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Review Article

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Translation Approaches Targeting Immune Pathways for the Prevention and Treatment of Metabolic Bone Disorders

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Abstract

Bone is a sensitive organ in our body that produces organisational proteins, reserves minerals and metabolises proteins controlled by certain influences. The last few years of discoveries have shown that there is a broad spectrum of communication between the bone and the immune system in maintaining skeletal equilibrium. Disorder of bone metabolism is a group of diseases that affects bone health.Disorder of bone metabolism can be further characterised into three disorders: Osteoporosis, Osteomalacia and Paget's Disease of Bone. Osteoporosis is a skeletal disease that is marked by a reduction in bone mass, which usually increases fracture risk. The occurrence of osteoporosis is mostly seen in post-menopausal women and older people. A broadened bone disorder identified as osteomalacia is characterised by reduced calcium absorption, resulting in a buildup of osteoid or unmineralized matrix in the skeleton. Osteomalacia causes musculoskeletal pain, skeletal abnormalities, weakness in muscles, and hypocalcaemia with warning signs. Osteomalacia is caused by a deficiency in Vitamin D. Vitamin D deficiency may cause malabsorption, liver disease and anticonvulsant medication. Paget's Disease of Bone is a disease that usually causes pain in the bone but often comes without symptoms. The pain is characterised by increased pain, and it affects one or several bones throughout the skeletal system.After emerging, the discoveries and the research highlight the immune system's crucial function in controlling bone metabolism, which has led to the study of Osteoimmunology. Osteoimmunology was contributed to due to the intensified bone loss caused by inflammatory diseases. The immune system plays a very important role in the process of bone remodelling. Osteoclasts are a type of multinucleated cell that helps the bones to grow and develop. The cytokines like IL-6, RANKL, and TNF-α help in bone resorption.The main objective of this paper is to review how immune signalling pathways can be targeted for the prevention and treatment of metabolic disorders.

Keywords: Osteoimmunology, Osteoporosis, Osteomalacia, IL-6, RANKL, TNF-α, Cytokines, Vitamin D, T-cells, B-cells

1. Introduction

Bones are solid calcified specialised connective tissue that are formed through processes such as endochondral ossification and intramembranous ossification. Endochondral ossification a process where bone tissue is produced during the development of the foetus or fixation of bones in the mammal's skeletal system. Intramembranous ossification is a process that is required during the natural healing of the bones. Decades later, it was found that there is a broad spectrum of communication between bones and the immune system. The immune system helps in bone regulation. Immunodeficiency syndromes can also lead to bone loss or abnormalities in the shape of bone [1]. After a lot of past investigation, one discovery came up which states that the presence of an immuno-skeletal interface (ISI), a centralisation of shared cells and cytokine effectors serving dual, but separate, functions within both the immune and skeletal systems.After all the discoveries are considered together, which basically highlights the function in controlling the metabolism of bone, has led to the

study of Osteoimmunology [2].

In the field of osteoimmunology, the association between T cells and osteoclasts is vital.

Osteoimmunology is a very crucial field, enabling the unmatched chance to comprehend conditions like rheumatic illnesses and arthritis.

The main objective of the paper is to review how translation approaches targeting immune pathways for the prevention and treatment of metabolic bone disorders.

1.1. Bone Biology

Bone Biology is the study of the development, structure and function of bones. Bones can be defined as specialised connective tissue. It undergoes bone remodelling, repair and growth for a lifetime.

1.2. Formation of Bone Tissue

Bone itself is known as a specialised connective tissue. Bone tissue is continuously renewed through the united actions of the cells of the bones. Two main cells basically help in the formation of bones: 1) Osteoclasts and 2) Osteoblasts.

1.3. Roles of Osteoblast and Osteoclast

- **Osteoclasts**

Osteoclasts are a type of bone cell that helps in the resorption of bone. Osteoclasts sense the mechanical forces generated within and outside the body. Osteoclasts are found basically on the surface of the bones that undergo resorption of bones. Osteoclasts play a vital role in maintaining, repairing and remodelling the bones. Two stages take place in the osteoclasts' resorption of the bone matrix: (1) the dissolution of the inorganic components (minerals) and (2) the breakdown of the organic components. An acidic environment is created by the osteoclast that helps in the increase of the solubility of the minerals of the bone, which helps in the reintegrating of the minerals of the bones into the cytoplasm. The activities performed by osteoclasts are controlled by hormones.

