Chapter 3
Descriptive and Analytic Epidemiology of Idiopathic Osteonecrosis of the Femoral Head in Japan

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Abstract Idiopathic osteonecrosis of the femoral head (ONFH) is a rare and multifactorial disease, which involves noninfectious and ischemic pathogenesis. ONFH has been designated as one of the targeted intractable diseases by the Ministry of Health, Labour and Welfare (MHLW) in Japan and its medical cost for treatment has been subsidized by public expenditure. Together with these policies, the epidemiology of ONFH in Japan has also been systematically elucidated by the Study Group on ONFH with academic support from the Study Group on Epidemiologic Research for Intractable Diseases (ERID), both of which are funded by the MHLW. This chapter summarizes the findings of descriptive and analytic epidemiology on ONFH which have been accumulated through collaborative efforts of the ONFH Study Group and the ERID Study Group. Methodologies in these epidemiologic studies include a nationwide epidemiologic survey and a hospital-based sentinel monitoring system to assess frequency and distribution of ONFH. Furthermore, case-control and cohort studies have been conducted to evaluate systemic steroid use and alcohol intake as two major risk factors for ONFH.

Keywords Osteonecrosis · Femoral head · Epidemiology · Steroid · Alcohol

3.1 Introduction

Idiopathic osteonecrosis of the femoral head (ONFH), also known as nontraumatic osteonecrosis or avascular osteonecrosis of the femoral head, is a rare and often progressive disease which typically involves noninfectious and ischemic pathogenesis. ONFH is considered to be a multifactorial disease and several potential mechanisms have been suggested including abnormal lipid or fat metabolism, nitric

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oxide-mediated apoptosis of osteoblasts and osteocytes, and thrombophilia or hypofibrinolysis [1–3]. The underlying etiology has not been fully elucidated, although some factors such as systemic steroid use and habitual alcohol consumption have been well known to be associated with ONFH development [1, 2]. Treatment options in the pre-collapse stage include osteotomy as a joint-preserving procedure, which is technically challenging because terminal blood flow in the femoral head is limited and biomechanical loads around the hip joint are complicated. Once collapse of the femoral head occurs, hip arthroplasty is needed and revision will be required in the future due to the survivorship of the artificial structures [3]. Eventually, bone destruction and loss of function in the hip joint substantially impair the patients' quality of life. In order to develop an appropriate strategy for disease prevention, treatment, and policy, it is fundamentally important to elucidate the epidemiology of ONFH in each country.

In Japan, the Ministry of Health and Welfare (later termed the Ministry of Health, Labour and Welfare [MHLW]) established a special program for "intractable diseases" in 1972. These are defined as rare diseases whose cause has not been determined and for which no specific medical treatment has been established. The program includes promoting research activities, eliminating patient co-payments for medical expenditures, and developing the necessary medical facilities. Under this program, the Study Group on Idiopathic Avascular Necrosis of the Femoral Head with support by a MHLW grant was launched in 1976. After 1982, this was re-named as "the Study Group on Idiopathic Osteonecrosis of the Femoral Head" (hereafter referred to as the ONFH Study Group). Later in 1992, ONFH was designated as one of the targeted intractable disease in Japan, and since then its medical costs have been subsidized by public expenditure [4].

Another study group funded by the MHLW, named "the Study Group on Epidemiologic Research for Intractable Diseases" (hereafter referred to as the ERID Study Group), was also launched in 1976 [5]. The ERID Study Group is comprised of epidemiologists and one of their missions is to provide academic support to other study groups on intractable diseases which are mainly comprised of clinicians. To date, the ONFH Study Group and the ERID Study Groups have cooperated with each other and a wide spectrum of epidemiologic studies has been employed. This chapter summarizes the main epidemiologic findings on ONFH in Japan from collaborative efforts of the two study groups, with the focus on two major risk factors for ONFH: systemic steroid use and habitual alcohol intake.

