


CASE REPORT

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Case report: primary osteonecrosis associated with thrombophilia-hypofibrinolysis and worsened by testosterone therapy

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Abstract

Background: Familial and acquired thrombophilia are often etiologic for idiopathic hip and jaw osteonecrosis (ON), and testosterone therapy (TT) can interact with thrombophilia, worsening ON.

Case presentation: Case 1: A 62-year-old Caucasian male (previous deep venous thrombosis), on warfarin 1 year for atrial fibrillation (AF), had non-specific right hip-abdominal pain for 2 years. CT scan revealed bilateral femoral head ON without collapse. Coagulation studies revealed Factor V Leiden (FVL) heterozygosity, 4G/4G plasminogen activator inhibitor (PAI) homozygosity, high anti-cardiolipin (ACLA) IgM antibodies, and endothelial nitric oxide (NO) synthase (eNOS) T786C homozygosity (reduced conversion of L-arginine to NO, required for bone health). Apixaban 5 mg twice daily was substituted for warfarin; and L-arginine 9 g/day was started to increase NO. On Apixaban for 8 months, he became asymptomatic. Case 2: A 32-year-old hypogonadal Caucasian male had 10 years of unexplained tooth loss, progressing to primary jaw ON with cavitation 8 months after starting TT gel 50 mg/day. Coagulation studies revealed FVL heterozygosity, PAI 4G/4G homozygosity, and the lupus anticoagulant. TT was discontinued. Jaw pain was sharply reduced within 2 months.

Conclusions: Idiopathic ON, often caused by thrombophilia-hypofibrinolysis, is worsened by TT, and its progression may be slowed or stopped by discontinuation of TT and, thereafter, anticoagulation. Recognition of thrombophilia-hypofibrinolysis before joint collapse facilitates anticoagulation which may stop ON, preserving joints.

Keywords: Osteonecrosis, Thrombophilia, Hypofibrinolysis, Testosterone, Anticoagulation

Background

Osteonecrosis (ON) is often secondary to high-dose, long-term steroids or alcoholism, with primary (idiopathic) ON defined when known secondary etiologies are ruled-out [1]. The development of primary ON appears to follow a sequence of events initiated by familial or acquired thrombophilia [2–4], venous occlusion causing osseous venous outflow obstruction, leading to increased intraosseous venous pressure, reduced arterial flow, ischemia, bone infarction and eventual joint collapse [3–7]. Venous occlusion is the initiating event in

experimental models of ON [8], and enoxaparin can prevent steroid induced ON [9]. Heritable or acquired thrombophilia-hypofibrinolysis alone, or augmented by testosterone therapy (TT) [9, 10] or clomiphene given to raise testosterone (in men) [10] are thought to lead to thrombotic venous occlusion and thence to osteonecrosis [3, 5–7]. In the current report, our specific aim was to describe the association of familial thrombophilia (Factor V Leiden heterozygosity), acquired thrombophilia (lupus anticoagulant, high anticardiolipin [ACLA] antibody IgM), and hypofibrinolysis (4G/4G homozygosity for the plasminogen activator inhibitor -1 mutation) with hip and jaw ON, and the interaction of TT with familial thrombophilia in ON.

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Methods

Studies were carried out following a protocol approved by the Institutional Review Board with signed informed consent.

Cases with idiopathic osteonecrosis and Controls

To provide a frame of reference for the two cases in the current report, thrombophilia-hypofibrinolysis measures in 240 cases with idiopathic osteonecrosis sequentially referred to our center for coagulation studies are provided, along with comparisons to 110 previously reported healthy, normal controls [11] (48 men, 62 women). Controls were selected from healthy hospital employees without osteonecrosis and without chronic disease states.

