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Mini Review

Bone Marrow Edema and Joint Overuse in Athletes: a Mini-Review

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Abstract

Bone marrow edema (BME) is defined as an area of low signal intensity on Tl-weighted MR images and associated with intermediate or high signal intensity findings on T2-weighted MR images. Although BME is clearly present at MRI in subjects who already experience joint pain, what makes it difficult to trace the origin of this clinical picture, and thus to establish the correct treatment, is the fact that BME is also found in asymptomatic patients. In fact, BME represents a typical imaging finding that characterizes stress-related bone injury, a common feature of athletes and military recruits, but also amateur athletes. There are several factors that contribute to the etiology of stress injuries, such as changes in an existing training regimen or, as is often seen in non-professional athletes, the undertaking of a new sport or activity. MRI plays a key role in the detection of bone abnormalities since this imaging technique allows detailed evaluation of BME as a consequence of physical performance. These bone changes detected at MRI can help in identifying the stress injuries at an early stage, and this is essential to avoid serious physical, professional, and financial consequences for professional athletes. The clinical significance of BME is still unclear, but it is important to correlate BME imaging findings with the clinical history of the patient and the specific sport performed; it is also crucial to clarify whether there is a specific threshold, during exercise-triggered bone remodeling, beyond which this condition degenerates into the clinical picture characterized by BME, pain and, in more severe cases, a stress fracture. This is necessary to help clinicians and trainees to ensure an accurate diagnosis and therapeutic treatment, and the proper workout adjustment respectively.

Keywords: Bone Marrow Edema; Magnetic Resonance Imaging; Athletes, Sport; Joint Overuse; Pain; Bisphosphonate

Abbreviations: BME: Bone Marrow Edema; BML: Bone Marrow Lesions; MRI: Magnetic Resonance Imaging; Pemfs: Pulsed Electromagnetic Fields; CPRS: Complex Pain Regional Syndrome.

Bone Marrow Edema (BME): on overview

Bone marrow edema (BME) on MRI is defined as an area of low signal intensity on Tl-weighted MR images and associated with intermediate or high signal intensity findings on T2-weighted MR images. The BME pattern is a non-specific finding with multiple etiologies [1]. Instead of BME, the term Bone Marrow Lesions (BML) is often used to describe a more heterogeneous clinical picture, which includes lesions that occur in the subchondral bone but also in other components of the osteochondral unit [2]. The altered signal pattern observed on MRI is probably related to the fact that the bone marrow is replaced by a water-rich material; it is replaced by aggregates of immune cells, in particular T and B lymphocytes, whose presence is associated with a high concentration of blood vessels. It is precisely this aspect, in fact, that determines the increased water content in BME that is detected at MRI [2-3]. From a clinical point of view, MRI (particularly in high-level athletes) has highlighted the presence of BME in both symptomatic and asymptomatic individuals [4]. Dual-energy CT can be useful too by creating bone edema mapping [5-6]. However, MRI is considered

the method of choice to depict bone marrow changes, being helpful in decision-making [7-8]. Orthopedics and sports medicine are showing a growing interest in bone marrow edema (BME) in the athletic population, with a steady increase in number of papers published yearly over those topics. BME onset has been linked to training. Training and sports-activity, even in the absence of trauma, can cause biomechanical joint overload and overuse. To correctly address the treatment, the clinician should take a careful patient' history and be able to differentiate traumatic and non-traumatic BME (by correlating pain onset, for example) [9]. It is important to underline how superficial soft tissue traumas could obscure clinical signs and symptoms of an underlying BME [10]. If the pain onset reported by an athlete could be caused by atraumatic BME, clinicians could use MRI to analyze elite athlete joints [11-12]. Some authors suggest that BME are part of the normal bone remodeling in response to regular overloads on the joints [13-14]. Specifically regarding atraumatic BME in the athletic population, the current hypothesis is that repetitive loading of submaximal forces and inadequate time for recovery lead to joint overuse. This biomechanical overuse causes bone stress reactions that can be clinically interpreted as pre-fractures. In either normal or impaired bone, pre-fractures could evolve into stress fractures [15]; this is why we consider important to study the link between BME and joint symptoms and prognosis for athletes: this will help clinicians and trainees to make the proper workout and therapeutic adjustments.

