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Bone disease in multiple myeloma and precursor disease: novel diagnostic approaches and implications on clinical management

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Abstract

The manifestations of bone involvement in patients with multiple myeloma (MM) can have devastating clinical effects and increase mortality. Recent studies demonstrate that patients with the precursor conditions smoldering MM (SMM) and monoclonal gammopathy of undetermined significance (MGUS) show evidence of bone disease and increased risk of fractures. The understanding of the pathogenesis of bone disease in MM has expanded in recent years. The traditional skeletal survey will probably be replaced by newer and more sensitive imaging techniques, which may have a prognostic impact and change our definition of MGUS and SMM. Bisphosphonates are recommended to prevent skeletal events in patients with MM, and have also been studied in SMM and MGUS. This article summarizes the current knowledge of bone disease in plasma cell disorders, and discusses the current standard and future role of novel imaging techniques, as well as the evidence and current guidelines for bisphosphonates in MM, SMM and MGUS.

Keywords

bisphosphonates; bone disease; fractures; MGUS; multiple myeloma; radiology; smoldering multiple myeloma

Bone disease in multiple myeloma

Multiple myeloma is a chronic, malignant B-cell disorder characterized by plasma cell infiltration in the bone marrow, and monoclonal immunoglobulins in the serum and/or urine [1]. Approximately 80% of multiple myeloma patients experience a pathological fracture over the course of their disease and 90% will have bone lesions [2]. The manifestations of bone involvement in patients with multiple myeloma include osteopenia, osteolytic lesions and fractures, which can have devastating clinical effects by increasing the morbidity of

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multiple myeloma patients. In addition, multiple myeloma patients who develop pathologic fractures have a 20% increased risk of death [3].

Research over the past decade has increased our understanding of the bone marrow micro-environment and the crucial mediators in the pathophysiology of bone disease in multiple myeloma, identifying an imbalance in the function of osteoblasts and osteoclasts, with increased bone resorption combined with decreased new bone formation. The bone disease is so severe in multiple myeloma because there is a multiplicity of factors driving osteoclastic bone destruction and blocking bone repair. The primary cause of abnormal bone remodeling is increased osteoclastic activity, which occurs in close proximity to active myeloma cells and decreased activity of the surrounding osteoblasts [4,5]. An increase in the activity and number of osteoclasts has been observed in histomorphometric studies [5,6]. By contrast, balanced bone remodeling with increased osteoclastogenesis combined with normal-to-increased bone formation exists in myeloma patients in areas of bone without tumor involvement [7]. Studies finding increased markers of bone resorption (e.g., C-terminal telopeptide of collagen type I and N-terminal telopeptide of collagen type I) and decreased markers of bone production (e.g., alkaline phosphatase and osteocalcin) support the evidence of dysregulated bone metabolism [8–10]. This interaction between multiple myeloma cells, osteoclasts, osteoblasts and other cells of the bone marrow microenvironment is very important in the pathogenesis of bone disease in multiple myeloma, as well as in the growth and survival of myeloma cells in the bone marrow [11]. Histologic studies of bone biopsies from patients with multiple myeloma suggest that increased osteoclast activity occurs in areas of focal myeloma involvement, while an absence of osteoclast activity is noted in areas without myeloma involvement [12,13]. The findings on histologic studies imply that local mediators released by myeloma cells play key roles in the stimulation of local osteoclasts. Key factors identified as contributing to increased osteoclastic activity in myeloma include receptor activator of NF- κ B ligand (RANKL), macrophage inflammatory protein-1 α (MIP-1 α), IL-6 and stromal-derived factor-1 α (SDF-1 α) [12].

