Vitamin D Deficiency in Multiple Myeloma: Prognostic Significance, Biological Mechanisms, and Clinical Implications

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Abstract

Background: Multiple myeloma is a clonal plasma cell malignancy characterized by bone marrow infiltration, monoclonal protein production, skeletal destruction, renal impairment, anemia, immune dysfunction, and recurrent relapse. Although advances in proteasome inhibitors, immunomodulatory agents, monoclonal antibodies, autologous stem cell transplantation, bispecific antibodies, and chimeric antigen receptor T-cell therapy have substantially improved survival, clinical outcomes remain heterogeneous. This variability has increased interest in identifying accessible prognostic biomarkers that may complement established staging systems, cytogenetic risk profiles, and measures of treatment response. Vitamin D deficiency is highly prevalent among patients with multiple myeloma and may be related to older age, reduced sunlight exposure, nutritional impairment, renal dysfunction, glucocorticoid therapy, limited mobility, and the metabolic consequences of active malignancy.

Vitamin D has important skeletal and extraskeletal functions relevant to multiple myeloma. Beyond regulating calcium and phosphate homeostasis, it influences osteoclast and osteoblast activity, immune-cell differentiation, inflammatory signaling, cellular proliferation, apoptosis, and interactions within the bone marrow microenvironment. Deficiency may therefore aggravate myeloma-related bone disease, impair immune regulation, enhance inflammatory cytokine activity, and potentially support disease progression. Clinical studies have associated low serum 25-hydroxyvitamin D concentrations with advanced disease stage, greater tumor burden, increased skeletal complications, poorer functional status, reduced treatment response, shorter progression-free survival, and inferior overall survival. However, these associations are not uniform across all populations and may be modified by ethnicity, renal function, disease activity, treatment exposure, nutritional status, and variation in the thresholds used to define deficiency.

This review aims to critically evaluate the prognostic significance of vitamin D deficiency in multiple myeloma, summarize the biological mechanisms that may link vitamin D status to disease behavior, and examine its relationship with bone disease, treatment outcomes, transplantation, and survival. It also discusses the potential clinical value of routine vitamin D assessment and supplementation.

Vitamin D deficiency appears to be a clinically relevant and potentially modifiable factor in multiple myeloma. Nevertheless, current evidence is largely observational and does not establish a direct causal relationship. Prospective studies and randomized trials are required to determine whether correction of deficiency improves disease-specific outcomes beyond its established benefits for musculoskeletal health.

Keywords: multiple myeloma; vitamin D deficiency; prognosis; bone marrow microenvironment

Introduction

Multiple myeloma is a biologically heterogeneous plasma cell malignancy characterized by clonal bone marrow infiltration, monoclonal immunoglobulin production, and progressive organ dysfunction. Its principal clinical manifestations include anemia, renal impairment, hypercalcemia, osteolytic bone disease, recurrent infections, and constitutional deterioration. The disease is usually preceded by monoclonal gammopathy of undetermined significance and, in some patients, an intermediate smoldering phase. Despite major therapeutic advances, multiple myeloma remains incurable in most patients because treatment-resistant subclones and interactions within the bone marrow microenvironment eventually promote relapse. [1]

The prognosis of multiple myeloma is conventionally assessed using disease stage, cytogenetic abnormalities, serum biomarkers, patient fitness, renal function, treatment response, and minimal residual disease status. The Revised International Staging System integrates serum β2-microglobulin, albumin, lactate dehydrogenase, and selected high-risk cytogenetic abnormalities; however, substantial variation in survival remains among patients within the same prognostic category. This heterogeneity has stimulated interest in additional biomarkers that are inexpensive, reproducible, biologically relevant, and potentially modifiable. Nutritional and metabolic abnormalities are especially attractive because they may reflect tumor burden, systemic inflammation, organ dysfunction, and general physiological reserve simultaneously. [2]