Measures of thrombophilia and hypofibrinolysis

PCR measures of the Factor V Leiden, Prothrombin, methylenetetrahydrofolate reductase (MTHFR), and plasminogen activator inhibitor (PAI-1 gene) mutations were done along with serologic measures of Lp (a), homocysteine, factors VIII and XI, antigenic proteins C, total S, free S, and antithrombin III, lupus anticoagulant, and anticardiolipin antibodies (ACLA) IgG and IgM, using previously reported methods [11, 12]. Serologic tests were done before anticoagulation. Plasminogen activator inhibitor-1 activity was not measured.

Statistical methods

The data were processed by SAS 9.4. Comparison of measures of thrombophilia-hypofibrinolysis between cases and controls was done by Chi-Square analysis, excepting those comparisons where the expected cell size was <5, when Fisher's exact X^2 tests were used.

Results

Case presentation

Case 1

A 62-year-old Caucasian male had a past history of deep venous thrombosis (DVT) in the right lower extremity (1995, after cervical laminectomy), and superficial venous thrombosis of the right greater saphenous vein (2003, after ablation procedure). He was receiving warfarin for 1 year for paroxysmal atrial fibrillation (AF) (status-post ablation and failed cardioversion). He was evaluated for abdominal-flank-hip pain progressing over a 2-year period. An abdominal CT scan revealed previously undiagnosed ON of both femoral heads without collapse (Ficat [13] stage I). In absence of alcoholism, high-dose long-term corticosteroid therapy, or any other causes of secondary ON [6], the ON was thought to be primary-idiopathic. Coagulation studies revealed thrombophilic Factor V Leiden (FVL) heterozygosity, hypofibrinolytic 4G/4G homozygosity for the PAI-1 gene,

thrombophilic elevated ACLA IgM (24 MPL, mid positive 20–80 MPL) and eNOS T786C homozygosity associated with reduced conversion of L-arginine to nitric oxide (NO), required for normal bone health [14]. The initial high ACLA IgM remained high on repeated testing. There were no other features of the antiphospholipid syndrome. Family screening revealed that both daughters were heterozygous for the FVL mutation, and one was homozygous for the PAI-1 4G/4G mutation. Because of difficulty maintaining an INR target of 2.5, Apixaban 5 mg twice daily was substituted for warfarin. L-arginine, 9 g/day, was given to increase NO production [15]. After 8 months on Apixaban, he was asymptomatic, but repeat imaging of the hips has not been done. We speculated that the warfarin, given for 1 year because of AF, may have concurrently stabilized his Ficat stage I ON.

Case 2

A 32-year-old hypogonadal Caucasian male had a 10-year history of unexplained progressive tooth erosion and tooth loss. Tooth loss accelerated 8-months after starting clomiphene (50 mg/day) to raise serum total and free testosterone, and a CT scan revealed cavitating ON of both jaws. The patient was referred to our center by his dental surgeon for evaluation. There were no etiologic factors for secondary ON. There was no evidence for excessive stomach acid or trauma (including teeth-grinding) related to tooth erosion, and no alcohol abuse, high-dose/long-term corticosteroids, or other secondary causes of ON. He had never received bisphosphonates, associated with jaw ON [16]. Coagulation studies revealed heterozygosity for the FVL mutation, homozygosity for the PAI-1 4G/4G mutation, and the lupus anticoagulant was positive, and remained positive on repeat testing.

TT was discontinued, with a sharp reduction in jaw pain within 2 months.

To provide a frame of reference to the two patients of the current report, Table 1 [17] displays comparisons of coagulation measures in 240 patients with primary ON versus those in 110 healthy normal controls. Over a period of 24 years beginning in 1992, we assessed 372 patients being referred for a new radiologic diagnosis of ON of either the hip or knee [17, 18] of whom 240 had primary idiopathic ON (not secondary to high dose-long term corticosteroids, alcoholism, sickle cell disease, dislocation, etc.). The 240 patients were compared against healthy normal controls ($n = 110$), except in the comparison of eNOS [14] mutations for which only 72 historical controls were evaluated. Due to diagnostic lab testing limitations, not every control or patient was able to be evaluated for every form of thrombophilia or hypofibrinolysis. These results allowed us to estimate the

