Current State of Diagnosis and Treatment of AVN of the Hip

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Abbreviations

ARCO	Association Research Osseous Circulation
AVN	Avascular necrosis
FSE	Fat-suppressed spin echo
GWAS	Genome-wide association study
JIC	Japanese Investigation Committee
MPSL	Methylprednisolone
MRI	Magnetic resonance imaging
ON	Osteonecrosis
ONFH	Osteonecrosis of the femoral head
ROM	Range of motion
SIF	Subchondral insufficiency fracture
STIR	Short T1 inversion recovery

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9.1 Introduction

"Death of all the cellular elements of bone indicates osteonecrosis (ON)" [1], and can be of traumatic or nontraumatic origin [2].

Nontraumatic AVN of the hip affects mainly young patients and leads to secondary arthritis of the hip. Additionally, the survival of total hip arthroplasties in those young patients with AVN of the hip is inferior [3] which still nowadays makes AVN of the hip a challenge for the orthopedic surgeon.

9.2 Epidemiology

ON accounts for about 10% of more than 500,000 total joint replacements performed annually in the United States [2]. The average age of the patients receiving total hip replacement for AVN is 38 years with only 20% of patients being more than 50 years old at the time of operation [4]. In our three-decade experience, the disease is underdiagnosed as many hips reach the state of secondary arthritis before the diagnosis of AVN. Especially in chemotherapy for leukemia associated with ON, the average patient age was as young as 14 years at the time of diagnosis [5].

As nontraumatic AVN of the hip affects both hips nonsimultaneously in up to 90% of the cases, it is mandatory also to examine the contralateral "silent hip" [6].

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Based on epidemiologic studies in Japan, the crude incidence rate has been reported to be 2.51 cases per 100,000 person-years, and the number of new nontraumatic AVN patients in Japan (population: ~120 million) was estimated to be around 3200 cases per year [7].

9.3 Etiology

In a prospective study, 20% of the patients were diagnosed with AVN of the hip 1 year after solid organ transplantation and associated glucocorticoid therapy [8], with renal transplantations having the highest risk. Cigarette smokers had an odds ratio of 10.3 for being affected by AVN of the hip over nonsmokers [9]. Further etiologies of ON are systemic lupus erythematosus [10], chronic inflammatory bowel disease [11], and multiple sclerosis [12].

In a retrospective study in 105 pediatric patients with chemotherapy because of acute lymphoblastic or myeloid leukemia and non-Hodgkin lymphoma, the average age was 8 years at leukemia diagnosis [5]. After 17 months, 4 boys und 4 girls each (7.6%) between 10 and 17 years had 18 osteonecrotic lesions, 12 of which affected the hip joint.

Further etiologies of AVN are sickle cell anemia [13], Caisson's disease of the divers [1], and Gaucher's disease [14]. Bone marrow edema syndrome and ON has also been reported in association with pregnancy and postpartum [15, 16].

9.4 Pathogenesis

Impaired femoral head blood flow and a procoagulatory state of plasma could be experimentally shown after high-dose steroid treatment [17]. Systemic fat embolism has been described after renal transplantation and associated glucocorticoid therapy [18]. Thrombophilia and hypofibrinolysis were described in 12 cases of steroid-induced ON [19].

Hypertrophy of bone marrow fat cells could be shown after steroid and alcohol application in vitro [20]. Fat-cell hypertrophy was postulated to increase intraosseous pressure, compress capillaries and sinus, and thereby decrease local bone blood flow in this study.

The necrotic area is typically located at the end of the lateral epiphyseal arteries within the femoral head. In these vessels, pathologic changes have been shown [21]. Later on, gene expression of factors of bone formation and remodeling as well as bone morphogenetic proteins 2 and 7 has been shown to rise [22].

As to the animal model for ON, corticosteroid-induced ON was firstly developed in rabbits, in which high-dose methylprednisolone (MPSL) (20 mg/kg) can induce multifocal ON in conjunction with thrombocytopenia, hypofibrinogenemia, and hyperlipidemia [23]. Based on this animal model for ON, several investigations for the prevention of AVN have been reported, including combined effects of warfarin and lipid-lowering agent [24], antiplatelet drug [25], statin [26], and anti-vasospasm agent [27, 28].

Recently, a genome-wide association study (GWAS) has been performed using 1602 ON cases and 60,000 controls. Stratified GWASs based on the three subgroups of ON of the femoral head (ONFH) (corticosteroids, alcohol, idiopathic) were also performed. A novel ON locus was identified at chromosome 20q12, and *LINC01370* was the best candidate gene in this locus [29].

