The proportion of patients with acetabular dysplasia was high especially among the younger patients. More than 90% of the patients were in their thirties to fifties. Even for patients in their seventies, it was more than 60%. The etiology of hip OA in the female patients was significantly different from that observed in the male patients. The female patients had more acetabular dysplasia than the male patients. Sex may therefore play a role in the development of acetabular dysplasia. The BMI of female patients was lower than that of male patients, with obesity being found in approximately one-fourth of the female patients. These data on obesity also suggest that acetabular dysplasia was a major cause for hip OA in the female patients.

Among the patients with a posterior pelvic inclination, it increased with increasing patient age. Posterior pelvic inclination causes uncovering of the acetabulum, resulting in a high prevalence of hip OA.[14] This is most likely due to lumbar kyphosis, which is caused by a compression deformity of the lumbar spine due to postmenopausal or senile osteoporosis. This change in pelvic inclination may be involved in the prevalence of hip OA, particularly in elderly patients.

The patients with hip OA in Japan were unique based on the age distribution, sex heterogeneity, and the frequency of acetabular dysplasia as the disease etiology in comparison to those in Caucasians. Hip OA in Caucasians is mainly due to aging, although OA hip joints with acetabular dysplasia are found to occur in younger generation patients. As most patients were assessed to have acetabular dysplasia as the etiology, the patient distribution thus appeared to peak for middle-aged patients and not elderly patients in Japan. Female patients also had more acetabular dysplasia than the male patients. Because most of the patients were female, the proportion of the patients with acetabular dysplasia was therefore also higher than that reported in previous studies. Therefore, these unique characteristics of the patients in Japan may be related to the occurrence of acetabular dysplasia in this patient population.

Acknowledgements. This study was supported by grants from the Japanese Orthopaedic Association-subsidized Science Project Research 2006-5 and the Japanese Hip Society.

References

1. Shima Y. Standard for evaluation of osteoarthritis of the hip. Nippon Seiekeigekagakkai Zasshi 1971;45:813–33 (in Japanese).
2. Doiguchi Y, Iwasaki K, Yamada K, Takahashi K, Teshima K, Sasamatsu T, et al. Correlation between pelvic inclination and radiological shape of the pelvic cavity. Orthop Traumatol 1992;41:641–5 (in Japanese).
3. Jorring K. Osteoarthritis of the hip. Acta Orthop Scand 1980; 51:523–30.
4. Danielsson L, Lindberg H, Nilsson BO. Prevalence of coxarthrosis. Clin Orthop 1984;191:110–5.
5. Van Sasse JLCM, Van Romunde LKJ, Cats A, Vandenbroucke JP, Valkenburg HA. Epidemiology of osteoarthritis: Zoetermeer survey — comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. Ann Rheum Dis 1989;48:271–80.
6. Ledingham J, Dawson S, Preston B, Milligan G, Doherty M. Radiographic progression of osteoarthritis of the hip. Ann Rheum Dis 1993;52:263–7.
7. Oliveria SA, Felson DT, Reed JI, Cirillo PA, Walker AM. Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. Arthritis Rheum 2005;38:1134–41.
8. Yoshimura N, Campbell L, Hashimoto T, Kinoshita H, Okayasu T, Wilman C, et al. Acetabular dysplasia and hip osteoarthritis in Britain and Japan. Br J Rheumatol 1998;37:1193–7.
9. Inoue K, Wicart P, Kawasaki T, Huang J, Ushiyama T, Hukuda S, et al. Prevalence of hip osteoarthritis and acetabular dysplasia in French and Japanese adults. Rheumatology 2000;39:745–8.
10. Tepper S, Hochberg MC. Factors associated with hip osteoarthritis: data from the first national health and nutrition examination survey (NHANES-1). Am J Epidemiol 1993;137:1081–8.
11. Nevitt MC, Xu L, Zhang Y, Lui LY, Yu W, Lane NE. Very low prevalence of hip osteoarthritis among Chinese elderly in Beijing, China, compared with whites in the United States: the Beijing Osteoarthritis Study. Arthritis Rheum 2002;46:1773–9.
12. Lian K, Lui L, Zmuda JM, Nevitt MC, Hochberg MC, Lee JM, et al. Estrogen receptor alpha genotype is associated with a reduced prevalence of radiographic hip osteoarthritis in elderly Caucasian women. Osteoarthritis Cartilage 2007;15:972–8.
13. Jingushi S, Sofue M, Hirota Y, Itoman, M, Matsumoto T, Hamada Y, et al. A prospective multi-institutional study about the etiology of hip osteoarthritis in Japan: the involvement of acetabular dysplasia. In: Transactions of the 56th annual meeting of the Orthopaedic Research Society, 2010. Poster no. 2016.
14. Offierski CM, MacNab I. Hip-spine syndrome. Spine 1983;8: 316–21.

J Orthop Sci (2011) 16:156–164
DOI 10.1007/s00776-011-0025-7

ORIGINAL ARTICLE

Osteoarthritis hip joints in Japan: involvement of acetabular dysplasia

Seiya Jingushi · Satoko Ohfuji · Muroto Sofue · Yoshio Hirota · Moritoshi Itoman · Tadami Matsumoto · Yoshiki Hamada · Hiroyuki Shindo · Yoshio Takatori · Harumoto Yamada · Yuji Yasunaga · Hiroshi Ito · Satoshi Mori · Ichiro Owan · Genji Fujii · Hirotsugu Ohashi · Yukihide Iwamoto · Keita Miyanishi · Toshiro Iga · Naonobu Takahira · Tanzo Sugimori · Hajime Sugiyama · Kunihiko Okano · Tatsuro Karita · Kenichi Ando · Takanari Hamaki · Teruhisa Hirayama · Ken Iwata · Satoshi Nakasone · Masanori Matsuura · Taro Mawatari

Received: 5 August 2010 / Accepted: 3 November 2010 / Published online: 26 February 2011

Abstract
Background We conducted a nationwide epidemiologic study regarding hip osteoarthritis (OA) in Japan, and a previous report found these patients to be unique in comparison to Caucasians. This report focused on the data regarding each hip joint, and the involvement of acetabular dysplasia with hip OA was analyzed.

Methods Seven hundred twenty OA hips were examined. Sixty-five joints with osteonecrosis of the femoral head and 215 non-OA contralateral joints of the unilateral patients were examined as controls. The revised system of stage classification for hip OA of the Japanese Orthopedic Association (JOA) was used according to the reproducibility in order to ensure reliable data from the multiple

S. Jingushi (✉) · M. Itoman · K. Miyanishi
Department of Orthopaedic Surgery, Kyushu Rosai Hospital of Japan Labour Health and Welfare Organization, 1-3-1 Takamatsu, Kuzuhara, Kokura-minami-ku, Kitakyushu 800-0296, Japan
e-mail: jingushi.orth@kyushuh.rofuku.go.jp

S. Ohfuji · Y. Hirota
Department of Public Health, Osaka City University Graduate School of Medicine, Osaka, Japan

M. Sofue · T. Iga
Orthopaedic Division, Nakajo Central Hospital, Niigata, Japan

T. Matsumoto · T. Sugimori
Department of Orthopaedic Surgery, Kanazawa Medical University, Uchinada, Japan

Y. Hamada
Orthopaedic Division, Mitsuwadai General Hospital, Chiba, Japan

H. Shindo · K. Okano
Department of Orthopaedic Surgery, Graduate School of Medicine, Nagasaki University, Nagasaki, Japan

Y. Takatori
Division of Science for Joint Reconstruction, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

H. Yamada · K. Ando
Department of Orthopaedic Surgery, Fujita Health University, School of Medicine, Toyoake, Japan

Y. Yasunaga · T. Hamaki
Department of Artificial Joints and Biomaterials, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan

H. Ito · T. Hirayama
Department of Orthopaedic Surgery, Asahikawa Medical College, Asahikawa, Japan

S. Mori
Department of Bone and Joint Surgery, Seirei Hamamatsu General Hospital, Hamamatsu, Japan

I. Owan · S. Nakasone
Department of Clinical Neuroscience, Orthopedic Surgery, School of Medicine, University of the Ryukyus, Nishihara, Japan

G. Fujii
Tohoku Hip Joint Center, Matsuda Hospital, Sendai, Japan

H. Ohashi · M. Matsuura
Department of Orthopedic Surgery, Saiseikai Nakatsu Hospital, Osaka, Japan

Y. Iwamoto · T. Mawatari
Department of Orthopaedic Surgery, Clinical Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

N. Takahira
Department of Rehabilitation, School of Allied Health Sciences, Kitasato University, Sagamihara, Japan

institutions. The acetabular dysplasia indexes were also chosen according to the reproducibility and measured in the radiograph of bilateral hip joints. The clinical score was assessed using the JOA scoring system. The relative risk of the grade of acetabular dysplasia indexes for hip OA was calculated as the odds ratio and the 95% confidence interval.