- **Osteoblasts**

Osteoblasts are single-nucleated bone cell and mesenchymal cells that helps in synthesizing bones and are also responsible for the bone matrix. Osteoblasts possess the receptors and catabolic enzymes required for metabolising and using circulating lipids [3]. Osteoblasts produce a high amount of bone mineral that mixes with the inorganic matrix, forming a dense tissue.

1.4. Bone Metabolism Regulation

The continuous process of formation of bones, in which the strength of the bone does not change and the amount of minerals present is stable, is defined as bone metabolism. The process also includes bone remodelling, closely controlled by hormones, nutrients, cells, and mechanical forces.

2. Immune System and Interaction of Bones

The interaction between the immune system and cells of bones is known as Osteoimmunology.

2.1. Role of T-Cells, B-Cells, and Macrophages in Bones

The main role of T- cells, B-cells and macrophages is to help in the remodelling or repairing of the bones. Here is the detailed function of all the cells that help in the repair of the bones.

2.1.1. Role of T-Cells

The role of T- cells is that it helps in the remodelling of the bones through the secretion of cytokines. The main role of T cells is to produce RANKL, and it also helps in the secretion of cytokines. The T-cells release cytokines like **TNF-α**, IL-**17** and **IFN-γ**. Depending on the situation, these cytokines can either promote or prevent bone resorption. The T cells also help in bone remodelling or repair of bones.

2.1.2. Role of B-Cells

The B-Cells are abundant and influence bone metabolism. If there is an abnormal B–cell activity, it can lead to certain bone diseases like Osteoporosis or rheumatoid arthritis by increasing osteoclast activity. The B-Cells produce a protein like Osteoprotegerin that inhibits the production of Osteoclasts.

2.1.3. Role of Macrophages

The main role of Macrophages is that they are closely associated with osteoclasts and play a significant role in controlling the reconstruction of bones. During bone injury and fracture healing, macrophages eliminate dead cells and tissue.

3. Theroles of Cytokines such as IL-6, TNF-α, and RANKL in Regulating Osteoblast and Osteoclast Activity

- **IL-6**

Interleukin-6 is a multifaceted cytokine (IL-6) regulates immunological responses and is essential for preserving physiological homeostasis. IL-6 is quickly produced and triggers acute-phase and immunological responses in situations of homeostasis disruption, such as infection or tissue damage, supporting host defence mechanisms. However, the pathophysiology of IL-6 production that is dysregulated, high, or persistent is associated with both acute systemic inflammatory response syndrome and chronic immune-mediated diseases [4].

Moreover, IL-6 links immune activation to bone resorption by increasing osteoclast development through elevation of RANKL expression [5]. Additionally, it triggers intracellular signalling pathways, especially the JAK/STAT pathway, which intensifies inflammatory cascades even more [6].

- **TNF- α**
- TNF-α is a versatile cytokine that is mostly produced by activated macrophages. Under physiological conditions, the precursor pro TNF-α, a type II transmembrane protein, is cleaved by proteases at the Ala76–Val77 bond to release the soluble TNF-α (mature protein).

- **RANKL**
- The TNF super-family includes the 317 amino acid protein RANKL, whose mRNA is mostly expressed in bone, bone marrow, and lymphoid tissues.

4. Metabolic Bone Disorder

Metabolic Bone disorder is a type of disease or disorder of the skeletal system that is usually causes due to the altering of the calcium and phosphorous of the homeostasis [7].

There are three types of disorders of bone metabolism: Osteoporosis, Osteomalacia and Paget's disease of the bone.

4.1. Osteoporosis

Osteoporosis is a skeletal disease that causes increased fracture risk and loss of bone mass. The major cause of osteoporosis is low bone mass. The most significant categories of causes include inadequate optimum bone density, women's menopause, slow bone loss from ageing processes, and a variety of sporadic environmental, nutritional, and behavioural factors that influence bone mass in certain individuals but not in others.

