

# Therapeutic and functional approach for the treatment of patients with bone marrow edema in Rehabilitation Medicine

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## Abstract

Bone marrow edema (BME) represents an imaging finding in various diseases, and often causes pain and significant dysfunction.

Although few data are available about its etiology, several hypotheses have been developed to explain the pathogenetic mechanisms of BME.

Increased intravascular pressure and capillary leakage within the bone marrow would lead to nerve irritation, causing pain. Bone turnover would increase locally, due to proinflammatory molecules driven by the primary cause of BME (trauma, ischemia, arthritis, *etc.*). In addition to imaging findings, the clinical

evaluation of a subject affected by BME should rely on an accurate functional assessment, as this condition often leads to transient disability. As regards therapeutic approaches, recent research works have reported benefits from the extracorporeal shock wave treatment (ESWT) and above all bisphosphonates.

A deeper knowledge of the pathophysiological bases of the BME combined with the classic physiatric approach can allow to select the subjects affected by BME who can benefit from therapies such as bisphosphonates and ESWT, and evaluate their clinical and functional effects.

## Introduction

The notion of bone marrow edema (BME) has drastically changed in recent years from being seen as an aspecific imaging finding, which can be secondary to a wide spectrum of conditions and diseases, to being considered a primary source of pain and even a central pathogenetic element of a group of nosological entities called bone marrow edema syndromes (BMES).<sup>1,2</sup> The histopathologic analysis of these conditions has shown that the *edema* is only a component of a complex and heterogeneous histological picture, which in a significant number of cases is also characterized by other alterations, such as bone marrow bleeding, remodeled osseous trabeculae, bone marrow fibrosis, ingrowth of fibrovascular tissue and lymphocytic infiltrate. Therefore, the Authors re-defined these nosological entities as bone marrow lesions (BMLs).<sup>3</sup>

In scientific literature BMEs and BMLs are currently considered as an important clinical issue, which can contribute significantly to clinical symptoms and negatively affect the natural history of the pathologies associated with bone edema<sup>4</sup> as well as the rehabilitation process of these patients.

## Etiology, pathogenetic mechanisms and classifications

BME and BMLs have been demonstrated in many different pathologies, despite they carry significant differences in terms of histopathological findings, causal mechanisms and prognosis. However, these conditions share a common denominator, which is a form of injury to the bone and bone marrow due to mechanical stress, inflammation or ischemia.<sup>5</sup>

From a pathogenetic point of view, BME and BMLs can be primary or secondary to a large number of diseases. The primary forms involve most frequently lower limb joints in a decreasing order: hip, knee, ankle, foot.<sup>6,7</sup> Secondary bone marrow lesions can be associated to inflammatory, degenerative, infective or neoplastic conditions, even though, in some cases, the exact

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causes and pathogenetic mechanisms cannot be easily identified.<sup>8</sup>

In particular, BME is the common distinctive feature shared by: i) osteitis (due to rheumatoid arthritis or spondyloarthropathies); ii) osteoarthritis (OA); and iii) BMES.

Bone marrow edema syndromes refer to transient, self-limited, clinical conditions characterized by the imaging pattern of BME, such as: transient osteoporosis of the hip, regional migratory osteoporosis, and complex regional pain syndrome (CRPS). While the etiology of BMES is still unclear, a growing number of hypotheses have been explored for the pathogenetic mechanisms.<sup>9</sup>

Magnetic resonance imaging is the main investigation for early diagnosis and monitoring the progression of the edema, whereas plain radiographs may reveal regional osseous demineralization. Laboratory tests and lesion histology are usually unnecessary. Early differentiation from other aggressive conditions with long-term sequelae, and above all from osteonecrosis, which requires a surgical approach, is of crucial importance.<sup>9</sup>

### Physiopathology and clinical features of bone marrow edema

The clinical significance of BME and BMLs is still being debated by experts, even if current evidence suggests an overall correlation between these conditions, patient's symptoms and disease progression.<sup>3</sup> Literature findings are variable and very little is known about the natural history and the progression of the lesions. Long-term follow-up studies are required for further evaluation, however numerous data show that the presence of BME and BMLs is associated with more severe pain and functional impairment in patients.<sup>10</sup>

Indeed, the clinical presentation of BME is mainly characterized by sudden or sometimes gradual onset of acute local pain, which may be unrelated to recent traumatic events. Acute local pain may be present during activities and limb loading, but also with the joint at rest and tends to worsen at night. This kind of bone pain can be associated with local swelling and become persistent,<sup>11-14</sup> thus limiting significantly daily life activities.