Non-Traumatic BME Onset

Stress-related bone injuries are common in athletes and in military recruits but given the considerable importance of physical activity to ensure a healthy lifestyle, this condition is no longer limited to professional athletes or military personnel [16]. In particular, in the adolescent athlete population, these types of injuries can occur in one of three ways: first, they can develop in athletes who increase rapidly their physical activity level, without adequate training; second, they can occur in inadequately trained children who do not have particular skills for any specific sport; third, they can manifest in athletes that do not allow the body to rest after a period of intense activity [17]. In athletes, also the type of training, the match load together with intrinsic and extrinsic risk factors, contribute to the etiology of the injury [18]. As mentioned, MRI plays a key role in the detection of bone abnormalities since this imaging technique allows detailed evaluation of BME as a consequence of physical performance. These bone changes, correlated to the clinical history of the patients, can help in identifying the stress injuries at an early stage; identifying these abnormalities at an early stage is essential to avoid serious physical, professional and financial consequences for professional athletes [16]. BME is optimally detected by T1-weighted and fat-suppressed T2-weighted MRI sequences, but the histopathological features observed on MRI are not clearly defined. It is the severity of the joint injury that determines the different histopathological aspects detectable at MRI: a less severe trauma causes BME appearance without detectable damage to the cellular elements, whereas with increasing severity of trauma, microfractures and hemorrhage are seen within the trabecular bone [14-19]. Changes in an existing training regimen, in equipment, or, as is often seen in non-professional athletes, the undertaking of a new sport or activity, are the common causes of stress injuries [16].

Etiopathogenesis of BME

Usually, BME associated with sports activities is characterized by a traumatic etiology but besides pure acute traumatic causes, it may result from repetitive or chronic trauma [14]. The cascade of events that leads to an osseous stress injury begins with a stress reaction or response by the bone, that progresses to a stress fracture and finally, to a complete fracture; these lesions are characterized by BME at MRI [16]. The basic principle of bone stress response is Wolff's law, which claims that changes in stress applied to the bone are reflected in changes in its internal architecture [18]. In professional athletes, however, the correlation between joint damage and BME is not so obvious, since the results of some studies have revealed that edema can also be common in asymptomatic athletes, as also described in the next paragraphs. [4]. In fact, in their study, Major and Helms analyzed at MRI the knee joint of high-level collegiate basketball players before the start of the season, in order to evaluate changes that could have been misinterpreted as abnormal when a player underwent the MRI during the season. Their study revealed that 14 out of 34 players were showing BME in at least one location. They concluded that the changes observed at the MRI were asymptomatic abnormalities; they also hypothesized that these lesions could be due to a microtrauma transmitted through the meniscus, dissipated by the cartilage and absorbed by the bone and that the continuous repetition of jumping and running eventually led to the appearance of edema [20]. Another study by Schueller-Weidekamm et al. conducted on asymptomatic marathon runners, showed the presence of BME in the knee in 13.6% of subjects but no increase in the extent of BME was found after the completion of a marathon. They concluded that marathon running is not the cause of BME appearance at MRI in well-trained individuals, with normal Body Mass Index. Moreover, trained runners such as marathoners have appropriate shoes that can properly distribute across the joint the stress due to repeated movement [21-22]. As mentioned above, stress applied repeatedly on the joint causes a stress reaction: the bone reacts to repetitive stress, which can be seen as hypertrophy and trabecular bone remodeling. The remodeling trabeculae show microfractures, which appear at MRI as areas characterized by BME. It is also hypothesized that the biomechanics related to the specific sport could be responsible for BME pattern observed at MRI [4-16]. The response of the bone to repetitive stress also results in an increase in the activity of osteoclasts at the expense of osteoblasts, resulting in weakening of the bone itself. The temporary adaptive response to this condition

is periosteal new bone formation to provide reinforcement but, if the source of the stress persists, the osteoclastic activity becomes predominant, leading, as mentioned above, to the appearance of microfractures [18]. These small lesions are extremely difficult to detect, so it is important to correlate imaging with the patient's medical history and pain localization when present [16].

