INTRODUCTION:
Osteoarthritis (OA) is a debilitating disease that affects over 40 million people in the United States at any given time. Virtually everyone over the age of 75 is affected in at least one joint by osteoarthritis, making this disease one of the most common health conditions in the country. Several theories of OA progression have been proposed. Mow et al. have suggested a primarily cartilage-based etiology for OA progression while Radin has proposed that initial subchondral bone changes precede cartilage degradation. While these groups have studied the different stages of cartilage degradation, early events of the disease process remain unclear. Recent work done by our group as well by Ghosh et al. suggests that thrombosis may play a role in the early etiology of OA. Our studies have shown hypercoagulability in patients with OA, suggesting a systemic contribution to local intraosseous thrombosis. Utilizing the Dunkin-Hartley guinea-pig model of spontaneous arthritis, we have shown a relationship between subchondral microthrombosis, subchondral bone plate thickness, and cartilage degeneration. We believe that such a relationship elucidates the time-course of progression of OA and furthers our understanding of the pathophysiology of the disease.

METHODS:
Duncan-Hartley guinea-pigs spontaneously and uniformly develop histologically evident OA. Animals were euthanized with phenobarbital at 4, 6, 8, or 12 months of age and their tibias were harvested (2 animals at each age group, 8 animals total). The tibias were first treated with a 1% bovine serum albumin solution at 4°C for 60-minutes for membrane stabilization. Specimens were then fixed in an aqueous buffered zinc formalin solution (Z-fix, Anatech, Ltd.) for ~24 hours. Specimens were then decalcified in a 5% nitric acid solution for ~24-hours, embedded in paraffin, and cut in the coronal plane. Slides were prepared with two different stains. Phosphotungstic acid-hematoxylin (PTAH) was utilized as a means to identify thrombosis in the subchondral vessels. Safranin-O / Fast-green stain was used for subchondral plate thickness evaluation and Mankin scoring. The number of vessels with thrombi were counted per unit area. The subchondral bone plate thickness was assessed with image-analysis software (Scion Image, 2000) as the ratio of medial to lateral thickness. The severity of OA was assessed by Mankin score. Statistical significance was determined by the Student’s t test.

RESULTS:
The number of thrombi and subchondral bone plate thickness increase simultaneously as the age of the animals increases (p<0.05). Cartilage degeneration begins several months before the appearance of subchondral thickening and microvascular thrombi appear however, it is relatively mild until 12 months of age at which time changes appear in the subchondral bone.

Figure 1: Mankin score, subchondral microthrombosis, and the subchondral bone plate thickness as a function of age. The scales for the Mankin score and thrombi appear on the left. The scale for the subchondral bone plate thickness appears on the right.

DISCUSSION:
Microvascular thrombosis has been shown to cause an increase in intraosseous pressure, which, in turn, has been shown to result in thickening of bony trabeculae. The results reported here suggests that this may be a pathogenic mechanism which contributes to cartilage degeneration in this model of spontaneous osteoarthritis. Hypercoagulability, observed in many patients with osteoarthritis, may contribute to the subchondral microvascular thrombosis. Current studies are attempting to elucidate this relationship. Microvascular thrombi may not be related to cartilage degeneration only by virtue of changes in the physical properties of the subchondral bone. Enzymes, such as thrombin and plasmin, fibrinopeptides, and cytokines released from platelets have effects on inflammation and generate matrix-degrading enzymes.

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REFERENCES: