Review

Influence of Vitamin D and C on Bone Marrow Edema Syndrome—A Scoping Review of the Literature

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Abstract: Bone marrow edema syndrome (BMES) is a rare disease with a largely unknown etiology. The aim of this scoping review is to systematically evaluate and combine the available evidence about vitamin D and C and BMES. The analysis of the manuscripts was based on country of origin, number of patients, gender, study type, epidemiology, localization, bone mineral density measurements, vitamin status and therapy. Sixty studies were included. The overall number of patients was 823 with a male-to-female ratio of 1.55:1 and a mean age of 40.9 years. Studies were very heterogeneous and of diverging scientific scope with a weak level of evidence. The hip was the most affected joint, followed by the foot and ankle and the knee; 18.3% of patients suffered from multifocal BMES. Sixteen studies reported on vitamin D levels, resulting in a high prevalence of vitamin D deficiency (47%) and insufficiency (17.9%) among BMES patients. Three BME manuscripts were associated with vitamin C deficiency. Current therapeutic interventions include conservative measures (mainly unloading), various osteoactive drugs and iloprost. In summary, data about BMES in association with vitamin status is limited. A causal relationship between vitamin D or vitamin C status, osteopenia, and BMES cannot be determined from the existing literature.

Keywords: lower extremity; regional transient osteoporosis; bone marrow edema; vitamin D; vitamin C; scoping review

1. Introduction

The term “bone marrow edema” (BME) describes an MR tomographic imaging phenomenon that is characterized by hypointensity on T1 weighted images and hyperintensity on STIR or fat-suppressed T2 weighted images. It was first recognized as a transient increase in bone marrow water content by Wilson in 1988 in 10 patients with hip or knee pain which he suspected due to the MRI pattern. “For lack of a better term and to emphasize the generic character of the condition”, he introduced the term “transient marrow edema syndrome” [1].

Currently, various pathologies of the bone are known that can lead to a secondary, reactionary bone marrow edema. Triggering pathologies can be traumatic (stress fracture, contusion, post-surgical), septic (osteomyelitis, septic arthritis), inflammatory (enthesitis), degenerative (osteoarthritis), neoplastic (benign or malignant bone tumors), ischemic/neurogenic (avascular necrosis, Charcot neuro-osteo-arthopathy) or metabolic [2]. In addition to these known causes, some patients with nonspecific subacute or chronic joint pain and the radiologic diagnosis of bone marrow edema may not have any known underlying pathology. In these cases, the term “bone marrow edema syndrome” (BMES) was used and the disease was recognized as a separate entity [3,4]. Various synonyms have been used to describe this disease. These terms are often stated in a confusing and inconsistent manner in the literature including “transient osteoporosis” (of the hip), “regional osteoporosis” (regional), “migratory osteoporosis”, “transient bone marrow edema” and “bone marrow edema syndrome”, to name the most common. The term “transient...
osteoporosis” was first used by Curtiss and Kincaid in 1959 [5]. This descriptive term of the pre-MRI-era was used for the affected joints of pregnant women, showing radiolucency interpreted as osteopenia on conventional radiographs [5].

BMES is described as a self-imitating disease with a spontaneous onset of debilitating joint pain, usually of the lower extremity, which worsens with weight bearing [3,6,7]. It is a rare disease, affecting mostly middle-aged men between 40 and 60 years, but epidemiological data are lacking [3,6,8]. The etiology and pathophysiology remain largely unknown [2,3].

Recent reports highlight the role of vitamins (vitamin K, B, C) in skeletal health and on bone mineral density [9–11]. Especially the role of vitamin D in osteoporosis, in bone metabolism and in the health of the bone microenvironment has often been demonstrated in the past [12]. This suggests a possible relationship between vitamin status and BMES. Therefore, the aim of this scoping review was to systematically evaluate and combine the available evidence about vitamins and BMES.

2. Materials and Methods

Protocol and registration: The scoping review was conducted using the PRISMA guidelines and the recommended checklist (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews; PRISMA-ScR; http://prisma-statement.org (accessed on 29 April 2022)). The scoping review was registered prior to data analysis on the platform “Open Science Framework” under the registration number 42HGX (https://doi.org/10.17605/OSF.IO/42HGX (accessed on 25 September 2022)).

Eligibility criteria: For this scoping review, we included published peer-reviewed journal papers that were written in English or German, included human participants and addressed vitamins in combination with BMES. Review articles and meta-analysis were excluded as research sources. Moreover, we excluded manuscripts that analyzed patients with secondary bone marrow edema, including osteochondral lesions, osteonecrosis, fractures, any kind of trauma and diabetic foot syndrome.

Information sources and search: To identify suitable articles for the scoping review, a database search was conducted. The database search was carried out on three databases (OVID, Pubmed and Web of Science). The search was drafted by the last author and further refined through team discussion. The search string we used was: “((migratory-osteoporosis) OR (bone-marrow-edema) OR (bone-marrow-oedema) textls[-5]OR (transient-osteopenia) OR (idiopathic-osteoporosis) OR (idiopathic-osteopenia) OR (transient-osteoporosis)) AND (vitamin)”. The search was performed on 29 April 2022, with a final update of the records identified on 25 September 2022. Duplicates were identified and excluded using Endnote 20 (Cleverbridge GmbH; Köln, Germany).

Selection of sources of evidence: Three authors screened all articles (title and abstract) for the predefined eligibility criteria. A manuscript was considered suitable for further analysis if two of the three authors (AE, ME, IS) agreed that the manuscript met the eligibility criteria (primary literature). In the next step, a full text analysis was performed, again considering the eligibility criteria. Additionally, we screened the literature of the finally eligible articles for relevant references. Reference articles were included in the final analysis if their core-statement was associated with eligibility criteria (secondary literature). Full texts were included in the quantitative synthesis, systematically analyzed and evaluated by the authors for the purpose of the scoping review.

Data charting process, data items, synthesis of results: Each full text was carefully read by two authors. The information contained in the manuscript was extracted, discussed and put into tabular form. We abstracted data into manuscript characteristics (country of origin, number of patients, gender, study type), levels of vitamin, affected bones, follow-up period, therapy and time to achieve therapeutic success. Finally, we grouped the studies by epidemiology, localization, bone mineral density measurement, laboratory analysis and therapy.
3. Results

Selection of sources of evidence: From the three database searches, we identified 235 articles. Upon removal of the duplicates, 102 papers remained. After application of the eligibility criteria, 19 relevant articles (primary literature) were identified for further analysis. For the primary literature, nine papers were case reports (1 patient per case report), eight papers were retrospective case series or retrospective observational studies (19.5 patients per study), one prospective observational study (12 patients) and one retrospective cross-sectional study (65 patients). The manuscripts of the primary literature were very heterogeneous and of diverging scientific scope. A synopsis of the primary literature would not be sufficient due to the limited evidence provided by the manuscripts. Therefore, we expanded the eligibility criteria to the references of the primary literature (secondary literature). Thus, an additional 41 papers could be identified and added into our scoping review. The total number of analyzed manuscripts was 60 (Figure 1).

Figure 1. Study selection for review: Illustration of literature search and selection with numbers of articles at each stage.

Bibliographic characteristics: All 60 studies are composed of 28 (47%) case reports, 18 (30%) retrospective studies, 11 (18%) prospective studies, 2 (3%) longitudinal studies and 1 (2%) randomized controlled phase III trial. The included total number of patients are 37 for the case reports (1.3 patients per report), 443 for the retrospective studies (24.6 patients per study), 207 for the prospective studies (18.8 patients per study), 88 for the longitudinal studies (44.0 patients per study) and 48 for the randomized controlled phase III trial. Most
of the studies were conducted in Germanophone countries (37% in Germany, Austria and Switzerland) followed by Italy (13%), USA (10%), Spain (5%) and Greece (5%).