Despite this condition is frequently under-reported and under-diagnosed, the epidemiological data suggest that primary BMES affect mainly people aged 40 to 60, without significant differences between genders. Moreover, a correlation exists between the specific BMES called *transient osteoporosis of the hip* and gestation (it tends to occur in the third trimester of pregnancy and has an uncertain incidence).<sup>6,15</sup>

When trying to investigate the *pathogenetic origin of pain* associated with BME and BMLs, researchers have assumed that it is caused by irritation or disruption of *sensory nerves* within the neurovascular bundles of the bone marrow. Irritation could derive from a significant increase in *intraosseous pressure* (even from 2030 mmHg to 5090 mmHg). Marrow edema is supposed to be caused by *capillary leakage* due to either local change in the capillary wall (e.g., trauma, tumor) or increased intravascular pressure. *Increased intravascular pressure* can be either hyperemic due to an increased blood flow to the marrow or congestive caused by decreased venous clearance of the marrow tissue.<sup>4,16,17</sup> The evidence available suggests that BME and BMLs can originate from two different major mechanisms: i) invasion of the marrow space from the outside in inflammatory lesions of rheumatoid arthritis (RA), spondyloarthritis and enthesitis; ii) localized increase in proinflammatory cytokines and vasoactive agents in the marrow space due to microtrauma or

ischemia in the area as seen typically in macro-fractures, local transient osteoporosis, bone bruises and OA.<sup>3</sup>

In these processes, cytokines play a key role in the formation of BME. This could explain the occurrence of pain as well as the effect of treatments such as corticosteroids or anti-tumor-necrosis-factor- $\alpha$  (anti-TNF $\alpha$ ) on the expression of cytokines. It has also been proven that peritumoral edema in bone tumors correlates with the level of prostaglandins and the expression of cyclo-oxygenase-2, which is involved in prostaglandin synthesis.<sup>18</sup> Histological studies on primary BMES highlight that *trauma stimulates a localized repair response with high bone turnover and increased vascularization*. Increased vascularization induced by angiogenic factors and capillary leakage caused by proinflammatory cytokines contribute to the magnetic resonance imaging (MRI) signal abnormality. The *localized high turnover* with increased levels of proinflammatory cytokines and vasoactive agents *may also explain the positive effects of antiresorptive drugs, like bisphosphonates and TNF antagonists on BME and BML extension and symptoms*. A reduction in turnover is supposed to help reduce the levels of proinflammatory cytokines and vasoactive peptides in the lesion.<sup>3,6,19</sup>

In recent years it has also been suggested that BMLs could be an increased risk factor for joint cartilage loss, therefore *treatments aimed at managing these lesions could contribute to the preservation of joint cartilage and early management of osteoarthritis*.<sup>20</sup>

Overall, the connection between the symptoms and the pathogenesis of BME is variable and may be due to acute or chronic trauma or even frequently without any history of obvious trauma.<sup>9,12,21</sup> The distinction between traumatic and non-traumatic BME and BML - especially in sports injuries - is primarily based on a clinical history of trauma, as imaging features are mostly indistinguishable.<sup>7</sup> Repeated micro-trauma and microfractures in the subchondral bone with resulting inflammation of the trabecular bone could also be involved in the origin of these lesions.<sup>3</sup> However, whether a stress fracture is the cause or the consequence of BME still remains controversial. Increased focal bone turnover may result in increased stress risers within the trabeculae, causing microdamage and leading to stress fractures.<sup>22</sup>

