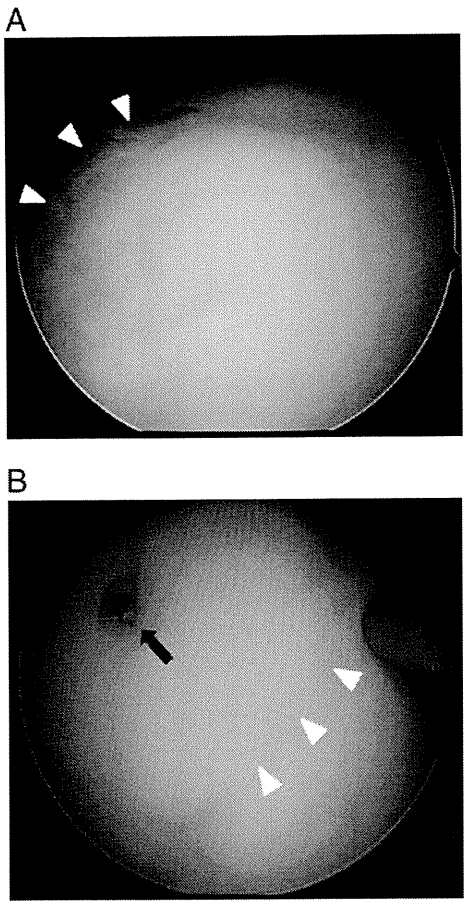

Fig. 3. (A) Second-look arthroscopic view of the medial border of the re-fixed chondral fragment, which remained fissured with marginal irregularity (white arrow-heads). (B) The lateral border, which was smoothly continuous to the adjacent articular cartilage (white arrow-heads), and a pin protrusion (arrow).

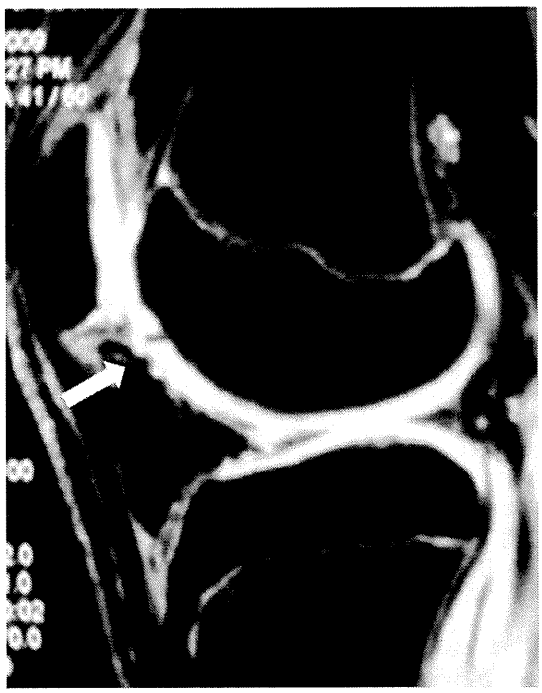

Fig. 4. T2* MRI sagittal view of the lateral femoral condyle 2 years after the operation, showing the persisting fixation pin (arrow) and the re-fixed fragment continuous to the bed without any abnormal intervention.

that not only osteochondral fractures but also fracture of pure chondral fragments from the articular cartilage may occur in adolescents as well as adults.

In this series, since the fragments were all detached from the lateral femoral trochlea, it was considered likely that a shearing force had been applied to the lateral facet by the collision of the patella generated by the twisting motion of the lower leg and/or contraction of the quadriceps. This is the same mechanism as that which causes patellar dislocation. Patellar dislocation generally occurs in patients with various contributory predisposing factors. However, these three cases had none of the common predisposing factors such as general joint laxity, abnormal Q angle, the type III patella of Wiberg's classification, shallow femoral trochlea or patella alta, etc. (Table 1). As the applied force was not released by dislocation of the patella due to the absence of any predisposing factor in these patients, it is likely that the force might instead be concentrated on to the lateral facet as a shearing force leading to this type of chondral injury (Fig. 5). We therefore consider that shearing of a chondral fragment from the articular cartilage of the knee might be a type of sports injury in adolescents, although it is likely to be very rare, in patients with no predisposing factors for patellar dislocation. Arthroscopically, a far inferior healing response was observed between the medial border of the re-fixed fragment and the adjacent articular cartilage in two of the three cases. This might be caused by intermittent shearing forces generated by contact of the central ridge of the patellar articular surface to this area of the lateral facet during activities of daily life leading to tearing off of the medial side of the re-fixed fragment.

In this series, only one case was accurately diagnosed by physical examination and routine MRI. We were not able to identify the fragment retrospectively in cases 1 and 3. Theoretically, a free fragment in the supra-patellar pouch or intercondylar notch could be palpated as a loose body or be easily detected by MRI. In reality, however, it might be missed depending on the location of the fragment. We believed that it was very difficult to recognize it as a stuck fragment and to distinguish it from the popliteal tendon, even though this injury with chondral fragment had been taken into consideration. Also, the unfamiliar images obtained using a different MRI machine at a different hospital could have caused the fragment to be missed. We should have examined the MRI scans again. In addition, a matching defect could be overlooked in chronic cases such as case 1 due to coverage by fibrous cartilage. Therefore, this injury should be considered as a possibility in adolescent patients with acute limitation of ROM of the knee joint.

We had no re-detached cases following this procedure and no symptoms such as effusion, catching or pain at the final follow-up

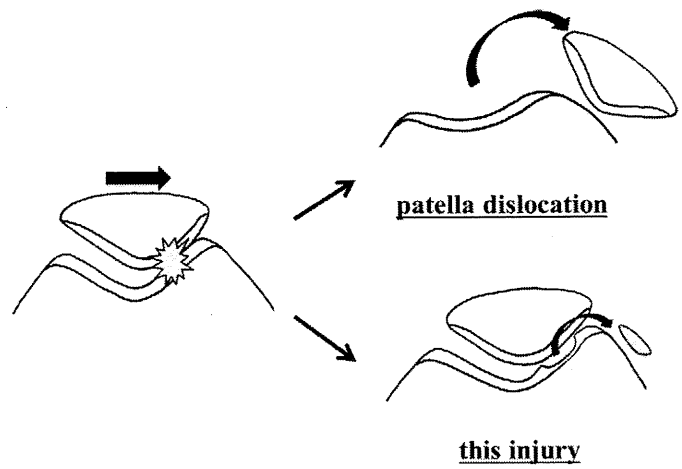

Fig. 5. Presumed injury mechanism.

examination, while case 1 transiently experienced joint effusion due to back-out of the pins. MRI showed a similar transition of signal intensity from the bone marrow to the lesion as the healthy surrounding area, and 2nd-look arthroscopy performed in two cases revealed a smoothly continuous surface of the lateral border of the re-fixed fragments. While histological evaluation was not performed in these cases, Nakamura et al. showed, by biopsy, a normally-reconstructed osteochondral junction analyzed histologically in their report [6]. Thus, we believe that fixation of a chondral fragment is clinically effective in terms of preservation of healthy hyaline cartilage and that this procedure should be the first choice of treatment for this injury, allowing the options of drilling or osteochondral transplantation if the fragment becomes re-detached. However, care must be taken to back-out the pins used in this procedure. There have been several reports of articular cartilage damage caused by protruding bio-absorbable pins, accompanied by joint effusion, pain or catching, after the pins were used for fixation of osteochondral fragments [2,7].

Finally, this series of cases suggested that a chondral fragment of articular cartilage of the lateral femoral trochlea of the knee joint in active adolescents, successfully treated with open reduction and fixation using bio-absorbable pins, should be recognized as a clear entity, although a rare injury.

4. Conflict of interest statement

We do not have any company affiliations and/or conflict of interest notifications.

