Review on Emerging Drug Delivery Approaches for Treatment of Osteoporosis

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Abstract

Osteoporosis is a systemic skeletal disease characterized by low bone density and micro architectural deterioration of bone tissue with a consequent increase in bone fragility. This disease can affect anyone, but it is more likely to develop in women, partially due to the increased rate of bone loss at the onset of menopause. Worldwide most of the population suffering from osteoporosis of the hip. The present review provide information on the all the currently and emerging approaches for marketed and researched drug delivery treatment options. Bisphosphonates are the most popular drug therapy in this category. But there are many other treatments that strive to prevent further bone resorption such as hormone therapy, estrogen agonist or antagonists, calcitonin, and denosumab. Other therapies approach the problem of bone loss by inducing the formation of new bone tissue to replace that lost to these pathologies. These include teriparatide, strontium ranelateand statins. These therapies are more effective but it produces the some systemic adverse and side effects. To overcome this problems, development of targeted drug delivery, Nanoparticles and controlled drug delivery through polymer has been investigated. These methods extends the drug half-life, bioavailability and therapeutic efficacy of the osteoporosis treatment.

Keywords: *Osteoporosis, Bisphosphonates, Hormone Therapy, Skeletal Disease, Targeted Drug Delivery*

1. INTRODUCTION

Osteoporosis is a disease characterized by low bone mass and deterioration of bone structure that causes bone fragility and leads to an increased risk of fracture. The World Health Organization has defined osteoporosis as a bone mineral density (BMD) value more than 2.5 standard deviations below the mean for a normal young Caucasian woman 10. The severity of the disease is determined by a rating system developed by the World Health Organization, called as T score. Currently, there are approximately 323 million globally over the age of fifty with osteoporosis, and another 34 million at risk of developing the disease and 1.55 billion will increase by 2050.T scores are used by physicians to determine the severity of the osteoporosis as well the risk of future fracture. Though very few people die from this disease, an estimated 1.5 million individuals suffer from an osteoporotic fracture each year. In fact, forty percent of all white women, and thirteen percent of white men, over fifty years of age will experience a fracture of the hip, spine or wrist within the remainder of their lifetime[1, 2].

Table 1. WHO Scoring on Osteoporosis

T Score	Diagnosis
0 to ±0.99	Normal
1 to ±2.499	Osteopenia
≤ ±2.5	Osteoporosis
≤ ±2.5 accompanied by fracture or history of fracture	Severe osteoporosis

Primary osteoporosis is a result of the cumulative bone loss and deterioration that occurs throughout life. This steady bone loss leads to compromised bone strength, predisposing the bone to an increased risk of fracture. During childhood bone mass increases linearly, reaching a peak in both males and females around twenty or thirty years of age. At this time, the trabecular layer within the bone begins to slowly thin, resulting in a slow, linear loss of cancellous bone mass with age. It is generally thought that this thinning of the trabecular layer is associated with an age-related

decline in the amount of matrix synthesized by local osteoblasts[3].

2. PATHOLOGY OF OSTEOPOROSIS

The exact pathology of osteoporosis is unknown, but there are many contributing factors causing the increased bone loss. One main factor in the reduction of bone mass is the inadequate intake and retention of calcium. As people age the intestinal absorption and renal conservation of calcium is insufficient to conserve enough calcium to sustain blood levels.

This retention rate is low due to the amount of calcium lost daily through shed skin, nail, hair, sweat, and urine. Because of all these factors, only four to eight percent of calcium is absorbed. This inadequate calcium intake contributes to osteoporosis by resulting in the thinning of the cortical layer as well as a decrease and thinning of trabecular. In addition to changing estrogen and calcium levels, there are many age-related highly interdependent hormonal and nutritional factors that attribute to osteoporotic bone loss.

Lastly, though the biochemical basis behind bone loss and osteoporosis is unknown, it has been discovered that there are many other diseases attributing to the increased bone loss. Some of these pathologies are hypercortisolism, gonadal insufficiency, thyroid disease, diabetes mellitus, hyperparathyroidism, as well as some gastrointestinal disorders[3, 4].

