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Femoral head collapse rate among Japanese patients with pre-collapse osteonecrosis of the femoral head

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Abstract

Objective: In this study, we aimed to elucidate the relationship between the duration from diagnosis to femoral head collapse and the collapse rate among patients with pre-collapse osteonecrosis of the femoral head (ONFH).

Methods: In this retrospective, observational, multicenter study, we analyzed 268 patients diagnosed with ONFH and classified them using the Japanese Investigation Committee classification. The primary endpoint was duration from the time of diagnosis to femoral head collapse for each type of ONFH.

Results: The 12-, 24-, and 36-month collapse rates among participants were 0%, 0%, and 0% for type A, respectively; 0%, 2.0%, and 10.8% for type B, respectively; 25.5%, 40.8%, and 48.5% for type C-1, respectively; and 57.4%, 70.3%, and 76.7% for type C-2 ONFH, respectively. A comparison of unilateral and bilateral ONFH, using Kaplan–Meier survival curves demonstrated similar collapse rates.

Conclusions: The lowest collapse rate was observed for ONFH type A, followed by types B, C-1, and C-2. Additionally, a direct association was observed between the collapse rate and location of the osteonecrotic lesion on the weight-bearing surface.

Keywords

Osteonecrosis, femoral head collapse, Kaplan–Meier survival analysis, osteonecrotic lesion, observational study, Japan

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Introduction

Osteonecrosis of the femoral head (ONFH) is an intractable disease caused by ischemia. Although the mechanism underlying femoral head ischemia in non-traumatic ONFH remains unknown, corticosteroid use, systemic lupus erythematosus, alcoholism, and smoking are related risk factors.[1–3] In this disease, a part of the femoral head develops avascular and aseptic necrosis owing to decreased vascular flow. Collapse due to ONFH generally progresses to secondary osteoarthritis (OA). Total hip arthroplasty (THA) is considered the final treatment option, even in young patients.[1–6] To the best of our knowledge, no known treatment can prevent femoral head collapse or can substitute THA. Hence, a novel method that prevents femoral head collapse is needed.

Recently, the results of a clinical trial among patients with pre-collapse ONFH who received a single local administration of recombinant human fibroblast growth factor-2-impregnated gelatin hydrogel were reported.[7] The next phase of the clinical trial was started in Japan using an open design (TRION, "Clinical trial of idiopathic osteonecrosis of the femoral head to evaluate the effectiveness and safety of trafermin [genetic recombinant] gelatin hydrogel"). In this trial, as per Japanese Regulatory Authority requirements, the evaluation was performed per patient rather than per hip. In bilateral ONFH, if the collapse is confirmed in either hip, the participant is considered to have a collapse. To appropriately assess this trial's efficacy, evaluating the natural course of ONFH prior to collapse using the aforementioned per-patient method is essential.

Some reports have attempted to evaluate the collapse rate of ONFH.[5,8–16] Although the follow-up duration was long in those reports, the data were relatively dated, and the time until femoral head collapse was unclear. In addition, these reports evaluated each hip in patients with bilateral ONFH, and the collapse rate could not be evaluated for each patient. Therefore, in this retrospective observational study, we aimed to elucidate the relationship between the duration from diagnosis to femoral head collapse and the collapse rate in patients with pre-collapse ONFH.

Methods

Study design and participants

We conducted a retrospective, observational, multicenter study using data collected between February 2017 and May 2018 at different university hospitals in Japan: Gifu University, The University of Tokyo, Kyoto University, Osaka University, Hokkaido University, Yamagata University, Yokohama City University, Kanazawa Medical University, Okayama University, and Kagoshima University. This study was approved by the ethics committees of Gifu University Graduate School of Medicine; the University of Tokyo Graduate School of Medicine; Kyoto University Graduate School and Faculty of Medicine; Osaka University Hospital; Hokkaido University Hospital; Yamagata University Faculty of Medicine; Yokohama City University Hospital; Kanazawa Medical University; Okayama University Hospital/Graduate School of Medicine, Dentistry and Pharmaceutical Sciences; and Kagoshima University Hospital (approval dates: December 7, 2016; May 12, 2017; February 28, 2017; December 28, 2016; February 3, 2017; January 5, 2017; June 1, 2017; January 31, 2017; January 27, 2017; and March 29, 2017, respectively). The study was conducted in accordance with the STROBE guidelines.[17]

The objective of this study was to elucidate the relationship between the duration from diagnosis of ONFH to femoral head collapse and the rate of collapse in patients with pre-collapse ONFH. In addition, the results of this study were to be used as an external control for the TRION clinical trials by administering a trafermin (genetic recombinant)-containing cross-linked gelatin product.

