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Multiple Myeloma: Impact on the Skeletal System- a Review of the Literature

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Abstract:
Background. Multiple myeloma is a cancerous disease of the hematopoietic system marked by the uncontrolled proliferation of monoclonal plasma cells within the bone marrow. Bone disease is a characteristic feature and a diagnostic criterion of multiple myeloma.
Aim. This paper aims to discuss the pathophysiological mechanisms underlying bone damage in multiple myeloma and to present current diagnostic and therapeutic approaches designed to improve clinical outcomes in patients affected by myeloma bone disease.
Material and methods. A review of the scientific literature from the past eight years was conducted using topic-specific keywords, primarily through databases such as PubMed and Google Scholar.
Results. Bone mass loss is a complex process that involves elevated osteoclast activity, impaired osteoblast function, and the release of pro-inflammatory cytokines, resulting in a disruption of the balance between bone resorption and formation. As a consequence, patients may develop chronic bone pain, pathological fractures, and postural changes. Therapeutic strategies that aim to slow the course of the disease and inhibit osteoclast activity are essential for minimizing the risk of skeletal-related complications and markedly enhancing patients' quality of life.
Conclusion. Multiple myeloma is a malignancy that frequently leads to bone damage. This review discusses the underlying mechanisms, diagnostic methods, and current treatments aimed at preventing skeletal complications and improving patient outcomes

Keywords: multiple myeloma; myeloma bone disease; osteoclastogenesis; osteoblasts; OPG; RANKL.

1. Introduction.

Multiple myeloma is a malignant hematologic disorder characterized by the unchecked proliferation of monoclonal plasma cells, which secrete monoclonal immunoglobulins. This leads to multiorgan damage and the suppression of the production of other blood cell lines in the bone marrow [1]. The disease accounts for less than 1% of all cancer diagnoses and 10% of hematologic cancers [2,3]. The annual incidence is 5 per 100,000 people, with a slightly higher frequency within males and Black people [2,3]. The highest incidence is observed in individuals in their seventh decade of life, and less than 3% of cases affect individuals under the age of 40 [2]. Multiple myeloma is more commonly diagnosed in highly developed countries, particularly in Australia, the USA, and Western Europe. The incidence is steadily increasing in these regions, with multiple myeloma accounting for 1.8% of all cancer diagnoses in the USA in 2020 [3]. Known risk factors for developing multiple myeloma aside from the mentioned statistical aspects are obesity and exposure to digoxin [4]. Currently, multiple myeloma is considered incurable, but treatment can significantly extend survival [4]. Bone lesions in multiple myeloma represent a major issue, affecting up to 90% of patients, with significant consequences for their health [5]. Pathological fractures and other bone damage contribute to substantial impairment of patients' functioning and increase the risk of death. In multiple myeloma, this imbalance between bone resorption and formation leads to lesions that fail to heal, even during complete remission. [6]. Understanding these mechanisms is crucial, as it provides better insight into the pathogenesis of the disease and facilitates the implementation of appropriate treatments that can help control these lesions, improve the general condition of patients, and minimize the consequences associated with bone damage.

2. Review methodology.

This article outlines the current understanding of how multiple myeloma affects the skeletal system. The analysis and review of existing literature were performed through searches in the PubMed and Google Scholar online databases. The following keywords were used to find relevant articles: multiple myeloma, myeloma bone disease, osteoclastogenesis, osteoblasts, OPG, RANKL. Publications in both the Polish and English languages were considered in the review. The majority of the sources (81%) were published within the past eight years.

3. Research results

The Importance of the Skeletal System in Multiple Myeloma. Bone disease is the most common clinical manifestation of multiple myeloma [5]. Patients often report severe bone pain and pathological fractures resulting from progressive bone mass loss [6]. These symptoms significantly affect the patients' functionality and contribute to an increased mortality rate, with an increase of up to 20% [6]. Moreover, bone disease in multiple myeloma can lead to hypercalcemia and spinal cord compression syndromes, which not only impact patients' quality of life but also their prognosis. The most common location for these lesions is the lumbar spine. Bone destruction confirmed by X-ray imaging is observed in up to 79% of patients [7].