Another aspect of multiple myeloma is that bone involvement results in permanent scarring of the bone. Persistent lytic lesions can be found in patients in remission with no evidence of marrow infiltration by malignant myeloma cells [14]. An antagonist of the Wnt signaling pathway, Dickkopf-related protein 1 (DKK1), is produced by myeloma cells and prevents osteoblast differentiation from bone marrow stromal cells [15]. Attempts to repair the bone by increasing bone production at sites of injury occurs via the differentiation of mesenchymal stem cells into osteoblasts [16]. Bone repair appears to be inhibited at sites of osteolytic lesions in multiple myeloma patients, most likely owing to inhibition of osteoblastic activity by DKK1 [12]. According to some studies, the proteasome inhibitor, bortezomib, may have a role in enabling bone repair by promoting bone formation, but these findings need to be confirmed in clinical trials [17]. The pathogenesis of bone disease in multiple myeloma has been covered in great detail in previous review articles [12,18].

Bone disease in monoclonal gammopathy of undetermined significance

Multiple myeloma is consistently preceded by a premalignant state, monoclonal gammopathy of undetermined significance (MGUS) or smoldering multiple myeloma [19,20]. MGUS is defined by a monoclonal protein spike less than 3 g/dl and less than 10% plasmacytosis in the bone marrow with no end organ damage (Table 1) [21]. While patients with MGUS are asymptomatic, they may have increased morbidity and mortality [22–24]. Smoldering multiple myeloma is defined by ≥ 3 g/dl monoclonal proteins in the blood and/or $\geq 10\%$ plasmacytosis in the bone marrow, in the absence of end organ damage (Table 1) [21]. The average risk of progression to multiple myeloma is approximately 1% per year for

patients with MGUS and 10% per year for patients with smoldering multiple myeloma [25,26].

We recently performed a population-based study on fracture risk in patients with MGUS [27]. We identified 5326 MGUS patients diagnosed from 1958 to 2006, and compared them with 20,161 matched controls. MGUS patients had a 1.6-fold increased risk of any fracture at 10 years, with a significantly higher risk of suffering axial (skull, vertebral/pelvis and sternum/costae) compared with distal (arm and leg) fractures. We further found that, among 2724 IgG/IgA MGUS patients, there was a slightly higher risk of fractures compared with that among 530 IgM MGUS patients; however, the difference was not significant. Similar to previous studies [28,29], we found no association between the concentration of M-protein and risk of fractures. Interestingly, MGUS patients with fractures (vs without) had no excess risk of multiple myeloma or Waldenström macroglobulinemia.

There are other published clinical studies on fractures in MGUS patients [2,22,29,30]. In a Danish study including 1535 MGUS patients, a significantly 1.4-fold increased risk of fracture was observed in MGUS patients compared with the general population. Patients with IgG and IgM MGUS were found to be associated with a higher risk of fractures [29]. In a study based on 488 MGUS patients diagnosed in Olmstead County (MN, USA), a 6.3-fold increased risk of fracture in MGUS patients was found, compared with expected rates in the community [28]. In this study, IgG MGUS was found to be protective. Furthermore, an increased risk was only observed for axial but not distal fractures. In a screening study from Olmstead County, based on 605 MGUS patients compared with 16,793 controls, a significantly increased risk was observed for vertebral, hip and clavicle fractures, whereas there was no increase in the risk for fracture of long bones [22]. Taken together, these data show that MGUS patients have an increased risk of fractures; however, the higher risk in axial sites suggests that the underlying mechanism may be related to the production of hematopoietic marrow, primarily seen in axial bones. These findings suggest that bone alterations are present in early myelomagenesis.

By using histomorphometric studies in bone biopsies from MGUS patients, evidence of abnormal bone degradation has been observed [31]. In addition, an increase in bone resorption markers has been found in some, but not all studies on MGUS patients [9,10,32–36]. Interestingly, characterization of markers such as RANKL has provided new insights into the pathophysiology of bone disease in multiple myeloma, and has also been shown to be affected in MGUS patients [30,37]. Furthermore, studies have not found an increased production of the Wnt-signaling antagonist DKK1 in MGUS, as has been observed in multiple myeloma [15,38]. Interestingly, in one study, the expression of DKK1 was found to be increased in MGUS patients compared with controls, and not in advanced multiple myeloma, suggesting that these inhibitors may mediate bone destruction in the early phase of multiple myeloma, or even in MGUS [15].