Table 1 Coagulation abnormalities in 240 patients with primary osteonecrosis, compared with 110 healthy normal controls

Coagulation measures	Abnormal range	Primary ON (n = 240)	Normal controls (n = 110)	Case vs control p ^a
Factor V Leiden	TC, TT	21/235 (9%)	2/109 (2%)	.014
Prothrombin gene	TC, TT	9/228 (4%)	3/110 (3%)	.76 (F)
MTHFR	TT	46/226 (20%)	32/109 (29%)	.068
PAI-1 gene	4G4G	66/225 (29%)	26/104 (25%)	.42
Homocysteine	Dated cut point ^b	32/212 (15%)	5/107 (5%)	.0061
ACLA IgG	Dated cut point ^c	11/210 (5%)	6/109 (6%)	.92
ACLA IgM	Dated cut point ^d	27/209 (13%)	2/109 (2%)	.0011
Lupus anticoagulant	positive	2/203 (1%)	2/110 (2%)	.61 (F)
Lp(a)	≥35 mg/dl	61/205 (30%)	21/107 (20%)	.054
Factor VIII	>150%	47/175 (27%)	7/103 (7%)	<.0001
Factor XI	>150%	15/169 (9%)	3/101 (3%)	.060
Protein C	<73%	10/204 (5%)	6/96 (6%)	.63
Protein S	<63%	1/206 (0.5%)	4/96 (4%)	.037 (F)
Free S	<66%	8/186 (4%)	2/96 (2%)	.50 (F)
Antithrombin III	<80	8/203 (4%)	2/96 (2%)	.51 (F)
			Compare with 72 controls	
eNOS	TC, TT	90/138 (65%)	28/72 (29%)	.0003

^acomparisons made by Chi-square test, unless there were cells which had expected counts <5 in 2 × 2 table where Fisher's exact test (F) was used

^bdated cut point for Homocysteine high: ≥15 (11/15/08-12/2/14); ≥10.4 (after 12/3/14)

^c dated cut point for IgG high: ≥23 GPL (before 10/31/12); ≥15 (after 11/1/12)

^d dated cut point for IgM high: ≥10 MPL (before 4/30/12); ≥13 (after 5/1/12)

prevalence of thrombophilia and hypofibrinolysis in the healthy controls without ON, and amongst patients with primary ON, Table 1.

The two patients of our current report were heterozygous for the FVL mutation, one had elevated ACLA, and one was homozygous for the eNOS T786C mutation [14]. Our 240 patients with primary ON differed from normal controls by having FVL heterozygosity (like the 2 patients in the current report), high homocysteine, high ACLA IgM, high Factor VIII, and heterozygosity for the eNOS T786C mutation, Table 1.

Discussion

Arthralgia of the hips [19] and knees [20] is a very common complaint in the outpatient setting, often requiring diagnostic imaging studies [21–23]. Primary ON [6] is not a common cause of arthralgia [24], and the diagnosis and therapy of ON remains poorly understood by many clinicians. While the prevalence of early-stage (pre-joint collapse) primary ON appears to be relatively low [25], it is important to diagnose, because, as we have shown, treatment with long-term anticoagulation in patients with familial or acquired thrombophilia-hypofibrinolysis and with primary ON (Ficat [13] stage I-II, pre-joint collapse) often results in complete symptomatic relief and long-term joint preservation of both knees [7] and hips [26], and may ameliorate osteonecrosis of the jaw [27]. The major clinical barrier to reaching this therapeutic

benefit is the lack of awareness of the association between thrombophilia- hypofibrinolysis with primary ON [1, 3, 14, 28–31] which we are addressing in the current report.

There appear to be etiologic associations between factor V Leiden heterozygosity [3, 28, 32], hyperhomocysteinemia [33], high ACLA IgM [34], high Factor VIII [35], hetero-homozygosity for the T786C eNOS mutation [14] and primary ON. ON, particularly multifocal, occurs in patients with the antiphospholipid antibody syndrome [36]. Exogenous testosterone therapy (TT) in patients with familial or acquired thrombophilia-hypofibrinolysis promotes development of ON [32, 37] of the femoral head [32] and jaw [10].

