ONFH in Patients with Hypercoagulability

Subjects: Pathology

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Osteonecrosis of the femoral head (ONFH) is a debilitating disease with major social and economic impacts. It frequently affects relatively young adults and has a predilection for rapid progression to femoral head collapse and end-stage hip arthritis. If not diagnosed and treated properly in the early stages, ONFH has devastating consequences and leads to mandatory total hip arthroplasty. The pathophysiology of non-traumatic ONFH is very complex and not fully understood. While multiple risk factors have been associated with secondary ONFH, there are still many cases in which a clear etiology cannot be established. Recognition of the prothrombotic state as part of the etiopathogeny of primary ONFH provides an opportunity for early medical intervention, with implications for both prophylaxis and therapy aimed at slowing or stopping the progression of the disease. Hereditary thrombophilia and hypofibrinolysis are associated with thrombotic occlusion of bone vessels. Anticoagulant treatment can change the natural course of the disease and improve patients' quality of life.

Keywords: osteonecrosis ; femoral head ; hereditary thrombophilia

1. Introduction

Osteonecrosis, avascular necrosis or aseptic necrosis of bone is defined as bone cell death following the compromise of blood flow to the bone [1]. The basic underlying mechanism is the cessation of circulation to a specific area [2]; both arteries and veins may be involved. The trauma leads to vascular interruption of arterial blood flow, which is mainly and directly responsible for bone ischemia. Glueck et al. [3] and Orth et al. [4] hypothesized that the intravascular coagulation which occurs in the thrombophilia-hypofibrinolysis states determines venous thrombotic occlusion—which leads initially to increased intraosseous venous pressure and subsequently to impaired arterial blood flow and bone ischemia. Regardless of the initiating mechanism, the interruption of blood flow leads to persistent osseous hypoxia and lack of nutrients, factors which are responsible for bone necrosis. The osteocytes die, leading to bone resorption and collapse of the articular surface.

Although it can occur in any bone, the most commonly affected site is the femoral head [5]. Osteonecrosis of the femoral head (ONFH) encompasses traumatic and nontraumatic causes, the first being by far the more prevalent [5]. The femoral head blood supply lies mainly on retinacular arteries and, to a lesser extent not exceeding 20%, on the artery of the ligamentum teres. Retinacular arteries (superior, inferior, anterior, posterior), originating from medial and lateral circumflex femoral arteries, wrap around the femoral neck on their way to the femoral head. Ligamentum teres is an intra-articular ligament between the femoral head and acetabulum. Traumatic lesions such as displaced femoral neck fractures and hip dislocations severely compromise the vascularity around the femoral head, leading to bone ischemia and ONFH [6].

Nontraumatic ONFH has traditionally been classified as idiopathic or secondary, depending on the absence or presence of known causes [5]. The pathophysiology of the nontraumatic ONFH is very complex, multifactorial and not fully known. Multiple risk factors have been associated with secondary ONFH. More than 80% of cases are a consequence of long-term corticosteroid use and excessive alcohol intake [5]. Hemoglobinopathies (such as thalassemia [7] and sickle cell anemia [8]) and coagulopathies, such as hemophilia [9] and congenital afibrinogenemia [10] are also associated with ONFH. The blood flow in the bone microcirculation is compromised by the rigid and less-deformable red blood cells in thalassemic patients [7] or by abnormally shaped and stiff red blood cells in patients with sickle cell anemia [8]. Blockages in microcirculation result in bone infarction. Acute hemarthrosis is associated with increased intra-articular pressure and impaired blood flow to the bone. Recurrent hemorrhages in the hip joint can lead to femoral head ischemia and ONFH in patients with congenital bleeding disorders [9][10]. Malignancies—including myeloproliferative disorders, autoimmune diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis), metabolic disorders (e.g., diabetes mellitus, hyperlipidemia, lipid storage diseases) and renal failure have all been shown to be involved in ONFH [5][11][12][13][14]. Currently, a wide range of modern antineoplastic medications are linked to bone necrosis, including tyrosine kinase

inhibitors [15][16][17], monoclonal antibodies [17][18], mammalian target of rapamycin inhibitors, radiopharmaceuticals, selective estrogen receptor modulators and immunosuppressants [17].

Still, in many studied cases, a clear etiology could not be established. ONFH was considered primary (idiopathic); however, it may be—at least in part—the consequence of hereditary thrombophilia or hypofibrinolysis.

In the early 1990s, it was suggested that the hypercoagulability state could be a risk factor for osteonecrosis [19]. Since then, much evidence has been gathered to support this hypothesis, including data from animal models [20][21][22] which confirmed that venous occlusion was a primary event. Recognition of the prothrombotic state as part of the etiopathogeny of primary ONFH provides an opportunity for early medical intervention, with implications for both prophylaxis and therapy aimed at slowing or stopping the progression of the disease. This is all the more important, as studies show that the highest incidence of nontraumatic ONFH is in relatively young adults (males aged 20 to 50 years) [6][23][24], and that hip joint destruction rapidly progresses into end-stage hip arthritis, requiring surgical intervention [25].

2. Hereditary Thrombophilia Associated with ONFH

Familial thrombophilia includes a broad spectrum of genetic abnormalities that interfere with the coagulation cascade. Differences have been noted in their prevalence and capacity to determine thrombosis. The highest frequency of heritable thrombophilia was recorded in individuals with ancestry from northern Europe [26] and some parts of the Middle East [27]. The most common and important thrombophilic states are: the factor V Leiden mutation, the prothrombin gene G20210A mutation, antithrombin III deficiency, protein C and protein S deficiency [28] and the methylenetetrahydrofolate reductase (MTHFR) C677T gene polymorphism [29]. It has also been noted that thrombosis may occur due to either a single dominant abnormality or to a combination of milder but multiple defects—as by association, their prothrombotic effects are potentiated.

