

# Factors Associated With the Course of Femoral Head Osteonecrosis; A Retrospective Study

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Received: February 22, 2015; Revised: March 20, 2015; Accepted: March 26, 2015

**Background:** An increased incidence of osteonecrosis of the femoral head (ONFH) has recently been observed in Iran, likely associated with the introduction of an illegal, steroid-containing opioid drug, Temgesic. The correlation of risk factors associated with the course of ONFH has yet to be determined.

**Objectives:** The purpose of the present study was to assess the effects of etiologic factors on the course of ONFH after emergence of symptoms.

**Patients and Methods:** We retrospectively assessed patients with untreated ONFH due to one of the four etiologies of steroid medication, Temgesic abuse, trauma and idiopathic. Patients with multiple risk factors and those without collapse at the last follow-up visit were excluded. The effect of age, gender, etiology of osteonecrosis, opium addiction and smoking on the time interval between pain onset and radiologic collapse were investigated.

**Results:** In total, 110 patients (174 hips) were categorized into four etiologic groups. The average time between onset of pain to radiologic collapse in different etiologic groups was 12.8 months for all groups, 12.4 months for steroid, 8.7 months for Temgesic, 18.5 months for trauma and 16.6 months for idiopathic groups. Thirteen hips had collapse in less than six months. Patients who used steroid and Temgesic had shorter time interval to collapse, which was statistically significant (P Values < 0.001 and < 0.001, respectively). Smoking had a statistically significant association with the time to femoral head collapse (P Value = 0.003).

**Conclusions:** Steroid medications and Temgesic abuse are associated with shorter time interval to femoral head collapse. Smoking is also a factor associated with shorter time interval to collapse. These factors should be considered in any joint preserving treatments for patients with FHON.

**Keywords:** Hip; avascular necrosis; Smoking

## 1. Background

Osteonecrosis of the femoral head (ONFH) is a devastating condition, which usually results in hip destruction in young and middle-aged patients (1). The outcome is collapse or arthritis in most patients (2).

Although ONFH can be idiopathic, some etiologic factors have been identified such as: trauma, steroid medication, alcohol abuse, coagulation and haematological disorders, radiation, chemotherapy, Human Immunodeficiency Virus (HIV) infection and sickle cell anemia (SCA) (3). Of note, there has been an increased incidence of osteonecrosis in drug abusers in Iran following the introduction of "Temgesic" to the illicit market several years ago (4). Temgesic is a combination of opioid and steroid medications and is used intravenously (5).

The natural history of ONFH and the time to collapse vary in different cases (1, 3, 6, 7). The impact of risk factors on the natural course of disease has not been clearly

determined. The confounding effects of different modifying factors and common accompaniment of more than one of these factors in a patient add to the complexity of the issue.

Literature concurs that without treatment, most hips affected by ONFH ultimately fail and need a salvage surgery (4). This finding accentuates the necessity of timely intervention to preserve the hip, since few hip preserving interventions are available after collapse (1). Having an estimation of the time to collapse would aid surgeons in determining the optimal course of action.

## 2. Objectives

The purpose of the present study was to assess the effects of etiologic factors on the course of ONFH after emergence of symptoms.

### 3. Patients and Methods

This study was approved by the local ethics board committee of the orthopedic surgery Department of the Iran University of Medical Sciences. Included patients had sustained femoral head osteonecrosis and presented to two referral hospitals in Tehran, Iran (Shafa and Milad hospitals) from September 2008 to February 2011. Documents of all patients who presented with the diagnosis of FHO were assessed. We excluded asymptomatic cases, cases with prior hip surgery (except for trauma-induced hips), those with any concomitant hip disease, those with more than one risk factor (e.g. patients under steroid therapy for Systemic Lupus Erythematosus (SLE)), those receiving medications suspected to affect the disease course (e.g. bisphosphonates) and patients who did not have X-rays before collapse or those in whom the date of collapse could not be determined with three months accuracy. Patients with uncommon etiologies were also excluded.

All patients were thoroughly investigated for presence of any known risk factors for ONFH to categorize them into different groups. A meticulous history was taken from each patient, focusing on any significant history of steroid medication, alcohol/drug abuse, smoking and trauma. Whenever possible, we verified patients' statements by his or her medical documents. The patients were also specifically studied for hyperlipidemia, hypercoagulation states, SCA and infection with HIV.

