METHYLPREDNISOLONE TREATMENT CAUSES HYPERCOAGULABILITY IN Pigs. A PATHOGENETIC LINK TO FEMORAL HEAD NECROSIS?

+*Drescher, W; *Li, H; *Donslund, S; **Ingerslev, J; *Hansen, E; *Bunger, C
+*Dept. of Orthopedics, Aarhus University Hospital, Aarhus, Denmark. Dept. of Orthopedics E, Aarhus University Hospital, DK-8000 Aarhus C, Denmark, ++45 8949 4136, Fax: ++45 8949 4150, wolddrescher@hotmail.com

Relevance to Musculoskeletal Conditions This study demonstrates that long term corticosteroid treatment induces a hypercoagulable state of possible significance for the pathogenesis of steroid-induced avascular necrosis of bone.

Introduction The pathogenesis of steroid-induced necrosis of the femoral head remains obscure. Disorders of fibrinolysis have been found in patients with osteonecrosis of different etiology(1). The effect of long term steroid treatment on the coagulation system in the normal organism was investigated in this study in pigs.

Materials and Methods Out of a total of 22 immature female Danish Landrace pigs from 11 litters, 11 animals received Medrol® (methylprednisolone) orally for 3 months (CS) at a daily dosage of 100 mg. Their 11 sister pigs served as controls and received no steroid treatment (NCS). In general anesthesia a 6F sheath was inserted unilaterally into the jugular vein from which three 5 ml citrate blood samples were taken immediately. The samples were centrifuged for 10 minutes at 4000 rotations per minute and 4 °C temperature. From the overlying plasma the prothrombin time (PT), the activated partial thromboplastin time (aPTT), fibrinogen, and antithrombin III (AT-III) levels were recorded on an ACL-3000 Coagulation Analyser (Instrumentation Laboratory, Milan, Italy). The mean and standard deviation were calculated for each group and compared by the Independent Samples t-test. Difference was considered significant at p < 0.05.

Results The CS animals received a cumulative dose of 9692 ± 502 mg methylprednisolone. The mean start dose was 3.6 mg/kg, the mean dose during the first, second, and third month of treatment was 3.0, 2.3, and 1.9 mg/kg bodyweight. Samples from 1 NCS pig showed hemolysis, 1 CS pig died during anesthesia, and samples from 2 CS pigs showed clotting before analysis. These 4 animals were excluded from the analysis. In CS pigs, the activated partial thromboplastin time (aPTT) was shortened to 50 % compared to control pigs (Table 1). Plasma fibrinogen displayed a non-significant tendency to increase in CS animals.

Table 1. Coagulation data given as mean ± S.D. in steroid-treated and non-treated animals.

<table>
<thead>
<tr>
<th>Coagulation parameter</th>
<th>Non-Steroid (NCS, n=10)</th>
<th>Steroid (CS, n=8)</th>
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<tbody>
<tr>
<td>PT [sec]</td>
<td>10.2 ± 5.8</td>
<td>10.0 ± 4.9</td>
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<tr>
<td>aPTT [sec]</td>
<td>34.5 ± 10.9</td>
<td>16.1 ± 6.0 (a)</td>
</tr>
<tr>
<td>fibrinogen [g/l]</td>
<td>6.1 ± 1.2</td>
<td>9.5 ± 5.0</td>
</tr>
<tr>
<td>AT-III [U/l]</td>
<td>0.9 ± 0.1</td>
<td>1.2 ± 0.5</td>
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Discussion In otherwise healthy pigs, CS treatment was accompanied by a hypercoagulable state. The activated partial thromboplastin time, that was significantly shortened in CS pigs, displays the global function of the intrinsic pathway of coagulation. This result points to the possibility that intravascular coagulation may be implicated in steroid-induced femoral head necrosis. Since the other global coagulation measure, the PT, was unchanged in CS treated pigs, suspicion is raised that one or more coagulation factors in the early intrinsic coagulation phase are affected by methylprednisolone. Hypofibrinolysis has previously been suggested as a possible cause of osteonecrosis in general (2). The porcine coagulation system consists of the same single factors as the human coagulation system (3). Our results in the untreated NCS pigs for PT, aPTT, AT-III, and the fibrinogen levels are not different from the corresponding human values (3,4).

Conclusion This study, utilising an animal pig model, illustrates that long-term high-dose steroid administration induces a hypercoagulable state with no apparent signs of an underlying disease. This finding points to a possible implication of coagulation in the pathogenesis of steroid-induced osteonecrosis.


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**Dept. of Clinical Immunology, Aarhus University Hospital, Aarhus, Denmark.

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