In patients with early stage primary-idiopathic ON, before segmental collapse of hips or knees has occurred (Ficat [13] stage I or II), with a heritable thrombophilia or hypofibrinolysis, anticoagulation therapy of at least 1 year has been shown to arrest progression of ON and lead to clinically significant pain relief [7, 26, 38, 39]. We have previously [26] reported that long term anticoagulation (4 to 16 years) stops progression of idiopathic hip ON associated with familial thrombophilia (5 patients with Factor V Leiden Heterozygotes and 1 patient with resistance to activated protein C). On 4–16 years anticoagulation, 9 hips in these 6 patients, 8 originally Ficat II, 1 Ficat I remained unchanged [26] in contrast to untreated ON Ficat stage II where 50–80% of hips progress

to collapse (Ficat III-IV) within 2 years of diagnosis [40, 41]. Left untreated, ON of the hip inevitably leads to irreversible segmental or total joint collapse [41] (i.e., Ficat III- IV) requiring joint replacement, typically within 2 years of initial diagnosis [40–45].

There were no clinically significant bleeding episodes [26]. Long term anticoagulation initiated in Ficat I II idiopathic hip in patients heterozygous for the Factor V Leiden mutation may change the natural history of the disease [26].

Long term anticoagulation is also effective in thrombophilic patients with early (pre-collapse) primary ON of the knee [7]. In 6 patients with knee osteonecrosis, all 6 with thrombophilia, 4 with concurrent hypofibrinolysis, we determined prospectively whether anticoagulation with Enoxaparin could prevent collapse, progression to osteoarthritis, ameliorate pain, and restore function [7]. The 6 patients were treated with Enoxaparin (40–60 mg/day for ≥ 3 months) as mandated by an FDA-approved protocol. In post-Enoxaparin prospective follow-up, patients were reassessed clinically every 4–6 months and X-rayed every year. The 6 patients had follow-up for 15.1, 7.5, 3.9, 2.25, 2, and 1 years [7]. None progressed to joint collapse or severe osteoarthritis; 4 became and remained asymptomatic at 2, 3.9, 7.5, and 15.1 year follow-up [7]. Thrombophilic-hypofibrinolytic patients with knee ON treated with Enoxaparin have had no collapse or progression to severe osteoarthritis; and most have had resolution of pain and restoration of full function [7].

In the jaw, when left untreated, ON leads to progressive tooth loss with failure to heal, jaw bone cavitation, and chronic pain syndromes [10, 16]. Paralleling the patient in our current report, we have previously reported a very similar case of primary ON of the jaw in a 55 year old Caucasian man [10]. He also had FVL heterozygosity, and rapid progression of disease 6 months after starting TT gel 50 mg/day, with development of high serum T (963 ng/dl, laboratory upper limit [46] 800 ng/dl) and high estradiol (50 pg/ml, laboratory UNL 42.6 pg/ml). As in our current patient, the development of jaw ON appeared soon (6 months) after initiation of TT therapy [10], which then interacted with the patient's familial and acquired thrombophilia and familial hypofibrinolysis, promoting and worsening the jaw ON [18, 32]. We have previously reported in a pilot study, that warfarin therapy in patients with both Factor V Leiden heterozygosity and osteonecrosis of the jaw was effective in reducing jaw pain [27].

In patients with thrombophilia-hypofibrinolysis and thrombotic events on TT, continuation of TT, even with adequate concurrent anticoagulation, leads to repetitive thrombotic events [47].

