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Evaluating the association between avascular necrosis of femoral head and oral corticosteroids use in Taiwan

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Abstract

The aim of this study was to assess a correlation between avascular necrosis of femoral head and oral corticosteroids use in the general population in Taiwan. A population-based case-control study was performed to analyze the database of Taiwan National Health Insurance Program. The study consisted of 3002 subjects aged 20 to 84 with newly diagnosed avascular necrosis of femoral head between 2000 and 2013 as the cases and 11279 sex-matched and age-matched subjects without avascular necrosis of femoral head as the matched controls. Use of oral corticosteroids was defined as subjects who had at least a prescription for oral corticosteroids before the index date. No use of oral corticosteroids was defined as subjects who did not have a prescription for oral corticosteroids before the index date. The logistic regression model revealed that subjects with avascular necrosis of femoral head were 1.65 times more likely to be exposed to oral corticosteroids than those subjects without avascular necrosis of femoral head (OR 1.65, 95% CI = 1.51–1.80). A sub-analysis revealed that there was a significant association between avascular necrosis of femoral head and increasing cumulative duration of oral corticosteroids for each additional month of use (OR 1.03, 95% CI = 1.02–1.03). A significant association is detected between avascular necrosis of femoral head and oral corticosteroids use in the general population in Taiwan. There is a duration-dependent effect of oral corticosteroids use on the risk of avascular necrosis of femoral head. Clinicians should be aware of the risk of avascular necrosis of femoral head when oral corticosteroids are prescribed for a long time.

Abbreviation: ICD-9 code = International Classification of Diseases, 9th Revision, Clinical Modification.

Keywords: avascular necrosis, case-control study, femoral head, oral corticosteroids, Taiwan National Health Insurance Program

1. Introduction

Avascular necrosis of femoral head is defined as a reduction of blood supply to femoral head resulting in cellular death, head collapse, and finally secondary osteoarthritis of hip joint.[1,2] Avascular necrosis of femoral head is a progressive debilitating disease with irreversible destruction of hip joint and eventually needing total hip arthroplasty.[3,4] From a view of preventive medicine, primary prevention, and early detection are important because the stage and location of avascular necrosis of femoral head will affect the prognosis.[4,5] To date, wide range of risk factors has been described, including trauma, alcohol consumption, and corticosteroids use.[6–8]

Some epidemiological studies have shown the correlation between avascular necrosis of femoral head and other comorbidities,[9–11] An observational study in Taiwan showed that corticosteroids use accounted for 21.7% of the etiologies for avascular necrosis of femoral head,[12] but this study only used

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CLL and KFL conducted data analysis.

Insurance reimbursement claims data used in this study were available for public access. Patient identification numbers were scrambled to ensure confidentiality. Patient informed consent was not required. This study was approved by the Research Ethics Committee of China Medical University and Hospital in Taiwan (CMUH-104-REC2-115).

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one hospital record and it could not be extrapolated to the general population in Taiwan. An observational study in Taiwan showed that avascular necrosis of femoral head was the leading cause of total hip replacement (accounting for 46.9% of cases with total hip replacement).[13] An observational study reported that at least 76% of the general population in Taiwan has ever used corticosteroids.[14] Based on the above review, we made a plausible hypothesis that there could be a link between avascular necrosis of femoral head and corticosteroids use in the general population in Taiwan. Given avascular necrosis of femoral head causing a serious outcome, if a link between avascular necrosis of femoral head and corticosteroids use really exists in the general population, active surveillance for femoral head and harm reduction program should be suggested among corticosteroid users. Therefore, a population-based study was performed to address the following objectives:

(1) Whether there is a possible correlation between avascular necrosis of femoral head and oral corticosteroids use in the general population in Taiwan?
(2) Whether there is a duration-dependent effect of oral corticosteroids use on the risk of avascular necrosis of femoral head?

2. Methods

2.1. Study design and data source

A population-based case-control study was conducted to analyze the database of the Taiwan National Health Insurance Program. The program was launched in March 1995 and has covered 99.7% of 23 million residents living in Taiwan.[15–17] The details of the program can be found in previous studies.[18–20]

2.2. Study subjects

Subjects aged 20 to 84 years with newly diagnosed avascular necrosis of femoral head during the period between 2000 and 2013 were selected as the cases (based on International Classification of Disease, 9th Revision of Clinical Modification [ICD-9] code 733.42). The diagnosis date of avascular necrosis of femoral head was defined as the index date. In addition, for every case with avascular necrosis of femoral head, approximately 4 subjects aged 20 to 84 years without a diagnosis of avascular necrosis of femoral head were selected from the same database as the controls. The cases and the controls were matched for sex, age (every 5-year span), comorbidities, and the year of the index date.