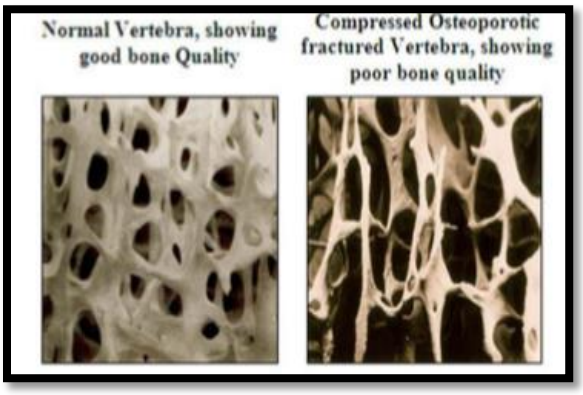

Fig. 1 Osteoporosis Pathogenesis

3. CURRENT DRUG DELIVERY APPROACHES FOR OSTEOPOROSIS

3.1 Anti-Catabolic Therapeutic Approaches

Anti-catabolic bone treatments block the activity of osteoclasts cells to prevent bone resorption and remodelling. This approach does not increase the amount of bone mineral content, its focus is to prevent any further pathological loss of bone structure[5].

3.1.1 Bisphosphonates

The most common drug therapy available for treatment of bone loss is a class of anti-catabolic drugs called bisphosphonates, these therapies are considered as a first-line treatment. These have affinity to bind to the surface of calcium phosphate hydroxyapatite crystals. These bisphosphonates surround the bone and act directly on osteoclasts by inhibiting recruitment and adhesion to the mineral matrix, shortening the osteoclasts lifespan and directly inhibiting the cellular activity. Commercially available bisphosphonates are alendronate, risedronate, Ibandronate, and zoledronic acid and additional bisphosphonate formulations are clodronate, etidronate, incadronate, minodronate, olpadronate, pamidronateand tiludronate[5, 6].

Bisphosphonates are the most common treatment in its drug class, coming in both oral and intravenous formulations. They are cnsidered as an appropriate and cost-effective therapy for both the treatment and prevention of osteoporosis[7].

3.1.2 Hormone Therapy

Estrogen, and the lack thereof, plays a large role in the onset of post-menopausal osteoporosis, and can also be used as a treatment option to prevent further development of the disease. Estrogen hormone therapy is an anti-catabolic treatment shown to not only preserve current bone mass, but the first one to two years of treatment often result in an increase in measured bone density. Currently, estrogen treatment therapies come in various formulations and routes of delivery.

In the cellular level, estrogen binds to osteoclasts receptors and stimulates the release of mediators that block further osteoclasts activity. In the initial weeks of therapy, biochemical markers of bone resorption slowly decline, followed by a slow and delayed decline in bone formation markers. In addition to a decreased resorption, estrogen also acts to rapidly reduce the activation of new remodeling sites within the bone. Estrogen hormone therapy can be used for both prevention and treatment of osteoporosis in post-menopausal women. It is shown to reduce the occurrence of both vertebral and non-vertebral fractures by thirty percent. Since estrogen is a naturally occurring molecule, it is distributed evenly throughout the body protecting the whole skeleton from further bone loss[8,9].

3.1.3 Estrogen Agonist or Antagonist

Another type of hormone-related anti-catabolic therapy for the treatment of various bone diseases is an estrogen modulator, raloxifene. This is the first-line treatment of both prevention and treatment of bone loss. It is a benzothiopenederivative that reduces bone resorption by mimicking estrogen's beneficial effects within bone, while having an anti-estrogen effect on the breast and uterus. These estrogen modulators also tend to lower serum cholesterol levels. Raloxifene is commonly prescribed because it provides the beneficial aspects of estrogen hormone therapy without the associated serious adverse effects.

Raloxifene acts by binding to estrogen receptors in the body and inhibiting the effects of estrogen on the uterus, while inducing estrogen-like effects on bone tissue but hormone therapy is known to increase the risk of breast cancer, endometrial or uterine cancer. Lasofoxifene and Bazedoxifene also used to hormonal therapy of osteoporosis[9, 10].