3.1. Diagnosis of Multiple Myeloma.

3.1.1. Criteria for the diagnosis of multiple myeloma

The expansion of abnormal plasma cells within the bone marrow results in the suppression of the production of other blood cells, including erythrocytes, which leads to anemia and considerable physical weakness. It also affects immune system cells, leading to immune dysfunction and an increased risk of infections. The development of the disease causes lytic bone lesions, which subsequently lead to painful fractures and hypercalcemia, damaging, among other organs, the kidneys. The M protein produced by circulating plasma cells can accumulate in the kidneys, leading to their failure [4]. These symptoms are part of the diagnostic criteria for multiple myeloma under the acronym CRAB, which describes organ damage. Bone-related changes are the second most common feature in CRAB [8]. The second part of the acronym, SLiM, refers to tumor biomarkers. For the diagnosis of multiple myeloma, there is a required presence statement of clonal plasma cells in the bone marrow (>10%) or a confirmed plasma cell tumor (either in the bone or extramedullary) in a biopsy. With it, at least one of the criteria defines multiple myeloma as described by the SLiM CRAB acronyms:

	S	At least 60% clonal plasma cells in the bone marrow or tissue biopsy
Tumor Biomarkers	Li	Presence of clonal free light chains in serum at a concentration of ≥100 mg/l and a clonal-to-non-clonal light chain ratio of ≥100
	M	At least 2 areas of plasma cell infiltrates ≥5 mm in size on magnetic resonance imaging (MRI)
	C	Increased serum calcium levels of ≥1 mg/dl above the upper normal limit or ≥11 mg/dl
	R	Serum creatinine levels >2 mg/dl, or creatinine clearance <40 ml/min
Organ Damage	A	Hemoglobin concentration 2 g/dl below the lower normal limit or <10 g/dl
	B	At least one osteolytic lesion confirmed by radiographic (X-ray), computed tomography (CT), or positron emission tomography-computed tomography (PET-CT) imaging

Table 1. Criteria for the diagnosis of multiple myeloma [9].

In addition to the classic symptomatic plasma cell myeloma (PCM), the 2016 WHO classification also recognizes other clinical variants of this disease.

Asymptomatic ("smoldering") myeloma	Characterized by an asymptomatic or minimally symptomatic course, meaning it does not meet the CRAB and SLiM criteria and lacks AL amyloidosis, despite the presence of monoclonal protein in serum ≥30 g/l or in urine >500 mg/24 h and/or clonal plasma cells in the bone marrow at 10–60%
Non-secretory myeloma	Characterized by the absence of monoclonal protein in serum and urine immunofixation, but in two-thirds of cases, elevated levels of monoclonal free light chains and/or an abnormal κ/λ free light chain ratio (minimally or poorly secretory), which allows for disease monitoring
Plasmacytic leukemia	The most advanced stage of plasma cell myeloma. It is diagnosed when the number of circulating clonal plasma cells exceeds 2000/μl and/or >20% of circulating leukocytes. It is an aggressive form with poor prognosis and a short survival time (<1 year). Plasmacytic leukemia can be classified as either primary or secondary – developing after a previously diagnosed multiple myeloma (MM) and most commonly occurring in its advanced stage

Table 2. Other clinical variants of multiple myeloma [10,11]

3.1.2. Other states not meeting PCM criteria.

There are disease states associated with plasma cell proliferation that do not meet the criteria for multiple myeloma, but may represent early forms or conditions with the potential to progress into myeloma. These include solitary plasmacytoma and monoclonal gammopathy.

1. Solitary plasmacytoma is a single tumor composed of plasma cells occurring in the bone (SPB - solitary plasmacytoma of bone), presenting with localized pain or pathological fractures, or developing outside the bones (EP - extramedullary plasmacytoma), which can occur anywhere in the body. This accounts for approximately 2% of all plasma cell neoplasms. It represents an intermediate phase between monoclonal gammopathy of undetermined significance and multiple myeloma [12].

2. Monoclonal gammopathy of undetermined significance (MGUS) is a condition characterized by the expansion of clonal plasma cells. For diagnosis, the following criteria must be met:

- Monoclonal protein concentration in serum <3 g/dl,
- Clonal plasma cells in the bone marrow <10%,
- Absence of organ damage as described by the CRAB acronym (hypercalcemia, renal insufficiency, anemia, and bone lesions) [13].

