Avascular necrosis of hematopoietic stem cell transplantation (HSCT): state of the art

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ABSTRACT

Avascular necrosis (AVN) is a complex, multifactorial disease that may affect one bone, several bones together, or different bones at different times and it can impair the patient's quality of life. It predominantly occurs in the femoral head, but also commonly affects other sites, especially the femur and knees, causing severe pain, bone necrosis, and, in extreme cases, even bone collapse. It can be diagnosed by magnetic resonance imaging analysis, and is usually staged using the Association of Research Circulation Osseus (ARCO) system or the Ficat system.

Currently, literature on the prevention and treatment of AVN is very scanty, and studies are based on retrospective analyses. The aim of this review is to analyze the state of the art with regard to risk factors and treatments for AVN in patients who have received a hematopoietic stem cell transplant.

KEYWORDS

Avascular necrosis, AVN, osteonecrosis, HSCT.

Introduction

Avascular necrosis (AVN), also known as osteonecrosis, is a complex, multifactorial disease that may affect one bone, several bones together, or different bones at different times. It predominantly occurs in the femoral head, but also commonly affects other sites, such as the proximal humerus, knees, carpus, and jaw. It is characterized by a temporary or permanent lack of adequate vascular perfusion of bone.

When bone tissue is not properly supplied with blood, it dies and the affected bone collapses. Alterations to the blood supply may occur for several reasons, and the most common nontraumatic causes are glucocorticoid (GLC) treatment and alcohol abuse. Alcohol abuse is related to AVN because it increases adipogenesis, inducing lipid metabolism disorders and promoting osteopenia and osteoporosis, resulting in an excess of microfractures. GLC treatment in AVN is associated with altered lipid metabolism, too, and an imbalance between osteogenesis and adipogenesis, resulting in an increased size and number of adipocytes. In addition, GLC treatment promotes the onset of inflammatory processes, vasoconstriction, and hypercoagulability associated with thrombosis [1].

Gaucher disease may also be related to AVN; in fact, patients who develop anemia and osteopenia in the course of this disease have a greater risk of developing AVN (they were found to be 60% more likely to develop it compared with the group of non-anemic patients) [2]. Although the mechanisms underlying AVN in Gaucher disease are not well understood, it is possible that chronic inflammation, splenectomy, and the high D-dimer levels that can be associated with this disease play a role in AVN [3].

AVN, especially in the craniofacial region, is an adverse effect of bisphosphonate therapy for osteoporosis. Bisphosphonates may be involved in the pathogenesis of AVN of the jaw through their direct toxicity and their role in inhibiting angiogenesis and altering the immune system [4].

Post-traumatic AVN occurs when the blood supply to the femoral head is cut off due to a fracture or dislocation of the femoral head. Generally, AVN is related to fractures in the subcapsular region of the femoral neck. Lesions in this region interrupt the anastomosis between the lateral epiphyseal vessels, decreasing the blood supply to the femoral head [5,6].

In addition to the above causes, AVN can occur in patients who have received a hematopoietic stem cell transplant (HSCT), particularly in childhood. The prevalence of AVN in pediatric patients after HSCT ranges from 3.9% to 29.5%. This range is partly attributable to the heterogeneity of the study population, the different approaches to transplantation, and the different conditions necessitating the transplant [7,8].

The timing of the onset of the disease varies from patient to patient, ranging from the first six months after transplantation to 10 years later, but on average, AVN occurs around the second year after HSCT [9].

The aim of this review is to analyze the state of the art in terms of risk factors and therapies for the treatment of AVN in patients undergoing HSCT.

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AVN diagnosis

Early diagnosis is essential in order to have a good chance of managing to delay or reverse the disease progression [10].

The diagnosis is often made by means of magnetic resonance imaging (MRI) rather than X-ray analysis because of the poor sensitivity of the latter in the early stages of AVN. MRI, in addition to its superior sensitivity, allows evaluation of the extent/location of the necrosis and makes it possible to predict further bone collapse [11].

Positron emission tomography, having a higher power of resolution, is much more sensitive than MRI and X-ray analyses, and therefore a better technology for diagnosing AVN in its earlier stages [12]. However, being costly and time consuming, it is not a technique that can be routinely used to rapidly diagnose AVN [13].