Results The stage of the OA joints deteriorated with increasing age. The clinical scores also decreased. The grade of the acetabular dysplasia indexes of the OA joints was significantly higher than that of the control joints. Each index of acetabular dysplasia demonstrated significantly increased odds ratios for hip OA. Among the OA joints, the deterioration of the OA stage was found to be significantly associated with an increasing grade of acetabular dysplasia. The odds ratio for OA deterioration in the acetabular dysplasia index was also obtained. The joints of females tended to have a higher grade and prevalence of acetabular dysplasia than those of males.

Conclusions These findings confirmed a high prevalence of acetabular dysplasia in hip OA joints in Japan. Acetabular dysplasia was one of the most important factors associated with hip OA.

Introduction

Osteoarthritis (OA) of the hip is a major disease that affects the healthy life span of a population. It is necessary to understand the patient condition before systematic treatment can be applied. A nationwide epidemiologic study regarding OA of the hip was conducted in Japan and reported previously [1]. This previous study showed the patients with hip OA in Japan to be unique based on the age distribution, the gender heterogeneity, and the disease etiology in comparison to the findings observed in Caucasians. There was a substantially larger number of female than male patients. The peak age of patients at presentation was in the 50s. The etiology was assessed to be acetabular dysplasia in most of the patients. Our study concluded that these unique characteristics of patients in Japan may be related to the occurrence of acetabular dysplasia.

The previous report [1] focused on the data regarding each patient and the current status of patients with hip OA in Japan. This report focused on the data regarding each hip joint, and the involvement of acetabular dysplasia with hip OA was analyzed.

H. Sugiyama
Department of Orthopaedic Surgery, Kanagawa Rehabilitation Hospital, Kanagawa, Japan

T. Karita
Department of Orthopaedic Surgery, Tokyo Metropolitan Tama Medical Center, Tokyo, Japan

K. Iwata
Department of Orthopaedic Surgery, Kagawa University Faculty of Medicine, Miki, Japan

Patients and methods

This study reevaluated the data obtained in a previous multi-institutional examination of patients with hip OA [1]. Data were collected from patients who were newly admitted to the orthopedic outpatient clinic of each institution. Fifteen institutions in five areas of Japan participated in the study. The patients were limited to those old enough to have hip joints that had completed closure of the growth plate. Patients were excluded if they had undergone an operation on both bilateral hip joints after growth plate closure. OA of the hip was defined as a symptomatic hip joint that had radiological evidence of OA changes. A symptomatic hip joint that had a deformity in the joint such as acetabular dysplasia or dislocation, but no OA changes was also included. Data were collected for 9 months after the study had received approval from the institutional review board, including the one at the first author's institution. Written informed consent was obtained from each patient.

Seven hundred twenty OA hips were examined in this study. The data from 65 joints in patients with osteonecrosis of the femoral head (ONFH) and 215 non-OA contralateral joints of the unilateral hip OA patients were collected in the same previous multi-institutional examination as controls. The proportions of female-to-male joints were 90:10, 46:54, and 87:13 in the OA, ONFH, and non-OA groups, respectively. The mean ages of the patients with OA joints, ONFH joints, and non-OA joints were 57.2 ± 14.3 (SD), 48 ± 15.1, and 61.1 ± 13.7 years, respectively.

The stage of hip OA was classified using the system based on the classification proposed by the Japanese Orthopedic Association's (JOA) committee [2] on evaluation criteria for this condition. It was revised according to the reproducibility in the previous preliminary study [3] in order to ensure reliable data from the multiple institutions. It defined four groups of hip OA: the pre-OA stage, the initial stage, the advanced stage, and the terminal stage. Briefly, when a symptomatic hip demonstrated no radiological OA changes but showed morphological changes of the acetabulum and/or proximal femur related to OA, it was assessed as being at pre-OA. The joints that had one or more OA changes and possible narrowing of the joint space were assessed as at the initial stage. An additional condition for the joints at the initial stage was that the width of the joint space was maintained at 2 mm or more throughout the weight-bearing area. The joint was assessed as being at

the advanced stage when the width was <2 mm at the thinnest point or loss of joint space was observed, and simultaneously when the width was <15 mm. The joints at the terminal stage showed gross loss of the joint space, and the width was 15 mm or more. Typical radiographs of the OA hip joints at each stage were used for reference to evaluate the stage of the OA joints.

Acetabular dysplasia indexes were also chosen according to the reproducibility for the multi-institutional examination [3] from the Sharp angle [4], the center edge angle [5], the acetabular roof obliquity angle [6], the acetabular head index (AHI) [7], and the approximate acetabular quotient [7]. Sharp angle, acetabular roof obliquity angle, and AHI were assessed as reproducible indexes and were measured in an antero-posterior view radiograph of the bilateral hip joints. The joints at the terminal stage were excluded because the severe OA deformity made measuring difficult.

The clinical score of the hip joints was assessed using the JOA scoring system [8]. The score was based on pain (40 points), range of motion (ROM) (20), gait (20), and ADL (20) scores. The clinical score data regarding pain and ROM were used for assessing each joint in this report. The ROM score was assessed by measuring the flexion and the abduction angle. The pain score was assessed as follows: no pain (40), slight pain just after a long walk (30), moderate pain while walking (20), infrequent resting pain (10), and continuous resting pain (0).

The joint's characteristics, including the clinical score and the stage classification, were compared across age categories or across stage categories, using a Kruskal-Wallis test (continuous variables) and a Mantel-Haenszel chi-square test (categorical variables). The index data of acetabular dysplasia in the hip OA joints were also compared with those in the control joints using a Wilcoxon rank sum test (continuous variables) and a Mantel-Haenszel chi-square test (categorical variables). The relative risk of the grade of acetabular dysplasia indexes for hip OA and the stage of deterioration was calculated as the odds ratio and the 95% confidence interval using logistic regression models and proportional odds models. All analyses were performed using the Statistical Analysis System® version 9.1 software program package (SAS Institute, Cary, NC). Differences with p values of <0.05 were considered to be statistically significant.

Results

The proportion of the OA joints at each stage varied depending on the age generation, although the proportions of OA joints at each stage in the whole group were not significantly different from each other. The OA stage significantly deteriorated with age (Table 1). The clinical scores for pain and ADL of the OA joints also decreased with the increasing age of the joints. Both the pain and ADL scores significantly decreased according to the stage of deterioration (Table 2).