MGUS is a precursor condition for multiple myeloma, Waldenström's macroglobulinemia, and AL amyloidosis. The risk of progression to multiple myeloma increases with the duration of the disease, reaching 17% after 10 years and 40% after 25 years [14].

3.2. Impact of Multiple Myeloma on the Skeletal System.

Bone changes in multiple myeloma are among the most severe and characteristic symptoms of this disease. They result from excessive bone resorption and the inhibition of repair processes. The most significant bone changes associated with multiple myeloma include osteolysis, pathological fractures, osteoporosis, and osteopenia.

Osteolysis can affect various parts of the skeletal system, but most commonly occurs in the spine, ribs, pelvis, and, less frequently, in the skull and long bones. This process is irreversible, meaning that bones do not regenerate, even if the patient achieves remission in the treatment of myeloma.

A pathological fracture refers to the disruption of bone continuity due to tissue altered by the disease process. It usually occurs because of minor trauma, often without an identifiable cause. In cases of bone destruction in the vertebrae, compression fractures can occur, leading to back pain, postural deformities, and mobility difficulties. Vertebral fractures may also cause compression of the spinal cord, resulting in neurological issues such as leg weakness, paralysis, and sensory disturbances [8]. Fractures of long bones (e.g., the femur) and ribs are also common and can occur after minor trauma. These fractures are associated with severe pain and difficulties in daily functioning.

Significant progress in the treatment of multiple myeloma in recent years has led to prolonged survival times for patients [15]. Despite advancements in treatment methods, patients still struggle with devastating symptoms that significantly reduce their quality of life, particularly due to changes resulting from tumor involvement of the skeletal system.

3.2.1. Mechanisms of Bone Damage.

Bone is a tissue that undergoes constant renewal throughout an individual's life. It performs many essential functions in the human body: the skeletal framework of the rib cage, consisting of the sternum, ribs, and thoracic vertebrae, forms a protective scaffold for vital internal organs. Bones act as sites of attachment for skeletal muscles, aiding in movement, and they participate in homeostasis by storing calcium and phosphate ions [16]. Continuous remodeling is essential for maintaining bone function by preventing damage accumulation and ensuring both the mechanical strength of bones and calcium homeostasis.

Remodeling involves replacing damaged bone tissue with osteoclasts, which dissolve collagen and other proteins using proteolytic enzymes, and replacing it with new bone tissue produced by osteoblasts. Osteoblasts produce extracellular proteins, including osteocalcin, alkaline phosphatase, and type I collagen, which make up over 90% of the bone matrix protein. The extracellular matrix is first secreted as unmineralized osteoid and later mineralized by the deposition of calcium phosphate in the form of hydroxyapatite. In multiple myeloma, this balance is disrupted [17].

3.2.1.1.Excessive Osteoclast Activity.

Osteoclasts are cells responsible for bone resorption. In multiple myeloma, there is excessive osteoclast activity, leading to bone mass loss and osteolysis. This mechanism is triggered by the stimulation of osteoclasts by various factors, including cytokines secreted by myeloma cells and bone marrow stromal cells, as well as molecules from the TNF family, such as RANK, RANKL, and osteoprotegerin, which play a significant role [17].

Cancer cells can cause osteolysis through three different mechanisms: by producing RANKL and directly stimulating osteolysis, indirectly by increasing RANKL expression by stromal cells, and by inhibiting osteoprotegerin production [17].

3.2.1.2. Role of RANKL (Receptor Activator of Nuclear Factor-kB Ligand).

RANKL is one of the key ligands that stimulate the differentiation and activity of osteoclasts. On the surface of osteoclasts, plasma cells, and stromal cells, there is the receptor RANK, which binds with RANKL to stimulate osteoclastogenesis and inhibit osteoclast apoptosis. Additionally, RANKL can bind to the TRAIL receptor on monoclonal plasma cells, inhibiting their apoptosis. Under physiological conditions, a balance exists between RANKL and its antagonist, osteoprotegerin [18]. Osteoprotegerin acts as a decoy receptor for RANKL, and by blocking RANK, it inhibits osteoclast formation.[17]. In myeloma, cancer cells increase RANKL expression and decrease osteoprotegerin expression by directly acting on cells responsible for osteoprotegerin synthesis- bone marrow stromal cells and endothelial cells in the bone marrow- leading to increased osteolysis [17,18].

