



Continuing medical education

## From bone marrow edema to osteonecrosis. New concepts \*

Guillermo Fernández-Cantón

Centro OSATEK, Unidad de Dr. Areilza, Bilbao, País Vasco, Spain

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## ABSTRACT

The widespread use of MRI in the diagnosis of articular pathology has allowed for an improved knowledge of a series of disturbances that occur with epiphyseal bone edema as a main radiological sign, featured as low signal intensity of the bone marrow on T1 and high signal on STIR and fat saturated T2 sequences. The new etiopathogenic theories postulate a clear differentiation between primary and secondary osteonecrosis. While secondary osteonecrosis is related to risk factors, primary osteonecrosis is a result of a subcondral insufficiency fracture. Both have different characteristic and MRI criteria. The pathogenesis of transient bone edema syndrome (BMES) is currently under discussion, divided between the biomechanic theory and the more classic one that relates to the complex and poorly understood mechanisms associated with complex regional pain syndrome type I (reflex sympathetic dystrophy). The BMES, classically considered a reversible form of osteonecrosis, has enough differentiated features to be considered as a distinct disease. Bone marrow edema can be as extensive in either insufficiency or fatigue stress fractures than in BMES. The diagnostic key is the display of a subcondral bone fracture. These can be resolved or occasionally evolve into a primary osteonecrosis.

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### Del edema de médula ósea a la osteonecrosis. Nuevos conceptos

## RESUMEN

El uso generalizado de la resonancia magnética (RM) en el diagnóstico de la enfermedad articular ha permitido conocer mejor una serie de trastornos que cursan con edema óseo epifisario como signo radiológico principal, caracterizado por una hiposeñal de la médula ósea en secuencias T1 e hiperseñal en STIR o saturación grasa T2. Los nuevos conceptos etiopatogénicos acerca de la osteonecrosis postulan una clara diferenciación entre osteonecrosis primaria y secundaria. Mientras que la osteonecrosis secundaria se relaciona con factores de riesgo, la osteonecrosis primaria es consecuencia de una fractura subcondral de insuficiencia. Ambas tienen criterios de imagen en RM característicos y diferentes. La etiopatogénesis del síndrome del edema óseo transitorio (SEOT) se debate actualmente entre la teoría biomecánica y la teoría más clásica que la relaciona con mecanismos complejos y poco conocidos asociados al síndrome de dolor regional complejo tipo I (algodistrofia simpática refleja). El SEOT, clásicamente considerado una forma reversible de osteonecrosis, tiene características suficientemente diferenciales como para considerarse una enfermedad con entidad propia y de curso distinto a la osteonecrosis. En las fracturas de estrés, ya sean de insuficiencia o de sobrecarga, el edema puede ser tan extenso como en el SEOT y la clave diagnóstica es la visualización de fractura del hueso subcondral. Éstas pueden resolverse o evolucionar ocasionalmente hacia una osteonecrosis primaria.

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## Palabras clave:

Osteonecrosis

Necrosis avascular

Síndrome del edema óseo transitorio de médula ósea

Fracturas de insuficiencia

Síndrome del dolor regional complejo tipo I

### Introduction

Bone edema is a pattern seen in magnetic resonance (MR) images characterized by a hyposeñal on T1 and STIR hypersignal in T2 fat saturation in the bone marrow, which are currently the useful sequences for this diagnosis. Its margins are imprecise and tend to

be peripherally attenuated. The pattern of edema defined in this manner is characteristic of any inflammatory process affecting the bone marrow, such as acute bone contusions, osteochondral stress or insufficiency lesions, osteitis, osteomyelitis, among other causes. Some present imaging differential characteristics but on occasion, clinical and laboratory tests are necessary to establish an adequate

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E-mail address: [gfernandez@osatek.es](mailto:gfernandez@osatek.es)

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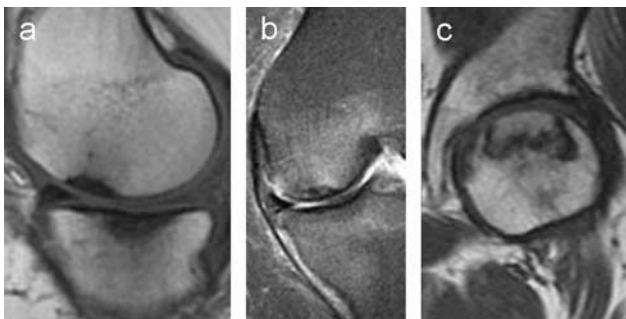
diagnosis. Although most of the cases of marrow edema can be explained by cartilage lesions or trauma, there are other cases in which no clear etiopathogenic cause is evident. This article centers on those causes of epiphyseal bone edema with a non-degenerative or traumatic cause, among which primary or spontaneous necrosis and transitory bone edema are included, as well as their relationship with subchondral insufficiency bone fractures.

