Epidemiology of Osteonecrosis in the USA

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5.1 Introduction

Osteonecrosis (ON) is an uncommon disease. It is therefore important to know the populations at high risk for ON and the anatomic sites most frequently involved in order to improve diagnostic acumen. Knowledge of the risk factors and etiology of ON lends insight into management and potentially prevention. Furthermore, the differences in the distribution of ON internationally may help highlight important topics for research and identify key areas of intervention to prevent the occurrence of disease.

5.2 Types of Osteonecrosis

5.2.1 Traumatic Osteonecrosis

The fractures most commonly associated with the subsequent development of ON are fractures of the femoral neck, scaphoid, and talus. The blood supply to these bones is unique in that one end portion of the bone is highly dependent upon vascular flow through a single, more central portion of the bone, and a fracture may disrupt this flow.

A major complication of femoral neck fractures is development of ON. This leads to revision surgery or hip arthroplasty. The major determinants of whether or not ON occurs are fracture displacement and, to a lesser degree, age, excessive valgus reduction, and timing of reduction of dislocation. The incidence of ON has been reported to be 50 % higher for displaced versus undisplaced fractures [1, 2]. In a series of 73 femoral neck fractures in patients between the ages of 15 and 50 years treated at a single institution, Haidukewych et al. found an overall frequency of osteonecrosis of 23 % [3] over a mean follow-up period of 6.6 years. Osteonecrosis developed in 27 % of displaced fractures and 14 % of nondisplaced fractures. Initial fracture displacement and the quality of reduction were found to affect results. In younger patients (ages 15–50 years) with femoral neck fractures, the overall incidence of osteonecrosis is reported to be 20–36 % over a mean follow-up period of 3–7 years [4, 5]. In older patients (65 years or older) with displaced femoral neck fractures, osteonecrosis is reported to be 15–33 % [6]. When evaluating healed fractures only, the reported incidence of ON is 12 % in displaced fractures versus 7 % in undisplaced fractures over a mean follow-up of greater than 2 years [1, 7]. Excessive valgus reduction has been associated with ON [8]. Bunata [9] found that excessive valgus reduction was associated with four times increased incidence of ON (42 %) as compared to those without excessive valgus.

The incidence of necrosis with nonunions has been reported to be four times greater than for united femoral neck fractures [10], while the incidence of ON was found to be about doubled for delayed unions [8]. Incidence of ON with nonunions is reported to be 60 % [11].

The incidence of anterior dislocation is far below that of the posterior variety, and there is a similar contrast in the incidence of associated necrosis. The reported incidence of osteonecrosis with anterior dislocations has been 3–9 %, whereas that for posterior dislocation has been 13–26 % over a mean follow-up period of 5 years [12]. Certain fracture-dislocation patterns increase the likelihood of osteonecrosis. Epstein [12] reported 11 % necrosis with type 1 dislocations (with, or without, minor fracture) as opposed to 42 % with type 4 injuries (with acetabular rim or floor fractures).

The relationship between the timing of reduction and the incidence of osteonecrosis has been very well documented [13, 14]. Stewart et al. [14] found ON in 14 (15.5 %) out of the 90 patients treated by closed reduction and in 11 (40 %)

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out of 28 patients in those treated surgically. The interval between the time of injury and close reduction averaged to 3 days, whereas that between injury and surgery averaged to 21 days. In a prospective study by McKee et al. [13] on 25 patients with irreducible dislocations of hip, ON was found to be associated with delay in reduction. Brav [15] reported 18 % ON for hips reduced within 12 h when compared to 57 % for hips subjected to greater delay.

The scaphoid is second only bone to the femoral head in its overall incidence of posttraumatic osteonecrosis [16–18]. Osteonecrosis is thought to occur in 13–40 % of all scaphoid fractures. The reported incidence varies according to the fracture location and amount of displacement. Fractures of the proximal third have the highest incidence of ON (14–100 % in different series) than the fractures of the middle third (30–50 % cases). Osteonecrosis develops in nearly all fractures of the proximal pole that involve the proximal one-fifth of the bone. Fracture displacement more than 1 mm has been associated with ON which occur in up to 50 % of such cases [16–18].

