て予後予測ツールを作成した（図1）。

２．考察

本研究で行った厚労省研究班による全国疫学調査は、規模別に無作為抽出された全国の医療機関から報告された特発性心筋症症例の大規模な集団を対象としており、現時点でのわが国の本症患者を代表する実態を知ることができる初めての調査といえる。この集団の予後調査から得られた結果は、現在のわが国の医療レベルにおける本症患者の予後の実態といえる。

特発性心筋症患者を診療する医師は、患者の各種検査データから予後を予測する必要があり、また、患者に適切な情報を伝える必要がある。また、患者の立場からも自らの意志決定のために予後を知る必要がある。これまで、多くの研究において本症の予後予測要因が報告されているが、ほとんどの研究が小規模なものであり、予後予測要因を網羅的に検討し予後予測モデルを作成した研究は国内外においてほとんどなかった。本研究から明らかになった現時点でのわが国の本症患者の予後予測モデルによる生存率予測は、臨床の現場において大変貴重な情報になると考えられる。

また、今回作成した予後予測モデルでは、心臓カテーテル検査や心筋生検など侵襲的検査の所見や特殊な検査所見を用いず、一般に広く行われる簡略な検査のみで予後予測ができるようなものとした。広く臨床の現場で用いやすくするためである。その結果、拡張型心筋症においては、性、年齢、NYHA機能分類、LVD index の 4 項目が予後予測スコアの因子となり、これらをもとに計算式を用いて推定10年生存率を算出することが可能となった。さらに表計算ソフトを用いてこれらの予後因子の実測値を直接入力するだけで予測 10 年生存率を計算するフォームは、臨床の現場で簡便に予後予測を可能とする手段であり、今後は広く一般臨床の現場で用いることができるようにインターネットなどを用いて広く公開することを検討中である。今回の予後予測式はあくまでもシミュレーション上での検討であることから、今後、臨床の現場からその有用性や妥当性を十分にフィードバックできる環境も整え、より有用で実用的な予後予測フォームに発展させていく必要があるであろう。

本研究で予測された生存率は、わが国の平均的な治療法が実施された時のものである。よりレベルの高い治療では生存率はさらに良好となり、一方、不適切な治療がなされた場合は生存率が低めになることが予想される。また、今後治療法、治療薬の進歩によりさらに予後が改善されることが十分あり得ることを考慮する必要がある。

E. 結論

全国疫学調査によりわが国を代表する特発性心筋症患者の予後および予後要因を明らかにし、その結果から表計算ソフトで簡便に使用できる予後予測フォームを作成した。拡張型心筋症では 4 項目の予後関連要因を用いて10 年生存率のシミュレーションを行った。簡便に 10 年生存率を予測することができるフォームは、わが国の本症の診療現場において活用が可能である。

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Ｅ．研究発表
１．論文発表（書籍を含む）
なし

２．学会発表
なし

Ｆ．知的財産権の出願・登録状況
（予定を含む）
１．特許取得
なし
２．実用新案登録
なし
３．その他

Ｇ．共同研究を行った他の難病研究班
該当なし

表１．拡張型心筋症の 10 年生存と関連する要因

	ハザード比	(95%信頼区間)	*P*
年齢（10 歳上昇あたり）	1.37	(1.25-1.51)	<0.001
性別（女性）	0.64	(0.47-0.87)	0.004
NYHA 心機能分類（１上昇あたり）	1.28	(1.10-1.48)	0.001
LVD index （10mm/m2 上昇あたり）	1.27	(1.11-1.45)	<0.001

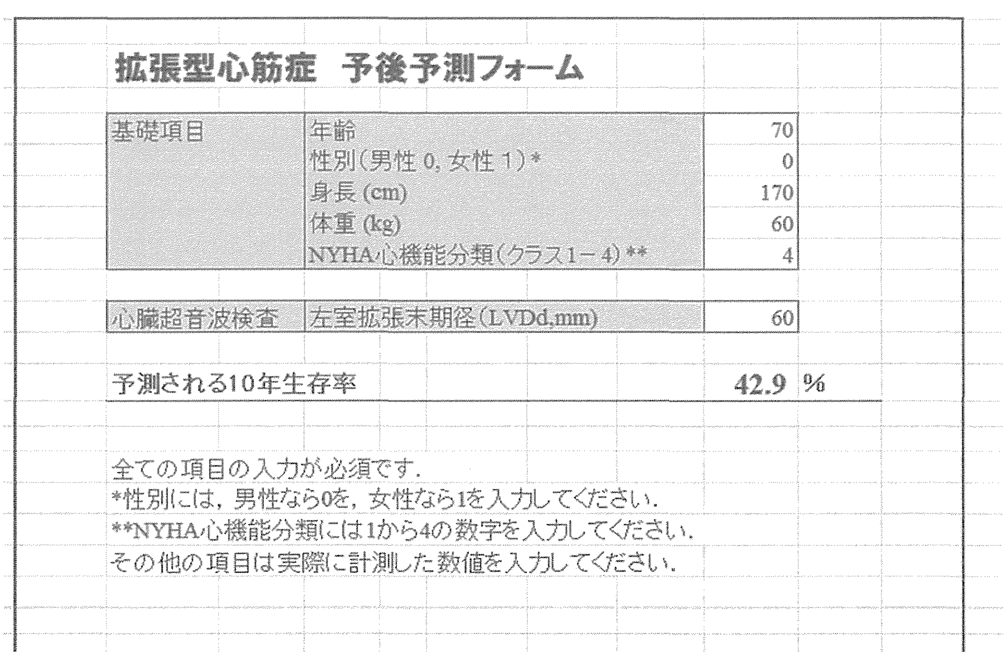
Cox 比例ハザードモデル，ステップワイズ変数選択法

表 2. 拡張型心筋症の 10 年生存と関連する要因の係数 β と平均値

	β	平均値
年齢　30-59 歳（30 歳未満と比較）	0.493	0.28
年齢　60 歳以上（30 歳未満と比較）	1.197	0.47
性別　（男=0, 女=1）	-0.330	0.28
NYHA class II　(class I と比較)	0.640	0.41
class III (class I と比較)	0.925	0.29
class IV　(class I と比較)	0.781	0.10
LVD index	0.015	39.4

Cox 比例ハザードモデル，強制投入法　全変数を同時に投入

図 1. 拡張型心筋症 10 年生存率　予測シート



拡張型心筋症　予後予測フォーム

基礎項目	年齢	70
	性別(男性 0, 女性 1)*	0
	身長 (cm)	170
	体重 (kg)	60
	NYHA心機能分類(クラス1－4)**	4

心臓超音波検査	左室拡張末期径(LVDd,mm)	60

予測される10年生存率　**42.9** %

全ての項目の入力が必須です．
*性別には，男性なら0を，女性なら1を入力してください．
**NYHA心機能分類には1から4の数字を入力してください．
その他の項目は実際に計測した数値を入力してください．