3.1.4 Overview on Anti Catabolic Treatments

These anti-catabolic treatments are extremely effective in lowering the risk of both vertebral and non-vertebral fractures and ceasing the bone resorption process. Risk of fracture is lowered up to sixty-eight percent and in some cases the bone mineral density can even increase around five percent. In some treatment forms, such as estrogen agonist / antagonists, these effects can be seen with very low dosages and after less than one year of treatment. Though these treatments are very effective and commonly used, they focus on retaining the density and structure the bone has at the initiation of treatment. If therapy is started at a more progressed stage of the disease, anti-catabolic treatments many not be as effective. Since these drugs act to prevent further damage they are very effective when administered early in the disease progression, but for patients with severe bone loss, an anabolic therapy may be more desirable.

3.1.5 Calcitonin

Calcitonin is a polypeptide hormone used as an anti-catabolic second-line treatment for patients who do not respond or have intolerable reactions to first-line treatments. Calcitonin is used to inhibit further bone resorption normally in women who are more than five years post-menopausal. Calcitoninis commercially available as a nasal spray under the names Fortical and Miacalcinby Upsher-Smith Pharmaceuticals and Novartis, respectively. But these therapies are not commonly used because though they are one of the safest therapies, they are also far less effective and have a much shorter duration than other treatments (11).

Calcitonin also inhibits osteoclastic acidic secretion of tartrate-resistant acid phosphatase (TRAP) and Na+-K- ATPasethat are necessary for mineral and collagen breakdown. Calcitonin produces effective cessation of bone resorption, but this effect generally does not last more than 24 hours, of which the direct effect on osteoclasts' function membrane and secretions only lasts for several hours. When prescribed and used correctly, calcitonin is able to prevent bone loss and lower the incidence of vertebral fracture, but it is seen as clinically impractical due to a need for strict patient compliance. It is generally only used only for women with at least five years post-menopausal who either cannot or choose not to use more potent therapies [1, 2].

3.1.6 Denosumab

The last anti-catabolic therapy for the treatment of bone loss is denosumab, an antibody that interacts with biological proteins in order to prevent bone resorption. This treatment is made by AMGEN and

marketed under the brand names Prolia and Xgeva. Though this isn't a common treatment for osteoporosis, it has been shown to be very effective at blocking bone loss. Denosumab is a human monoclonal antibody that binds to the receptor activator of nuclear factor-kappa β ligand (RANKL). The protein RANKL is essential to the formation and function of osteoclasts, with the binding of denosumab this protein is deactivated. The inhibition of this protein leads to a blockage of bone resorption. Denosumab works in a similar way as bisphosphonates, this antibody targets a different step in the bone remodelling process[8, 12].

3.2 Anabolic Therapeutic Approaches

Anabolic methods of treatment focus on inducing osteoblasts to lay down new ECM, to be mineralized and increase the skeleton bone mineral density. The goal of these therapies is to replace any lost tissue with new mineralized bone[13].

3.2.1 Teriparatide

Parathyroid hormone naturally plays a role in the body by maintaining calcium levels and stimulating both bone formation and resorption. As a therapeutic treatment, recombinant forms of parathyroid hormone have been shown to have anabolic properties and act to rebuild bone tissue. Currently, the available parathyroid hormone therapy is a recombinant intravenous injectable drug teriparatide. The early increase in bone mineral density suggests a rapid stimulation of osteoplastic activity through the activation of existing osteoblasts and the induction of differentiation of bone lining cells. Another advantageous effect seen from the use of teriparatide is the lack of influence of other hormones. Fluctuating levels of estrogen and testosterone constantly influence natural parathyroid hormone, while the responsiveness of osteoblasts was unchanged with teriparatide [14, 25].