Bone imaging in multiple myeloma

The skeletal survey, a series of plain films including the chest, skull, humeri, femora, pelvis, as well as antero-posterior and lateral images of the whole spine, has been the gold standard imaging modality to detect osteolytic lesions in multiple myeloma (Table 2 & Figure 1) [39]. However, the skeletal survey requires at least 30% cortical bone destruction for the detection of osteolytic lesions [40]. As the skeletal survey is based on 20 separate films, the patient typically spends a lengthy period of time on the radiographic table. This may be cumbersome for multiple myeloma patients suffering from skeletal pain as they are rotated and positioned for multiple radiographic images [39]. Furthermore, the skeletal survey cannot be used to assess response as osteolytic lesions usually do not change

radiographically following therapy. Owing to these limitations, there is an increasing interest in improving imaging techniques in multiple myeloma. Features of an optimal imaging technique include high sensitivity for detecting lytic bone lesions and infiltrative focal lesions in the bone marrow, reliable detection of extramedullary disease, low radiation, and being able to assess response to treatment. Newer modalities that have been tested in multiple myeloma include CT scan, PET, MRI and others.

Multidetector computed tomography (MDCT) allows for whole-body imaging and great anatomic detail. MDCT was studied in 18 patients with Durie–Salmon stage III multiple myeloma and compared with the skeletal survey [41]. In the study, a total of 325 vertebrae were examined. The skeletal survey was found to detect bone lesions in 207 vertebrae as compared with 231 lesions by MDCT. In addition, MDCT detected twice as many lesions at risk of fracture (defined as a lytic lesion with >50% volume loss) compared with the skeletal survey. A major disadvantage of MDCT, however, is high radiation doses (>35 milliseverts [mSv]).

Another approach is the use of low-dose computed tomography (LDCT) where the average dose is approximately 3.3 mSv. In one study using LDCT, 34 patients with biopsy-confirmed multiple myeloma and five patients with MGUS or smoldering multiple myeloma were enrolled [42]. All patients underwent a LDCT and a skeletal survey. LDCT was found to detect more osteolytic lesions, allowing the restaging of 25 cases (20 cases were upstaged). These two studies, although small, show that CT appears to be superior to the skeletal survey for the detection of osteolytic lesions.

The fusion of anatomic imaging with functional imaging in the form of PET/CT can also be performed in patients with multiple myeloma (Figure 2). ^{18}F -fluorodeoxyglucose (FDG) PET/CT has the ability to detect osteolytic lesions, focal lesions in the bone marrow, as well as extramedullary disease in patients [43]. When ^{18}F -FDG-PET/CT was compared with the skeletal survey, a higher number of lesions was found in 16 out of 28 newly diagnosed multiple myeloma patients [44]. Furthermore, in nine out of the 16 patients, the skeletal survey was normal while ^{18}F -FDG-PET/CT detected one or more lytic bone lesions. Various studies have reported the sensitivity of ^{18}F -FDG-PET/CT in detecting osteolytic lesions in multiple myeloma to be approximately 80–90%, with a specificity of 80–100% [45,46]. Interestingly, Zamagni *et al.* recently showed that the persistence of FDG uptake after autologous stem-cell transplantation was associated with an inferior progression-free survival and overall survival [47].

Bone scintigraphy has a very limited role in patients with multiple myeloma owing to the lack of osteoblastic response to lytic lesions. Its sensitivity in detecting myeloma bone disease was found to range only between 40 and 60% [48]. When compared with the skeletal survey, radionuclide imaging has been shown to be inferior to conventional x-rays in the detection of bone lesions [48]. This is in contrast to ^{18}F -fluoride PET/CT, which has been found to be sensitive to both osteoblastic as well as osteolytic lesions, allowing its use in multiple myeloma [49]. Further studies are required to investigate its clinical utility in the detection of myeloma bone disease.