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SMARTT
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CASE REPORT Open Access

Knee hemarthrosis after arthroscopic surgery in an athlete with low factor XIII activity

Akira Tsujii[1], Yoshinari Tanaka[1], Yasukazu Yonetani[1], Yoshiki Shiozaki[2], Yoshiaki Tomiyama[3] and Shuji Horibe[4*]

Abstract

We report a thirteen-year-old tennis player with knee hemarthrosis caused by low factor XIII activity. She visited our hospital because of medial peripatellar pain for two years. Although there was no abnormal sign in X-ray or MRI, diagnostic arthroscopy was performed. It revealed some cartilage debris, medial plica and complete septum of suprapatellar plica. Removing the debris by washing out and resecting the medial plica, she could return to play tennis without perioperative symptom. Two months after the first operation, her knee got swelling without any apparent cause. Since 20 ml blood was aspirated twice and MRI revealed suprapatellar mass, we performed arthroscopy again. Suprapatellar mass was old blood clot covered with complete suprapatellar plica. Resection of suprapatellar plica and washing out blood clot were performed, and severe postoperative hemarthrosis was progressively occurred. As factor XIII level was 54% preoperatively, we diagnosed that this condition was caused by low activity level of the factor and administered factor XIII concentrates. The level got improved to 129% and then hemarthrosis gradually relieved. She had no signs of recurrence. We should keep in mind of low factor XIII activity case in case of unexplained postoperative hemarthrosis after arthroscopy because consumption of the factor might promote this condition.

Background

Hemarthrosis is one of the most common complications after knee arthroscopy [1]. Hemarthrosis is generally not severe except in coagulation factor deficiency. In case of hemophilia this complication is critical, and standard coagulation studies can reveal this disorder. But deficiency of factor XIII cannot be suggested with those studies. Therefore, it is necessary to test factor XIII activity or clot solubility test for diagnosing this disorder. Factor XIII is known as fibrin stabilizing factor, which acts in the terminal phase of the coagulation cascade. The disorder presents clinically with bleeding diathesis, and impaired wound healing. Congenital deficiency of factor XIII was first described in 1960 by Duckert [2] and acquired deficiency of the factor was also reported in some articles [3-5]. However, there are few literatures associated with deficiency of factor XIII especially in the field of orthopedic surgery [6]. We here present a case of postoperative hemarthrosis caused by low activity level of this factor.

Case presentation

A thirteen-year-old junior tennis player, who had had no past history of disorder and played several hours a day since 6 years old, visited our hospital with the chief complaint of left knee pain after tennis games for two years. She had a medial peripatellar pain and knee flexion angle was slightly restricted. Although X-ray and MRI revealed no abnormal findings, we performed diagnostic arthroscopy because she and her parents had strong desire to receive arthroscopic inspection. Arthroscopy showed that the ACL and menisci were intact, but there were some cartilage debris. In addition, there were the medial plica and the suprapatellar plica (plica synovialis suprapatellaris, PSSP) with a complete septum, then the debris was washed out and the medial plica was resected. Her knee flexion angle got improved postoperatively, followed by return to the tennis court. Two months after the operation, her left knee got swelling after a long distance walk. Approximately 20 ml of bloody effusion was aspirated by joint puncture twice, and after this procedure the knee swelling increased. T2 weighted MR images revealed high intensity mass in the suprapatellar pouch, indicating of hematoma (Figure 1). As knee flexion angle was gradually restricted again to 110°, we decided to perform arthroscopic removal of the

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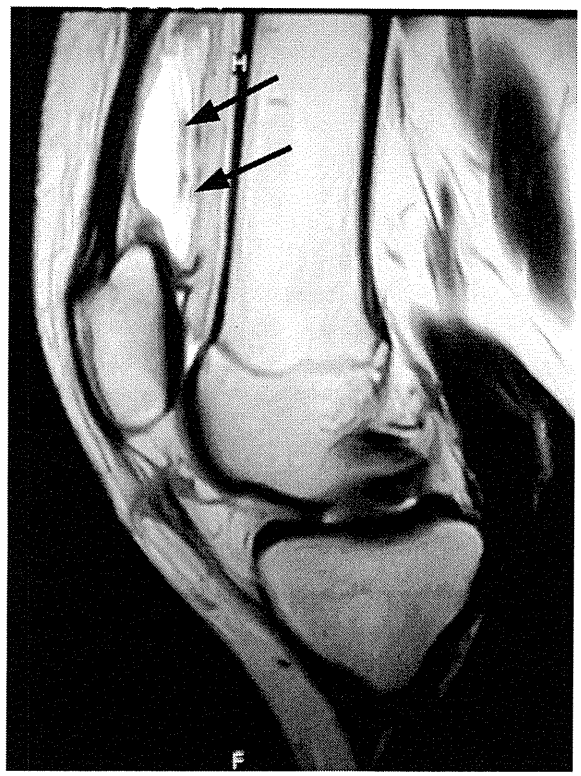

Figure 1 T2 weighted MR image shows high intensity mass in the suprapatellar pouch (arrows).

hematoma. In order to investigate the cause of unexplained hematoma, we examined factor XIII preoperatively and the level was 54% which was slightly low (normal; over 70%), with no abnormal findings in the standard coagulation studies. At arthroscopy, there was no bloody effusion or hemosiderin deposit within the joint, but in the proximal side of PSSP complete septum there seemed to be blood like content. Resecting the septum with shaver, old blood clot was flowed out (Figure 2). Complete resection of the septum and old blood clot was performed as possible. On the next day, there was no bleeding from the wound and total drainage volume was 90 ml, then we removed the drainage tube. However, her knee got swelling progressively and the flexion angle was severely restricted to 30°. Hemoglobin was decreased from 13.5 g/dl preoperatively to 10.3 g/dl on postoperative days (POD) 7 and blood loss estimated to about 800 ml [7]. After discussion with a hematologist, we diagnosed that this condition was caused by low activity level of factor XIII and administered factor XIII concentrates on POD 7 to 9. The level got improved to 129% and then the knee swelling gradually relieved (Table 1). After 3 months postoperatively, she returned to play tennis and after 5 months she completely returned to the game. There was no recurrence but the level of factor XIII returned to preoperative level (57%), which was slight low, three months after the second operation.

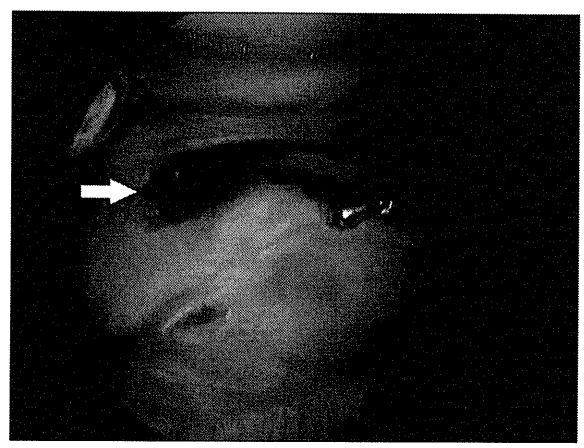

Figure 2 Bloody content flowed out from suprapatellar pouch (arrow).

Discussion

We presented a case of severe knee hemarthrosis after knee arthroscopy. Although hemarthrosis is one of the most common complications after knee arthroscopy [1], it is generally not severe and often relieved spontaneously, except in coagulation factor deficiency. In case of hemophilia, which deficit factor VIII or IX, this complication is critical, and preoperative standard coagulation studies can reveal this disorder. But deficiency of factor XIII cannot be suggested with the standard coagulation examination, including prothrombin time, partial prothrombin time, thrombin time, bleeding time, platelet count, and qualitative platelet function assays. Therefore, it is necessary to test factor XIII activity or clot solubility test for diagnosing this condition.