### Osteonecrosis

The term osteonecrosis refers to a pathological process that leads to the death of the constituents of the bone marrow (osteocytes, bone marrow, and hematopoietic tissue). Although avascular necrosis, osteonecrosis, septic necrosis, and bone infarction are equivalent terms due to their localization and tend to translate as bone death, osteonecrosis is usually differentiated from a bone infarction by its localization. Osteonecrosis is reserved for the epiphyseal affection involving the bone cortex, while bone infarction is reserved for metaphysodiaphyseal localizations in which the necrosis only affects bone marrow bone.

Radiologists currently recognize there are significant differences between primary and secondary osteonecrosis.<sup>1</sup> Secondary osteonecrosis is a lesion with an ischemic origin and is currently related to predisposing factors such as trauma, and diseases such as alcoholism, steroid use, infections, barotraumas, deposit diseases, bone-marrow infiltrating diseases, coagulation abnormalities, and hematological disease. The half-moon sign is the characteristic image on x-rays (RX) and represents the fracture of subchondral bone that defines stage III osteonecrosis. The characteristic and earliest sign on the MR is a ring of low-intensity signal on T1 in a subchondral localization which represents the repair process interphase between ischemic and normal bone (Figure 1). Its natural history is not well established although it can progress toward joint deterioration.

In primary, spontaneous or idiopathic osteonecrosis, these predisposing factors are absent and it is believed that it represents a consequence of the fracture due to insufficiency of the subchondral bone.<sup>2,3</sup> This hypothesis is based on the demonstration of fractures on pathological studies obtained from bones of patients who received a prosthesis,<sup>2</sup> as well as the occasional presence of lines running parallel to subchondral bone as seen on MR.<sup>4</sup> Epidemiological and clinical factors seem to strengthen this hypothesis and have been undergone particular study in the case of the knee: they are associated with advanced age, obesity, and predominate in women (risk of osteoporosis). Patients refer spontaneous, acute onset pain that is presumably of a mechanic origin. It has a predilection for the weight-bearing surface of the medial condyle and is associated to meniscus lesions. Osteoarthritis is also a predisposing factor, probably



**Figure 1.** a and b) Primary or spontaneous osteonecrosis of the knee. Sagittal T1, coronal STIR. A pseudo-thickening of the cortex represents necrotic bone on both sides of the joint. On the coronal (STIR) plane there is a line representing probable fracture of the subchondral bone and intense bone edema. c) Coronal T1 scan of the hip showing the characteristic ringed appearance of avascular necrosis.

related to chondral damage.<sup>5</sup>

In spontaneous osteonecrosis, the necrosis foci are interposed between the fracture line and the subchondral plateau, demonstrating the fact that fracture is the primary factor.<sup>2,6</sup>

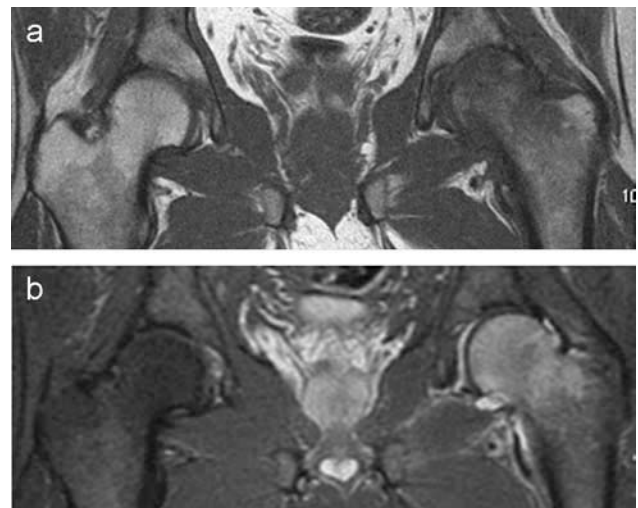
The most common finding on the MR is an area of focal hypointense signal causing a false cortical thickening (Figure 1). Other findings are a straightening or depression of the subchondral plateau, liquid-filled subchondral fractures (equivalent to the half-moon sign), or subchondral cysts.

