Medical Treatment of Osteonecrosis of the Knee Associated With Thrombophilia-Hypofibrinolysis

CHARLES J. GLUECK, MD; RICHARD A. FREIBERG, MD; PING WANG, PHD

abstract

In 6 patients with stage II knee osteonecrosis, all 6 with thrombophilia and 4 with concurrent hypofibrinolysis, the authors prospectively determined whether anticoagulation with enoxaparin could prevent collapse and progression to osteoarthritis, ameliorate pain, and restore function. The 6 patients were treated with enoxaparin (40 to 60 mg/d for 3 or more months) as mandated by a US Food and Drug Administration–approved protocol. In post-enoxaparin prospective follow-up, patients were reassessed clinically every 4 to 6 months, and radiographs were obtained every year. The 6 patients followed up at 15.1, 7.5, 3.9, 2.25, 2, and 1 year, respectively. None progressed to joint collapse or severe osteoarthritis. Four became and remained asymptomatic at 2-, 3.9-, 7.5-, and 15.1-year follow-up, respectively. A fifth patient did not progress to collapse or severe osteoarthritis but had residual pain at 2.25-year follow-up. The sixth patient had no symptomatic benefit on enoxaparin but improved on rivaroxaban at 1-year follow-up. Two patients had recurrences of knee pain 1 and 4 years after their initial treatment with enoxaparin. One resolved after a second course of enoxaparin, and the other, with a second recurrence 1 year after the second course, resolved after a third course. Pretreatment, all 6 patients required canes, crutches, or wheelchairs, but after enoxaparin, no patient required them, and walking was unrestricted. Thrombophilia-hypofibrinolysis contributes to the pathogenesis of knee osteonecrosis. Thrombophilic-hypofibrinolytic patients with stage II knee osteonecrosis treated with enoxaparin have had no collapse or progression to severe osteoarthritis, and most have had resolution of pain and restoration of full function. This represents a major improvement compared with the natural history of untreated spontaneous knee osteonecrosis.

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The pathogenesis of osteonecrosis (ON) of the hip often reflects a multiple-etiology model.\textsuperscript{1-8} The current authors\textsuperscript{9-13} and others\textsuperscript{1,14-23} have postulated a sequence for the development of ON in which osseous venous outflow obstruction is caused by venous thrombosis due to thrombophilia-hypofibrinolysis,\textsuperscript{1,9,12,24} leading to increased intraosseous venous pressure, reduced arterial flow, ischemia, and bone death.\textsuperscript{1-5,15,17,25-27} Experimental models of ON\textsuperscript{2-7} confirm venous occlusion as a primary event.

Procoagulant risk factors for ON of the hips, jaw,\textsuperscript{28} and knees\textsuperscript{14} in adults\textsuperscript{9,15,16,18,20-22,25,29} and in children with Legg-Calve-Perthes disease\textsuperscript{23,30} include heritable thrombophilia-hypofibrinolysis or, in adults, reduction of nitric oxide production by the T-786C mutation of the endothelial nitric oxide synthase gene (eNOS).\textsuperscript{9,31} The current authors have speculated that anticoagulation in thrombophilic-hypofibrinolytic patients with ON facilitates lysis of intraosseous thrombi, reducing elevated intraosseous venous pressure, improving arterial flow, reversing hypoxia, stopping bone death, and allowing bone healing.\textsuperscript{12,24}

Nontraumatic knee osteonecrosis includes 4 distinct conditions\textsuperscript{32,33}: idiopathic ON, secondary ON (predominantly after high-dose, long-term steroids), spontaneous ON in elderly women,\textsuperscript{34} and post-arthroscopic ON.\textsuperscript{35}

The association of heritable thrombophilia-hypofibrinolysis with ON is important because the diagnosis has led to therapy, which has decreased the frequency of total hip arthroplasty\textsuperscript{12,24} by using anti-coagulation with enoxaparin to stop progression of Ficat stage I and II primary ON of the femoral head. This experience\textsuperscript{12,24} led the current authors to investigate whether 3 or more months of therapy with enoxaparin in patients with knee ON and with thrombophilia-hypofibrinolysis would have similar results.