The modern view of hemostasis grants the platelets a very important role in thrombus formation [30]. In the cell-based coagulation model, platelet and coagulation factors are strongly interconnected, since platelets provide rich phosphatidylserine-exposing surfaces on which high levels of thrombin are produced and, in turn, thrombin causes more platelet activation [31]. Congenital thrombocytopathies may disrupt the platelet hemostatic mechanisms, leading to bleeding [32] or, in rare cases, to thrombosis. For instance, sticky platelet syndrome is characterized by hyperaggregability that leads to arterial and venous thrombotic events [33].

2.1. Factor V Leiden

Factor V (FV) plays an important role in the coagulation process, acting as a cofactor for factor Xa in the prothrombinase complex and leading to thrombin generation. A single nucleotide polymorphism (1691G>A) in the FV gene determines the synthesis of an abnormal protein: the FV Leiden. The procoagulant activity of FV Leiden is not affected, but the arginine-to-glutamine substitution occurs at an important protein's cleavage site and significantly reduces the rate at which FVa is deactivated by activated protein C (APC) [34][35]. Factor V Leiden also decreases the APC cofactor activity of FV in the deactivation of factor VIIIa. The association between impaired FVa and VIIIa deactivation results in a prothrombotic state [36].

Factor V Leiden represents the most frequent cause of inherited thrombophilia. The prevalence is 3–5% in the general population, 20% in patients with deep venous thrombosis and about 50% in patients with familial thrombophilia [37][38]. In the general population, the prevalence of FV Leiden varies considerably with geographic area, ethnic group, and the degree of ethnic mixture within ethnic groups [39][40][41]. The highest prevalence is found in Caucasians and the lowest in Asians.

An association between ONFH and the genetic polymorphisms in FV has also been reported. One prospective cohort study assessed 244 USA patients with ONFH (unilateral or bilateral disease) and found that 9.3% of 161 patients with idiopathic ONFH and 9.6% of 83 patients with secondary ONFH (known trauma, alcoholism or long-term and/or high-dose corticosteroids) had FV Leiden, thereby supporting the hypothesis that FV Leiden is a risk factor for ONFH [42].

Another study evaluated 68 adult patients with ONFH, of which 63 had nontraumatic etiologies. Out of 33 patients with secondary ONFH (known trauma, alcoholism or corticosteroids use), only one patient had FV Leiden. Meanwhile, out of 35 patients with idiopathic ONFH, 8 patients had FV Leiden, including one patient who also had the prothrombin 20210A gene mutation [43]. In all cases, the patients were heterozygous for the gene mutations. In patients with idiopathic ONFH, FV Leiden was significantly more prevalent than in patients with corticosteroid-induced or alcohol-induced ONFH [43]—and doubly as prevalent as in the control group, where 32 cases of FV Leiden were identified among 282 healthy volunteers

[26]. This increased prevalence can be explained by the characteristics of the population enrolled in the study, which was from southern Sweden—a region where the prevalence of FV Leiden is 10%, one of the highest rates in the world.

In a study that enrolled 72 consecutive Caucasian Greek patients with nontraumatic ONFH and 300 healthy subjects [44], FV Leiden was present in 18.0% of ONFH patients (all heterozygous) and in 4.6% in the control group (4.3% heterozygous, 0.3% homozygous), with OR 4.5 (95% CI: 2.0–10.0), thus directly linking the procoagulant status determined by FV Leiden to ONFH. The prevalence of FV Leiden was significantly increased both in primary and secondary ONFH patients, with the highest (21.7%) in the idiopathic ONFH subgroup, who showed a significant OR of 5.7 (95% CI: 1.8–17.5).

A European study of unrelated adult Caucasians of Polish origin included 45 patients with idiopathic ONFH and 23 patients with secondary ONFH, and reported no association between FV Leiden and ONFH [45].

Major thrombophilic mutations like FV Leiden have been identified as risk factors for nontraumatic ONFH in Caucasians, but have not been confirmed in Asian populations. Not only is prevalence of FV Leiden very low in the general Asian population [39], but studies in Asian populations did not confirm any association between FV Leiden and ONFH. In the Korean general population, the mutation has not been identified—nor has it been identified in ONFH patients or control subjects [46]. This finding supports the results of a previous study, in which 418 Koreans (including normal individuals, with thrombotic diseases and with nonthrombotic disorders) were screened for the presence of FV Leiden. The mutation was not identified in any case [47]. Similar results were provided by a Chinese study that included 267 patients with venous thromboembolism (VTE) and 102 control subjects. Although FV Leiden is a known risk factor for VTE, none of the Chinese patients enrolled was a carrier of FV Leiden [48]. Therefore, the presence of FV Leiden can be considered a risk factor for ONFH primarily in Caucasians. Its existence should be sought in patients with idiopathic ONFH within this ethnic group.

2.2. Prothrombin G20210A Mutation

The presence of the G20210A prothrombin gene mutation is responsible for high levels of prothrombin, which leads to an increased generation of thrombin and to a prothrombotic state. This mutation is present in 1–5% of Caucasians and is associated with deep venous thrombosis [49] and pulmonary embolism [50].

A prospective North American cohort study that evaluated the presence of prothrombin G20210A mutation in 235 patients with idiopathic and secondary ONFH found that 8 (3.4%) were heterozygous for prothrombin G20210A. This was similar to the control group, where 3 of 104 subjects (2.9%) had the mutation [42]. Therefore, in this study, the prothrombin G20210A mutation alone was not a significant risk factor for ONFH, which confirmed the same author's previous results [51].