The mean Sharp angle and the mean acetabular roof obliquity angle of the OA joints were significantly larger than that of the ONFH joints or than that of the non-OA joints (Table 3). The mean AHI of the OA joints was significantly lower than that of the ONFH joints or than that of the non-OA joints. A comparison of the proportion of each category in various acetabular indexes revealed that the proportion of the relatively large Sharp angle or acetabular roof obliquity angle was higher in the OA joints than that in the ONFH joints or than that in the non-OA joints. The proportion of the relatively small AHI was higher in the OA joints than that in the ONFH joints or than that in the non-OA joints. Furthermore, the mean acetabular roof obliquity angle of the non-OA joints was significantly larger than that of the ONFH joints. The proportion of the relatively larger acetabular roof obliquity angle was

Table 1 Stage classification and clinical scores of the OA joints

	Total (N = 720)	<30 years old (N = 34)	30–39 (N = 50)	40–49 (N = 108)	50–59 (N = 199)	60–69 (N = 161)	70–79 (N = 142)	≥80 (N = 26)	p value
Stage [number (%)]									
Pre-OA	167 (23)	22 (65)	31 (62)	33 (31)	40 (20)	25 (16)	15 (11)	1 (4)	<0.0001*
Initial	124 (17)	12 (35)	15 (30)	26 (24)	31 (16)	21 (13)	17 (12)	2 (8)	
Advanced	168 (23)	0 (0)	2 (4)	25 (23)	71 (36)	31 (19)	34 (24)	5 (19)	
Terminal	261 (36)	0 (0)	2 (4)	24 (22)	57 (29)	84 (52)	76 (54)	18 (69)	
Clinical score [mean (SD)]									
Pain	21.3 (12.2)	25.7 (12.1)	29.1 (11.1)	21.6 (12.5)	20.7 (12.1)	19.6 (12.0)	21.0 (11.6)	14.8 (12.0)	<0.0001**
ROM	15.1 (4.8)	18.9 (2.1)	19.0 (2.0)	16.2 (4.4)	14.7 (5.2)	14.3 (4.9)	14.1 (4.7)	12.7 (3.4)	<0.0001**

* Mantel-Haenszel chi-square test

** Kruskal-Wallis test

Table 2 Relationship between the stage and the clinical scores

	Stage				*p* value
	Pre-OA ($N = 167$)	Initial ($N = 124$)	Advanced ($N = 168$)	Terminal ($N = 261$)	
Pain [mean (SD)]	31.2 (10.6)	24.5 (12.4)	17.8 (10.7)	15.6 (9.3)	<0.0001*
ROM [mean (SD)]	19.3 (1.8)	18.2 (2.4)	14.5 (3.8)	11.5 (4.6)	<0.0001*

* Kruskal-Wallis test

Table 3 Indexes of acetabular dysplasia in the OA joints compared with those in the control joints

	OA joints ($N = 407$)	ONFH joints ($N = 61$)	Non-OA joints ($N = 198$)	*p* value (OA vs. ONFH)	*p* value (OA vs. non-OA)	*p* value (ONFH vs. non-OA)
SHARP angle						
Mean (SD)	45.0 (5.1)	39.8 (4.0)	40.6 (5.1)	<0.0001*	<0.0001*	0.089*
<40	54 (13.3)#	26 (42.6)	66 (33.3)	<0.0001**	<0.0001**	0.101**
40–44	116 (28.5)	29 (47.5)	99 (50.0)			
45–49	166 (40.8)	6 (9.8)	32 (16.2)			
50+	71 (17.5)	0 (0)	1 (0.5)			
Acetabular roof obliquity angle						
Mean (SD)	20.3 (8.4)	9.9 (6.4)	12.2 (6.0)	<0.0001*	<0.0001*	0.001*
<10	38 (9.3)	35 (57.4)	60 (30.3)	<0.0001**	<0.0001**	0.005**
10–19	153 (37.6)	21 (34.4)	121 (61.1)			
20–29	163 (40.1)	4 (6.6)	16 (8.1)			
30+	53 (13.1)	1 (1.6)	1 (0.5)			
AHI (%)						
Mean (SD)	69.7 (12.0)	83.3 (6.8)	81.1 (8.4)	<0.0001*	<0.0001*	0.076*
80+	78 (19.2)	45 (73.8)	117 (59.1)	<0.0001**	<0.0001**	0.031**
70–79	144 (35.4)	15 (24.6)	71 (35.9)			
60–69	102 (25.1)	1 (1.6)	9 (4.5)			
<60	83 (20.4)	0 (0)	1 (0.5)			

* Wilcoxon rank sum test

** Mantel-Haenszel chi-square test

\# Percentage in parentheses

higher in the non-OA joints than that in the ONFH joints. The proportion of the relatively smaller AHI was higher in the non-OA joints than in the ONFH joints.

An analysis of the joints of the OA patients including the OA and non-OA joints determined the odds ratio for OA in each index of acetabular dysplasia. Sharp angles of more than 45° or 50° had significantly increased odds ratios of 6- or 87-fold greater for hip OA, respectively, in comparison to the joints in which the Sharp angles were <40° (Table 4). The corresponding age-adjusted ratio was approximately 5- or 65-fold greater, respectively. Either crude odds ratio or the age-adjusted odds ratio increased with an increase of the Sharp angle. The odds ratio of the joints in which the acetabular roof obliquity angle was more than 10°, 20°, or 30° was approximately 2-, 16-, or 84-fold greater, respectively, in comparison to the joints where the angles were <10°. The age-adjusted odds ratio was approximately 2-, 16-, or 83-fold greater, respectively. The association between higher acetabular roof obliquity angle and hip OA was dose respondent in crude and age-adjusted analyses. The odds ratio of the joints in which the AHIs were less than 80, 70, or 60% was approximately 3-, 17-, or 125-fold greater, respectively, in comparison to the joints in which the AHIs were higher than 80%. The age-adjusted odds ratio was approximately 3-, 15-, or 100-fold greater, respectively. Either the odds ratio or the age-adjusted odds ratio increased with a decrease of AHI.

There was a significant relationship between the acetabular roof obliquity angle and the stage of the OA joints (Table 5). The acetabular roof obliquity angle increased according to the stage of deterioration. The AHI also significantly decreased with the stage of deterioration.

Table 4 The relative risk of the grade of acetabular indexes for hip OA

	OA joints ($N = 407$)	Non-OA joints ($N = 198$)	Univariate			Age-adjusted		
			OR	95% CI	p value	OR	95% CI	p value
Sharp angle [number (%)]								
<40	54 (13)	66 (33)	1.00			1.00		
40–44	116 (29)	99 (50)	1.43	0.91–2.24	0.117	1.29	0.82–2.04	0.277
45–49	166 (41)	32 (16)	6.34	3.76–10.7	<0.0001	4.99	2.88–8.66	<0.0001
50+	71 (17)	1 (1)	86.8	11.7–645	<0.0001	65.4	8.70–492	<0.0001
			(Trend $p < 0.0001$)			(Trend $p < 0.0001$)		
Acetabular roof obliquity angle								
<10	38 (9)	60 (30)	1.00			1.00		
10–19	153 (38)	121 (61)	2.00	1.25–3.20	0.004	2.07	1.27–3.38	0.004
20–29	163 (40)	16 (8)	16.1	8.36–31.0	<0.0001	16.2	8.31–31.7	<0.0001
30+	53 (13)	1 (1)	83.6	11.1–630	<0.0001	83.1	11.0–630	<0.0001
			(Trend $p < 0.0001$)			(Trend $p < 0.0001$)		
AHI (%)								
80+	78 (19)	117 (59)	1.00			1.00		
70–79	144 (35)	71 (36)	3.04	2.03–4.56	<0.0001	2.70	1.79–4.08	<0.0001
60–69	102 (25)	9 (5)	17.0	8.12–35.6	<0.0001	14.5	4.88–30.6	<0.0001
<60	83 (20)	1 (1)	125	17.0–913	<0.0001	100	13.6–737	<0.0001
			(Trend $p < 0.0001$)			(Trend $p < 0.0001$)		

However, there was no significant relationship between the Sharp angle and the stage of classification.

An analysis of the OA joints excluding the OA joints at the terminal stage showed the odds ratio for the stage of deterioration in each index of acetabular dysplasia. The odds ratio of the joints in which the angle was more than 20° or 30° was approximately 3- or 15-fold greater, respectively (Table 6), in comparison to the joints in which the acetabular roof obliquity angle was <10°. The age-adjusted odds ratio was approximately 3- or 18-fold greater, respectively. Either the crude odds ratio or the age-adjusted odds ratio increased with an increase of the angle. The odds ratio of the joints in which AHIs were <60 was approximately threefold greater in comparison to the joints in which the AHIs were more than 80. The age-adjusted odds ratio of the joints that were less than 70 or 60 was approximately two- or six-fold greater, respectively. Either the crude odds ratio or the age-adjusted odds ratio increased with a decrease of AHI. The data of the Sharp angle were not statistically significantly associated with the OA deterioration stage.