3.2.2 Statins

Statins are a class of commonly prescribed drugs that act as competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase in order to decrease hepatic cholesterol biosynthesis. These molecules acts as a rate limiting step in cholesterol synthesis by blocking conversion of HMG-CoA to mevalonate, resulting in lowered serum cholesterol levels for the treatment of high cholesterol and coronary heart disease. Recently, studies have shown that statins also increase the expression of bone morphogenic protein 2 (BMP-2) in osteoblasts, inducing osteoblast differentiation, and subsequently stimulating bone formation. These treatments are currently being investigated and researched by many different groups for possible use as a therapy for bone loss, reversing the acquired skeletal fragility. Stains also increases the collagen availability which further enhances the ability for newly differentiated osteoblasts to lay down osteoid. Alkaline phosphatase, necessary for bone mineralization, concentration was also elevated in cells treated with statin drugs[15, 16].

3.2.3 Strontium Ranelate

The last treatment option widely researched is strontium ranelate, a conjugate of strontium and ranelic acid. The mechanism of action behind strontium ranelateis not well known. *In vitro* and *in vivo*. Studies have shown both anabolic and anti-catabolic properties, it is proven to both increase bone formation and decrease resorption. While not approved for sale in the United States, an oral form of strontium ranelate is marketed for use in prevention of vertebral and hip fractures in abroad under the name Protelos.

Strontium ranelate has also been associated with a decrease in the numbers of mature osteoclasts and bone resorption. It is thought that this decrease in bone resorption is achieved by strontium ranelate's total disruption of the actin cytoskeleton of osteoclasts. The disruption of this protein structure prevents the cells from attaching to the apatite minerals, a necessary step in the mineral breakdown.

3.2.4 Limitations of Anabolic Treatments

The ability to enhance bone mineral density and repair pathological damage is an optimum treatment path for bone disease therapies. The only anabolic treatment approved for use in the United States is a form of recombinant parathyroid hormone, teriparatide. Though teriparatide is very effective at increasing bone density, upon cessation

of treatment bisphosphonates are needed to prevent continued breakdown of the tissue. Statins have shown remarkable success in the induction of bone formation through the increased expression of biological markers, but much more research must be completed before this can be considered a potential treatment for bone pathologies. Lastly, strontium ranelate acts in two ways to increase formation and decrease resorption and has shown increases in bone density.

4. CONTROLLED DRUG DELIVERY

4.1 Nanoparticles Delivery Vehicles

Nanoparticles are commonly investigated for their ability to transport drug therapies and release the drug treatments directly into the cell. These nanoparticles are so effective because they are much smaller than a cell; these particles are taken up by the cell, transported across the cell membrane and released into the cytosol for delivery to cell organelles.

Many materials are being researched for the fabrication and loading of nanoparticles. A large focus has been placed on polymers because of the lack of inflammatory or immune response and the proven biodegradability of some bio inert polymers. For therapeutic delivery to bone tissue, an emphasis has been placed mainly on three different polymers, N-(2-hydroxypropyl) methacrylamide copolymer (HPMA), polyurethane (PU), and poly(lactide-co-glycolide)-poly(ethylene glycol) copolymer (PLGA-PEG) (20, 21).

4.1.1 N - (2-hydroxypropyl) Methacrylamide Copolymer (HPMA)

HPMA copolymer nanoparticles were successfully formulated with a proper molecular size such that they were efficiently cleared from the body by the liver, with minimal accumulation in the heart and lungs. It has been shown that a larger molecular weight increased the particle accumulation in bone, but decreased the specificity of the targeted delivery.

These HPMA particles were also used to deliver prostaglandin, known to have anabolic effects on bone, to the tissue with a large portion of the drug being release in the cellular osteoclast environment.

4.1.2 Polyurethane (PU)

Biodegradable PU scaffolds have also been a topic of research for the delivery of statins to bone tissue. The use of a scaffold prevents a large amount of the drug from being lost due to first-pass metabolism. It was shown that two hundred micrograms of lovastatin was a sufficient dose to enhance new bone formation without any adverse inflammatory reactions.

4.1.3 Poly (Lactide-Co-Glycolide) - Poly (Ethylene Glycol) Copolymer (PLGA-PEG)

Biocompatible polymers for bone drug delivery such as PLGA-PEG. PEG is commonly used in nanoparticle formulations to provide additional biocompatibility and increased blood circulation time compared to non-PEG ylated particles. It was also showed that altering the proportions of PLGA to PEG within the copolymer could change the bio distribution of the particles.