Vitamin D is a fat-soluble secosteroid whose biological activity extends beyond calcium and phosphate regulation. Its active metabolite, 1,25-dihydroxyvitamin D, binds to the vitamin D receptor and influences gene transcription in numerous tissues, including immune cells, osteoblasts, osteoclasts, and bone marrow stromal cells. Through these pathways, vitamin D contributes to skeletal remodeling, immune regulation, cellular differentiation, apoptosis, and inflammatory control. These functions are directly relevant to multiple myeloma, in which malignant plasma cells depend on complex interactions with stromal, immune, and bone cells for survival, proliferation, treatment resistance, and osteolytic disease development. [3]

Vitamin D deficiency is common in patients with multiple myeloma. Contributing factors include advanced age, limited sunlight exposure, reduced dietary intake, impaired mobility, renal dysfunction, systemic inflammation, glucocorticoid exposure, and the metabolic consequences of active cancer. A scoping review of the available literature reported that vitamin D deficiency affected a substantial proportion of studied patients, although prevalence estimates varied according to population characteristics, disease setting, season, laboratory method, and the serum 25-hydroxyvitamin D threshold applied. This variability complicates comparisons among studies and highlights the need for standardized definitions when evaluating vitamin D as a prognostic biomarker. [4]

Clinical investigations have associated deficient vitamin D levels with advanced disease stage, increased bone marrow plasma cell infiltration, abnormal bone metabolism, skeletal morbidity, peripheral neuropathy, reduced treatment response, and inferior survival. Nevertheless, findings have not been fully consistent. Some studies suggest that vitamin D deficiency independently predicts poorer progression-free or overall survival, whereas others indicate that the association may be influenced by ethnicity, renal impairment, performance status, disease burden, or other unmeasured confounders. Vitamin D deficiency may therefore represent a direct biological contributor to adverse outcomes, a surrogate marker of aggressive disease and poor general health, or a combination of both mechanisms. [5]

The central research gap is the absence of definitive evidence establishing whether vitamin D deficiency has an independent and causal effect on multiple myeloma outcomes. Most available studies are retrospective, single-center, observational, or based on administrative data. They also differ in the timing of vitamin D measurement, deficiency thresholds, patient ethnicity, treatment regimens, transplantation status, and adjustment for established prognostic variables. Furthermore, evidence that vitamin D supplementation improves myeloma-specific treatment response, progression-free survival, or overall survival remains insufficient. This review therefore aims to critically examine the prevalence and

determinants of vitamin D deficiency in multiple myeloma, its biological links with myeloma pathophysiology, and its associations with disease severity, bone complications, treatment outcomes, transplantation, and survival. It also evaluates the potential clinical role of vitamin D screening and replacement while identifying priorities for future prospective and interventional research. [6]

Multiple Myeloma: Overview and Current Prognostic Landscape

Multiple myeloma (MM) is a hematologic malignancy characterized by the uncontrolled proliferation of clonal plasma cells within the bone marrow, resulting in excessive production of monoclonal immunoglobulins and progressive organ dysfunction. It accounts for approximately 10% of hematologic malignancies and remains the second most common blood cancer worldwide. Although remarkable therapeutic advances have transformed MM into a chronic yet treatable disease for many patients, relapse remains inevitable in most cases because of persistent minimal residual disease, clonal evolution, and the protective role of the bone marrow microenvironment. Consequently, identifying additional prognostic biomarkers beyond conventional staging systems has become an important area of clinical research. [7]

MM develops through a multistep process beginning with monoclonal gammopathy of undetermined significance (MGUS), progressing to smoldering multiple myeloma (SMM), and eventually evolving into symptomatic disease characterized by end-organ damage. While MGUS progresses at an average rate of approximately 1% annually, SMM carries a substantially greater risk during the first five years following diagnosis. This stepwise evolution reflects the gradual accumulation of cytogenetic abnormalities, epigenetic alterations, and microenvironmental changes that ultimately promote malignant plasma cell expansion and immune escape. Understanding these precursor stages is important because biological factors, including vitamin D status, may influence disease progression long before symptomatic MM develops. [8]