9.5 Pathology

One of the most characteristic pathologic findings in ON is a zone formation, comprising necrotic, reparative, and viable tissue [30]. A wedge-shaped necrotic area is seen in a subchondral area, which is surrounded by reparative tissue. This reparative tissue continues to the normal viable bone and bone marrow tissue (Fig. 9.1).

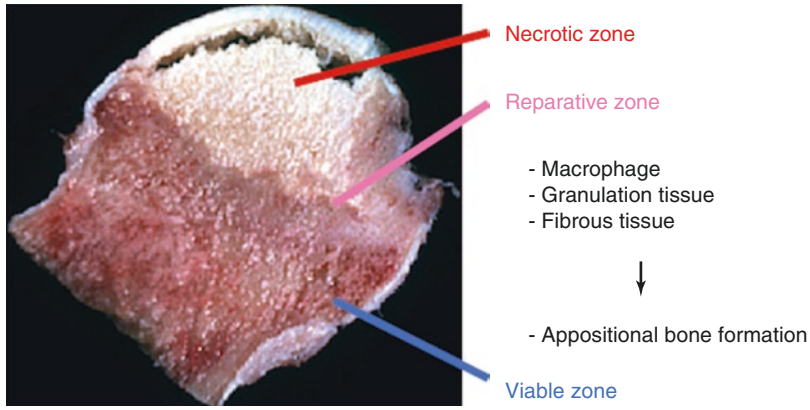


Fig. 9.1 Zone formation in ON. A wedge-shaped necrotic area is seen in a subchondral area, which is surrounded by the reparative tissue. This reparative tissue continues to the normal viable bone and bone marrow tissue. In the early phase of ON, the reparative tissue generally consists of infiltration macrophage, granulation tissue, and fibrous tissue, which can only be recognized on magnetic resonance imaging (MRI). Thereafter, bony repair such as appositional bone formation and creeping substitution occur, when radiograph can detect these bony changes as a sclerotic change

9.6 Diagnostic Criteria

First symptoms often are spontaneous groin pain eventually radiating to the knee [31]. According to the experience of the authors, the pain is extremely strong, unrelated to mechanic stress/weight bearing, and often occurs spontaneously in the night. At clinical examination of the range of motion (ROM), the hip often is extremely painful in many directions.

9.7 The ARCO and JIC Classification Systems

Very much established today is the ARCO classification consented by the Association Research Circulation Osseous (Table 9.1) [4]. The JIC classification for clinical differential therapy has been worked out by the Japanese Investigation Committee. Both systems are presented here as they very much supplement each other.

Stage ARCO 0 can only be detected histologically [32]. It is defined as a reversible stage without clinical symptoms. It should be thought of, when the contralateral hip has a later stage AVN as both hips are affected in up to 90% in an unsynchronized fashion. In this case, MRI of both hips is warranted.

In the reversible early stage ARCO 1, X-rays are without pathological findings. Gold standard is the MRI, preferably T1-weighted spin-echo and T2-weighted fat-suppressed spin-echo (FSE) or short T1 inversion recovery (STIR) sequences [33]. On MRI, stage 1 is characterized by unspecific signal changes.

An important differential diagnosis in this early stage is bone marrow edema syndrome [34, 35]. By peculiar history taking, especially searching for etiologic factors of ON, a detailed clinical examination, and simply thinking of AVN as a differential diagnosis, the early stage ARCO 1 can be secured by MRI examination.

Early diagnosis is very important; as for stage ARCO 1, a high rate of healing has been reported after the simple surgical therapy of core drilling [36].

ARCO stage 2 is the irreversible early stage (ARCO 2) In this stage, AVN of the hip can be diagnosed by X-ray examination. Enhanced bone

Table 9.1 The ARCO classification of AVN of the hip [4]

Stage		Characteristics
0		Bone biopsy results consistent with AVN (Ficat 1985) without radiographic pathology
I		Positive scintiscan or MRI, or both; lesions subdivided into medial, central, or lateral depending on the location of involvement of femoral head; no radiographic pathology
	I-A	<15% involvement of the femoral head
	I-B	15–30% involvement of the femoral head
	I-C	>30% involvement of the femoral head
II		Radiographic abnormalities (mottled appearance of the femoral head, osteosclerosis, cyst formation, and osteopenia); no signs of collapse of the femoral head on radiographs or computed tomography (CT) scan; positive scintiscan and MRI; no changes in acetabulum; lesions subdivided into medial, central, or lateral depending on the location of involvement of femoral head
	II-A	<15% involvement of the femoral head
	II-B	15–30% involvement of the femoral head
	II-C	>30% involvement of the femoral head
III		Crescent sign; lesions subdivided into medial, central, or lateral depending on the location of involvement of femoral head
	III-A	<15% crescent sign or <2 mm depression of femoral head
	III-B	15–30% crescent sign or 2–4 mm depression of femoral head
	III-C	>30% crescent sign or 4 mm depression of femoral head
IV		Articular surface flattened radiographically and joint space shows narrowing; changes in acetabulum with evidence of osteosclerosis, cyst formation, and marginal osteophytes