Comparing the indices of acetabular dysplasia in the joints of females and males, the mean acetabular roof oblique angle was significantly higher in the joints of females than in those of males (Table 7). The mean AHI tended to be lower in the joints of females than in those of males. The proportion of the relatively larger Sharp angle or acetabular roof obliquity angle was higher in the joints of females than in those of males. An analysis of the joints of the female OA patients, including OA and non-OA joints, revealed a significant odds ratio for OA in each index of acetabular dysplasia (Table 8).

Discussion

The analysis of the stage classification for OA joints revealed that the severity of OA joints increased with increasing age. The clinical scores of pain and ROM for the joints also declined with increasing age, and there was a significant relationship between the classification stage and the clinical score. These data indicated that the natural course of OA hip joints generally deteriorated with aging. In addition, the high proportion of OA joints with acetabular dysplasia may strengthen this tendency, as previously reported [1] and as shown in this study. Acetabular dysplasia of the hip joints usually develops prior to early adolescence, and the period that acetabular dysplasia can influence the etiology of hip OA increases with aging.

The OA joints had a statistically significant tendency to have acetabular dysplasia in comparison to the control joints, based on the indexes measured in the hip radiographs. The acetabulum of the ONFH control joints remained intact, and the acetabular dysplasia indexes of the ONFH joints were equivalent to those in the hip joints in the normal population. The significantly high grade of

Table 5 Relationship between the stage of classification and the indexes of acetabular dysplasia in the OA joints

	Pre-OA (N = 157)	Initial stage (N = 106)	Advanced stage (N = 144)	p value
SHARP angle				
Mean (SD)	45.1 (4.0)	45.3 (5.6)	44.5 (5.8)	0.435*
<40	16 (10.2)#	13 (12.3)	25 (17.4)	0.361**
40–44.9	47 (29.9)	27 (25.5)	42 (29.2)	
45–49.9	77 (49.0)	41 (38.7)	48 (33.3)	
50–54.9	17 (10.8)	24 (22.6)	28 (19.4)	
55–59.9	0 (0.0)	1 (0.9)	1 (0.7)	
Acetabular roof obliquity angle				
Mean (SD)	17.1 (6.7)	20.0 (7.5)	23.9 (9.2)	<0.0001*
<10	24 (15.3)	8 (7.5)	6 (4.2)	<0.0001**
10–14.9	29 (18.5)	18 (17.0)	14 (9.7)	
15–19.9	46 (29.3)	21 (19.8)	25 (17.4)	
20–24.9	38 (24.2)	26 (24.5)	36 (25.0)	
25–29.9	16 (10.2)	22 (20.8)	25 (17.4)	
30–34.9	3 (1.9)	8 (7.5)	19 (13.2)	
35–39.9	1 (0.6)	3 (2.8)	9 (6.3)	
40+	0 (0)	0 (0.0)	10 (6.9)	
AHI (%)				
Mean (SD)	73.2 (9.4)	69.8 (11.0)	65.9 (14.1)	<0.0001*
<40	0 (0)	0 (0.0)	4 (2.8)	<0.0001**
40–49	0 (0)	3 (2.8)	15 (10.4)	
50–59	16 (10.2)	18 (17.0)	27 (18.8)	
60–69	35 (22.3)	27 (25.5)	40 (27.8)	
70–79	73 (46.5)	34 (32.1)	37 (25.7)	
80–89	26 (16.6)	21 (19.8)	15 (10.4)	
90+	7 (4.5)	3 (2.8)	6 (4.2)	

* Kruskal-Wallis test

** Mantel-Haenszel chi-square test

Percentage in parentheses

acetabular dysplasia of the OA joints in comparison to the ONFH control joints indicated a significantly high proportion of joints with acetabular dysplasia in the OA joints. In contrast, the non-OA joints were in the contralateral joints of the unilateral hip OA patients. These would include the joints that had acetabular dysplasia but had not developed OA yet. The significantly high grade of acetabular dysplasia of the OA joints in comparison to the non-OA joints indicated that the grade of acetabular dysplasia correlated with the incidence of the OA joints. In addition, the non-OA joints tended to have a higher grade of acetabular dysplasia than the ONFH control joints. This suggests that many hip OA patients have acetabular dysplasia in both of the joints, regardless of whether they have OA or non-OA disease. Our previous report [1] clarified that there is a high proportion of bilateral involvement of hip OA, as well as a high proportion of acetabular dysplasia, especially in young patients. These findings suggest that acetabular dysplasia may therefore have a genetic cause, although the details still remain to be elucidated.

The current study indicated that the grade of acetabular dysplasia was related to significant risk for hip OA. The joints that had significant increased odds ratios were those with a Sharp angle of more than 45°, an acetabular roof obliquity angle of more than 10°, and an AHI <80%. The proportions of OA joints with such acetabular dysplasia among all the OA joints were 58, 91, and 81%, respectively. This indicates that most of the OA joints had acetabular dysplasia with a significant risk for the incidence of OA. These proportions are similar to that shown in the previous report based on the etiology study [1]. The proportion of hip OA joints with acetabular dysplasia in the countries other than Japan has been reported to be relatively low. In previous reports from England [9], South Africa [10], and the United States [11], the proportions were 21%, approximately 20%, and more than 40%, respectively. The current study confirmed a high prevalence of acetabular dysplasia in hip OA joints in Japan.

A previous study that examined radiographic and patient factors associated with pre-radiographic OA in hip dysplasia found that OA was associated with increasing age as well as with the severity of dysplasia [12]. Another study using white women aged 65 and above with and without radiographic hip OA did not obtain a statistically

Table 6 The relative risk of the grade of acetabular dysplasia indexes for the stage of deterioration of hip osteoarthritis

	Pre-OA stage ($N = 157$)	Early stage ($N = 106$)	Advanced stage ($N = 144$)	Univariate			Age-adjusted		
				OR	95% CI	p value	OR	95% CI	p value
SHARP angle [number (%)]									
<40	16 (10)	13 (12)	25 (17)	1.00			1.00		
40–44	47 (30)	27 (25)	42 (29)	0.63	0.35–1.15	0.131	0.77	0.41–1.43	0.405
45–49	77 (49)	41 (39)	48 (33)	0.47	0.27–0.84	0.010	0.88	0.47–1.62	0.67
50+	17 (11)	25 (24)	29 (20)	0.98	0.51–1.88	0.940	2.08	1.02–4.26	0.044
				(Trend $p = 0.731$)			(Trend $p = 0.021$)		
Acetabular roof oblique angle									
<10	24 (15)	8 (8)	6 (4)	1.00			1.00		
10–19	75 (48)	39 (37)	39 (27)	1.81	0.89–3.63	0.100	1.64	0.79–3.41	0.185
20–29	54 (34)	48 (45)	61 (42)	3.38	1.67–6.83	0.001	3.41	1.65–7.06	0.001
30+	4 (3)	11 (10)	38 (26)	14.8	6.08–35.8	<0.0001	17.6	6.97–44.3	<0.0001
				(Trend $p < 0.0001$)			(Trend $p < 0.0001$)		
AHI (%)									
80+	33 (21)	24 (23)	21 (15)	1.00			1.00		
70–79	73 (46)	34 (32)	37 (26)	0.79	0.47–1.32	0.368	1.02	0.60–1.75	0.945
60–69	35 (22)	27 (25)	40 (28)	1.54	0.89–2.66	0.120	2.33	1.30–4.15	0.004
<60	16 (10)	21 (20)	46 (32)	3.10	1.72–5.59	0.0002	6.07	3.19–11.6	<0.0001
				(Trend $p < 0.0001$)			(Trend $p < 0.0001$)		

Table 7 A sex difference in the indexes of acetabular dysplasia in the OA joints

	Male ($N = 40$)	Female ($N = 367$)	p value
SHARP angle			
Mean (SD)	43.2 (6.4)	45.1 (4.9)	0.067**
<40	11 (28)#	43 (12)	0.048*
40–44	9 (23)	107 (29)	
45–49	15 (38)	151 (41)	
50+	5 (13)	66 (18)	
Acetabular roof obliquity angle			
Mean (SD)	15.5 (8.4)	20.8 (8.2)	0.001**
<10	11 (28)	28 (7)	0.0002*
10–19	15 (38)	138 (38)	
20–29	13 (33)	150 (41)	
30+	1 (3)	52 (14)	
AHI (%)			
Mean (SD)	73.1 (10.7)	69.4 (12.1)	0.051**
80+	11 (28)	67 (18)	0.115*
70–79	15 (38)	129 (35)	
60–69	8 (20)	94 (26)	
<60	6 (15)	77 (21)	

* Mantel-Haenszel chi-square test

** Wilcoxon rank sum test

Percentage in parentheses

significant odds ratio for the incidence of OA [13]. In contrast, a similar study of elderly white women found the odds ratio for the association of abnormal center-edge angle and acetabular dysplasia with incident hip OA to be 3.3 and 2.8, respectively [14]. The current study found a tendency for crude odds ratios for hip OA to be higher than the age-adjusted one. However, the age-adjusted odds ratios using any acetabular dysplasia indexes were high enough to show the involvement of acetabular dysplasia in hip OA. Acetabular dysplasia as well as aging is an important etiology for hip OA caused by abnormal loading and abnormal instability [15].