Epidemiology: Altogether, 823 patients are included in all studies. The distribution of males to females is 1.55♂/♀. Most of the included studies do not focus on a specific age group. Only six studies/case reports exclusively focus on BMES in children, although children were included in several studies. The mean age of all patients is 40.9 years. The youngest patient observed with BMES is seven years old, the oldest 79 years old. Nine patients were pregnant during onset of symptoms or while being diagnosed with BMES. The mean age of patients included in case reports is 36.1 years. In the case reports, more female patients were reported (n = 21) than male patients (n = 14).

Localization: Bone marrow edema syndrome almost exclusively affects the weight-bearing regions of the body. In all 60 included articles, 296 patients suffered from BME of the proximal femur, making the hip joint the most commonly affected site (Table 1). Most of the remaining cases are shared between the other two big weight-bearing joint regions, namely the foot and ankle (244 patients) and the knee (198 patients). Few cases could be observed at the weight-bearing axial skeleton, i.e., the pelvis (os sacrum, os pubis, acetabulum; 15 patients) and the lumbar spine (3 patients). Only three cases were reported at the upper extremities: two at the hand and one at the sternum. Interestingly, both cases affecting the hand were observed in children [13,14], with one due to vitamin C deficiency. Of the 823 patients, 151 suffered from multifocal BMES, which means the involvement of two or more joints, mostly bilateral BMES of the hip or more than one affected bone at the same region. As a result, altogether 1146 bones were affected. Multiple bone involvement mostly concerned the foot and ankle with 530 bones in 244 patients. At the foot and ankle, the talus was the most affected bone (n = 145), followed by the tarsus (os naviculare, os cuboideum, ossa cuneiforma; n = 111), the calcaneus (n = 57), metatarsals (n = 47) and the distal part of the tibia (n = 27).

Table 1. Localization of the bone marrow edema, total number of patients and number of bones.

| Localisation     | Number of Patients | Number of Bones |
|------------------|--------------------|-----------------|
| Pelvis           | 15                 | 20              |
| Proximal femur   | 296                | 340             |
| Knee             | 198                | 241             |
| Foot/Ankle      | 244                | 530             |
| Lumbar Spine     | 3                  | 3               |
| Hand             | 2                  | 3               |
| Sternum          | 1                  | 1               |
| Not specified    | 73                 | 8               |
| Multifocal       | 151                | -               |
| Total            | 823                | 1146            |

Vitamin levels: The vitamin D levels of patients with BMES were reported in 16 studies (223 patients). Ten studies were conducted in northern Europe and the USA. According to the definition of the Endocrine Society, 105 patients (47.1%) had a vitamin D deficiency (<20 ng/mL), 40 patients (17.9%) had a vitamin D insufficiency (21–29 ng/mL) and 78 patients (35.0%) had normal vitamin D values (>30 ng/mL). Three case reports (1 patient each publication) associated vitamin C with BMES. In all cases, the patients had reduced serum levels of vitamin C due to malnutrition or restrictive eating habits and were successfully treated with vitamin C supplementation.

Bone mineral density measurement: 15 of 60 articles reported bone mineral density (BMD) measurements, but of the 232 patients included in those articles, only 148 received BMD measurements. Dual energy X-ray absorptiometry (DXA) of the lumbar spine and
proximal femur was the most used BMD test, being used in 142 patients. Other BMD tests included high-resolution quantitative computed tomography (HR-pQCT) of the distal radius and distal tibia, as well as quantitative ultrasound of the calcaneus. Seven articles are case reports with a maximum of three patients, the remaining eight articles include ten or more patients with BMD measurements; the largest cohort was reported by Oehler et al. [7] with 57 DXA and 37 HR-pQCT measurements. Thus, data about BMD in patients with BMES is rare. Results of BMD measurements are reported as T- and Z-scores, absolute BMD values or categories (“normal”, “osteopenic” or “osteoporotic”), making comparisons between studies difficult. If categorized according to the WHO definition of osteopenia (T-score $–2.5$ to $–1$) and osteoporosis (T-score $< 2.5$), 126 of the reported patients are classifiable: 35.7% of patients with BMES have normal BMD, 38.9% are osteopenic and 25.4% suffer from osteoporosis. Varenna et al. report on 16 patients with BMES of the hip who received DXA measurements of the affected as well as the unaffected hip. BMD of the unaffected hip showed normal values according to age and gender, whereas the involved hip had a significant median decrease in BMD: 16.6% for the total hip and 22.5% for the femoral neck. This finding supports the term of “transient regional osteoporosis” as a synonym for BMES. During therapy, BMD increases significantly after 2 and 4 months in the affected hips [15]. An increase of BMD or a decrease in the difference between affected and unaffected hip after therapy is confirmed by other authors [16–19].

Therapy: Apart from three studies [7,20,21], all articles report on therapies of BMES, but among all remaining 57 articles, only one randomized, controlled phase III trial (level of evidence I) exists [22]. Most other are case reports, retrospective case series and few observational studies, mostly retrospective. Therefore, evidence on therapies and their efficiency in BMES is weak. Among the different therapy strategies, nearly all authors report on reducing weight of the affected extremity, reaching from bed rest to non-weight-bearing (NWB), partial weight-bearing (PWB) and avoiding intense activities. Another common component of therapy is the substitution of vitamin D and calcium. Most authors report on dosages of at least 800 IU vitamin D and 600 to 1000 mg calcium per day. To systematically analyze the treatment options for the BMES, we grouped the therapeutic approaches into “conservative”, “osteoactive drugs”, “iloprost” and “others”. All studies with their therapeutic regimen and results are summarized in Table 2.

Conservative therapy: In this group, therapies are summarized which consist of a combination of limited weight-bearing, analgesics, mostly NSAIDs, physical therapy and vitamin D substitution; 13 articles can be assigned to this group, and among those are 10 case reports with three or fewer patients. Pieropan et al., Orr et al. and Radke et al. [23–25] report on 13, 14 and 10 patients, respectively, in a retrospective, observational way. Duration of therapy mostly lasts from 3 to 6 months or until the patient is asymptomatic. Results are reported by MRI control and clinically without objectivation by scores. Healing is described to take between weeks and 1 year, mostly around 3 to 6 months.

Osteoactive drugs: Osteoactive drugs include bisphosphonates and teriparatide, a recombinant form of parathyroid hormone, and 22 reports can be assigned to this group; 19 about bisphosphonates, including those studies with the highest number of patients and the highest level of evidence. Alendronate, ibandronate, zolendronate, pamidronate, neridronate and clodronate are the bisphosphonates being used. Three articles only indicate “bisphosphonates” without specification. Therapy regimens differ from a mid-term oral application, namely alendronate 70 mg/week for 1 to 6 months, a single i.v./s.c. application (zolendronate, teriparatide) or a short-term i.v. application (ibandronate, 1–3 times). Success of therapy is mostly controlled clinically and by MRI; healing time differs, mostly between 1 and 6 months with a peak around 2 and 3 months.

Iloprost: The use of iloprost, a vasodilating prostacyclin analogon, which is used for thromangiitis obliterans, pulmonal hypertension and M. Raynaud, is reported in 10 articles. Among them, five are from the same working group [26–30]. The application is i.v., mostly on 5 consecutive days, in a dosage of 20 to 50 µg/d. The occurrence of side effect is common, apparently depending on dosage. Nevertheless, most studies report a quick decrease in
pain levels within the first days of treatment with an overall healing time from weeks to 3 months.

Others: Further therapy regimens of BMES include calcitonin, vitamin C substitution, core decompression and extracorporeal shock wave therapy. Vitamin C substitution is described in three case reports [13,31,32], all of them with an etiology of proven vitamin C deficiency. All authors report positive results of their therapies, but altogether, the number of reports and cases is small (s. Table 2).