Study participants had been diagnosed with ONFH after 2002, according to the 2001 Japanese Investigation Committee (JIC) guidelines, as per the Ministry of Health and Welfare Classification System.[18,19] Staging of ONFH and localization of necrotic lesions were determined based on the JIC classification; this classification comprises four types of ONFH: A, B, C1, and C2. The classification is based on the central coronal section of the femoral head on T1-weighted magnetic resonance imaging (MRI); staging is based on the anteroposterior and lateral views of the femoral head on radiological images. Stage 1 is defined as the absence of abnormal findings related to osteonecrosis on radiographs but the presence of specific findings on MRI, bone scintigraphy, or histology. Stage 2 is defined as the observation of demarcating sclerosis without femoral head collapse. Stage 3 (defined as the presence of femoral head collapse, including the crescent sign, without joint space narrowing) is sub-classified into two stages: stage 3A (extent of femoral head collapse <3 mm) and stage 3B (extent of femoral head collapse ≥ 3 mm).

Stage 4 is defined as the presence of secondary OA-related changes following femoral head collapse. The extent of osteonecrotic lesions was classified into the aforementioned four types (i.e., types A, B, C1, and C2) based on the size and

location of the lesions on T1-weighted MRI or radiography.[18,19] In this study, ONFH was classified as stage 1 or 2 and assessed using a T1-weighted 1.5 Tesla MRI or more to determine its extent, classified as one of the four types (A, B, C-1, and C-2). Patients for whom the precise timing of femoral head collapse diagnosis was unavailable and those who had undergone surgery for pre-collapse ONFH were excluded from the study. All participant data were treated with confidentiality. This study was conducted in accordance with the Declaration of Helsinki.

Study procedure

Using patient medical records at each research facility, we selected 271 consecutive participants who had been diagnosed with ONFH $\geq$24 months before the date of approval by the ethics committee of each facility. We extracted information from the medical records at the time of diagnosis and during the observation period. We collected radiographs and MRI images acquired at the time of diagnosis. The need for informed consent was waived considering the retrospective and observational nature of the study. An opt-out approach was used, with the disclosure provided on the website of each hospital. All patients provided verbal consent to receive treatment for ONFH.

Endpoints

The primary endpoint was the duration from the time of diagnosis to femoral head collapse for each type of ONFH. In bilateral ONFH, if collapse was confirmed in either femoral head, the patient was considered to have collapse. Collapse was defined as progression from JIC stage 1 or 2 to stage 3 or 4. The main secondary endpoints were the duration from diagnosis to femoral head collapse for each type and stage of ONFH in patients with unilateral or bilateral ONFH.

Statistical methods

The total number of participants registered in this study was defined as the full analysis set (FAS). However, participants in the electronic data capture deemed ineligible after data fixing were excluded from the study.

The target number of participants was determined based on feasibility. Approximately 30 patients were diagnosed with ONFH at Gifu University and had not yet shown collapse by 2002. Because we planned to collect data for this study from 10 university hospitals, we estimated that at least 200 participants should be included. Moreover, we conducted exact one-to-one matching wherein participants with type C-1 or C-2 status in the FAS were matched to each participant in the TRION clinical trial. If the proportion of patients with type C-1 or C-2 status was 80% and the proportion of participants selected in this study for matching was 50%, 200 participants would be sufficient to be matched with 64 participants in the TRION clinical trial.

To confirm our estimate of the proportion of matched participants, we conducted an interim analysis when the number of enrolled patients reached approximately 112, which was twice the statistically estimated sample size (n=56) in the TRION trial. If the proportion of participants matched with the 64 participants in the TRION trial was more than 30% in the interim analysis, we continued enrollment until the target number of participants was reached. Otherwise, we reviewed the target number.

We estimated survival curves for each endpoint using the Kaplan–Meier method. In addition, using these curves, we calculated the incidence of femoral head collapse at 12, 24, and 36 months after diagnosis for

each endpoint and their two-sided 95% confidence interval.