Osteonecrosis of the talus is a complication of talar neck fractures [19]. Nondisplaced talar neck fractures have an approximately 10 % chance of developing osteonecrosis, whereas displaced fractures have an associated disruption of the subtalar articulation, carrying an approximate 40 % risk of osteonecrosis. Displaced fractures with incongruity of both the ankle and subtalar joints have an approximate 90 % incidence of osteonecrosis [20]. Canale and Kelly [21] further reported that extrusion of the talar body and subluxation of the talonavicular joint virtually guarantees osteonecrosis.

5.2.2 Nontraumatic Osteonecrosis

The epidemiology of nontraumatic ON is completely different than traumatic ON. As the etiology is unrelated to a precipitating traumatic fracture, the affected populations, risk factors, and demographic distribution are all different.

5.3 Epidemiology of Nontraumatic Osteonecrosis in the USA

The risk factors associated with ON are slightly different comparing Asian to North American and Western European populations. In several studies, the proportion of patients with ethanol-related disease is higher in Asian populations [22, 23].

5.3.1 Incidence

The epidemiology of nontraumatic ON is variable according to the risk factors of the disease. It is difficult to describe the exact incidence of nontraumatic osteonecrosis in the USA because many early asymptomatic cases are not diagnosed or reported. However, there have been few studies that have attempted to study the occurrence of ON. Various described risk factors for osteonecrosis include corticosteroids, alcohol intake, systemic lupus erythematosus (SLE), organ transplantation, chemotherapy and/or radiation, human immunodeficiency virus (HIV) infection, hemoglobinopathies, pancreatitis, hyperuricemia or gout, and childhood history of slipped capital femoral epiphysis (SCFE). Other miscellaneous causes include decompression sickness, autoimmune diseases causing vasculitis, coagulopathy such as thrombophilia or disseminated intravascular coagulation, Gaucher's disease, hyperlipidemia, fat embolus syndrome, treatment of developmental hip dysplasia, and chronic liver disease. In one-fourth of the cases, no associated conditions or diseases can be found [24, 25].

5.3.2 Steroids and Osteonecrosis

Steroids have been known to be a risk factor for ON since 1957 [26]. The incidence of ON is thought to vary with the dose of steroids given; therefore, the prevalence varies from 10 to 60 % of patients in multiple large demographic studies [24, 27]. This variance is likely due to the different populations of patients commonly receiving large doses of steroids either sporadically or on a long-term basis [28, 29].

5.3.2.1 Steroid Immunosuppression for Solid Organ Transplantation

The reported incidence of ON after renal transplantation is 4–37 % [30–34]. The highest reported incidence was 37 % reported by Cruess et al. [30] who have since found a drastic reduction by changing from divided to single dose steroids. In a study carried by Martson et al. [35] on fifty-two patients (103 hips) who had undergone a solid organ transplant, survivorship analysis revealed that, at 1 year after the transplant, 89 % ± 7 % of the hips and 80 % ± 13 % of the patients were free of osteonecrosis of the femoral head. The prevalence of osteonecrosis 1 year after transplantation was 11 % or 20 %, respectively. Using an abbreviated screening MRI, Mulliken et al. [36] found a prevalence of ON of the femoral head of 7.6 %. This prevalence of 7.6 % agrees closely with that reported recently by Tervonen et al. [37], who discovered 6.0 % of asymptomatic renal transplants had ON using a similar abbreviated MRI. Both of these figures are lower than previous reports, possibly due to decreased steroid dosing or other factors. Kopecky et al. [38] studied MR findings in 104 patients up to 24 months after transplantation and found that MR lesions in seven hips (in five asymptomatic patients) regressed in size; in six hips, the MR images returned to normal. They suggested that some patients with MR evidence of ON of the hip have spontaneous improvement.

5.3.2.2 Steroid Treatment for Acute Lymphoblastic Leukemia

The incidence of ON related to allogeneic bone marrow transplant or acute lymphoblastic leukemia (ALL) varies from about 1–72 % [39–41] based on study design, primary diagnosis, symptomatic versus asymptomatic cases, and osteonecrosis definition used. Reports based on symptomatic cases [39–41] and those using radiographic evaluation typically report a lower incidence of osteonecrosis than those prospectively monitoring its development with contemporary MR techniques [40]. In the Childhood Cancer Survivor Study consisting of 9,261 patients and a random sample of 2,872 siblings, 52 (0.56 %) survivors of childhood cancer self-reported osteonecrosis developing in 78 joints; 60 % reported multiple joint involvement [39]. The reported incidence of symptomatic ON in ALL in a study by Mattano et al. [41] ranged from 1.8 % 5-year cumulative incidence to a 3-year life-table incidence of 9.3 %. Kawedia et al. [40] reported a cumulative incidence of osteonecrosis involvement in hips or knees in 72 % of prospectively monitored patients with ALL while on therapy, irrespective of symptoms. ON appears to involve the periarticular knee sites more commonly than the femoral head.