Comparative studies: In eight articles, different therapy forms are compared. The only RCT by Seefried et al. compares the use of zoledronate plus PWB and vitamin D/calcium substitution to placebo and PWB vitamin D/calcium. A significant difference in the edema volume reduction in favor of zoledronate is stated, as well as a significant reduction of pain level after 3 and 6 weeks by zoledronate [22]. Bartl et al. conducted a prospective observational study, comparing ibandronate to a conservative regimen [33]. Both therapy forms could significantly reduce pain after 6 and 12 months with a better reduction by ibandronate as well as a significant (ibandronate) versus a non-significant (conservative) edema volume reduction after 6 months.

4. Discussion

In this scoping review about BMES and vitamins, 19 sources could be identified by primary research and an additional number of 41 by secondary research. Thus, a total number of 823 patients was included. The overall evidence is poor, especially concerning the role of vitamins in BMES: 223 of the included patients had vitamin D analysis and only 3 patients were associated with vitamin C deficiency. Additionally, the study quality is poor with 47% of the included articles being case reports.

Our review shows, that the prevalence of vitamin D deficiency and insufficiency among patients with BMES is high with 47.1% and 17.9%, respectively, and thus only 35.0% of patients with normal vitamin D values. This is even more striking, considering the young patient’s average age of 40.6 years. Therefore, a pathophysiological relationship between vitamin D deficiency and BMES seems likely, but all included studies reporting vitamin D status are lacking an age-, sex- and seasonal-matched control group. Almost all studies were conducted on the northern hemisphere, namely central Europe and North America. Vitamin D deficiency is known to be of a high prevalence in those countries [34–36]. In a recent survey, Rabenberg et al. report 32.8% of vitamin D deficiency and 28.7% insufficiency in men aged between 18 and 44 years in Germany and 28.9% of vitamin D deficiency and 27.0% of insufficiency for women in the same age group [34]. Furthermore, vitamin D levels are known to highly depend on season and latitude as well as other factors like age, BMI, sports activity and media consumption [34–36]. Therefore, it is difficult to conclude a causal relationship between vitamin D deficiency and BMES without a reference population.

Similar results could be observed in this review regarding bone mineral density. The prevalence of osteopenia and osteoporosis was high among the study population, with 38.9% (osteopenia) and 25.4% (osteoporosis), but only 148 of all 823 patients received BMD measurements. A transfer of those results to the general population suffering from BMES is therefore problematic as some authors report on selection of patients for BMD measurements. Karantanas et al. state that only men > 70 years and women > 60 years were indicated to DXA, and according to Singh et al., only patients with “risk factors” received BMD tests [37,38]. Thus, a selection bias with overestimation of the prevalence of osteoporosis is possible. Furthermore, analogous to vitamin D levels, no control groups exist to distinguish between co-existing osteopenia/osteoporosis due to general prevalence and causal osteoporosis.

Regarding the role of vitamin C in BMES, three case report were available. All patients suffered not only from BME but also from other symptoms of scurvy due to severe vitamin C deficiency because of their eating habits (malnutrition due to alcoholism, anorexia nervosa, diet lacking fresh fruit and vegetables) [13,31,32]. Because vitamin C deficiency is a well-
known cause of scurvy, it is reasonable to assume that there could be a causal correlation between scurvy and bone marrow edema. It is still not clear if, in those cases, the patients suffered from a secondary bone marrow edema due to scurvy or had a “bone marrow edema syndrome” in its classical meaning. A recent review by Rowe et al. highlights, that vitamin C deficiency is common in low- and middle-income countries and still existent in high-income countries [39]. The prevalence in an age group comparable to this review ranges between 1% (France [40,41]), 1.4% (England [42,43]), <3% (Canada [44]) and 8.4% (USA [45]). Apart from the abovementioned case reports, vitamin C levels in patients suffering from primary BMES have not been published yet. It would be interesting and a possible focus for further research if the prevalence of vitamin C deficiency in patients with BMES is higher than in the general population and if there is a pathophysiologic relationship.

As the pathophysiology of BMES remains largely unknown, no causal therapy exists. The best evidence is available for bisphosphonates and iloprost therapy, but the overall evidence is poor due to lacking RCTs. Vitamin D substitution is common in many therapy protocols, again assuming a pathophysiologic relationship, but no study compares vitamin D substitution against no substitution. Reducing weight and vitamin D substitution appear in a plethora of combinations among other therapeutically measures in most studies, so that the role of those measures is not evaluable within the existing data.

All studies report on successful treatment of BMES. Publication bias may be one cause, but additionally, as BMES is considered a self-limiting disease, the influence of therapy is difficult to demarcate against spontaneous healing when lacking control groups. When comparing healing times, the time between onset of symptoms and beginning of therapy has to be considered, as this time is already part of the spontaneous healing time. As the analyzed studies are heterogenous and poor in quality, a meta-analysis for therapies is not feasible.

This review has a few limitations. As the primary search strategy focused on the literature about BMES and vitamins, the secondary literature might not be complete, especially regarding therapies. Furthermore, we did not focus on subgroups such as pregnancy-associated bone marrow edema or growth-associated BME in children as it is still unclear whether they represent a separate entity or are part of bone marrow edema syndrome. As the definition and nomenclature of BMES is sometimes challenging and some authors do not clearly define the origin of the BME they report on, it is possible that secondary BME is included in this analysis.
Table 2. Summary of all studies.