Although whole-body (WB)-MRI is inferior to MDCT when it comes to detecting bony lesions, its strength lies in its ability to image the bone marrow directly and to detect the pattern and extent of bone marrow infiltration in the absence of osteolytic lesions [50]. Unlike conventional MRIs, WB-MRI enables an expanded field of view encompassing all or nearly all of the body. In a study on 60 patients with multiple myeloma, the entire axial skeleton was imaged with both WB-MRI and conventional radiographs [51]. They found that WB-MRI revealed additional areas of abnormalities and that the greatest discordance

between the two methods was the detection of diffuse disease infiltration on the WB-MRI, which was not detectable on the skeletal survey. Thus, 68% of the patients had their disease stage upgraded by the WB-MRI. When the authors looked at the group of patients requiring further therapy (24 out of 60 patients), WB-MRI was the most important factor in ten out of the 24 patients in prompting the initiation of further therapy because it detected extra-medullary lesions in six out of the ten patients and impending fractures in three patients. In addition, in a prospective study on 668 patients with multiple myeloma using pre- and post-treatment imaging evaluations with both a skeletal survey and an MRI of the axial bone marrow, the authors found that MRI detected focal lesions in 139 patients who had normal skeletal surveys [52]. Computed tomography-guided fine-needle aspiration of the lesions confirmed focal osteolysis in 97% of these patients. They also found that MRI had a higher sensitivity for detecting focal lesions in the spine, sternum and pelvis, leading them to the conclusion that MRI should be used to complement the skeletal survey in assessing patients with multiple myeloma [52].

Technetium (^{99m}Tc)-sestamibi has a propensity to accumulate in tissues with high cell density and mitochondrial activation, making it suitable for studying malignant tumors [53]. It has been used to detect focal infiltrative bone marrow lesions in myeloma [54–56]. In one of these studies, 39 patients with multiple myeloma (29 with active disease and ten in remission) underwent ^{99m}Tc -sestamibi scans. These scans were then classified as normal, diffuse uptake, focal uptake, or diffuse and focal uptake [54]. In their results, the authors found 32 abnormal scans and seven normal scans. All the normal scans were found in patients in remission after chemotherapy, while 91% of the abnormal scans were found in patients with active disease. They also found that patients with low disease burden had scans with low-intensity diffuse uptake while those with a higher stage disease had focal or high-intensity diffuse uptake. The authors concluded that ^{99m}Tc -sestamibi was a potentially useful technique in the detection of myeloma in the bone marrow, and that the type and intensity of uptake correlated with disease severity.

New imaging modalities will probably change the future management of multiple myeloma patients as they are more sensitive and have the potential to detect lesions not identified using the traditional skeletal survey. The association of detecting early bone lesions using more sensitive techniques and progressive disease needs to be addressed in future studies. In addition, the impact of earlier treatment for bone disease in multiple myeloma and the effect on prognosis will have to be determined in prospective clinical trials.

Bone imaging in monoclonal gammopathy of undetermined significance & smoldering multiple myeloma

Since our current definition of multiple myeloma and precursor states relies heavily on recognizing the presence of end organ damage (Table 1), sensitive studies designed to detect disease at early stages of disease have had a great impact on prevalence and treatment outcomes. More importantly, advancing technology may provide an opportunity to capture early events and processes previously unrecognized, thus perhaps creating unique treatment options.

In a study on 38 newly diagnosed smoldering multiple myeloma patients, MRIs of the thoracic and lumbosacral spine were found to be normal in 19 patients, while the remaining patients had variegated, diffuse or focal patterns [57]. The median time to progression to symptomatic multiple myeloma for all patients was 29 months; however, the median time to progression was far longer in the patients with normal MRIs versus abnormal MRIs (43 vs 16 months). Therefore, according to the authors, abnormal MRI patterns in patients with smoldering multiple myeloma may justify the initiation of systemic treatment. In another

study on 24 patients with MGUS who underwent an MRI of the thoracolumbar spine, all patients had normal scans, compared with only 86% of patients with smoldering multiple myeloma [58].