Results

In the interim analysis, 29.3% (36 of 123) of the cases were matched. Based on these results, we continued enrollment without changing the target number. We registered 271 patients, of which 3 were excluded because they were deemed ineligible after data fixing. Finally, 268 patients were included in the FAS.

Demographics

Seventy-six participants had bilateral ONFH and 192 had unilateral ONFH. In total, 194 patients (72.4%) had steroid use; 48 (17.9%) had alcohol consumption; 4 (1.5%) had both steroid use and alcohol consumption; and 22 (8.2%) had idiopathic disease (Table 1).

Collapse rate

In total, we analyzed 268 patients with pre-collapse ONFH. The Kaplan–Meier curves of collapse rates for each type of ONFH are shown in Figure 1. The 12-, 24-, and 36-month collapse rates were 0%, 0%, and 0%, respectively, for type A; 0%, 2.0%, and 10.8%, respectively, for type B; 25.5%, 40.8%, and 48.5%, respectively, for type C-1; and 57.4%, 70.3%, and 76.7%, respectively, for type C-2 (Table 2). The collapse rates at 12, 24, and 36 months were highest for patients with type C-2 ONFH.

In this study, the central image confirmation committee conducted a blind review of the staging and type of ONFH in patients, based on the X-ray and MRI images at the time of diagnosis. For some patients, the diagnosis at each research facility was different from that established by this committee. The collapse rate for each type judged through the central image confirmation

Table 1. Patient demographics.

Parameter	ONFH type A N (%)	ONFH type B N (%)	ONFH type C-1 N (%)	ONFH type C-2 N (%)
Total	19 (100.0%)	50 (100.0%)	98 (100.0%)	101 (100.0%)
Sex				
Female	9 (47.4%)	26 (52.0%)	53 (54.1%)	47 (46.5%)
Male	10 (52.6%)	24 (48.0%)	45 (45.9%)	54 (53.5%)
Age, years				
Mean age (SD)	46.8 (13.0)	45.3 (13.9)	43.2 (14.8)	43.0 (14.5)
Hip joint				
Unilateral	16 (84.2%)	40 (80.0%)	73 (74.5%)	63 (62.4%)
Bilateral	3 (15.8%)	10 (20.0%)	25 (25.5%)	38 (37.6%)
Background factors				
Steroids	10 (52.6%)	33 (66.0%)	75 (76.5%)	76 (75.2%)
Alcohol	8 (42.1%)	8 (16.0%)	15 (15.3%)	17 (16.8%)
Idiopathic	1 (5.3%)	9 (18.0%)	5 (5.1%)	7 (6.9%)
Steroids + alcohol	0 (0.0%)	0 (0.0%)	3 (3.1%)	1 (1.0%)
Stage at initial diagnosis				
Stage 1	15 (78.9%)	28 (56.0%)	39 (39.8%)	38 (37.6%)
Stage 2	4 (21.1%)	22 (44.0%)	59 (60.2%)	63 (62.4%)

SD, standard deviation; OHFH, osteonecrosis of the femoral head.

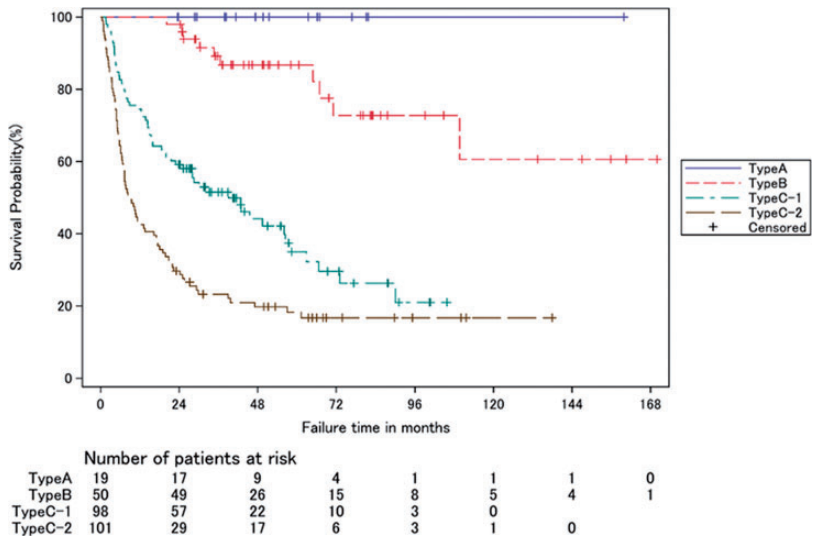

Figure 1. Kaplan–Meier curves from diagnosis to collapse for each type of osteonecrosis of the femoral head.