| Author          | Year  | Country | Study Type | n  | Therapy                                                                 | Duration of Therapy | Result Clinically | Result Radiologically (MRI) | Healing Time | Follow Up Time |
|-----------------|-------|---------|------------|----|-------------------------------------------------------------------------|--------------------|-------------------|-----------------------------|--------------|----------------|
| **Conservative**|       |         |            |    |                                                                         |                    |                   |                             |              |                |
| Alsaed O. [46]  | 2018  | Qatar   | CR         | 1  | Avoid prolonged WB, NSAID, Vit. D                                       | 3 m                | asymptomatic      | “few weeks”                | 3 m          |                |
| Kaspiris A. [47] | 2019  | Greece  | CR         | 1  | Avoid WB, NSAID, Vit.D                                                  | 6 m                | asymptomatic      | 6 months: normal           | 6 m          | 6 m            |
| Pieropan S. [23]| 2019  | Italy   | RCS        | 13 | Avoid intense activity, analgetics, PT, Vit. D, cortisone p.o.          | 3 m                | asymptomatic      |                             | 3 m          | 3 m            |
| Orr, JD. [24]   | 2010  | USA     | RCS        | 14 | PWB ± cast, NSAID, PT                                                  | asymptomatic (86%) | 4/14: 75% normal  | 4 m (up to 18 m)           | 20.7 (3.5–43) m |                |
| Axt-Fiedler R. [48] | 2001 | Germany | CR         | 1  | Bedrest, PWB, analgetics, PT                                           | n.r.               | improved          |                             | post partum   | n.r.           |
| Daniel RS. [49] | 2009  | USA     | CR         | 1  | Analgetics                                                             | n.r.               | n.r.              |                             | 12 months: reduction | 12 m          | 12 m          |
| Diwanji SR. [18]| 2008  | Korea   | CR         | 2  | NWB, NSAID, PT                                                         | n.r.               | asymptomatic      | 9 months: normal           | 3–7 m        | 10–22 m        |
| Escolà A. [50]  | 2009  | Spain   | CR         | 1  | PWB, deflazacort                                                       | n.r.               | asymptomatic      | 6 months: normal           | 3 m          | 12 m          |
| García Garzón JR [51] | 2005 | Spain   | CR         | 1  | “conservative treatment”                                               | n.r.               | asymptomatic      | 5 m                         | 5 m          |                |
| Joshi V. [52]   | 2014  | USA     | CR         | 1  | Limit intense activity,                                                | asymptomatic       |                    |                             | 4 m          | 8 m            |
| Palit G. [53]   | 2006  | Belgium | CR         | 1  | Avoid physical activity, paracetanol                                   | n.r.               | asymptomatic      |                             | 6 w post partum | n.r.           |
| Radke S. [54]   | 2001  | Germany | PCS        | 10 | PWB, analgetics core decompression after 1–2 months                    | n.r.               | n.r.              | Weber ankle score improvement from 52 to 95 | 3–9 m CD: 3–12 m | 12 m          |
| Yamasaki S. [55]| 2003  | Japan   | CR         | 3  | PWB, NSAID                                                             | n.r.               | asymptomatic      | 2–8 months: normal         | 2–8 m        | n.r.           |
| **Osteoactive Drugs** |       |         |            |    |                                                                         |                    |                   |                             |              |                |
| Emad Y. [56]    | 2021  | Egypt   | CR         | 1  | Alendronate 70 mg/week p.o. PWB, Vit. D, calcium                       | 6 m                | improvement       | 3 months: almost total regression | 3 m          | 3 m            |
| Emad Y. [57]    | 2012  | Egypt   | PCS        | 8  | Alendronate 70 mg/week p.o. NWB, Vit. D, calcium                       | 6 m                | n.r.              | 6 months: normal           | 6 m          | 6 m            |
| Evangelatos G. [58] | 2019 | Greece  | RCS        | 9  | Alendronate 5 mg i.v. single PWB, Vit. D, calcium                      | 1 m                | asymptomatic (100%) | 3 months: 100% normal      | 1.1 ± 0.5 m  | 60.7 ± 34.4 m |
| Karantanas AH. [37]| 2008 | Greece  | LDS        | 65 *| Alendronate 10 mg/d p.o. NWB, NSAID, calcium                           | 3 m                | improvement (100%) |                             | 8.4 (±3.9) m | 3 y            |
| Kibbi L. [59]   | 2007  | USA     | CR         | 3  | Alendronate 70 mg/week p.o.                                           | asymptomatic       |                    | 5 months: normal           | 3 w–2 m      | n.r.           |
| Milten O. [60]  | 2003  | Germany | CR         | 1  | Alendronate 70 mg/week p.o. NWB, Vit. D, calcium                       | asymptomatic       |                    | 3 months: normal           | 9 w          | 3 m            |
| Simon MJ. [61]  | 2014  | Germany | RCS        | 25 | Bandronate 3 mg i.v. single; 2nd/3rd application after 4–6 weeks optional PWB, Vit. D, calcium |                             | pain reduction after 2 weeks: 64% | return to competition time 102.6 ± 65.2 d | n.r.    | 102.6 ± 65.2 d | 395 ± 269.7 d |
| Author          | Year | Country     | Study Type | n  | Therapy                                                                 | Duration of Therapy | Result Clinically                              | Result Radiologically (MRI) | Healing Time | Follow Up Time |
|-----------------|------|-------------|------------|----|------------------------------------------------------------------------|---------------------|-----------------------------------------------|-----------------------------|--------------|----------------|
| Ringe JD [16]   | 2005 | Germany     | POS        | 12 | Ibandronate 4 mg i.v. single; 2 mgibandronate after 3 months optional Vit. D, calcium | decrease in pain score 43.3% (1 month), 78.4% (3 months), 94.3% (6 months) | DXA: increase lumbar spine BMD 4% | 6 m            |              |                |
| Carty S. [62]   | 2007 | Great Britain | CR        | 2  | Pamidronate 60 mg i.v. single                                          | asymptomatic        | 1 months: normal/reduced                                      | n.r.                       | 2-4 w        | n.r.           |
| Varenna M. [15] | 2002 | Italy       | PCS        | 16 | Pamidronate 45 mg i.v. 3× every 3rd day                              | asymptomatic: 43.8% (1 month), 87.5% (2 months); significant improvement VAS and FUI score after 1 month | 3 months: normal                    | 1-2 m        | 39.5 ± 17.7 m |
| La Montagna G. [63] | 2005 | Italy      | CR         | 1  | Neridronate 25 mg/month i.m. Bed rest, Vit. D, calcium            | 6 m                 | asymptomatic                                       | 4 months: normal            | 2 m          | 4 m            |
| Trevisan C. [64] | 2002 | Italy      | CR         | 3  | Clodronate 100 mg/d i.v., Calcitonin 100 U/d NWB, NSAID, PT        | 2-6 m               | asymptomatic                                       | 1-10 m                     |              |                |
| Springhorn AE. [65] | 2011 | Australia  | RCS        | 10 | “Bisphosphonates” Walker, Vit. D, calcium                            | 5-10 m              | asymptomatic                                       | 5-10 m (4-21) m            |              |                |
| Vaishya R. [66] | 2017 | India      | RCS        | 12 | “Bisphosphonates” PWB, NSAID, Vit. D, calcium                      | n.r.                | asymptomatic                                       | 17.1 (13-25) w            | 1.3 (1-2.5) y |                |
| Trevisan C. [67] | 2016 | Italy      | ROCS       | 23 | “Bisphosphonates” PWB                                               | n.r.                | “healing”                                          | 4.3 (2-7) m               |              |                |
| Rolvien T. [68] | 2017 | Germany    | ROS        | 14 | Teriparatide 66mg s.c. single Vit. D; 2/14 + Core decompression     | significant decrease (VAS) | 6-12 weeks: completely resolved: 50%, reduced: 43%, constant: 7% | 6-12 w                    |              |                |
| Fabbriciani G. [19] | 2010 | Italy      | CR         | 1  | Teriparatide20 µg/d PWB, Vit. D                                    | 1 m                 | asymptomatic                                       | 2 months: almost normal      | 1 m          | n.r.           |
| Geith T. [69]   | 2015 | Germany    | CR         | 1  | Teriparatide 60 mg s.c. single                                      | asymptomatic        | 2 months: normal                                    | 2 m                        |              |                |
| Iloprost        |      |             |            |    | Iloprost 50 µg i.v. on 5 consecutive days                          | Mazur score improvement from 58 to 91 (1 month), 93 (3 months) | 3 months: normal (100%)          | 5 (3-6) w                  | 6 m          |                |
| Aigner N. [29]  | 2001 | Austria     | PCS        | 6  | Iloprost 50 µg i.v. on 5 consecutive days                          | pain relief: 79%; non-responder: 21%; Mazur score improvement from 54.9 to 87.8 | 3 months: 63% completely resolved, 16% subtotal regression, 21% no improvement | 3 m                      |              |                |
| Aigner N. [26]  | 2003 | Austria     | PCS        | 19 | Iloprost 50 µg (6/19), Iloprost 20 µg (13/19) i.v. on 5 consecutive days PWB if needed | 6 weeks: almost complete resolution 12 weeks: normal | 2 w                                      | 6 m                      |              |                |
| Aigner N. [27]  | 2002 | Austria     | CR         | 1  | Iloprost 20 µg i.v. on 5 consecutive days                          | asymptomatic        | 3 months: nearly complete resolution                | 3 m                        | 2.5 y        |                |
| Arazi M. [70]   | 2006 | Turkey      | CR         | 1  | Iloprost 40 µg i.v. on 5 consecutive days                          | asymptomatic        | 3 months: nearly complete resolution                | 3 m                        |              |                |
| Author                | Year | Country | Study Type | n   | Therapy                                                                 | Duration of Therapy | Result Clinically                                                                 | Result Radiologically (MRI) | Healing Time | Follow Up Time |
|-----------------------|------|---------|------------|-----|-------------------------------------------------------------------------|---------------------|----------------------------------------------------------------------------------|-----------------------------|--------------|----------------|
| Hörterer H. [71]      | 2018 | Germany | OCS        | 11  | Iloprost 20 µg dL, 40 µg 42–5 WB as tolerated, Analgetics, PT           | 3 months: 56% pain decrease, 38% no pain relief | 3 months: 83% considerable decrease                                              |                             | 28 ± 19 m   |                |
| Meizer R. [30]        | 2005 | Austria | ROS        | 27  | Iloprost 20–50 µg/d on 5 consecutive days PWB                           | 4 months: 75.2% pain decrease                         | 4 months: 92.6% significant improvement                                          | 4 m                          | 4 m          |                |
| Tosun HB. [72]        | 2020 | Turkey  | RCS        | 23  | Iloprost 20 µg i.v. on 5 consecutive days, Alendronate 70 mg/week, FWB, ASS 150 mg, Vit. D, calcium | 3 m               | significant reduction VAS after 3 and 6 months (from 9.1 to 2.4), significant improvement FMS score | 3 months: 60.9% complete regression, 17.4% minimal edema, 21.7% moderate edema | n.r.         |                |