厚生労働科学研究費補助金（難治性疾患等政策研究事業（難治性疾患政策研究事業））
難治性疾患の継続的な疫学データの収集・解析に関する研究（H26-難治等(難)-一般-089 ）
分担研究　２０１４年度　終了報告書

「運動失調症の医療基盤に関する調査研究班」への研究協力について

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研究要旨：「運動失調症の医療基盤に関する調査研究班（政策班）」への研究協力について、現時点での進捗状況および今後の方針について報告する。運動失調症政策班では、現在、脊髄小脳変性症（SCD）を対象に、臨床情報の収集と遺伝子検査データ等を統合した患者登録システム J-CAT を構築し、患者の自然歴を調査する患者追跡研究を計画中である。現在、J-CAT のプロトコール作成、生体資料のロジスティクス整備、自然歴調査における評価項目の選定、Clinical research coordinator (CRC)による電話インタビュー体制など、平成 27 年度より患者登録が開始できるように準備を進めているところである。本研究での自然歴調査は、疫学班に求められる研究協力領域としての「予後調査」に該当することから、本研究の計画段階からメンバーに加わり、協力していく方針である。

A．研究目的

「運動失調症の医療基盤に関する調査研究班（政策班）」への研究協力について、平成 26 年度は次年度からの研究協力体制構築と今後の計画であり、現時点での進捗状況および今後の方針について報告する。

B．研究方法

運動失調症政策班では、現在、脊髄小脳変性症（SCD）を対象に、臨床情報の収集と遺伝子検査データ等を統合した患者登録システム J-CAT(Japan Consortium of ATaxia) を構築し、患者の自然歴を調査する患者追跡研究を計画中である。患者登録システムに関しては、既に筋疾患を対象としたクラウドサーバーを用いた Web 患者登録システムが構築されており [1)]、このシステムを用いた患者登録・追跡研究が計画されている。現在、J-CAT のプロトコール作成、生体資料のロジスティクス整備、自然歴調査における評価項目の選定、Clinical research coordinator (CRC) による電話インタビュー体制など、平成 27 年度より患者登録が開始できるように準備を進めているところである。

（倫理面への配慮）現在プロトコール作成中であり、文部科学省・厚生労働省の「人を対照とする医学研究に関する倫理指針」に基づき、十分な倫理的配慮を行う方針である。

C．研究結果と考察

本年度は次年度に向けた研究協力体制と計画ということで、平成 27 年 1 月 14 日、15 日に行われた政策班および実用化班の合同研究報告会に参加することにより、臨床班全体としての研究内容や進捗状況について情報収集を行った。

J-CAT 運営委員会の中には自然歴・遺伝子解析・臨床指標・リハビリテーションの４つの subcommittee を設定し、J-CAT を基盤とした総合的な研究の推進が行われることとなっている。この中でも特に、「自然歴調査」に関しては、疫学班に求められる研究協力領域としての「予後調査」に該当することから、本研究の計画段階からメンバーに加えていただいて、円滑な研究遂行のため協力していく方針である。

自然歴調査において考慮すべき点としては、１）登録時臨床情報に関しては、必要最小限の項目を満たしかつ簡便に行うことのできる内容とする、２）追跡調査の方法として 6ヶ月ごとの CRC による電話インタビューと 1 年ごと医師による定期診察を予定しているが、その際の調査内容について、３）評価項目（アウトカム指標）の設定として ADL・QOL

指標や運動失調評価スケールの検討、４）他の医療機関を受診するあるいは通院が中断されるようなアウトカムを起こした場合の確認方法の検討などが考えられる。

またJ-CATに限らず、今後の政策班における新たな研究の計画や分析方法に対する助言など幅広く協力を行っていくこととしている。

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Ｅ．研究発表

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２．学会発表　なし

Ｆ．知的財産権の出願・登録状況

（予定を含む）

１．特許取得　なし

２．実用新案登録　なし

３．その他　なし

Ｇ．共同研究を行う他の難病研究班

「運動失調症の医療基盤に関する調査研究班」研究代表者：水澤英洋（国立精神・神経医療研究センター）

Ⅲ．研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
Wakaba Fukushima, Yoshio Hirota	Alchol	Kyung-Hoi Koo et al.	Osteonecrosis	Springer	Berlin	2014	95-99

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Shinji Takahashi, Wakaba Fukushima et al.	Temporal Trends in Characteristics of Newly Diagnosed Nontraumatic Osteonecrosis of the Femoral Head From 1997 to 2011: A Hospital-Based Sentinel Monitoring System in Japan	J Epidemiol	In press		2015
Yoshikazu Nakamura, Ryusuke Ae, et al.	Descriptive Epidemiology of Prion Disease in Japan : 1999-2012	J Epidemiol	25(1)	8-14	2015
Yoko Kano, Mikiko Tohyama, et al.	Sequelae in 145 patients with drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms: Survey conducted by the Asian Research Committee on Severe Cutaneous Adverse Reactions(ASCAR)	J Dermatol	42(3)	276-282	2015
Masayuki Amagai, Akiko Tanikawa, et al.	Japanese guidelines for the management of pemphigus	J Dermatol	41(6)	471-486	2014
黒沢美智子	特集　重症薬疹の診断と治療アップデート　II.我が国の重症薬疹の疫学	ｱﾚﾙｷﾞｰ・免疫	21(8)	1197-1207	2014

Ⅳ．研究成果の刊行物・別刷り

Kyung-Hoi Koo
Michael A. Mont
Lynne C. Jones
Editors

Osteonecrosis

Springer

Alcohol

13

Wakaba Fukushima and Yoshio Hirota

13.1 Introduction

Osteonecrosis is a condition of bone death leading to joint pain, bone destruction, and loss of function. Nontraumatic osteonecrosis, a disease entity in which the underlying etiology and pathogenesis have not been fully elucidated, commonly involves the femoral heads. Although a wide spectrum of conditions, including systemic steroid administration, that are potentially related to nontraumatic osteonecrosis of the femoral head (ONFH) have been reported so far [1–5], alcohol consumption continues to be important as an environmental factor. In this chapter, we present a summary of the descriptive and analytic epidemiology regarding alcohol-induced ONFH, as well as related issues including potential mechanisms for disease etiology and influences of alcohol-associated factors.

13.2 Descriptive Epidemiology of Alcohol-Induced ONFH

According to published reviews, the association of alcoholism with osteonecrosis was first described in 1922 [1, 4]. Several studies have examined the frequency of ONFH among alcoholics and found that the prevalence was low. A study from the USA assessed 790 patients who were hospitalized for treatment of alcoholism. ONFH was diagnosed in 2 patients, resulting in a prevalence of 0.3 % [6]. In Yugoslavia, among 1,157 patients who had been treated for excessive alcohol consumption, 92 sites in 62 patients (5 %) were diagnosed as nontraumatic osteonecrosis. Of these, 82 sites were found to be ONFH [7].

