**INTRODUCTION:** It has been reported that osteonecrosis (ON) of the hip occurs more frequently in patients who receive high-dose corticosteroid therapy for several diseases. Establishing a prophylaxis against corticosteroid-induced ON is an important theme. Various hypotheses have been proposed regarding the mechanism by which corticosteroid induce ON such as hyperlipidemia, hypercoagulable condition and vascular endothelial dysfunction. Recently, it was reported that oxidative injury was present in the bone shortly after corticosteroid administration in a rabbit model prior to the development of ON. Accordingly, we set up a hypothesis that antioxidative substances alleviate oxidative injury following corticosteroid administration and thus prevent ON. Vitamin E has potent antioxidant properties. Alpha-tocopherol (TCP) has the highest biopotency of the known vitamin E homolog. Thus α-TCP should have the greatest potential for a prophylaxis against ON. In this study, we examined the potential of α-TCP to reduce the incidence of corticosteroid-induced ON in an animal model. We also examined whether α-TCP exerts some effects on disorders of lipid metabolism, lipid peroxidation and vascular damage, which is a predisposing factor for both hypercoagulation and hypofibrinolysis, after corticosteroid administration.

**METHODS:** All protocols were performed in accordance with the guidelines of Animal Care and Use Committee of our institution. Fifty male Japanese white rabbits were divided into two groups; the control group was fed a normal diet and the experimental group was fed α-TCP-supplemented diet in which α-TCP (600 mg/kg diet) was added to the normal diet. To induce ON, high-dose methylprednisolone acetate (MPSL) (20 mg/kg body weight) was injected once into the right gluteus medius muscle of all rabbits. Four weeks after the injection of MPSL, the presence or absence of ON of bilateral femurs was examined histopathologically. The number of ON which developed ON (ON group) and the rabbits which not developed ON (ON group).

To examine the development of lipid peroxidation and vascular damage in bone, the femurs were stained immunohistochemically with clone 1F83 (anti malondialdehyde monoclonal antibody). The effect of α-TCP on lipid peroxidation and vascular damage was assessed by comparing immunohistochemical data between the control group and the experimental group. The effect of corticosteroid-induced lipid peroxidation and vascular damage on ON was also assessed comparing the following ON (ON group) and the rabbits which not developed ON (ON group). The TCP/T-cho ratios in the experimental group significantly increased (P<0.05) that in the control group at Week 4 were significantly higher (P<0.01) than the baseline level, respectively. The plasma levels of TG were significantly increased (P<0.01) during the period from Week 0 to Week 4. In plasma levels of TG, there was no difference between the groups at the same point.

**DISCUSSION:** Alpha-TCP significantly decreased the incidence of ON in this rabbit model of corticosteroid-induced ON. This finding suggests that the intake of α-TCP may prevent corticosteroid-induced ON. No significant difference was observed in disorders of lipid metabolism. These results indicate that there are some other ON-preventing mechanisms by α-TCP than disorders of lipid metabolism which has been reported by other researchers. Alpha-TCP reduced oxidative stress in the serum and in the blood vessels. We inferred that this is one of the mechanisms through which α-TCP prevented the development of steroid-induced ON.

It was reported that α-TCP is a very safe agent and its upper limit of no observed adverse effect level in humans when used as a medicine is 1600 mg/day. The amount of α-TCP that each rabbit consumed in this study was equivalent to about 1200 mg/day for a man (60 kg) and is considered to be a safe dose.

Our study has the following limitations. Because the occurrence of ON was evaluated at only one time point, it is possible that ON was repaired before this time point or that the development of ON was delayed, both of which can not be ruled out. Because we limited the content of α-TCP to 600 mg/kg diet, we were unable to determine the optimum level of α-TCP that can suppress the development of ON. Therefore, future studies should determine the timing of ON development and the level of α-TCP required to elicit this suppressive effect on ON-development.

Alpha-TCP was administered orally via the diet to rabbits at a safe dose and it suppressed corticosteroid-induced ON. Since α-TCP is safe and is frequently used in clinical settings, we believe this agent could be easily tested in clinical trials to confirm its effect on prevention of ON in humans, although further studies are required before that.

**REFERENCES:**