In a retrospective study of 66 patients with plasma cell disease (14 with MGUS) that were imaged using whole-body ^{18}F -FDG-PET, all patients with active multiple myeloma had an abnormal PET scan, despite 25% presenting with a negative skeletal survey [59]. Furthermore, all the MGUS patients had negative scans.

Dynamic contrast-enhanced MRI of the lumbar spine in 222 patients with MGUS, smoldering multiple myeloma and multiple myeloma, and 22 healthy controls were used in one study [60]. A statistically significant abnormal rate constant (a marker for microcirculation) between normal controls and those with smoldering multiple myeloma was observed, as well as between normal controls and those with multiple myeloma, with a higher difference in value between the normal controls and those with multiple myeloma. The authors also found a correlation between the dynamic contrast-enhanced MRI peak intensity and bone marrow plasmacytosis. Because of their findings, the authors propose that dynamic contrast-enhanced MRI can be used to recognize patients at higher risk for progression, and that these patients should be considered for the initiation of early therapy. However, this has not been shown in prospective trials and at this time is not recommended outside research protocols.

Clinical management of multiple myeloma bone disease

The diagnosis and treatment of bone disease is critical in the management of patients with multiple myeloma. Current guidelines in the treatment of bone disease in multiple myeloma recommend the use of bisphosphonates. The primary mechanism of action of bisphosphonates is osteoclast inhibition, which leads to reduced bone resorption. In patients with active multiple myeloma and at least one lytic lesion, intravenous bisphosphonates have been shown in large, double-blind, randomized trials to decrease skeletal-related events and pain, improve performance status and maintain quality of life [61–63]. In a recent randomized clinical trial based on 1970 patients with symptomatic multiple myeloma, treatment with zoledronic acid compared with oral clodronic acid was found to improve overall survival independently of prevention of skeletal-related events, indicating that zoledronic acid has antimyeloma effects in addition to improving or delaying bone disease [64].

There are four major peer-reviewed guidelines published on the use of bisphosphonates in multiple myeloma [65–68]. The choice of the two intravenous bisphosphonates, pamidronate and zoledronic acid, is left to the discretion of the treating physician and the patient. Zoledronic acid is more potent than pamidronate and has the advantage of a more rapid infusion time. However, some of the guidelines favor the use of pamidronate owing to the concern of increased risks for osteonecrosis of the jaw with zoledronic acid therapy compared with pamidronate [67,69]. In a large trial comparing zoledronic acid and clodronic acid, there was a higher rate of osteonecrosis of the jaw in the zoledronic acid arm (4 vs 1%) [64]. Most of the treatment guidelines restrict the duration of bisphosphonates therapy to 2 years in patients with responsive or stable disease owing to the risk of osteonecrosis from cumulative exposure to bisphosphonates. The optimal duration of bisphosphonate treatment is not known, and other factors such as complications need to be taken into account. Some published guidelines recommend bisphosphonate therapy beyond 2 years in patients with active disease who have not achieved a response or who have threatening bone disease, and recommend to decrease the frequency to every 3 months [67]. Others leave this decision to the discretion of the treating physician. In a recent double-blind, randomized clinical trial

from the Nordic Myeloma Study Group, 504 patients with multiple myeloma were randomized to either 90 mg pamidronate (standard dose) or 30 mg every month for at least 3 years. The clinical end points in this study, physical function and time to first skeletal-related event, did not differ between the two doses of pamidronate, and the authors therefore recommend 30 mg of pamidronate monthly as a new standard [70]. An important side effect of bisphosphonates is osteonecrosis of the jaw, with pain and localized infection, loosening of teeth and soft tissue ulceration [68,71,72]. Known risk factors include dental extractions and long-term use of bisphosphonates, with the type of bisphosphonates used being an important variable, with intravenous use having a higher incidence [73,74]. Treatment is mostly supportive with good oral hygiene, use of antibiotics and pain relief. Prevention is of the greatest importance, and dental procedures are recommended before initiating therapy. In patients who are already receiving bisphosphonates, a conservative approach is of importance, with the avoidance of dental procedures if possible [68,75,76].

