

# COAGULATION DISORDERS IN PATIENTS WITH FEMORAL HEAD OSTEONECROSIS

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## ABSTRACT

**Objective:** To compare the occurrence of thrombophilic disorders in patients with idiopathic osteonecrosis of the femoral head and patients with secondary osteonecrosis of the femoral head. **Methods:** Twenty-four consecutive patients were enrolled, with eight of them presenting idiopathic osteonecrosis and 16 presenting secondary osteonecrosis. The tests for detection of thrombophilic disorders were measurements of protein C, protein S and antithrombin levels and detection of prothrombin and factor V gene mutations. We compared the results using the odds ratio statistics for the thrombophilic disorders between the two groups. **Results:** The odds ratio for the protein S deficiency

and protein C deficiency between the idiopathic and secondary groups were 5 and 2.14, respectively. Thus, an individual with idiopathic osteonecrosis has 5 times more chance of presenting protein S deficiency and 2.14 times more chance of presenting protein C deficiency than an individual with secondary osteonecrosis. **Conclusion:** Patients with idiopathic osteonecrosis have more chances of presenting thrombophilias than those with secondary osteonecrosis, suggesting these coagulation disorders can play an important role in the pathogenesis of the osteonecrosis in cases where there was no initial risk factor recognized. **Level of Evidence III, Case-Control Study.**

**Keywords:** Femur head necrosis. Osteonecrosis. Thrombophilia.

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## INTRODUCTION

Femoral head osteonecrosis (FHO) is an ischemic bone disorder that can lead to joint degeneration and is associated with a variety of risk factors such as corticosteroid therapy, alcoholism, hemoglobinopathies, hip trauma, vasculitis, dysbarism, autoimmune diseases, neoplasias, irradiation, hyperuricemia and even pregnancy.<sup>1,2</sup> Despite some proposed theories, several aspects relating to the etiology and pathogenic mechanisms are not completely clear and about 5 to 40% of cases are still classified as idiopathic.<sup>3,4</sup>

In the last two decades some studies<sup>5-14</sup> have demonstrated that blood clotting disorders, more specifically thrombophilias, can also constitute a risk factor for the development of FHO and that a significant proportion of cases thitherto classified as idiopathic in actual fact were associated with these disorders, which are caused by genetic changes and that lead to a state of hypercoagulability and possibly to the formation of thrombi in the microcirculation. The most frequent thrombophilic disorders include G1691A mutation in the factor V gene (the so-called factor V Leiden), G20210A mutation in the prothrombin gene, protein

S deficiency, protein C deficiency and antithrombin deficiency.<sup>15</sup> The aim of this study is to compare the occurrence of these thrombophilias in patients with idiopathic osteonecrosis of the femoral head, i.e., where no risk factor was initially identified, with regards to occurrence in patients with secondary osteonecrosis of the femoral head.

## MATERIALS AND METHODS

The study included 24 consecutive patients who were admitted to the Adult Hip Outpatient Service (AORQ) of Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo (HCFMRP-USP) between February and August 2011 and were diagnosed with FHO. The diagnosis hypothesis of FHO was generated through the clinical history, physical examination and plain radiographs of the pelvis in the anteroposterior and frog-leg views, with confirmation through nuclear magnetic resonance scanning of all the patients. There was no exclusion criterion. The study met the ethical standards of the Declaration of Helsinki from 1995.

Based on the data obtained in the clinical history, the patients

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were divided into two groups, according to the presence or absence of risk factors for FHO. The idiopathic group was formed by the patients where there was no risk factor present, while the secondary group was formed by the patients where some risk factor was identified. The risks factors considered in this study were alcoholism, use of corticosteroids, previous hip trauma and hemoglobinopathies, according to criteria already established in the literature.<sup>11,16</sup> (Table 1) Hemoglobin electrophoresis was performed on all the patients with the intention of detecting hemoglobinopathies ignored by them and in all the cases presented normal results.

**Table 1.** Criteria used for classification of FHO as secondary.

Risk factor	Characteristics
Alcoholism	Ingestion above 400ml of ethyl alcohol per week
Use of corticosteroids	Over 20mg/day of prednisone (or equivalent dosage of other corticosteroid) for more than one month
Hemoglobinopathies	Sickle cell anemia, falcemic trace or thalassemias
Trauma	Fracture of the femoral neck or coxofemoral luxation

Eight patients constituted the idiopathic group, made up of seven men and one woman, aged between 26 and 75 years (averaging 50.5 years) and with four of these patients presenting bilateral involvement. According to the Ficat and Arlet classification<sup>17</sup> ten hips were in stage IV and two in stage III.

Sixteen patients constituted the secondary group, made up of 13 men and three women, aged between 26 and 65 years (averaging 44.8 years) and with ten of these patients presenting bilateral involvement. According to the Ficat and Arlet classification,<sup>17</sup> one hip was in stage I, four in stage II, seven in stage III and 14 in stage IV. Alcoholism was the most common risk factor in this group and was identified in 11 patients, followed by the use of corticosteroids in five patients; none of the patients presented previous hip trauma or hemoglobinopathy.

Blood samples were drawn from the 24 patients for the performance of the laboratory tests for investigation of thrombophilic disorders. The tests performed were levels of free protein S, protein C chromogenic and chromogenic antithrombin, and detection of G20210A mutation in the prothrombin gene and of G1691A mutation in the factor V gene (factor V Leiden). All these tests, as well as the hemoglobin electrophoresis carried out as a triage test for possible hemoglobinopathies, were performed at the Hematology Laboratory of HCFMRP-USP.

To compare the results statistically we calculated the odds ratio (OR) of the thrombophilias between the two groups, using SAS<sup>®</sup> software, version 9.2 (Cary, NC, USA). The OR is an association measure used in case-control studies to compare occurrences of events.

## RESULTS

Two of the eight patients (25%) in the idiopathic group and two of the 16 patients (12.5%) in the secondary group had thrombophilic disorders. In the idiopathic group, one of the patients presented protein S deficiency and the other presented protein S and C deficiency. In the secondary group, one of the patients presented protein S and C deficiency and the other presented mutation in the factor V gene (factor V Leiden). None of the 24

patients studied presented antithrombin deficiency or mutation in the prothrombin gene. (Table 2)

Based on these data we were able to determine that the ORs for protein S deficiency and protein C deficiency between the idiopathic and secondary groups were respectively 5 and 2.14. (Table 3) Therefore, an individual with idiopathic osteonecrosis has a five times higher chance of presenting protein S and a 2.14 times higher chance of presenting protein C deficiency than an individual with secondary osteonecrosis. It was not possible to calculate the OR of the other thrombophilias investigated owing to the prevalence equal to zero in one or both groups, in our casuistry.

**Table 2.** Frequencies of thrombophilias in the different groups.

	Protein C deficiency	Protein S deficiency	Antithrombin deficiency	G20210A mutation in the prothrombin gene	G1691A mutation in the factor V gene
Idiopathic (n=8)	1	2	0	0	0
Secondary (n=16)	1	1	0	0	1

**Table 3.** Odds ratio of some thrombophilias between the studied groups.

	Comparison	OR (CI 95%)
protein S deficiency	Idiopathic vs. Secondary	5 (0.38 – 66.01)
protein C deficiency	Idiopathic vs. Secondary	2.14 (0.12 – 39.47)

OR = Odds ratio - CI 95% = Confidence interval 95%.

## DISCUSSION

Since the 1990s, different authors<sup>5-14</sup> have associated femoral head osteonecrosis with thrombophilic disorders and other hypercoagulable states that predispose to thrombi formation in the microcirculation, either through an increase in the function of the procoagulant factors, such as factor V or prothrombin, or through the decrease in the activity of the endogenous anticoagulants, such as antithrombin, protein C and protein S.

The thrombophilias found most frequently in the general population include G1691A mutation in the factor V gene (the so-called factor V Leiden), G20210A mutation in the prothrombin gene, protein S deficiency, protein C deficiency and antithrombin deficiency.<sup>15</sup>

Antithrombin is a protein whose anticoagulant effect consists of inactivating thrombin and factors IX and X; thus, its deficiency facilitates intravascular coagulation.<sup>7</sup> Protein C or protein S deficiencies lead to an increase in coagulant activity by means of the reduction of the inactivation of the prothrombotic factors V and VIII.<sup>13</sup> G1691A mutation in the factor V gene is also called factor V Leiden; in this condition, the mutant factor V is inactivated in a less effective manner by the protein C.<sup>18</sup> Finally, G20210A mutation in the prothrombin gene brings about an increase in the serum levels of this factor and an increment of their procoagulant function.<sup>18</sup>

These disorders often evolve subclinically, manifesting when associated with environmental or epigenetic events and evidencing a probable multifactorial pathogenesis of many

cases thitherto classified as idiopathic PFO.<sup>13,19</sup> To the best of our knowledge, this is the first study in the national literature to seek a possible association between FHO and thrombophilias in adult individuals.

Undoubtedly the greatest limitation of our study is the small number of patients studied; moreover, ideally, research into thrombophilias in a second control group composed of individuals without FHO would be useful for additional comparisons. Such limitations occurred due to the high costs of the laboratory tests. The proportion of patients with idiopathic FHO in our casuistry (eight cases out of a total 24 patients or 33.3%) is consistent with the distribution found in the literature, which reports that 5 to 40% of the cases fit into this condition.<sup>3,4</sup> We observed that four of the 24 patients (16.7%) with FHO had some form of thrombophilia, a rate compatible with the wide margin mentioned in the literature, which ranged from 10 to 83%.<sup>2,4,9,11-14</sup> Through the calculation of the OR, we verified that patients with idiopathic FHO have higher chances of presenting thrombophilias, specifically protein S deficiency (5 times higher) and protein C deficiency (2.14 times higher), than the patients with secondary FHO; as already reported, we were unable to calculate the OR of the other thrombophilic disorders investigated due to the prevalence equal to zero in at least one of the two groups. Studies with more numerous groups are necessary to elucidate this matter, as we did not find in literature any studies that have calculated the OR values comparing the occurrence of thrombophilias between patients with idiopathic and secondary FHO, as was the case here. Anyway, in our casuistry we observed an increased prevalence of some thrombophilias in individuals from both groups, idiopathic and secondary, in relation to

the prevalence of these disorders in the general population according to data from literature<sup>4,14,15,20,21</sup> (Table 4), which suggests that a possible association between hypercoagulability and FHO may be present not only in the cases classified as idiopathic, but also in the secondary cases, whereas such a fact is also reported by several other authors.<sup>2,9,12,14</sup> By contrast, two studies carried out on Asian populations did not find greater prevalence of thrombophilias in the patients with FHO, indicating a possible ethnic influence on the genetic profile of risk for the development of this disease.<sup>18,22</sup>

**Table 4.** Comparison between the prevalence of thrombophilias found in this study and in the general population.

	Protein C deficiency	Protein S deficiency	Antithrombin deficiency	G20210A mutation in the prothrombin gene	G1691A mutation in the factor V gene
Idiopathic	12.5%	25%	0%	0%	0%
Secondary	6.25%	6.25%	0%	0%	6.25%
General population*	0.2 to 0.4%	0.03 to 0.13%	0.02%	1 a 4%	2 a 5%

\*Data obtained from the literature series.<sup>4,14,15,20,21</sup>

## CONCLUSION

The results obtained show that patients with idiopathic FHO are more likely to present protein S deficiency and protein C deficiency than those with secondary FHO, suggesting that these thrombophilias may play an important role in the pathogenesis of FHO cases where there is no identifiable risk factor at first.

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