

# Increased level of apolipoprotein B/apolipoprotein A1 ratio as a potential risk for osteonecrosis

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## Abstract

**Objective**—This study was performed to investigate whether a high ratio of apolipoprotein B to apolipoprotein A1 (apo B/apo A1 ratio) is significantly associated with the risk of developing non-traumatic osteonecrosis of the femoral head (ON).

**Methods**—Fifty consecutive non-traumatic ON cases were compared with 50 age and sex matched controls, using both univariate and stepwise discriminant analyses, regarding the factors of corticosteroid, alcohol, cigarettes, cholesterol, triglyceride, and apo B/apo A1 ratio. To eliminate the possibility that ON or osteoarthritic change itself can increase the apo B/apo A1 ratio, a further 32 consecutive cases comprising nine traumatic ON and 23 osteoarthritis (OA) patients were analysed using Scheffe's test.

**Results**—There was a significant association between a high apo B/apo A1 ratio and the development of non-traumatic ON with both univariate ( $p=0.0001$ ) and stepwise discriminant analyses (partial  $r^2=0.1239$ ,  $p=0.0004$ ). The apo B/apo A1 ratio in the non-traumatic ON group was significantly higher than that in the traumatic ON ( $p<0.01$ ), control ( $p<0.001$ ), or the OA groups ( $p<0.001$ ).

**Conclusion**—A high apo B/apo A1 ratio is significantly associated with the risk of developing ON. This ratio may be useful for assessing the potential risk of developing osteonecrosis.

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As a useful serological marker of cholesterol transport, the ratio of apolipoprotein B to apolipoprotein A1 (apo B/apo A1 ratio) has been emphasised mainly in the field of ischaemic heart disease. A high apo B/apo A1 ratio is considered to reflect prominent cholesterol transport to peripheral tissue.<sup>1</sup>

Osteonecrosis of the femoral head (ON) is thought to be the result of ischaemic insult to bone and bone marrow tissue.<sup>2,3</sup> This study was designed to determine whether a high apo B/apo A1 ratio is significantly associated with the risk of developing non-traumatic ON.

## Methods

### PATIENTS AND CONTROLS

In this study, none of the patients had any history of obesity, ischaemic heart disease, hypertension, diabetes mellitus, or the use of diuretics or  $\beta$  blockers, as verified by body mass

index,<sup>4</sup> clinical history, electrocardiogram, and haematological and urinary examinations.

### Non-traumatic ON group

The non-traumatic ON group consisted of 50 consecutive Japanese patients, who had been referred to Kyushu University Hospital between August 1996 and September 1997 with the diagnosis of non-traumatic ON, as confirmed by roentgenography, bone scintigram, magnetic resonance imaging (MRI), and histopathological examination.<sup>2,3,5</sup>

This group consisted of three subgroups, corticosteroid, alcohol, and idiopathic groups. The corticosteroid group (20 patients) had a history of corticosteroid treatment for underlying diseases. The alcohol group (18 patients) was defined based on a report that the consumption of over 400 ml of ethanol per week results in a significant risk of developing ON.<sup>6</sup> The remaining 12 patients were categorised as idiopathic, as they had no associated risk factors for ON.<sup>2</sup>

### Control group

This group consisted of 50 randomly selected healthy Japanese volunteers who had no history of corticosteroid use, alcohol abuse, or associated risk factors for ON.

### Traumatic ON group and osteoarthritis of the hip group

The traumatic ON group consisted of nine consecutive Japanese patients, who had been referred to our hospital during the same period. The osteoarthritis (OA) group consisted of 23 consecutive Japanese patients who had also been referred to our hospital during the same period, among whom secondary OA after collapsed ON had been excluded.<sup>7</sup> Patients in both groups had no risk factors for ON.