Pain related to bone disease causes significant morbidity and impacts on quality of life in patients with multiple myeloma [77]. Assessment of pain as well as pharmacological and nonpharmacological interventions for pain relief should be employed. Guidelines for pain management of multiple myeloma have recently been published [75].

Local radiotherapy is effective for treating pain caused by bone lesions in multiple myeloma [78,79]. Approximately 70% of myeloma patients with bone disease receive radiation therapy during the course of their illness; however, data on radiotherapy after the introduction of novel agents are lacking. The exact dose has not been established in clinical trials. In nonrandomized studies, 91–97% of patients have experienced pain relief with a dose of 3–60 Gy [78,79]. Low-dose radiation, for example, a single fraction of 8 Gy, has been recommended [75].

Recent studies have shown that vertebroplasty is safe and effective in the treatment of vertebral localization of myeloma [80]. Recent randomized clinical trials on the use of vertebroplasty in osteoporotic vertebral fractures (not myeloma patients) were equally effective in control groups [81,82]. In a multicenter clinical trial, 134 patients with cancer were randomized to balloon kyphoplasty versus nonsurgical fracture management for the treatment of painful vertebral body compressions [83]. A total of 49 patients had multiple myeloma. The authors showed that kyphoplasty was safe and effective, and rapidly reduced pain and improved function.

Management of bone disease in MGUS & smoldering multiple myeloma

There are few published studies examining the effects of bisphosphonates in smoldering multiple myeloma or MGUS (Table 3), and all of the current guidelines restrict the use of bisphosphonate therapy to patients with active symptomatic multiple myeloma and/or evidence of bone disease. In a pilot study, Martin *et al.* treated 12 patients with smoldering multiple myeloma with 12 courses of pamidronate, and found an increase in bone density but no significant anti-tumor effect [84]. In a prospective study, Musto *et al.* treated 43 patients with smoldering multiple myeloma with pamidronate monthly for 1 year and then every 3 months until progression, and compared with historical controls [85]. They found no difference in progression rate to multiple myeloma, but at progression 42% of the pamidronate-treated patients had evidence of bone lesions compared with 85% of the control subjects. In another study, Musto *et al.* examined the use of zoledronic acid in previously untreated patients with smoldering multiple myeloma in an open-label, Phase III, randomized trial [86]. A total of 163 patients were enrolled and randomized to zoledronic acid ($n = 81$ patients) for 1 year at a monthly dose of 4 mg versus observation only ($n = 82$ patients). The rates of progression to symptomatic multiple myeloma were similar at a

median follow-up of 65 months. However, at time of progression to multiple myeloma, skeletal-related events were significantly lower in the zoledronic acid groups compared with the observational arm, at 56 and 78%, respectively [86]. In a randomized trial, 90 patients with smoldering multiple myeloma were treated with pamidronate versus observation for 1 year [87]. As in the previous study, there was no difference in the rate of progression; however, there were fewer skeletal-related events in the pamidronate group. Recently, the results of this study were reported with more patients enrolled and longer follow-up [88]. A total of 177 smoldering multiple myeloma patients were included with a minimum follow-up of 5 years for live patients and, similar to previously published studies, there was no difference in progression to multiple myeloma, being 63% in both arms. Overall survival was also similar in the two groups; however, there were fewer skeletal-related events in the pamidronate-treated patients. Thus, all published studies on bisphosphonates in smoldering multiple myeloma show that these agents are effective at decreasing bone disease, but do not seem to change the natural history of the disease.