A kind of microfracture, which could be linked to BME and BMLs, is defined by British authors as *Subchondral Insufficiency Fracture* (SIF) associated with *functional overload*, but also *joint derailment*: the meniscus undergoes a subluxation, loses its cushioning function and exposes the articular bone to a concentration of non-physiological loads.<sup>4,23</sup> As a result of the dynamics described in these types of bone marrow edema and lesions, these conditions do not exclusively affect elderly patients, but can also occur in younger patients due to a single trauma or repeated micro-trauma capable of causing micro-fractures. Therefore, among patients at risk for this condition, there can be sportsmen/sportswomen who practice training or physical maximal intensity activity. An example could be amateur athletes, who are trained for a short-distance race, yet suddenly decide to participate in a marathon: the consequence can be a very significant bone edema.<sup>7</sup>

### Considerations on clinical manifestations and diagnostic imaging in bone marrow edema

The pain associated with BME has usually a spontaneous onset and can range from a vague and insidious onset to rapidly progressive severe pain that can cause variable degrees of dis-

ability.<sup>6</sup> If a lower limb joint is involved, walking can be painful, and occasionally impossible. Pain due to bone marrow edema is also exacerbated by weight bearing.<sup>4,14,15,23,24</sup> In case of upper limb involvement, manual skills and overhead movements could be compromised.<sup>25</sup> Also negligible or small effusion associated with subcutaneous edema can be found, when peripheral joints, such as knee, ankle or foot, are involved.<sup>14,15,24</sup>

Trophic or vasomotor changes are usually absent in primary BMES, whereas patients suffering from algodystrophy show much more significant autonomic nervous involvement.<sup>26</sup>

The joint affected by BME is usually painful under passive and active mobilization. Percussion of the affected bone has been reported to be more painful than in the normal contralateral side, especially if the knee is involved, and is described as a useful clinical clue to this condition.<sup>27</sup> However, the symptoms may not be very significant in all cases, as they may often be barely perceptible. Indeed, a key clinical feature is that pain and disability are often disproportionate compared to the imaging findings.<sup>6</sup>

In primary BMES the duration of symptoms is variable - from weeks to months - depending mainly on both initial severity and extent of bone involvement and the initiation of an early treatment. Typically the initial phase in these syndromes consists of local pain with functional impairment and is followed by a gradual resolution of symptoms.<sup>6,8</sup>

From a diagnostic point of view BME is a relatively recently recognized condition, as conventional imaging techniques are unable to detect bone marrow edema.<sup>7</sup> The gold standard for the diagnosis of bone marrow edema is MRI, which demonstrates BME with a low signal intensity on T1-weighted images and high-signal intensity on fluid sensitive images (fat suppressed PD and T2-weighted as well as short tau inversion recovery).<sup>8</sup> Therefore, *magnetic resonance imaging is the main exam for early diagnosis and progression monitoring in BME*, whereas *plain radiographs* may reveal regional *osseous demineralization*. Laboratory tests and lesion histology are usually unnecessary.<sup>9</sup>

Purely morphological imaging information may be unspecific, therefore history and clinical details are necessary in most cases for a complete diagnostic picture.<sup>28</sup> Due to its unspecific symptoms, an accurate diagnosis is often delayed, thus leading to more severe pain, functional impairment and poor quality of life.

A key factor in patient management is the distinction between reversible and irreversible conditions and the correct diagnosis of the underlying pathology.<sup>3</sup> Early differentiation from other aggressive conditions with long-term sequelae and above all osteonecrosis is of crucial importance.<sup>9</sup> There still remains some controversy about the question as to whether BMES are a separate entity or represent an early stage of avascular necrosis (AVN). Very few cases ever progress to AVN, and not all cases of AVN are associated with BMES, thus suggesting a potential miscategorization.<sup>14,15,29</sup> Moreover, a review of the literature can reveal a long-standing scientific debate on the differential diagnosis between FH-AVN and aBMEs and there is still no consensus among the Authors on this topic.<sup>4,30</sup>