Some ONFH control joints included those that had sufficient acetabular dysplasia to have a significant risk for OA. The proportions of the ONFH joints with such acetabular dysplasia in all of the ONFH joints were 10, 43, and 26.2%, respectively, according to the grade of Sharp angle, acetabular roof obliquity angle, and AHI. In addition, the proportion of ONFH joints that had a more than ten-fold greater odds ratio for OA according to the grade of the acetabular dysplasia indexes of the acetabular roof obliquity angle and AHI were 8 and 2%, respectively. Therefore, some hip joints with sufficiently severe acetabular dysplasia to be at risk for OA may be included in the normal population. This proportion of hip joints with acetabular dysplasia in the normal population is relatively high com-

Table 8 The relative risk of the grade of acetabular dysplasia indexes for hip OA in the joints of females

	OA joints ($N = 367$)	Non-OA joints ($N = 172$)	Univariate			Age-adjusted		
			OR	95% CI	p value	OR	95% CI	p value
Sharp angle [number (%)]								
<40	43 (12)	55 (32)	1.00			1.00		
40–44	107 (29)	88 (51)	1.56	0.95–2.54	0.077	1.38	0.84–2.27	0.209
45–49	151 (41)	28 (16)	6.90	3.91–12.2	<0.0001	5.20	2.84–9.51	<0.0001
50+	66 (18)	1 (1)	84.4	11.3–633	<0.0001	60.4	7.93–460	<0.0001
			(Trend $p < 0.0001$)			(Trend $p < 0.0001$)		
Acetabular roof obliquity angle								
<10	28 (7)	49 (29)	1.00			1.00		
10–19	138 (38)	106 (62)	2.36	1.39–4.03	0.002	2.55	1.45–4.46	0.001
20–29	150 (41)	16 (9)	17.0	8.47–34.2	<0.0001	17.9	8.69–36.8	<0.0001
30+	52 (14)	1 (1)	94.3	12.3–721	<0.0001	97.1	12.6–750	<0.0001
			(Trend $p < 0.0001$)			(Trend $p < 0.0001$)		
AHI (%)								
80+	67 (18)	103 (60)	1.00			1.00		
70–79	129 (35)	61 (36)	3.25	2.11–5.01	<0.0001	2.86	1.84–4.46	<0.0001
60–69	94 (26)	8 (5)	18.1	8.24–39.6	<0.0001	15.0	6.81–33.2	<0.0001
<60	77 (21)	0 (0)	NA			NA		
			(Trend $p < 0.0001$)			(Trend $p < 0.0001$)		

pared to reports from other countries. In France, the proportion is reported to be approximately one half of that in Japan [16]. The proportions of hip joints with <25° of the center edge angle were 16 and 4% of men in Japan and Britain, respectively [17]. According to the degree of the center edge angle, they were reported to be 3.3, 10.4, and 4.5% in Nigerian [18], Turkish [19], and Chinese men [20], respectively.

Several previous prospective studies showed acetabular dysplasia is associated with a significant risk of hip OA. A prospective cohort study [21] found that hip joints with acetabular dysplasia (the center edge angle <25°) had a 4.3-fold increased risk for OA. A study using non-OA hip joints of the unilateral hip OA patients [22] showed that hips with an abnormal acetabular roof obliquity angle had a significantly increased probability to develop OA (OR 5.96). Although the current study was not prospective, the grade of the odds ratio was consistent with these earlier studies. In addition, there was a significant tendency of an increased odds ratio according to the grade of acetabular dysplasia. At most, the odds ratio was up to approximately 100-fold. Furthermore, the stage classification data revealed that the grade of acetabular dysplasia of the OA joints had a significant relationship with deterioration of OA. The OA joints that had a high grade of acetabular dysplasia had a significant risk for OA deterioration. These data indicated that acetabular dysplasia is one of the most important factors associated with hip OA.

The joints of females tended to have a higher grade and prevalence of acetabular dysplasia than the joints of males. The etiology study in the previous report also showed that acetabular dysplasia is present in more than 80% of female patients in contrast to approximately half of the male patients [1]. The estrogen receptor genotype is involved in the prevalence of hip OA [23]. Therefore, the sex difference in the involvement of acetabular dysplasia may also depend on genetic differences. The relative risk of the grade of acetabular dysplasia indices for hip OA in the female joints was similar to that in all joints. This is because of the high percentage of female joints in all of the OA hip joints in our study and the high prevalence of acetabular dysplasia in the joints of females. An analysis limited to the joints of females confirmed the involvement of acetabular dysplasia in hip OA.

Although the prevalence of normal control joints in the ONFH joints was indicated in the current study, the correct prevalence of hip OA in the normal population was not shown. Although the relative risk for OA depending on the grade of acetabular dysplasia was shown in the current study, the relative risk for OA incidence was not indicated, since it was not a cohort study. This nationwide and multi-institutional epidemiological study showed the existence of both a high grade and prevalence of acetabular dysplasia in Japan, especially in the joints of females, and acetabular dysplasia is therefore considered to be closely involved with hip OA.

Acknowledgments This study was supported by grants from the JOA (Japanese Orthopaedic Association)-Subsidized Science Project Research 2006-5 and the Japanese Hip Society.