Some epidemiological studies reported the frequency of alcohol-induced ONFH among all ONFH patients on the basis of country. In Japan, a nationwide survey was conducted by stratified random sampling from all orthopedic departments to estimate the number of patients with ONFH who sought medical care during 2004 and to reveal their basic characteristics [8]. Of 1,502 patients from whom clinical information was obtained, 31 % had a history of habitual alcohol use, 51 % had a history of systemic steroid administration, 3 % had both histories, and 15 % had neither history. After stratification by gender and age group, the proportions of patients with a history of habitual alcohol use were 47 % for males and 6 % for females and 27 % for patients aged <40 years, 36 % for those aged 40–64 years, and 17 % for those aged ≥65 years (Table 13.1). Another nationwide survey in Korea estimated the prevalence of osteonecrosis of the femoral head, including posttraumatic cases, between 2002 and 2006 using medical claims and population data from the National Health Insurance Corporation of Korea [9]. Regarding a subset of the validation data with 185 hospitalized patients for whom a diagnosis was confirmed, 32.4 % had a history of alcohol abuse, 14.6 % had a history of steroid use, and 1.6 % had a history of hip fracture.

Although frequency of alcohol-induced ONFH among all ONFH patients is likely to be described among study participants in clinical studies that evaluated outcomes of operative or therapeutic procedures, this is not always the case. Even when described, the frequency varied across the studies. For example, with respect to several recent reports, the proportion[1] was 27/52 patients (52 %) [10], 6/23 patients (26 %) [11], 5/28 patients (18 %) [12], 18/80 patients (23 %) [13], 1/19 patients (5 %) [14], 37/100 patients (37 %) [15], 26/32 patients (81 %) [16], 16/42 hips (38 %) [17], and 11/71 hips (15 %) [18]. In addition to differences in ethnicity,

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[1]Note: If patients with posttraumatic osteonecrosis of the femoral head were included in the study, the authors excluded the subjects and recalculated the proportion of alcohol-induced ONFH patients (hips) among all patients (hips).

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Table 13.1 Distribution of potential causative factors among ONFH patients: a nationwide epidemiological survey in Japan, 2004

	All patients	Stratified by gender[a]		Stratified by age (years) at diagnosis[a]		
	(n = 1,502)	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

Reproduced with permission and copyright © of the *Association of Bone and Joint Surgeons* [8; Table 2]
Some totals of "%" do not equal 100 % attributable to rounding
ONFH nontraumatic osteonecrosis of the femoral head
[a]There was no available information regarding gender for five patients and for age at diagnosis for 95 patients

diagnostic criteria, and definitions for eligibility and exclusion in each study, no universal definition regarding alcohol-induced ONFH explains the different frequencies among studies. Some studies defined alcohol-induced ONFH as having a history of greater than 400 mL of pure ethanol consumption per week [16] or equivalent consumption for at least 6 months [10]. However, even less alcohol consumption might increase the risk of ONFH, because a threshold of alcohol consumption for alcohol-induced ONFH is unknown, and the causal mechanisms of alcohol intake have not been fully proven.

13.3 Analytic Epidemiology of Alcohol-Induced ONFH

13.3.1 Alcohol Consumption as a Risk Factor for ONFH

Although cohort, case-control, and cross-sectional studies can all be used to determine the factors associated with ONFH, the case-control approach is particularly suited to evaluate alcohol intake as a risk factor for development of ONFH. Possible reasons for this are that ONFH is an uncommon disease, and it is crucial to obtain a detailed history of alcohol consumption in each subject. Several hospital-based case-control studies have been reported from Japan [19–22]. In all studies, patients with ONFH without a history of systemic steroid treatment and control patients were recruited at departments of orthopedic surgery.

A case-control study by Matsuo et al. recruited 112 cases with ONFH and 168 controls from 4 collaborating hospitals in Western Japan [19]. Later, Hirota et al. reported results from another case-control study in which 118 cases and 236 controls were recruited from 20 collaborating hospitals all over Japan [20]. These two studies are highly comparable with respect to case definition, control selection, matching conditions between cases and controls (gender, age, ethnicity, date of initial examination/diagnosis, and hospital), and statistical analysis. According to the results by Hirota et al.

Table 13.2 Adjusted relative risks of alcohol drinking for ONFH: a case-control study in Japan, 1988–1990

	Cases		Controls			
Characteristics	No.	%	No.	%	Relative odds[a]	95 % CI
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	
<3,200	15	12.8	62	26.7	2.2	0.7–6.9
3,200–7,999	25	21.4	36	15.5	9.7	2.6–36.1
≥8,000	54	46.2	47	20.3	12.9	3.8–43.4
					Trend: $p < 0.001$	

Reproduced with permission and copyright © 1993 by the *Johns Hopkins University School of Hygiene and Public Health* [20;Tables 2 and 3]
ONFH nontraumatic osteonecrosis of the femoral head, *CI* confidence interval
[a]Adjusted for cigarette smoking, occupational energy consumption, body mass index, and liver dysfunction, using conditional logistic regression model

[20], the odds ratios (ORs) of former, occasional, and regular drinkers were 1.0, 3.2, and 13.1, respectively, compared to never drinkers (trend $p < 0.001$). Likewise, elevated ORs with a clear dose–response relationship were observed with respect to weekly ethanol consumption (ORs 2.8, 9.4, and 14.8 for <320, 320–799, and ≥800 g/week, respectively, in comparison to nondrinker; trend $p < 0.001$) and cumulative alcohol consumption (ORs 2.2, 9.7, and 12.9 for <3,200, 3,200–7,999, and ≥8,000 drink-years, respectively, in comparison to never drinker; trend $p < 0.001$) (Table 13.2). Similar findings were also seen in the

Table 13.3 Multiplicative or additive interaction between current drinking status and 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[b]	Synergy index[c] (95 % CI)
	Cases (*n*)/controls (*n*)	Adjusted OR (95 % CI)[a]	Cases (*n*)/controls (*n*)	Adjusted OR (95 % CI)[a]		
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)

Reproduced with permission and copyright © of the *British Editorial Society of Bone and Joint Surgery* [29; Table IV]
ONFH nontraumatic osteonecrosis of the femoral head, *OR* odds ratio, *CI* confidence interval
[a]Adjusted for gender, age, smoking, and past history of liver disease, hyperlipidemia, and gout, using logistic regression model
[b]Wald test for each interaction term (DF = 1)
[c]Synergy index >1 indicates additive interaction

earlier study by Matsuo et al. [19]. Later, two case-control studies confirmed the positive association between alcohol intake and ONFH [21, 22].