Table 2. Collapse rate at the initial diagnosis for each type of ONFH.

		Collapse rate (95% confidence interval)		
ONFH type	N	12 months	24 months	36 months
Type A	19	0.0%	0.0%	0.0%
Type B	50	0.0%	2.0% (0.3–13.4)	10.8% (4.6–24.1)
Type C-1	98	25.5% (18.0–35.4)	40.8% (31.8–51.2)	48.5% (38.8–59.1)
Type C-2	101	57.4% (48.1–67.2)	70.3% (61.3–78.9)	76.7% (68.0–84.5)

ONFH, osteonecrosis of the femoral head.

committee is shown in Table 3. There were no notable differences between the collapse rates for each type diagnosed at the different research facilities and those judged by the central image confirmation committee.

The Kaplan–Meier curves for the duration from diagnosis of unilateral or bilateral ONFH of each type and stage until femoral head collapse are shown in Figure 2. These curves demonstrate similar collapse rates for patients with unilateral or bilateral ONFH.

The 12-, 24-, and 36-month collapse rates of unilateral or bilateral ONFH for each type are shown in Table 4. For both unilateral and bilateral ONFH, the collapse rates were highest in patients with type C-2 ONFH, followed by those with type C-1 and type B.

Discussion

In this study, we evaluated the collapse rate per patient in different types of ONFH and found this rate increased in the following order: type A<B<C-1<C-2 (Figure 1 and Table 2). Similarly, we evaluated the collapse rate per hip joint. The rates for

Table 3. Collapse rate for each type of osteonecrosis of the femoral head based on initial diagnosis by the central image confirmation committee

		Collapse rate (95% confidence interval)		
ONFH type	N	12 months	24 months	36 months
Type A	16	0.0% (0.0–0.0)	0.0% (0.0–0.0)	6.3% (0.9–36.8)
Type B	33	0.0% (0.0–0.0)	3.0% (0.4–19.6)	6.3% (1.6–22.8)
Type C-1	104	19.2% (12.9–28.2)	33.7% (25.5–43.6)	42.1% (33.0–52.6)
Type C-2	115	54.8% (46.0–64.0)	66.1% (57.4–74.6)	72.9% (64.4–80.8)

ONFH, osteonecrosis of the femoral head.

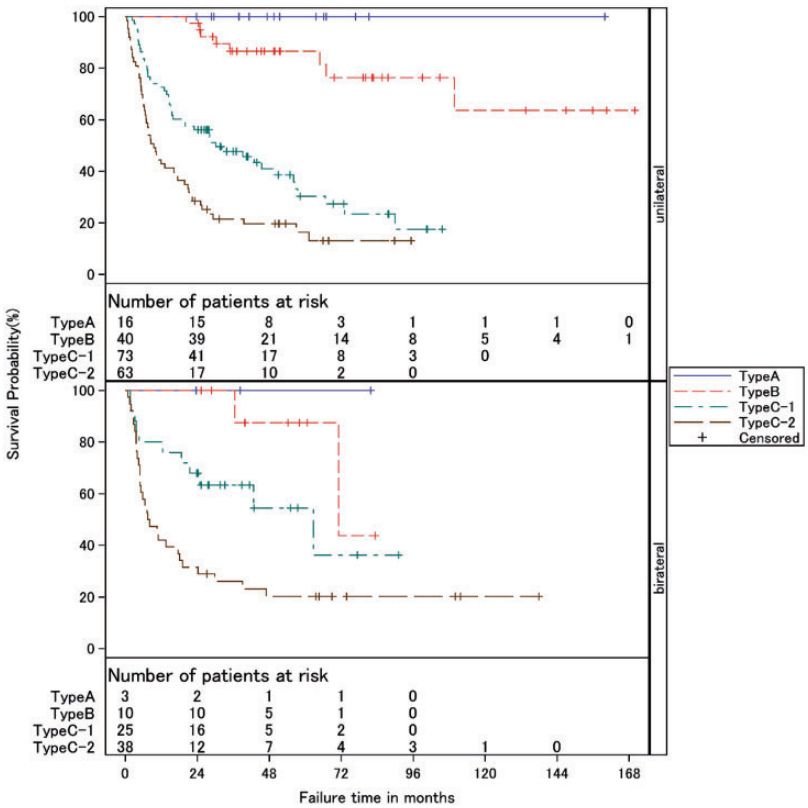

Figure 2. Kaplan–Meier curves from diagnosis to collapse for each type of osteonecrosis of the femoral head.