apposition on necrotic trabeculae makes the necrotic area less radiolucent. On MRI, the necrotic area is now delineated, and the "double-line sign" in T2-weighted sequences is pathognomonic [37]. The outer line of low signal intensity represents reactive bone while the inner line of higher signal intensity represents the vascularized zone of reparation.

Stage ARCO 3 is characterized by advancing resorption of dead bone trabeculae with mechanic weakening, subchondral fracture, and depression of the femoral head. The narrow radiolucent subchondral line on X-ray is pathognomonic for stage 3, and is termed "crescent sign" [37]. In case of uncertainty about the subchondral fracture, CT is recommended [38]. An important differential diagnosis in stage ARCO 3 is subchondral insufficiency fracture (SIF) in elderly osteoporotic and renal transplant patients [39]. The low-signal-intensity band in the T1-weighted coronary MR sequence is distinctive here [40].

The late stage ARCO 4 denominates secondary arthritis of the hip.

The stages ARCO 1–3 are subclassified by medial, central, or lateral localization of the necrotic lesion also addressing its size (Table 9.1).

The Japanese Investigation Committee (JIC) of ON proposed criteria for the diagnosis, classification, and staging of ON in 2001, by the working group of the Specific Disease Investigation Committee under the auspices of the Japanese Ministry of Health, Labor and Welfare [41].

9.8 Diagnosis: JIC criteria

The following five criteria were selected for the diagnosis of ON, since they all showed high specificity:

1. Collapse of the femoral head (including crescent sign) without joint space narrowing or acetabular abnormality on X-ray images
2. Demarcating sclerosis in the femoral head without joint space narrowing or acetabular abnormality
3. "Cold in hot" on bone scans
4. Low-intensity band on T1-weighted MRI (bandlike pattern)
5. Trabecular and bone marrow necrosis on histology

ON can be diagnosed if the patient fulfills two of these five criteria and does not have bone tumors, SIF, or dysplasia.

9.9 Differential Diagnosis

9.9.1 Subchondral Insufficiency Fracture

The entity of SIF has been described in both the osteoporotic elderly and renal transplant recipients [39, 42]. At the onset of pain, plain radiographs show no obvious findings but MRI reveals a bone marrow edema pattern with an associated irregular serpiginous low-signal-intensity line on the T1-weighted images. This irregular low-intensity line is one of the characteristic appearances in SIF [43]. Based on histological re-examination, the prevalence of SIF in cases with a preoperative diagnosis of osteoarthritis was 6.3% (460 out of 7349), and with ON was 11.1% (41 out of 369) [44].

9.10 The JIC 2001 Classification

The classification scheme consists of four types, based on their location on T1-weighted images or X-ray images.

1. Type A lesions occupy the medial one-third or less of the weight-bearing portion.
2. Type B lesions occupy the medial two-thirds or less of the weight-bearing portion.
3. Type C1 lesions occupy more than the medial two-thirds of the weight-bearing portion but do not extend laterally to the acetabular edge.
4. Type C2 lesions occupy more than the medial two-thirds of the weight-bearing portion and extend laterally to the acetabular edge. Staging is based on anteroposterior and lateral views of the femoral head on X-ray images.

Based on this classification, the collapse rate on each type has been reported (Fig. 9.2) [45].

9.11 Therapy

Core drilling (core decompression) is indicated for AVN patients with the reversible stage ARCO 1. This procedure leads to relief of intraosseous pressure and improvement of microcirculation. Neovascularization occurs in the necrotic lesion by penetrating the boundary of necrotic lesion. Wirtz et al. reported that a restitutio ad integrum can be achieved by core decompression of the femoral head in cases with transient bone marrow edema [36]. In stages ARCO 1 and 2, cases with less than 30% of necrotic lesion within the femoral head have the best prognosis.

Stem cell therapy is discussed in Chaps. 11 and 12 of this book.