Osteoporosis is now known to be significantly influenced by chronic low-grade inflammation, especially in postmenopausal women and the elderly.

Because osteoporosis is a clinically silent condition until it shows up as a fracture, it is frequently undertreated [8].
There are two types of osteoporosis:

- Primary Osteoporosis
- Secondary Osteoporosis

4.1.1. Primary Osteoporosis

Primary Osteoporosis is usually defined as a genetic underlying disease, or it can be well explained as a disease that is caused by ageing or usually found in post menopausal women. Primary osteoporosis basically affects post menopausal women due to the changes that occur and affects the person [9]. Apoptosis, or programmed cell death, causes primary ovarian failure, which leads to menopause, a natural physiological phenomenon [10].

4.1.2. Secondary Osteoporosis

Secondary osteoporosis usually occurs due to a bad lifestyle or due to a medical condition that affects the body and causes bone mass loss.

4.2. Osteomalacia

Osteomalacia is the least common bone disease in bone biology. Osteomalacia causes musculoskeletal pain and weakness in the muscles. The primary cause of osteomalacia is vitamin D deficiency, which is typically brought on by decreased cutaneous vitamin D production in elderly people who are confined to their homes [11]. Osteomalacia is frequently caused by abnormal vitamin D metabolism, resistance to vitamin D's action, or harmful effects on osteoblast function.

4.3. Paget's disease of bones

Paget's Disease of bones is a chronic metabolic disease where usually the bones break down, and when it remodels itself, the bones start growing rapidly at a very fast speed and form irregular shapes. In this disease, both the osteoclast and osteoblast are highly active.

5. Nutritional & Micro-Bio Based Translational Approach

5.1. Role of Calcium and Vitamin D in bone Remodelling

Calcium and Vitamin D play a very important role in bone remodelling. The deficiencies in calcium and vitamin D lead to osteoporosis, which usually causes loss of bone mass and increases fracture risk. Calcium is a very vital element that helps to reduce the loss of bone mass and lowers the risk. Callus mineralisation requires calcium, with 1.7–2.3 g of hydroxyapatite deposition required per cm3 of bony callus, as shown by measuring calcium kinetics in rats during callus development using radioactive Ca45. Consequently, vitamin D and calcium deficiencies likely have a detrimental effect on fracture healing [12-15].

5.2. Importance of zinc, magnesium, and vitamin K

- **Magnesium -:**
- The main role of magnesium is that it acts as a cofactor, and it is a very essential element. Magnesium supports bone density and helps to regulate blood glucose [16].
- **Zinc-:**
- Zinc acts as a catalytic component and helps in bone formation. Zinc helps in immune defence and cell proliferation. Zinc also helps in stabilising cell membranes and helps in the growth of bones [16].
- **Vitamin K2-:**

Vitamin K2 directs calcium to where it is needed, bones and teeth. Vitamin K2 is a fat-soluble vitamin, and it is a group of molecules with distinct side chains but a common methylated naphthoquinone ring. Menaquinone-n (MK-n) is a group of distinct compounds that make up vitamin K2 (VK2). The length of the unsaturated isoprene side chain in the molecule varies from MK-2 to MK-15; the most researched menaquinones are MK-4, MK-7, and MK-9 [16].

6. Translational Approach for Metabolic Bone Disorder

Translating fundamental biological research results into clinical interventions and diagnostic tools is the aim of translational research. Dietary changes are important to encourage bone reabsorption and regeneration and reduce fracture risk, although supplementation of essential minerals, including calcium, phosphate, and vitamin D are often needed. Although these treatments are frequently successful, genetic factors make hereditary bone illnesses particularly difficult to treat. Emerging technologies that provide higher-resolution insights into bone architecture and quality are increasingly complementing traditional diagnostic methods such as dual-energy X-ray absorptiometry (DXA) [17].