When the thrombus-promoting TT therapy is stopped, and anticoagulation started, we speculate that venous outflow is restored, increased venous pressure in the bone is reduced, facilitating increased arterial flow, reducing osseous ischemia [7, 26]. This is accompanied, as in our current case of jaw ON, by reduction of symptoms, and, in longer term anticoagulation studies, by stopping and reversing osteonecrosis [7, 26]. It is relevant that experimental models of ON have shown venous occlusion to be the initiating event [8, 48], and that treatment with enoxaparin in experimental animals has the potential to prevent steroid-associated ON [48]. Giving TT to mice hetero- and homozygous for the Factor V Leiden mutation [49, 50] and also having experimental antiphospholipid syndrome [50], and using animal models of venous occlusion and ON [8, 48] would allow basic science studies of the relationship of TT and thrombophilia to ON [18].

Historically, in adults with primary ON of weight bearing joints, the most common treatments include invasive forms of secondary and tertiary prevention, including core decompression [51] with or without stem cell infusion [52], vascularized fibular graft [53], and ultimately total joint replacement [54]. Hence, new diagnoses of ON, initially made by the radiologist and confirmed by the orthopedic or dental surgeon or clinician [55], rarely undergo a rigorous workup for thrombophilia or hypofibrinolysis [5]. This represents a clinically important missed-opportunity as many patients may be inadequately treated for their joint pain [56] while thrombophilia-hypofibrinolysis, a treatable [7, 26] causative etiology of primary ON (Ficat Stages I-II), goes unaddressed [5].

Conclusion

Primary ON is often caused by underlying familial and acquired thrombophilia and hypofibrinolysis, and can be worsened by TT or testosterone-elevating clomiphene. In patients with primary ON, it is important for diagnostic and therapeutic reasons to determine whether thrombophilia-hypofibrinolysis are present, and whether TT is being used. To stop progression of early primary ON at Ficat Stage I or II before joint collapse in patients with thrombophilia-hypofibrinolysis, discontinuing TT is essential and may slow or stop progression of the ON. Initiating anticoagulation may stop progression of ON in thrombophilic patients without joint collapse and without progression to jaw cavitation, thus, avoiding the usual natural history of untreated ON, which is total joint replacement within 2 years of initial diagnosis, and in the jaw, chronic pain syndrome with jaw cavitation and recurrent supra-infection.

Abbreviations

ACLA: Anti-cardiolipin IgM antibodies; AF: Atrial fibrillation; DVT: Deep venous thrombosis; eNOS: endothelial nitric oxide synthase; FVL: Factor V Leiden; MTHFR: Methylene tetrahydrofolate reductase; NO: Nitric oxide; ON: Osteonecrosis; PAI: Plasminogen activator inhibitor; TT: Testosterone therapy

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Availability of data and materials

Available on request from Ping Wang PhD (pxwang@mercy.com).

Authors' contributions

MAJ participated in data collection, editing, and writing. KL participated in data collection, editing, and writing. AK participated in data collection, editing, and writing. SM participated in data collection, editing, and writing. IL participated in data collection, editing, and writing. CM participated in data collection, editing, and writing. AH participated in data collection, editing, and writing. AM participated in data collection, editing, and writing. CJG participated in data collection, editing, statistics, and writing. PW participated in data collection, editing, statistics, and writing. All authors read and approved the final manuscript.

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Competing interests

The authors declare no competing interests.

Consent for publication

Written consent for publication of the patients' details were obtained.

Ethics approval and consent to participate

Studies were carried out following a protocol approved by the Jewish Hospital Institutional Review Board with signed informed consent.