### Focus on a particular bone lesion: osteonecrosis

Femoral head osteonecrosis is considered the *coronary disease* of the hip, as it consists in the ischemic death of bone marrow and therefore of bone cells. It can be due to trauma (hip dislocation, subcapital fracture of femoral neck), decompression

syndrome, steroid therapy, alcohol and smoking abuse, coagulopathies and myoglobinopathies, irradiation.<sup>31</sup> Six hours of anoxia are sufficient to cause bone marrow death, while osteocytes, osteoblasts and osteoclasts can still survive after 48 weeks. Over this same period the macroscopic appearance of the femoral head shows no changes.<sup>32</sup> However, the death of the bone tissue triggers an inflammatory response, which determines the affixing between the necrotic and vital areas of a reactive interface with fibrous tissue, neoangiogenesis and bone resorption, which in reality leads to subchondral fracture and cartilage infringement. In the absence of treatment, 70% of femoral heads with osteonecrosis collapse, leading to joint failure and the need for prosthetic replacement within 3-4 years. The *staging* of osteonecrosis of the femoral head, according to *Ficat and Arlet* and to *Steinberg's* classification starts from pre-clinical and pre-radiographic *stage 0*, in which the lesion is suspected, when the other hip is affected. Stage I follows, in which radiographic signs of sclerosis or bone cysts are not yet present, but there are symptoms (groin pain, radiating to the anterior or medial anterior face of the thigh or to the gluteus, with functional limitation in the various directions with respect to the contralateral hip) and/or signs of osteonecrosis on MRI or scintigraphy with Tc99m. After the first stage, radiological signs appear, *i.e.* a progressive increase in radiopacity of the necrotic area with respect to the surrounding bone (which may develop osteopenia), followed by the formation of a radiolucent ring around the necrotic area, due to resorption and apposition of healthy bone. Finally, there is the *sign of the crescent*, a line of subchondral radiolucency to the supero-external pole of the femoral head, which indicates joint degeneration.<sup>32</sup> For a correct diagnosis of a subject with a clinical suspicion of osteonecrosis for over 6 weeks, it is recommended to perform antero-posterior and lateral X-rays of the pelvis in the projection of Lauenstein (*frog-leg lateral view*). In case of a negative result, the best diagnostic method is MRI, as osteonecrosis will appear hypointense and hyperintense respectively in T1 and T2 scans.<sup>32</sup> As regards the treatment of osteonecrosis, among the approaches that have shown to improve the clinical picture and postpone surgery, there are physical methods, such as *shock waves* (able to reduce edema and intraosseous pressure, restore blood flow and oxygenation tissue) and *pulsed electromagnetic fields* (which inhibit bone resorption and stimulate neof ormation). On the contrary, data on *hyperbaric oxygen therapy* are considered ambivalent.<sup>32</sup> As mentioned above, the most important parameter to be able to save the hip from collapsing is to diagnose the condition at an early stage based on an accurate physiatric evaluation of bilateral joint excursion. Furthermore, it is necessary to set up a *program of exercises* at an early stage, which are specific for the individual pain and joint function, and should be gradually increasing in duration and intensity, in order to improve hip excursion by preserving the tone and trophism of the flexor-extensor, intra- and extra-rotator hip muscles.

### Role of functional evaluation of bone marrow edemas and lesions

A full understanding of BMLs will be mandatory in the near future in order to develop appropriately-targeted treatments.<sup>10</sup> A combination of *history, clinical examination and imaging findings* is required in each case to *reach an accurate diagnosis*. Therefore, a rather complex and appropriate differential diagnosis, which may require a multidisciplinary approach and in-



involve multiple specialists, such as radiologists, orthopedists, rheumatologists and psychiatrists, should be considered.

The psychiatric clinical evaluation for diagnostic purposes also includes the characterization of the functional impairment, with a specific assessment of the transitory motor disabilities related to these conditions, and in particular a plan for rehabilitation and physical therapy within the framework of an individual rehabilitation project, intended to offer the patient a comprehensive holistic treatment.

Despite the functional impairment in patients affected by BMES can be disabling, the impact of these syndromes in performing physical work and activities of daily life (ADL) has not received extensive attention in literature, with the exception of CRPS. This syndrome is characterized by severe pain, that tends to become chronic with functional and even serious limitations and a significant impact on the quality of life of these patients. In terms of function, the majority of patients affected by CRPS felt that symptoms caused *substantial interference* with general activities (74.2%), mood (74.2%), mobility (67.7%), normal work (74.2%), relations (64.5%), sleep (67.7%), enjoyment (71%), recreational activities (77.4%), and social activities (74.2%). Interference in self-care was identified by 45.2% of patients.<sup>33</sup> Moreover, a survey of CRPS patients conducted by the RSD Foundation found that 23% of the respondents had to stop daily activities occasionally and 74% had to stop them frequently due to pain. These findings suggest that *chronic pain associated with CRPS affects function across the social, recreation/leisure, physical, and emotional domains of the quality of life*.<sup>34</sup> When assessing functional abilities to perform work activities or ADL in patients with BMES and CRPS, it is important first of all to assess difficulties associated with the measurement of pain and functional limitations.<sup>35</sup>