Prognostic criteria on MR that seem to indicate a benign course are the absence of a focal depression of the epiphyseal lining and the absence of deep, low intensity signal line on the condyles.<sup>7</sup> The progression toward collapse is related with a damaged surface exceeding 5 cm<sup>2</sup> on the condyle.<sup>8</sup>

### Transitory bone edema syndrome

The term transitory bone edema (TBE) is relatively new, being proposed by Wilson to define a group of 10 patients with knee pain and an RX with or without osteopenia and an abnormal MR image in which the symptoms ceded spontaneously.<sup>9</sup>

In transitory bone edema syndrome (TBED) of the bone marrow, soft tissue edema and a joint effusion usually accompany bone edema, as occurs in other inflammatory processes. In addition, it is usually manifested in characteristic localizations: hips, knees, and feet. The main symptoms are non-specific: pain, inflammation, and functional limitation manifested as limping. Edema can migrate to other joints in up to 33% of cases, although it varies according to the published series and follow-up time.<sup>10,11</sup> The diagnosis is made after excluding clinical signs of infection, trauma in relation to the degree of edema or joint or systemic inflammatory diseases. In general, no complementary or special testing is needed. Simple RX have a limited value and are useful for demonstrating the accompanying osteoporosis that characterizes this syndrome. Bone scans are seldom employed because of their low yield in detecting and differentiating the problem when confronted with an MR. TBES is manifested on the MR as an intense and extensive edema that starts on the subchondral bone but extends through the bone marrow to zones distal from it (for example the femoral neck, the intertrochanteric region, the condyle, etc) (Figure 2). It is usually not accompanied by a focal lesion of the subchondral bone and is spontaneously cured in a period of weeks to months.



**Figure 2.** Transitory bone edema syndrome of the hip. The left femoral head and neck show a T1 sequence hyposignal (a) and a hypersignal in STIR b) no focal lesions are seen on the subchondral bone.

Most of the cases of TBES respond to conservative treatment, although bone decompression has also been shown as effective in the treatment of TBES to reduce symptoms and time of recovery. Curiously, it has also shown to be effective in one case of BES that affected several tarsal bones in which a biopsy-forage of the astragalus was performed.<sup>12</sup> However, it is an invasive and seldom used technique because TBES is self-limited, although it should be considered in patients that require a faster reintegration to daily activities.

Early avascular necrosis should be included in the etiopathogenic discussion and the differential diagnosis, as well as subchondral stress fractures and bone edema of a biomechanical nature, as follows.

#### *Transitory bone edema syndrome and avascular necrosis*

Before TBES was described, patients were treated with surgical decompression, considering it an early stage of osteonecrosis in an attempt to avoid the progression to advanced stages. It has more recently been used as a way to shorten the period of healing.<sup>7,13</sup> This surgical technique has allowed obtaining of biopsies of the femoral head that allow us to determine the histopathological characteristics of TBES, although other biopsy studies of other anatomic localizations yield similar results.<sup>7,14</sup> These have similar findings to those of initial forms of osteonecrosis (Ficat's classification stage I and II). In TBES there is fat necrosis and an increase in bone neoformation, but what really differentiates it is the lack of bone necrosis. The reduction in bone density is due to a loss of mineralization. Therefore, Penk et al<sup>14</sup> propose the term of transitory demineralization, which better describes what occurs in this syndrome. These findings have led to the formulation of the classic hypothesis in which TBES is a reversible form of osteonecrosis, something that has helped with the confusion that reigns in these diseases, although there is consistent evidence that currently shows they are different entities.<sup>15</sup>