Another important method for diagnosing AVN is lesion staging. Several staging systems exist, and the Ficat, Association of Research Circulation Osseus (ARCO), and Steinberg systems are all commonly used [11]. The first ARCO staging system for non-traumatic osteonecrosis of the femoral head (ONFH) was established in 1994 and revised in 2019 [10,14] (Tables I and II).

Risk factors in HSCT patients

Risk factors for AVN in post-HSCT patients may include high doses of glucocorticoids (GLCs) for the treatment of graft-versus-host disease (GVHD) [9,15,16], calcineurin inhibitors [17], an underlying diagnosis of acute myeloid leukaemia (AML) or chronic myeloid leukemia (CML) [18,19], young age [20], female sex [21,22], and the use of total body irradiation (TBI) as a conditioning regimen [18,21,23,24].

High doses of GLCs, such as those prescribed for patients undergoing HSCT, can cause reduced blood flow by promoting hypercoagulability, which in turn can cause AVN. GLCs, increasing lipid synthesis, also induce hypertrophy of adipocytes [25,26]. This cellular increment induces intraosseous hypertension, especially at proximal femoral level, leading to intravascular coagulation due to compression of the venous sinusoids. Then, arterial blood flow is blocked, and ischemia occurs. All this adds up to an ischemic cascade (Fig.1) [10,14,27-29] that can be summarized in the following steps:

1) Hyperplasia of bone marrow fat cells.
2) Intra-osseous hypertension.
3) Vascular compression.
4) Intravascular coagulation.
5) Blocked or impaired blood flow.
6) Necrosis of bone marrow and osteocytic death.
7) Fibrovascular reparative process around the necrotic zone.

Once the fibrovascular reparative process around the necrotic zone has occurred, the lesion is irreversible [14,28,30].

The result is that the necrotic bone becomes saponified and mechanically weak, and the risk of stress fractures increases [30-32]. Ischemic lesions do not always progress to irreversible osteonecrosis. It depends on the degree of blood perfusion

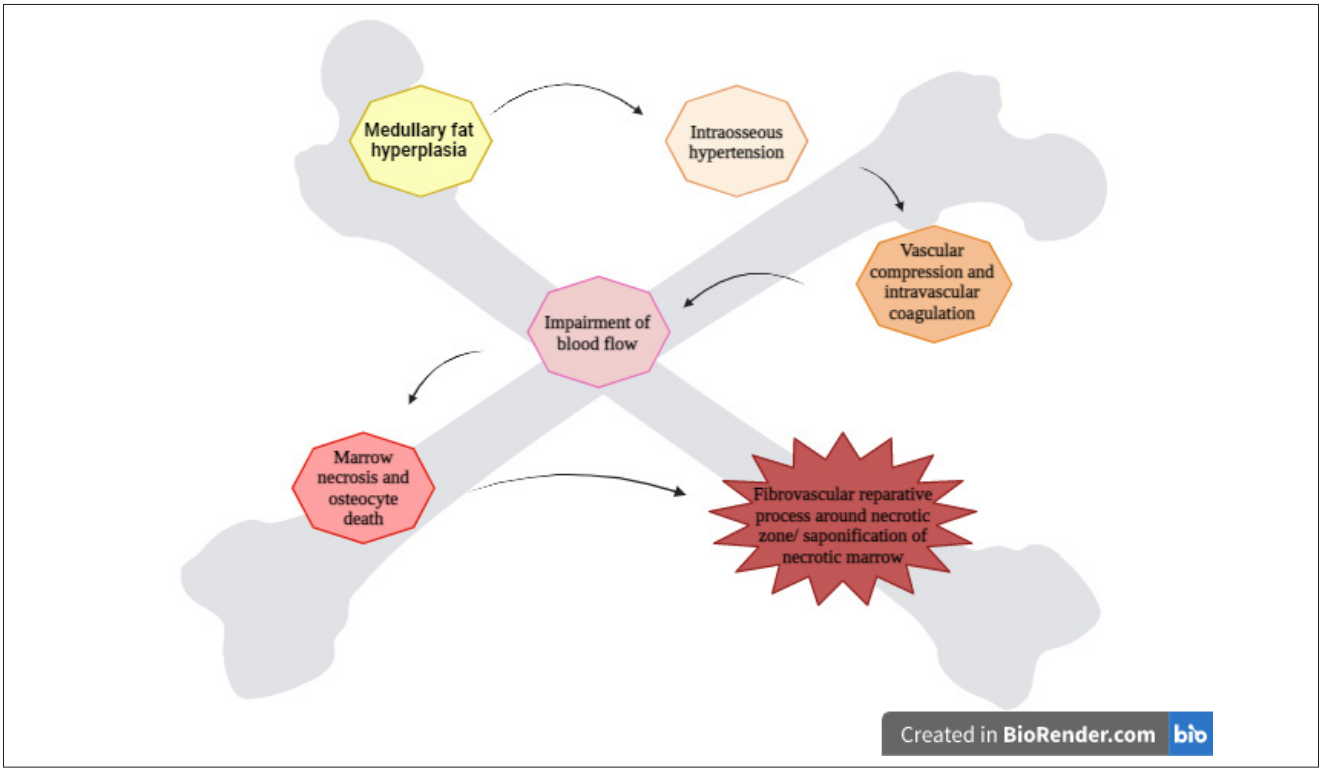
Table 1 The ARCO classification.