5.3.2.3 Steroid Immunosuppression After Bone Marrow Transplantation

Osteonecrosis is a potentially persistent and debilitating complication after allogeneic bone marrow transplantation (alloBMT) [42, 43]. The reported incidence of ON in alloBMT of any joint ranges from 3.9 to 44.2 % [44–46]. Recently, nearly 22 % of prospectively monitored pediatric patients, irrespective of clinical symptoms, were found to have MR-documented osteonecrosis of the hips or knees. Nearly 50 % of those with osteonecrosis had at least one third of the epiphysis involved [46]. The probable risk factors, such as acute or chronic graft versus host disease (GvHD) requiring steroids, increasing age, and a primary diagnosis of aplastic anemia or acute leukemia, have been documented in post-BMT settings in mixed populations [42].

5.3.2.4 Steroids in Other Medical Conditions

There is no definitive evidence to suggest that steroid inhalers used for chronic obstructive pulmonary disease, occasional Medrol Dosepak for rash or other inflammatory conditions, and locally administered steroids (e.g., steroid injections) cause osteonecrosis. However, oral intake of steroids above certain dose and duration is a risk factor for ON. Straightforward dose dependent association with steroid intake and ON has been demonstrated. Cumulative intravenous methylprednisolone, at doses of >2 g for >3 months, significantly increased the risk for ON [47]. More recently, a statistically significant association was described between ON incidence and the total dose of steroids during the first 2 months after renal transplantation [48].

5.3.3 Alcohol and Osteonecrosis

Ethanol abuse was described as a risk factor in osteonecrosis of the femoral head in 1922. In one study of 57 patients, the incidences of alcohol-associated osteonecrosis of the femoral head and of idiopathic osteonecrosis were 29 and 12 %, respectively [49]. Orlic et al. [50] studied risk factors in a total of 172 patients for the development and progression of osteonecrosis after alcohol use and idiopathic osteonecrosis. They found that patients with alcohol-induced osteonecrosis were significantly older than patients with idiopathic osteonecrosis (average age, 49 years versus 40 years), were men (97 %), and presented with collapsed femoral heads (90 %). In another study group, 164 patients with alcohol-induced osteonecrosis were analyzed for different factors [51]. The average duration of alcohol abuse was 9.5 years, 28 % of patients were younger than 40 years of age, and 76 % were younger than 50 years. Bilateral necrosis of femoral heads was present in 45 % of patients, and within 3 years of the diagnosis, multifocal osteonecrosis became evident in 23 cases at distant sites (shoulders and knees). Elevated cholesterol and triglyceride levels were found in 38 % of cases. Serum amylase was elevated in 33 (20 %) patients, liver dysfunction was present in 50 (30 %), hepatomegaly was found in 32 (20 %), and biopsy-confirmed cirrhosis was present in 22 (13 %) cases.

5.3.4 Systemic Lupus Erythematosus and Osteonecrosis

The incidence of ON in systemic lupus erythematosus (SLE) has been reported to occur in 40 % of patients if silent cases are included. Approximately 15 % of patients develop symptomatic osteonecrosis [4, 52]. Weiner and Abeles [53] reported on 28 of 172 patients (16 %) with SLE who developed ON. Cozen and Wallace [54] reported on their experience over 47 years. ON was found in 26 of 488 (5 %) patients with SLE. In a review of the Hopkins Lupus Cohort, Petri [55] noted a prevalence of ON of 14.5 %. One possible explanation for the differences in these percentages may be the variability of severity of SLE, ranging from mild cases in a private practice setting to severe cases in tertiary referral centers. Glucocorticoid use is considered a risk factor for the occurrence of osteonecrosis in general, but particularly in patients with SLE [56]. Other factors may also be implicated in its development, as osteonecrosis has been described in SLE patients who have not received glucocorticoids [57]. Additional risk factors have been variably identified by

different investigators [54, 56, 58]; these include a Cushingoid body habitus, smoking, thrombophlebitis, vasculitis, Raynaud's phenomenon, arthritis, presence of certain autoantibodies (antiphospholipid, anti-Ro plus anti-RNP, or anti-topoisomerase I), or disease-related fibrinolytic abnormalities.