Because both current consumption and cumulative consumption were positively associated with ONFH, effects of alcohol on ONFH are likely to be immediate, as well as cumulative [20]. However, detailed pathogenesis for alcohol-induced ONFH has not been well established. Some studies observed morphological changes in the bone marrow of the femoral head among alcohol-treated animals: an induced adipogenesis and decreased osteogenesis [23] and an increased fat cell size and higher bone marrow pressure [24]. These studies also reported an elevated serum cholesterol or triglyceride [23, 24]. Likewise, a recent experimental study in rabbits revealed abnormalities in lipid status both in bone marrow and in blood after intragastric administration of different doses of alcohol. In addition, these abnormalities were more pronounced in rabbits with higher doses of alcohol [25]. An increased level of serum cortisol in patients with alcohol-induced ONFH has been reported as another hematological change [26]. With respect to in vitro studies, suggested mechanisms include nitric oxide-mediated apoptosis of osteoblasts and osteocytes [27] and a decreased ability in osteogenic differentiation of mesenchymal stem cells isolated from the bone marrow [28].

13.3.2 Interaction Between Alcohol Consumption and Other Factors

Pathogenesis of ONFH is likely to be multifactorial. However, little is known about the interaction of alcohol consumption with other factors in the development of ONFH.

Recently, we reported results from a hospital-based case-control study that examined the risk of ONFH due to interactions between oral corticosteroid use and alcohol intake [29]. Among 71 cases with ONFH and 227 controls, we evaluated multiplicative interaction and additive interaction, as proposed by Rothman [30], using a two-by-two table of "nondrinker vs. drinker" for alcohol intake and "never user vs. user" for oral corticosteroids. Compared to nondrinkers without steroid use, an elevated but nonsignificant OR was observed for drinkers without steroid use (OR 2.79). In contrast, we found a substantially elevated OR in nondrinkers with steroid use (OR 31.5). However, no further increase in OR was seen for the combined effect of alcohol and steroid use (OR 31.6). As a result, we did not detect any significant multiplicative or additive interaction (Table 13.3). Although pharmacokinetic interaction 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 in the development of ONFH.

Our case-control study also demonstrated the importance of stratification by steroid use [29]. When we evaluated the effects of cumulative alcohol intake on ONFH among all subjects, a positive relationship (OR of the highest category of cumulative consumption: 3.93) was weaker than that in previous reports by Matsuo et al. [19] or Hirota et al. [20]. After we limited the analysis to those subjects who had never used steroids, we obtained a pronounced positive association between cumulative intake and ONFH (OR 11.1), which was comparable to the results from the previous two reports. An association between factors of interest and ONFH may be masked if subjects with a history of steroid administration are included in the study. A similar finding was also observed in a study that evaluated the effect of smoking on the risk of ONFH [31].

13.3.3 Alcohol-Associated Factors and ONFH: Activities of Aldehyde Dehydrogenases and History of Liver Dysfunction

Alcohol consumption can be influenced by the activities of alcohol dehydrogenases and aldehyde dehydrogenases. Aldehyde dehydrogenase 2 (ALDH2), a key enzyme in the elimination of acetaldehyde, has a genetic polymorphism that is prevalent in East Asians, but rare in Caucasians or Africans [32]. The mutant ALDH2*2 allele encodes a catalytically inactive subunit, and the molecules containing 1 or 2 ALDH2*2 allele subunits (i.e., ALDH2*1/*2 or ALDH2*2/*2) are considered to be inactive. Those with inactive ALDH2 are likely to experience facial flushing responses due to acetaldehydemia after drinking alcohol, resulting in reduced alcohol intake with respect to both frequency and amount [33–36]. In a case-control study, Shibata et al. examined whether facial flushing pattern (i.e., flusher or non-flusher), as a proxy measure for sensitivity of alcohol, was independently associated with ONFH among 64 male cases and 128 male controls who were recruited from five collaborating hospitals in Japan [21]. Compared to flushers, the crude OR of non-flushers was significantly elevated (OR 2.08). However, no association was shown after adjustment for several confounders including alcohol consumption (OR 0.73). Sakata et al. directly assayed ALDH2 genotypes among 34 male cases and 68 male controls in a single-center case-control study in Japan [22]. Although the crude OR of ALDH2*1/*1 for ONFH was significantly elevated (OR 3.31) in comparison to ALDH2*1/*2 or ALDH2*2/*2, the authors did not find a significant association in the multivariate analyses (OR 1.51). Because non-flushers or those with active ALDH2 are likely to drink heavily, the findings from these two studies clearly showed that an apparent association in the univariate analysis was confounded by alcohol consumption. Interaction of flushing pattern or ALDH2 polymorphism with alcohol consumption was not evaluated due to the small numbers of subjects.

It has been reported that a history of liver dysfunction was positively associated with ONFH. The OR was increased approximately fivefold after simultaneous adjustment for alcohol consumption, as well as other covariates, in the multivariate analysis [19]. Some studies also found a similar association, although a statistical significance was not achieved [20, 21, 37]. Clinicians may question whether such an association can be substantially attributed to alcohol consumption as a risk factor of ONFH because alcohol consumption per se induces liver dysfunction. However, if a history of liver dysfunction was truly an intermediate step between alcohol consumption and ONFH, the positive association in these studies would disappear in the multivariate analyses due to multicollinearity. Thus, the positive relationship of liver diseases with subsequent ONFH risk is likely to be independent, although the influence of residual confounding cannot be ruled out. It should be noted that, in general, laboratory testing for liver dysfunction as a part of routine medical examinations is rarely performed for control subjects because they have no clinical signs of liver diseases. In some studies, subjects were considered to have a history of liver dysfunction if they had received treatment for three or more months for any diseases of the liver [19, 20, 37]. Self-reported information may be unacceptable as a surrogate for laboratory data in clinical settings. However, this approach would be useful in epidemiological studies in order to retain comparability between cases and controls and thus provide some clues for disease etiology.

13.4 Summary

Alcohol consumption is one of the important underlying factors for the development of ONFH. A history of habitual alcohol use or alcohol abuse was frequently observed among patients with ONFH, although the prevalence of ONFH among alcoholics seemed to be low. Several analytic epidemiological studies have consistently found a strong positive association between alcohol consumption and ONFH. However, compared to steroid-induced ONFH, less is known about the pathogenesis or mechanisms of alcohol-induced ONFH. Exploring possible interactions between alcohol consumption and other potential risk factors also could contribute to a better understanding of the etiology of ONFH. Other issues to be proven include determining a threshold of alcohol consumption, which would lead to the definition of a universal criterion of alcohol-induced ONFH and thus increase comparability across studies.