3.2.1.3. Role of M-CSF (Macrophage Colony-Stimulating Factor).

The immune system plays a vital modulatory role in the initiation and progression of cancer. Among various immune cells, macrophages are the most abundant population in tumor tissues and play critical roles in tumor formation, progression, metastasis, and response to therapy [19]. M-CSF, also known as CSF-1, is a cytokine that selectively stimulates the proliferation of hematopoietic stem cells, promoting their differentiation into mononuclear phagocytes [19]. M-CSF, together with RANKL, directly induces osteoclastogenesis and inhibits osteoclast apoptosis by binding to RANK on osteoclast precursors and mature osteoclasts. Furthermore, myeloma cells exhibit an anti-apoptotic effect on osteoclasts by secreting large amounts of M-CSF [20].

3.2.1.4. Role of MIP-1α.

MIP-1α is a protein that induces osteoclast formation independently of RANKL and amplifies the activity of RANKL and IL-6. The level of MIP-1α in the serum of patients with multiple myeloma correlates with the severity of osteolysis, as well as resorption markers and RANKL levels [20].

3.2.1.5 Inhibition of Osteoblast Function.

In multiple myeloma, osteoblast activity is inhibited by blocking the differentiation of precursor cells into mature osteoblasts. Myeloma cells secrete inhibitory factors such as DKK-1 (Dickkopf-related protein 1), which is an inhibitor of the Wnt signaling pathway, preventing the differentiation of precursor cells into osteoblasts.

Osteoblasts differentiate from mesenchymal stem cells, and this process is known as the canonical Wnt pathway. Wnt is a group of glycoproteins that bind the Frizzled receptor and its coreceptor, LRP-5/6 [17]. This interaction induces the canonical Wnt pathway, influencing cell function by regulating β-catenin levels. β-catenin transport to the nucleus regulates gene expression and stimulates osteoblast differentiation and proliferation. During the development of multiple myeloma, the Wnt/β-catenin pathway is inhibited by extracellular Wnt antagonists, such as DKK-1 and sFRP-1. DKK-1 binds to the LPR 5/6 coreceptor, and sFRP-1 directly binds to the Wnt protein, blocking osteoblast proliferation [17,20].

Moreover, osteoblast apoptosis is significantly increased due to high cytokine levels and physical interactions between osteoblasts and cancer cells. Myeloma cells inhibit the transcription factor Runx2/Cbfa1 in osteoblast progenitors within the bone marrow, leading to impaired synthesis and differentiation of osteoblasts, as well as increased apoptosis [17]. As a result, new bone tissue is not generated in response to resorption processes [18]. This leads to normal or low levels of bone formation markers, such as osteocalcin or alkaline phosphatase, with increased bone resorption. In patients with multiple myeloma without bone changes, bone formation markers are normal or elevated [21].

3.2.1.6. Harmful Effects of Cytokines.

Cytokines are low-molecular-weight soluble proteins released by various cells, especially immune system cells. They play a role in immune responses as mediators and are used as biomarkers in diseases [22].

- Interleukin 7 (IL-7) is a cytokine produced by bone marrow stromal cells, which acts as an independent factor capable of stimulating RANKL production and bone resorption. Additionally, IL-7 secreted by bone marrow stromal cells inhibits the activity of the Runx2/Cbfa1 promoter, an essential transcription factor for osteoblast formation [8].
- Interleukin-6 (IL-6): A cytokine involved in inhibiting the apoptosis of multiple myeloma cells, it also plays a role in regulating RANKL production through a mutual interaction between IL-6 and IL-7. IL-6 stimulates IL-7 production, while IL-7 stimulates bone marrow cells to produce IL-6 [17].
- Interleukin-1 (IL-1): IL-1 also stimulates osteoclast activity, leading to increased bone resorption. It is produced by myeloma cells and cells of the bone marrow microenvironment [23].