A North European study evaluated 68 adult patients with idiopathic and secondary ONFH (known trauma, alcoholism or corticosteroid use). Only four patients had the prothrombin G20210A mutation (three with idiopathic ONFH and one with posttraumatic ONFH) [43]. Therefore, an independent association of prothrombin G20210A mutation with ONFH could not be established. However, when analyzed together, the presence of FV Leiden and prothrombin G20210A mutation in patients with idiopathic ONFH showed a clear pattern. These two major thrombophilic mutations occurred with more than twice the frequency of the control subjects [26][52] and were 10 times more common than in patients with corticosteroid-induced or alcohol-induced ONFH (OR 10.8; 95% CI, 1.4–84) [43], suggesting that the presence of a thrombophilic substrate is a favoring factor for ONFH.

In a study that enrolled 72 consecutive Caucasian Greek patients with nontraumatic ONFH and 300 healthy subjects [44], prothrombin G20210A mutations were identified in 4.2% of ONFH patients (1.4% heterozygous, 2.8% homozygous) and in 2.6% in the control group (2.3% heterozygous, 0.3% homozygous), with OR 1.6 (95% CI 0.4–6.1). Although statistical significance was not achieved and no significant association between prothrombin G20210A mutation and ONFH could be established, a considerably higher prevalence of prothrombin G20210A mutation (8.7%) was found in patients with idiopathic ONFH [44]. A European study of unrelated adult Caucasians of Polish origin included 45 patients with idiopathic ONFH and 23 patients with secondary ONFH. It also reported no association between prothrombin G20210A mutation and ONFH [45].

The mutation has not been identified in Korean populations, ONFH patients, or control subjects [46]. Similar, a Chinese study that included 267 patients with VTE and 102 control subjects showed that none of the patients enrolled was a carrier of the prothrombin G20210A mutation [48].

Important conclusions can be drawn from the available studies; namely, that the prevalence of the G20210A mutation in the prothrombin gene in patients with ONFH varies between ethnic groups and that it alone is not a risk factor for ONFH. However, it exerts a thrombogenic effect when added to other thrombophilic mutations.

2.3. Antithrombin III Deficiency

Antithrombin III (ATIII) is a circulating anticoagulant glycoprotein synthetized in the liver and secreted in plasma [53]. The main action of ATIII is the inhibition of thrombin and factor Xa. It also has minor inhibitory effects on factors IXa, XIa, and XIIa. The two ATIII active sites are the reactive site, responsible for its proteolytic function, and the heparin binding site. In the presence of heparin, the ATIII anticoagulant activity is increased more than 1000-fold [54], thus enhancing the inactivation of thrombin and factor Xa.

The ATIII deficiency can be inherited or acquired. The inherited form is an autosomal dominant condition caused by a defected allele of the *SERPIN1* gene, and is classified into two types. Type 1 is defined by the absence of gene product in a homozygous state, while in the heterozygous case, normal antithrombin activity is approximately halved. Type 2 is characterized by a qualitative inadequate protein. Various conditions may lead to acquired ATIII deficiency, including liver disease, malnutrition, nephrotic syndrome, sepsis and treatment with L-asparaginase [54][55].

ATIII deficiency leads to a hypercoagulable state that significantly increases thrombotic risk [56]. In fact, ATIII deficiency has been associated with a 16.3-fold increase in the VTE risk) compared to nonthrombophilic individuals) [57].

The association between ATIII deficiency and ONFH was also considered in different clinical settings [58][59][60][61]. Chotanaphuti et al. identified two cases of ATIII deficiency out of 40 Thai patients with idiopathic ONFH [60]. In Canadian patients with nontraumatic ONFH, Séguin et al. found that the ATIII deficiency was present in only one patient out of 49 included [62]. It is of note that, in their study, all hypercoagulability markers had low prevalence. The study of Garcia et al. enrolled 24 Brazilian patients with ONFH and identified zero cases with ATIII deficiency [63]. Very recent published data by Rathod et al. [59] showed a lower prevalence of ATIII deficiency in idiopathic ONFH patients compared to healthy controls (11% vs. 22%), suggesting that, when familial thrombophilia is considered a substrate of primary ONFH, the involvement of ATIII deficiency is unlikely.

Although the incidence of ATIII deficiency has been intensively investigated in idiopathic and secondary ONFH, studies have proved the scarcity of ATIII deficiency among ONFH patients, implying that its contribution is a minor one in the development and progression of the disease.

2.4. Protein C and Protein S Deficiency and Resistance to Activated Protein C

Protein C is a glycoprotein synthesized by hepatocytes through a vitamin K-dependent pathway and circulates in blood as zymogen [64]. It is activated by thrombin bound to thrombomodulin, which is a catalytic cofactor present on endothelial cells' surface membranes [65]. APC exerts its anticoagulant effect by degrading factors Va (FVa) and VIIIa (FVIIIa) on the surface of negatively charged phospholipid membranes using lipid and protein cofactors. Protein S, also a vitamin K-dependent plasma protein, is synthesized by the liver, endothelial cells and megakaryocytes. It is a cofactor for APC, enhancing the inactivation of factors Va and VIIIa on phospholipid surfaces.

While for FVa inactivation, only protein S is an important APC cofactor, inactivation of FVIIIa is more complex, and requires both protein S and the intact FV molecule as synergistic APC cofactors [66]. Therefore, mutations in FV genes can disrupt the functionality of the C protein pathway. The Gln506 mutation of the FV gene is common and results in FV Leiden, while Arg306 mutation of the FV gene is less common and results in resistance to activated protein C [67]. It can be considered that FV Leiden and resistance to activated protein C represent the same type of thrombophilia, as they are the consequences of different mutations of the FV gene. While FV Leiden is commonly associated with the pathogenesis of ONFH, there is no data showing a link between acquired activated protein C resistance and the risk of ONFH—although it has been described as a risk factor for thrombosis [60][68][69][70].