3.2 Descriptive Epidemiology (1): Nationwide Epidemiologic Survey

Since the mid-1990s, the prevalence of ONFH in Japan has been systematically clarified according to "a protocol for a nationwide epidemiologic survey on intractable diseases" as proposed by the ERID Study Group [6–9]. The procedure involves two stages: the first-stage survey, which estimates the number of patients visiting

hospitals, and the second-stage survey, which reveals their demographic and clinical features. Nationwide epidemiologic surveys on ONFH have been conducted in 1995 [4, 10], 2005 [11], and 2015 [12]. It is noteworthy that the ONFH Study Group conducted nationwide epidemiologic surveys every 10 years from 1995 to 2015. Furthermore, using the same protocol in each survey enabled us to evaluate secular trends during the past two decades.

The targets in each survey were selected from all orthopedic departments in all hospitals in Japan by stratified random sampling according to inpatient bed numbers and hospital characteristics. Sampling fractions for each strata were as follows: 5% for general hospitals with 99 or fewer beds; 10% for 100 to 199 beds; 20% for 200 to 299 beds; 40% for 300 to 399 beds; 80% for 400 to 499 beds; 100% for 500 or more beds, university hospitals irrespective of the number of beds, and special departments where ONFH patients were likely to visit. The first-stage surveys were performed in January in 1995, 2005, and 2015, respectively, and the target departments were asked whether or not patients with ONFH visited their departments during the preceding 1 year (i.e., 1994, 2004, and 2014, respectively). The diagnostic criteria for ONFH, which had been proposed by the ONFH Study Group [13], was used with satisfying any two of the following five criteria: (1) collapse of the femoral head without joint space narrowing or acetabular abnormality on radiographs, including the crescent sign; (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 magnetic resonance imaging (MRI), which was described as a "band-like pattern"; and (5) trabecular and marrow necrosis on histology. The sensitivity and specificity of the inclusion criteria were 91% and 99%, respectively, in comparison to histological diagnosis of ONFH as gold standard [14]. The estimated number of patients was initially calculated within each stratum according to the following formula: the estimated number of patients = the reported number of patients / (selection rate × response rate). Then, the estimated number of patients in each stratum was added to obtain the annual number of prevalent ONFH patients in Japan, and 95% confidence intervals (CI) were calculated with an assumption of multinominal hypergeometric distribution. The estimated annual prevalence of ONFH was further obtained using the total population of Japan as a denominator. Additionally, the estimated annual number of incident ONFH patients, which was defined as newly diagnosed ONFH patients during the year surveyed (i.e., 1994, 2004, and 2014, respectively), was calculated.

Table 3.1 shows the summary of the first-stage survey in three nationwide epidemiologic surveys. From 1994 to 2004, the estimated annual number of prevalent ONFH patients, the estimated annual prevalence of ONFH, and the estimated annual number of incident ONFH patients have increased approximately 1.5-fold (7400 patients to 11,400 patients, 5.9 per 100,000 population to 8.9 per 100,000 population, and 1500 patients to 2200 patients, respectively). Similarly, from 2004 to 2014, there was an approximate twofold increment in the estimated annual number of prevalent ONFH patients and the estimated annual prevalence of ONFH (11,400 patients to 23,100 patients, 8.9 per 100,000 population to 18.2 per 100,000 population, respectively). However, this was not observed for the estimated annual number

Table 3.1 Summary of the first-stage survey in three nationwide epidemiologic surveys of ONFH

Year conducted [reference No]	Year surveyed	Number of responding orthopedic departments (response rate, %)	Reported number of cases	Estimated annual number of prevalent cases during the year surveyed (95% CI)		Estimated annual prevalence during the year surveyed (per 100,000 population)	Estimated annual number of incident cases during the year surveyed[a] (95% CI)
1995 [4, 10]	1994	605 (57)	4271	7400	(6700–8200)	5.9	1500
2005 [11]	2004	577 (58)	5602	11,400	(10,100–12,800)	8.9	2200
2015 [12]	2014	738 (60)	13,563	23,100	(20,800–25,300)	18.2	2100

ONFH idiopathic osteonecrosis of the femoral head

[a]Defined as newly diagnosed ONFH cases during the year surveyed (i.e., 1994, 2004, and 2014, respectively)

of incident ONFH patients (2200 patients to 2100 patients). Explanations for this substantial increase in each figure from 1994 to 2004 could be that ONFH became a well-known disease in Japan after it was earmarked for financial support by the MHLW in 1992 and that diagnostic techniques advanced dramatically with the introduction of MRI. In contrast, possible reasons for the discrepancy between the increased number of prevalent cases and the stable number of incident cases during the most recent 10 years may be that ONFH is not a fatal disease in spite of frequent onset among those of middle-age, and therefore postoperative patients may have been accumulated over time. Nevertheless, the series of nationwide epidemiologic surveys clearly conveyed the disease burden of ONFH in Japan during the past two decades.