The role of bisphosphonates in MGUS has also been examined in clinical studies (Table 3). Pepe *et al.* performed a non-randomized study where they separated 100 MGUS patients into two groups based on the presence or absence of vertebral fractures and/or osteoporosis [89]. Patients with signs of bone disease were treated with alendronate plus calcium and cholecalciferol, while the other MGUS patients were treated with calcium and cholecalciferol only. After 18 months, the mean bone-mineral density (BMD) of the lumbar spine and total femur had increased by 6.1 and 1.5%, respectively, in the alendronate-treated patients. In the other patients, the BMD increased by 1.2% in the lumbar spine and decreased by 1.2% in the total femur. In addition, there was a significant decrease in bone markers in favor of the alendronate-treated patients [89]. In a Phase II open-label study, 54 patients with MGUS and osteopenia or osteoporosis were treated with zoledronic acid 4 mg intravenously at 0, 6 and 12 months [90]. DEXA scans and skeletal surveys were performed at time of screening and 1 month after the final zoledronic acid injection. Lumbar spine T-scores improved by a median of +0.27, corresponding to a median increase in BMD of 15%, and hip BMD improved by 6%. No fractures were reported during the study.

Taken together, the role of bisphosphonates in multiple myeloma precursor disease (MGUS and smoldering multiple myeloma), with the aim to prevent future skeletal-related events, needs to be better defined in randomized, prospective clinical trials.

Expert commentary

Bone disease is an important issue in multiple myeloma and there is emerging evidence that patients with smoldering multiple myeloma and MGUS also have increased risk of skeletal-related events. New imaging modalities have improved the detection of lytic lesions and may have an effect on prognosis and treatment strategies. In addition, novel agents active against multiple myeloma – such as bortezomib which seems to have anabolic effects and agents specifically inhibiting osteoclastogenesis – will probably decrease the morbidity and hopefully prolong survival of multiple myeloma patients in the future.

Five-year view

The survival of patients with multiple myeloma has improved in recent years owing to novel treatment options. New agents that are currently in clinical trials will hopefully lead to an even longer survival. At the same time, it is important to diminish skeletal-related events. With optimal use of currently available bisphosphonates as well as novel agents such as denosumab [91] (a monoclonal antibody that binds to RANKL) and BHQ-880 [92] (an anti-

DKK1 monoclonal antibody), we may alter our way of managing bone disease in multiple myeloma.

In addition, biochemical markers of bone metabolism, such as N-terminal and C-terminal cross-linking telopeptide of type I collagen, deoxypyridinoline and CTX generated by matrix metalloproteinases, have been used in multiple myeloma to assess bone turnover and bone destruction [93–99]. These have been used to follow bone disease during treatment. Although not in routine clinical practice, they will probably be increasingly used in the near future to evaluate the extent of bone turnover and response to treatment. In addition, they may be used for smoldering multiple myeloma to reveal patients at high risk of progression [94].

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Key issues

- The manifestations of bone involvement in patients with multiple myeloma can have devastating clinical effects and increase mortality.
- Patients with smoldering multiple myeloma and monoclonal gammopathy of undetermined significance have evidence of bone disease and increased risk of fractures.
- The skeletal survey has traditionally been the gold-standard imaging modality to detect osteolytic lesions in multiple myeloma.
- Newer modalities that have been tested in multiple myeloma, including computed tomography, PET and MRI, are more sensitive in detecting osteolytic lesions and extramedullary disease, which may have prognostic impact in individual patients.
- Current guidelines in the treatment of bone disease in multiple myeloma recommend the use of bisphosphonates in patients with active multiple myeloma and at least one lytic lesion.
- Intravenous bisphosphonates have been shown in large, double-blind, randomized trials to decrease skeletal-related events and pain, improve performance status and maintain quality of life.
- Published studies on bisphosphonates in smoldering multiple myeloma and monoclonal gammopathy of undetermined significance show that these agents are effective in decreasing bone disease, but do not seem to change the natural history of the disease.