Protein C and protein S deficiency, as well as activated protein C resistance, through the hypercoagulability status that they induce, may underlie the pathogenic mechanism that leads to bone necrosis in patients with ONFH [60][68][69][71].

The first case of protein S deficiency associated with ONFH in adults was reported in 1997 by Pierre-Jacques et al. [72]. In the same year, Glueck et al. reported that protein S deficiency was found in 7% of the adults with ONFH from the study group, while protein C deficiency was identified in 2–13% of cases [68]. Zalavras et al. found that patients with idiopathic ONFH had decreased protein C and S levels compared to control group. Protein C deficiency was present in 29.4% of cases with primary ONFH and in 21.6% of cases with secondary ONFH. Protein S deficiency was present in 5.9% of

cases with primary ONFH and in 11.8% of cases with secondary ONFH [73]. Similar, Garcia et al. found that patients with idiopathic ONFH were 5 times more likely to have protein S deficiency and 2.14 times more likely to have protein C deficiency than patients with secondary ONFH [63].

In 106 patients with ONFH, Korompilias et al. identified 88 cases with coagulation abnormalities: 35 patients (33%) showed resistance to activated protein C alone and 2 patients (1.9%) had protein S deficiency [74]. Rathod et al. also confirmed the association between protein C or S deficiency and ONFH, with statistically significant differences between ONFH patients and the control group (p value = 0.028 for protein C deficiency and p value = 0.038 for protein S deficiency) [59].

All the available and relevant data demonstrate a strong association between protein C and protein S deficiency—as well as activated protein C resistance and ONFH. Studies have shown that the most common familial thrombophilia associated with osteonecrosis are the FV Leiden mutation and/or RAPC. These were found in 15.5% of cases in a series of 535 patients with ONFH [75].

2.5. MTHFR C677T Gene Polymorphism

The enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR) is vital to the homocysteine metabolism pathway. Gene mutations can reduce the activity of the enzyme and cause the accumulation of homocysteine in the blood, which leads to an increased production of peroxides and oxygen free radicals via self-oxidation of homocysteine. Reactive oxygen species injure endothelial cells and disrupt the balance between vasodilator and vasoconstrictor endothelium-derived factors by increasing endothelin-1 secretion and decreasing relaxing factor and prostaglandin secretion. This imbalance further triggers thrombosis [76]. Moreover, the thrombomodulin's action on the endothelial surface is reduced, leading to a decrease in protein C activity and the inhibition of factors Va and VIIIa. The thrombin generation is thus intensified, resulting in increased fibrin formation [77]. Conversion of fibrinogen to insoluble polymer fibrin gives structural stability, strength, and adhesive surfaces for growing blood clots [78].

Since MTHFR C677T gene polymorphism leading to hyperhomocysteinemia has been associated with deep venous thrombosis and pulmonary embolism [79][80][81], special attention has been paid to its potential influence on ONFH occurrence. While some studies have shown a correlation between MTHFR C677T gene polymorphism and ONHF [44][45][46][82], others have had neutral [51] or opposite results [83][84].

A meta-analysis that included eight studies evaluating the relation between MTHFR C677T gene polymorphism and ONFH (778 cases and 1162 controls) reported the absence of a significant association when all subjects were analyzed, but highlighted the presence of an ethnicity-dependent risk. There was an association between MTHFR C677T gene polymorphism and ONFH risk in non-Asian populations (OR = 1.72; 95% CI: 1.21–2.43), but not in Asian populations (OR = 0.88; 95% CI: 0.66–1.66) [85].

The most recent meta-analysis that investigated the correlation between MTHFR C677T gene polymorphism and nontraumatic ONFH analyzed the results of 11 studies and confirmed the association between this genetic substrate and the risk of ONFH. The OR was 0.72; 95% CI: 0.54–0.96 for the entire population included. In an analysis of different ethnic groups, MTHFR C677T gene polymorphism was associated with ONFH, especially in Caucasian subjects. Caucasians with the CC genotype had a lower risk for ONFH than subjects with CT+TT genotype, with an OR = 0.65 [86].

These results can be explained by the variable prevalence of the mutation with ethnicity. The prevalence is high among Caucasians (32.2–44%) and Asians (30.5–42%) and low in Africans (6–10.3%) [87][88]. Moreover, the level of homocysteine in the blood is influenced by a series of factors, such as drugs, smoking, alcohol consumption and diet. Because MTHFR participates in the homocysteine metabolism alongside folates and vitamin B12 [89], persistent low levels of folates and B12 may lead to hyperhomocysteinemia and increased thrombotic risk. Therefore, regional eating habits (resulting in diets deficient in these compounds) and alcoholism may be associated with increased homocysteine levels and can influence the prevalence of ONFH related to MTHFR gene polymorphism.

In the presence of many confounding factors, it is very difficult to separate and accurately analyze the contribution of the genetic substrate, independent of environmental factors. Therefore, the magnitude of its impact on the onset of ONFH cannot be accurately assessed—although we know that the MTHFR C677T gene polymorphism has thrombogenic potential.