If target departments responded in the first-stage survey to report that they had a patient(s), they were invited to the second-stage survey to provide information on demographic and clinical characteristics for each patient using a structured questionnaire. Regarding the nationwide epidemiologic survey that was conducted in 2005, the second-stage survey gathered the information on 1502 ONFH patients, who were randomly sampled from the reported patients in the first-stage survey (i.e., prevalent cases who visited the target departments during 2004) [11]. The peak in the distribution of age at diagnosis was observed in those in their 40s among all subjects, in males in their 40s, and in females in their 30s (Fig. 3.1), which highlighted that ONFH frequently occurs in the middle-aged population. Table 3.2 shows the distribution of two major risk factors for ONFH patients: systemic steroid use and habitual alcohol intake. The proportion of each history was 51% for systemic steroid use, 31% for habitual alcohol intake, 3% for both steroid and alcohol

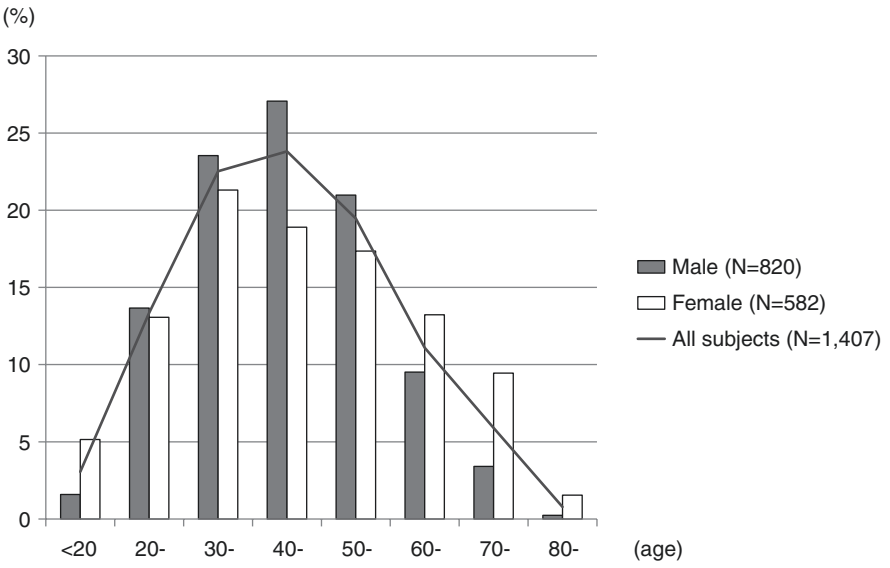

Fig. 3.1 Distribution of age at diagnosis is shown. Analysis is based on the subjects whose age at the time of diagnosis was available. There was no available information regarding gender for five subjects. [Source: Fukushima W, Fujioka M, Kubo T, Tamakoshi A, Nagai M, Hirota Y. Nationwide epidemiologic survey of idiopathic osteonecrosis of the femoral head. Clin Orthop Relat Res. 2010;468:2715–24]

Table 3.2 Distribution of potential causative factors among ONFH patients: a result from the second-stage survey in a nationwide epidemiologic survey in Japan, 2004

	All patients (n = 1502)		Stratified by gender[a]				Stratified by age (years) at diagnosis[a]					
			Male (n = 885)		Female (n = 612)		<40 (n = 548)		40–64 (n = 706)		≥65 (n = 153)	
Variables	n (%)		n (%)		n (%)		n (%)		n (%)		n (%)	
Systemic steroid administration	760	(51)	295	(34)	462	(76)	325	(60)	340	(48)	58	(38)
Habitual alcohol use	456	(31)	415	(47)	39	(6)	146	(27)	253	(36)	26	(17)
Both	47	(3)	39	(4)	8	(1)	16	(3)	24	(3)	6	(4)
Neither	225	(15)	127	(15)	98	(16)	59	(11)	85	(12)	62	(41)
Unknown/not filled-in	14		9		5		2		4		1	

