INTRODUCTION

The natural history of ON generally involves a progressive collapse which often results in secondary degenerative osteoarthritis (1). To treat this condition, prosthetic replacement is one of the surgical options. However, a higher rate of early failure has been reported in younger ON patients (1). Thus there is a need for the development of preventative methods, which requires that the pathogenesis of ON be clarified (2).

Gender differences have been proposed in many diseases such as cardiovascular disease (2). In this experimental study, we investigated the development of steroid-induced ON in male and female rabbits.

METHODS

We studied 47 adult (defined as animals with closed growth plate; male, n = 24; female, n = 23) Japanese white rabbits, ranging in age from 28 to 32 weeks. The rabbits were injected once with 20 mg/kg body weight of methylprednisolone (MPSL) acetate intramuscularly into the gluteus medius muscle before the start of the investigation (week 0) (3). Two weeks after the MPSL injection, the rabbits were sacrificed and tissue specimens were prepared as described (3). The diagnosis of ON was determined at 2 weeks after steroid administration. The complete areas of the proximal one-third and distal condyle of both the femora and humeri were examined histologically for the presence of ON. Diagnosis of ON was made on the basis of the diffuse empty lacunae or pyknotic nuclei of osteocytes within the bone trabeculae, accompanied by surrounding bone marrow cell necrosis (3).

Calculation of the size of bone marrow fat cells.

We calculated the size of bone marrow fat cells as the average of the maximal diameters of 100 fat cells in randomly selected fields (1 field = 4 x 10^-3 meters^2) from viable areas, using NIH Image software, as previously described (4).

Laboratory data examination.

We examined the following plasma lipid levels: low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), triglycerides, and the ratio of LDL cholesterol to high-density lipoprotein (HDL) cholesterol (LDL:HDL cholesterol ratio), which is considered a potential risk factor for corticosteroid-induced ON in rabbits (5).

RESULTS

Prevalence of ON.

The incidence of ON in the male rabbits was 66.7% (16 of 24), while that in the female rabbits was 21.7% (5 of 23). There was a significant difference in the rate of incidence of ON between male and female rabbits (P = 0.0032) (Figure 1A). Figure 1B. Histological appearance of ON was similar in male and female rabbits. In the metaphysis and diaphysis of both genders, yellowish areas were observed in which an accumulation of bone marrow cell debris was seen and the bone trabeculae showed empty lacunae (Figure 2).

Sizes of bone marrow fat cells.

The bone marrow fat cells of the male rabbits (61.5 ± 5.6 μm) were significantly larger than those of the female rabbits (58.9 ± 3.7 μm) (P = 0.0102). Among male rabbits, the average size of bone marrow fat cells was significantly larger in rabbits with ON (62.9 ± 5.9 μm) than in those without ON (58.8 ± 5.9 μm) (P = 0.0058). Similarly, among female rabbits, the average size of bone marrow fat cells was significantly larger in rabbits with ON (62.2 ± 4.0 μm) than in those without ON (57.9 ± 3.0 μm) (P = 0.0218). There was no significant difference in the size of bone marrow fat cells between ON-positive male and female rabbits (P = 0.9772).

Laboratory data examination. LDL (Figure 1B).

The levels of plasma LDL between male and female rabbits had a significant interaction with gender (P = 0.0069). The levels of LDL in male rabbits at 1 week were significantly higher than those in female rabbits (P = 0.0001). In male rabbits, plasma levels of LDL were significantly increased at 1 (*P = 0.0001), and 2 weeks (**P = 0.0001) in comparison to those at week 0. In female rabbits, plasma levels of LDL were significantly increased at 2 weeks (**P = 0.0200) in comparison to week 0, while no significant difference was observed at 1 week (P = 0.4370). C LDL:HDL cholesterol ratio between male and female rabbits had no significant interaction with gender (P = 0.3330). Plasma levels of LDL:HDL cholesterol ratio in male rabbits at 1 week were significantly higher than that in female rabbits (P = 0.0001).

DISCUSSION

Several mechanisms have been implicated in the pathogenesis of ON. Hyperlipidemia has been identified as a possible contributor to ON. A previous study showed the adipocytes within the femoral heads of steroid-treated rabbits had a 2% greater increase in fat content relative to untreated rabbits (6).

On the other hand, a higher LDL:HDL cholesterol ratio apparently reflects increased lipid transport to the peripheral tissue, a potential risk factor for corticosteroid-induced ON in rabbits (5). In the present study, 1 week after the MPSL injection, the plasma LDL:HDL cholesterol ratios of the female rabbits were significantly lower than those of the male rabbits. In addition, the bone marrow fat cells of the female rabbits were significantly smaller on average than those of the male rabbits. Therefore, we speculate that the gender differences on the development of ON might be partly explained by a gender difference in lipid deposition in bone marrow fat cells.

We believe that gender differences are critical to understanding the pathogenesis of steroid-induced ON.

REFERENCES