References

1. Cooper, C.; Steinbuch, M.; Stevenson, R.; Miday, R.; Watts, N.B. The epidemiology of osteonecrosis: Findings from the GPRD and THIN databases in the UK. Osteoporos. Int. 2010, 21, 569–577.
2. Mont, M.A.; Cherian, J.J.; Sierra, R.J.; Jones, L.C.; Lieberman, J.R. Nontraumatic Osteonecrosis of the Femoral Head: Where Do We Stand Today? A Ten-Year Update. J. Bone Jt. Surg. Am. 2015, 97, 1604–1627.
3. Glueck, C.J.; Freiberg, R.A.; Wang, P. Role of thrombosis in osteonecrosis. Curr. Hematol. Rep. 2003, 2, 417–422.
4. Orth, P.; Anagnostakos, K. Coagulation abnormalities in osteonecrosis and bone marrow edema syndrome. Orthopedics 2013, 36, 290–300.
5. Assouline-Dayan, Y.; Chang, C.; Greenspan, A.; Shoenfeld, Y.; Gershwin, M.E. Pathogenesis and natural history of osteonecrosis. Semin. Arthritis Rheum. 2002, 32, 94–124.
6. Baig, S.A.; Baig, M.N. Osteonecrosis of the Femoral Head: Etiology, Investigations, and Management. Cureus 2018, 10, e3171.
7. Thulasidhar, A.N.; Kumar, S.; Aroor, S.; Mundkur, S. Avascular Necrosis of Femoral Head in a Child with Beta Thalassaemia Major. J. Clin. Diagn. Res. 2016, 10, SL03.
8. Adesina, O.; Brunson, A.; Keegan, T.H.M.; Wun, T. Osteonecrosis of the femoral head in sickle cell disease: Prevalence, comorbidities, and surgical outcomes in California. Blood Adv. 2017, 1, 1287–1295.
9. Rodriguez-Merchan, E.C. Effects of hemophilia on articulations of children and adults. Clin. Orthop. Relat. Res. 1996, 328, 7–13.
10. Simurda, T.; Kubisz, P.; Dobrotova, M.; Necas, L.; Stasko, J. Perioperative Coagulation Management in a Patient with Congenital Afibrinogenemia during Revision Total Hip Arthroplasty. Semin Thromb Hemost 2016, 42, 689–692.
11. Abu-Shakra, M.; Buskila, D.; Shoenfeld, Y. Osteonecrosis in patients with SLE. Clin. Rev. Allergy Immunol. 2003, 25, 13–24.
12. Kang, J.S.; Park, S.; Song, J.H.; Jung, Y.Y.; Cho, M.R.; Rhyu, K.H. Prevalence of osteonecrosis of the femoral head: A nationwide epidemiologic analysis in Korea. J. Arthroplast. 2009, 24, 1178–1183.
13. Glueck, C.J.; Freiberg, R.A.; Wang, P. Heritable thrombophilia-hypofibrinolysis and osteonecrosis of the femoral head. Clin. Orthop. Relat Res. 2008, 466, 1034–1040.
14. Kim, H.; Cho, C.; Cho, Y.; Cho, S.; Yoon, K.; Kim, K. Significant associations of PAI-1 genetic polymorphisms with osteonecrosis of the femoral head. BMC Musculoskelet. Disord. 2011, 12, 160.
15. Yassin, M.A.; Moustafa, A.H.; Nashwan, A.J.; Soliman, A.T.; El Derhoubi, H.; Mohamed, S.F.; Mudawi, D.S.; ELkourashy, S.; Asaari, D.R.; Gutierrez, H.L.; et al. Dasatinib Induced Avascular Necrosis of Femoral Head in Adult Patient with Chronic Myeloid Leukemia. Clin. Med. Insights Blood Disord. 2015, 8, 19–23.
16. Thekkudan, S.F.; Nityanand, S. Nilotinib induced avascular necrosis of femoral head in an adult chronic myeloid leukemia patient. J. Clin. Orthop. Trauma 2018, 9, S26–S28.
17. King, R.; Tanna, N.; Patel, V. Medication-related osteonecrosis of the jaw unrelated to bisphosphonates and denosumab—A review. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. 2019, 127, 289–299.
18. Bennardo, F.; Buffone, C.; Giudice, A. New therapeutic opportunities for COVID-19 patients with Tocilizumab: Possible correlation of interleukin-6 receptor inhibitors with osteonecrosis of the jaws. Oral Oncol. 2020, 106, 104659.
19. Jones, J.P., Jr. Intravascular coagulation and osteonecrosis. Clin. Orthop. Relat. Res. 1992, 277, 41–53.
20. Boss, J.H.; Misselevich, I. Osteonecrosis of the femoral head of laboratory animals: The lessons learned from a comparative study of osteonecrosis in man and experimental animals. Vet. Pathol. 2003, 40, 345–354.
21. Bejar, J.; Peled, E.; Boss, J.H. Vasculature deprivation—Induced osteonecrosis of the rat femoral head as a model for therapeutic trials. Biol. Med. Model. 2005, 2, 24.
22. Laroche, M. Intraosseous circulation from physiology to disease. Jt. Bone Spine 2002, 69, 262–269.
23. Petek, D.; Hannouche, D.; Suva, D. Osteonecrosis of the femoral head: Pathophysiology and current concepts of treatment. Efort Open Rev. 2019, 4, 85–97.
24. Cohen-Rosenblum, A.; Cui, Q. Osteonecrosis of the Femoral Head. Orthop. Clin. N. Am. 2019, 50, 139–149.
25. Glueck, C.J.; Freiberg, R.A.; Sieve, L.; Wang, P. Enoxaparin prevents progression of stages I and II osteonecrosis of the hip. Clin. Orthop. Relat. Res. 2005, 164–170.
26. Svensson, P.J.; Zoller, B.; Mattiasson, I.; Dahlback, B. The factor VR506Q mutation causing APC resistance is highly prevalent amongst unselected outpatients with clinically suspected deep venous thrombosis. J. Intern. Med. 1997, 241,

379–385.