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Original Article

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Temporal Trends in Characteristics of Newly Diagnosed Nontraumatic Osteonecrosis of the Femoral Head From 1997 to 2011: A Hospital-Based Sentinel Monitoring System in Japan

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ABSTRACT

Background: Nontraumatic osteonecrosis of the femoral head (ONFH) is a rare disorder caused by ischemic necrosis of unknown etiology. A few studies have demonstrated trends in the number of patients with ONFH. However, there are no data on temporal trends in characteristics such as age, gender, and causative factors. To investigate this, we examined data from a multicenter hospital-based sentinel monitoring system in Japan.

Methods: A total of 3041 newly-diagnosed ONFH patients from 34 participating hospitals who were reported to the system from 1997–2011 were analyzed. We examined age at diagnosis, potential causative factors, and underlying diseases for which patients received systemic steroid administration. Their temporal trends were assessed according to date of diagnosis in 5-year intervals (1997–2001, 2002–2006, and 2007–2011).

Results: The gender ratio and distribution of potential causative factors did not change. Regarding underlying diseases requiring steroid administration, the proportion of patients with systemic lupus erythematosus decreased in males (10% to 6.4%) and in females (37% to 29%). Proportion of patients with renal transplantation fell consistently across the study period in both males (3.8% to 1.2%) and females (3.2% to 0.8%). In contrast, the proportion of patients receiving steroids for pulmonary disease (except asthma) significantly increased in both males (0.5% to 5.5%) and females (0.5% to 3.6%).

Conclusions: This large descriptive study is the first to investigate temporal trends in the characteristics of ONFH, which provide useful information for future studies.

Key words: nontraumatic osteonecrosis of the femoral head; temporal trends; a multicenter hospital-based sentinel monitoring system

INTRODUCTION

Nontraumatic osteonecrosis of the femoral head (ONFH) is a disorder of unknown pathogenesis that often progresses to hip joint destruction and physical disability.[1] Once the destruction occurs, surgical interventions, such as osteotomy and hip replacement, are required. ONFH is a rare disease, and its annual incidence in Japan has been reported to be an average of 2.51 cases per 100 000 persons between 1999 and 2008.[2] Some epidemiologic studies have shown an increase in the number of patients with ONFH in recent years.[3–5] Kang et al[3] conducted a nationwide survey between 2002 and 2006 using medical claims data from the National Health Insurance Corporation to estimate the prevalence in Korea. They reported that the prevalence increased from 20.53 per 100 000 persons in 2002 to 37.96 in 2006 (a 1.8-fold increase). Another survey from Japan reported that the estimated number of patients with ONFH who sought medical care in 2004 was 1.5 times higher than that in 1994.[4,5] However, even for well-known risk factors, such as corticosteroid use and alcohol intake,[6–9] the temporal trends in the characteristics of ONFH have not been investigated.

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In the present study, using data collected in a multicenter hospital-based sentinel monitoring system in Japan over a period of 15 years, we evaluated temporal trends in ONFH with respect to basic characteristics, including gender ratio, age at diagnosis, potential causative factors, and underlying diseases treated by systemic steroid administration. The trends were examined according to gender because the characteristics of ONFH differ considerably between male and female patients.[5]

METHODS

Since 1972, the Ministry of Health, Labour and Welfare in Japan has carried out a special program against so-called "intractable diseases," which are defined as rare diseases without any established therapy. The program includes eliminating patients' copayments for medical expenditures and promoting research activities. The Research Committee on Idiopathic Osteonecrosis of the Femoral Head, which consists of hip surgeons and experts in epidemiology, biology, and genetics from all parts of Japan, was established in 1975 under the program. The research committee started a multicenter hospital-based sentinel monitoring system for ONFH (hereafter referred to as the monitoring system) in June 1997 to elucidate the descriptive epidemiology of ONFH. The monitoring system is ongoing, and a total of 34 hospitals, including 31 university hospitals and three highly specialized medical centers, have participated up to November 2012.

When a patient was newly diagnosed with ONFH at one of the participating hospitals, the demographic and clinical information of the patient was reported to the monitoring system. Patients were also reported if they had been diagnosed in previous hospitals and then referred to the participating hospitals. The diagnosis of ONFH was made by hip surgeons based on the criteria proposed by the research committee.[10] The diagnostic criteria had a sensitivity of 91% and a specificity of 99% when histologic diagnosis was used as the gold standard.[10] Patients with caisson disease or trauma history of the hip joint were excluded because of secondary osteonecrosis due to external factors. The study protocol was approved by the ethics committees of each participating hospital.

Data collection

A structured form was used to collect patients' information on demographic and clinical characteristics. The form included the following as basic information: date of birth, gender, date of disease diagnosis, potential causative factors, and any underlying disease for which patients received systemic steroid administration. Assessment of potential causative factors comprised four categories, which were a combination of two major risk factors for ONFH: history of systemic steroid administration, history of habitual alcohol intake, history of both, and history of neither. All of the underlying diseases for which steroids were administered were reported. We did not use any specific definition of habitual alcohol intake because there is no universal criterion of alcohol-induced ONFH. As additional information, data on the amount and duration of alcohol intake among ONFH patients was available for those who were reported to the monitoring system after 2009. A representative hip surgeon in each participating hospital was asked to complete or recheck the data if the information was missing or lacked consistency.

Data analysis

All analyses were performed based on the calendar year of diagnosis. Among the patients reported up to November 2012, those who were first diagnosed with ONFH between January 1997 and December 2011 (a total of 15 years) were extracted for the present study. The date of diagnosis was further divided into 5-year intervals, resulting in three periods to assess trends in the characteristics: the first period, 1997–2001; the second period, 2002–2006; and the third period, 2007–2011. We further excluded the following patients: patients with missing data on gender or age; patients who were reported to the monitoring system more than 3 years after diagnosis, because a longer period since diagnosis could introduce a reverse relationship between causative factors or underlying disease treated with steroids and development of ONFH; and patients aged 15 years or less, to avoid the possible inclusion of Perthes disease.

Underlying diseases treated by steroid administration were categorized as follows: systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), polymyositis/dermatomyositis, mixed connective tissue disease, Sjögren syndrome, other types of collagen disease, nephrotic syndrome, nephritis, renal transplantation, other organ transplantation (except renal transplantation and bone marrow transplantation), hematological malignancy, thrombocytopenic purpura, aplastic anemia, inflammatory bowel disease, hepatitis, bronchial asthma, pulmonary disease (except asthma), skin disease, eye disease, ear disease, facial palsy, and other disease. In patients with two or more underlying diseases treated by steroid administration, each disease was counted in the analyses. Information on the dosage and duration of steroid administration was not obtained.