The clinical manifestations of MM are primarily explained by plasma cell infiltration and monoclonal protein production. Patients commonly present with the CRAB features of hypercalcemia, renal impairment, anemia, and osteolytic bone disease. Additional complications include recurrent infections, peripheral neuropathy, hyperviscosity syndrome, extramedullary disease, and thromboembolic events. Skeletal involvement is particularly important because approximately 80% of patients exhibit osteopenia, lytic lesions, or pathological fractures at diagnosis, substantially impairing functional status and quality of life. Since vitamin D plays a central role in bone remodeling and mineral homeostasis, deficiency may further aggravate these complications. [9]

Modern prognostic assessment integrates both disease burden and disease biology. The Revised International Staging System (R-ISS) combines serum β2-microglobulin, albumin, lactate dehydrogenase, and high-risk cytogenetic abnormalities, including del(17p), t(4;14), and t(14;16). More recently, additional abnormalities such as gain 1q and TP53 alterations have further refined risk stratification. Nevertheless, patients classified within the same prognostic category frequently demonstrate markedly different responses to therapy and survival outcomes, indicating that additional biological and host-related factors contribute to prognosis. [10]

Host-related variables have increasingly been recognized as modifiers of clinical outcome in MM. Advanced age, frailty, renal dysfunction, nutritional status, chronic inflammation, sarcopenia, and metabolic disturbances influence tolerance to therapy, immune competence, and recovery following treatment. Among these potentially modifiable factors, vitamin D deficiency has attracted growing attention because of its high prevalence and its biological effects on bone metabolism, immune regulation, inflammatory signaling, and tumor cell behavior. These observations provide the rationale for investigating vitamin D as a complementary prognostic biomarker that may improve risk assessment while representing a readily correctable clinical abnormality. [11]

Vitamin D Physiology and Biological Relevance in Multiple Myeloma

Vitamin D is a fat-soluble secosteroid hormone synthesized primarily in the skin following ultraviolet-B exposure, with smaller amounts obtained through dietary intake. It undergoes sequential hydroxylation in the liver to form 25-hydroxyvitamin D [25(OH)D], the principal circulating marker of

vitamin D status, and subsequently in the kidneys to generate the biologically active metabolite, 1,25-dihydroxyvitamin D (calcitriol). Calcitriol exerts its effects by binding to the vitamin D receptor (VDR), a nuclear transcription factor expressed in osteoblasts, osteoclasts, immune cells, bone marrow stromal cells, and plasma cells, thereby regulating hundreds of genes involved in mineral metabolism, immune function, cellular differentiation, and apoptosis. [12]

Beyond maintaining calcium and phosphate homeostasis, vitamin D plays an essential role in preserving skeletal integrity through coordinated regulation of bone formation and bone resorption. In multiple myeloma, malignant plasma cells disrupt this balance by stimulating osteoclast activity while suppressing osteoblast differentiation, leading to progressive osteolytic lesions. Vitamin D deficiency may further amplify these abnormalities by impairing bone mineralization, increasing secondary hyperparathyroidism, and promoting excessive bone turnover, thereby worsening skeletal morbidity and fracture risk. [13]

The biological effects of vitamin D extend to both innate and adaptive immunity. Vitamin D suppresses excessive inflammatory responses by reducing the production of cytokines such as interleukin-6, interleukin-1β, and tumor necrosis factor-α while promoting regulatory immune pathways. Since IL-6 is a critical growth and survival factor for myeloma cells, inadequate vitamin D levels may indirectly facilitate disease progression through persistent inflammatory activation within the bone marrow microenvironment. These immunomodulatory properties provide an important biological explanation for the observed relationship between vitamin D deficiency and adverse clinical outcomes in MM. [14]