Comparative Studies

| Seefried L. [22]      | 2022 | Germany | RCT        | 48  | (1) Zolendronate 5 mg i.v. single; PWB, Vit. D, calcium (2) Placebo; PWB, Vit. D, calcium | (1) significant pain reduction week 3 and 6 (2) non-significant reduction week 3 and worsening week 6 | 6 weeks: volume reduction from (1) 69.7 cm³ to 25.2 cm³ (2) 44.0 cm³ to 19.6 cm³ Significant difference between groups; Decrease/complete resolution of edema (1) 76.5%/38.2% (2) 50%/21.4% | 3 m                          |              |                |
| Pabinger C. [73]      | 2012 | Austria | CR         | 1   | (1) NWB, PT (2) Iloprost 300 µg/d for 5 d, followed by pamidronate 30 mg/d for 3 days, Vit. D, calcium | (1) 3 m (2) 3 m | (1) asymptomatic (2) asymptomatic                                              | (1) 3 m (2) 2 w             | 10 m         |                |
| Bartl C. [33]         | 2012 | Germany | POS        | 50  | (1) Ibandronate 6mg i.v./months 3× (n = 30) (2) 3 weeks NWB, NSAID (n = 20) | (1) 3 m                   | VAS decrease from (1) 8.5 to 1.6 (6 months) and 1.2 (12 months) (2) 8.1 to 4.6 (6 months) and 4.0 (12 months) Scores: significant improvement in both groups (6 + 12 months); Ibandronate vs. Conservative sign. better | (1) 3 m (2) not defined       | 1 y          |                |
| Radke S. [74]         | 2003 | Germany | ROS        | 43  | (1) PWB, NSAID (2) Core decompression, NWB | n.r.                    | HHS improvement from (1)38.6 to 80.6 (2) 48.5 to 77.2                        |                             | 2–10 y       |                |
| Singh D. [38]         | 2015 | Great Britain | ROS | 18  | (1) PWB alone (n = 7) (2) PWB, then Zolendronate 5 mg i.v. (n = 9) (3) PWB, then Alendronate p.o.(n = 2) | n.r.                   |                             | (1) 25.6 w (2) 13.8 w (3) 24.0 w                                         |                             | 5.75 y       |                |
Table 2. Cont.

| Author            | Year | Country | Study Type | n   | Therapy                                                                 | Duration of Therapy | Result Clinically | Result Radiologically (MRI) | Healing Time | Follow Up Time |
|-------------------|------|---------|------------|-----|-------------------------------------------------------------------------|--------------------|-------------------|-------------------------------|--------------|----------------|
| Muller F. [75]    | 2020 | Switzerland | ROS | 34  | (1) Ibandronate i.v. multiple (n = 9) (2) Zoledronate i.v. single (n = 12) (3) Ibandronate i.v. multiple followed by Zoledronate iv single (n = 7) (4) Teriparatide s.c. single (n = 3) (5) Alendronate p.o. (n = 3) | response to treatment (1) 89% (2) 100% (3) 86% (4) 100% (5) 100% | 18/34: Edema reduction (1) 67% (2) 92% (3) 86% (4) 67% (5) 100% | 18/34: Edema reduction | n.r.          |                |
| Aigner N. [28]    | 2005 | Austria | ROS | 36  | (1) Iloprost 20 µg i.v. on 5 consecutive days, PWB (n = 18) (2) Core decompression, NWB (n = 20) | HHS improvement from (1) 64.7 to 97 (3 m) (2) 53.7 to 95.1 (3 m) | (1) normal (100%) (2) 70% complete remission, 20% residual edema, 10% progression to avascular necrosis | (1) 4 (0–12) w (2) 6 w | n.r.          |                |
| Baier C. [76]     | 2012 | Germany | ROS | 20  | (1) Iloprost 1 d 20 µg, 1 d 30 µg, 3 d 40 µg (2) Ibandronate 6 mg/month | (2) 3 m VAS: significant improvement (1) from 6.4 to 1.1 (3 months), 1.1 (12 months) (2) from 5.6 to 2.6 (3 months), 1.5 (12 months) WOMAC: significant improvement (1) 53.6 to 13.4 and 12.1 (2) 59.5 to 27.5 and 20.8 | (1) 43% complete regression, 43% reduction, 14% non-responder, 50% reduction, 17% non-responder | (1) first days—4 w (2) first days—3 m | 12 (10–17) months |
| Others            |      |         |           |     |                                                                         |                    |                                |                               |              |                |
| Laktasic-Zerjavic N. [77] | 2007 | Croatia | CR | 1   | Calcitonin 200 IU/d nasal; PWB, Vit. D, calcium | 2 m asymptomatic | 1 y: normal | 2 m                              | 1 y          |                |
| Arayssi TK. [17]  | 2003 | Lebanon | CR | 2   | Calcitonin 200 IU/d sc/nasal; PWB, Vit. D, calcium | n.r. mild symptomatic/asymptomatic | normal | 6–9 w                              |              |                |
| Fernandez-Canton OC. [78] | 2003 | Spain | LDS | 25  | Calcitonin, rest, NSAID, Vit. D, calcium | n.r. 76% asymptomatic | 72% resolution, 20% partial improvement, 8% no improvement | 9–13 m                     |              |                |
| Berger CE. [79]   | 2003 | Austria | PCS | 37  | Core decompression | recovered (100%) | 3 m: normal (100%) | 6 w                              | 12 (12–48) m |                |
| Radke S. [74]     | 2003 | Germany | PCS | 18  | Core decompression, 6 weeks NW, 6 weeks PWB | 12 w pain free (100); significant HHS improvement from 37.2 to 93.7 | 6 m: 91% normal | 7.2 (1–30) d | 6 m |                |
| D’Agostino C. [80] | 2014 | Italy | PCS | 20  | Extracorporal shock waves 2× (after 48 h), PWB | 1 m HHS: significant improvement after 2 and 3 months from 39.0 to 81.3 (2 m), 91.8 (3 m), 95.1 (6 m) | significant edema reduction after 2 and 6 m | 3 m 15.5 ± 1.9 m |                |
| Amar SK. [31]     | 2021 | Great Britain | CR | 1   | Vitamin C substitution | asymptomatic |                         | 3 w                              | 3 m          |                |
| Liebling EJ. [13] | 2020 | USA | CR | 1   | Vitamin C 100 mg 3×/d for 7 days, 100 mg/d | 3 w asymptomatic |                             | 3 w                              | 3 w          |                |
| Rodriguez S. [32] | 2007 | USA | CR | 1   | Vitamin C substitution, NSAID, PT | Lost to FU |                             |                         |              |                |
Table 2. Cont.

| Author          | Year | Country | Study Type | n   | Therapy                                                                 | Duration of Therapy | Result Clinically   | Result Radiologically (MRI) | Healing Time | Follow Up Time |
|-----------------|------|---------|------------|-----|-------------------------------------------------------------------------|--------------------|----------------------|-------------------------------|--------------|----------------|
| Sconza C. [81]  | 2022 | Italy   | CR         | 1   | Neridronate 100 mg i.v. 4x every 3 days, extracorporal shockwaves 3×/week, NWB, NSAID, PT, Vit. D, calcium | 4 m                | asymptomatic          | 4 m: normal                   | 4 m          | 4 m            |
| Kroger L. [14]  | 2004 | Finland | CR         | 1   | n.r.                                                                   |                     | asymptomatic          | 8 m: normal                   | 3 m          | 8 m            |
|                  |      |         |            |     | Without therapeutical intervention                                     |                     |                      |                               |              |                |
| Hadidy AM. [20] | 2009 | Jordan  | RCS        | 17  |                                                                         |                     |                      |                               |              |                |
| Horas K. [21]   | 2017 | Germany | RCS        | 31  |                                                                         |                     |                      |                               |              |                |
| Oehler N. [7]   | 2018 | Germany | RXS        | 65  |                                                                         |                     |                      |                               |              |                |

Abbreviations: w: week(s); m: month(s); y: year(s); CR: case report; RCS: retrospective case series; PCS: prospective case series; POS: prospective observational study; ROS: retrospective observational study; RCT: randomized controlled trial; LDS: longitudinal study; ROCS: retrospective observational cohort study; RXS: retrospective cross-sectional study; PT: physical therapy; WB: weight bearing; PWB: partial weight bearing; NWB: non weight bearing; CD: core decompression n.r.: not reported; VAS: visual analogue scale; HHS: Harris Hip Score.