Factor XIII, also known as fibrin stabilizing factor, is an enzyme required for normal fibrin clot formation. It acts in the terminal phase of the coagulation cascade, after thrombin has converted fibrinogen to fibrin. In the absence of factor XIII a clot is easily soluble, so its deficiency leads to prolonged bleeding which is characteristically delayed 12–36 h after stop bleeding. Congenital deficiency of factor XIII was first described in 1960 by Duckert [2]. The disorder presents clinically with bleeding diathesis, and impaired wound healing. And it is also reported about acquired deficiency of factor XIII, caused by formation of antibody or unknown reason [3-5]. According to the European data, the most common bleeding symptoms were subcutaneous bleeding, muscle hematoma, hemorrhage after surgery, hemarthrosis, and intracerebral bleeding [8]. Decreased

Table 1 Changes of Hemoglobin (g/dl) and XIII activity (%)

	Pre	POD 7	POD 8	POD 9	POD 13	PO 3mo
Hemoglobin (g/dl)	13.5	10.3	10.8	10.6	10.8	13.1
XIII activity (%)	54	-	98	129	-	57

* Factor XIII concentrates administered on postoperative days (POD) 7, 8, and 9.

enzymatic activity of factor XIII was discussed as a cause of unexplained intraoperative and/or postoperative hematoma in abdominal, gynecological, plastic, and urological surgery and also recently in the field of neurosurgery [9]. To the best of our knowledge, however, there were few literatures about periarticular hematoma due to factor XIII deficiency or decreased activity level of factor XIII during perioperative phase. In this present case, low activity level of the factor seemed to be the cause of unexplained bleeding. As its concentration was recovered by administering the factor XIII concentrates, it was highly unlikely that the condition was associated to autoimmune antibody. In addition to the preoperative low activity level, consumption of the factor was likely to aggravate bleeding diathesis. As described by Korte, acquired factor XIII deficiency in the perioperative setting might be frequent [10]. Furthermore, Spahn demonstrated that blood loss could be reduced with administration of a single dose of factor XIII given within 15 min commencement of surgery [11].

As for perioperative level of factor XIII, no report has clearly revealed when we should administer factor XIII concentrates. In general, it is considered sufficient to keep 10% in small bleed, or 20-30% in muscle hematoma. But in severe bleeding case or major surgery, increasing use of the factor in the wound, it is recommended to keep 100% preoperatively [12]. Gerlach et al. reported the average postoperative decrease in factor XIII was approximately 18% in the neurosurgery patients [9]. Furthermore, they concluded the risk of postoperative hematoma is increased in patients with factor XIII < 60%. Taking the conclusion into account, the perioperative low activity level of factor XIII might have been the risk of the hemarthrosis following arthroscopy.

Conclusion

We report a case of postoperative hemarthrosis caused by low factor XIII activity. Decreased activity of the factor seemed to be the cause, and the consumption might have an effect on bleeding diathesis. We should be in careful about managing this condition perioperatively as coagulation factor activity can decrease by increasing consumption of the factor.

Consent

Written informed consent was obtained from the patient for publication this case report and the images.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors co-wrote the paper and discussed the results for the manuscript preparation. All authors have read and approved the final manuscript.

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〈Original Article〉

Epidemiological study of the relationship between C-reactive protein and diabetes in Japanese females

Rikio Takao, Hirokazu Oguro, Emi Yamashita, Makihiko Kuhara, Yukiko Ogawa, Yukie Yoshida and Shuji Horibe

Summary Recent evidence suggests that a small percentage of chronic inflammations are associated with the onset of diabetes. Based on this association, C-reactive protein (CRP), an inflammatory marker, has been garnering attention as a new risk factor for diabetes. However, according to reports from a large-scale epidemiological study conducted in the US and Europe, no conclusive evidence was found linking CRP levels and diabetes. Therefore, we conducted an epidemiological study of Japanese females from Habikino City during routine medical examinations and found through cross-sectional and longitudinal analysis that CRP levels and diabetes are indeed linked in these women.

Key words: C-Reactive Protein (CRP), A1C, Diabetes, Medical examination.

1. Introduction

The growing number of people affected by diabetes is a worldwide concern. In November 2011, the International Diabetes Federation (IDF) published the Volume 5 of the Diabetes Atlas, which estimated that 366 million adults between the ages 20-79 years were affected with diabetes, a figure that is expected to rise to 552 million by 2030[1]. Japan is the sixth-most affected country in the world with 10.67 million diabetic adults. Considering this situation, early detection of diabetes is exceedingly important for increasing the healthy lifespan of Japanese citizens.

A mechanistic understanding of the onset of diabetes and its mode of affecting a patient has not been completely elucidated. However, clinical and epidemiological studies have reported that age, obesity, high blood pressure, abnormal glucose tolerance, and insulin resistance are all risk factors for diabetes[2-10]. Furthermore, an association between chronic inflammation and onset of diabetes has been recently reported[11, 12] and the levels of the inflammatory marker C-reactive protein (CRP) has been suggested as a risk factor for diabetes. Interestingly, large-scale clinical studies conducted in the US and Europe did not find any conclusive evidence linking CRP levels and diabetes[13-15]. Moreover, CRP levels vary depending on ethnic group and sex, which can affect

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the risk of onset of diabetes[16].

Relatively few Japanese studies with healthy adults have been conducted regarding the relationship between CRP levels and diabetes, compared to the US or European countries. Data from a large-scale clinical study centered on the Japanese population are required to determine the validity and effectiveness of using CRP levels as a risk factor for the onset of diabetes. Here, we report the results of an epidemiological study of Japanese females from Habikino City during routine medical examinations to study the relationship between CRP levels and the onset of diabetes.

2. Subjects and Methods

Our CRP reference values for the Japanese population were obtained from the findings of Nakamura et al.[17]. The normal value was set to 0.2 mg/dl; the study population was divided into 2 target groups: a low CRP cohort (measured CRP less than 0.2 mg/dl) and a high CRP cohort (measured CRP more than 0.2 mg/dl). The values for glycated hemoglobin (HbA1c) were converted to corresponding values by the National Glycohemoglobin Standardization Program (NGSP) using the guidelines and basic policies for international standardization[18] these values are referred to as A1C. We classified subjects with an A1C value above 6.5% as diabetic, according to the diagnostic criteria set by the American Diabetes Association (ADA).

1. Cross-sectional study

Of the 7,105 female participants from Habikino City who underwent a standard medical examination in the year 2000, 6,729 were selected (average age, 60.3 ± 10.5 years) on the basis of completeness of measured variables for CRP, body mass index (BMI), systolic/diastolic blood pressure, total cholesterol, triglycerides, HbA1c, and drinking and smoking habits. Further, 376 of the 7,105 were excluded from the study because their CRP levels were above 1.0 mg/dl, which is indicative of systemic inflammatory disease. We performed a multiple regression analysis using A1C as the target variable and age, BMI, blood pressure, total cholesterol, triglycerides, CRP, and drinking and smoking history as the dependent variables. We set the ratio of onset of diabetes for the low CRP cohort to 1 and calculated the adjusted odds ratio (OR) and that for confidence interval (CI) for conciseness when representing the data in the results section. (adjusted factors: age, BMI, and total cholesterol) for the high CRP cohort using logistic regression analysis.

2. Longitudinal study

We selected 2,164 non-diabetic participants who had complete records of the measured variables for the period between 2001 and 2005 and whose CRP values were below 1.0 mg/dl. The participants were grouped into the low CRP or high CRP cohorts, depending on the CRP values measured in the year 2000. Using the Kaplan-Meier estimation, we calculated the cumulative rate of incidence of diabetes during the 5-year follow-up period from 2000. Adjusted OR were calculated for the high CRP cohort (adjusted factors: age, BMI, and total cholesterol) for each year of the 5-year periods (2000-2001, 2000-2002, 2000-2003, 2000-2004, and 2000-2005), and the onset of diabetes for the low CRP cohort was set to 1. Additionally, we monitored changes in CRP levels for each participant that developed diabetes during the study period in both cohorts. All statistical analyses were performed using IBM SPSS version 19.0 for Windows, with a significance level of 5%.