In order to evaluate the potential bias of hospitals newly participating in the monitoring system, we conducted an additional analysis by limiting the data to that collected by the 11 hospitals that regularly reported patients throughout the study period (Asahikawa Medical University Hospital, Kanazawa Medical University Hospital, Kyoto Prefecture University Hospital, Kyushu University Hospital, Kurume University Hospital, Nagasaki University Hospital, Nagoya University Hospital, Osaka University Hospital, Saga University Hospital, Shinshu University Hospital, and Showa University Fujigaoka Hospital).

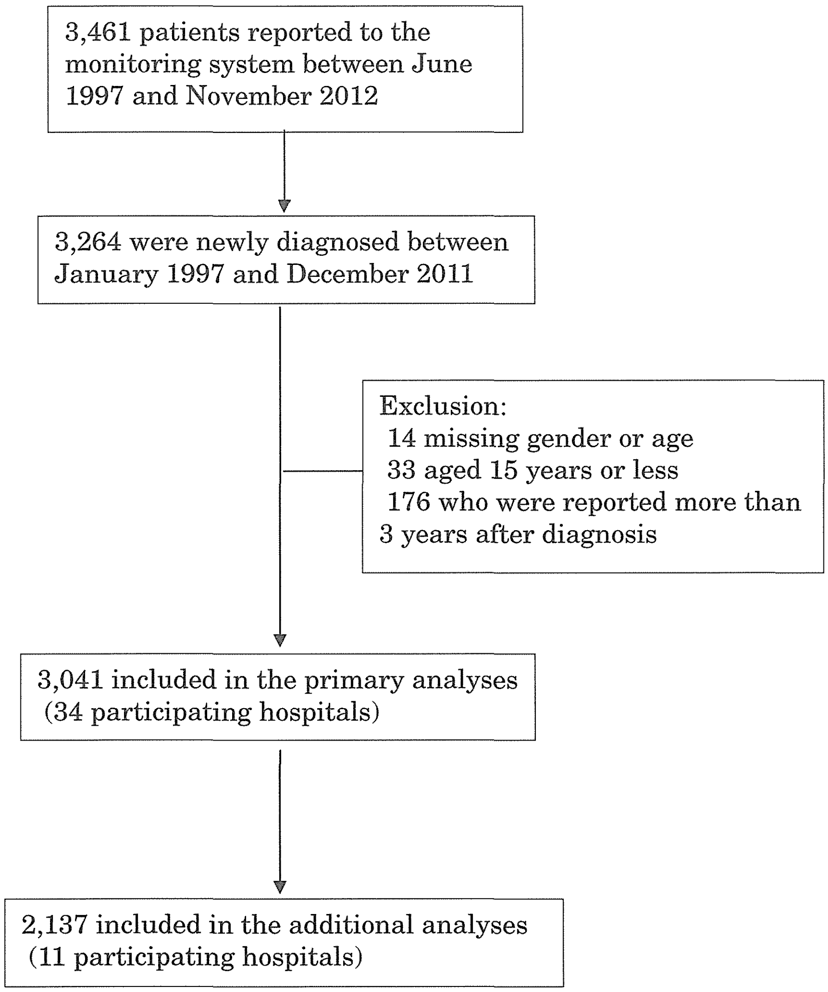

Figure 1. Flow diagram of the selection of subjects for analyses of trends in nontraumatic osteonecrosis of the femoral head. The additional analyses included 11 hospitals that regularly reported patients throughout the study period.

Trends in gender, age, potential causative factors, and underlying diseases treated by steroid administration were examined using the Cochran-Armitage test. Statistical tests were employed with the significance level set at 0.05. All *P* values were two-sided. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

RESULTS

Figure 1 shows the flow diagram of the present study. A total of 3264 patients were diagnosed between January 1997 and December 2011 in 34 participating hospitals. Ultimately, 3041 patients were subjected to the primary analyses, and 2137 patients who were reported by the 11 hospitals were included in additional analyses.

The annual number of patients diagnosed at the 11 participating hospitals increased substantially for both genders throughout the study period (Figure 2). However, the increase became fairly subtle after 2006. The number of patients appeared to decline in 2011 because the present analysis did not include those patients who had been diagnosed before 31st December 2011 but had not been reported by November 2012.

The gender ratio (male:female) was 1.7 over the entire period and remained consistent throughout the study period (Table 1). In males, the proportion of patients aged 40–49 years significantly decreased. The proportions of patients aged 50–59, 60–69, and ≥70 years increased, although the differences were not significant. In females, a significant decrease in the proportion of patients aged 16–29 years and significant increases in those aged 30–39 and 60–69 years were observed. Regarding assessment of the distribution of potential causative factors in males, the proportion of patients with habitual alcohol intake was the highest (48%), followed by systemic steroid administration (35%), neither factor (9.6%), and both factors (7.9%). In females, those with systemic steroid administration accounted for the majority of the causes (70%), while a higher proportion of females than males reported neither cause (17%). The average age of males with a history of habitual alcohol intake was 45 (standard deviation [SD], 12) years. Regarding patients treated by steroid administration, the average (SD) age of SLE and non-SLE males was 37 (13) years and 44 (14) years, respectively. In females, the average (SD) age of patients with a history of habitual alcohol intake was 42 (12) years. The average

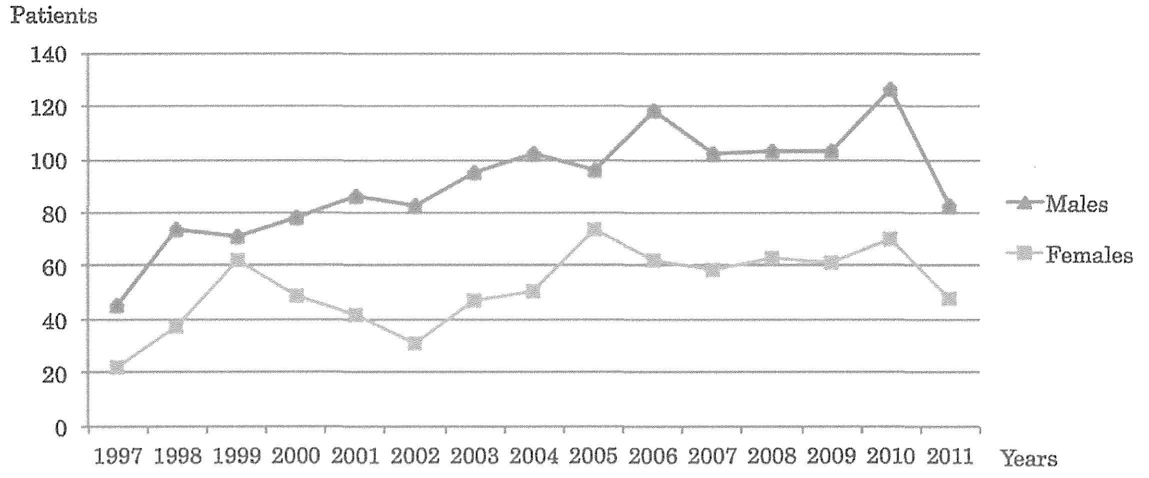

Figure 2. Annual trends in the reported number of newly diagnosed patients with nontraumatic osteonecrosis of the femoral head from 1997–2011 according to gender. The trends are presented for the 11 hospitals which regularly reported patients throughout the study period. The number of patients gradually increased for both sexes until 2006.