### LABORATORY TESTS

All preoperative blood samples were obtained from each of the ON and OA patients between 7 and 8 am, after a 12 hour recumbent fasting period. Blood samples from the controls were obtained under the same conditions. Total serum cholesterol and triglyceride were measured by enzymatic methods<sup>8</sup> with high precision (coefficients of variation were 0.3% for cholesterol and 0.5% for triglyceride). Serum levels of apolipoprotein A1 (apo A1) and apolipoprotein B (apo B) were measured by turbidimetric immunoassay,<sup>9</sup> with a coefficient of variation of 2.3% for apo A1 and 1.1% for apo B.

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Table 1 Univariate (top) and multivariate (bottom) analyses of risk factors for developing osteonecrosis of the femoral head

Risk factor*	ON		p†
	+	- (n=50)	
Corticosteroid			
+	20	0	
-	30	50	0.0001
Sex			
male	34	34	
female	16	16	1.0000
Age (y)	44.4 (14.9)	44.4 (14.5)	1.0000
Alcohol (ml/week)‡	388.0 (401.0)	82.9 (142.0)	0.0001
Cigarettes (no/day)	17.6 (19.0)	7.4 (13.3)	0.0027
Cholesterol (mg/dl)	192.7 (34.1)	203.8 (34.1)	0.1081
Triglyceride (mg/dl)	121.9 (39.9)	109.9 (46.1)	0.1685
Apo B/apo A1 ratio	0.85 (0.24)	0.62 (0.18)	0.0001
Risk factor	partial r <sup>2</sup> §		p§
Corticosteroid	0.2500		0.0001
Alcohol	0.3163		0.0001
Apo B/apo A1 ratio	0.1239		0.0004
Cigarettes	0.0005		0.8327
Cholesterol	0.0067		0.4268
Triglyceride	0.0000		0.9938

\*Corticosteroid and sex are listed as numbers of subjects. The other factors are given as means (SD). †Univariate analyses were performed by means of Fisher's exact test for corticosteroid,  $\chi^2$  test for sex, and Student's *t* tests for age, alcohol, cigarettes, cholesterol, triglyceride, and the apo B/apo A1 ratio. ‡Values are given as weekly ethanol consumption. §Stepwise discriminant analysis was used. Apo B/apo A1 ratio = apolipoprotein B/apolipoprotein A1 ratio; ON = osteonecrosis of the femoral head.

#### STATISTICAL ANALYSIS

Univariate analyses between the non-traumatic ON and the control groups were performed by means of Fisher's exact test and  $\chi^2$  test for the differences in proportions of corticosteroid history and sex, respectively, and Student's *t* tests for numerical data of age, alcohol, cigarettes, cholesterol, triglyceride, and the apo B/apo A1 ratio. Factors except for those with a *p* value of 1.0000 were further analysed by multivariate analysis using stepwise discriminant analysis,<sup>10</sup> where adjustments for all confounding factors including corticosteroid, alcohol, and age were performed.

To eliminate the possibility that ON or OA itself can increase the level of the apo B/apo A1 ratio, multiple comparisons of the apo B/apo A1 ratio were performed using Scheffe's test with *p*<0.05 being considered significant.

All the analyses were performed with the SAS software (SAS Institute Ltd, Tokyo, Japan).

#### Results

##### CHARACTERISTICS OF THE STUDY SAMPLE

The mean (SD) age in the non-traumatic ON group was 44.4 (14.9) years. The corticosteroid group consisted of nine men and 11 women, ranging from 20 to 70 years of age (mean (SD) 40.9 (15.9) years), of whom nine

Table 2 Multiple comparisons of apolipoprotein B/apolipoprotein A1 ratio

Group	Apolipoprotein B/apolipoprotein A1 ratio
Non-traumatic ON	0.85 (0.24)
Corticosteroid	0.85 (0.20)
Alcohol	0.86 (0.29)
Idiopathic	0.84 (0.24)
Control	0.62 (0.18)*
Traumatic ON	0.59 (0.16)**
OA	0.63 (0.18)*