STAGE	RADIOLOGICAL FINDINGS	SUBCLASSIFICATION
0	All diagnostic studies normal. Diagnosis by histology only	
I	Plain radiographs and CT normal. MRI and biopsy ++	Extent: A (15%), B (15–30%), C (30%) Location: 1 (medial third), 2 (median third), 3 (lateral third)
II	Radiographs +	Extent/location as above
III	Subchondral fracture	Extent/location as above
IV	Flattening of the femoral head	Depression of femoral head: A (2 mm), B (2–4 mm), C (4 mm)
V	Flattening of the femoral head. Osteoarthritic changes Joint space and acetabular changes	Depression as above
VI	Joint destruction	

Table 2 The Ficat classification.

STAGE	MRI	X-RAY	CT
0	Formation of the subchondral linear band	-	-
I	Linear and defined double subchondral band	-	-
II	Thick double subchondral band	Fuzzy osteorarefaction	Segmental osteorarefaction
III	Loss of sphericity. Chondral fragmentation	Loss of sphericity	Subchondral thickening. Loss of sphericity
IV	Subchondral bone collapse Cartilage destruction, etc.	Loss of sphericity, etc.	Subchondral collapse, erosions, etc.

Figure 1 The ischemic cascade.



restoration and the capacity for replacement of ischemic bone [10,30]. In recent studies, it has, however, been reported that a predisposition to hypercoagulability/hypofibrinolysis and/or hypo-angiogenesis decreases the restoration of blood circulation within necrotic bone [32,33].

Several studies have confirmed the correlation between treatment with GLCs and the occurrence of AVN in patients who have been transplanted with hematopoietic stem cells. Campbell *et al*. [17], published a retrospective study of 1346 HSCT patients (all treated with prednisone-based therapies, immunosuppressants and/or calcineurin inhibitors) with a mean age of 34 years. 75 patients developed AVN in 160 joints. The researchers found that the incidence of osteonecrosis in the 10 years following HSCT was 2.9% in patients treated with autograft, 5.4% in those treated with allograft, and 15% in patients who had received a transplant from an unrelated donor. In another follow-up [15], 74 HSCT patients with AVN and 147 HSCT patients without AVN (controls), all treated with prednisone, were analyzed. It was shown that cumulative GLC doses < 3870 mg increased the risk of developing AVN 4-fold, doses 3870 mg < X < 9735 mg increased the risk 5.6-fold, while doses > 9735 mg increased it 8.6-fold. The authors thus found a dose-dependent incidence [15].

In a large retrospective study by Socié *et al*., conducted in 4,388 HSCT patients, severity of GVHD was directly related to a higher frequency of AVN [23]. As we have mentioned, AVN has been encountered in hematological malignancies. HSCT treatment in diseases such as AML and CML may be a risk factor associated with AVN. In fact, a group of researchers has demonstrated that the risk of osteonecrosis in AML and CML patients treated with HSCT is 7 and 10% respectively [18]. Others have reported a 15% risk of AVN in the 15 years following transplantation in CML patients with GVHD [19].