BME and Pain

Symptoms are non-specific but include pain onset and sensitivity during sports activity: pain is initially bearable and does not interfere with physical activity. At this stage, the athlete continues to train, increasingly stressing the joint, thinking of a mild muscle injury. As a result, the risk is that the stress reaction has no way to heal, and can degenerate into a stress fracture [16]. The clinical significance of BME is still unclear, but in order to ensure an accurate diagnosis and a therapeutic treatment, it is necessary to correlate the clinical history of the patient with the specific sport performed and the imaging findings [14-16]. Even if there are no studies in the literature analyzing the correlation between BME and athletic performance we could consider that the latter is reduced due to pain and temporary avoidance of physical activity. No single sport activity is spared of BME: in the literature there are studies over runners, basketball players, volleyball, and others [23- 25]. The type of sport activity involved influence BME location: rugby players tend to have BME focused on the tibiofemoral joint (e.g. medial condyle) while runners tend to have the patellofemoral joint mostly included due to a more linear movement [24-26]. This stress distribution could also explain why some bony areas (like the carpal bones) are relatively spared from BME [27]; Lutter et al. shown that less strain is transmitted along the carpal bone while it is conducted more through the ligaments to the distal radius and ulna. They proceeded to study n= 31 rock climbers reporting pain, where carpal bones have been the subject of thenar and hypothenar muscle strength: 28 climbers had associated BME of one or more carpal bone and nonoperative treatment with a break from rock climbing of around 4 months determined pain reliving [28]. However, it is difficult to compare the studies present in the literature: a limit is the athletic population heterogeneity: the age intervals, the proportion of male and female studies, and the workout profiles. Another difficulty found in the studies analyzed is the quantification of the training intensity; in a study by Mandalia et al. including 25 asymptomatic university athletes, the total training time and its intensity were significantly associated with BME appearance ($p<0.05$) [26]. The study group states the challenge to measure the severity of repeated impacts and the exact duration of repetitive impacts as the most relevant influencing factor for BME appearance. Again, this same study highlights how high-contacts athletes have an increased BME incidence (5 out of 13 rugby players had BME while none of the swimmers) showing how the type of sport activity dictates BME incidence [26]. When looking for the correlation between BME and clinical symptoms, we have not found a consensus, with some studies founding statistical significance connection while other did not. A study by Sims et al. analyzed lumbar vertebral bodies MRI-detected BME in 65 healthy male cricket players for lower back symptoms and lumbar stress injuries. They have found a correlation between the BME signal intensity and symptomatic lumbar stress fractures: a signal intensity of 2 or more in the vertebral body was suggestive of symptomatic relevant BME [8]. Differently, a 2-year follow-up study with 102 elite players (soccer, ice-hockey and bandy) by Paajanen et al. found no statistical significance between BME and groin pain as 50% of both symptomatic and asymptomatic players had pubic BME joint at MRI imaging. Again, this study highlight how BME origin is linked to joint overuse and/or subclinical contact injury: bandy players had a less frequent direct pelvic contact than soccer and ice-hockey players, and subsequently had a lower frequency pubic BME [29]. In our research we have included also 2 studies involving military personnel involved because, they endure a structured uninterrupted physical training over their military service. Varkas et al. studied 22 military recruits for BME of the sacroiliac joints before and after 6 weeks of intense standardized physical training. At the end of the observation period the BME size did not increase and no statistically significant relationship was found between back pain and BME [30]. As mentioned above, in some cases, the term BME is replaced by the more generic definition of BML; according to numerous studies, the signal detected by the MRI is not only due to the presence of edema, which is not always present in histological samples, but also to alterations occurring in the surrounding tissues [2]. Pattern imaging is usually more complex and, in addition to edema, involves the entire osteochondral unit, particularly subchondral bone: at MRI it can be observed a fibrotic appearance, lymphocytic infiltrates and increased vascularization [31]. At this purpose, it is noteworthy that the formation of new blood vessels is also linked to neurogenesis by some pathways, which involve the release of proangiogenic factors. Angiogenesis could therefore contribute to the genesis of new nerves, and consequently to the perception of pain, in patients characterized by BML and BME at MRI [32]. In this regard, a study conducted by Kuttapitiya et al. has shown that BML is characterized by increased expression of genes involved in pain sensitization, inflammatory process and neurogenesis, thus giving further evidence of the correlation of these lesions with the pain perceived by patients suffering from osteoartrosis. During total knee replacement (TKR), bone tissue samples were taken to be subsequenlty analyzed through microarray technique. From this analysis, it was found that the most upregulated gene was STMN2 (Stathmin 2), a phosphoprotein involved in responsiveness to Nerve Growth Factor (NGF), neuronal growth and osteogenesis. The upregulation of this gene within BML could thus lead to the formation of new neuronal structures in the bone tissue affected by osteoarthrosis, thus increasing pain perception [33]. These results suggest that the increase in vascularization, which is itself the