ONFH idiopathic osteonecrosis of the femoral head
Some totals of "%" do not equal 100% attributable to rounding
[a]There was no available information regarding gender for five patients and for age at diagnosis for 95 patients. [Source: Fukushima W, Fujioka M, Kubo T, Tamakoshi A, Nagai M, Hirota Y. Nationwide epidemiologic survey of idiopathic osteonecrosis of the femoral head. Clin Orthop Relat Res. 2010;468:2715–24]

intake, and 15% for neither steroid nor alcohol intake. Stratification by age at diagnosis revealed that there was a higher proportion of history of systemic steroid use in the younger age group (60% among those aged <40 years, 48% among those aged 40 to 64 years, and 38% among those aged ≥65 years). Among ONFH patients with history of systemic steroid use, systemic lupus erythematosus (SLE) was the most frequent underlying illness requiring steroid therapy (31%). Since SLE is characterized by early onset during the life course, these findings emphasized the importance of preventative strategies for ONFH among the younger population, including better steroid administration regimens for SLE.

3.3 Descriptive Epidemiology (2): A Hospital-Based Sentinel Monitoring System

A methodology for the nationwide epidemiologic survey on intractable diseases, which has been proposed by the ERID Study Group, is useful to understand the descriptive epidemiology in a specific country. However, it may not be the best method to evaluate secular trends of disease characteristics periodically due to significant effort and expensive costs. The ONFH Study Group therefore started a multicenter hospital-based sentinel monitoring system for ONFH (hereafter referred to as the ONFH sentinel monitoring system) in 1997 as an option to elucidate the descriptive epidemiology of ONFH. The monitoring system is currently ongoing and as of October 2017, a total of 35 hospitals from the ONFH Study Group are participating. The system is similar to the sentinel surveillance for infectious disease. The participating hospitals report the information on patients' characteristics when a newly diagnosed ONFH patient is confirmed or when an operation is conducted for ONFH patients in each hospital.

Using data from the ONFH sentinel monitoring system over a period of 15 years, a temporal trend of newly diagnosed ONFH patients with respect to basic characteristics were assessed. This included gender ratio, distribution of age at diagnosis, major risk factors, and underlying diseases treated by systemic steroid administration [15]. A total of 3041 newly diagnosed ONFH patients who were reported from 34 collaborating hospitals between 1997 and 2011 were analyzed. The temporal trends of the disease characteristics were assessed in 5-year intervals according to the date of diagnosis (1997–2001, 2002–2006, and 2007–2011). In order to confirm the robustness of the trend, an additional analysis was employed by confining the data to that from 11 hospitals, which regularly reported ONFH patients to the monitoring system throughout the study period.

A notable trend was observed in underlying diseases requiring steroid therapy among ONFH patients with history of systemic steroid use. Across the study period, the proportion of patients with SLE decreased in females (from 1997–2001 to 2007–2011: 37% to 29%, $p = 0.022$). The proportion of patients with renal transplantation also decreased both in males (3.8% to 1.2%, $p = 0.047$) and in females

(3.2% to 0.8%, $p = 0.038$). In contrast, the proportion of patients with pulmonary disease (except for bronchial asthma) increased both in males (0.5% to 5.5%, $p = 0.022$) and in females (0.5% to 3.6%, $p = 0.027$). An increase in the proportion of patients with skin diseases was observed in females (2.2% to 4.4%, $p = 0.046$). Limiting the data to 11 hospitals, additional analysis demonstrated that the results were almost unchanged, although the trends of SLE and renal transplantation were no longer statistically significant due to the reduced number of subjects.

These findings indicate that the distribution of underlying diseases requiring systemic steroid use, which pose a higher risk for ONFH, has gradually changed over time. Current national statistics showed that both the number of SLE patients receiving public financial aid for treatment and the number of patients with renal transplantation have increased in Japan [16, 17]. These trends are inconsistent with those from the ONFH sentinel monitoring system, probably because steroid regimens for SLE treatment or after renal transplantation have evolved so that less are administered [18–20].