2.3. Definition of oral corticosteroids use

Oral corticosteroids in Taiwan during 2000–2013 were included as follows: cortisone, dexamethasone, fludrocortisone, methylprednisolone, prednisolone, and triamcinolone. The definition of oral corticosteroids use was adapted from previous studies.[21–23] Use of oral corticosteroids was defined as subjects who had at least a prescription for oral corticosteroids before the index date. No use of oral corticosteroids was defined as subjects who did not have a prescription for oral corticosteroids before the index date.

2.4. Comorbidities studied

Comorbidities before the index date were selected as follows: alcohol-related disease, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, hyperlipidemia, and hypertension, as well as cardiovascular disease including coronary artery disease, heart failure, cerebrovascular disease, and peripheral atherosclerosis. All comorbidities were diagnosed based on ICD-9 codes, which have been well assessed in previous studies.[24–28]

To increase the analysis validity, subjects having at least 2 episodes of the same diagnosis for avascular necrosis of femoral head and comorbidities during the ambulatory care and/or having at least one episode of hospitalization diagnosis could be included in the study. Principal diagnosis and secondary diagnosis were equally applied. Such stringent criteria were adapted from previous studies.[14,29]

2.5. Statistical analysis

The differences of the demographic status, oral corticosteroids use, and comorbidities between the cases and the matched controls were assessed by using the Chi-square test for categorized variables and the *t* test for continuous variables. All variables were tested by the logistic regression model. The odds ratio and the 95% confidence interval were used to assess the correlation between avascular necrosis of femoral head and oral corticosteroids use. A further analysis was conducted to assess the correlation between avascular necrosis of femoral head and cumulative duration of oral corticosteroids use. Analyses were performed by using the SAS 9.2 version (SAS Institute Inc., Carey, North Carolina), with $P < .05$ as statistically significant.

3. Results

3.1. Basic information of the study population

Table 1 revealed the distributions of sex, age, oral corticosteroids use, and comorbidities between the cases and the matched controls. The study included 3002 cases with avascular necrosis of femoral head and 11279 matched controls, with similar distributions of sex and age. The mean ages (standard deviation) of the study subjects were 52.9 (14.6) in the cases and 52.7 (14.8) in the matched controls, without statistical significance (*t* test, $P = .45$). The cases had a higher proportion of use of oral corticosteroids than the matched controls, with statistical significance (71.2% vs 60.0%, Chi-square test, $P < .001$). The proportions of comorbidities were equally distributed in the cases and the matched controls (Chi-square test, $P > .05$).

3.2. Association between avascular necrosis of femoral head and oral corticosteroids use

Table 2 revealed the association between avascular necrosis of femoral head and oral corticosteroids use. Because other variables studied were not significantly associated with avascular necrosis of femoral head in a univariable logistic regression model, the multivariable logistic regression model was not performed. The univariable logistic regression model revealed that there was a significant association between avascular necrosis of femoral head and oral corticosteroids use (OR 1.65, 95% CI= 1.51–1.80). A sub-analysis in Table 3 revealed that there was a significant association between avascular necrosis of femoral head and increasing cumulative duration of oral corticosteroids for each additional month of use (OR 1.03, 95% CI= 1.02–1.03).

Table 1

Basic information of subjects with and without avascular necrosis of femoral head.

	Avascular necrosis of femoral head				
	No N = 11279		Yes N = 3002		
Variable	n	(%)	n	(%)	*P* value*
Sex					.65
Female	3364	29.8	908	30.3	
Male	7915	70.2	2094	69.7	
Age group, yr					.99
20–39	5081	45.1	1351	45.0	
40–64	3477	30.8	930	31.0	
65–84	2721	24.1	721	24.0	
Age, yr, mean ± standard deviation†	52.7 ± 14.8		52.9 ± 14.6		.45
Use of oral corticosteroids	6768	60.0	2138	71.2	<.001
Comorbidities before index date					
Alcohol-related disease	1719	15.2	489	16.3	.16
Cardiovascular disease	3241	28.7	874	29.1	.68
Chronic kidney disease	900	7.98	252	8.39	.46
Chronic obstructive pulmonary disease	2386	21.2	643	21.4	.75
Diabetes mellitus	862	7.64	236	7.86	.69
Hyperlipidemia	3131	27.8	840	28.0	.81
Hypertension	4554	40.4	1221	40.7	.77

Data are presented as the number of subjects in each group, with percentages given in parentheses.

* Chi-square test, and.

† *t* test comparing subjects with and without avascular necrosis of femoral head.