origin of BME, is determined by an increase in angiogenesis, which in turn is related to neurogenesis. It would therefore be interesting to treat athletes in whom BME has been detected associated with pain, with anti-NGF antibodies, and investigate whether inhibition of the neurogenesis process can also block angiogenesis and consequently, the formation of edema.

How Training Influence BME Size

A breakthrough was the finding that physical training on athletes could influence BME size and, ultimately, its disappearance; a study by Horga et al. analyzed both knees of 71 middle-aged asymptomatic marathon runners 6 months before and half a month after the marathon: a size reduction of subchondral BME was observed after the marathon for 19 of the 58 previously detected BME. To our knowledge this is the first study showing lesion reversibility following training but the short follow-up cannot exclude, in our opinion, BME reversibility [34]. Other similar studies focusing on runners have found stable or increased BME incidence after a marathon [35, 36]. An appearing-and-vanishing pattern has been observed in a study by Kornaat et al. analyzed 16 professional asymptomatic runners over 7 months to investigate BME clinical and radiological progression: only 14 runners already have BME at the beginning of the study (mostly located at the foot and ankle joint), 96% graded as 1 or 2. As the end of the observation period, 58% of BME showed a fluctuation pattern (20% appeared and 22% disappeared) without causing any clinical symptoms. According to the authors, this could explain how BME are part of the physiological bone remodeling process and that, at least within 7 months, cannot cause symptoms [24]. The bone remodeling theory has been taking over again in a case-study by Matiotti et al. In 87 asymptomatic adolescent (age range 14-17) a higher prevalence of BME (41.3%, prevalent in the medial femoral condyle) was found in the knee of those adolescents that were soccer players rather than in the control group (7%). Alongside BME other abnormalities were found but with no statistical significance: joint effusion, tendon injury, patellar chondral lesion and edema of the iliotibial band. Also a study by Solder et al. found a higher BME prevalence in soccer players (50%) rather than control group (3.6%). Both authors agree on identify a causal connection between BME and knee bone remodeling [37]. Similarly, a study by Hadid et al. on 55 Israeli recruits found BME lesions in 26 of 55 recruits (47.3%) at entry and only nine (16.4%) following basic training [38].

Update On BME Therapeutic Management

Regarding treatment, most studies generally recommended a temporary halt to work out without additional treatment based on empiric observation. This management is widely accepted probably because of the lack of correlating symptoms and BME. Specifically, there is a paucity of studies in the literature focusing on BME in the athletic population. A study with 25 symptomatic high-performance soccer players with BME found a reduction of the 50% (from 124.4 days to 63.8 days) in the recovery time and return to competition by the administration of intravenous bisphosphonate (specifically ibandronate) and high-dose vitamin D [39]. Among bisphosphonates, a recent study by Müller et al. on 34 patients with painful knee BME proved how Zolendronate was more efficacious in reducing pain when compared to other biphosponates or monoclonal antibodies [40]. Also Iloprost (a vasodilator used for treating pulmonary hypertension) has been found promising in reducing BME pain with bisphosphonates [41]. Other studies focus on BME treatment but with non-athletes focus groups; extracorporeal shock wave therapy is promising in reducing pain [42-43]. Pulsed electromagnetic fields (PEMFs) have been studied as well [44]. A paper by Martinelli et al. on BME affecting the talus revealed how, in 5 out of 7 patients, there was a decrease in pain and BME already 1 month of magnetic field therapy, with complete BME lesion regression at 3 months [45]. It is essential to identify the cause of BME to administer the right treatment: for example primary inflammatory or rheumatic BME can also be treated with pharmacologically (e.g. NSAIDs, corticosteroids, bisphosphonates, etc.) while a degenerative BME (e.g. caused by osteoarthritis) could be treated with physical therapy as eccentric exercises [46]. Complex regional pain syndrome (CRPS) management could be useful even if the relationship between BME and CPRS in not fully elucidated. CPRS criteria include the Harden 2010 Budapest criteria: allodynia, limb pain, hyperalgesia, limb functional impairment, edema. etc. [47]. BME syndrome is an incomplete self-limited form of CRPS: having an atraumatic pathogenesis it is a self-limited condition [48, 49]. PEMFs and physical exercises have been proven effective for the treatment of both CRPS and BME syndrome [47]. Neridronate, a bisphosphonate for treating CRPS, has been found useful to treat BME in a study by Lurati et al. on 73 patients with painful BME.: the administration of Neridronate has been found to decrease BME size and reported pain, demonstrating how research should focus on bisphosphonates to treat BME [50].