Experimental studies have further demonstrated that vitamin D influences tumor biology through inhibition of cellular proliferation, induction of apoptosis, promotion of cellular differentiation, and suppression of angiogenesis. Activation of the vitamin D receptor may also alter signaling pathways that regulate plasma cell survival and interactions between malignant cells and bone marrow stromal cells. Although these findings have been demonstrated mainly in laboratory and preclinical models, they support the hypothesis that vitamin D deficiency may contribute to a microenvironment favorable for myeloma growth and treatment resistance. [15]

Collectively, the pleiotropic actions of vitamin D on bone metabolism, immune regulation, inflammation, and cellular proliferation provide a strong biological rationale for investigating its prognostic significance in multiple myeloma. While current evidence does not establish a direct causal relationship, these mechanisms support the possibility that vitamin D deficiency is more than a simple nutritional abnormality and may actively influence disease behavior and clinical outcomes. [16]

Prevalence and Determinants of Vitamin D Deficiency in Multiple Myeloma

Vitamin D deficiency is highly prevalent in patients with multiple myeloma, with most studies reporting deficiency or insufficiency in more than half of newly diagnosed patients. Although prevalence varies depending on geographic location, ethnicity, season, laboratory methodology, and the serum 25(OH)D threshold used, published data consistently demonstrate that vitamin D deficiency is considerably more common in MM than in the general population. This high prevalence suggests that vitamin D deficiency represents an important comorbidity that deserves routine clinical attention. [17]

Several disease-related and patient-related factors contribute to the development of vitamin D deficiency in MM. Advanced age, reduced outdoor activity, poor nutritional intake, renal impairment, prolonged corticosteroid therapy, chronic inflammation, obesity, and decreased physical performance all reduce vitamin D synthesis or metabolism. Furthermore, renal dysfunction, which is common in MM, impairs the conversion of 25(OH)D to its biologically active form, further aggravating deficiency. [18]

The disease itself may also influence vitamin D homeostasis. Progressive bone destruction, cytokine dysregulation, and alterations within the bone marrow microenvironment may increase metabolic demand while disrupting normal vitamin D signaling pathways. Elevated inflammatory cytokines, particularly IL-6, may interfere with vitamin D metabolism and receptor activity, creating a reciprocal relationship in which aggressive disease promotes deficiency while deficiency further enhances inflammation and skeletal damage. [19]

Several observational studies have demonstrated that patients with lower serum vitamin D

concentrations frequently exhibit more advanced disease characteristics at diagnosis, including higher International Staging System (ISS) stage, elevated β2-microglobulin, greater bone marrow plasma cell infiltration, and more extensive osteolytic disease. Although these findings do not establish causality, they consistently support an association between vitamin D deficiency and greater disease burden. [20] Because vitamin D deficiency is common, inexpensive to detect, and readily correctable, routine measurement of serum 25(OH)D at diagnosis and during follow-up may provide valuable clinical information. Standardized assessment could facilitate early identification of patients at increased risk for skeletal complications and poor functional status while providing an opportunity for timely nutritional intervention as part of comprehensive supportive care. [21]

Association Between Vitamin D Deficiency and Disease Severity

Growing evidence suggests that vitamin D deficiency is associated with a more aggressive clinical phenotype in multiple myeloma. Patients with low serum 25(OH)D concentrations are more likely to present with advanced ISS or R-ISS stage, elevated β2-microglobulin, higher lactate dehydrogenase levels, greater plasma cell infiltration, and extensive skeletal involvement. These findings indicate that vitamin D deficiency may reflect increased tumor burden and a more unfavorable biological profile at diagnosis. [22]

Bone disease is one of the strongest clinical manifestations associated with vitamin D deficiency in MM. Deficient patients have a higher frequency of osteolytic lesions, pathological fractures, vertebral compression fractures, and chronic bone pain. Vitamin D deficiency further impairs calcium homeostasis and bone remodeling, amplifying the imbalance between osteoclast activation and osteoblast suppression that characterizes myeloma bone disease. Consequently, deficient patients often experience greater skeletal morbidity and reduced quality of life. [23]