* 98 patients included in study, but only 63 with BMES. ** 42 patients included in study with different etiologies of BME, only 11 patients with BMES. *** 104 patients included in study, with different etiologies of BME, only 27 patients with BMES.
5. Conclusions

There is limited data on BMES in association with vitamin status. A high prevalence of vitamin D deficiency and osteopenia among patients with BMES suggests a pathophysiological connection, but a causal relationship between vitamin D status, osteopenia and BMES cannot be made within the existing literature. Vitamin C deficiency seems to be causal for BME in patients suffering from scurvy, but no data exists about the prevalence of acute or subacute vitamin C deficiency in patients suffering from primary BMES. Various different therapy regimens are successful, with bisphosphonates and iloprost as the most promising candidates in reducing healing time. For further research and better understanding of this disease, epidemiological data with a special focus on vitamin status and bone mineral density compared to a matched control population, as well as randomized, controlled trials for therapy evaluation, are needed.

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References
1. Wilson, A.J.; Murphy, W.A.; Hardy, D.C.; Totty, W.G. Transient osteoporosis: Transient bone marrow edema? Radiology 1988, 167, 757–760. [CrossRef] [PubMed]
2. Baumbach, S.F.; Pfahler, V.; Bechtold-Dalla Pozza, S.; Feist-Pagenstert, I.; Furmetz, J.; Baur-Melnyk, A.; Saller, M.M.; Straube, A.; Schmidmaier, R.; et al. How We Manage Bone Marrow Edema-An Interdisciplinary Approach. J. Clin. Med. 2020, 9, 551. [CrossRef] [PubMed]
3. Patel, S. Primary bone marrow oedema syndromes. Rheumatology 2014, 53, 785–792. [CrossRef]
4. Thiryayi, W.A.; Thiryayi, S.A.; Freemont, A.J. Histopathological perspective on bone marrow oedema, reactive bone change and haemorrhage. Eur. J. Radiol. 2008, 67, 62–67. [CrossRef] [PubMed]
5. Curtiss, P.H., Jr.; Kincaid, W.E. Transitory demineralization of the hip in pregnancy. A report of three cases. J. Bone Jt. Surg. Am. 1959, 41-A, 1327–1333. [CrossRef] [PubMed]
6. Mirghasemi, S.A.; Trepman, E.; Sadeghi, M.S.; Rahimi, N.; Rashidinia, S. Bone Marrow Edema Syndrome in the Foot and Ankle. Foot Ankle Int. 2016, 37, 1364–1373. [CrossRef]
7. Oehler, N.; Mussawy, H.; Schmidt, T.; Rolvien, T; Barvencik, F. Identification of vitamin D and other bone metabolism parameters as risk factors for primary bone marrow oedema syndrome. BMC Musculoskelet. Disord. 2018, 19, 451. [CrossRef] [PubMed]
8. Craiovan, B.S.; Baier, C.; Grifka, J.; Gotz, J.; Schaumburger, J.; Beckmann, J. Bone marrow edema syndrome (BMES). Orthopade 2013, 42, 191–204. [CrossRef] [PubMed]
9. Capozzi, A.; Scambia, G.; Lello, S. Calcium, vitamin D, vitamin K2, and magnesium supplementation and skeletal health. Maturitas 2020, 140, 55–63. [CrossRef] [PubMed]
10. Dai, Z.; Koh, W.P. B-vitamins and bone health—A review of the current evidence. Nutrients 2015, 7, 3322–3346. [CrossRef] [PubMed]
11. Rondanelli, M.; Peroni, G.; Fossari, F.; Vecchio, M.; Faliva, M.A.; Naso, M.; Perna, S.; Di Paolo, E.; Riva, A.; Petrangolini, G.; et al. Evidence of a Positive Link between Consumption and Supplementation of Ascorbic Acid and Bone Mineral Density. Nutrients 2021, 13, 1012. [CrossRef] [PubMed]
12. Reid, I.R. Osteoporosis: Evidence for vitamin D and calcium in older people. Drug Ther. Bull. 2020, 58, 122–125. [CrossRef] [PubMed]
13. Liebling, E.J.; Sze, R.W.; Behrens, E.M. Vitamin C deficiency mimicking inflammatory bone disease of the hand. Pediatr. Rheumatol. Online J. 2020, 18, 45. [CrossRef] [PubMed]
14. Kroger, L.; Arikoski, P.; Komulainen, J.; Seuri, R.; Kroger, H. Transient bone marrow oedema in a child. Ann. Rheum. Dis. 2004, 63, 1528–1529. [CrossRef] [PubMed]
15. Varenna, M.; Zacchi, F.; Binelli, L.; Failoni, S.; Gallazzi, M.; Sinigaglia, L. Intravenous pamidronate in the treatment of transient osteoporosis of the hip. *Bone 2002*, *31*, 96–101. [CrossRef]

16. Ringe, J.D.; Dorst, A.; Faber, H. Effective and rapid treatment of painful localized transient osteoporosis (bone marrow edema) with intravenous ibandronate. *Osteoporos. Int.* *2005*, *16*, 2063–2068. [CrossRef] [PubMed]

17. Arayssi, T.K.; Tawbi, H.A.; Usta, I.M.; Hourani, M.H. Calcitonin in the treatment of transient osteoporosis of the hip. *Semin. Arthritis Rheum.* *2003*, *32*, 388–397. [CrossRef]

18. Diwanji, S.R.; Cho, Y.J.; Xin, Z.F.; Yoon, T.R. Conservative treatment for transient osteoporosis of the hip in middle-aged women. *Singap. Med. J.* *2008*, *49*, e17–e21.

19. Fabbriciani, G.; Pirro, M.; Manfredelli, M.R.; Bianchi, M.; Sivolella, S.; Scarponi, A.M.; Mannarino, E. Transient osteoporosis of the hip: Successful treatment with teriparatide. *Rheumatol. Int.* *2012*, *32*, 1367–1370. [CrossRef]

20. Hadidy, A.M.; Al Ryalat, N.T.; Hadidi, S.T.; Tarawneh, E.S.; Hadidi, M.T.; Samara, O.A.; Abu-Labn, D.M.; Al-Rousan, L.M.; Hiyasat, D.A.; Hamamy, H.A. Male transient hip osteoporosis: Are physicians at a higher risk? *Arch. Osteoporos.* *2009*, *4*, 41–45. [PubMed]

21. Horas, K.; Fraissler, L.; Maier, G.; Jakob, F.; Seefried, L.; Konrads, C.; Rudert, M.; Walcher, M. High Prevalence of Vitamin D Deficiency in Patients with Bone Marrow Edema Syndrome of the Foot and Ankle. *Foot Ankle Int.* *2017*, *38*, 760–766. [CrossRef]

22. Seefried, L.; Genest, F.; Baumann, J.; Heidemeier, A.; Meffert, R.; Jakob, F. Efficacy of Zoledronic Acid in the Treatment of Nonmalignant Painful Bone Marrow Lesions: A Triple-Blind, Randomized, Placebo-Controlled Phase III Clinical Trial (ZoMARS). *J. Bone Miner Res.* *2022*, *37*, 420–427. [CrossRef] [PubMed]