27. Eid, S.S.; Shubeilat, T. Prevalence of factor V Leiden, prothrombin G20210A, and MTHFR G677A among 594 thrombotic Jordanian patients. Blood Coagul. Fibrinolysis 2005, 16, 417–421.
28. Ali, N.; Ayyub, M.; Khan, S.A. High prevalence of protein C, protein S, antithrombin deficiency, and Factor V Leiden mutation as a cause of hereditary thrombophilia in patients of venous thromboembolism and cerebrovascular accident. Pak. J. Med. Sci. 2014, 30, 1323–1326.
29. Liu, F.; Silva, D.; Malone, M.V.; Seetharaman, K. MTHFR A1298C and C677T Polymorphisms Are Associated with Increased Risk of Venous Thromboembolism: A Retrospective Chart Review Study. Acta Haematol. 2017, 138, 208–215.
30. Hoffman, M. A cell-based model of coagulation and the role of factor VIIa. Blood Rev. 2003, 17 (Suppl. 1), S1–S5.
31. Brouns, S.L.N.; van Geffen, J.P.; Campello, E.; Swieringa, F.; Spiezia, L.; van Oerle, R.; Provenzale, I.; Verdoold, R.; Farndale, R.W.; Clemetson, K.J.; et al. Platelet-primed interactions of coagulation and anticoagulation pathways in flow-dependent thrombus formation. Sci. Rep. 2020, 10, 11910.
32. Mohan, G.; Malayala, S.V.; Mehta, P.; Balla, M. A Comprehensive Review of Congenital Platelet Disorders, Thrombocytopenias and Thrombocytopathies. Cureus 2020, 12, e11275.
33. Sokol, J.; Skerenova, M.; Ivankova, J.; Simurda, T.; Stasko, J. Association of Genetic Variability in Selected Genes in Patients with Deep Vein Thrombosis and Platelet Hyperaggregability. Clin. Appl. Thromb. Hemost. 2018, 24, 1027–1032.
34. Kalafatis, M.; Rand, M.D.; Mann, K.G. The mechanism of inactivation of human factor V and human factor Va by activated protein C. J. Biol. Chem. 1994, 269, 31869–31880.
35. Kalafatis, M.; Mann, K.G. Factor V Leiden and thrombophilia. N. Engl. J. Med. 1995, 332, 1382–1383.
36. Castoldi, E.; Brugge, J.M.; Nicolaes, G.A.; Girelli, D.; Tans, G.; Rosing, J. Impaired APC cofactor activity of factor V plays a major role in the APC resistance associated with the factor V Leiden (R506Q) and R2 (H1299R) mutations. Blood 2004, 103, 4173–4179.
37. Zoller, B.; Svensson, P.J.; He, X.; Dahlback, B. Identification of the same factor V gene mutation in 47 out of 50 thrombosis-prone families with inherited resistance to activated protein C. J. Clin. Investig. 1994, 94, 2521–2524.
38. Rees, D.C.; Cox, M.; Clegg, J.B. World distribution of factor V Leiden. Lancet 1995, 346, 1133–1134.
39. Ridker, P.M.; Miletich, J.P.; Hennekens, C.H.; Buring, J.E. Ethnic distribution of factor V Leiden in 4047 men and women. Implications for venous thromboembolism screening. JAMA 1997, 277, 1305–1307.
40. Gregg, J.P.; Yamane, A.J.; Grody, W.W. Prevalence of the factor V-Leiden mutation in four distinct American ethnic populations. Am. J. Med. Genet. 1997, 73, 334–336.
41. Jadaon, M.M. Epidemiology of activated protein C resistance and factor v leiden mutation in the mediterranean region. Mediterr. J. Hematol. Infect. Dis. 2011, 3, e2011037.
42. Glueck, C.J.; Freiberg, R.A.; Boriel, G.; Khan, Z.; Brar, A.; Padda, J.; Wang, P. The role of the factor V Leiden mutation in osteonecrosis of the hip. Clin. Appl. Thromb. Hemost. 2013, 19, 499–503.
43. Bjorkman, A.; Svensson, P.J.; Hillarp, A.; Burtscher, I.M.; Runow, A.; Benoni, G. Factor V leiden and prothrombin gene mutation: Risk factors for osteonecrosis of the femoral head in adults. Clin. Orthop. Relat. Res. 2004, 425, 168–172.
44. Zalavras, C.G.; Vartholomatos, G.; Dokou, E.; Malizos, K.N. Genetic background of osteonecrosis: Associated with thrombophilic mutations? Clin. Orthop. Relat Res. 2004, 422, 251–255.
45. Gagala, J.; Buraczynska, M.; Mazurkiewicz, T.; Ksiazek, A. Prevalence of genetic risk factors related with thrombophilia and hypofibrinolysis in patients with osteonecrosis of the femoral head in Poland. BMC Musculoskelet. Disord. 2013, 14, 264.
46. Chang, J.D.; Hur, M.; Lee, S.S.; Yoo, J.H.; Lee, K.M. Genetic background of nontraumatic osteonecrosis of the femoral head in the Korean population. Clin. Orthop. Relat Res. 2008, 466, 1041–1046.
47. Kim, Y.W.; Yoon, K.Y.; Park, S.; Shim, Y.S.; Cho, H.I.; Park, S.S. Absence of factor V Leiden mutation in Koreans. Thromb. Res. 1997, 86, 181–182.
48. Jun, Z.J.; Ping, T.; Lei, Y.; Li, L.; Ming, S.Y.; Jing, W. Prevalence of factor V Leiden and prothrombin G20210A mutations in Chinese patients with deep venous thrombosis and pulmonary embolism. Clin. Lab. Haematol. 2006, 28, 111–116.
49. Rosendaal, F.R.; Doggen, C.J.; Zivelin, A.; Arruda, V.R.; Aiach, M.; Siscovick, D.S.; Hillarp, A.; Watzke, H.H.; Bernardi, F.; Cumming, A.M.; et al. Geographic distribution of the 20210 G to A prothrombin variant. Thromb. Haemost. 1998, 79,

706–708.