Values are means (SD). ON = osteonecrosis of the femoral head; OA = osteoarthritis. \**p*<0.001, \*\**p*<0.01 compared with non-traumatic ON.

patients had received corticosteroid treatment for systemic lupus erythematosus, three for aplastic anaemia, three for nephrosis, two for idiopathic thrombocytopenic purpura, one for uveitis, one for rheumatoid arthritis, and one for adrenal dysfunction. The alcohol group consisted of 18 men, ranging from 26 to 67 years of age (mean (SD) 44.0 (9.8) years), the idiopathic group consisted of seven men and five women, ranging from 26 to 73 years of age (mean (SD) 51.0 (18.5) years), and the traumatic ON group consisted of five men and four women, ranging from 12 to 45 years of age (mean (SD) 30.3 (10.9) years), of whom seven patients had antecedent femoral neck fracture, one had femoral head fracture, and one had fracture dislocation of the hip.

The control group consisted of 34 men and 16 women, ranging from 20 to 78 years of age (mean (SD) 44.4 (14.5) years), while the OA group consisted of seven men and 16 women, ranging from 22 to 74 years of age (mean (SD) 45.7 (16.5) years).

#### ASSOCIATION BETWEEN RISK FACTORS AND NON-TRAUMATIC ON

Table 1 summarises the results of univariate and multivariate analyses. Those factors that were significantly associated with non-traumatic ON in the multivariate analysis were corticosteroid, alcohol, and the apo B/apo A1 ratio.

#### MULTIPLE COMPARISONS OF THE APO B/APO A1 RATIO BETWEEN THE SUBGROUPS

The apo B/apo A1 ratio in the non-traumatic ON group was significantly higher than that in the traumatic ON (*p*<0.01), control (*p*<0.001), or the OA groups (*p*<0.001), but there was no significant difference between the latter three groups. The apo B/apo A1 ratio was not significantly different between the corticosteroid, alcohol, and idiopathic groups (table 2).

#### Discussion

Patients with a history of corticosteroid treatment or alcohol abuse have a higher risk of developing ON compared with healthy people,<sup>2</sup> and as such it is not uncommon for cases initially diagnosed as not having ON based on MRI or biopsy to then develop ON several months later. It is thus difficult to define the end point at which there is no risk of suffering from ON in such cases. To exclude such false negative cases, patients who had a history of corticosteroid treatment or alcohol abuse were not included in the control group in this study.

Multivariate analysis proved that the apo B/apo A1 ratio was associated with the risk of ON independently of corticosteroid and alcohol. This view is supported by several clinical reports. The apo B/apo A1 ratio in SLE patients has been reported to show no remarkable change after corticosteroid treatment.<sup>11</sup> A low apo B/apo A1 ratio has been reported in alcoholics.<sup>12</sup> We thus conclude that the apo B/apo A1 ratio had actually been raised from the outset in the corticosteroid and alcohol ON cases.

The apo B/apo A1 ratio has been reported to increase gradually over a lifetime. In the multiple comparison, the ages in each group were not exactly matched. The mean age in the idiopathic ON group was seven years older than that in the control group, however, a span of seven years around the age of 50 seems to show no significant difference in the level of the apo B/apo A1 ratio.<sup>13</sup> The mean age in the traumatic ON group was 14 years younger than that in the non-traumatic ON group. The traumatic ON group was included to refute the hypothesis that an increased apo B/apo A1 ratio is the result of ON. We therefore believe that the non-increased apo B/apo A1 ratio in the traumatic ON group was meaningful in that it could at least refute such a hypothesis despite the difference in age.

The abnormal lipid deposition in bone and bone marrow tissue that has been reported both in human ON cases<sup>14</sup> and in an animal model,<sup>15</sup> may conceivably be related to prominent lipid transport to bone tissue resulting from a high apo B/apo A1 ratio. It is our belief that the apo B/apo A1 ratio may be useful not only for assessing the potential risk of developing ON, but also for exploring the possible mechanism of ON.

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