Table 1. Trends in the distribution of demographic data and potential causative factors according to gender from 1997–2011

	Study period[a]				P^b
	Entire period *n* = 3041	First period *n* = 678	Second period *n* = 1039	Third period *n* = 1324	
Number of participating hospitals	33	16	21	30	
Gender ratio (male:female)	1.7	1.6	1.7	1.6	0.963
Males	*(n = 1902)*	*(n = 418)*	*(n = 661)*	*(n = 823)*	
Age (years)					
16–29	250 (13)	63 (15)	91 (14)	96 (12)	0.078
30–39	510 (27)	105 (25)	188 (28)	217 (26)	0.821
40–49	489 (26)	120 (29)	175 (26)	194 (24)	0.043
50–59	385 (20)	80 (19)	120 (18)	185 (22)	0.092
60–69	194 (10)	37 (8.9)	62 (9.4)	95 (12)	0.105
≥70	74 (3.9)	13 (3.1)	25 (3.8)	36 (4.4)	0.270
Potential causative factors					
Systemic steroid administration	660 (35)	152 (36)	237 (36)	271 (33)	0.184
Habitual alcohol intake	906 (48)	193 (46)	319 (48)	394 (48)	0.631
Both	150 (7.9)	32 (7.7)	43 (6.5)	75 (9.1)	0.227
Neither	182 (9.6)	41 (9.8)	59 (9.0)	82 (10)	0.821
Unknown	4	0	3	1	
Females	*(n = 1139)*	*(n = 260)*	*(n = 378)*	*(n = 501)*	
Age (years)					
16–29	213 (19)	62 (24)	81 (21)	70 (14)	0.001
30–39	236 (21)	40 (15)	74 (20)	122 (24)	0.003
40–49	197 (17)	49 (19)	62 (16)	86 (17)	0.642
50–59	186 (16)	48 (18)	69 (18)	69 (14)	0.062
60–69	175 (15)	32 (12)	55 (15)	88 (18)	0.048
≥70	132 (12)	29 (11)	37 (9.8)	66 (13)	0.288
Potential causative factors					
Systemic steroid administration	789 (70)	184 (71)	263 (70)	342 (69)	0.548
Habitual alcohol intake	124 (11)	22 (8.5)	48 (13)	54 (11)	0.468
Both	31 (2.7)	2 (0.8)	10 (2.7)	19 (3.8)	0.015
Neither	187 (17)	51 (20)	55 (15)	81 (16)	0.352
Unknown	8	1	2	5	

Values are expressed as numbers (%).
[a]Study period was divided into first (1997–2001), second (2002–2006), and third (2007–2011) periods.
[b]The Cochran-Armitage test.

Table 2. Trends in the distribution of underlying diseases for which patients received steroid therapy during 1997–2011 in males

	Study period[a]				P^b
	Entire period $n = 810$	First period $n = 184$	Second period $n = 280$	Third period $n = 346$	
Systemic lupus erythematosus	73 (9.0)	19 (10)	32 (11)	22 (6.4)	0.077
Rheumatoid arthritis	13 (1.6)	5 (2.7)	5 (1.8)	3 (0.9)	0.103
Polymyositis/dermatomyositis	31 (3.8)	6 (3.3)	13 (4.6)	12 (3.5)	0.991
Mixed connective tissue disease	7 (0.9)	3 (1.6)	1 (0.4)	3 (0.9)	0.506
Sjögren syndrome	6 (0.7)	1 (0.5)	2 (0.7)	3 (0.9)	0.663
Other type of collagen disease	45 (5.6)	6 (3.3)	10 (3.5)	29 (8.4)	0.005
Nephrotic syndrome	66 (8.1)	15 (8.2)	23 (8.2)	28 (8.1)	0.984
Nephritis	39 (4.8)	6 (3.3)	16 (5.7)	17 (4.9)	0.475
Renal transplantation	16 (2.0)	7 (3.8)	5 (1.8)	4 (1.2)	0.047
Other organ transplantation[c]	4 (0.5)	0 (0)	2 (0.7)	2 (0.6)	0.433
Hematological malignancy	66 (8.1)	11 (6.0)	25 (8.9)	30 (8.7)	0.313
Thrombocytopenic purpura	33 (4.1)	10 (5.4)	10 (3.6)	13 (4.8)	0.434
Aplastic anemia	12 (1.5)	2 (1.1)	3 (1.1)	7 (2.0)	0.321
Inflammatory bowel disease	50 (6.7)	12 (6.5)	21 (7.5)	17 (4.9)	0.373
Hepatitis	13 (1.6)	2 (1.1)	6 (2.1)	5 (1.4)	0.868
Bronchial asthma	61 (7.5)	11 (6.0)	20 (7.1)	30 (8.6)	0.225
Pulmonary disease[d]	26 (3.2)	1 (0.5)	10 (3.6)	15 (5.5)	0.022
Skin disease	38 (4.7)	9 (4.9)	8 (2.9)	21 (6.1)	0.328
Eye disease	39 (4.8)	8 (4.3)	15 (5.4)	16 (4.6)	0.936
Ear disease	37 (4.6)	11 (6.0)	11 (3.9)	15 (4.3)	0.487
Facial palsy	11 (1.4)	2 (1.1)	4 (1.4)	5 (1.4)	0.739
Other disease	151 (19)	38 (21)	50 (18)	63 (18)	0.606
Unknown	6	1	1	4	

Values are expressed as numbers (%).
[a]Study period was divided into first (1997–2001), second (2002–2006), and third (2007–2011) periods.
[b]The Cochran-Armitage test.
[c]Except renal transplantation and bone marrow transplantation.
[d]Except asthma.

(SD) age of SLE and non-SLE females with a history of steroid administration was 37 (13) years and 49 (14) years, respectively.

With respect to alcohol consumption in patients who were reported to the monitoring system after 2009, the average (SD) alcohol intake per day was 74 (55) g of ethanol and the average drinking period was 20 (12) years. All the patients who were reported after 2009 had a history of alcohol consumption of three days a week or more.