An objective assessment of functional capacity plays a key role in linking self-reported and examination findings to the inability to work.<sup>36,37</sup> Furthermore, the inquiry into how patient minimizes discomfort while pursuing activities of daily living, including bathing and dressing, is also useful to guide functional restoration efforts.<sup>38</sup> Although there is still no specific and shared model for an objective functional assessment of patients affected by primary BMES, there exist models for assessing functional capacities in patients affected by pathologies coexisting with BME, such as in CRPS patients with upper or lower extremity involvement (Table 1).<sup>35</sup> These models can also be used in other disabling conditions associated to BME and BMLs.

The ability to use the upper extremities for grasping and manipulating, that could be limited by some types of BMES, is as critical to the performance of highly skilled managerial and professional activities in the age of computer keyboards, as it is for the unskilled worker doing hand assembly jobs.<sup>35</sup>

Moreover, as described before, BME and BMLs affecting the lower extremities can lead to difficulty in walking. The exam of the interaction between function across the quality of life domains and changes in pain-related symptomatology must be complete, accurate and scrupulous mostly in patients with bone marrow edema in the context of a CRPS, because of the aforesaid functional implications of this pathology.<sup>35,39</sup>

### Focus on complex regional pain syndrome

A brief focus on CRPS, which is a multiple-system dysfunction causing severe and chronic pain and disability may be helpful before discussing functional assessment. It can be distinguished into 2 categories. Type I CRPS, also defined as reflex sympathetic dystrophy (RSD), develops after a noxious event, with a *disproportionate spontaneous pain or allodynia/hyperalgesia* spread over the course of a single peripheral nerve, with *local edema, aberrant inflammation, vasomotor dysfunction, shiny skin and abnormal sudomotor activity and maladaptive neuroplasticity*. In type II CRPS, or causalgia, in addition to the clinical picture described above, also *nerve injury* occurs.

The main risk factors for the development of CRPS are: fractures (45%), sprains (18%), elective surgery (12%).<sup>40</sup> The traumatic event that is most frequently complicated with CRPS is Colles' fracture of the distal radius, where CRPS occurs in up to 37% of cases. However, it is not yet clear whether the appearance of the syndrome depends on the severity of the fracture, on its reduction methods or the immobilization procedure. Further risk factors for CRPS are represented by immobilizations, cerebral ischemia, neurosurgical interventions, pleuropulmonary disorders, myocardial infarction, arteriography, angiography, neoplasms, drugs (anti-tuberculosis, anti-convulsants), intra-articular maneuvers (arthocentesis, arthroscopy, infiltrations).<sup>40</sup>

The pathogenetic pattern of CRPS includes a process of neuroinflammation, followed by dysfunction of the microcirculation and microvascular damage. The combination of abnormalities that are typical in this condition includes limb-confined inflammation and tissue hypoxia, sympathetic dysregulation, small-fiber damage, serum autoantibodies, central sensitization and cortical reorganization.

In the limb affected by a trauma, a local release of proinflammatory neuropeptides, such as nerve growth factor, determines a greater antidromic secretion of neuropeptides from sensory nerve endings (substance P, calcitonin gene-related peptide), as well as autoimmune mediators and autoantibodies, which contribute both to vasodilatation, increased vascular permeability and interstitial edema, with a regional change of sensory nerve function, and axonal sensory degeneration. The result is structural and functional changes that can lead to further up-