A strength of the ONFH monitoring system includes the strict diagnostic criteria because all diagnoses were confirmed by orthopedic hip surgeons who were members of the ONFH Study Group. Less expensive costs and fewer efforts to operate the system in comparison to a nationwide epidemiologic survey are also attractive aspects. For example, as of October 2017, we found that there were 222 newly diagnosed ONFH patients who had been reported to the ONFH sentinel monitoring system, whose diagnosis had been confirmed during 2014. According to the results from the nationwide epidemiologic survey (Table 3.1), the estimated annual number of incident ONFH patients during 2014 in Japan was 2100. Thus, we can expect that newly diagnosed ONFH patients in the ONFH sentinel monitoring system would cover approximately 10% of the incident ONFH patients in Japan overall (222/2100). The ONFH sentinel monitoring system is a useful alternative to evaluate descriptive epidemiology of ONFH both continuously and efficiently.

3.4 Analytic Epidemiology (1): Habitual Alcohol Intake as a Risk Factor

Although descriptive epidemiology of ONFH showed that the history of systemic steroid use and habitual alcohol intake are very prevalent in ONFH patients, analytic epidemiology is required to evaluate whether or not these factors are associated with an increased risk of ONFH.

With respect to evaluation of habitual alcohol intake, a case-control approach is considered particularly suitable because ONFH is a rare disease and a history of alcohol intake in each subject throughout the lifetime can be obtained using a self-administered questionnaire. In Japan, Matsuo et al. were the first to report the association between habitual alcohol intake and ONFH [21]. From 1980 to 1985, they recruited 112 ONFH cases without history of systemic steroid use and 168 matched

controls from 4 collaborating hospitals in Japan. They revealed that alcohol drinking status, weekly ethanol consumption, and cumulative ethanol consumption significantly increased the risk of ONFH with evident dose-response relationships. Later, the ONFH Study Group conducted another case-control study where 118 ONFH cases without history of systemic steroid use and 236 matched controls were recruited from 20 collaborating hospitals throughout Japan between 1988 and 1990 [22]. They also found that alcohol drinking status, weekly ethanol consumption, and cumulative ethanol consumption were significantly associated with ONFH. The odds ratios (ORs) were 1.0, 3.2, and 13.1 for former, occasional, and regular drinkers, respectively, in comparison to never drinkers (trend $p < 0.001$); 2.8, 9.4, and 14.8 for <320, 320–799, and ≥800 g/week, respectively, in comparison to nondrinkers (trend $p < 0.001$); 2.2, 9.7, and 12.9 for <3200, 3200–7999, and ≥8000 drink-years, respectively, in comparison to never drinkers (trend $p < 0.001$) (Table 3.3). Similar findings were further confirmed in three case-control studies from Japan [23–25]. The effects of alcohol on ONFH may be immedi-

Table 3.3 Adjusted relative risks of alcohol drinking for ONFH: a case-control study in Japan, 1988–1990

Characteristics	Cases		Controls		Relative odds[a]	95% CI
	No.	%	No.	%		
Alcohol drinking						
Never	23	19.5	87	36.9	1.0	
Former	4	3.4	10	4.2	1.0	0.2–6.2
Occasional	26	22.0	80	33.9	3.2	1.1–9.2
Regular	65	55.1	59	25.0	13.1	4.1–42.5
					Trend: $p < 0.001$	
Weekly ethanol intake (g/week)						
Nondrinker	27	22.9	97	41.1	1.0	
< 320	24	20.3	87	36.9	2.8	1.0–7.8
320–799	49	41.5	45	19.1	9.4	3.0–29.0
≥ 800	18	15.3	7	3.0	14.8	3.8–57.2
					Trend: $p < 0.001$	
Drink-years						
Never drank	23	19.7	87	37.5	1.0	
< 3200	15	12.8	62	26.7	2.2	0.7–6.9
3200–7999	25	21.4	36	15.5	9.7	2.6–36.1
≥ 8000	54	46.2	47	20.3	12.9	3.8–43.4
					Trend: $p < 0.001$	

ONFH idiopathic osteonecrosis of the femoral head, *CI* confidence interval

[a]Adjusted for cigarette smoking, occupational energy consumption, body mass index, and liver dysfunction, using a conditional logistic regression model

ate and cumulative because both current consumption and cumulative consumption increased the risk of ONFH [22].