3.3. Bone Lesion Diagnosis in Multiple Myeloma.

The diagnosis of bone lesions in multiple myeloma is a crucial element in assessing the patient's condition, as these changes significantly impact the quality of life, prognosis, and therapeutic decisions. Various imaging techniques are used to accurately evaluate bone damage, detect lytic bone lesions, monitor disease progression, identify areas potentially at risk for pathological fractures, and evaluate treatment response. The most commonly used methods in the diagnosis of bone lesions in multiple myeloma are:

3.3.1 X-ray.

For many years, radiography was the preferred method for diagnosing bone disease in the course of multiple myeloma.

However, it is now being replaced by more advanced techniques due to several limitations, including: lower sensitivity compared to other diagnostic methods (at least 30% loss of bone mineral density is necessary to detect a lytic lesion), difficulties in assessing changes in the pelvis or spine, challenges in distinguishing pathological fractures due to myeloma from fractures secondary to osteoporosis, and the inability to assess treatment response - lytic lesions rarely regress even in patients with sustained complete remission [8,24]. Due to these limitations, conventional radiography is insufficient for diagnosing multiple myeloma.
Current imaging techniques include: whole-body low-dose tomography (WBLDCT), positron emission tomography with computed tomography (PET/CT) and magnetic resonance imaging (MRI) – all of which are used in the diagnosis of symptomatic myeloma according to the SLiM CRAB criteria, as well as for tracking disease progression and evaluating treatment response.

3.3.2. Whole-Body Low-Dose Computed Tomography (WBLDCT).

This examination uses a low dose of radiation, even 2-3 times lower than standard computed tomography, and allows for the evaluation of the entire skeleton for osteolytic changes. It has higher sensitivity and resolution compared to WBXR (whole-body X-Ray). The short data acquisition time is a desirable feature for patients who have difficulty tolerating long-duration procedures. A disadvantage of this test is its low specificity in assessing osteopenia and the inability to evaluate treatment response [25].

3.3.3. Positron emission tomography/computed tomography (PET/CT).

The PET/CT scan combines morphological and metabolic diagnostics by performing a low-dose computed tomography of the whole body alongside evaluating the metabolism of a radiotracer that indicates disease activity. Given the ability of FDG-PET/CT to distinguish between active and inactive disease, it is an excellent imaging tool for assessing tumor metabolic activity and monitoring treatment response. It enables precise anatomical localization of hypermetabolic changes both within and outside the bone marrow [25].

3.3.4. Magnetic Resonance Imaging (MRI).

MRI broadens the scope of imaging while avoiding exposure to ionizing radiation [26]. To prevent missing bone changes, it is necessary to perform magnetic resonance imaging that includes the axial skeleton and the upper parts of the limbs [26]. The extended data acquisition time limits its use in patients who cannot tolerate remaining still for extended periods, which increases the risk of motion artifacts. MRI has been recognized as the first-choice method for assessing the extent of bone marrow infiltration, while WBXR and CT detect bone destruction. This technique is also used for evaluating spinal involvement and identifying soft tissue masses. MRI is especially indicated in individuals presenting with neurological symptoms suggestive of spinal cord or nerve root compression. With its high resolution, MRI can reveal bone marrow infiltration features before changes are visible on X-ray and CT scans [25]. The detection of at least two focal lesions on MRI is considered the most significant adverse prognostic factor and is included in the diagnostic criteria for myeloma, serving as a tumor biomarker. [25].

3.4. Methods of Treating Bone Lesions in Multiple Myeloma.

3.4.1 Pharmacological Treatment.

Pharmacological treatment of bone lesions in multiple myeloma aims to reduce pain, prevent further bone tissue loss, and improve the quality of life. Bone damage in multiple myeloma results from excessive bone resorption by osteoclasts, and the primary goal of therapy is to control this process.

One of the drugs used in multiple myeloma therapy is bortezomib - a selective, reversible proteasome inhibitor. It inhibits the activity of the 26S proteasome, preventing the proteolysis of the ubiquitin-proteasome complex, which disrupts intracellular signaling and leads to cell apoptosis. Cancer cells are more susceptible to this mechanism than healthy cells. Bortezomib also affects the ability of monoclonal plasma cells to interact with the bone marrow microenvironment. Studies have shown that proteasome inhibitors, such as bortezomib, enhance osteoblast differentiation and function by stimulating the activity of Runx2/Cbfa1, as indicated by increased alkaline phosphatase expression [8].