The protocol of this study was approved by the Institutional Review Board of Osaka Prefecture University. All data were collected by health center of Habikino City, which allowed Osaka Prefecture University to use these data for analysis.

3. Results

1. Cross-sectional study

Table 1 shows the baseline characteristics of both low and high CRP cohorts. A significantly higher A1C value was observed for the high CRP cohort (5.4 ± 2.6%) than the low CRP cohort (5.1 ± 1.4%) ($p < 0.001$). Multiple regression analysis using A1C as the objective variable is shown in Table 2. An

independent positive correlation was observed between CRP levels and A1C. Furthermore, the same positive correlation was observed between A1C and age, BMI, and total cholesterol. The adjusted OR for the onset of diabetes was significantly higher for the high CRP cohort (2,164; 95% CI, 1.194-1.893) than the low

Table 1 Characteristics of participants based on C-reactive protein (CRP) levels

Variables	Low CRP (n=5,312)		High CRP (n=1,417)		*P*-value
	Mean	SD	Mean	SD	
Age (y)	59.8	10.3	62.2	10.4	<0.001
BMI (kg/m^2)	22.7	3.0	24.0	3.6	<0.001
Systolic BP (mmHg)	129.3	18.6	133.0	18.1	0.312
Diastolic BP (mmHg)	76.4	10.8	77.6	10.6	0.342
Total-Choresterol (mg/dl)	213.3	33.1	216.9	34.5	0.016
HDL-Choresterol (mg/dl)	64.5	14.9	60.0	14.8	0.822
Triglyceride (mg/dl)	114.2	59.7	134.4	71.5	<0.001
A1C (%)	5.1	1.4	5.4	2.6	<0.001
Current smoking (%)	4.1	–	5.4	–	0.052
Current drinking (%)	10.7	–	8.0	–	0.003

SD: Standard Deviation. BMI: Body Mass Index. BP: Blood Pressure.
HDL: High Density Lipoprotein. LDL: Low Density Lipoprotein

Table 2 Multiple regression analysis using A1C as the objective variable

Explanatory Variables	A1C (Objective variable)			*P*-value
	Regression Coefficient	SE	95% CI	
Age	0.007	0.002	0.003 – 0.012	0.002
BMI	0.029	0.008	0.014 – 0.044	<0.001
Systolic BP	0.002	0.002	-0.002 – 0.005	0.297
Diastolic BP	-0.002	0.003	-0.008 – 0.004	0.457
Total-Choresterol	0.003	0.001	0.001 – 0.004	0.001
HDL-Choresterol	-0.002	0.002	-0.006 – 0.001	0.191
Triglyceride	0.001	0.001	-0.001 – 0.002	0.124
C-Reactive Protein	0.538	0.177	0.191 – 0.885	0.002
Current smoking	-0.067	0.077	-0.217 – 0.084	0.385
Current drinking	-0.029	0.113	-0.250 – 0.191	0.793

SE: Standard Error. BMI: Body Mass Index. BP: Blood Pressure.
HDL: High Density Lipoprotein. LDL: Low Density Lipoprotein

Table 3 Adjusted odds ratio for onset of diabetes based on C-reactive protein (CRP)

Follow up	Crude OR		95%CI	*P*-value	Multiple adjusted OR*		95%CI	*P*-value
	Low CRP (n = 1,748)	High CRP (n = 416)			Low CRP (n = 1,748)	High CRP (n = 416)		
2000-2001	1.00	2.53	1.54 – 4.34	<0.005	1.00	2.13	1.24 – 3.64	0.006
2000-2002	1.00	1.83	1.22 – 2.74	0.003	1.00	1.46	0.96 – 2.21	0.077
2000-2003	1.00	2.04	1.44 – 2.87	<0.001	1.00	1.56	1.09 – 2.23	0.015
2000-2004	1.00	1.93	1.40 – 2.66	<0.001	1.00	1.50	1.07 – 2.09	0.018
2000-2005	1.00	1.86	1.37 – 2.54	<0.001	1.00	1.43	1.03 – 1.98	0.031

*Adjusted for Age, BMI, Total Choesterol
OR: Odds Ratio. CI: Confidence Interval.

CRP cohort (adjusted OR, 1.00; $p < 0.001$).

2. Longitudinal study

During the follow-up period, 223 participants developed diabetes. The cumulative rate of incidence for the high CRP cohort (18.5%) was significantly higher than that for the low CRP cohort (9.9%) (Fig. 1). Moreover, when the adjusted OR for the onset of diabetes for the low CRP cohort was set to 1, the adjusted OR for each year of the 5-year period for the high CRP cohort were 2.212 (95% CI, 1.240-3.640; 2000-2001), 1.456 (95% CI, 0.961-2.208; 2000-2002), 1.557 (95% CI, 1.090-2.225; 2000-2003), 1.497 (95% CI, 1.072-2.090; 2000-2004), and 1.429 (95% CI, 1.033-1.977; 2000-2005) (Table 3). Average CRP levels in the low CRP cohort rose continuously leading

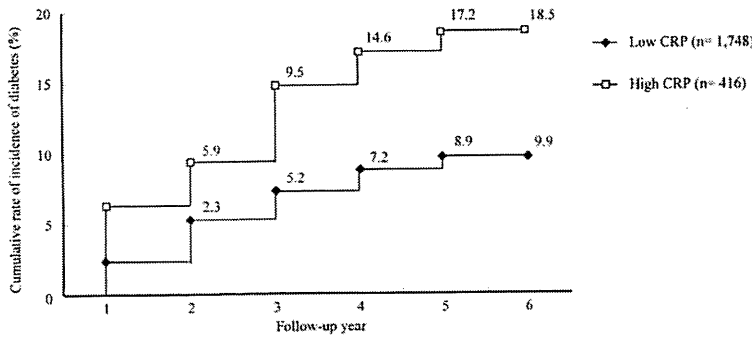

Fig. 1 Kaplan-Meyer curve of cumulative incidence of diabetes during follow-up.

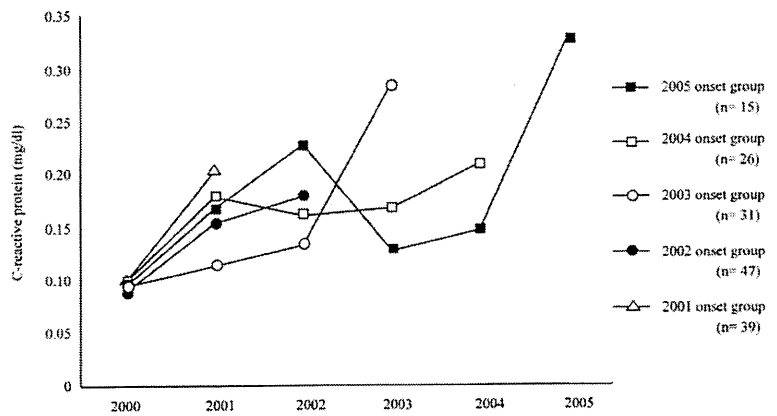

Fig. 2 Changes in the C-reactive protein (CRP) Levels in the low CRP cohort until the onset of diabetes.