Patients were assigned to groups according to the presumed etiologic factors. Four etiologic groups were determined including steroid-induced, Temgesic-induced, trauma-induced and idiopathic ONFH. Demographic data and smoking habit were evaluated in all groups. Smoking was defined as consuming at least one cigarette per day.

Only those steroid-receiving patients who had taken a minimal Prednisone-equivalent dose of 2000 mg of a corticosteroid were included, since literature is not conclusive about the causative role of lesser amounts on ONFH (8). In addition, patients with a history of steroid intake due to vasculitic diseases like SLE and Wegener disease were excluded to eliminate the confounding effect of these underlying diseases.

Although Temgesic is a steroid-containing drug, we considered it a separate etiologic factor because of unclear role of other ingredients in causing osteonecrosis.

In the trauma-induced group, we included only hips with documented history of pure dislocation or united femoral neck fracture. Cases of ONFH following hip fracture-dislocation, femoral-head fracture or unhealed femoral-neck fractures were excluded.

Patients were required to have serial radiographs in three month intervals or less. The radiographs were evaluated for collapse by two of the authors (MA and MRS) who were blind to the etiologies, using the radiological classification system recommended by Ficat and Allert (9). All attempts were used to determine the earliest time of radiologic collapse. Ficat IIB was regarded as early collapse (10).

Statistical analysis: Student's t-test and Pearson's Chi-square tests were used for continuous variables and categorical variables, respectively, to examine differences of characteristics among the four etiologic groups. P Value of equal or less than 0.05 was regarded as significant. Multivariate linear regression analysis was used to identify the predictors of time to radiologic collapse. The idiopathic group was used as the reference among the etiologic groups. Temgesic and steroid-induced groups were separately compared to each other.

### 4. Results

Overall, 223 patients with femoral head collapse due to ONFH were visited during the study period. Of these, 113 patients met at least one of the exclusion criteria. There were 14 patients taking less than 2000 mg cumulative dose of steroids, 11 patients with SLE or Wegener disease, 23 trauma-induced cases not fulfilling the inclusion criteria, eight smokers with no other risk factors, seven alcohol-induced cases and nine patients due to other rare etiologies. Forty-one patients were already receiving bisphosphonate therapy or had undergone a surgical intervention and were excluded. 110 remaining patients (174 hips) met the inclusion criteria and were assessed for etiology of osteonecrosis, time interval to collapse and smoking. The mean age of patients was 32.6 years (ranged 18 to 65) at the time of pain onset. Ninety patients (142 hips) were male and 20 (32 hips) were female. Table 1 shows demographic and categorical characteristics of the four groups. Table 2 includes data regarding the outcome and statistical analysis. Some information specific to individual groups is discussed separately.

**Table 1.** Characteristics of the Study Groups

Group	Number of Male Female Patients			Age $\pm$ SD, y	Smokers (%)	Number of Hips	Stage IIB at Final Visit	Stage III at Final Visit	Stage IV at Final Visit
<b>Steroid-induced</b>	45	32	13	30.6 $\pm$ 8.8 (19-65)	17 (37.7%)	77	15	21	41
<b>Temgesic-induced</b>	27	26	1	33 $\pm$ 6.4 (20-45)	25 (89.8%)	49	5	8	36
<b>Trauma-induced</b>	21	17	4	34 $\pm$ 9.5 (26-51)	8 (38.1%)	21	2	5	14
<b>Idiopathic</b>	17	15	2	35.9 $\pm$ 11.3 (24-50)	0 (0%)	27	5	4	18
<b>Total</b>	110	90	20	32.4 $\pm$ 8.9 (19-65)	50 (28.7%)	174	27	38	109

**Table 2.** Time From Pain Onset to Collapse and Statistical Analysis With Idiopathic Group as the Reference

Group	Pain to Collapse $\pm$ SD, mo
Steroid-induced	12.4 $\pm$ 7.0
Temgesic-induced	8.7 $\pm$ 2.9
Trauma-induced	18.5 $\pm$ 6.4
Idiopathic	16.6 $\pm$ 12.0
P Value	< 0.001

#### 4.1. Steroid Induced

All patients had received a minimum total dose of 2000 mg of prednisone or its equivalent. At the time of pain onset, which was 13.4 (5 to 32) months after starting steroid medication, the mean total amount of steroid patients received was 7430 mg (ranged 2300 to 19200). Some were previously healthy patients taken steroids for odd reasons such as gaining weight and others had medical problems not known to predispose to ONFH (e.g. multiple sclerosis, rheumatoid arthritis). Twelve patients (20 hips) were opium-dependent and 18 patients (29 hips) were smokers as well. Addiction to opioids did not affect the time period between pain onset and radiological collapse (P Values, 0.085).