Figure 1. An 82-year-old female with IgA monoclonal gammopathy of undetermined significance and a vertebral fracture in L5

Figure 2. ¹⁸F-fluorodeoxyglucose-PET/computed tomography imaging in a patient with smoldering multiple myeloma

A 65-year-old male with smoldering multiple myeloma. The patient had no lesions on skeletal survey. (A) CT scan of the patient's right lower extremity that shows a lytic lesion in the right distal femur. (B) PET image that demonstrates increased ¹⁸F-fluorodeoxyglucose (FDG) uptake in the PET image at the corresponding region. The ¹⁸F-FDG-PET also shows two additional areas of increased uptake probably representing early lytic changes. (C) A composite image derived from the CT scan and FDG-PET images.

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Table 1
Diagnostic criteria for monoclonal gammopathy of undetermined significance, smoldering multiple myeloma and multiple myeloma

Disease	M-protein (g/l)	Clonal bone marrow plasmacytosis (%)	Additional criteria
MGUS	Serum M-protein <30	<10	No other B-cell lymphoproliferative disorders
Smoldering (asymptomatic) myeloma	Serum M-protein >30 and/or	>10	No related organ and tissue impairments
Multiple myeloma	M-protein in the serum or urine	Clonal bone marrow plasmacytosis or plasmacytoma	Related organ and tissue impairment [†]

[†] Hypercalcemia defined as: serum calcium >2.75 mmol/l; renal dysfunction: serum creatinine >173 mmol/l; anemia: hemoglobin 2 g/dl below lower limit of normal; lytic bone lesions (CT scan and MRI may be used to identify suspicious findings on plain films); symptomatic hyperviscosity; amyloidosis; recurrent bacterial infections (more than two episodes in 1 year).

MGUS: Monoclonal gammopathy of undetermined significance.

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Table 2
Comparison of standard imaging modalities in multiple myeloma

Modality	Radiological detection of			Advantages	Disadvantages
	Extramedullary disease	Bone marrow focal lesions	Osteolytic lesions		
Metastatic bone survey	Yes	No	No	Widely available Historical standard	Poor sensitivity Poor interobserver reliability Poor tolerance by patients (multiple positions, long duration)
CT	Yes	No	No	Very sensitive for osteolytic lesions No repositioning Rapid test Better assessment for pathologic fracture risk	Relatively high radiation dose
MRI	No	Yes	No	Very sensitive for bone marrow focal lesions No radiation exposure	High cost Not widely available Long duration of examination Limited fields of view
PET/CT	Yes	Yes	Yes	Widely available	High cost Limited sensitivity in spine

CT: Computed tomography.
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Table 3
Clinical trials on bisphosphonates in smoldering or early-stage multiple myeloma and monoclonal gammopathy of undetermined significance

Study (year)	Design	Bisphosphonates	Patients (n)	Effect on bone disease	Effect on progression	Ref.
<i>SMM</i>						
Martin <i>et al.</i> (2002)	Prospective, single arm	Pamidronate 60–90 mg monthly for 1 year	12 SMM	Increased bone density at 1 year	No	[84]
Musto <i>et al.</i> (2003)	Prospective, historical control	Pamidronate 60 mg monthly for 1 year then every 3 months	43 stage IA or SMM	Decreased skeletal-related events in treatment arm	No	[85]
Musto <i>et al.</i> (2008)	Prospective, Phase III, randomized	Zoledronic acid 4 mg monthly for 1 year	163 SMM	Decreased skeletal-related events at progression	No	[86]
D'Arena <i>et al.</i> (2011)	Prospective, Phase III, randomized	Pamidronate 60–90 mg monthly for 1 year	177 SMM	Decreased skeletal-related events at progression	No	[88]
<i>MGUS</i>						
Pepe <i>et al.</i> (2008)	Prospective, nonrandomized	Calcium and cholecalciferol ± alendronate 70 mg weekly for 18 months	100 MGUS	Increased bone density at 18 months	NA	[89]
Berenson <i>et al.</i> (2008)	Phase II, single arm	Zoledronic acid 4 mg at months 0, 6 and 12	54 MGUS	Increased bone density at 1 year	NA	[90]

MGUS: Monoclonal gammopathy of undetermined significance; NA: Not applicable; SMM: Smoldering multiple myeloma.

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