Table 2 and Table 3 show underlying diseases treated by systemic steroid administration. In males (Table 2), the most frequent disease was SLE (9.0%), followed by nephrotic syndrome (8.1%), hematological malignancy (8.1%), and bronchial asthma (7.5%). In females (Table 3), SLE was again the most frequent underlying disease treated by steroids (34%), followed by bronchial asthma (6.1%), polymyositis/dermatomyositis (5.7%), and thrombocytopenic purpura (5.5%). The proportion with SLE declined in the third period in both males and females ($P = 0.077$ and $P = 0.022$, respectively). The proportion of patients receiving steroid treatment for renal transplantation fell consistently across the study period in both males and females ($P = 0.047$ and $P = 0.038$, respectively). In contrast, the proportion of patients with pulmonary disease (except asthma) showed consistent increases in both males and females ($P = 0.022$ and $P = 0.027$, respectively). In females, an increase in the proportion of patients receiving steroids for skin disease was observed during the third period ($P = 0.046$).

In the additional analysis, which included data from 11 hospitals (eTable 1), the results were unchanged in comparison to the primary analyses except for the following: the change in the proportion of potential causative factors in males was statistically significant, with a decrease from 36% to 27% in systemic steroid administration ($P = 0.002$) and an increase from 47% to 53% in habitual alcohol intake ($P = 0.104$) (eTable 1); regarding underlying diseases treated by steroid administration in males, the proportion of patients treated for RA significantly decreased from 3.2% to 0% ($P = 0.026$), while decreases in the proportion of patients treated for SLE and renal transplantation did not reach statistical significance (eTable 2 and eTable 3).

DISCUSSION

This study, which analyzed the data of over 3000 patients who were newly diagnosed with ONFH during a 15-year period in Japan, is the first to investigate temporal trends in the characteristics of ONFH. The strengths of our monitoring system include the strict diagnostic criteria, in which all diagnoses were carried out by hip surgeons who were members of the research committee. It has been shown that, in Japan, 12% of patients who had been diagnosed with

Table 3. Trends in the distribution of underlying diseases for which patients received steroid therapy during 1997–2011 in females

	Study period[a]				P^b
	Entire period n = 820	First period n = 186	Second period n = 273	Third period n = 361	
Systemic lupus erythematosus	275 (34)	69 (37)	102 (37)	104 (29)	0.022
Rheumatoid arthritis	11 (1.3)	1 (0.5)	3 (1.1)	7 (1.9)	0.160
Polymyositis/dermatomyositis	47 (5.7)	11 (6.0)	14 (5.1)	22 (6.1)	0.870
Mixed connective tissue disease	31 (3.8)	4 (2.2)	13 (4.8)	14 (3.9)	0.395
Sjögren syndrome	23 (2.8)	5 (2.7)	5 (1.8)	13 (3.6)	0.413
Other type of collagen disease	48 (5.9)	4 (2.2)	10 (3.7)	34 (9.4)	<0.001
Nephrotic syndrome	34 (4.1)	7 (3.8)	11 (4.0)	16 (4.4)	0.711
Nephritis	29 (3.5)	4 (2.2)	13 (4.8)	12 (3.3)	0.675
Renal transplantation	15 (1.8)	6 (3.2)	6 (2.2)	3 (0.8)	0.038
Other organ transplantation[c]	4 (0.5)	1 (0.5)	1 (0.4)	2 (0.6)	0.931
Hematological malignancy	39 (4.8)	10 (5.4)	18 (6.6)	11 (3.0)	0.120
Thrombocytopenic purpura	45 (5.5)	14 (7.5)	13 (4.8)	18 (5.0)	0.263
Aplastic anemia	8 (1.0)	2 (1.1)	1 (0.4)	5 (1.4)	0.556
Inflammatory bowel disease	20 (2.4)	8 (4.3)	5 (1.8)	7 (1.9)	0.124
Hepatitis	16 (2.0)	2 (1.1)	4 (1.5)	10 (2.8)	0.143
Bronchial asthma	50 (6.1)	10 (5.4)	17 (6.2)	23 (6.4)	0.682
Pulmonary disease[d]	20 (2.4)	1 (0.5)	6 (2.2)	13 (3.6)	0.027
Skin disease	22 (2.7)	4 (2.2)	2 (0.7)	16 (4.4)	0.046
Eye disease	21 (2.6)	5 (2.7)	6 (2.2)	10 (2.8)	0.896
Ear disease	15 (1.8)	2 (1.1)	5 (1.8)	8 (2.2)	0.389
Facial palsy	8 (1.0)	1 (0.5)	5 (1.8)	2 (0.6)	0.742
Other disease	86 (10)	16 (8.6)	28 (10)	42 (12)	0.280
Unknown	3	0	0	3	

Values are expressed as numbers (%).
[a]Study period was divided into first (1997–2001), second (2002–2006), and third (2007–2011) periods.
[b]The Cochran-Armitage test.
[c]Except renal transplantation and bone marrow transplantation.
[d]Except asthma.

ONFH and had been reported to the medical claim system were misdiagnosed because some physicians were unfamiliar with ONFH.[11] Using standardized and consistent criteria over the study period also enhanced the reliability of observed trends. In addition, the monitoring system has many advantages with respect to costs and labor in comparison to a nationwide epidemiologic survey involving random sampling of participating hospitals.[5]

We observed an increase in the annual number of newly-diagnosed patients among the 11 participating hospitals from 1997 to 2006. This finding is consistent with previous reports[3–5] and may be partly explained by the spread of the use of magnetic resonance imaging (MRI), which has contributed to accurate diagnosis of ONFH. Organization for Economic Co-operation and Development (OECD) health data showed that the availability of MRI units has increased in most OECD countries over the past two decades.[12] In Japan, the number of MRI units per million people showed a sharp increase from 1996 to 2005 (23.2 units and 40.1 units, respectively), whereas the increase levelled off in 2008 (43.1 units). Our study also suggests no further increase in the number of patients after 2006.

We investigated trends in patient characteristics, both in all participating hospitals and in the subset of 11 hospitals, to assess potential biases that may have been introduced by newly participating hospitals. Because we did not observe a substantial difference between the two datasets, the results of the primary analyses are discussed below.

The age at disease diagnosis shifted from a younger age toward an older age across the study period, especially in females. One possible reason is the decreased proportion of patients receiving steroid treatment for SLE, which was the most frequent underlying disease treated by steroid administration in the present study and is likely to affect the younger population because the average age of patients treated for SLE was younger than that of non-SLE patients. Another possible reason is the aging population in Japan. The proportion of the population aged 16–29 years among those aged 16 years or older decreased from 23% in 2000 to 17% in 2010, while the proportions of the population aged 30–39 and 60–69 years increased from 13% to 14% and 11% to 13%, respectively.[13]

The proportion of patients with a history of habitual alcohol intake did not show apparent trends. Additional information of patients with ONFH who were reported after 2009 showed that all patients who had a history of alcohol consumption did so on three days a week or more. According to the National Health and Nutrition Survey in Japan, the prevalence of those who drink three days a week or more has been decreasing: in males, values were 53% in 1999, 38% in 2004, and 36% in