#### 4.2. Temgesic Abuse

The mean duration of abuse was 8.3 months (ranged 3 to 22) at the time of pain onset and the average dose was 7.7 injections (ranged 3 to 18) per day.

#### 4.3. Trauma Induced

Of 21 included hips, six had pure hip dislocation, while united femoral-neck fracture was found in the rest. The average pain free interval after trauma was 11.8 months (ranged 4 to 28).

#### 4.4. Statistical Analysis

Multivariate analysis did not show statistically significant effect of gender, age and opium addiction on the time interval from onset of pain to femoral head collapse (P Value > 0.05). Smoking was associated with earlier collapse as an independent factor (P Value, 0.003). After omitting the effect of this variable, Cox-regression analysis was performed to compare different etiologic groups. With the idiopathic group as a reference, steroid (P Value = 0.007) and Temgesic (P Value < 0.001) groups showed significantly faster courses to collapse after pain onset. The trauma-induced group did not show significantly different (P Value = 0.847) time interval between pain onset and collapse compared to idiopathic group. The Temgesic group showed a significantly faster time-course to collapse compared to the steroid group (P Value < 0.01).

**Table 3.** Multivariate Regression Model on the Effect of Four Etiologic Groups and Other Predictors on the Time to Collapse<sup>a</sup>

Variables	B <sup>b</sup>	SE <sup>b</sup>	P Value <sup>b</sup>
<b>Etiology</b>			
Temgesic	-12.58 <sup>c</sup>	2.64	<.0001
Trauma	0.48	2.45	0.847
Steroid (reference: idiopathic)	-5.78 <sup>c</sup>	2.10	0.007
<b>Age</b>	0.02	0.08	0.839
<b>Gender</b>			
Female (reference: male)	-0.31	1.80	0.863
<b>Smoking</b>			
Yes (reference: no)	-5.33 <sup>c</sup>	1.76	0.003
<b>Intercept</b>	16.05	3.31	<.0001
<b>F ratio</b>	5.81		
<b>Adjusted R-square</b>	0.199		
<b>N</b>	117		

<sup>a</sup> Abbreviations: B, coefficient estimate; N, sample size; SE, standard error.

<sup>b</sup> Time to radiologic collapse

<sup>c</sup> Statistically significant.

## 5. Discussion

ONFH runs a faster course to collapse when caused by steroid intake or Temgesic abuse. Smoking also showed to be an independent risk factor for earlier collapse.

Systemic corticosteroids are strongly associated with osteonecrosis (11, 12). In the present study, earlier radiographic collapse and osteoarthritis might be due to concomitant osteoporosis and systemic effect of medication in the steroids-taking group (13, 14).

The systemic and musculoskeletal complications of Temgesic abuse imposed a heavy burden on the health-care system in the recent years (4, 5). This drug has been widely abused as a result of its low cost and its ability to mask the typical malnourished appearance of opium-dependent patients. Temgesic vials contain corticosteroids and almost all abusers have signs of hypercortisolism, such as striae on their abdominal skin (4). Biochemical studies revealed that the available product in Iran consists of diacetylmorphine, acetylcodeine, pheniramine and heroin (4, 5, 15). As each vial contains 0.4mg Dexamethasone (4), patients of the present study had received an average of 767 mg (ranged 299 to 1792) Dexamethasone by the time of pain onset, which is equivalent to 5061 mg (ranged 1973 to 11827) of prednisone (16).