50. Varga, E.A.; Moll, S. Cardiology patient pages. Prothrombin 20210 mutation (factor II mutation). Circulation 2004, 110, e15–e18.
51. Glueck, C.J.; Fontaine, R.N.; Gruppo, R.; Stroop, D.; Sieve-Smith, L.; Tracy, T.; Wang, P. The plasminogen activator inhibitor-1 gene, hypofibrinolysis, and osteonecrosis. Clin. Orthop. Relat. Res. 1999, 133–146.
52. Hillarp, A.; Zoller, B.; Svensson, P.J.; Dahlback, B. The 20210 A allele of the prothrombin gene is a common risk factor among Swedish outpatients with verified deep venous thrombosis. Thromb. Haemost. 1997, 78, 990–992.
53. Bravo-Perez, C.; de la Morena-Barrio, M.E.; Vicente, V.; Corral, J. Antithrombin deficiency as a still underdiagnosed thrombophilia: A primer for internists. Pol. Arch. Intern. Med. 2020, 130, 868–877.
54. Maclean, P.S.; Tait, R.C. Hereditary and acquired antithrombin deficiency: Epidemiology, pathogenesis and treatment options. Drugs 2007, 67, 1429–1440.
55. Patnaik, M.M.; Moll, S. Inherited antithrombin deficiency: A review. Haemophilia 2008, 14, 1229–1239.
56. Bucciarelli, P.; Rosendaal, F.R.; Tripodi, A.; Mannucci, P.M.; De Stefano, V.; Palareti, G.; Finazzi, G.; Baudo, F.; Quintavalla, R. Risk of venous thromboembolism and clinical manifestations in carriers of antithrombin, protein C, protein S deficiency, or activated protein C resistance: A multicenter collaborative family study. Arter. Thromb. Vasc. Biol. 1999, 19, 1026–1033.
57. Di Minno, M.N.; Ambrosino, P.; Ageno, W.; Rosendaal, F.; Di Minno, G.; Dentali, F. Natural anticoagulants deficiency and the risk of venous thromboembolism: A meta-analysis of observational studies. Thromb. Res. 2015, 135, 923–932.
58. Cenni, E.; Fotia, C.; Rustemi, E.; Yuasa, K.; Caltavuturo, G.; Giunti, A.; Baldini, N. Idiopathic and secondary osteonecrosis of the femoral head show different thrombophilic changes and normal or higher levels of platelet growth factors. Acta Orthop. 2011, 82, 42–49.
59. Rathod, T.N.; Tayade, M.B.; Shetty, S.D.; Jadhav, P.; Sathe, A.H.; Mohanty, S.S. Association of Thrombophilic Factors in Pathogenesis of Osteonecrosis of Femoral Head in Indian Population. Indian J. Orthop. 2020, 54, 33–38.
60. Chotanaphuti, T.; Heebthamai, D.; Chuwong, M.; Kanchanaroek, K. The prevalence of thrombophilia in idiopathic osteonecrosis of the hip. J. Med. Assoc. Thai 2009, 92 (Suppl. 6), S141–S146.
61. Kubo, T.; Tsuji, H.; Yamamoto, T.; Nakahara, H.; Nakagawa, M.; Hirasawa, Y. Antithrombin III deficiency in a patient with multifocal osteonecrosis. Clin. Orthop. Relat. Res. 2000, 306–311.
62. Seguin, C.; Kassis, J.; Busque, L.; Bestawros, A.; Theodoropoulos, J.; Alonso, M.L.; Harvey, E.J. Non-traumatic necrosis of bone (osteonecrosis) is associated with endothelial cell activation but not thrombophilia. Rheumatology 2008, 47, 1151–1155.
63. Garcia, F.L.; Ramalli, E.L.; Picado, C.H. Coagulation disorders in patients with femoral head osteonecrosis. Acta Ortop. Bras. 2013, 21, 43–45.
64. Dahlback, B.; Villoutreix, B.O. Regulation of blood coagulation by the protein C anticoagulant pathway: Novel insights into structure-function relationships and molecular recognition. Arter. Thromb. Vasc. Biol. 2005, 25, 1311–1320.
65. Esmon, C.T. The protein C pathway. Chest 2003, 124, 26S–32S.
66. Shen, L.; Dahlback, B. Factor V and protein S as synergistic cofactors to activated protein C in degradation of factor VIIIa. J. Biol. Chem. 1994, 269, 18735–18738.
67. Williamson, D.; Brown, K.; Luddington, R.; Baglin, C.; Baglin, T. Factor V Cambridge: A new mutation (Arg306-->Thr) associated with resistance to activated protein C. Blood 1998, 91, 1140–1144.
68. Glueck, C.J.; Freiberg, R.; Tracy, T.; Stroop, D.; Wang, P. Thrombophilia and hypofibrinolysis: Pathophysiologies of osteonecrosis. Clin. Orthop. Relat. Res. 1997, 334, 43–56.
69. Lykissas, M.G.; Gelalis, I.D.; Kostas-Agnantis, I.P.; Vozonelos, G.; Korompilias, A.V. The role of hypercoagulability in the development of osteonecrosis of the femoral head. Orthop. Rev. 2012, 4, e17.
70. Cui, Q.; Jo, W.L.; Koo, K.H.; Cheng, E.Y.; Drescher, W.; Goodman, S.B.; Ha, Y.C.; Hernigou, P.; Jones, L.C.; Kim, S.Y.; et al. ARCO Consensus on the Pathogenesis of Non-traumatic Osteonecrosis of the Femoral Head. J. Korean Med. Sci. 2021, 36, e65.
71. Rosen, S.B.; Sturk, A. Activated protein C resistance—A major risk factor for thrombosis. Eur. J. Clin. Chem. Clin. Biochem. 1997, 35, 501–516.
72. Pierre-Jacques, H.; Glueck, C.J.; Mont, M.A.; Hungerford, D.S. Familial heterozygous protein-S deficiency in a patient who had multifocal osteonecrosis. A case report. J. Bone Jt. Surg. Am. 1997, 79, 1079–1084.