### Materials and Methods

**Study Design**

Signed informed consent was obtained using a protocol approved by

<table>
<thead>
<tr>
<th>Patient No./Race/Sex/Age, y</th>
<th>Smoker</th>
<th>Stage</th>
<th>No. of Knees</th>
<th>Homocysteine</th>
<th>PAI-1 Gene</th>
<th>Protein C</th>
<th>ACLA IgM</th>
<th>Factor VII</th>
<th>Factor XI</th>
<th>Lp(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/AV/F/56</td>
<td>N</td>
<td>II</td>
<td>1</td>
<td>4G4G</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/AV/M/65</td>
<td>N</td>
<td>II</td>
<td>1</td>
<td>4G4G</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/AV/M/33</td>
<td>N</td>
<td>II</td>
<td>2</td>
<td>16.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/AV/M/53</td>
<td>Y</td>
<td>II</td>
<td>2</td>
<td>166</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/AV/F/28</td>
<td>Y</td>
<td>II</td>
<td>1</td>
<td>183</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6/AV/F/49</td>
<td>N</td>
<td>II</td>
<td>2</td>
<td>19.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ACLA IgM, anticardiolipin antibody immunoglobulin M; F, female; M, male; N, no; PAI-1, plasminogen activator inhibitor activity; W, White; Y, yes.

*Only abnormal measures shown.

*Normal range, <15 µmol/L.

*Normal range, >60%.

*Normal range, <13 MPL/mL.

*Normal range, >150%.

*Normal range, <1 mg/dL.

*Hypofibrinolytic abnormality.

*Thrombophilic abnormality.
the Jewish Hospital institutional review board.

Initial treatment with enoxaparin in patients with thrombophilia-hypofibrinolysis was restricted by the US Food and Drug Administration–approved protocol to 40 to 60 mg/d for 3 or more months. Separate treatment courses (1.5 mg/kg/d in 2 divided doses) were repeated in 2 patients, the first because of recurrent symptoms and the second because of the development of ON in the contralateral knee.

The data of these 6 patients have not been previously reported.

In all patients, after an overnight fast, blood was drawn in the seated position for assessment of thrombophilia and hypofibrinolysis.

### Patients

In the temporal sequence of their referral, the authors assessed only those patients whose idiopathic ON involved the knee(s). The authors excluded patients who had taken high-dose, long-term steroids; alcoholics; elderly women with spontaneous ON of the knee; and those with postarthroscopy ON. All 6 patients had been diagnosed as having unilateral or bilateral knee ON by referring orthopedists using radiographs and magnetic resonance imaging (MRI).

Knee ON was staged per Lotke and Ecker and Carpintero et al as follows:

- **Stage I:** Radiographs normal, increased uptake in bone scans, subchondral areas of abnormal marrow signal intensity by MRI.
- **Stage II:** Radiographs and MRIs abnormal, cystic-sclerotic changes, flattening of the medial or lateral femoral condyle or tibial plateau.
- **Stage III:** Radiographs abnormal, fracture of the medial femoral condyle, the medial rim of the medial tibial plateau, tibial plateau collapse, or articular cartilage loose.
- **Stage IV:** Bone collapse on radiographs, articular cartilage destroyed, joint space narrowed, bone spur formation.