Vitamin D deficiency has also been associated with adverse laboratory parameters that reflect disease activity and systemic illness. Several studies have reported correlations between low vitamin D levels and anemia, hypoalbuminemia, impaired renal function, elevated inflammatory markers, and poorer performance status. Although these abnormalities may partly result from advanced disease rather than vitamin D deficiency itself, they reinforce the close relationship between vitamin D status and overall disease severity. [24]

The biological basis for these clinical observations is supported by experimental evidence demonstrating that vitamin D modulates inflammatory cytokines, immune-cell function, osteoclastogenesis, and bone marrow stromal cell interactions. Deficiency may therefore promote a microenvironment favorable for plasma cell survival, angiogenesis, immune escape, and progressive bone destruction, providing mechanistic support for its association with aggressive disease. [25]

Despite these consistent associations, current evidence remains predominantly observational. Differences in study design, vitamin D cut-off values, ethnicity, renal function, treatment exposure, and seasonal variation limit direct comparison between studies. Therefore, vitamin D deficiency should currently be regarded as a promising prognostic biomarker associated with disease severity rather than an established independent determinant of aggressive myeloma. [26]

Prognostic Impact of Vitamin D Deficiency on Treatment Response and Survival

The relationship between vitamin D deficiency and clinical outcomes has become an area of increasing interest in multiple myeloma research. Several observational studies have demonstrated that patients with deficient serum 25(OH)D levels experience inferior therapeutic responses, shorter progression-free survival (PFS), and reduced overall survival (OS) compared with patients who have sufficient vitamin D levels. Although these findings are not entirely consistent across all cohorts, the overall evidence suggests that vitamin D status may provide additional prognostic information beyond conventional clinical and laboratory markers. [27]

Vitamin D deficiency has been associated with reduced rates of complete response and very good partial response following first-line therapy. This observation may be explained by impaired immune surveillance, persistent inflammatory activation, and altered interactions between myeloma cells and the bone marrow microenvironment, all of which may reduce treatment sensitivity. Furthermore, deficient

patients often present with poorer performance status and greater disease burden, factors that may further compromise therapeutic efficacy. [28]

The prognostic significance of vitamin D appears particularly relevant in patients undergoing autologous stem cell transplantation (ASCT). Emerging studies suggest that pre-transplant vitamin D deficiency may delay immune reconstitution and be associated with inferior post-transplant clinical outcomes. Although these observations require confirmation in larger prospective studies, they indicate that optimization of vitamin D status before transplantation may represent a simple supportive intervention worthy of further investigation. [29]

Not all studies have demonstrated an independent association between vitamin D deficiency and survival after adjustment for established prognostic variables. Differences in ethnicity, treatment regimens, renal function, vitamin D cut-off values, and study methodology likely contribute to these inconsistent findings. Nevertheless, the reproducible association between vitamin D deficiency and adverse clinical characteristics supports its potential role as an adjunctive prognostic biomarker rather than a replacement for established staging systems. [30]

Overall, current evidence indicates that vitamin D deficiency identifies patients at greater risk of unfavorable clinical outcomes, although causality remains unproven. Well-designed prospective multicenter studies and randomized clinical trials are required to determine whether correction of vitamin D deficiency can improve treatment response, prolong survival, or enhance quality of life in patients with multiple myeloma. [31]

Mechanistic Basis Linking Vitamin D Deficiency to Multiple Myeloma Progression

Several biological mechanisms may explain the association between vitamin D deficiency and adverse outcomes in multiple myeloma. Vitamin D receptor (VDR) activation regulates genes involved in cell-cycle control, apoptosis, and differentiation. Experimental studies have shown that activation of VDR suppresses myeloma cell proliferation while promoting apoptosis, suggesting that deficiency may weaken these protective antitumor effects. [32]