The average time to collapse was shorter for the Temgesic group compared to the steroid group. There are four possible explanations. One is the presence of a real difference in the course of ONFH between the groups. Heroin is known to induce vasoconstriction at high doses, an effect able to potentiate the effect of steroids in causing ONFH

(17, 18). The possible presence of unknown impurities that influence the pathogenesis of the disease cannot be excluded. Another explanation is a possible recall inaccuracy in the drug-addicted group with their characteristic psychosocial problems. The next possible reason could be the slightly higher monthly dosage of steroids that Temgesic-addicted patients had received (610 versus 550 mg/month for steroid and Temgesic groups, respectively) ( $P = 0.599$ ). The final possibility is that the analgesic effect of drug inhibits the pain sensation in early stages of the disease.

Smoking was indicated as an independent risk factor for a more rapid collapse, as it had already been suggested to initiate the process of ONFH (19). In previous studies, an increased risk was found for ONFH in current smokers (20, 21). The inhaled gases during smoking have been demonstrated to activate osteoclasts (22), which have an important role in the resorption of necrotic bone and consequent collapse in the pathogenesis of osteonecrosis (23). We did not perform a quantitative measurement for smoking and cannot deduce whether reduction in the frequency of smoking is helpful.

The average interval from pain onset to collapse for patients in all etiologic groups was 12.8 months, which is in agreement with a study conducted by Hernigou et al. (2) who reported this time as 12 months (more than 6 months in all cases). In the present study, pain was always preceded by collapse, but sometimes for as short as three months. In total, 13 hips collapsed in less than six months from pain onset; all but one of these cases were in steroid or Temgesic groups. This discrepancy may be due to the fact that the aforementioned study investigated very small asymptomatic osteonecroses that might have followed a longer course to collapse.

The prognostic factors that may play a role in the course of ONFH have been widely studied. One differentiating factor among the studies on ONFH is their reference for prognosis. Some investigate the proportion of osteonecrotic hips that fail either radiologically or clinically (survival studies), while others evaluate the temporal course that hips run to failure (temporal-course studies) (10, 24-26). It is of crucial importance to differentiate these two types when referring to ONFH prognosis. Two separate hips that ultimately collapse are considered prognostically the same by a survival study, but in a temporal-course study, they are considered different if one fails earlier than the other. The present study was a temporal-course study with no assessment of survival rate of hips.

Previous studies on the natural course of ONFH are mostly survival studies that show no correlation between the disease course and the cause (25-29). In studies on asymptomatic ONFH, Bradway (27) and Min (30) found no difference in the course of ONFH for different etiologies. In another study on 50 hips, different etiologic groups were not different regarding the rate or pattern of clinical deterioration (28). Similarly, studies regarding

the time course of ONFH have mostly failed to detect any influence of etiologies (2, 10, 30, 31). In an extensive literature review, Mont et al. reported that ONFH in SLE cases was associated with a better prognosis, whereas a worse prognosis was detected in SCA (25). Other etiologies did not show any significant modifying effects on prognosis. In contrast, we found that ONFH due to steroids and Temgesic ran a faster course after pain onset, resulting in earlier collapse compared with idiopathic ONFH. The authors would like to mention the following features of the current study that might explain this discrepancy. Only symptomatic hips were investigated and every effort was made to make the groups uniform regarding etiologies. To investigate the natural history of the disease, only non-treated patients were included. We also excluded patients with more than one etiology to avoid confounding results. For instance, the relatively better prognosis associated with SLE-induced ONFH might be skewed by the adverse effects of steroids in a patient with SLE treated by steroids. Another strength of the present study was that every attempt was made to find occult underlying etiologies before labelling patient as idiopathic ONFH. Furthermore, the confounding effect of smoking was eliminated using multivariate analysis.

The study had some weaknesses. One is that due to its retrospective nature, recall bias may have been introduced. Especially, the amount of drug abuse might have been under- or over-reported by abusers. However, McElrath et al. (32) revealed that retrospective self-reports from injection drug abusers in their series had acceptable reliability and consistency. Second, we used plain radiography to detect femoral head collapse, which is known to be inferior to MRI in accuracy (11). However, regular MRI study every three months was not a feasible option. Also, any potential delay in detecting collapse probably occurred for all groups with little effect on the comparative results. Another limitation was that the authors did not take the duration and dose of smoking into account. In addition, some common risk factors, such as alcohol abuse, were not available in sufficient numbers for investigation. Moreover, trauma-induced cases were commonly treated by restricted weight bearing for variable periods of time. This, rather than the nature of trauma-induced ONFH, might have resulted in later collapse.

