INTRODUCTION:
Non-traumatic osteonecrosis of femoral head (ONFH) is an intractable disease. Many ONFH cases develop in association with steroid treatment. We found that single nucleotide polymorphism (SNP) of the ATP binding cassette B1 (ABCB1) gene and Lipoprotein(a) phenotype is related to ONFH (we reported at 50th and 52nd Annual Meeting of the ORS). Since multiple factors are involved in the risk of ONFH, it is necessary to clarify other related genetic polymorphisms. Steroid-induced ONFH has been reported to be related to lipid metabolism abnormalities. Associations of lipid parameters, major SNPs of lipoproteins and coronary artery disease (CAD) have been reported.

In this study, we examined the relationships between lipoprotein polymorphisms, lipid parameters, and steroid-induced ONFH, in order to clarify the risk factors for steroid-induced ONFH.

METHODS:
The current study examined 33 patients with ONFH (case) and 122 patients who did not develop ONFH (reference group) following renal transplantation in our university from 1983 to 2004. We retrospectively examined patient gender, age at transplantation, type of transplantation (living or cadaveric), status of acute rejection, type of immunosuppressant used after transplantation (cyclosporine or tacrolimus), and steroid administration protocol. Four SNPs which were reported to be related to CAD include C7623T and G12619A for the ApoB gene and G75A and C83T for the ApoA1 gene. These SNPs were analyzed using polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) and Taqman® real-time PCR chemistry. Also, serum levels of Low-density lipoprotein (LDL), high-density lipoprotein (HDL), ApoB and ApoA1 were measured. ApoB/ApoA1 and LDL/HDL ratios were calculated. The relationships among these SNPs, lipid parameters and ONFH development were statistically evaluated. The crude and adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated by a logistic regression model. These analyses were all conducted using the Statistical Analysis System (SAS, ver 9.0).

RESULTS:
A significant relationship was observed between ONFH development and C7623T of the ApoB gene, with a significantly increased risk of ONFH development with the T allele (Table 1). No significant relationship was observed between other SNPs and ONFH development. Regarding lipid parameters, a significant relationship was observed between ApoB/ApoA1 ratio and ONFH development (Table 2). No association was observed between ONFH and serum levels of LDL, LDL, ApoB and ApoA1, as well as the LDL/HDL ratio. The lipid parameters were compared with 4 gene polymorphisms. Lipid parameters were not related to ApoB C7623T (Figure 1), ApoB G12619A, and ApoA1 G-75A. Significant relationships were found between ApoA1 C83T and serum ApoB level, ApoB/ApoA1 ratio has been emphasized mainly as a risk factor for CAD.

DISCUSSION:
Regarding the relationship to CAD, de Padua et al. reported that people with 7623CC are more susceptible, and those with 7623TT are less susceptible despite their higher serum lipid levels. Boekholdt et al. reported that the T allele of C7623T alters the structure of ApoB particle, which increases the serum level of LDL which is less likely to cause arteriosclerosis. This study showed significantly higher risk of ONFH in patients with 7623CT or 7623TT than those with 7623CC. No significant relationship was observed in this study between ONFH and other genes which are associated with CAD. There may be different pathological mechanisms involved in the process of steroid-induced ONFH compared with those in CAD.

As for the relationship between ONFH and serum apolipoprotein levels, Miyazaki et al. reported the relationship between ONFH and a serum ApoB/ApoA1 ratio in a study of Japanese subjects. In the current study, although no relationship was observed between ONFH and serum ApoB level, a significant relationship was also observed between ONFH and serum ApoB/ApoA1 ratio (P=0.045). As a useful serological marker of cholesterol transport, ApoB/ApoA1 ratio has been emphasized mainly in the field of ischemic heart disease. Since it is reported that accumulation of lipids in the bone affects the development of ONFH, high serum ApoB/ApoA1 ratios observed in this study may have affected ONFH through increased transport of lipids to the periphery.

REFERENCES: