

# Role of Thrombotic and Fibrinolytic Alterations in the Pathogenesis and Treatment of Osteonecrosis



Osteonecrosis is a devastating disease that leads to joint collapse and arthritis of the hip, knee, shoulder, ankle, and other joints<sup>1,2</sup>. It has been noted to be responsible for more than 10% of the hip replacements performed in the United States. Previously, the only successful treatments for this disease have been surgical. However, an understanding of its pathogenesis might lead to prevention and early medical treatment.

One of the most common risk factors for osteonecrosis is the use of corticosteroids. Multivariate analysis has shown that corticosteroid use<sup>3,4</sup>, especially in high doses, is an important risk factor for the disease<sup>5</sup>. Over the past decade, multiple studies have not only tried to elucidate the pathogenesis of the disease but have also examined the use of various pharmacological agents such as lipid-lowering drugs, anticoagulants, vasodilators, and bisphosphonates for the treatment of osteonecrosis<sup>6-9</sup>. To date, the best treatment option for preventing joint replacement in this disease is diagnosing patients in the earlier stages before biomechanical compromise, e.g., joint collapse. This emphasizes the importance of identifying high-risk patients.

Recently, published data suggest that heritable thrombophilia and decreased fibrinolysis may play an important role in the pathogenesis of osteonecrosis. Table 1 lists a large number of proposed thrombotic and fibrinolytic alterations associated with the development of this disease. Lipoprotein(a) [Lp(a)] is predominantly a genetic trait whose level remains constant after puberty. To date, more than 13 phenotypes of Lp(a) have been identified, having a molecular weight of 300 to 800 kDa. Lp(a) has been shown to play an important role not only in fibrinolysis, but also in thrombogenesis and in atherogenesis<sup>10</sup>. High plasma levels of Lp(a) have been found in coronary heart disease, stroke, and other atherosclerotic diseases. Concerning the musculoskeletal system, alterations in Lp(a) levels have been

found in Legg-Calvé-Perthes disease (juvenile osteonecrosis) and bone marrow edema syndrome, as well as osteonecrosis. Glueck, *et al* postulated that hypofibrinolytic high levels of Lp(a) may cause thrombotic venous occlusion, which may lead to intramedullary hypertension, reduced arterial perfusion, hypoxia-anoxia, and osteonecrosis of the femoral head<sup>11</sup>. In a study of 30 patients with idiopathic and secondary osteonecrosis, the same authors reported that the average Lp(a) was much higher (60 mg/dl) in the 18 patients with secondary osteonecrosis compared to a mean Lp(a) of 16 mg/dl ( $p = 0.001$ ) in the 12 patients with idiopathic osteonecrosis. Similar findings have been reported by various centers<sup>12,13</sup>. Still other investigators failed to demonstrate a relationship between high levels of Lp(a) and osteonecrosis<sup>14-16</sup>. Jones, *et al* studied thrombophilia and decreased fibrinolysis in 45 patients diagnosed with osteonecrosis compared to 40 healthy individuals<sup>15</sup>. They found that 37 of the 45 patients (82.2%) with osteonecrosis had at least one coagulopathy, versus 12 of the 40 controls (30%;  $p < 0.0001$ ). Patients with osteonecrosis had high levels of hypofibrinolytic plasminogen activator inhibitor activity (42% compared to 3%;  $p < 0.0001$ ), and high anticardiolipin antibody IgG (34% compared to 10%;  $p = 0.008$ ). However, the investigators did not detect altered serum levels of Lp(a) in the 2 groups. Only 8 of the 45 patients (18%) and 5 of 40 controls (12.5%;  $p > 0.05$ ) demonstrated elevated Lp(a) serum levels. Similarly, Mont and coinvestigators studied 103 patients with systemic lupus erythematosus and found that 31 patients (30%) had developed osteonecrosis<sup>16</sup>. They showed positive correlations between a high prednisone dose, elevated anticardiolipin antibodies, and the development of osteonecrosis. However, they did not find a statistical difference in elevated Lp(a) levels between the 31 lupus patients (14 of the 31 exhibited elevated levels, 45%)

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Table 1. Thrombotic and fibrinolytic alterations implicated in the pathogenesis of osteonecrosis.