5.3.5 Human Immunodeficiency Virus Infection and Osteonecrosis

Recent retrospective case studies of human immunodeficiency virus (HIV)-infected patients have reported incidences ranging from 0.03 to 0.37 cases per 100 person-years [59, 60]. The true incidence of symptomatic osteonecrosis, however, has not been well defined. Morse et al. [61] found an incidence of ON in HIV to be 0.65 cases per 100 patient-years for asymptomatic patients and 0.26 cases per 100 patient-years for symptomatic patients. This is 100-fold higher than the estimated incidence in the general population [62, 63]. They also found a rapid progression of disease in symptomatic patients (59 %) needing THR [61]. In a study by Assouline-Dayan et al. [57], the prevalence of osteonecrosis in the initial cohort of 339 asymptomatic patients who were evaluated by MRI was found to be extraordinarily high at 5.6 %. In another study by Wallis et al. [64], osteonecrosis was identified by MRI in 2 (18 %) of 11 asymptomatic patients, highlighting the potential risks in this population and further emphasizing how corticosteroids must be used cautiously in HIV-infected patients.

5.3.6 Hematologic Conditions and Osteonecrosis

Osteonecrosis has been associated with several hemoglobinopathies (hemoglobin SS, hemoglobin SC, and sickle thalassemia) and coagulation disorders (thrombophilia and hypofibrinolysis). The reported prevalence of osteonecrosis in these populations has been 4–20 % [24, 65, 66]. At least one coagulation factor abnormality was found in 82 % of patients with osteonecrosis of the femoral head compared with 30 % of controls ($p < .0001$). Two or more abnormalities were identified in 21 patients (47 %) compared with 2.5 % of controls ($p < .0001$) [65]. Glueck et al. [66] found a high prevalence of plasminogen activator inhibitor-1 coagulation abnormalities in patients with osteonecrosis. In a study [67] on multifocal ON, rate of coagulation disorders was found to be similar to rates reported in the literature. Eighty percent to 90 % of patients tested with osteonecrosis had hypofibrinolysis and thrombophilia or both. Patients with single joint involvement are just as likely to have a coagulation disorder as are patients with more joint involvement [67].

5.3.7 Rare Disorders and Osteonecrosis

Additional rare disorders may be associated with ON. As these diseases occur infrequently, the exact incidence of ON among these populations is difficult to discern. Report indicates that ON may be seen with hyperlipidemia (9 %), liver disease (4 %), Gaucher's disease (2 %), and dysbarism (2 %) of all the ON cases [24].

5.4 Age Distribution

The age range of patients is reported from 15 to 83 years, with the vast majority under 50 years for overall nontraumatic osteonecrosis. For alcohol-associated ON, age at the time of diagnosis is reported from 19 to 67 years with 72 % less than 50 years of age [24, 49, 50]. For steroid-related ON, age at diagnosis of ON is reported from 15 to 63 years with 60 % below 50 years of age [24, 63, 68]. The mean age of patients with SLE first diagnosed with ON generally ranges from 25 to 35 years [56, 69]. In a study [24] on US population, pancreatitis-associated ON was found in age group 36–61 years with 82 % less than 50 years of age. For hyperuricemia-associated ON, age at the time of diagnosis of ON ranged from 19 to 81 years with 57 % less than 50 years of age. All patients with sickle cell ON were reported to be less than 50 years at the time of diagnosis [24]. Ages ranged from 31 to 62 years in ON associated with liver disease with the majority less than 50 years old. For hyperlipidemia, ages at the time of diagnosis of ON ranged from 32 to 67 years and 52 % were less than 50 years old. Sixty-seven percent of patients were under 50 years of age when ON was apparent for Gaucher's disease. For multifocal osteonecrosis, a mean age at presentation of 36 years (range, 15–75 years) has been reported [24, 67].

5.5 Gender Distribution

There has been male dominance with ratio of around 4:1 as compared to females for overall osteonecrosis [24, 57, 70]. In a study of 75 patients with steroid-associated ON, 31 % were found to be females [24]. In other series of 72 steroid-treated patients, Fisher and Bickel [68] observed a higher incidence of female involvement (44 %).