Biochemical markers of bone metabolism, such as serum osteocalcin and C-terminal telopeptide levels, can also be used to quantify bone remodelling. Other laboratory tests that should

be used to rule out secondary osteoporosis include sedimentation rate (SR), blood count, alkaline phosphatase (ALP), ionised calcium, creatinine, serum 25-hydroxyvitamin D (S-25OHD), transglutaminase antibodies, thyroid-stimulating hormone (TSH), and testosterone in men [17].

Bone-resorbing cells (osteoclasts) can be slowed down by bisphosphonates such as risedronate, ibandronate, alendronate, and zoledronic acid. Hormone replacement treatment (HRT) and other compounds that resemble oestrogen, like the selective oestrogen receptor modulator (SERM) raloxifene, can effectively prevent bone loss. Antibodies like denosumab stop bone loss by targeting receptor activators of nuclear factor kappa B ligand (RANKL), a protein necessary for osteoclast development. Teriparatide is an anabolic steroid that increases bone density and strength.

7. Immune Pathways Involved in Bone Disorder

Osteoporosis is a skeletal disease that usually results in fractures or loss of bone when there is an increase in osteoclast cells, which usually break the bones. After a lot of decades and a lot of research, it was found that there is a connection between the bones and the immune system, which is known as Osteoimmunology, where signals are shared between the bones and the immune system by cytokines. Both the immune cells and the bone cells arise from the bone marrow, so they share a common origin of cells. The Immune system releases cytokines (protein structures) that control the cells of the bones, such as T-Cells, B-Cells, and also send signals such as RANKL and OPG. Cytokines are protein structures that act as chemical messengers. Cytokines like TNF, IL-1 and IL-6 increase bone loss, and there are some anti-inflammatory cytokines that help to prevent bone damage and help in bone formation. Interleukin–10, TGF-B, Interleukin–4 (IL-4), and Interleukin -13, that reduces inflammation and protect bones.

• **RANKL (Receptor Activator of NF-κB Ligand)** is a signalling system that is formed by osteoblasts (bone-forming cells) and bone marrow cells to control osteoclast formation. The Osteoclast breaks the bones, and so to balance it Osteoblast are produced to maintain the balance of the cells and to prevent fracture risk. RANKL acts as a messenger molecule.

• **RANK is** a receptor found on the osteoclast herald. It acts as a latch to the osteoclasts.

• **OPG** is **OSTEOPROTEGERIN**, a protein that is secreted by bone-forming cells and functions as a soluble receptor mimic, capturing RANKL molecules and suppressing RANK-RANKL signalling.

The understanding of bone diseases underwent an enormous shift when genetic enquiries revealed that the receptor activator of NF-κB (RANK), its ligand RANKL, and the decoy receptor OPG are crucial, key regulators of osteoclast growth and osteoclast function [18]. Osteoprotegerin is a protein that is secreted by osteoblasts, and it maintains skeletal stability and increases the degradation of bones by suppressing the RANKL-RANK signalling.

8. Origin and Progression of Metabolic Bone Disease

Increased bone breakdown, decreased bone production, and increasing structural degradation are the hallmarks of metabolic bone diseases, which are caused by abnormalities in the mineral, hormonal, or immunological regulation of bone remodelling. The main cause of a metabolic disorder is due to the presence of low calcium and Vitamin D, which leads to diseases like Rickets and Osteomalacia. Hormonal changes, such as reduced estrogen or the presence of excess parathyroid hormone, lead to this kind of metabolic bone disorder.Even the presence of low Osteoprotegerin can lead to such a disease. Inflammation, poor nutrition, decreased lean body mass, immobility, and the side effects of medicines, particularly glucocorticoids, are all direct causes of bone loss. Systemic skeletal deterioration is frequently linked to persistent inflammatory disorders. The intricate and interconnected mechanisms at play are mainly mediated by disturbances in the kinetics of bone remodelling. Inflammation often affects both routes and increases osteoclastic activity while limiting osteoblastic function [19]. This review describes how immune responses and bone metabolism interact and assesses treatment strategies for inflammation-induced bone loss. A catabolic state that encourages the breakdown of lean body mass and reduces bone formation is associated with the majority of chronic inflammatory diseases [20,21].