A recent meta-analysis by Yoon et al. summarized the evidence regarding alcohol intake as a risk factor for ONFH [26]. From 1127 articles which had been published up to January 2016, 5 case-control studies were selected [21–25], all of which were coincidentally Japanese studies and identical to the aforementioned articles. Using the Newcastle-Ottawa Scale (a maximum of 9 stars), the quality assessment showed that each study had a score of 8–9 stars, indicating sufficient quality for evaluation. A conventional meta-analysis to obtain the summary estimate of drinking habits found an increased risk of ONFH among those with former drinkers with marginal significance (OR = 2.62, $p = 0.055$) and a significantly increased risk of ONFH among current drinkers (OR = 3.63, $p < 0.001$ in occasional drinkers; OR = 5.90, $p < 0.001$ in daily drinkers). The dose-response meta-analysis using restricted cubic spline models with four knots revealed that the risk of ONFH significantly increased by 35.3% for every 100 g/week and by 44.1% for every 500 drink-years. Very interestingly, the pattern of dose-response was not J-shaped, but an ever-increasing pattern which indicated that higher alcohol intake resulted in a higher risk of ONFH. In other words, the risk of ONFH is elevated even with a lower alcohol intake level. Since there is no universal consensus regarding the critical dose of alcohol intake which may be necessary for ONFH development, further studies should focus on the threshold of alcohol intake in terms of prevention of ONFH.

3.5 Analytic Epidemiology (2): Systemic Steroid Use as a Risk Factor

To date, associations between systemic steroid use and the risk of ONFH have been assessed mainly among patients with SLE and renal transplantation. However, these findings are not consistent with each other. Information on a complete history of steroid administration in each patient is quite challenging to obtain, especially for total dose and average dose. A single center study may be more convenient for collecting accurate information on steroid therapy compared with a multicenter study, while such a single center study is likely to miss a significant finding due to predefined standard regimens for steroid therapy in each center.

Using a case-control study approach, the ONFH Study Group evaluated systemic steroid use on ONFH risk among SLE patients [4, 27]. They recruited 49 ONFH cases with SLE and 69 matched controls with SLE from 14 collaborating hospitals between 1985 and 1993. Cases and controls were matched for gender, birth year, outpatient department where they received treatment for SLE, and the age at diagnosis of SLE. History of systemic steroid use was collected during the period from the date of diagnosis of SLE to the date of diagnosis of ONFH for cases, and during the period from the date of diagnosis of SLE to the same date of the matched cases for controls. Total dose, maximum dose, and average daily dose

were evaluated after being classified into two levels: the lowest and the middle tertile vs. the highest tertile. A significantly elevated OR was found for average daily dose of ≥16.6 mg (vs. < 16.6 mg, OR = 3.7, $p = 0.01$) but not for total dose of ≥28.4 g (vs. < 28.4 g, OR = 2.2, $p = 0.40$) and maximum daily dose of ≥80 mg (vs. < 80 mg, OR = 2.4, $p = 0.06$). With respect to the number of pulse therapies, OR of one dose of pulse therapy was significantly elevated (3.2, $p = 0.02$), while OR of two or more doses of pulse therapy was not significantly associated with ONFH (1.2, $p = 0.80$). Lack of a dose-response relationship between the number of pulse therapies and ONFH risk may indicate that the individual susceptibility to steroids was also associated with ONFH. This interpretation is consistent with a report that patients with lower midazolam clearance showed a significantly higher prevalence of steroid-associated ONFH [28]. Midazolam clearance is a proxy variable of hepatic cytochrome P450 (CYP) 3A, which metabolizes corticosteroids.