Thalidomide and its analogs lenalidomide and pomalidomide are widely used in the anti-cancer treatment of multiple myeloma. Their uniqueness lies in their immunomodulatory properties, which are particularly advantageous in managing cancers such as multiple myeloma that lead to immune system paralysis, and consequently, the loss of immune surveillance over the tumor. This is due to the production of cytokines such as TGF-beta, IL-6, and VEGF by bone marrow stromal cells. These cytokines cause B and T cell suppression, weaken lymphocyte co-stimulation by dendritic cells, increase NK cell numbers, activate the CD4+ T cell subpopulation, leading to increased secretion of IL-2 and IFN-γ, and induce apoptosis in myeloma cells by activating caspase 8. Lenalidomide and pomalidomide also enhance antibody-dependent cytotoxicity (ADCC) [27]. Importantly, in the context of bone disease, immunomodulatory drugs (IMiDs) like lenalidomide and pomalidomide reduce RANKL production by blocking its production and specifically inhibiting osteoclast formation [8].

Among the drugs counteracting osteoblastic bone loss, bisphosphonates play a key role. This class of drugs has a high affinity for the mineral components of bones, as they bind to hydroxyapatite crystals. As a result, the retention of bisphosphonates in the bone system depends on the availability of binding sites on hydroxyapatite. These drugs are especially effective in diseases characterized by increased bone turnover, as they preferentially bind to areas of active bone remodeling. If they are not adapted into bone tissue, they are removed from circulation by the kidneys [28]. By binding to hydroxyapatites, they block their breakdown, thereby preventing osteolysis [29]. For this reason, they are highly effective in patients with multiple myeloma who exhibit bone lesions such as osteolysis, osteopenia, bone pain, or the risk of pathological fractures. They also play a significant role in palliative care, reducing the occurrence of painful bone complications and decreasing the frequency of hypercalcemia [29]. Currently, one of two drugs is used: zoledronic acid or pamidronate. These are given intravenously once a month, with the option to decrease the frequency of administration after two years of treatment. Despite the clear advantages of bisphosphonate therapy, potential side effects should be considered. In patients undergoing long-term bisphosphonate therapy, there is a risk of jawbone necrosis, a serious and painful side effect characterized by exposed, necrotic bone in the jaw and facial area, persisting for eight weeks and developing because of bisphosphonate therapy [8].

Among all cancer patients treated with bisphosphonates, those with multiple myeloma exhibit the highest incidence of jawbone necrosis [29]. To reduce the risk of this complication, all dental caries should be treated before starting bisphosphonate therapy, dental procedures should be avoided, and if necessary, prophylactic antibiotics should be administered, with bisphosphonate therapy being halted for three months before and up to three months after invasive dental procedures [25]. Due to the benefits outweighing the potential risks, bisphosphonate treatment is recommended for all multiple myeloma patients undergoing chemotherapy, with zoledronic acid being the drug of choice, as randomized trials have shown a link to prolonged survival [30]. If intravenous treatment is not possible, clodronate therapy should be considered. During intravenous bisphosphonate therapy, oral calcium and vitamin D supplementation are recommended. To prevent kidney failure caused by hypercalcemia, calcium levels and markers of kidney damage should be monitored. In case of disease relapse, it is advisable to resume bisphosphonate therapy.

A new drug used both in bone disease treatment in multiple myeloma and in osteoporosis is denosumab. This is a monoclonal antibody targeting the RANKL molecule on the surface of osteoclasts. Denosumab has a high affinity for the RANKL molecule, preventing the activation of the RANK receptor present on osteoclast precursors and mature osteoclasts, thus inhibiting the function, formation, and survival of osteoclasts, thereby reducing osteolysis. [31].

3.4.2. Supportive Treatment.

Compression fractures of the vertebrae are a common complication of osteolysis in multiple myeloma. These lead to severe pain and impaired daily functioning. In cases of vertebral compression fractures, a patient may be referred by an orthopedic surgeon for vertebroplasty or kyphoplasty procedures. Vertebroplasty involves injecting polymethyl methacrylate into the damaged vertebral body, while kyphoplasty additionally restores vertebral height by using an inflatable balloon before injecting the substance to fill the bone void [32]. This significantly reduces pain and restores normal functioning.