23. Pieropan, S.; Antoniazzi, F.; Tadiotto, E.; Caldonazzi, F.; Maschio, M.; Aiello, G.; Melotti, G.; Cavarzere, P.; Piacentini, G. Bone Marrow Foot Oedema in Adolescents: The Role of Vitamin D. *J. Bone Metab.* *2019*, *26*, 241–246. [CrossRef]

24. Orc, J.D.; Sabesan, V.; Major, N.; Nunley, J. Painful bone marrow edema syndrome of the foot and ankle. *Foot Ankle Int.* *2010*, *31*, 949–953. [PubMed]

25. Radke, S.; Rader, C.; Kenn, W.; Kirschner, S.; Walther, M.; Eulert, J. Transient marrow edema syndrome of the hip: Results after core decompression. A prospective MRI-controlled study in 22 patients. *Arch. Orthop. Trauma Surg.* *2003*, *123*, 223–227. [CrossRef] [PubMed]

26. Aigner, N.; Meizer, R.; Stolz, G.; Petje, G.; Krasny, C.; Landsiedl, F.; Steinboeck, G. Iloprost for the treatment of bone marrow oedema of the talus. *J. Bone Jt. Surg. Br.* *2001*, *84*, 1050–1052. [CrossRef]

27. Aigner, N.; Petje, G.; Schneider, W.; Krasny, C.; Grill, F.; Landsiedl, F. Juvenile bone-marrow oedema of the acetabulum treated by iloprost. *J. Bone Jt. Surg. Br.* *2002*, *84*, 1050–1052. [CrossRef]

28. Aigner, N.; Petje, G.; Schneider, W.; Wilk, M.; Kotsaris, S.; Knahr, K.; Landsiedl, F. Bone marrow edema syndrome of the femoral head: Treatment with the prostacyclin analogue iloprost vs. core decompression: An MRI-controlled study. *Wien. Klin. Wochenschr.* *2005*, *117*, 130–135. [CrossRef] [PubMed]

29. Aigner, N.; Petje, G.; Steinboeck, G.; Schneider, W.; Krasny, C.; Landsiedl, F. Treatment of bone-marrow oedema of the talus with the prostacyclin analogue iloprost. An MRI-controlled investigation of a new method. *J. Bone Jt. Surg. Br.* *2001*, *83*, 855–858. [CrossRef]

30. Meizer, R.; Radda, C.; Stolz, G.; Kotsaris, S.; Petje, G.; Krasny, C.; Wilk, M.; Mayerhofer, M.; Landsiedl, F.; Aigner, N. MRI-controlled analysis of 104 patients with painful bone marrow edema in different joint localizations treated with the prostacyclin analogue iloprost. *Wien. Klin. Wochenschr.* *2011*, *117*, 278–286. [CrossRef]

31. Amar, S.K.; Melath, S. Scurry: A Rare Cause of Bone Marrow Edema. *J. Clin. Rheumatol.* *2021*, *27*, e41. [CrossRef] [PubMed]

32. Rodriguez, S.; Paniagua, O.; Nugent, K.M.; Phy, M.P. Regional transient osteoporosis of the foot and vitamin C deficiency. *Clin. Rheumatol.* *2007*, *26*, 976–978. [CrossRef] [PubMed]

33. Bartl, C.; Imhoff, A.; Bartl, R. Treatment of bone marrow edema syndrome with intravenous ibandronate. *Arch. Orthop. Trauma Surg.* *2012*, *132*, 1781–1788. [CrossRef] [PubMed]

34. Rabinenberg, M.; Scheidt-Nave, C.; Busch, M.A.; Rieckmann, N.; Hintzpeter, B.; Mensink, G.B. Vitamin D status among adults in Germany—Results from the German Health Interview and Examination Survey for Adults (DEGS1). *BMC Public Health* *2015*, *15*, 641. [CrossRef] [PubMed]

35. Rucker, D.; Allan, J.A.; Fick, G.H.; Hanley, D.A. Vitamin D insufficiency in a population of healthy western Canadians. *CMAJ* *2002*, *166*, 1517–1524.

36. Chapuy, M.C.; Preziosi, P.; Maamer, M.; Arnaud, S.; Galan, P.; Hercberg, S.; Meunier, P.J. Prevalence of vitamin D insufficiency in an adult normal population. *Osteoporos. Int.* *1997*, *7*, 439–443. [CrossRef]

37. Karantanas, A.H.; Drakonaki, E.; Karachalios, T.; Korompilias, A.V.; Malizos, K. Acute non-traumatic marrow edema syndrome in the knee: MRI findings at presentation, correlation with spinal DEXA and outcome. *Eur. J. Radiol.* *2008*, *67*, 22–33. [CrossRef]

38. Singh, D.; Ferrero, A.; Rose, B.; Goldberg, A.; Cullen, N. Bone Marrow Edema Syndrome of the Foot and Ankle: Mid- to Long-Term Follow-up in 18 Patients. *Foot Ankle Spec.* *2016*, *9*, 218–226. [CrossRef] [PubMed]

39. Rowe, S.; Carr, A.C. Global Vitamin C Status and Prevalence of Deficiency: A Cause for Concern? *Nutrients* *2020*, *12*, 2008. [CrossRef]

40. Faure, H.; Preziosi, P.; Roussel, A.M.; Bertras, S.; Galan, P.; Hercberg, S.; Favier, A. Factors influencing blood concentration of retinol, alpha-tocopherol, vitamin C, and beta-carotene in the French participants of the SU.VI.MAX trial. *Eur. J. Clin. Nutr.* *2006*, *60*, 706–717. [CrossRef]
41. Galan, P.; Viteri, F.E.; Bertrais, S.; Czernichow, S.; Faure, H.; Arnaud, J.; Ruffieux, D.; Chenal, S.; Arnault, N.; Favier, A.; et al. Serum concentrations of beta-carotene, vitamins C and E, zinc and selenium are influenced by sex, age, diet, smoking status, alcohol consumption and corpulence in a general French adult population. *Eur. J. Clin. Nutr.* 2005, 59, 1181–1190. [CrossRef] [PubMed]

42. Canoy, D.; Wareham, N.; Welch, A.; Bingham, S.; Luben, R.; Day, N.; Khaw, K.T. Plasma ascorbic acid concentrations and fat distribution in 19,068 British men and women in the European Prospective Investigation into Cancer and Nutrition Norfolk cohort study. *Am. J. Clin. Nutr.* 2005, 82, 1203–1209. [CrossRef] [PubMed]

43. McCall, S.J.; Clark, A.B.; Luben, R.N.; Wareham, N.J.; Khaw, K.T.; Myint, P.K. Plasma Vitamin C Levels: Risk Factors for Deficiency and Association with Self-Reported Functional Health in the European Prospective Investigation into Cancer-Norfolk. *Nutrients* 2019, 11, 1552. [CrossRef]

44. Langlois, K.; Cooper, M.; Colapinto, C.K. Vitamin C status of Canadian adults: Findings from the 2012/2013 Canadian Health Measures Survey. *Health Rep.* 2016, 27, 3–10. [PubMed]

45. Schleicher, R.L.; Carroll, M.D.; Ford, E.S.; Lacher, D.A. Serum vitamin C and the prevalence of vitamin C deficiency in the United States: 2003-2004 National Health and Nutrition Examination Survey (NHANES). *Am. J. Clin. Nutr.* 2009, 90, 1252–1263. [CrossRef]

46. Alsaed, O.; Hammoudeh, M. Recurrent Migratory Transient Bone Marrow Edema of the Knees Associated with Low Vitamin D and Systemic Low Bone Mineral Density: A Case Report and Literature Review. *Case Rep. Rheumatol.* 2018, 2018, 7659702. [CrossRef] [PubMed]