ONFH types A, B, C-1, and C-2 were 3.7% (1/27), 15.9% (7/44), 46.0% (58/126), and 73.6% (92/125), respectively. Consistent with previous studies,[5,8–16] we observed a direct association between the collapse rate and location of the osteonecrotic lesion on the weight-bearing surface.

Among previous studies, the study on Japanese patients with ONFH published by Kuroda et al. in 2019[16] was similar to

Table 4. Collapse rate of unilateral or bilateral ONFH for each type.

Affected hip joint			Collapse rate (%)		
	ONFH type	N	12 months	24 months	36 months
Unilateral	A	16	0.0% (0.0–0.0)	0.0% (0.0–0.0)	0.0% (0.0–0.0)
	B	40	0.0% (0.0–0.0)	2.5% (0.4–16.5)	13.5% (5.8–29.4)
	C-1	73	27.4% (18.6–39.2)	43.8% (33.4–55.9)	52.2% (41.0–64.4)
	C-2	63	57.1% (45.4–69.5)	71.4% (60.0–81.9)	78.4% (67.4–87.7)
Bilateral	A	3	0.0%	0.0%	0.0%
	B	10	0.0%	0.0%	0.0%
	C-1	25	20.0% (8.9–41.6)	32.0% (17.5–53.9)	36.5% (20.9–58.6)
	C-2	38	57.9% (43.0–73.6)	68.4% (53.6–82.3)	73.9% (59.4–86.6)

ONFH, osteonecrosis of the femoral head.

Table 5. Collapse rates at initial diagnosis of ONFH, based on background factors.

			Collapse rate (%)		
	ONFH type	N	12 months	24 months	36 months
Alcohol	A	8	0.0%	0.0%	0.0%
	B	8	0.0%	0.0%	0.0%
	C-1	15	26.7% (10.9–56.4)	40.0% (20.3–68.2)	47.5% (26.0–74.8)
	C-2	17	58.8% (37.4–81.4)	64.7% (43.0–85.5)	64.7% (43.0–85.5)
Steroids	A	10	0.0%	0.0%	0.0%
	B	33	0.0%	3.0% (0.4–19.6)	16.4% (7.1–35.0)
	C-1	75	25.3% (17.0–36.8)	41.3% (31.2–53.3)	49.4% (38.5–61.5)
	C-2	76	56.6% (45.8–67.8)	71.1% (60.7–80.7)	78.4% (68.4–87.0)

ONFH, osteonecrosis of the femoral head.

our study in terms of the number of patients, inclusion of Japanese patients, and evaluation of the relationship between the duration from diagnosis to femoral head collapse and the collapse rate. However, there were some differences between these studies: our study included a higher number of university hospitals (10 vs. 3); additionally, the main analysis of collapse in our study was performed per patient rather than per hip. In our study, the central image confirmation committee conducted a blind review of the stage and type of ONFH in the included patients on the basis of radiographs and MRI images acquired at the time of diagnosis.

The collapse rates in patients with pre-collapse ONFH were compared based on differences in background factors, such as steroid and alcohol use (Table 5), and no significant differences were observed.

Our study has some limitations, given its retrospective observational design. First, selection bias cannot be excluded. However, on the day the ethics committee of each facility approved the study, we selected up to 50 consecutive participants with the latest diagnosis date from that facility. Similarly, participants were required to satisfy the inclusion criterion of $\geq$24 months having passed since diagnosis. Finally, the date of collapse was not

always accurate, depending on the frequency of medical examination. Therefore, we established the inclusion criterion that image evaluation be performed at least once a year after the diagnosis of ONFH to improve accuracy.

Conclusions

Our results suggested that the collapse rates per participant and hip joint were the highest for type C-2 ONFH, followed by type C-1 and type B ONFH. Similarly, our findings suggested a direct association between the collapse rate and location of the osteonecrotic lesion on the weight-bearing surface.

Availability of data and materials

The data used in this study are available from the author upon reasonable request.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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