Radiotherapy is recommended for uncontrolled pain or symptomatic spinal cord compression or pathological fractures [33,25]. Occasionally, low-dose radiotherapy is also used, which has an exceptionally good pain-relieving effect and reduces the risk of bone fractures and the formation of new lesions.

3.4.3. Pain Management.

Pain control is crucial for multiple myeloma patients. Non-opioid anti-inflammatory drugs have limited use due to their nephrotoxic effects. Paracetamol is allowed and effective for mild pain. In cases of severe cancer pain, opioid medications are necessary. Morphine and codeine also exhibit nephrotoxic effects, so in cases of severe kidney failure, buprenorphine and fentanyl should be used [34].

Bortezomib therapy itself may lead to the development of peripheral neuropathy: finger pain, paresthesia, numbness, and even sensory ataxia. Selective serotonin reuptake inhibitors, tricyclic antidepressants, norepinephrine reuptake inhibitors, gabapentin, and duloxetine are used for neuropathic pain management. Local applications of lidocaine or capsaicin may also be used. The last step is to reduce the bortezomib dose [34].

3.4.4. Vitamin D.

Vitamin D deficiency (<10 ng/mL) correlates with an increased number of cancer cells in the bone marrow, and the risk of disease progression, bone disease development, and in patients with normal vitamin D levels [35]. Therefore, vitamin D supplementation is recommended for patients with multiple myeloma. To prevent toxic hypercalcemia, doses should be adjusted according to serum vitamin D levels.

3.4.5. Future Prospects for Multiple Myeloma Treatment.

Romosozumab is a biologic drug used in the treatment of osteoporosis, particularly in postmenopausal women with a high fracture risk. It is a monoclonal antibody that works by inhibiting the activity of sclerostin, a protein that inhibits Wnt/β-catenin signaling [36]. Sclerostin naturally inhibits new bone formation, and Romosozumab works by blocking it, thus stimulating bone formation and increasing bone density.

Romosozumab is used in the treatment of osteoporosis, a condition marked by low bone mass and an increased susceptibility to fractures.. It enhances osteoblast activity while simultaneously reducing bone resorption by osteoclasts [36]. This dual action improves bone formation and reduces bone loss.

Currently, there are no clinical trials confirming its effectiveness and safety in treating multiple myeloma, but numerous preclinical studies have shown that antibodies against sclerostin stimulate bone formation in multiple myeloma [37]. Therefore, focusing research on using Romosozumab in multiple myeloma therapy holds promising prospects, especially in improving bone mass and reducing fracture risk.

4. Conclusions

Multiple myeloma is a disease that contributes to the development of bone damage such as osteolysis, osteoporosis, and pathological fractures, primarily due to progressive bone tissue loss. The pathophysiological mechanisms responsible for these changes involve an imbalance between bone resorption and bone formation processes. Early detection of bone lesions and ongoing monitoring of disease progression are essential for preventing complications such as pathological fractures and neurological damage.

Modern imaging techniques, including MRI, CT, and PET-CT, play a key role in evaluating the disease, enabling the detection of bone changes at initial stages. Currently, the mainstay of treatment for myeloma-related bone disease includes medications that reduce osteoclast proliferation, such as bisphosphonates and denosumab. A promising therapeutic option for the future may be the use of Romosozumab, a drug that stimulates the formation of new bone tissue; however, there is currently insufficient clinical evidence to confirm its safety in this context.

Vitamin D supplementation supports the maintenance of proper bone mineral density and reduces fracture risk, though it requires an individualized approach based on serum levels. While available therapies significantly improve bone condition, they do not lead to complete recovery. Therefore, there is an ongoing need for further research into new treatment and prevention strategies for bone damage. Studies on the efficacy and safety of emerging drugs and therapeutic approaches, such as Romosozumab, are necessary.

The management of bone disease in multiple myeloma should not only focus on controlling skeletal complications but also on treating the underlying myeloma. A comprehensive, multidisciplinary approach that addresses both oncological and orthopedic aspects is crucial for improving patients' quality of life and reducing the risk of bone-related complications.

Disclosure:

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The authors declare no conflict of interest.

Declaration of Generative AI and AI-Assisted Technologies

During the preparation of this work, the authors used ChatGPT (OpenAI) to improve grammar and language clarity. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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