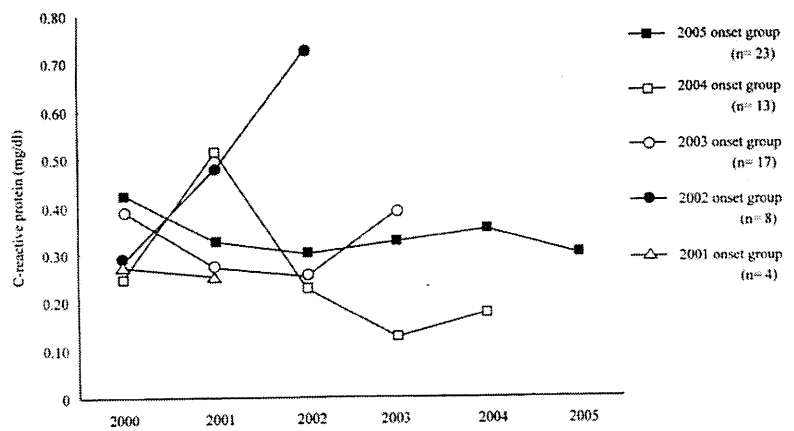

Fig. 3 Changes in the C-reactive protein (CRP) levels in the high CRP cohort until the onset of diabetes.

up to the year of onset of diabetes and reached its peak value during that year (Fig. 2). On the other hand, CRP levels for the high CRP cohort were stable above 0.2 mg/dl for most of the study period (Fig. 3).

4. Discussion

Based on the data above, a significant association between CRP cohorts and unadjusted rates of incidence of diabetes was observed in Japanese female adults from Habikino City surveyed in 2000, suggesting that CRP levels and the onset of diabetes are correlated. A significant correlation was also observed using the predictive power of the logistic regression model, adjusted for age, BMI, and total cholesterol. This suggests that CRP levels can be used as an independent risk factor to predict the onset of diabetes, similar to its use in other large-scale epidemiological studies conducted in Japan[19, 20]. Considering that 9.9% of participants in the low CRP cohort developed diabetes within 5 years of the study and that their CRP levels rose as they neared the onset of diabetes, monitoring CRP levels with age can be an important aspect of mitigating the onset of diabetes.

Studies have shown that CRP levels are higher among subjects with diabetes than among those without; even among unaffected people, a high A1C level is correlated with high CRP levels[21, 22]. Furthermore, Festa et al.[23] showed that an independent interrelationship exists between CRP levels and insulin resistance. In addition, high blood glucose is known to accelerate chronic inflammation[24, 25]. These studies confirm our results regarding the relationship between rising CRP levels and the onset of diabetes.

Although our study did not analyze highsensitive CRP values, a relationship between conventional CRP levels and diabetes was observed, similar to that reported by King et al.[26] We believe that monitoring conventional CRP levels and A1C during routine examinations can lead to early diagnosis of diabetes.

5. Conclusions

CRP levels were associated with the onset of diabetes in Japanese female adults. Even a clinically non-relevant CRP level (0.2-0.3 mg/dl) can be a risk factor for diabetes; therefore, we believe that careful monitoring of both CRP and A1C levels with aging can lead to early detection of diabetes.

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[Original Article]

Epidemiology Study into the Connection Between C-Reactive Protein and Dyslipidemia

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Summary

Atherosclerosis is widely viewed as a state of chronic blood vessel inflammation that can be monitored by the serum level of C-reactive protein (CRP), which has been shown to be a reliable predictive factor for circulatory diseases. In contrast to Western countries, there have been limited large-scale studies in Japan investigating the association between CRP levels and dyslipidemia, a disorder of lipoprotein metabolism that is closely linked to circulatory diseases. Therefore, in the present study, we conducted a large-scale epidemiological study on CRP levels and their association with dyslipidemia using results obtained from health examinations conducted in city H every year since 2000. In contrast to the Western population, the mean CRP level of local residents was 0.11 mg/dL, showing a deviation to the lower end of the normal range in other ethnicities. It was also shown that the CRP levels observed in individuals falling under a larger number of diagnostic criteria for dyslipidemia were significantly higher.

(Med Biol **156:** 585-591 2012)

Key words: Health examination, Dyslipidemia, C-reactive protein (CRP), High-sensitivity CRP test

Introduction

In Japan, circulatory diseases, including cardiovascular and cerebrovascular disorders, rank among the highest causes of mortality and long-term morbidity among people aged 65 years and older. Thus, it is crucial to prevent these diseases in order to maintain health and extend life expectancy.

Although atherosclerosis is largely involved in the development of circulatory diseases, its development and progression remains unclear. However, after the completion of the Framingham Study, which proposed the risk factor concept in the US[1,2], obesity[3,4], hypertension[5,6], diabetes[7,8], and lipid metabolism disorders[9,10] have been established as risk factors for atherosclerosis in numerous other studies. Moreover, the accumulation of these risk factors is reported to be largely involved in the development of circulatory diseases[11,12].

Recently, Ross proposed that atherosclerosis is a chronic blood vessel inflammation[13], and this theory has been widely accepted. Moreover, the inflammatory C-reactive protein (CRP) level has also gained attention as a reliable indicator of the disease. CRP levels have already been reported in the U.S. to be a predictive factor for circulatory diseases[14-16], which led to their usage as a valuable prognostic factor for the onset of cerebrovascular and cardiac diseases by the Ceners for Disease

Control and Prevention (CDC) and the American Heart Association (AHA).

However, a wide disparity between ethnicities has been reported regarding the distribution of CRP levels and their evaluation as a risk factor[17,18]. Therefore, it is necessary to accumulate evidence from Japanese-based, large-scale clinical studies in order to incorporate CRP levels as a predictive factor for circulatory diseases in Japan. In the present study, we analyzed the association between CRP levels and dyslipidemia using the results of basic health examinations conducted over eight years from 2000 residents of city H.

Subjects and Methods

In city H, Conventional CRP levels were measured as part of routine health examination in patients from 2000 to 2005, whereas high-sensitivity CRP levels were only measured since 2006. In order to compare normal and high-sensitivity CRP levels, subjects were selected by excluding those with potential systemic inflammatory diseases (CRP ≥1.00 mg/dL) from 8,016 individuals who had undergone health examinations in 2005 and 2006 to minimize secular variation, which resulted in a study cohort of 7,674 subjects for analysis. The analytical methods are shown below.

1. Descriptive epidemiology: We collected baseline patient information including CRP levels, age, body mass index (BMI), blood pressure, total cholesterol (TC) levels, high-density lipoprotein cholesterol (HDL-C) levels, triglycerides (TG) levels, low-density lipoprotein cholesterol (LDL-C) levels, hemoglobin A1c (HbA1c) levels, drinking rate, and smoking rate between 2005 and 2006. These characteristics were then compared between men and women.

2. Cross-sectional study: We divided the subjects into four groups (zero applicable item group, one applicable item group, two applicable items group, and three applicable items group) on the basis of the number of applicable items in the diagnostic criteria for dyslipidemia adopted from the Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases (LDL-C ≥140 mg/dL, HDL-C <40 mg/dL, and TG ≥150 mg/dL) and performed one-way analysis of variance (ANOVA) on the CRP levels from each group. All statistical analyses were conducted using IBM SPSS v.19.0 for Windows software (SPSS Inc., Chicago, IL, USA) and a p-value of <0.05 was considered statistically significant.

Results

1. Descriptive epidemiology: The baseline study results from 2005 and 2006 are shown in Tables 1 and 2. Biochemical test values were within normal ranges in both years. The mean CRP level in 2005 and 2006 in men was 0.15 mg/dL and 0.13 mg/dL, respectively, while the mean CRP level in women was 0.13 mg/dL and 0.11 mg/dL, respectively. The CRP levels were higher in men than in women (statistically significant). The distribution of CRP levels is shown in Figures 1 and 2. Both men and women showed a similar tendency, with the mean value in them showing a deviation to the lower end of the normal range in other ethnicities.