In summary, the present study demonstrated that osteonecrotic hips due to steroid medication and Temgesic abuse follow a faster course to collapse after pain onset than those due to trauma or unknown causes. It is possible for steroid or Temgesic-induced ONFH to collapse in less than six months after pain onset. Furthermore, smoking is a powerful independent risk factor of faster collapse. The findings should be considered in planning for any hip preserving procedures in the treatment of ONFH. Table 3 depicts multivariate regression model on the effect of four etiologic groups and other predictors on the outcome.

## Acknowledgements

We thank Dr. Mohsen Sadeghi and Prof. Kazem Mohammadi for their generous contribution to the statistical analysis and Dr. Abas Behgoo for recruiting his patients for this study.

## Authors' Contributions

Study concept, design and supervision: Allan Edward Gross, Mohammad Taghi Ghazavi, Mansour Abolghasemian and Oleg Safir, Acquisition of data, drafting of the manuscript and critical revision of the manuscript for important intellectual content: Mansour Abolghasemian, Mehdi Ramezan Shirazi, Mohammad Taghi Ghazavi, Kaveh Gharanizadeh and Ali Yeganeh, Analysis and interpretation of data: Mansour Abolghasemian, Mehdi Ramezan Shirazi and Kaveh Gharanizadeh.

## References

- Aldridge J3, Urbaniak JR. Avascular necrosis of the femoral head: etiology, pathophysiology, classification, and current treatment guidelines. *Am J Orthop (Belle Mead NJ)*. 2004;**33**(7):327-32.
- Hernigou P, Poignard A, Nogier A, Manicom O. Fate of very small asymptomatic stage-I osteonecrotic lesions of the hip. *J Bone Joint Surg Am*. 2004;**86-A**(12):2589-93.
- Mont MA, Jones LC, Hungerford DS. Nontraumatic osteonecrosis of the femoral head: ten years later. *J Bone Joint Surg Am*. 2006;**88**(5):1117-32.
- Azizi F, Jahed A, Hedayati M, Lankarani M, Bejestani HS, Esfahanian F, et al. Outbreak of exogenous Cushing's syndrome due to unlicensed medications. *Clin Endocrinol (Oxf)*. 2008;**69**(6):921-5.
- Koushesh HR, Afshari R, Afshari R. A new illicit opioid dependence outbreak, evidence for a combination of opioids and steroids. *Drug Chem Toxicol*. 2009;**32**(2):114-9.
- Malizos KN, Karantanas AH, Varitimidis SE, Dailiana ZH, Bargiotas K, Maris T. Osteonecrosis of the femoral head: etiology, imaging and treatment. *Eur J Radiol*. 2007;**63**(1):16-28.
- Lieberman JR, Berry DJ, Mont MA, Aaron RK, Callaghan JJ, Rajadhyaksha AD, et al. Osteonecrosis of the hip: management in the 21st century. *Instr Course Lect*. 2003;**52**:337-55.
- Colwell CJ, Robinson CA, Stevenson DD, Vint VC, Morris BA. Osteonecrosis of the femoral head in patients with inflammatory arthritis or asthma receiving corticosteroid therapy. *Orthopedics*. 1996;**19**(11):941-6.
- Ficat RP. Idiopathic bone necrosis of the femoral head. Early diagnosis and treatment. *J Bone Joint Surg Br*. 1985;**67**(1):3-9.
- Ohzono K, Saito M, Takaoka K, Ono K, Saito S, Nishina T, et al. Natural history of nontraumatic avascular necrosis of the femoral head. *J Bone Joint Surg Br*. 1991;**73**(1):68-72.
- Shigemura T, Nakamura J, Kishida S, Harada Y, Ohtori S, Kamikawa K, et al. Incidence of osteonecrosis associated with corticosteroid therapy among different underlying diseases: prospective MRI study. *Rheumatol*. 2011;**50**(11):2023-8.
- Kaushik AP, Das A, Cui Q. Osteonecrosis of the femoral head: an update in year 2012. *World J Orthop*. 2012;**3**(5):49-57.