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References

- Glueck CJ, Freiberg R, Tracy T, Stroop D, Wang P. Thrombophilia and hypofibrinolysis: pathophysiologies of osteonecrosis. *Clin Orthop Relat Res.* 1997;1997:43–56.
- Glueck CJ, Freiberg RA, Fontaine RN, Tracy T, Wang P. Hypofibrinolysis, thrombophilia, osteonecrosis. *Clin Orthop Relat Res.* 2001;2001:19–33.
- Bjorkman A, Burtscher IM, Svensson PJ, Hillarp A, Besjakov J, Benoni G. Factor V Leiden and the prothrombin 20210A gene mutation and osteonecrosis of the knee. *Arch Orthop Trauma Surg.* 2005;125:51–5.
- Orth P, Anagnostakos K. Coagulation abnormalities in osteonecrosis and bone marrow edema syndrome. *Orthopedics.* 2013;36:290–300.
- Glueck CJ, Freiberg RA, Wang P. Detecting Thrombophilia, Hypofibrinolysis and Reduced Nitric Oxide Production in Osteonecrosis. *Semin Arthroplasty.* 2007;18:184–91.
- Glueck CJ, Freiberg RA, Wang P. Heritable thrombophilia-hypofibrinolysis and osteonecrosis of the femoral head. *Clin Orthop Relat Res.* 2008;466:1034–40.
- Glueck CJ, Freiberg RA, Wang P. Medical treatment of osteonecrosis of the knee associated with thrombophilia-hypofibrinolysis. *Orthopedics.* 2014;37:e911–6.
- Boss JH, 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;40:345–54.
- Beckmann R, Shaheen H, Kweider N, Ghassemi A, Fragoulis A, Hermanns-Sachweh B, Pufe T, Kadyrov M, Drescher W. Enoxaparin prevents steroid-related avascular necrosis of the femoral head. *Sci World J.* 2014;2014:347813.
- Pandit RS, Glueck CJ. Testosterone, anastrozole, factor V Leiden heterozygosity and osteonecrosis of the jaws. *Blood Coagul Fibrinolysis.* 2014;25:286–8.
- Freedman J, Glueck CJ, Prince M, Riaz R, Wang P. Testosterone, thrombophilia, thrombosis. *Transl Res.* 2015;165:537–48.
- Glueck CJ, Wang P, Fontaine RN, Sieve-Smith L, Lang JE. Estrogen replacement therapy, thrombophilia, and atherothrombosis. *Metabolism.* 2002;51:724–32.
- Ficat RP. Idiopathic bone necrosis of the femoral head, Early diagnosis and treatment. *J Bone Joint Surg (Br).* 1985;67:3–9.
- Glueck CJ, Freiberg RA, Oghene J, Fontaine RN, Wang P. Association between the T-786C eNOS polymorphism and idiopathic osteonecrosis of the head of the femur. *J Bone Joint Surg Am.* 2007;89:2460–8.
- Glueck CJ, Munjal J, Khan A, Umar M, Wang P. Endothelial nitric oxide synthase T-786C mutation, a reversible etiology of Prinzmetal's angina pectoris. *Am J Cardiol.* 2010;105:792–6.
- McMahon RE, Bouquot JE, Glueck CJ, Griep J. Beyond bisphosphonates: thrombophilia, hypofibrinolysis, and jaw osteonecrosis. *J Oral Maxillofac Surg.* 2006;64:1704–5.
- Glueck CJ, Freiberg RA, 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.
- Glueck CJ, Riaz R, Prince M, Freiberg RA, Wang P. Testosterone Therapy Can Interact With Thrombophilia, Leading to Osteonecrosis. *Orthopedics.* 2015;38:e1073–8.
- Christmas C, Crespo CJ, Franckowiak SC, Bathon JM, Bartlett SJ, Andersen RE. How common is hip pain among older adults? Results from the Third National Health and Nutrition Examination Survey. *J Fam Pract.* 2002;51:345–8.
- Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. *Ann Rheum Dis.* 2001;60:91–7.
- Murphey MD, Roberts CC, Bencardino JT, Appel M, Arnold E, Chang EY, Dempsey ME, Fox MG, Fries IB, Greenspan BS, et al. ACR Appropriateness Criteria Osteonecrosis of the Hip. *J Am Coll Radiol.* 2016;13:147–55.
- Berquist TH, Dalinka MK, Alazraki N, Daffner RH, DeSmet AA, El-Khoury GY, Goergen TG, Keats TE, Manaster BJ, Newberg A, et al. Chronic hip pain. American College of Radiology. ACR Appropriateness Criteria. *Radiology.* 2000;215:391–6.
- Pavlov H, Dalinka MK, Alazraki N, Berquist TH, Daffner RH, DeSmet AA, El-Khoury GY, Goergen TG, Keats TE, Manaster BJ, et al. Nontraumatic knee pain. American College of Radiology. ACR Appropriateness Criteria. *Radiology.* 2000;215:311–20.
- Mont MA, Hungerford DS. Non-traumatic avascular necrosis of the femoral head. *J Bone Joint Surg Am.* 1995;77:459–74.
- Naranje SMC EY, et al. Epidemiology of Osteonecrosis in the USA. In: K-H K, Mont MA, editors. *Osteonecrosis*. 1st ed. Heidelberg: Springer-Verlag Berlin Heidelberg; 2014. p. 39–45.
- Glueck CJ, Freiberg RA, 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.
- Glueck CJ, McMahon RE, Bouquot JE, Tracy T, Sieve-Smith L, Wang P. A preliminary pilot study of treatment of thrombophilia and hypofibrinolysis and amelioration of the pain of osteonecrosis of the jaws. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1998;85:64–73.
- Bjorkman A, Svensson PJ, Hillarp A, Burtscher IM, 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;2004:168–72.
- Glueck CJ, Freiberg R, Tracy T, Stroop D, Wang P. Thrombophilia and hypofibrinolysis: pathophysiologies of osteonecrosis. *Clin Orthop.* 1997;1997:43–56.