The ONFH Study Group also conducted several cohort studies among patients with renal transplantation to evaluate steroid therapy as a risk factor. A study with 150 subjects who received renal transplantation between 1988 and 1999 evaluated the development of ONFH prospectively and routinely using MRI during 1 year after renal transplantation [29]. For total steroid dose during 2 weeks, 4 weeks, 6 weeks and 8 weeks after renal transplantation, a significant association with dose-response relationship was found for total steroid dose during the 8 weeks after renal transplantation (OR of >1795 mg vs. ≤1400 mg: 7.4, $p = 0.01$, trend $p = 0.02$) but not for total steroid dose during 2 weeks, 4 weeks, and 6 weeks. In contrast, the same study with 286 subjects in which recruitment period had been extended until 2007 showed that the most pronounced association with dose-response relationship was found for total steroid dose during the 2 week period after renal transplantation (OR of >600 mg vs. ≤520 mg: 4.9, $p < 0.01$, trend $p < 0.01$) [30].

Although patients with SLE or renal transplantation seem to be suitable populations for evaluating systemic steroid use on ONFH risk, they can only provide effect estimates comparing high doses and low doses of steroids. Thus, the ONFH Study Group conducted another case-control study to evaluate the extent of ONFH risk between steroid users and non-steroid users. They recruited 73 ONFH cases irrespective of history of systemic steroid use and 250 matched controls and found that history of oral corticosteroid use was significantly associated with development of ONFH approximately 20-fold [31]. Using a very similar dataset, interactions between oral corticosteroid use and alcohol intake were evaluated [25]. Among 71 ONFH cases and 227 matched controls, multiplicative interaction and additive interaction were assessed using a two-by-two table of "nondrinker vs. drinker" for alcohol intake and "never-user vs. user" for oral corticosteroids. When nondrinkers without steroid use were set as a reference group, an elevated but non-significant OR was observed for drinkers without steroid use (OR: 2.79). In contrast, nondrinkers with steroid use showed a substantially elevated OR (OR: 31.5). However, no further increase in OR was observed for drinkers with steroid use (OR: 31.6). Consequently, any significant multiplicative or additive interaction was

Table 3.4 Multiplicative or additive interaction between current drinking status and history of oral corticosteroid use for ONFH: a case-control study in Japan, 2002–2004

Variables	Never user of oral corticosteroids		User of oral corticosteroids		*p*-value for multiplicative interaction[a]	Synergy index[b] (95% CI)
	Cases (n)/ controls (n)	Adjusted OR (95% CI)[c]	Cases (n)/ controls (n)	Adjusted OR (95% CI)[c]		
Current drinking status						
Nondrinker	4/79	1	22/15	31.5 (9.05–109)		
Drinker	23/122	2.79 (0.89–8.77)	22/11	31.6 (8.67–115)	0.19	0.95 (0.32–2.80)

ONFH idiopathic osteonecrosis of the femoral head, *OR* odds ratio, *CI* confidence interval

[a]Wald test for each interaction term (DF = 1)
[b]Synergy index >1 indicates additive interaction
[c]Adjusted for gender, age, smoking and past history of liver disease, hyperlipidemia and gout, using a logistic regression model

detected (Table 3.4). Although pharmacokinetic interactions between steroids and alcohol is possible, the most plausible interpretation may be that the added effect of alcohol intake was too small to make any significant difference in the presence of the overwhelming effect of steroids on ONFH risk. Together with the findings from descriptive epidemiology in which ONFH is frequently observed among middle-aged individuals and younger ONFH cases are likely to have a greater history of systemic steroid use, the development of preventative strategies especially for steroid-associated ONFH is urgently sought.

3.6 Summary

The ONFH Study Group and the ERID Study Groups have conducted a variety of epidemiologic studies together and have systematically elucidated the epidemiology of ONFH in Japan. Although the underlying mechanisms of ONFH are still controversial, epidemiologic findings can contribute to policy and provide a clue for experimental or clinical studies regarding pathogenesis and effective treatment. Several methodologies that have been proposed by the ERID research group could be helpful in understanding epidemiology on other intractable diseases. Regarding ONFH, specific issues to be evaluated in further epidemiologic studies include periodic updating of descriptive epidemiology, determining “safe” thresholds of alcohol

intake and steroid dosages for elevated risk of ONFH, while other potential factors associated with ONFH should also be explored. Continuous efforts to collaborate effectively between the ONFH Study Group and the ERID Study Groups should result in accumulation of further evidence.

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