Iloprost A long-term follow-up study showed that intravenous iloprost could relieve pain and reduce the necrotic lesion or bone marrow edema. However, there was no convincing evidence of prognostic improvement for AVN [46].

Bisphosphonates A prospective randomized multicenter study demonstrated that zoledronate had no protective effect on the onset of ON or the decrease of cases with surgical indication [47].

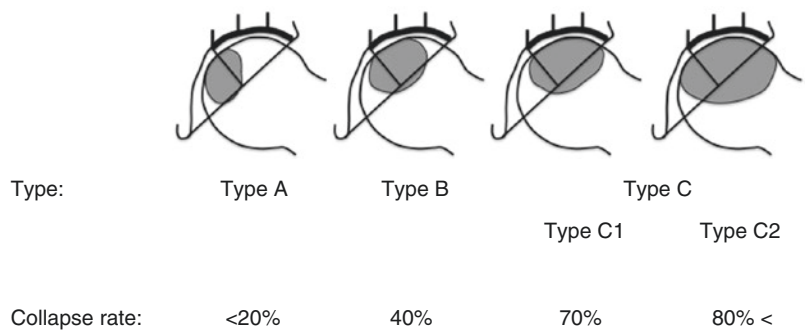


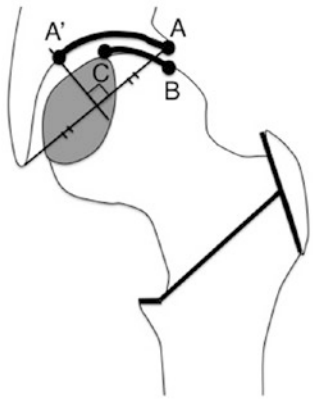
Fig. 9.2 Necrotic area location [45]

Intertrochanteric Osteotomy Previous reports have described various survival rates of intertrochanteric osteotomy. Flexion osteotomy is the most commonly used intertrochanteric osteotomy technique. We previously evaluated 70 hips treated with intertrochanteric flexion osteotomy, reporting that a 5-year survival rate was 90%, and after 10 years it was 81% [48]. A better survival rate was obtained in cases in stage ARCO 2 and with a necrotic angle of less than 200°. Reck et al. examined lower benefit of flexion osteotomy because of its poor prognosis [49]. They reported a 10-year survival rate of only 42.5%. It should be taken into account that the subsequent hip replacement is considerably difficult after osteotomy. Another report showed superior results at 10-year follow-up of cementless short-stem arthroplasty as an alternative treatment of intertrochanteric osteotomy [50].

In Japan, two operative procedures to preserve the original hip joint have been performed. One is intertrochanteric curved varus osteotomy of the femur, and the other is rotational osteotomy of the femoral head [51]. Both operations are performed in patients with a postoperative intact area of 34% or higher (Fig. 9.3) [52] according to the position and size of the intact area (Fig. 9.4).

Transtrochanteric Rotational Osteotomy The areas of necrosis can be accurately identified by using anteroposterior radiographs of the hip joint and Lauenstein radiographs (flexion, 90°; abduction, 45°). Osteotomy is performed in patients with a postoperative intact area ratio to the acetabular weight-bearing area of 34% or higher (Fig. 9.4). If the necrotic area is anteriorly located or is located in the middle or back of the head, an anterior rotational osteotomy, wherein the intact area remaining in the posterior portion is moved to the weight-bearing area, and a posterior rotational osteotomy, wherein the intact area remaining in the anterior portion is moved to the weight-bearing area, are performed, respectively. The femoral head can be rotated up to 90° anteriorly and up to 140° posteriorly. Several good clinical results have been reported [51–54].

Transtrochanteric Curved Varus Osteotomy This procedure is indicated in cases with a residual intact area in the lateral part of the femoral head with an intact area ratio to the acetabular weight-bearing area of 34% or more in a maximum abduction position. Good clinical results [55, 56] as well as leg-length discrepancies after this procedure have been reported [57].



$$\text{Postoperative intact ratio (\%)} = \frac{B - C}{A - A'} \times 100$$

Fig. 9.3 Postoperative intact ratio. This is a calculation of the postoperative intact ratio. It is essential that the postoperative intact ratio be 34% or higher [52]