The inheritance of confusion has persisted in medical literature for several years, confusing aspects of etiology, prognosis, and treatment between primary and secondary osteonecrosis and TBES. The medical community has not begun to distinguish between both forms of osteonecrosis until recently. Until then it is easy to find studies in which the patient selection criteria to evaluate the natural history or the response to treatment, especially surgical decompression, do not comply with that comply with the more modern criteria and mixes them in a totum revolutum. Classic papers that show the efficacy of surgical decompression in initial stages of osteonecrosis of the femoral head have tended to confuse it with TBES, creating a false link between their satisfactory findings regarding the prevention of femoral collapse to an erroneous diagnosis. In this way, when faced with a pattern of bone edema, radiologists have included TBES and early osteonecrosis in the differential diagnosis, although no continuity between both entities has been proven.<sup>16,17</sup> The use of more modern MR equipment incorporating high resolution surface coils, helps define more clearly whether or not there are subchondral bone lesions, allowing to differentiate the diagnosis from insufficiency fractures or small foci of subchondral osteonecrosis.

Gadolinium, MR studies have been done with the idea of demonstrating areas that lack uptake of contrast as indicating areas of infarction or as early signs of osteonecrosis that permit the differentiation of TBES from osteonecrosis in its edema stage,<sup>18</sup> although its usefulness without contrast is limited.

Another reason that leads to thinking that osteonecrosis and TBES are different diseases is the behavior of the latter on the foot. In this localization there can be one or several bones affected and a progression to osteonecrosis has not been shown in any case. Characteristic osteonecrosis of foot bones, such as navicular osteonecrosis (Köhler or Müller-Weiss disease) and astragalus osteonecrosis are easily recognizable due to their radiological pattern.

A different evolution over time is also evident. Osteonecrosis occurs very rapidly after ischemia. Pathology studies have shown that after 6 to 12 h there is necrosis of the red marrow, between 12 and 48 h there is osteocyte and osteoblast necrosis and, finally, between days 2 and 5 there is fat necrosis.<sup>19</sup> The first MR manifestations occur from this point onward, but the time of appearance of the ring sign is not known, although it is believed to be an early occurrence. In an experimental study on dogs, MR signs were manifested from the first week and were present in all cases by the fourth week.<sup>20</sup> In TBES, the pattern of edema remains the same for weeks without the appearance of this sign. Patients that present hip pain usually undergo an MR several weeks after the onset of symptoms. In these cases, with no clear radiological criteria of osteonecrosis on the MR, it should be excluded from the differential diagnosis if it is estimated that the early phase of osteonecrosis does not last more than a few days.

#### *Transitory bone edema syndrome and subchondral stress fractures*

It has been proposed that TBES has a biomechanical origin due to its analogy to subchondral fractures and corresponds to a response to stress.<sup>21</sup> Stress fractures can occur if normal bones receive abnormal stress (fatigue or overload fractures), or if normal stress is applied to weakened bone (insufficiency fractures). In addition, they may be reversible and be cured without complications or evolve into osteonecrosis and collapse. In stress fractures, the edema can be as extensive as the TBES and the diagnostic clue is the observation of an irregular band of signal parallel to subchondral bone (equivalent to the half-moon sign on the RX).

Although it is common that in TBES no focal epiphyseal lesions are seen, fine lines parallel to subchondral bone or small focal areas of altered signal can be seen in TBES and interpreted as subchondral fractures. Paradoxically, these patients may have a faster recovery than patients with evident bone edema without subchondral fractures.<sup>22</sup> When only one bone is affected, the differential diagnosis between TBES and stress fracture can be impossible and other alternatives must be considered. Clinical data may clear up this if an abrupt onset is demonstrated showing the moment of fracture. Subchondral microlesions may also be seen in cases of bone edema of the foot, but in these cases the distribution into multiple bones presenting bone edema clears up the diagnosis of TBES. These findings do not mean that the primary cause of TBES is necessarily a subchondral fracture, because this can also be a consequence of the former. In fact, the resulting demineralization results in bone weakening in TBES and can lead to a greater susceptibility to insufficiency fractures.

Subchondral stress fractures are differentiated from avascular necrosis in that the ring sign (reactive margin) is not present outside the fracture line.<sup>21</sup>

Bone edema can be produced by overloading the joints, which is demonstrated in volunteers in situations such as the use of plantar footpads to force hyperpronation or in athletes who run 50 miles a week.<sup>23,24</sup> However, the clinical history of patients with TBES does not usually mention intense stress nor does its recovery time seem similar to the abovementioned studies.