References

1. Jingushi S, Ohfuji S, Sofue M, Hirota Y, Itoman M, Matsumoto T, Takatori Y, Tamada H, Yasunaga Y, Ito H, Mori S, Owan I, Genji F, Ohashi H, Iwamoto Y, Miyanishi K, Iga T, Takahira N, Sugimori T, Sugiyama H, Okano K, Karita T, Ando K, Hamaki T, Hirayama T, Iwata K, Nakasone S, Matsuura M, Mawatari T. A multi-institutional epidemiologic study regarding osteoarthritis of the hip in Japan. J Orthop Sci. 2010;15(5):626–31.
2. Ueno R. Staging of osteoarthritis of the hip joint according to the roentgenographic findings. J Jpn Orthop Assoc. 1971;45:826–8 (in Japanese).
3. Takatori Y, Ito K, Sofue M, Hirota Y, Itoman M, Matsumoto T, Takatori Y, Tamada H, Yasunaga Y, Ito H, Mori S, Owan I, Genji F, Ohashi H, Iwamoto Y, Miyanishi K, Iga T, Takahira N, Sugimori T, Sugiyama H, Okano K, Karita T, Ando K, Hamaki T, Hirayama T, Iwata K, Nakasone S, Matsuura M, Mawatari T, Jingushi S. An analysis of interobserver reliability for radiographic staging of coxarthrosis and indexes of acetabular dysplasia—a preceding study. J Orthop Sci. 2010;15:14–9.
4. Sharp IK. Acetabular dysplasia. The acetabular angle. J Bone Joint Surg Br. 1961;43:268–72.
5. Wiberg G. Studies on dysplastic acetabula and congenital subluxation of the hip joint with special reference to the complication of osteoarthritis. Acta Chir Scand Suppl. 1939;58:1–135.
6. Massie WK, Howorth MB. Congenital dislocation of the hip. Part I. Method of grading results. J Bone Joint Surg Am. 1950;32:519–31.
7. Heyman CH, Herndon CH. Legg-Perthes disease. A method for the measurement of the roentgenographic result. J Bone Joint Surg Am. 1950;32:767–8.
8. Shima Y. Standard for evaluation of osteoarthritis of the hip. Nippon Seiekeigekagakkai Zasshi. 1971;45:813–33 (in Japanese).
9. Lloyd-Roberts GC. Osteoarthritis of the hip. A study of the clinical pathology. J Bone Joint Surg. 1953;37B:8–45.
10. Solomon L. Patterns of osteoarthritis of the hip. J Bone Joint Surg. 1976;58B:176–83.
11. Harris WH. Etiology of osteoarthritis of the hip. Clin Orthop. 1986;213:20–33.
12. Jessel RH, Zurakowski D, Zilkens C, Burstein D, Gray ML, Kim Y-J. Radiographic and patient factors associated with pre-radiographic osteoarthritis in hip dysplasia. J Bone Joint Surg Am. 2009;91:1120–9.
13. Lane NE, Nevitt MC, Cooper C, Pressman A, Gore R, Hochberg M. Acetabular dysplasia and osteoarthritis of the hip in elderly white women. Ann Rheum Dis. 1997;56:627–30.
14. Lane NE, Lin P, Christiansen L, Gore LR, Williams EN, Hochberg MC, Nevitt MC. Association of mild acetabular dysplasia with an increased risk of incident hip osteoarthritis in elderly white women. Arthritis Rheum. 2000;43:400–4.
15. Maeyama A, Naito M, Moriyama S, Yoshimura I. Evaluation of dynamic instability of the dysplastic hip with use of triaxial accelerometry. J Bone Joint Surg Am. 2008;90:85–92.
16. Inoue K, Wicart P, Kawasaki T, Huang J, Ushiyama T, Hukuda S, Courpied J-P. Prevalence of hip osteoarthritis and acetabular dysplasia in French and Japanese adults. Rheumatology. 2000;39:745–8.
17. Yoshimura N, Campbell L, Hashimoto T, Kinoshita H, Okayasu T, Wilman C, Coggon D, Croft P, Cooper C. Acetabular dysplasia and hip osteoarthritis in Britain and Japan. Br J Rheumatol. 1998;37:1193–7.
18. Ali-Gombe A, Croft PR, Silman AJ. Osteoarthritis of the hip and acetabular dysplasia in Nigerian men. J Rheumatol. 1996;23:512–5.
19. Goker B, Sancak A, Haznedaroglu S. Radiographic hip osteoarthritis and acetabular dysplasia in Turkish men and women. Rheumatol Int. 2005;25:419–22.
20. Lau EM, Lin F, Lam D, Silman A, Croft P. Hip osteoarthritis and dysplasia in Chinese men. Ann Rheum Dis. 1995;54:965–9.
21. Reijman M, Hazes JMW, Pols HAP, Koes BW, Bierma-Zeinstra SMA. Acetabular dysplasia predicts incident osteoarthritis of the hip. Arthritis Rheum. 2005;52:787–93.
22. Vossinakis IC, Georgiades G, Kafidas D, Hartofilakidis G. Unilateral hip osteoarthritis: can we predict the outcome of the other hip? Skeletal Radiol. 2008;37:911–6.
23. Lian K, Lui L, Zmuda JM, Nevitt MC, Hochberg MC, Lee JM, Li J, Lane NE. Estrogen receptor alpha genotype is associated with a reduced prevalence of radiographic hip osteoarthritis in elderly Caucasian women. Osteoarthr Cartil. 2007;15:972–8.

総説（Review Article）：膜（MEMBRANE），35（5），217-223（2010）

●特集　境界領域シンポジウム「材料と細胞および生体成分との相互作用」

細胞膜模倣ポリマーマテリアルのナノバイオ機能

石原一彦[1, 2, 3)]*・井上祐貴[1)]・松野亮介[1, 3)]

1）東京大学大学院工学系研究科　マテリアル工学専攻　〒113-8656 東京都文京区本郷7-3-1
2）東京大学大学院工学系研究科　バイオエンジニアリング専攻　〒113-8656 東京都文京区本郷7-3-1
3）科学技術振興機構　戦略的創造研究推進事業　〒102-0075 東京都千代田区三番町5番地

Nanobiofunctions on Cell Membrane–inspired Polymer Materials

Kazuhiko Ishihara[1, 2, 3)]*, Yuuki Inoue[1)], and Ryouske Matusno[1, 3)]

1) Department of Materials Engineering, School of Engineering, The University of Tokyo
7-3-1, Hongo, Bunkyo–ku, Tokyo 113-8656, Japan
2) Department of Bioengineering, School of Engineering, The University of Tokyo
7-3-1, Hongo, Bunkyo–ku, Tokyo 113-8656, Japan
3) Core Research for Evolutional Science and Technology (CREST), Japan Science and Technology Agency (JST)
5 Sanban–cho, Chiyoda–ku, Tokyo 102-0075, Japan

Preparation and characterization of the cell membrane–inspired polymer materials, which contain 2–methacryloyloxyethyl phosphorylcholine (MPC) unit, are reviewed. The MPC polymer can provide the biointerface to suppress completely the interactions with proteins and cells. Also, on the surface, the biomolecules are immobilized without significant reduction of the their biological activity. Polymer nanoparticles covered with the biointerface and contained quantum dot (QD) s is prepared as the novel bioimaging devices. The kinetic behavior in cytoplasm of the polymer nanopartcles is discussed. Although this nanoparticles can avoid the nonselective cellular uptake from mammalian cells, when bioactive molecules are immobilized, the nanoparticles can provide the various information about the specific interaction between biomolecules and cells. From these findings, it is concluded that the nanoparticles are candidates for the role of stable and highly sensitive fluorescent bioimaging probes in the fields of nanomedicine. Controlling interactions with cells is receiving considerable importance in biomedical fields, including nanobioengineering and cell and tissue engineering. The biointerface described here are a promising design for revealing a universal platform that integrates polymer chemistry; material science; and engineering, biochemistry, cell biology, and nanofabrication.

Key words : phospholipid polymer／nanobiodevice／cell／materials interaction／polymer particle／quantum dots

1. はじめに

生体親和性界面を創製することは，医療デバイスを利用して疾患を治療する際に生じる好ましくない生体反応を避けることができる表面を提供でき，医療デバイスの機能維持と生体に対する侵襲の低減の観点から極めて重要な課題である．現在は，界面での生体応答を避けることができないために，抗凝固剤や免疫抑制剤などの併用が必要である．はたして生体親和性マテリアルの創製は実現できるのであろ

* Corresponding Author
Tel: +81-3-5841-7124
Fax: +81-3-5841-8647
E-mail: ishihara@mpc.t.u-tokyo.ac.jp

うか？

これまで多くのマテリアル界面が提案されてきている[1]．古くは疎水性，親水性といった界面特性に基づく解析がなされてきた．しかしながらいずれの性質も生体反応を阻止できる決め手とはなっていない．また，ポリマー多相系の特徴であるミクロ層分離構造が，生体親和性を高めるという観点から検討がなされてきており，親水／疎水型，結晶／非晶，正／負荷電など相反する性質のミクロ層分離構造が創出された．また，水溶性ポリマーを表面に結合させて界面近傍でのポリマー鎖の膨潤特性，運動性などを生体親和性のパラメーターとした研究や，生理活性分子の表面への固定化による生体親和性の確保などが研究されている．一部，短期間の使用を目的とした医療デバイスには利用されている表面もあるが，完全な生体親和性の獲得には至っていない．

筆者らはこれらの研究とは異なり，細胞膜表面の構造に着目して人工細胞膜表面を持つ生体親和性マテリアルを創製してきている．細胞膜は厚み7～10 nmのリン脂質二分子膜構造を基本としており，これにタンパク質や多糖類が組み合わされて高度な生体機能発現するインターフェイスとして働いている．細胞外には電荷が中和されたホスホリルコリン（PC）基が多く存在しており，その割合はリン脂質の約80%である．タンパク質や多糖類は外部からのシグナル分子を捕捉し，細胞内に信号伝達する機能を有しており，この機構を正確にするためにはこれらの分子が埋め込まれているマトリックス表面には，外部からのシグナル分子の非特異的な反応が生じてはならない．この点に着目すると，PC基の表面は生物的に不活性であると考えられる．