2. Cross-sectional study: The comparison of CRP levels between the four groups based on the number of applicable items in the diagnostic criteria is shown in Tables 3 and 4. In both years, men and women indicated a similar tendency in which the CRP levels of individuals falling under a larger number of diagnostic criteria for dyslipidemia were significantly higher.

Discussion

Tina et al. reported[18] that CRP levels largely differ between ethnicities. The mean CRP levels of different ethnicities were as follows: African descent: 0.299 mg/dL, Hispanic: 0.277 mg/dL, South Asian: 0.263 mg/dL; and Caucasian: 0.226 mg/dL. In contrast, the mean CRP level of subjects

in the present study (0.113 mg/dL) was lower compared to that of other ethnicities as previously reported. Furthermore, the distribution pattern showed a deviation of the mean value to the lower end of the mean of other ethnicities, which is also in accordance with a previous Japanese-based report[19]. Several large-scale studies including The World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease MONICA Project[20] have concluded that the incidence rates of circulatory diseases are significantly lower in Japan when compared with other developed countries, which may be associated with the low CRP levels in Japanese population compared with those in the Western population.

The cross-sectional study revealed significantly high CRP levels in individuals falling under a larger number of diagnostic criteria for dyslipidemia in both years. The differences between the minimum and maximum CRP levels

Table1. Comparisons of Baseline Characteristics between Men and Women in 2005

	Male (n=2,228)		Female (n=5,446)			All (n=7,674)	
	mean	(SD)	mean	(SD)	P-value	mean	(SD)
Age (years)	66.2	(9.2)	64.7	(10.0)	<0.001	65.9	(9.9)
Body Mass Index (kg/m^2)	23.8	(9.3)	23.4	(11.5)	0.193	23.5	(10.9)
Systolic BP (mmHg)	133.2	(18.0)	130.5	(18.6)	<0.001	131.3	(18.5)
diastolic BP (mmHg)	77.1	(11.6)	75.1	(11.1)	<0.001	75.6	(11.3)
Total-cholesterol (mg/dL)	200.8	(34.0)	218.8	(33.5)	<0.001	213.6	(34.6)
HDL-cholesterol (mg/dL)	55.7	(15.2)	63.7	(16.1)	<0.001	61.4	(16.2)
Triglycerides (mg/dL)	138.6	(90.6)	120.2	(71.3)	<0.001	125.5	(77.8)
LDL-cholesterol (mg/dL)	117.6	(33.2)	131.3	(31.6)	<0.001	127.3	(32.5)
HbA1c (%)	5.5	(3.3)	5.3	(2.6)	0.620	5.4	(2.8)
CRP (mg/dL)	0.15	(0.13)	0.13	(0.10)	<0.001	0.11	(0.12)
Current drinking (%)	52.5		8.7		<0.001	21.4	
Current smoking (%)	31.1		7.1		<0.001	14.1	

SD : Standard Deviations. HDL : High Density Lipoprotein. LDL : Low Density Lipoprotein.
BP : Blood Pressure. CRP : C-Reactive Protein

Table2. Comparisons of Baseline Characteristics between Men and Women in 2006

	Male (n=2,228)		Female (n=5,446)			All (n=7,674)	
	mean	(SD)	mean	(SD)	P-value	mean	(SD)
Age (years)	67.2	(9.2)	65.7	(10.0)	<0.001	66.1	(9.8)
Body Mass Index (kg/m^2)	23.3	(3.0)	22.8	(3.4)	<0.001	23.0	(3.3)
Systolic BP (mmHg)	132.7	(17.5)	129.4	(17.8)	<0.001	130.4	(17.8)
diastolic BP (mmHg)	76.8	(10.6)	74.5	(10.5)	<0.001	75.1	(10.6)
Total-cholesterol (mg/dL)	200.4	(32.4)	219.4	(34.0)	<0.001	213.9	(34.6)
HDL-cholesterol (mg/dL)	56.7	(15.2)	65.3	(16.1)	<0.001	62.8	(16.3)
Triglycerides (mg/dL)	137.5	(88.2)	118.6	(65.8)	<0.001	124.1	(73.5)
LDL-cholesterol (mg/dL)	116.5	(30.9)	130.5	(31.9)	<0.001	126.4	(32.2)
HbA1c (%)	5.6	(4.6)	5.3	(1.7)	0.370	5.4	(2.9)
CRP (mg/dL)	0.136	(0.135)	0.107	(0.109)	<0.001	0.113	(0.118)
Current drinking (%)	52.3		8.3		<0.001	21.1	
Current smoking (%)	28.0		6.8		<0.001	13.0	

SD : Standard Deviations. HDL : High Density Lipoprotein. LDL : Low Density Lipoprotein.
BP : Blood Pressure. hs-CRP : high sensitive C-Reactive Protein

in 2005 and 2006 were extremely small (men, 0.03 mg/dL and 0.06 mg/dL, respectively; and women, 0.04 mg/dL and 0.03 mg/dL, respectively). However, the Hisayama study[21], a large-scale cohort study conducted in Japan, reported that the slight differences in CRP levels, when compared against baseline values, increased the risk of coronary artery disease, total mortality rate, death caused by cardiovascular disease, and death by other causes after 14 years. A slight variation in CRP levels should therefore be noted in terms of disease prevention.

Both conventional and high-sensitivity CRP levels showed similar trends when their usefulness was compared for disease prognosis. Therefore, by combining with other risk factors including age, BMI, blood pressure, and smoking history, conventional CRP levels may be a useful predictive factor for circulatory disease prevention.

Atherosclerosis occurring as a result of lipid metabolism disorders progresses quietly without any subjective symptoms. Therefore, we believe that CRP levels measured during annual health examinations would be effective predictive factors for disease prevention, rather than other specialized examinations. We hope to conduct further analyses on health examination results for