### Coagulation Measures: Laboratory Assessment of Thrombophilia and Hypofibrinolysis

**Polymerase Chain Reaction Assays.** Polymerase chain reaction measures

### Table 2

**Treatment in 6 Thrombophilic-Hypofibrinolytic Patients With Idiopathic Osteonecrosis of the Knee**

<table>
<thead>
<tr>
<th>Patient No./Race/Sex/Age, y</th>
<th>Initial Stage</th>
<th>No. of Knees</th>
<th>Rx</th>
<th>Progress</th>
<th>Asymptomatic FU, y</th>
<th>Stage at End of FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/W/F/56</td>
<td>II</td>
<td>1</td>
<td>Enoxaparin 40 mg/d for 6 mo</td>
<td>Improved in 2.6 y</td>
<td>Asymptomatic in 3.1 y</td>
<td>II</td>
</tr>
<tr>
<td>2/W/M/65</td>
<td>II</td>
<td>1</td>
<td>Enoxaparin 60 mg/d for 3 mo</td>
<td>Improved in 3 mo</td>
<td>Asymptomatic in 1.1 y</td>
<td>II</td>
</tr>
<tr>
<td>3/W/M/33</td>
<td>II</td>
<td>2</td>
<td>Enoxaparin 40 mg/d for 5 mo</td>
<td>R improved</td>
<td>L asymptomatic in 4 mo</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Enoxaparin 40 mg/d for 3 mo</td>
<td>Both R and L pain returned</td>
<td>Asymptomatic in 1 mo</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Enoxaparin 40 mg/d for 2 mo</td>
<td>Both R and L pain returned</td>
<td>Asymptomatic in 5 mo</td>
<td>II</td>
</tr>
<tr>
<td>4/W/M/53</td>
<td>II</td>
<td>2</td>
<td>Enoxaparin 40 mg/d for 3 mo</td>
<td>R pain resolved in 4 mo</td>
<td>Remained asymptomatic for 7.5 y</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Enoxaparin 60 mg/d for 3 mo</td>
<td>L pain resolved in 5 mo</td>
<td>Remained asymptomatic for 7.5 y</td>
<td>II</td>
</tr>
<tr>
<td>5/W/F/28</td>
<td>II in 1 knee</td>
<td></td>
<td>Enoxaparin 60 mg/d for 3 mo</td>
<td>R improved, L remained painful</td>
<td></td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>III in 1 knee</td>
<td></td>
<td>Enoxaparin 60 mg/d for 10 mo</td>
<td>Both knees improved, enoxaparin throughout pregnancy</td>
<td></td>
<td>III</td>
</tr>
<tr>
<td>6/W/F/49</td>
<td>II</td>
<td>2</td>
<td>Enoxaparin 60 mg/d + Metanx^a 2 tablets/d for 3 mo</td>
<td>No pain relief in 3 mo</td>
<td></td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rivaroxaban 10 mg for 8 mo</td>
<td>Pain improved in 2 mo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: F, female; FU, follow-up; L, left; M, male; R, right; Rx, prescription; W, White.

^aMetanx=L-methylfolate (6 mg), vitamin B6 (70 mg), vitamin B12 (4 mg).
are shown in Table 1. Osteonecrosis of the knee was stage II in 5 patients (8 knees), and, in the sixth patient (patient 5 in Table 1), it was stage II in 1 knee and stage III in the other.

No patient underwent knee surgery, including core decompression, before or during the study period.

**Thrombophilia and Hypofibrinolysis**

All 6 patients had thrombophilia. Two patients (patients 1 and 5) had high factor XI, 1 (patient 4) had high factor VIII, 1 (patient 2) had high anticardiolipin antibody immunoglobulin M, 1 (patient 3) had high homocysteine, and 1 (patient 6) had both low protein C and high homocysteine (Table 1).

Hypofibrinolysis was also present in 4 patients (patients 1-4), accompanying their thrombophilia, including 4G4G homozygosity of the PAI-1 gene in 2 (patients 1 and 2) and hypofibrinolysis Lp(a) in 2 (patients 3 and 4) (Table 1).

**Response to Enoxaparin**

Of the 6 patients with thrombophilia-hypofibrinolysis treated with enoxaparin for 3 or more months, 5 improved and 4 (patients 1-4) became asymptomatic after enoxaparin and remained asymptomatic through 2-, 3-, 5-, and 7.5-month follow-up, respectively (Table 2; Figure). Of the 6 patients receiving enoxaparin and having follow-up at 1 year or more, none had disease progression or required surgery (Table 2; Figure).

Patient 3 had 3 separate treatment periods (Table 2; Figure). In the 3 treatment periods (at 4, 1, and 5 months, respectively, after starting enoxaparin), he became asymptomatic (Table 2; Figure), and his initial knee stage remained unchanged at 15.1-year follow-up.

Prior to his 2 separate treatments, the first for the right knee and the second for the left knee, patient 4 could walk only 1 block with a cane and required opiates for pain relief. After the first enoxaparin treatment, pain resolved in the right knee in 4 months (Table 2; Figure). Four years later, the left knee became very painful, he could walk only a few steps with a cane, and he had to use opiates for pain relief (Table 2). After the second enoxaparin treatment, his left knee pain resolved in 5 months (Table 2; Figure). At the end of 7.5-year follow-up, both knees remained stage II.