**Table 1. Model for functional assessment of complex regional pain syndrome.**<sup>35</sup>

Domain	Tasks
Mobility/exercise tolerance	Walking, steps, getting in/out of bed or chairs, heavy housework, stooping, crouching, kneeling
Upper extremity	Rising arms overhead, grasp/handle, lifting/carrying, turning a key in a lock, preparing meals
Instrumental activities of daily life	Using the telephone, light housework, preparing meals, shopping
Self-care activities of daily life	Dressing, bathing/showering, using the toilet, eating

heaval by creating a vicious circle. In particular, some of these changes can be amplified by tissue ischemia. In chronic cases these factors can determine low activation of the sensory nerves leading to a central sensitization of the posterior horn.<sup>41</sup>

An example of a global evaluation model for patients affected by CRPS is the reflex sympathetic dystrophy-score and the shoulder hand syndrome-score.<sup>42</sup> It is also important for a physician who is assessing the impact of CRPS on the ability to perform work functions or daily life activities to address issues such as the use of a support device, such as a walker, crutch, wheelchair, or orthosis.<sup>35</sup>

Without prejudice to the above, and considering the importance of a holistic assessment of the person affected by these syndromic pictures (an approach typical of the physical and rehabilitation medicine specialist), the psychiatric examination of these patients must obviously include also a segmental assessment of both muscles and joints, associated with range of motion analysis and an accurate kinesiological evaluation.

Then objective findings on examination and observable changes in life function should lead to investigate aspects that are considered to be most closely related to CRPS or BMES.<sup>43</sup> A complete assessment in cases of CRPS should cover the following areas: pain, sensation, swelling, movement (also considering the presence of dystonia), function.<sup>39,44</sup> A complete examination of neuro-motor function and abilities associated with daily-life activities in patients affected by bone marrow edema syndromes is also important to improve clinical decision making and to plan the rehabilitation treatment. In addition, also functional outcome scores and measures should be used in order to determine treatment and rehabilitation goals and to assess treatment efficacy.<sup>44</sup>

### Clinical management of bone marrow edema in Rehabilitative Medicine: physical therapy and pharmacological treatment

As mentioned above, BME syndromes are associated with pain, which can be caused either by the edema related to an inflammatory infiltrate in RA, or a real edema with reduced bone mineralization, or associated to fibrosis and marrow necrosis in advanced OA,<sup>45</sup> or related to an increased marrow blood flow (hyperaemic) or a reduced vascular drainage (congestive), which both lead to a rise in intraosseous pressure, hypoperfusion and hypoxia.<sup>45</sup>

Although many studies highlighted a relationship between BME and pain, and a reduction of pain with decreasing BME, the presence of BME is detected on MRI images only in 50-73% of painful knees as well as in few painless knees.<sup>46</sup> Biomechanical problems due to malalignment, which are at the origin of several cases of OA, lead to microfractures of the subcondral metaphyseal bone and BME, with a progression of the OA process.<sup>46,47</sup>

Among the conservative approaches to treat BME in OA, other than reducing the weight-bearing load, also the extracorporeal shock wave treatment can result in pain and functional improvement, despite it requires surface anesthesia or intravenous analgesia.<sup>48</sup> The second option is the use of bisphosphonates (BPs), the osteoclast inhibitors that seem to act by regulating the increased bone turnover, thus slowing down disease progression.<sup>49</sup> In a sample of knee OA patients, the degree of BME decreased over a 12-month follow up period more significantly in the group who underwent SSWT compared to the group treated with oral alendronate.<sup>46</sup>

A meta-analysis of randomized controlled trials<sup>50</sup> comparing bisphosphonates (in particular risedronate) vs placebo in knee OA, excluding those using concomitant steroids or opioid therapies revealed that BPs, even if displaying good tolerability, did not lead to statistically significant differences in pain relief, nor defer radiographic progression compared to placebo. This poor efficacy of BPs in OA knee could depend on the low grade of bone turnover that characterizes the late stages of OA, which is not compatible with the mechanism of action of BPs. Therefore, subcondral bone turnover should be analyzed in OA patients in order to select those who could benefit from BPs and investigate their effects.<sup>50</sup>

However, a randomized, double-blind, placebo-controlled study<sup>51</sup> conducted on 64 patients with acute painful knee OA reported the efficacy of four i.v. infusions of 100 mg neridronate both in terms of pain control, as assessed by VAS, WOMAC, McGill pain questionnaire and SF-36 and of reduction of the whole-organ MRI score (WORMS) for knee OA for BME.