47. Kibbi, L.; Touma, Z.; Khoury, N.; Arayssi, T. Oral bisphosphonates in treatment of transient osteoporosis. *Clin. Rheumatol.* 2005, 24, 299–302. [CrossRef] [PubMed]

48. Escola, A.; Pons, M.; Pasarin, A.; Majo, J. Idiopathic transient osteoporosis of the pelvis in a non-pregnant young woman: A case study. *HPI Int.* 2009, 19, 71–74. [CrossRef]

49. Kibbi, L.; Touma, Z.; Khoury, N.; Arayssi, T. Oral bisphosphonates in treatment of transient osteoporosis. *Clin. Rheumatol.* 2005, 24, 299–302. [CrossRef] [PubMed]

50. Garcia Garzon, J.R.; Medic, C.G. Consecutive bone scintigraphy in bilateral hip migratory transient osteoporosis. *Clin. Nucl. Med.* 2005, 30, 677–679. [CrossRef] [PubMed]

51. Yoshida, A.; Kogure, K.; Sugimoto, K.; Hidaka, H.; Miyamoto, N.; Yamada, T.; Ohashi, S.; Watanabe, K.; Tanaka, H. Transient bilateral osteoporosis of the hip in pregnancy. *Brit. J. Rheumatol.* 1990, 29, 50–53. [CrossRef]

52. Palit, G.; Kerremans, M.; Gorissen, J.; Jacquemyn, Y. Transient bone marrow oedema of the femoral head in pregnancy—Case report. *Clin. Exp. Obstet. Gynecol.* 2006, 33, 244–245. [PubMed]

53. Radke, S.; Vispo-Seara, J.; Walther, M.; Ettl, V.; Eulert, J. Transient bone marrow oedema of the femoral head in pregnancy—Case report. *Clin. Exp. Obstet. Gynecol.* 2006, 33, 244–245. [PubMed]

54. Kibbi, L.; Touma, Z.; Khoury, N.; Arayssi, T. Oral bisphosphonates in treatment of transient osteoporosis. *Clin. Rheumatol.* 2005, 24, 299–302. [CrossRef] [PubMed]

55. Yamasaki, S.; Masuhara, K.; Miki, H.; Fuji, T. Three cases of regional migratory osteoporosis. *Arch. Orthop. Trauma Surg.* 2003, 123, 439–441. [CrossRef]

56. Emad, Y.; Ragab, Y.; Saad, M.A.; Rasker, J.J. Transient regional osteoporosis of the hip with extensive bone marrow edema (BME): Dramatic improvement after three months of Alendronate therapy. *Radiol. Case Rep.* 2021, 16, 2487–2490. [CrossRef]

57. Emad, Y.; Ragab, Y.; El-Shaarawy, N.; Rasker, J.J. Transient osteoporosis of the hip, complete resolution after treatment with alendronate as observed by MRI description of eight cases and review of the literature. *Clin. Rheumatol.* 2012, 31, 1641–1647. [CrossRef]

58. Danie, R.; Madrigal, E.; Velazquez, M.; Oliva, A.; Navarro, B.; Arroyo, A.; Saura, M.R.; Ortega, E.; Gomar, J.; Carmona, J.; et al. Transient osteoporosis of the hip: A mysterious cause of hip pain in men. *J. Clin. Rheumatol.* 2006, 12, 505–508. [CrossRef]

59. Vaishya, R.; Agarwal, A.K.; Kumar, V.; Vijay, V.; Vaish, A. Transient Osteoporosis of the Hip: A Mysterious Cause of Hip Pain in Adults. *Indian J. Orthop.* 2017, 51, 455–460. [CrossRef]
67. Trevisan, C.; Klumpp, R.; Compagnoni, R. Risk factors in transient osteoporosis: A retrospective study on 23 cases. *Clin. Rheumatol.* 2016, 35, 2517–2522. [CrossRef]

68. Rolvien, T.; Schmidt, T.; Butscheidt, S.; Amling, M.; Barvenciak, F. Denosumab is effective in the treatment of bone marrow oedema syndrome. *Injury* 2017, 48, 874–879. [CrossRef]

69. Geith, T.; Mutschler, W.; Berger, F. Therapy of bone marrow edema syndrome in the knee with denosumab. Case report. *Unfallchirurg* 2015, 118, 230–232. [CrossRef]

70. Arazi, M.; Yel, M.; Uguz, B.; Emlik, D. Be aware of bone marrow edema syndrome in ankle arthroscopy: A case successfully treated with iloprost. *Arthroscopy* 2006, 22, 909.e1–909.e3. [CrossRef]

71. Horterer, H.; Baumbach, S.F.; Gregersen, J.; Kriegelstein, S.; Gottschalk, O.; Szeimies, U.; Walther, M. Treatment of Bone Marrow Edema of the Foot and Ankle With the Prostacyclin Analog Iloprost. *Foot Ankle Int.* 2018, 39, 1183–1191. [CrossRef] [PubMed]

72. Tosun, H.B.; Uludag, A.; Demir, S.; Serbest, S.; Yasar, M.M.; Oznam, K. Effectiveness of Iloprost in the Treatment of Bone Marrow Edema. *Cureus* 2020, 12, e10547. [CrossRef] [PubMed]

73. Pabinger, C.; Heu, C.; Frohner, A.; Dimai, H.P. Pregnancy- and lactation-associated transient osteoporosis of both hips in a 32 year old patient with osteogenesis imperfecta. *Bone* 2012, 51, 142–144. [CrossRef] [PubMed]

74. Radke, S.; Kirschner, S.; Seipel, V.; Rader, C.; Eulert, J. Treatment of transient bone marrow oedema of the hip—A comparative study. *Int. Orthop.* 2003, 27, 149–152. [CrossRef] [PubMed]

75. Muller, F.; Appelt, K.A.; Meier, C.; Suhm, N. Zoledronic acid is more efficient than ibandronic acid in the treatment of symptomatic bone marrow lesions of the knee. *Knee Surg. Sport. Traumatol. Arthrosc.* 2020, 28, 408–417. [CrossRef] [PubMed]

76. Baier, C.; Schaumburger, J.; Gotz, J.; Heers, G.; Schmidt, T.; Griefka, J.; Beckmann, J. Bisphosphonates or prostacyclin in the treatment of bone-marrow oedema syndrome of the knee and foot. *Rheumatol. Int.* 2013, 33, 1397–1402. [CrossRef] [PubMed]

77. Laktasic-Zerjavic, N.; Curkovic, B.; Babic-Naglic, D.; Potocki, K.; Prutki, M.; Soldo-Juresa, D. Transient osteoporosis of the hip in pregnancy. Successful treatment with calcitonin: A case report. *Z. Rheumatol.* 2007, 66, 510–513. [CrossRef]

78. Fernandez-Canton, G.; Casado, O.; Capelastegui, A.; Astigarraga, E.; Larena, J.A.; Merino, A. Bone marrow edema syndrome of the foot: One year follow-up with MR imaging. *Skeletal. Radiol.* 2003, 32, 273–278. [CrossRef]

79. Berger, C.E.; Kroner, A.H.; Minai-Pour, M.B.; Ogris, E.; Engel, A. Biochemical markers of bone metabolism in bone marrow edema syndrome of the hip. *Bone* 2003, 33, 346–351. [CrossRef]

80. d’Agostino, C.; Romeo, P.; Lavanga, V.; Pisani, S.; Sansone, V. Effectiveness of extracorporeal shock wave therapy in bone marrow edema syndrome of the hip. *Rheumatol. Int.* 2014, 34, 1513–1518. [CrossRef]

81. Sconza, C.; Coletta, F.; Magarelli, N.; D’Agostino, M.C.; Egan, C.G.; Di Matteo, B.; Respizzi, S.; Mazziotti, G. Multimodal conservative treatment of migrating bone marrow edema associated with early osteonecrosis of the hip. *SAGE Open Med. Case Rep.* 2022, 10, 2050313X211067617. [CrossRef] [PubMed]