Discussion: What Is New For The Clinician

The purpose of our review is to summarize the current knowledge on what could be the causes of BME and what could be the clinical significance of this phenomenon in athletes: we would like to be able to give a small trigger to what could become in the future the guidelines for the management of this clinical picture, and at the same time encourage research in this field, given the scarcity of literature data on the subject. In support of this, Table 1 specifies the Level Of Evidence (LOE) for each article cited in our review. As the table shows, the articles cited by us are all characterized by a LOE 4 or 5. This means that to be able to develop sound guidelines for the management of BME in the future, more studies with the highest LOE value will be needed, and therefore characterised by the highest possible degree of recommendation. Then, further research is needed to correlate BME influence on athletes' health: the lack of guidelines challenges BME management. The very first

thing for BME assessment is a careful clinical history: clinicians should take note for any history trauma. In case no indirect or direct trauma could be traced back, the clinician must investigate other possible causes (septic inflammatory, rheumatic, neoplastic and, especially for athletes mechanical/degenerative BME). Pain characterization should have a careful inspection: the intensity, its chronicity or acute onset and its association with physical therapy must be recorded. Once joint overuse due to physical activity is identified as the primum movens, training intensity and modalities should be noted as well as break periods from physical activity. Further imaging analysis (with MRI being the gold-standard) are strongly recommended for differential diagnosis. In the literature no articles are studying BME treatment in the athletes. Because of that we strongly recommend that BME should be treated in the context of each individual's characteristics: musculoskeletal maturation, injury history, mechanics, and force-load. The baseline treatment for athletic population is a hiatus from sport activities both in asymptomatic and symptomatic individuals. The fact that some studies point at a reduction on BME size upon training is promising even if there is a need of longer continuous follow-ups to generate consensus. If the patient reports symptoms such as pain without any acute trauma, the first approach is a conservative treatment: short-period immobilization, resting from training halt and NSAIDs; surgical options could be recommended in case of failing of non-operative treatments [46]. A possible limitation of the present review is the use of various imaging clinics and machines, with variations on MRI acquisition protocols.

Conclusions

On the basis of the results obtained from the various studies presented in our work, we can therefore ascertain that physical exercise performed at high intensity and over time, triggers a phase of bone remodeling. Once a certain threshold is exceeded, the normal balance between bone apposition and resorption is unbalanced: this alters the internal architecture of the bone itself, initially leading to a condition of BME visible at MRI, and then to the perception of pain in more advanced cases. What we have to ask ourselves is: are there any warning signs that predict the occurrence of this condition? Is MRI a sufficient evaluation tool for this type of phenomenon, or is it necessary to resort to further diagnostic strategies? The purpose of this work is in fact to suggest that studies should be expanded along these lines, in order to arrive to an early diagnosis.

The role of joint overuse during the workout for the developing and progression of BME is in fact still debated. While some authors consider BME as part of the normal remodeling process, others look at BME as bone abnormalities that should be treated and alter workout training. Moreover, BME as a direct cause of pain is not fully understood: finding a possible causal connection should be the subjects of future studies. We strongly encourage studies to highlight the link between athletes and BME in order to identify athletes that should be treated.

Conflict of Interest

The Authors declare that there is neither conflict of interest nor economic interest in the paper submitted.

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