Thrombophilia	Hypofibrinolysis
Antigen-presenting cell resistance	Elevated plasminogen activator inhibitor-1
Factor V Leiden mutation	Low stimulated tissue plasminogen activator
Protein C deficiency	Plasminogen deficiency
Protein S deficiency	Dysfibrinogenemia
Anticardiolipin antibodies	High lipoprotein(a) levels
Homocysteine mutation	
Antithrombin III deficiency	
MTHFR mutation	
Platelet glycoprotein IIA P1A1/A2 polymorphism	
Platelet glycoprotein Ia	
Lupus anticoagulant	
Elevated Factor VIII levels	

MTHFR: methylenetetrahydrofolate reductase.

that developed osteonecrosis and the 72 control patients (33 of the 72 controls demonstrated elevated levels, 46%).

In this issue of *The Journal*, Hirata and colleagues from Japan present some interesting data identifying a strong relationship between the low molecular weight apolipoprotein(a) [apo(a)] isoform and the incidence of osteonecrosis in 112 renal transplant patients<sup>17</sup>. This report has important implications for the diagnosis and treatment of this disease. The authors studied patients who had corticosteroid treatment and no evidence of osteonecrosis before renal transplantation. Over the posttransplant years, 20 patients developed osteonecrosis and could be compared to the group of patients that did not develop the disease. The authors analyzed Lp(a) serum levels and high and low molecular weight isoforms, as well as characterizing genetic polymorphisms. They found a strong relationship between the low molecular weight form of apo(a) and osteonecrosis development. They did not find a significant relationship between plasma levels of Lp(a) and the single nucleotide polymorphisms.

Although there is a strong statistical correlation between low molecular weight apo(a) and osteonecrosis, this was not a universal finding. Osteonecrosis occurred in 10 of the 24 patients (41.7%) with the low molecular weight isoform as opposed to 10 of the 88 high molecular weight patients (11.4%;  $p = 0.0016$ ). Therefore, one should realize that there may be several genetic and environmental factors besides the apo(a) molecular weight phenotype that can be related to pathogenesis of osteonecrosis. This type of study certainly deserves additional investigation to further elucidate the pathogenesis of this disease. It is possible that thrombotic and fibrinolytic alterations are a missing link joining otherwise seemingly unrelated risk factors for osteonecrosis. If this is the case, then the precipitating factor with the specific thrombotic and fibrinolytic alteration becomes the etiology and the intravascular coagulation disorder becomes the first event in a pathogenic cascade that leads to the clinical disease.

The authors did not find a relationship between serum

Lp(a) and the development of osteonecrosis. However, they did find that mean levels of Lp(a) were increased in the osteonecrosis patients (19.4 mg/dl) versus the reference group (12.9 mg/dl). There was no statistically significant difference ( $p = 0.56$ ), although with greater numbers of patients studied this might have yielded statistical significance. This difference from other studies where this factor was found to be related might be explained by a number of unique features of the Hirata study. Lp(a) levels were measured in the periods between 13 and 268 months after renal transplantation, and thus we would not expect these levels to be stable throughout a patient's lifespan. Another reason for the difference might be a racial difference between Caucasian patients in previous studies and the Asian population in the Hirata study. In addition, various other environmental factors may affect plasma Lp(a) levels.

Hirata, *et al* also found no relationship between corticosteroid use and the incidence of osteonecrosis. This may be explained because the transplant centers in this study used very narrow dosage ranges of corticosteroids, which did not provide a wide spectrum of dosages to analyze.

In summary, the study by Hirata, *et al* is important because preoperative analysis of apo(a) phenotype may predict posttreatment osteonecrosis development. Although conducted only in renal transplant patients, the results may be relevant to patients with other conditions such as rheumatoid arthritis or systemic lupus erythematosus. The results of these tests would allow tailoring of treatment to include the avoidance or reduction of corticosteroid use or other risk factors such as smoking in these patients, to hopefully reduce the overall disease risk. This study should also encourage further investigation of other coagulation factors that potentially cause osteonecrosis, which may allow amelioration of the disease process. In addition, this line of investigation may open avenues for future pharmacological interventions. One cannot overemphasize the importance of this study: it assesses risk factors before patients actually developed osteonecrosis. Most reports in this field analyzed

patients after onset of osteonecrosis. Therefore, there is always a question of whether the disease itself may lead to the alteration in coagulation parameters. Another strength of the study is that the isoforms of Lp(a) would not be expected to be altered environmentally, but would be stable in a patient's lifetime, thus making Lp(a) an important marker for this disease. Moreover, the possible role of antithrombotic and profibrinolytic medications may shift the treatment algorithm from a historical surgical-based approach to a more pharmacological approach.

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