Patient 5, having the most advanced ON of the group (stage II in 1 knee and stage III in the other [Tables 1-2]) improved on enoxaparin but did not become asymptomatic (Table 2; Figure).

Patient 6 was restricted to walking 1 block with a cane before treatment and had no pain relief after 3 months on enoxaparin and Metanx (Pamlab, Covington, Louisiana) to reduce homocysteine levels. Because she had failed to improve on enoxaparin, for 9 months she received rivaroxaban along with Metanx. After 2 months on Metanx and rivaroxaban (10 mg/d), she had pain improvement, and at 1-year follow-up she could walk without difficulty (Table 2; Figure). Her pretreatment knee stage (II) remained unchanged after 1-year follow-up (Table 2).

There were no side effects of enoxaparin, aside from frequent bruising at subcutaneous injection sites; no changes in hematocrit or hemoglobin; and no thrombocytopenia. There were no side effects of rivaroxaban.

**DISCUSSION**

Having documented the long-lasting benefits of 3 months of enoxaparin in stage I or II idiopathic hip ON, the current authors found that comparable benefit could be obtained in stage I or II idiopathic knee ON. Of 6 enoxaparin-treated patients, none had joint collapse and none had rapid progression to osteoarthritis. This represents a major improvement compared with the natural history of untreated spontaneous knee ON reported by Satku et al.

Of 6 patients, 4 became asymptomatic on enoxaparin, with no change in their pre-
treatment knee stage. A fifth enoxaparin-treated patient with the most severe pre-treatment ON (stage II in 1 knee and stage III in the other) had improvement in pain with reduced pain and no change in knee stage after 2.25-year follow-up. Pretreatment, all 6 patients required canes, crutches, or wheelchairs, but after enoxaparin, no patient required them, and walking was unrestricted.

Two patients (stage II ON) had recurrences of knee pain. One resolved with a second course of enoxaparin, and the other after a third course. In agreement with the authors’ data on the effectiveness of enoxaparin in ON of the hips,12,24 3 months or more of enoxaparin therapy in patients with thrombophilia-hypofibrinolysis may be similarly effective for knee ON. The effects of repeated courses or nonstop treatment with enoxaparin or oral Xa inhibitors (rivaroxaban) must be further evaluated. In 2 patients heterozygous for the factor V Leiden mutation, the authors showed that on continuous anticoagulation with warfarin or rivaroxaban, there was no change from a pretreatment Ficat I to II ON hip at 6- and 13-year follow-up, stopping progression of ON.43

Enoxaparin works by binding antithrombin III, producing a confirmational change, which accelerates its ability to inactivate the coagulation enzymes thrombin (factor IIa), factor Xa, and factor IXa.44 Rivaroxaban competitively inhibits factor Xa and, unlike enoxaparin, does not require cofactors (such as antithrombin) to exert its anticoagulant effect. Rivaroxaban inhibits both free and clot-bound factor Xa, as well as prothrombinase activity.45

High homocysteine and B vitamin deficiency in the presence of MTHFR C677T homozygosity or compound C677T-A1298C heterozygosity are pro-thrombotic,46 and high homocysteine can be normalized by L-methylfolate-vitamin B6-vitamin B12 therapy with reduction of thrombotic potential.47,48

The authors have studied 300 patients with idiopathic hip ON9,49-52 but have encountered only 15 with idiopathic ON limited solely to the knees, demonstrating its rarity, the need for investigation of its etiology, and the need for development of improved treatment regimens. A limitation of this study is the small number of patients treated with enoxaparin. Although prospective follow-up of radiographs and MRIs allowed comparison of the patients with a study of the natural history of knee ON,36 an optimal study would be double-blind for enoxaparin, which was not feasible with the small number of patients. Also, the authors’ assessment of pain and knee function was not systematically quantitated using the validated outcome measures of the Knee Society Clinical Rating System or the Oxford Knee Score.53,54

CONCLUSION

In the current study, thrombophilic-hypofibrinolytic patients with idiopathic knee ON, predominantly stages I and II, treated selectively with enoxaparin had no collapse or progression to severe osteoarthritis, and most had resolution of pain and restoration of full functionality.

REFERENCES