2.　細胞膜模倣ポリマーマテリアルの設計

筆者らはマテリアルとしての観点から分子設計し，重合性，安定性，加工性，安全性あるいは汎用性と血液適合性を併せ持つポリマーバイオマテリアルを創製した[2]．分子内にPC基と重合性に優れたメタクリル酸エステルを有する2－メタクリロイルオキシエチルホスホリルコリン（MPC）は通常のラジカル重合によりポリマーを与える（Fig. 1）．最近では，リビングラジカル重合を利用して，分子構造が明確なポリマー群が得られるほか，表面開始グラフト重合によるバイオ界面創製にも利用されている[3]．MPCポリマーの化学構造や分子量を調節することにより水に対する溶解性，基材表面での成膜性など特性を幅広く変化させることができる．このMPCポリマーを利用すると，医療デバイス表面に溶媒キャスト法

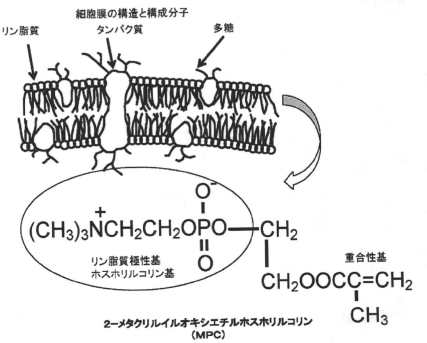

Fig. 1　Chemical structure of MPC.

により簡便に処理することができ，表面に“人工細胞膜構造”を構築することが可能である．ここでは血液凝固反応や免疫反応などの，いわゆる生体反応が回避できることが示されている．これらの生体反応は，表面でのタンパク質の構造変化が引き金となり開始される．MPCポリマー表面におけるタンパク質の吸着量はMPCユニット組成の増加に伴い減少する傾向となった．この結果はMPCポリマーとタンパク質との相互作用が極めて弱いことを表わしている[4,5]．

タンパク質の吸着はタンパク質の持つ結合水とポリマー表面に水和している水の共有化反応を伴う，いわゆる疎水性相互作用が重要な役割を果たしている[6]．ポリマー表面に結合水がないまたは少ない場合には，交換する水分子が存在しないことにより，表面に接触した場合にも直ちに水相へと再拡散するために，安定な吸着（不可逆的吸着）が起こり難くなる．タンパク質分子は分子内でのアミノ酸残基の相互作用により血液や緩衝溶液など水を溶媒とした系では一定のコンホメーションを維持しているが，油水界面に吸着（接触）した場合，コンホメーション変化を起こす．最近のバイオ工学においてタンパク質を安定にマテリアルに固定化し，これをバイオ素子として利用することも多くなってきている．この場合においても，固定化したタンパク質の機能低下につながる構造変化を阻止することは大切である．

タンパク質のポリマー表面への吸着現象に周囲の水が影響しているという仮説を証明するために，ポリマーの含水率及び自由水含率とタンパク質吸着量との関係を明らかにした[7]．ポリマーの自由水含率の増加に伴い明らかにタンパク質吸着量が低下する傾

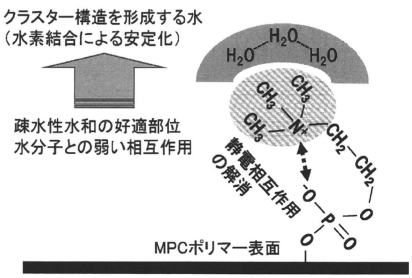

Fig. 2 Hydration state on MPC polymer surface.

向となった．特に，70%以上が自由水で占められているMPCポリマーの表面ではタンパク質吸着量が単分子吸着層形成までも至っていないことが認められた．最近，ポリマーブラシ構造を持つ表面に対するタンパク質の吸着力を直接計測したところ，MPCポリマーでは0.2 nNと，通常の表面（3.0 nN）に比較して極めて低いことが示された[8]．さらに吸着したタンパク質の構造変化について検討したところ，MPCポリマー表面ではほとんど変化が起こらないことが明らかとなった．

北野らは様々なポリマーを溶解した水溶液中の水の構造についてラマン分光法を利用して解析した[9]．その結果，疎水性基の周囲に形成される疎水性水和により水分子間の水素結合を促進する場合と，液体中に形成される水分子のネットワーク構造中にはまり込んで水の構造を維持する2種類のポリマーが比較的水の構造を保持するとされた．MPCユニットを考えてみると，PC基に存在する正負電荷は分子内で塩を形成する（ζ-電位は-0.4 mVとほぼゼロで電荷は中性である）（Fig. 2）．原子がちょうど正負電荷間で6個配列され，6員環を形成することになり，安定化される．この際にアンモニウム基に結合している3個のメチル基が水相側に配向する．ここに疎水性水和構造が形成される．したがって，MPCユニット近傍の水分子は，水分子間での水素結合が優位になりクラスター構造をとると考えられる．これはバルク水中で水分子が形成する構造と同じであるため，ポリマーと相互作用しているにもかかわらず，比較的自由水に近い構造で存在している．この水は比較的大きな運動性を持ち動的平衡状態をとる．この点が同様な親水性ポリマーであるポリエチレンオキシド（PEO）と決定的に異なる点である．PEOの場合は主鎖に存在する酸素原子に水分子が強く水素結合し，結合水として存在する．事実，無機塩をポリマー濃厚溶液に添加し，加熱した場合，PEOではポリマーが沈殿する．これは添加した塩のイオン性水和能がPEOと水分子との水素結合能を上回ることによる現象である．一方，MPCポリマーでは全く溶解性に影響を受けない．したがって，MPCポリマーの溶解には結合水のように強く相互作用する水は必要ないものと考えられる．これらのことは，タンパク質との疎水性や静電的な相互作用が弱いことを示しており，MPCポリマーのタンパク質吸着抑制効果が理解できる．

3. 細胞膜模倣表面を持つポリマーナノ粒子

MPCポリマーを利用して粒子を作製すると，非特異的な細胞応答を阻止できる．そこで，水溶性で両親媒性のMPCポリマーを設計し，これを乳化剤，表面処理剤としてポリマー粒子を作製した．粒子の直径は，MPCポリマー溶液の濃度により制御できる．表面には親水性のMPCユニットが存在し，水媒体に対する分散安定性も良好で，室温下においても数ヶ月間は沈殿することはない．さらに，活性エステルである*p*-ニトロフェニルエステル基を有するMPCポリマー（PMBN）は，表面に酵素，抗体などのタンパク質やDNAなどの特異的な分子認識機能を有するバイオ分子を，活性を低下させない温和な条件で反応，固定化できる[10]．このポリマーを水に溶解し，ここに核となるポリ乳酸（PLA）やポリスチレン（PSt）を水に混和しない低沸点有機溶媒（塩化メチレンなど）に溶解した溶液を混合し，超音波照射により分散乳化する．この分散液を減圧下にて加温することで有機溶媒を揮散させると，ポリマー粒子の分散液が生成する．MPCポリマーナノ粒子（PMBN/PLA-NP）は高い水分散安定性，血清タンパク質の非特異的吸着抑制能，表面に固定化された抗体の活性保持機能を持ち，これらの特性を最大限に生かすことで標的タンパク質を高選択性かつ高S/N比で回収できることがわかった．したがって，PMBN/PLA-NPはバイオアフィニティーナノ粒子として優れた適性を備えている．

また，PMBN/PLA-NP表面に固定化した抗体の活性が典型的な疎水性表面を有するPStナノ粒子上に固定した抗体の活性に比べると，結合定数から見積もった抗原／抗体複合体の安定性がオーダーにして2桁高く，この値は生体内における抗原／抗体複合体の形成定数と同程度であることが明らかとなった[11]．このような現象がナノ粒子上で起こることはこれまでに報告されておらず，これはMPCポリマーの効果

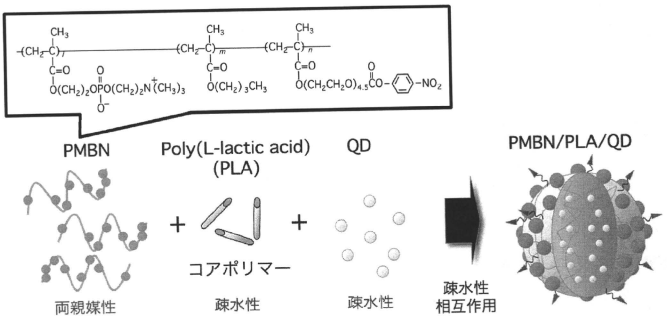

Fig. 3　Structure of polymer nanoparticles including QD.