- Weinstein RS. Glucocorticoid-induced osteoporosis and osteonecrosis. *Endocrinol Metab Clin North Am*. 2012;**41**(3):595-611.
- Heffernan MP, Saag KG, Robinson JK, Callen JP. Prevention of osteoporosis associated with chronic glucocorticoid therapy. *JAMA*. 2006;**295**(11):1300-3.
- Wu D, Song D, Ni J, Dai R. Avascular necrosis of the femoral head due to the bilateral injection of heroin into the femoral vein: A case report. *Exp Ther Med*. 2013;**6**(4):1041-3.
- Sparrow A, Geelhoed G. Prednisolone versus dexamethasone in croup: a randomised equivalence trial. *Arch Dis Child*. 2006;**91**(7):580-3.
- Jensen R, Olsen TS, Winther BB. Severe non-occlusive ischemic stroke in young heroin addicts. *Acta Neurol Scand*. 1990;**81**(4):354-7.
- Niehaus L, Meyer B. Bilateral borderzone brain infarctions in association with heroin abuse. *J Neurol Sci*. 1998;**160**(2):180-2.
- Matsuo K, Hirohata T, Sugioka Y, Ikeda M, Fukuda A. Influence of alcohol intake, cigarette smoking, and occupational status on idiopathic osteonecrosis of the femoral head. *Clin Orthopaedics Relat Res*. 1988;**234**:115-23.
- Hirota Y, Hirohata T, Fukuda K, Mori M, Yanagawa H, Ohno Y, et al. Association of alcohol intake, cigarette smoking, and occupational status with the risk of idiopathic osteonecrosis of the femoral head. *Am J Epidemiol*. 1993;**137**(5):530-8.
- Takahashi S, Fukushima W, Kubo T, Iwamoto Y, Hirota Y, Nakamura H. Pronounced risk of nontraumatic osteonecrosis of the femoral head among cigarette smokers who have never used oral corticosteroids: a multicenter case-control study in Japan. *J Orthop Sci*. 2012;**17**(6):730-6.
- Henemyre CL, Scales DK, Hokett SD, Cuenin MF, Peacock ME, Parker MH, et al. Nicotine stimulates osteoclast resorption in a porcine marrow cell model. *J Periodontol*. 2003;**74**(10):1440-6.
- Powell C, Chang C, Gershwin M. Current concepts on the pathogenesis and natural history of steroid-induced osteonecrosis. *Clin Rev Allergy Immunol*. 2011;**41**(1):102-13.
- Merle D'Aubigne R, Postel M, Mazabraud A, Massias P, Gueguen J, France P. Idiopathic necrosis of the femoral head in adults. *J Bone Joint Surg Br*. 1965;**47**(4):612-33.
- Mont MA, Zywiell MG, Marker DR, McGrath MS, Delanois RE. The natural history of untreated asymptomatic osteonecrosis of the femoral head. *J Bone Joint Surg*. 2010;**92**(12):2165-70.
- Mont MA, Hungerford DS. Non-traumatic avascular necrosis of the femoral head. *J Bone Joint Surg Am*. 1995;**77**(3):459-74.
- Bradway JK, Morrey BF. The natural history of the silent hip in bilateral atraumatic osteonecrosis. *J Arthroplasty*. 1993;**8**(4):383-7.
- Musso ES, Mitchell SN, Schink-Asciani M, Bassett CA. Results of conservative management of osteonecrosis of the femoral head. A retrospective review. *Clin Orthop Relat Res*. 1986(207):209-15.
- Nam KW, Kim YL, Yoo JJ, Koo KH, Yoon KS, Kim HJ. Fate of untreated asymptomatic osteonecrosis of the femoral head. *J Bone Joint Surg Am*. 2008;**90**(3):477-84.
- Min BW, Song KS, Cho CH, Lee SM, Lee KJ. Untreated asymptomatic hips in patients with osteonecrosis of the femoral head. *Clin Orthop Relat Res*. 2008;**466**(5):1087-92.
- Jergesen HE, Khan AS. The natural history of untreated asymptomatic hips in patients who have non-traumatic osteonecrosis. *J Bone Joint Surg Am*. 1997;**79**(3):359-63.
- McElrath K, Chitwood DD, Griffin DK, Comerford M. The consistency of self-reported HIV risk behavior among injection drug users. *Am J Public Health*. 1994;**84**(12):1965-70.