The rationale for using bisphosphonates in acute OA lies in the fact that OA is a degenerative disease with chronic inflammation and BME. Its epicenter is probably represented by the subchondral bone. Pain and function are scarcely controlled by paracetamol and opioids, whereas sulfate glucosamine is useful only if associated for a long time with chondroitinsulphate or Boswellia. Neridronate and clodronate have shown to reduce pain and edema in hand and knee OA.<sup>51-56</sup> Moreover clodronate has proven to have an anabolic effect on articular cartilage by increasing the extracellular matrix by 90%,<sup>53</sup> and to be able to stimulate the chondrogenic differentiation of mesenchymal cells in vitro in a dose-dependent manner.<sup>57</sup> The pharmacodynamic features that make clodronate suitable for OA patients are: absence of contraindications in case of kidney chronic impairment, safety regarding ONJ risk, proven anti-flogistic activity on Interleukin-1 and -6 and on metalloproteinases, its central analgesic effect, and its efficacy against BME.<sup>52</sup>

Moreover, according to a 4-year follow-up randomized study, clodronate also proved to reduce knee prosthetic migration by decreasing the risk of loosening.<sup>58</sup>

As regards the acute type 1 (CRPS-1), a multi-centric randomized double-blind placebo-controlled trial<sup>59</sup> conducted on 82 patients has shown a significant reduction of the Visual Analogue Scale score and a benefit in the SF-36 questionnaire in patients treated with the amino-bisphosphonate neridronate 100 mg i.v. compared to the placebo group.

The main potential mechanisms by which the amino-bisphosphonates may improve clinical signs and function of CRPS-1, regardless the inhibition of osteoclasts - not involved in the physiopathology of this condition- are supposed to be those reported in Table 2.<sup>60-64</sup>

Most studies reported that the response to BPs is significant in the early phases of CRPS-1, when scintigraphy highlights a major local accumulation of the drug, whereas scarce benefits have been shown in pediatric cases, long lasting disease, or a primarily cold disease, where the bone scan is often negative at a late stage.<sup>64</sup>

Moreover, safety of BPs is as important as efficacy. BPs have no reported serious side effects so far in the above-mentioned studies, such as osteonecrosis of the jaw or atypical fractures, when used in CRPS or knee OA therapeutic regimens, without prejudice to the recommendation of assessing serum calcium levels and renal function before BPs infusion and eventually correct any vitamin D deficiency.<sup>65</sup>

**Table 2. Mechanisms of action of amino-bisphosphonates leading to complex regional pain syndrome type 1 benefits.**<sup>53-57</sup>

Amino-bisphosphonates effects on bone marrow edema due to complex regional pain syndrome type 1	
• Decrease of lactic acid production (due to tissue hypoxia and increased anaerobic glycolysis), <sup>53</sup> which allows to:	– Prevent hydroxyapatite crystal dissolution in the acid milieu – Reduce the antidromic release of CGRP and SP from nociceptive afferents, thus reducing vasodilatation, edema and pain
• Inhibition of proliferation, activation and function of monocytes and macrophages <sup>54</sup>	– Reducing inflammation, nociceptive sensitization and microvascular disturbances
• Inhibition of farnesyl synthase and GTPase function	– Thus slowing the nociceptive signaling
• Chelation of calcium ions	– Thus reducing hyperalgesia and allodynia and the local release of CGRP and SP
• Prevention of bone cell apoptosis <sup>55,56</sup>	– Preserving osteoblasts and osteocytes from apoptosis <sup>55</sup> – Reducing the production of tumor necrosis factor- $\alpha$ <sup>56</sup>

CGRP, calcitonin-gene-related peptide; SP, substance P.

## Conclusions

Bone marrow edema is an important clinical issue deriving from several conditions and leading to severe bone pain and functional impairment. The physiatrist plays a pivotal role in various stages, from the diagnosis to the etiopathogenetic assessment, to the choice of a conservative therapy. In addition to physiotherapy and rehabilitation, today a safe and effective therapeutic weapon is available to treat BMLs at an early stage, *i.e.* bisphosphonates.

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