SLE-associated ON shows a female preponderance when compared with other risk factors [4, 58, 69, 71]. In the multicenter study on multifocal ON, there was a trend toward a greater proportion of women versus men in the systemic lupus erythematosus group (32 women, 6 men) as compared with the remaining study group (43 women, 20 men) ($p = 0.076$) [67]. This is similar to numbers of women in

other studies, which are weighted toward patients with systemic lupus erythematosus and other inflammatory disorder [58], but dissimilar to incidences reported in studies [51] where there is a preponderance of patients who use alcohol, in which more men are seen. Complete (100 %) male dominance was reported for pancreatitis- and sickle cell-associated ON [24]. For hyperuricemia, hyperlipidemia, and Gaucher's disease, 83 % male dominance has been reported [24]. In case of liver disease-associated ON, 60 % patients were found to be males [24].

5.6 Race Distribution

Overall, a white versus black predominance exceeding 3:1 has been reported [24, 70, 72]. The reported distribution among patients with steroid-associated ON was 84 % whites in contrast to 64 % blacks for pancreatitis-associated ON. Race distribution also showed 77, 60, 87, and 100 % white dominance for hyperuricemia, liver disease, hyperlipidemia, and Gaucher's disease, respectively [24].

5.7 Anatomical Location

5.7.1 Bilateral Osteonecrosis

Symptomatic osteonecrosis is often unilateral although when asymptomatic disease is considered, bilateral disease is common. The likelihood of bilateral disease, regardless of the presence of symptoms, has been studied in specific patient populations and in the femoral head, ranges from 34 to 80 % [24, 68, 72–74]. In an abbreviated MRI screening study of renal transplant patients' hips, lesions were bilateral 50 % of the time [36]. In other disease cohorts, symmetrical bilateral disease developed in 90 % (SLE), 36 % (pancreatitis and hyperuricemia), 13 % (sickle cell disease), 30 % (liver disease), 17 % (hyperlipidemia), and 17 % (Gaucher's disease) [24].

5.7.2 Multifocal Osteonecrosis

In contrast to bilateral involvement of a single joint, when a patient has diffuse, multifocal ON (i.e., three or more disease sites), the presence of bilateral disease is markedly increased. A multicenter study of multifocal ON revealed bilateral involvement in 98 % (femoral heads), 87 % (knees, distal femur, or proximal tibia), 83 % (proximal humerii), 61 % (distal tibia or talus), and 42 % (peri-elbow) [67]. The overall distribution of disease sites found in this multicenter study is shown in Table 5.1. Common risk factors for the presence of multifocal disease are a history of SLE (20 %) [58], ALL (74 %) [41], or bone marrow transplantation (44 %) [45]. When ON affects knee, shoulder, and ankle joints, multifocal disease should be suspected [75].

Table 5.1 Distribution of multifocal osteonecrotic lesions [67]

Anatomical location	Frequency (%)
Hip	200 (99)
Knee	179 (87)
Shoulder	146 (72)
Ankle	71 (35)
Elbow	17 (8)
Wrist	8 (4)
Calcaneus	6 (3)
Tarsal navicular	2 (1)
Cuneiform	1 (0.5)
Cuboid	1 (0.5)
Metacarpal head	1 (0.1)

5.8 Stage Distribution at Time of Presentation

In a study on multifocal osteonecrosis [67], plain radiography or MRI revealed that most (69 %) joints presented in a precollapse stage. Eighty-five of 200 (43 %) hips had collapse (59 hips) or osteoarthritis (26 hips). Only 17 % of 179 knees, 38 % of 146 shoulders, and 24 % of 71 ankles had collapse or arthritis. Approximately 30 % of the lesions were diagnosed solely by MRI. There was a higher incidence of these asymptomatic lesions in the knee (38 %), shoulder (30 %), and ankle (44 %) than in the hip (18 %). The incidence of negative radiographic findings but positive MRI scans was highest in the ankle (44 %) and knee (38 %) and lower in the shoulder (30 %) and hip (18 %).

5.9 Summary

In summarizing the epidemiology of osteonecrosis in the USA, it is evident that the prevalence and incidence vary according to the risk factor of disease and the population being studied. Traumatic osteonecrosis is associated with specific fractures, and the incidence depends upon many factors such as age, displacement, type of fracture, and method of treatment. Nontraumatic ONFH can be idiopathic but is usually associated with corticosteroid usage, ethanol abuse, systemic lupus erythematosus, barotrauma, or marrow packing disorders such as sickle cell disease and Gaucher's disease. The proportion of patients with steroid-related ONFH is increasing as solid organ and bone marrow transplantation are becoming more commonplace.

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