73. Zalavras, C.; Dailiana, Z.; Elisaf, M.; Bairaktari, E.; Vlachogiannopoulos, P.; Katsaraki, A.; Malizos, K.N. Potential aetiological factors concerning the development of osteonecrosis of the femoral head. Eur. J. Clin. Investig. 2000, 30, 215–221.
74. Korompilias, A.V.; Ortel, T.L.; Urbaniak, J.R. Coagulation abnormalities in patients with hip osteonecrosis. Orthop. Clin. N. Am. 2004, 35, 265–271.
75. Glueck, C.J.; Freiberg, R.A.; Wissman, R.; Wang, P. Long term anticoagulation (4–16 years) stops progression of idiopathic hip osteonecrosis associated with familial thrombophilia. Adv. Orthop. 2015, 2015, 138382.
76. Xu, J.; Li, K.; Zhou, W. Relationship between genetic polymorphism of MTHFR C677T and lower extremities deep venous thrombosis. Hematology 2019, 24, 108–111.
77. Brezovska-Kavrakova, J.; Krstevska, M.; Bosilkova, G.; Alabakovska, S.; Panov, S.; Orovchanec, N. Hyperhomocysteinemia and of Methylenetetrahydrofolate Reductase (C677T) Genetic Polymorphism in Patients with Deep Vein Thrombosis. Mater. Sociomed. 2013, 25, 170–174.
78. Simurda, T.; Brunclikova, M.; Asselta, R.; Caccia, S.; Zolkova, J.; Kolkova, Z.; Loderer, D.; Skornova, I.; Hudecek, J.; Lasabova, Z.; et al. Genetic Variants in the FGB and FGG Genes Mapping in the Beta and Gamma Nodules of the Fibrinogen Molecule in Congenital Quantitative Fibrinogen Disorders Associated with a Thrombotic Phenotype. Int. J. Mol. Sci. 2020, 21, 4616.
79. Ekim, M.; Ekim, H.; Yilmaz, Y.K.; Kulah, B.; Polat, M.F.; Gocmen, A.Y. Study on relationships among deep vein thrombosis, homocysteine & related B group vitamins. Pak. J. Med. Sci. 2015, 31, 398–402.
80. Herrmann, M.; Whiting, M.J.; Veillard, A.S.; Ehnholm, C.; Sullivan, D.R.; Keech, A.C.; Investigators, F.s. Plasma homocysteine and the risk of venous thromboembolism: Insights from the FIELD study. Clin. Chem. Lab. Med. 2012, 50, 2213–2219.
81. den Heijer, M.; Koster, T.; Blom, H.J.; Bos, G.M.; Briet, E.; Reitsma, P.H.; Vandenbroucke, J.P.; Rosendaal, F.R. Hyperhomocysteinemia as a risk factor for deep-vein thrombosis. N. Engl. J. Med. 1996, 334, 759–762.
82. Glueck, C.J.; Freiberg, R.A.; Fontaine, R.N.; Tracy, T.; Wang, P. Hypofibrinolysis, thrombophilia, osteonecrosis. Clin. Orthop. Relat Res. 2001, 19–33.
83. Asano, T.; Takahashi, K.A.; Fujioka, M.; Inoue, S.; Ueshima, K.; Hirata, T.; Okamoto, M.; Satomi, Y.; Nishino, H.; Tanaka, T.; et al. Relationship between postrenal transplant osteonecrosis of the femoral head and gene polymorphisms related to the coagulation and fibrinolytic systems in Japanese subjects. Transplantation 2004, 77, 220–225.
84. Kim, T.H.; Hong, J.M.; Kim, H.J.; Park, E.K.; Kim, S.Y. Lack of association of MTHFR gene polymorphisms with the risk of osteonecrosis of the femoral head in a Korean population. Mol. Cells 2010, 29, 343–348.
85. Shang, X.F.; Su, H.; Chang, W.W.; Wang, C.C.; Han, Q.; Xu, Z.W. Association between MTHFR C677T polymorphism and osteonecrosis of the femoral head: A meta-analysis. Mol. Biol. Rep. 2012, 39, 7089–7094.
86. Zhang, T.; Ye, S.; Chen, Z.; Ma, Y. Association between MTHFR C677T polymorphism and non-traumatic osteonecrosis of the femoral head: An update meta-analysis. Pteridines 2020, 31, 38–45.
87. Rosenberg, N.; Murata, M.; Ikeda, Y.; Opare-Sem, O.; Zivelin, A.; Geffen, E.; Seligsohn, U. The frequent 5,10-methylenetetrahydrofolate reductase C677T polymorphism is associated with a common haplotype in whites, Japanese, and Africans. Am. J. Hum. Genet. 2002, 70, 758–762.
88. Sadewa, A.H.; Sunarti, S.R.; Hayashi, C.; Lee, M.J.; Ayaki, H.; Sofro, A.S.; Matsuo, M.; Nishio, H. The C677T mutation in the methylenetetrahydrofolate reductase gene among the Indonesian Javanese population. Kobe J. Med. Sci. 2002, 48, 137–144.
89. Ueland, P.M.; Hustad, S.; Schneede, J.; Refsum, H.; Vollset, S.E. Biological and clinical implications of the MTHFR C677T polymorphism. Trends Pharm. Sci. 2001, 22, 195–201.