Several studies have analyzed possible risk factors for AVN in pediatric allogeneic HSCT recipients. Li *et al*. [20] performed a case-control study within a population study of 6,244 patients aged 21 years or younger who had received their first allogenic HSCT between 1990 and 2008 in the United States and survived six months or more after transplantation. They found increasing age at transplant, development of GVHD, and female gender to be important factors contributing to the occurrence of osteonecrosis; in contrast, absence of GVHD and an underlying disease of non-malignant origin reduced the risk of AVN [20]. Another important risk factor related to AVN in HSCT patients is TBI in addition to corticosteroid treatment. Nowadays, with the number of HSCT survivors increasing, it is mandatory to identify and understand the musculoskeletal complications related to HSCT and TBI.

In the light of all that has been described, it seems clear that the establishment of AVN in patients undergoing HSCT appears to be closely related to the ischemic processes caused by the transplantation itself and the immunosuppressive therapies these patients receive.

Therapeutic strategies

Pharmacological agents such as statins, bisphosphonates, iloprost, acetylsalicylic acid, and enoxaparin have been tested to assess their effect in terms of reversing or delaying the progression of AVN [34-38], but none of them can yet be considered a pharmacological treatment for AVN.

Given the absence of an adequate pharmacological treatment, to date only surgery is considered standard, serving to prevent disease progression by modulating and preserving diseased joints or even replacing them.

Core decompression (sometimes associated with autologous or allogeneic bone grafts) is a technique used mainly in the early stages of AVN, when there is not yet any bone collapse. It involves removing the necrotic part of the bone to relieve pressure and stimulate repair. It has been shown that core decompression can be combined with bone marrow aspirate transplantation [10,39-41]. The efficacy of bone marrow grafts may be related to the immediate availability of mesenchymal and endothelial stem cells endowed with osteogenic and angiogenic properties that can promote sufficient repair to render lesions reversible in the early stages of the disease [42-44]. Unfortunately, it is not yet possible to localize the bone marrow cells after the injection; consequently, larger studies are needed to demonstrate that bone repair might originate from bone marrow cells transplanted into the necrotic bone [44].

A superior technique to core decompression is vascularized fibular grafting (VFG) [6], which leads to neovascularization within the necrotic areas, promoting integrity of the femoral head [22,45].

Several research studies suggest osteotomy as a treatment. With osteotomy, the bone is reshaped to reduce the load exerted on the necrotic area [46]. If osteotomy is not possible, arthroplasty can be performed. Arthroplasty consists of surgical reconstruction or replacement of the damaged elements in order to restore proper functioning of the joint itself, and it can be applied to various joints. In young HSCT patients who require joint replacement, it is necessary to consider the wear and tear of the replaced joint over time and future procedures for joint preservation. To date, the most widely used technique is hemi-resurfacing arthroplasty [9], in which the acetabulum and femoral head are metal coated; this reduces bone loss and the subsequent need for total hip arthroplasty (a very likely scenario considering that 50% of HSCT patients with AVN undergo such surgery) [47,48].

The treatment management of HSCT patients with AVN should be individualized according to age, comorbidities, anti-GVDH GLC treatment, the patient's medical history, and the location of the affected joint [9]. A multidisciplinary therapeutic approach involving orthopedic surgeons and physiotherapists is necessary to achieve the goal of preserving the affected joint for as long as possible through the use of non-steroidal analgesic and anti-inflammatory therapy [49] and a crutch or wheelchair to limit loading of the joint.

Careful observation and conservative management are required in both symptomatic and asymptomatic injuries (respectively, 15% and 30% of those involving the femoral head. An appropriate treatment might be core decompression (with or without bone grafting) along with avoidance of high-impact activities involving the injured joint. A more aggressive therapeutic approach, such as VFG or hemi-resurfacing in younger, active patients, is preferably envisaged for lesions of the hip or at ARCO stage II or III; in older patients, total hip arthroplasty is envisaged in the case of subchondral collapse and in lesions causing or involving degradation of the acetabulum [6].

Conclusion

AVN is a bone complication that can easily occur in patients who have undergone HSCT, especially when treated with steroid therapy. Currently, the strategy for AVN prevention is based on ongoing vigilance on the part of physicians caring for HSCT survivors, and analysis of known risk factors that may present as symptoms in new patients. The literature on the risk of developing this disease and its treatment is mainly based on retrospective clinical studies and is still scanty. More in-depth studies could be helpful for physicians caring for HSCT survivors. Also, further in vitro studies might help to clarify the molecular and cellular bases of this bone complication, offering the opportunity to identify new molecular targets that might be useful for the development of new therapies.

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