9. Relationship Between Bones and Microbiome

A diverse and changeable community of microorganisms living in a particular niche—the gastrointestinal tract (GIT)—is referred to as the gut microbiota. The entire collection of genetic material found inside this microbial community is referred to as the gut microbiome, which is frequently used interchangeably with the term "gut microbiota."[22]. This "extended genome" is made up of millions of microbial genes. This group comprises unicellular eukaryotic species, viruses, archaea, and bacteria. Gut Microbiota influences the function of distal organs by producing multiple compounds. Gut Microbiota is a diverse system that changes with the passage of time. During infancy and early childhood, the GM changes quickly, and other variables like food and antibiotics may also contribute to its formation. The Immune system comprises a variety of cells that protect the organism from foreign particles. Gut Microbiota can interact with a lot of immune cells, produce molecules and maintain proper bone health. Gut Microbiota maintains proper bone health by increasing calcium health and by producing gut serotonin [23]. The gut microbiota constitutes a complex ecosystem that regulates calcium and vitamin D absorption while influencing intestinal permeability, hormonal activity, and immune function. Critical roles are played by T helper 17 cells, tumour necrosis factor (TNF), interleukin-17, and the RANKL system [24].

Probiotics are live organisms that provide health benefits to the host. Their key features include tolerance to acidic conditions and bile, enabling survival within the gastrointestinal tract (GIT), along with phenotypic and genetic stability, the ability to adhere to the mucosal lining, resistance to antibiotics, and the production of antimicrobial substances capable of suppressing known pathogens.

Fortified fermented dairy products, which also include calcium, protein, phosphorus, and other minerals, are a source of probiotics [25].

10. Therapeutic Approaches

In addition to the importance of academia's role in target identification and drug discovery, design, and development, translational drug discovery necessitates collaboration between clinical and pharmacological research. There are certain drugs developed to reduce bone loss, like anti-resorptive drugs, which basically reduce bone loss, Anabolic drugs, which help to build bone and biological therapies, for example, denosumab; these target the immune pathways (like RANKL) for blocking osteoclast formation.Vitamin D also acts as an immunomodulator by controlling immune responses and helps in the remodelling of the bones. Pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1, play a central role in mediating the inflammatory response in rheumatoid arthritis. Osteoclast activation and osteoblast differentiation can be directly or indirectly triggered by the proinflammatory cytokines involved, which can result in bone loss and osteoporosis. Osteoclast genesis has been directly linked to cytokines such as interleukin (IL)-1β, IL-6, IL-8, and IL-11[26]. Osteoclast production or osteoblast inhibition may be indirectly impacted by other cytokines such as TNF-α, IL-7, and IL-15. Furthermore, by releasing matrix metalloproteinases (MMPs), persistent inflammation might cause osteoporosis. One of the main cytokines that may be influenced in the pathophysiology of RA bone loss and cartilage injury is the receptor activator of nuclear factor-κB ligand (RANKL). Denosumab is a biological therapy; if we take a single dose, it will work up to 6 months.

11. Advanced Translational Approach

Precision medicine plays an important role and has the potential for doing betterment and having a positive impact on the endocrine disorder. The most extensively used biomarker of growth hormone secretion is insulin-like growth factor I (IGF-I). However, the accuracy of IGF-I tests can be affected by a number of circumstances, and their predictive value for response to recombinant human growth hormone administration is minimal. Biomarkers may act as either (i) clinical endpoints, which represent how the patient feels, functions, or survives, or (ii) surrogate endpoints, which are meant to replace a clinical endpoint that might take longer than the study period to manifest and are appropriate for forecasting the anticipated benefit (or lack thereof) based on scientific evidence [27]. AI Technology has a great potential which can help in doing drug discovery process a lot faster with the . of technology and high data and by giving appropriate data within a short period of time. Drug Discovery is a great process and is much required for developing medicines, and it is a bit time-consuming, but with the help of AI, it can be a lot faster. So, AI plays an important role in the Drug Discovery process.

These issues may be resolved by a variety of AI-based algorithms, such as reinforcement, evolutionary or rule-based algorithms, and supervised and unsupervised learning techniques. These techniques are usually predicated on the examination of vast volumes of data that can be used in many ways [28].