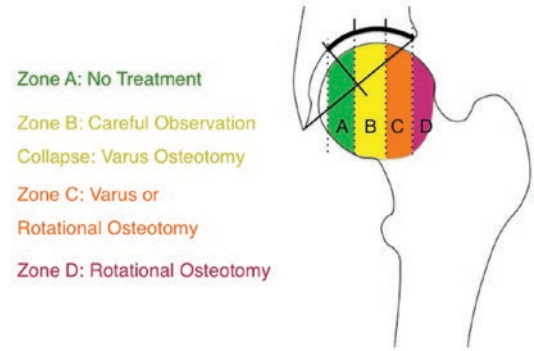


Fig. 9.4 Indication for femoral osteotomy. In principle, a curved varus osteotomy is performed in patients with an intact area ratio to the weight-bearing area of around 34% in a maximum abduction position, and an anterior rotation osteotomy or posterior rotation osteotomy is performed in patients other than those mentioned

Nonvascularized Bone Transplantation Rijnen et al. have suggested that this straightforward procedure does not impair subsequent total hip replacement [58]. A bone cylinder is obtained by a hollow drill from the lateral side of proximal femoral cortex to the necrotic lesion within the femoral neck. First, the necrotic lesion is completely removed, and is finally filled with impacted autograft bone chips. Rijnen et al. prospectively evaluated 28 hips in 27 patients in stages ARCO 2–4 at a mean follow-up of 42 months, reporting that subsequent hip replacement was performed in 8 hips. Of the remaining 20 hips, 90% of cases were clinically successful and 70% were radiologically successful. Patients aged less than 30 years had a better radiological outcome, while patients with subchondral collapse and a history of corticosteroid use had a poor prognosis. Seyler et al. reported that 18 of 22 hips in stage ARCO 2 survived at a mean follow-up of 36 months [59]. Mont et al. reported the contribution of bone substitute material (a combination of demineralized bone matrix, processed allograft bone chips, and a thermoplastic carrier) with bone morphogenetic protein through a window at the femoral head-neck junction [60]. Eighteen of 21 hips with a mean follow-up of 48 months were clinically successful at latest follow-up.

Vascularized Fibula Transplantation Previous studies showed good results of the vascularized grafting of fibular or iliac crest bone in the stage ARCO 2 or 3. A minimum 10-year follow-up study reported that the Harris hip score improved after vascularized fibular grafting, whereas only 10.5% of cases failed treatment and underwent conversion to total hip replacement [61]. In this study, postoperative subtrochanteric fracture was reported in two hips. Advanced surgical skill is required to insert grafting at the central position. In practice, revision surgery after vascularized fibular grafting is more difficult. The risk of fracture and the difficulty of revision surgery are similar to those of trabecular metal from the tantalum implant (Trabecular metal ON intervention implant, Zimmer Biomet, Warsaw/In, USA) [62]. Flörkemeier et al. reported that the survival rate with tantalum implant insertion was not superior to that of core decompression alone [63].

Short-Stem Hip Arthroplasty Short-stem hip arthroplasty is suitable for a sustainable long-term treatment strategy in young AVN patients, because it preserves the femoral neck. Short-stem hip arthroplasty is recommended to AVN patients due to encouraging midterm results [50]. In these cases, it seems to be important to evaluate the involvement of femoral head and neck on MRI. The increase of osteoblast formation and the alteration of trabecular bone properties in histopathology need to be taken into account even though these findings do not directly indicate ON [64].

Total Hip Arthroplasty In previous reports, complications and loosening after total hip replacement in AVN were variously described [65]. AVN associated with steroid, renal osteopathy, or sickle cell anemia has been reported to cause a higher rate of stem loosening after total hip replacement. Patients with immunosuppression have a higher rate of infection after total hip replacement. Regardless of etiology, 158 hips in 141 AVN patients had a mean Harris hip score of 84 at a mean follow-up of 103 months, and revision surgery was needed in 8.9% of these cases [66]. Recently, Kim et al. investigated 64 hips in 55 patients with a minimum 15 years of follow-up, reporting that the survivorship with an end point of revision of cementless modular stem was 93.8% at 16.8 years [67]. The good midterm results for ceramic-on-ceramic bearings were also prospectively reported in advanced AVN [68]. In addition, a previous study reported favorable midterm results of cementless short stems with ceramic-on-ceramic bearings [69].

Final Considerations of the Different Methods In our opinion, collateral damage of the selected technique has to be taken into account as the common end point will be total hip arthroplasty. The technique of free vascularized fibular grafting described by Urbaniak et al. requires drilling of a 2 cm wide channel from the lateral proximal femur through the femoral neck [70]. This involves the risk of subtrochanteric fracture [61].

Additionally, this makes a subsequent short-stem implantation impossible. Standard total hip arthroplasty can be even more difficult.

Flexion osteotomy can complicate or make subsequent hip arthroplasty very difficult.

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