#### *Transitory bone edema syndrome and transitory osteoporosis*

Transitory osteoporosis defines a self-limited disease characterized by joint pain with osteopenia that is visible on the x-ray in the weeks after the onset of symptoms. It is currently recognized that transitory osteoporosis and TBES are equivalent terms. During the first years after the description of the syndrome there were some doubts as to the fact that not all of the patients with TBES presented osteoporosis. There is no doubt that the detection of osteoporosis in simple RX is many times subjective. Radiographic plates are not always of the necessary quality and may complicate diagnosis in those cases in

which osteoporosis is mild or moderate if there is no comparative RX of the contralateral limb. In addition, osteoporosis can appear weeks after the diagnosis of TBES, as occurs in transitory osteoporosis.

#### *Transitory bone edema syndrome and reflex sympathetic dystrophy*

The relationship between TBES and reflex sympathetic dystrophy, currently known as type I complex regional pain syndrome (CRPS), is more difficult to explain. Some authors, especially the French, believe it is the same thing although others disagree.<sup>25,26,27</sup> The clinical definition of type I CRPS is complicated and non-specific.<sup>28,29</sup> The main signs and symptoms of type I CRPS, such as pain, edema, and inflammatory changes in soft tissue, as well as movement disorders, are present in TBES. Other, such as hypersensitivity, vasomotor manifestations, temperature and skin changes, and a progression toward atrophy are less constant<sup>30</sup> and their incidence has not been studied in TBES. Bone scans are usually positive in active phases, as occurs in TBES. Bone edema on the MR can be found in 46% to 100% of patients in the warm phase of type I CRPS, but is never present in the dystrophic phase. Therefore, the absence of bone edema does not rule out type I CRPS.<sup>31,32,33</sup> In this author's experience, many patients diagnosed as bone edema are sent from their specialists' clinic with the clinical suspicion of reflex sympathetic dystrophy. Agreement regarding the finding of osteopenia on a simple RX and the migratory forms of both diseases reaffirm the hypothesis that TBES is a manifestation of type I CRPS.

#### **Conclusion**

Differential characteristics among the different epiphyseal lesions currently recognized are exposed on Table. In many occasions, their precise distinction does not affect clinical treatment because it is usually conservative in early stages, although it does affect prognosis. An adequate categorization of patients with epiphyseal bone edema would allow us to better determine its prognosis and define the therapeutic options.

#### **Table**

Differential characteristics of epiphyseal lesions with bone edema

	TBES	ON primary	Avascular necrosis	Stress fracture
Equivalent terms	Transitory osteoporosis RSD?	Spontaneous ON Idiopathic ON	ON Secondary ON Aseptic necrosis	Fatigue (healthy bone) Stress (weak bone)
Pathology	Demineralization Fat necrosis Increase in osteoid No osteocyte necrosis	Subchondral microfractures Focal necrosis underlying the fracture (similar to secondary ON)	Necrosis of all of the components of the bone marrow (osteocytes, bone marrow, and hematopoietic tissue)	Subchondral fracture
Etiology	CRPS type I Unknown factors Biomechanical?	Mechanical trauma Insufficiency fracture Osteoarthritis	Ischemic trauma Predisposing factors: fractures, steroid use, alcohol, etc	Mechanic trauma
Progression	Spontaneous resolution 1/3 Migratory pattern	Irreversible Subchondral collapse in relation to the affected area	Irreversible Deterioration possible with varying degrees of joint damage	Reversible Possible progression to ON
Radiological findings	Bone edema Soft tissue edema and joint effusion Possible affection of multiple bones Occasional insufficiency fracture Integral cartilage	± fracture Subchondral bone lesion  Bone edema Soft tissue edema and joint effusion Osteoarthritis and chondral damage	RX: half-moon MR: ring  Bone edema Soft tissue edema and joint effusion Cartilage lesion in advanced stages	RX and MR: half-moon Bone edema  Soft tissue edema and joint effusion

CRPS indicates complex regional pain syndrome; ON, osteonecrosis; MR, magnetic resonance; RX, x-ray; RSD, reflex sympathetic dystrophy; TBES, transitory bone edema syndrome.

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