The bone marrow microenvironment is fundamental to myeloma progression. Malignant plasma cells interact continuously with stromal cells, osteoclasts, osteoblasts, endothelial cells, and immune cells through cytokines and adhesion molecules. Vitamin D modulates these interactions by reducing IL-6, TNF-α, and other pro-inflammatory mediators that promote plasma cell survival and drug resistance. Deficiency may therefore create a microenvironment that favors tumor growth and disease progression. [33]

Vitamin D also influences skeletal remodeling through the RANK/RANKL/osteoprotegerin pathway. In MM, excessive RANKL activity stimulates osteoclastogenesis while suppressing osteoblast function, resulting in progressive osteolytic lesions. Vitamin D deficiency amplifies this imbalance, contributing to accelerated bone resorption, pathological fractures, hypercalcemia, and persistent skeletal morbidity. [34]

Immune dysregulation represents another important mechanism. Vitamin D enhances innate immunity, regulates T-cell differentiation, improves natural killer cell activity, and suppresses chronic inflammation. Deficiency may impair antitumor immune surveillance, allowing malignant plasma cells to evade immune-mediated elimination while promoting chronic inflammatory signaling within the bone marrow niche. [35]

Although these mechanistic pathways strongly support a biological role for vitamin D in MM progression, most evidence originates from experimental and observational studies. Further translational and clinical research is required to determine whether correcting vitamin D deficiency can directly modify these pathways and translate into improved patient outcomes. [36]

Therapeutic Implications and Future Perspectives

Given the high prevalence of vitamin D deficiency in patients with multiple myeloma, routine assessment of serum 25(OH)D at diagnosis and during follow-up has become increasingly advocated as part of comprehensive supportive care. Vitamin D measurement is inexpensive, widely available, and may identify patients at increased risk for skeletal complications, impaired physical function, and

potentially inferior clinical outcomes. Current evidence supports correction of deficiency primarily to optimize bone health rather than as an established antimyeloma therapy. [37]

Vitamin D supplementation is recommended for deficient patients, particularly those receiving bisphosphonates or denosumab for myeloma-related bone disease. Adequate vitamin D status facilitates calcium homeostasis, reduces the risk of osteomalacia and secondary hyperparathyroidism, and may improve musculoskeletal function. Careful monitoring of serum calcium and renal function remains important because hypercalcemia may occur in patients with active myeloma or excessive supplementation. [38]

Whether vitamin D supplementation improves progression-free survival, overall survival, or treatment response remains uncertain. Most available evidence consists of retrospective studies, observational cohorts, and small prospective investigations, while randomized controlled trials specifically evaluating survival outcomes are lacking. Therefore, vitamin D replacement should currently be regarded as an evidence-based supportive intervention rather than a disease-modifying treatment. [39]

Future research should prioritize large multicenter prospective studies using standardized definitions of vitamin D deficiency and uniform measurement of serum 25(OH)D. Clinical trials should determine whether early correction of deficiency influences minimal residual disease, response to novel therapies, transplantation outcomes, progression-free survival, and overall survival. Further investigation into vitamin D receptor polymorphisms, molecular biomarkers, and personalized supplementation strategies may also improve patient stratification and optimize supportive management in multiple myeloma. [40]

Conclusion

Vitamin D deficiency is highly prevalent among patients with multiple myeloma and is consistently associated with advanced disease, increased skeletal complications, and poorer clinical outcomes. Its biological effects on bone remodeling, immune regulation, inflammatory signaling, and the bone marrow microenvironment provide a plausible mechanistic basis for these associations. Although current evidence supports vitamin D deficiency as a clinically relevant prognostic biomarker, most available data remain observational and do not establish a causal relationship between deficiency and adverse survival outcomes. Routine assessment and correction of vitamin D deficiency should therefore be considered an important component of supportive care, particularly in patients with bone disease or those receiving antiresorptive therapy, while adequately powered prospective studies and randomized clinical trials are needed to determine whether vitamin D optimization can improve treatment response, progression-free survival, and overall survival in multiple myeloma.

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