4.1.4 Other Copolymers

Rather than using inert polymers, an emphasis has also been placed on the use of physiological materials such as hydroxyapatite and other calcium orthophosphates for the delivery of drug therapies, especially to bone tissues. Hydroxyapatite and other calcium phosphate molecules are chemically similar to the inorganic component of bone, eliciting no immune response and allowing them to chemically bond to the bone tissue. Because of the chemical likeness to native bone tissue, the use of hydroxyapatite as a particle allows for targeted delivery for, these particles preferentially to deposit in bone tissue. Once these particles bind to the bone they are actively transported into bone cells where the loaded drug can be released for treatment of various conditions.

5. TARGETING APPROACHES

In order to enhance specificity of polymer and hydroxyapatite delivery to bone, many different targeting techniques have been investigated.

Delivery specificity is extremely important because drug absorption in unwanted tissues can cause serious adverse effects, as was the problem with estrogen therapy. There are two main approaches to locally target drug delivery with nanoparticles, passive and active targeting[23].

5.1 Passive Targeting

Passive targeting is often used for delivery to tumours because it utilizes characteristic physiological tumour biology. Tumours experience an increase in vascular fenestrations due to enhanced permeability and retention effect, allowing for the increased delivery of nutrients to the tumour due to the accelerated growth rate. Passive targeting relies on this increased permeability to allow for more nanoparticles to be delivered to the tumour site. Though effective, passive targeting is difficult to control because of the randomness of the approach. For delivery to non-tumorous tissues active targeting must be utilized.

5.2 Active Targeting

Active targeting approaches use the conjugation of small molecules to the surface of the nanoparticles. These molecules are specially chosen to bind to overexpressed antigens or receptors at the site of targeted delivery. Targeting agents generally fall within one of the following categories: proteins, including antibodies, nucleic acids, peptides, vitamins or carbohydrates.

6. DRUGS BINDING IN TARGETED DELIVERY

There are many molecules used to provide bone targeting specificity, mainly tetracycline, bisphosphonates, peptide sequences and various bone proteins. Tetracycline is a crystalline amphoteric substance that has the ability to bind to the surface of bone apatite crystals by chelation with surface calcium ions. These molecules bind strongly to bone mineral with minimal dissociation, but tetracycline has a poor chemical stability during modification. This instability eliminates the ability to conjugate drugs to the targeting molecule, making tetracycline an unusable targeting agent.

Bisphosphonates have been successfully conjugated to free drug 88, HPMA, and PEG for controlled drug delivery. Bisphosphonates have also been altered to form a liposome to control the release of therapeutic agents from a scaffold material. The use of bisphosphonates allows for a cost effective and efficient method to target bone tissue, but these delivery vehicles must be specially designed to block the anti-resorptive effects of the bisphosphonate itself.

Another common bone targeting agent is a D-aspartic acid octapeptide (Asp8). This peptide sequence can distinguish between functional domains of the skeleton and preferentially bind to resorptive sites. In recent studies targeting with Asp8 resulted in longer circulation half-lives, preferential binding to eroded surfaces and targeted bio distribution with over sixty percent of particles binding to the skeleton. Polymalonic acid has also been under investigation for use in a targeted drug delivery system because it has a strong affinity to bind to hydroxyapatite. Though it has been successfully modified on the surface of drugs, no therapeutic effects have been reported.

7. CONCLUSIONS

- Presently, there are many treatment options that can prevent osteoporosis and even increase the bone mineral density slightly.
- More focus must be placed on anabolic treatments to allow the recovery and rehabilitation of lost tissue.
- Statins have promising results for the induction of bone formation by the increase in BMP-2 mRNA. With these nHA-PGA-PEG nanoparticles, these statin molecules could be delivered directly to the skeleton to allow for a quick and efficient increase in the natural bone formation process. These particles have proven abilities to be loaded with drug and release that loaded drug with a controllable profile.
- Hydroxyapatite particles are known to target bone due to the chemical likeness of the molecules, but to enhance the targeting, peptide sequences have been tested for binding efficiency and specificity. It is shown that both peptides tested can exclusively target bone and remain bound to the surface

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