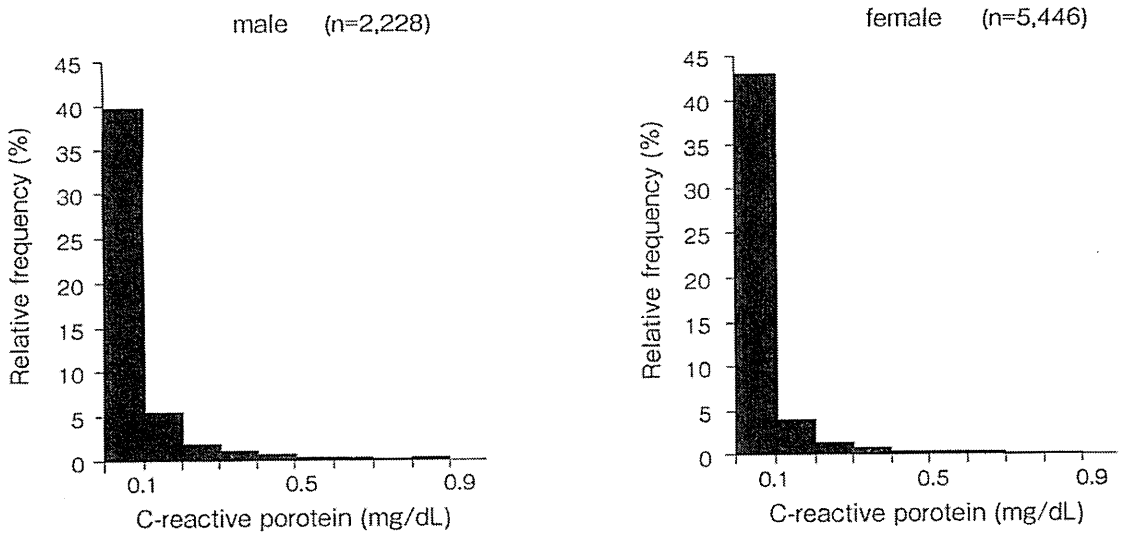

Figure1. Distribution of C-reactive protein levels in 2005

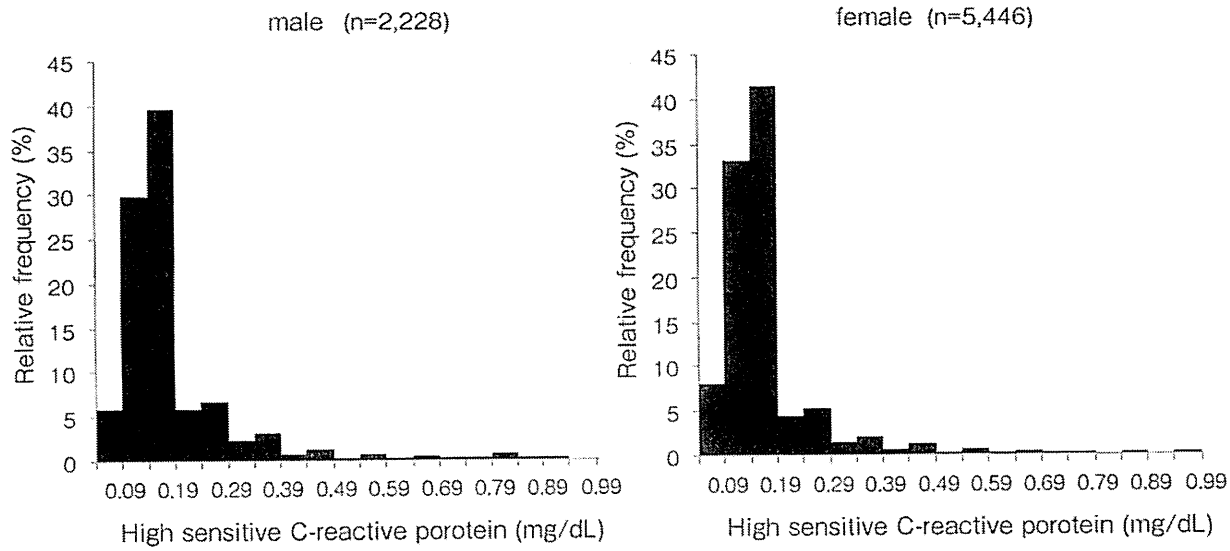

Figure2. Distribution of high sensitive C-reactive protein levels in 2006

disease prevention in local residents.

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Table3. Relation between the number of dyslipidemia and CRP in 2005

Gender	The number of dyslipidemia	n	CRP (mg/dL) mean	(SD)	P-value
male (n=2,228)	0	1,094	0.14	(0.12)	**
	1	831	0.15	(0.13)	
	2	274	0.16	(0.12)	
	3	29	0.17	(0.15)	
female (n=5,446)	0	2,662	0.13	(0.10)	* * *** **
	1	2,136	0.13	(0.10)	
	2	579	0.15	(0.14)	
	3	69	0.17	(0.15)	

SD : Standard Deviations. CRP : C-Reactive Protein
P-value:*p<0.05, **p<0.01, ***p<0.001

Table4. Relation between the number of dyslipidemia and hs-CRP in 2006

Gender	The number of dyslipidemia	n	hs-CRP (mg/dL) mean	(SD)	P-value
male (n=2,228)	0	1,144	0.120	(0.129)	*
	1	804	0.132	(0.139)	
	2	254	0.147	(0.145)	
	3	26	0.183	(0.203)	
female (n=5,446)	0	2,662	0.100	(0.103)	*** *** *
	1	2,207	0.107	(0.106)	
	2	544	0.137	(0.134)	
	3	33	0.156	(0.128)	

SD : Standard Deviations. hs-CRP : high sensitive C-reactive protein
P-value:*p<0.05, **p<0.01, ***p<0.001

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アスリートに対する半月板治療の選択 －外側半月板損傷を中心に－

堀部秀二[*1]，田中美成[*2]，米谷泰一[*2]，塩崎嘉樹[*3]

はじめに

アスリートの半月板損傷は，前十字靱帯(以下ACL)損傷に合併することが多いため，ロッキングを除き，ACL再建術時，鏡視所見を基に外科的治療法を決定していることが多い．さらに，ACL不全により二次的に生じた半月板損傷の形態は，内側であれ外側であれ，中～後節部の縦断裂が多いため，一般的な縫合術の適応(体部に変性の少ない，1cm以上の不安定な外周辺部1/3の縦・斜断裂)[1~3]をあてはめやすい．一方，単独損傷例に対しては，どのタイミングで手術を行うのか，どのような術式をとるのかなど，曖昧な点も少なくない．特に比較的頻度の高い単独外側半月板(以下LM)損傷は，損傷形態がさまざまであるにもかかわらず，損傷形態別の手術適応はよくわかっておらず，切除後の圧変化が大きく[4]，軟骨破壊が急激に進行すること[5,6]もあり，問題点も多い．ここでは，アスリートの単独LM損傷を取り上げ，損傷形態別の治療法の選択を中心に，最近の我々の考え方を述べる．

損傷形態

アスリートによくみられる損傷形態としては，前節部の縦・変性断裂，中節部の横断裂，後節部の縦断裂やhypermobile meniscus，円板状半月板損傷，がある．

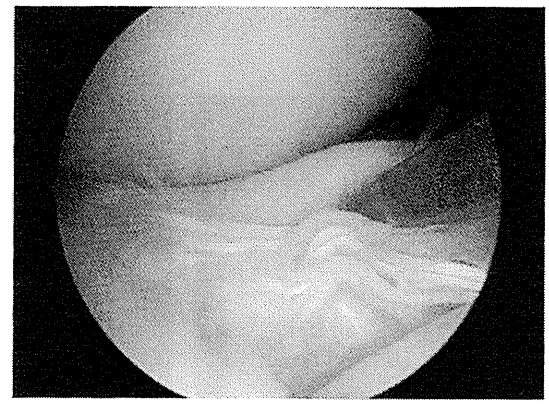

図1 ◆前節部変性断裂の鏡視所見
前節部はさばけており，変性断裂を疑う．

1．前節部の縦(変性)断裂(図1)

ボールを蹴る動作を繰り返し行うサッカー[7]やラグビー競技で多く，無症状なことも少なくない．

2．中節部の横断裂(図2)

スライディングなど膝を強く捻った時に生じることが多い．

3．後節部の縦断裂やhypermobile meniscus

外傷歴のある場合もあるが，膝窩筋腱溝周辺のhypermobile meniscus(図3)のように，明らかな外傷歴がないものもある．

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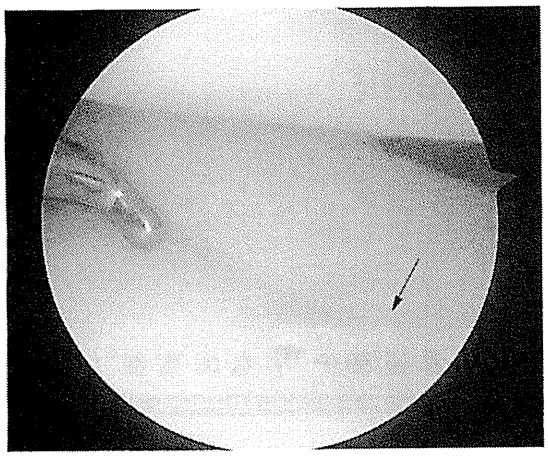