12. Challenges and Limitations

After a lot of research and decades later, a lot of pharmaceutical therapies were found that promote bone formation and treatment of osteoporosis, such as antiresorptive drugs, anabolic therapies and biological therapies such as denosumab. Antiresorptive drugs help in bone formation, and anabolic therapies help in the formation of new bones. Antiresorptive and bone anabolic medicines are linked to both common and uncommon side effects, which are especially crucial to address because these medications are used for long-term treatment in many patients, many of whom are older and/or have many medical conditions. Additionally, bisphosphonates have been repurposed as a cancer preventative medicine, and antiresorptive medications are used to avoid skeletal events in cancer patients or to limit bone resorption in patients with malignant hypercalcaemia. Antiresorptive drugs such as Bisphosphonates, Denosumab, selective oestrogen receptor modulator and anabolic therapy such as Teriparatide, Abaloparatide, Romosozumab. NPs (Nanoparticles) serve as versatile drug delivery platforms for diverse diseases, including malignancies and inflammatory or tissue-repair conditions. Since NPs may form persistent connections with various ligands, boost the drug loading effectiveness of both hydrophilic and hydrophobic molecules, and regulate the delivery of micro- and macromolecules, they have demonstrated a favourable platform for selective tissue targeting [29]. Specifically, NPs guarantee (i) enhanced drug solubility; (ii) prolonged drug stability due to the protective shield that lowers drug metabolism after administration and prevents rapid clearance by filtering organs; (iii) improved transport ability across cell membranes; (iv) reduction of drug resistance mediated by extrusion pumps; and (v) targeted delivery of therapeutics to targeted tissue. By selectively blocking RANKL, targeted therapies—especially monoclonal antibodies like Denosumab—have proven impressive clinical efficacy in improving bone mineral density and lowering fracture risk Denosumab is a biological therapy which is a long-term safety concern and leaves a mark working for a long term if a person has taken a single dose, it eventually works upto 6 months and it is safe [30].Therapies can be sometimes expensive and sometimes cost-friendly, like oral bisphosphonates, which are cost-friendly and biological therapies may be a bit expensive, like denosumab, Teriparatide and the most expensive treatment is Bone marrow transplant, which costs up to lakhs.It usually depends on the type of treatment that is done.

13. Future Perspective

The future of metabolic bone disorder treatment lies in personalised and combination therapies that target multiple pathways simultaneously. Advances in biomarker discovery and multi-omics technologies will further enhance our understanding of disease mechanisms. Continued research in osteoimmunology will lead to more precise and effective therapeutic strategies.

14. Conclusion

By demonstrating the essential role of osteoimmunological systems in bone remodelling, translational medicine research

that targets immune pathways has greatly revolutionised the prevention and treatment of metabolic bone diseases. Significant discoveries show that inflammatory mediators, including the RANK/RANKL/OPG signalling axis and cytokines (such as IL-6, IL-17, and TNF-α), directly control osteoclast development and activity, which in turn affects bone resorption. By selectively blocking RANKL, targeted therapies—especially monoclonal antibodies like Denosumab—have proven impressive clinical efficacy in improving bone mineral density and lowering fracture risk. These methods represent a change from conventional symptomatic therapies to mechanism-based interventions that target the disease's fundamental development of disease. Despite significant improvements, there are still several issues. The development of highly targeted therapies with few adverse effects is hampered by the complexity of immune pathways. The situation is further exacerbated by concerns including long-term safety, expensive therapy, and restricted access. Furthermore, it is still very difficult to close the gap between lab research and clinical application. This paper basically indicates the translational drug development targeting immune pathways and promising a strategy that helps in the reduction of metabolic bone disease and reduction in health issues by providing proper medication for the prevention of metabolic bone disease. This paper also indicates how the disease can be treated by proper lifestyle and the new treatments that are being developed. There are some biological therapies, antiresorptive medicines and anabolic therapies that help to reduce the loss of bone and the fracture risk of bones. It also shows how new technologies and AI are helping for the treatment work properly and how it is helpful.

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