4. Discussion

In this present study, subjects with avascular necrosis of femoral head were 1.65 times more likely to be exposed to oral corticosteroids than those subjects without avascular necrosis of femoral head, which was compatible with previous studies.[8,30] In a further analysis, subjects with avascular necrosis of femoral head were 1.55 times more likely to be exposed to oral corticosteroids <12 months than those without avascular necrosis of femoral head, which was partially compatible with a previous study revealing that patients would develop avascular necrosis of femoral head within 12 months of initiating corticosteroids use.[31] In addition, subjects with avascular necrosis of femoral head were 4.7 times more likely to be exposed to oral corticosteroids ≥12 months than those without avascular necrosis of femoral head. These findings indicate that there appears to a duration-dependent effect of oral corticosteroids use on the risk of avascular necrosis of femoral head. That is, the longer the duration of oral corticosteroids use, the greater the risk of avascular necrosis of femoral head.

Table 2

Odds ratio and 95% confidence interval of association between avascular necrosis of femoral head and oral corticosteroids use.

Variable	OR	(95% CI)
Sex (male vs female)	0.98	(0.90, 1.07)
Age (every 1 yr)	1.00	(0.99, 1.00)
Use of oral corticosteroids (no use as a reference)	1.65	(1.51, 1.80)
Comorbidities before index date (yes vs no)		
Alcohol-related disease	1.08	(0.97, 1.21)
Cardiovascular disease	1.02	(0.93, 1.11)
Chronic kidney disease	1.06	(0.91, 1.22)
Chronic obstructive pulmonary disease	1.02	(0.92, 1.12)
Diabetes mellitus	1.03	(0.89, 1.20)
Hyperlipidemia	1.01	(0.92, 1.11)
Hypertension	1.01	(0.93, 1.10)

Because other variables studied were not significantly associated with avascular necrosis of femoral head in a univariable model, the multivariable model was not performed.
CI = confidence interval, OD = Odds ratio.

The current literature on the mechanisms underlying the association between avascular necrosis of femoral head and oral corticosteroids use was summarized as follows. The animal models revealed that hyperlipidemia and increased free fatty acids were detected in rabbits with corticosteroid-induced avascular necrosis of femoral head.[32–34] These circulating lipids are likely to develop systemic fat emboli, which slow blood flow and compromise blood supply to the affected femoral head, and eventually cause death of affected bone cells.[1,35,36] These

Table 3

Odds ratio and 95% confidence interval of association between avascular necrosis of femoral head and cumulative duration of oral corticosteroids use.

Variable	Case number /control number	OR	(95% CI)
No use of oral corticosteroids as a reference	864/4511	1.00	(reference)
Cumulative duration of oral corticosteroids use (increase in duration for every one month)	2138/6768	1.03	(1.02, 1.03)
Cumulative duration of oral corticosteroids use <12 mo	1947/6556	1.55	(1.42, 1.69)
Cumulative duration of oral corticosteroids use ≥12 mo	191/212	4.70	(3.82, 5.80)

Because other variables studied were not significantly associated with avascular necrosis of femoral head in a univariable model, the multivariable model was not performed.
CI = confidence interval, OD = Odds ratio.

mechanisms represent a potential pathway of corticosteroid-associated avascular necrosis of femoral head. It can be partially supported by the evidence that statins are lipid-lowing agents, which can be associated with reduced risk of corticosteroid-related avascular necrosis of femoral head in animal and human studies.[37–40]

5. Limitation

Some limitations should be discussed. First, due to inborn limitation of the database, socioeconomic factors and traditional medicines use were not recorded in the database. It was unable to quantify the use of traditional medicines, which might contain undeclared corticosteroids. In addition, alcohol-related disease was used instead of alcohol consumption. This point has been mentioned in previous studies.[41,42] Second, due to the same limitation, the etiologic factor of avascular necrosis of femoral head was not recorded in the database. The traumatic or non-traumatic cause could not be differentiated. Third, due to a case-control design, whether the timing of corticosteroids use was before or after the onset of avascular necrosis of femoral head could not be differentiated. However, cases in this present study were those subjects with newly diagnosed avascular necrosis of femoral head, so corticosteroids really were used before the diagnosis of avascular necrosis of femoral head.

6. Conclusion

A significant association is detected between avascular necrosis of femoral head and oral corticosteroids use in the general population in Taiwan. There is a duration-dependent effect of oral corticosteroids use on the risk of avascular necrosis of femoral head. Clinicians should be aware of the risk of avascular necrosis of femoral head when oral corticosteroids are prescribed for a long time.

Author contributions

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