30. Glueck CJ, Freiberg RA, Boppana S, Wang P. Thrombophilia, hypofibrinolysis, the eNOS T-786C polymorphism, and multifocal osteonecrosis. *J Bone Joint Surg Am.* 2008;90:2220–9.
31. Glueck CJ, Freiberg RA, Fontaine RN, Tracy T, Wang P. Hypofibrinolysis, thrombophilia, osteonecrosis. *Clin Orthop.* 2001;2001:19–33.
32. Glueck CJ, Prince M, Patel N, Patel J, Shah P, Mehta N, Wang P. Thrombophilia in 67 Patients With Thrombotic Events After Starting Testosterone Therapy. *Clin Appl Thromb Hemost.* 2016;22:548–53.
33. Elishkewich K, Kaspi D, Shapira I, Meites D, Berliner S. Idiopathic osteonecrosis in an adult with familial protein S deficiency and hyperhomocysteinemia. *Blood Coagul Fibrinolysis.* 2001;12:547–50.
34. Mehsen N, Barnetche T, Redonnet-Vernhet I, Guerin V, Bentaberry F, Gonnet-Gracia C, Schaevebeke T. Coagulopathies frequency in aseptic osteonecrosis patients. *Joint Bone Spine.* 2009;76:166–9.
35. Kamphuisen PW, Eikenboom JC, Vos HL, Pablo R, Sturk A, Bertina RM, Rosendaal FR. Increased levels of factor VIII and fibrinogen in patients with venous thrombosis are not caused by acute phase reactions. *Thromb Haemost.* 1999;81:680–3.
36. Gorshtein A, Levy Y. Orthopedic involvement in antiphospholipid syndrome. *Clin Rev Allergy Immunol.* 2007;32:167–71.
37. Glueck CJ, Friedman J, Hafeez A, Hassan A, Wang P. Testosterone, thrombophilia, thrombosis. *Blood Coagul Fibrinolysis.* 2014;25:683–7.
38. Glueck CJFR, Wang P. Treatment of osteonecrosis of the hip and knee with enoxaparin. In: Koo K-H, Mont M, Jones LC, editors. *Osteonecrosis*. Berlin: Springer Verlag; 2014.
39. Glueck CJ, Freiberg RA, Sieve L, Wang P. Enoxaparin prevents progression of stages I and II osteonecrosis of the hip. *Clin Orthop Relat Res.* 2005;2005:164–70.
40. Bradway JK, Morrey BF. The natural history of the silent hip in bilateral atraumatic osteonecrosis. *J Arthroplasty.* 1993;8:383–7.
41. Mont MA, Zywiol MG, Marker DR, McGrath MS, Delanois RE. The natural history of untreated asymptomatic osteonecrosis of the femoral head: a systematic literature review. *J Bone Joint Surg Am.* 2010;92:2165–70.
42. Kang JS, Moon KH, Kwon DG, Shin BK, Woo MS. The natural history of asymptomatic osteonecrosis of the femoral head. *Int Orthop.* 2013;37:379–84.
43. Stulberg BN, Davis AW, Bauer TW, Levine M, Easley K. Osteonecrosis of the femoral head. A prospective randomized treatment protocol. *Clin Orthop.* 1991;140:151.