図2 ◆中節部横断裂の鏡視所見
中節部の横断裂(赤矢印)を認める．

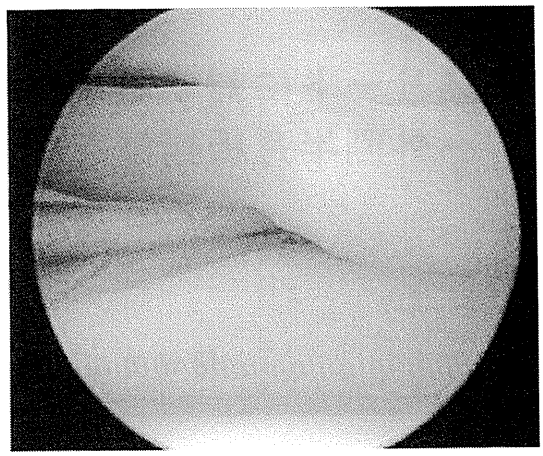

図3 ◆hypermobile meniscus の鏡視所見
膝窩筋腱溝にプローベをかけると，半月板は外顆を越えて前方に引き出される．

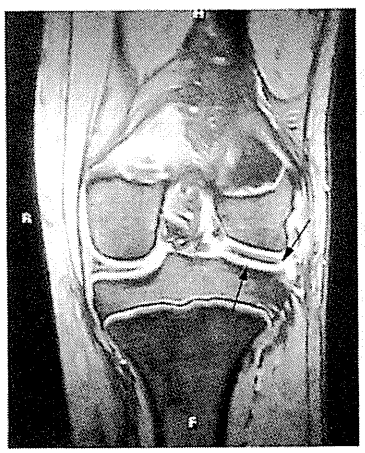

図4 ◆円板状半月板損傷
外側は大きく(赤矢印)．周辺部は高輝度陰影を認め(黒矢印)，外側円板状半月板の周辺部損傷を疑う．

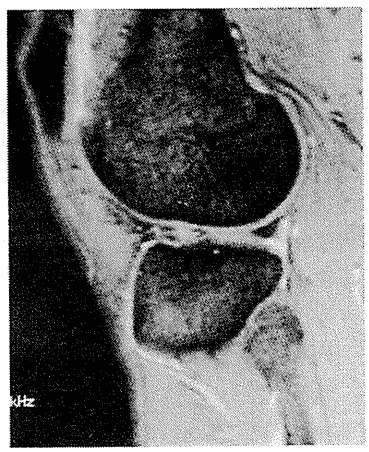

図5 ◆前節部縦断裂の MRI 所見
前節部実質内に高輝度陰影を認める(赤矢印)．

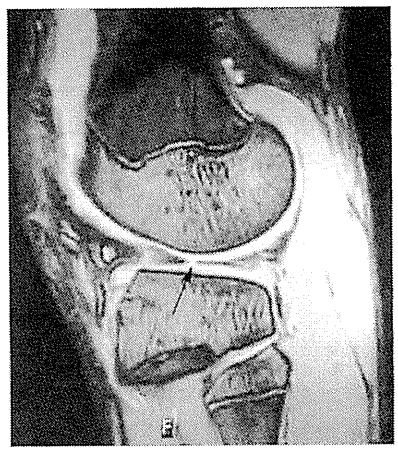

図6 ◆中節部横断裂の MRI 所見
関節包付近の矢状面で実質内に高輝度陰影を認める(赤矢印)．

4．円板状半月板損傷(図4)

日本人にはその頻度が高く[8]，体部の変性[9]や体部の膠原線維の配列異常[10]などもあり，損傷を受けやすい．

MRI 診断

MRI 検査は損傷半月板の診断に必須で，損傷しているかどうかの診断だけでなく，靱帯や軟骨損傷などの合併損傷の有無，損傷形態，術式予測(縫合可能か否か)[11]について検討することも重要である．

1．合併損傷の有無

ACL 損傷や軟骨損傷合併の有無は治療方針決定に関係してくるので重要である．

2．損傷形態

受傷機転や臨床症状(主にロッキングや関節裂隙圧痛の部位)も参考にしながら，損傷形態を MRI にて診断する．MRI での診断率は内側より低く，特に前節部断裂(図5)，中節部横断裂

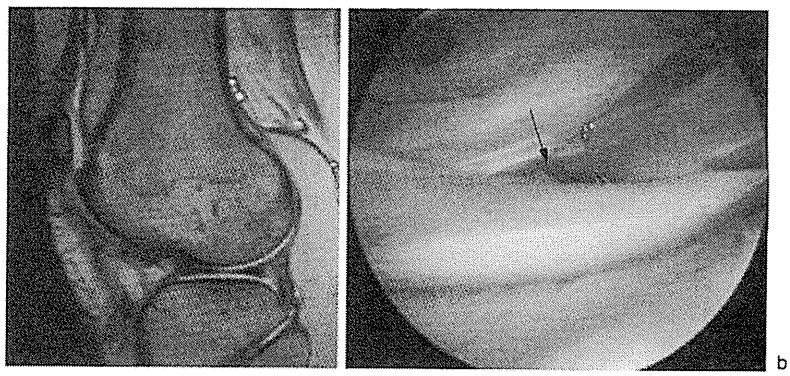

図7 ➔後節部縦断裂のMRI所見(a)と鏡視所見(b)
MRIでは明らかな高輝度陰影を認めず，縦断裂の診断は困難であるが，鏡視では膝窩筋腱溝の前方に縦断裂を認め，同部位にプローベが入る(赤矢印)．

a　b

(図6)，膝窩筋腱溝周囲の縦断裂(含hypermobile meniscus)(図7)は診断困難な場合も少なくない．

3．術式予測

半月板実質内部に高輝度陰影があり，水平断裂，横断裂，体部の変性が著しい症例は修復不能．縦断裂で体部に明らかな高信号を認めない症例は修復可能．と判定すれば，損傷半月板に対する術式をある程度予測できる[11]．ただ，最近は縫合術の工夫[12～14]により縫合術の適応が広がりつつあるので，必ずしも当てはまらない場合もあり，今後の検討課題である．

治療選択

どのような治療を行うかは，アスリートの希望やドクターの考え方などにより異なるが，選手のニーズ，損傷形態，縫合可能の有無，などを考慮して治療法を選択する必要がある．

1．治療の目的

損傷半月板治療の目的は，それに起因する症状(疼痛，水腫，可動域制限，膝周囲筋の筋力低下など)の緩和と，半月板機能の改善である．

2．切除術の問題点

"早期のスポーツ復帰なら切除術"という風潮もあるが，内側と比較して成績が不良[15]，切除後の急激な軟骨破壊[5,6]，縫合術のスポーツ復帰率が高い[16]，という報告もあり，アスリートの場合，高いパフォーマンスが切除後維持できるかについては疑問も残る．高いパフォーマンスが求められるアスリートに対し，安易に切除術を施行することは慎むべきかもしれない．

3．保存治療[17]

損傷半月板に起因する症状緩和を目的とした保存療法は，効果や期間など不確定な要素も少なくないが，安易に切除術を行うよりは，受傷後数ヵ月間は試みても良い方法である．ただ，漫然と行うのでなく，経過中に効果判定を必ず行い，保存治療法の変更や外科治療への切り替えを行う必要はある．

4．縫合術の適応

血行野である外周辺部1/3の1cm以上の不安定な縦・斜断裂が縫合術の良い適応[1～3,18]とされているが，これは，ACL損傷に合併している中～後節部の縦断裂に対して，"再建術のついで"に鏡視所見で決定する場合には有用であるが，損傷形態がさまざまなLM損傷の場合に当てはまるかどうかは疑問が残る．実際，最近ではさまざまな症例に対して縫合術が工夫[12～14,19,20]されるようになってきているため，縫合術の適応は今後変わる可能性がある．

損傷形態別の縫合術

1．後節部の縦断裂やhypermobile meniscus(図7)

これは，縫合術の良い適応で，体部が変性していなければ成績も良好であるため，診断できれば早期の縫合術が推奨される[18]．

2．前節部の縦(変性)断裂(図5)

症状が軽いことも少なくなく，どの時期に手術