44. Hofmann S, Mazieres B. Osteonecrosis: natural course and conservative therapy. *Orthopade.* 2000;29:403–10.
45. Koo KH, Kim R, Ko GH, Song HR, Jeong ST, Cho SH. Preventing collapse in early osteonecrosis of the femoral head. A randomised clinical trial of core decompression. *J Bone Joint Surg (Br).* 1995;77:870–4.
46. Montella BJ, Nunley JA, Urbaniak JR. Osteonecrosis of the femoral head associated with pregnancy, A preliminary report. *J Bone Joint Surg Am.* 1999;81:790–8.
47. Glueck CJ, Lee K, Prince M, Jetty V, Shah P, Wang P. Four Thrombotic Events Over 5 Years, Two Pulmonary Emboli and Two Deep Venous Thrombosis, When Testosterone-HCG Therapy Was Continued Despite Concurrent Anticoagulation in a 55-Year-Old Man With Lupus Anticoagulant. *J Investig Med High Impact Case Rep.* 2016;4:2324709616661833.
48. 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:S141–6.
49. Luley L, Schumacher A, Mulla MJ, Franke D, Lottge M, Fill Malfertheiner S, Tchaikovski SN, Costa SD, Hoppe B, Abrahams VM, Zenclussen AC. Low molecular weight heparin modulates maternal immune response in pregnant women and mice with thrombophilia. *Am J Reprod Immunol.* 2015;73:417–27.
50. Katzav A, Grigoriadis NC, Ebert T, Touloumi O, Blank M, Pick CG, Shoenfeld Y, Chapman J. Coagulopathy triggered autoimmunity: experimental antiphospholipid syndrome in factor V Leiden mice. *BMC Med.* 2013;11:92.
51. Sadile F, Bernasconi A, Russo S, Maffulli N. Core decompression versus other joint preserving treatments for osteonecrosis of the femoral head: a meta-analysis. *Br Med Bull.* 2016;118:33–49.
52. Gangji V, Toungouz M, Hauzeur JP. Stem cell therapy for osteonecrosis of the femoral head. *Expert Opin Biol Ther.* 2005;5:437–42.
53. Ding H, Gao YS, Chen SB, Jin DX, Zhang CQ. Free vascularized fibular grafting benefits severely collapsed femoral head in concomitant with osteoarthritis in very young adults: a prospective study. *J Reconstr Microsurg.* 2013;29:387–92.
54. Lee GW, Park KS, Kim DY, Lee YM, Eshnazarov KE, Yoon TR. Results of Total Hip Arthroplasty after Core Decompression with Tantalum Rod for Osteonecrosis of the Femoral Head. *Clin Orthop Surg.* 2016;8:38–44.
55. Lee GC, Khoury V, Steinberg D, Kim W, Dalinka M, Steinberg M. How do radiologists evaluate osteonecrosis? *Skeletal Radiol.* 2014;43:607–14.
56. Assouline-Dayana Y, Chang C, Greenspan A, Shoenfeld Y, Gershwin ME. Pathogenesis and natural history of osteonecrosis. *Semin Arthritis Rheum.* 2002;32:94–124.

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