であると考えられる．一方，従来のPStナノ粒子を利用した免疫分析では，抗体の活性低下により分析精度が低下している可能性を示唆している．MPCポリマーを利用して作製された人工細胞膜表面では，媒体中のタンパク質の非特異的吸着を抑制し，かつ表面に固定化したタンパク質が活性を損なうことなく本来の機能を発現し得ることがわかる．すなわち，高感度バイオ分析を行う上で最適なプラットフォームを提供でき，バイオ工学や臨床検査・診断など様々な用途において高い潜在性を持つ．

4. 蛍光イメージング機能を搭載したポリマーナノ粒子

MPCポリマーナノ粒子であるPMBN/PLA–NPは表面に最適なバイオ分子を結合させることで，バイオアフィニティーを発現できることが明らかとなった．さらなる機能化を試み，ポリマー粒子の内部に磁性ナノ粒子や量子ドット（QD）を導入することで，新たなナノバイオデバイスの構築が可能と考えた．

半導体のナノ結晶であるQDはその魅力的な蛍光特性から，バイオイメージングツールとして期待されている．しかしながら，QD（ここでは疎水性のリガンドであるトリオクチルホスフィン（TOPO）で表面を修飾されたZnS CdSe–core QDを指すものとする）はそのままでは有機溶媒にしか分散できないため，バイオ環境で使用するためには表面処理が必要である．チオール基とZnSが結合を形成することを利用してTOPOと交換する手法が考案された[12]．しかし，この方法ではQDの安定性維持に問題があり，QDが崩壊して蛍光強度が著しく減少したり，強い細胞毒性を示したりする．続いて，両親媒性分子によるカプセル化が考案された．カプセル物質としてPEO鎖を有するブロックポリマーが最も有望視されている[13]．実際に市販されているものはこのタイプのQDである．しかし，修飾用PEOの合成に手間がかかることや，PEOであるためサイズが大きくなる（30 nm），バイオ分子固定化のため官能基を導入すると著しく毒性が発現するといった問題がある．

そこで，PMBN及びPLAを用いて，QD内包ポリマーナノ粒子を調製した（PMBN/PLA/QD）[14]（Fig. 3）．動的光散乱（DLS）測定より得られたPMBN/PLA/QDの流体力学的サイズは約20 nmであり，その粒径分布は十分小さい．またAFM観察結果よりPMBN/ PLA/QDは球状の20 nmナノ粒子であることがわかり，そのサイズはDLS測定の結果とほぼ一致している．さらにTEM観察からナノ粒子一つあたりに6～8個のQDが内包されていることが明らかとなった．PMBN/PLA/QD表面はPC基で覆われ，水およびリン酸緩衝液中で優れた分散性を示した．PMBN/ PLA/QDの吸収及び蛍光スペクトルはトルエン中に分散している未処理のQDのそれとほぼ同じである．また，1年間以上4 ℃で保存したPMBN/PLA/QDの分散性及び蛍光強度はほぼ変化がない．さらにバイオ分野で用いられるpH域では蛍光強度が減少することなく非常に安定である．QDの特徴の一つである，蛍光寿命においても有機色素であるフルオレセイン（FITC）と比較すると，FITCでは経時的に蛍光強度が減衰するが，PMBN/PLA/QDでは6時間以上も初期値の95%以上の蛍光強度が観察され，極めて安定であることがわかった．

細胞に対するバイオ分子の機能解明を妨げている最大の原因の一つに，分析用のプローブ（蛍光タンパク質や蛍光ナノ粒子）の非選択的な細胞取り込み

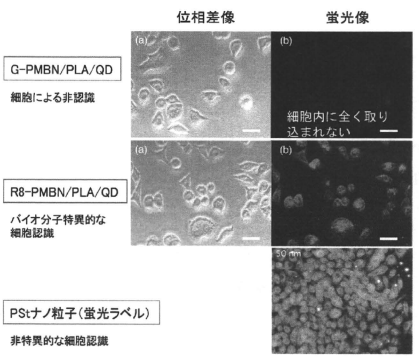

Fig. 4 Cellular uptake of polymer nanoparticles including QD.

が挙げられる．バイオ分子の正確な情報はしばしば非選択的な細胞取り込みによって発生したアーティファクトにより曖昧となる．したがって，非選択的な細胞取り込みに対して耐性を持ち，非侵襲的なイメージング技術により継続的に追跡可能な生体親和型プローブが望まれる．*in vitro* にてPMBN/PLA/QDの細胞取り込みを検討した．PMBN/PLA/QD表面の活性エステル基が培地中の血清タンパク質と結合することを防ぐために，予め表面の活性エステル基にグリシン（G）を反応させた（G–PMBN/PLA/QD）．ポリマー粒子をHeLa細胞の培地中に添加し，その取り込みを観察した．対照とした直径50 nmの蛍光標識PStナノ粒子をHeLa細胞と24時間インキュベートした結果，HeLa細胞内に粒子の取り込みが観察された（Fig. 4下：非特異的な細胞認識）．一方，G–PMBN/PLA/QDでは細胞内に全く取り込まれていない（Fig. 4上：細胞による非認識）．PMBN/PLA/QDが非特異的な細胞取り込みを完全に回避することは驚くべきものである．このように細胞取り込みの完全回避はリン脂質分子による修飾例を除いて報告されていない[15]．また，PMBN/PLA/QDはマクロファージ前駆細胞であるJ774.1細胞の細胞取り込みも回避しており，すなわちファゴサイトシスも起こさないことを意味している．

PMBN/PLA/QDのバイオイメージングプローブとしての特性を調べるため，バイオ分子のモデルとして合成膜透過ペプチドとして知られるオクタアルギニン（R8）を固定し，その膜透過機能を検討した．HIVウィルス（HIV–1）が持つTatタンパク質の48～60配列のペプチドが細胞膜透過性を有している．これらのペプチドは膜透過ペプチドと呼ばれ，難細胞膜透過性の細胞外由来タンパク質の細胞内輸送に役立つと期待されている．近年，Tat–（48–60）（GRKKRRQRRRPPQ）中に多くのアルギニンが含まれることに着目し，人工的に合成されたR8の細胞膜透過性が発見された．R8はマクロピノサイトシス機構により細胞内に取り込まれることが明らかとなっている．

PMBN/PLA/QDにR8を反応させた粒子（R8–PMBN/PLA/QD）とインキュベートしたHeLa細胞を蛍光観察した結果，R8–PMBN/PLA/QDはHeLa細胞内に遍在していた（Fig. 4中：バイオ分子特異的な細胞認識）．この結果より，G–PMBN/PLA/QDでは全く細胞に取り込まれないのにもかかわらず，R8のような膜透過ペプチドを固定するとその機能を発現した．これよりPMBN/PLA/QDはバイオ分子の機能のみを正しく評価できるプローブとしての機能を有していることが示された．

細胞取り込みを速度論的に定量解析できることはイメージングプローブとしても欠かせない能力のひとつである．G–PMBN/PLA/QDはインキュベーション時間経過によらず全く細胞に取り込まれない．一方，R8に誘起された細胞取り込みはPMBN/PLA/QDは添加後15分間以内に始まっており，その後緩やかになり，1時間で飽和に達することがわかった．このことからもPMBN/PLA/QDが生体分子機能を動的に評価できるといえる．共焦点レーザー顕微鏡によりナノ粒子の細胞内動態を解析した結果，添加して5分間以内に細胞膜表面に接着し，15分間から30分間以内にエンドソーム内に取り込まれ，エンドソーム内に取り込まれるR8–PMBN/PLA/QDの量が1時間から3時間で増加し，最終的に5時間でR8–PMBN/PLA/QDが全てエンドソーム内に取り込まれる様子が観察された．さらに，共焦点顕微鏡により励起光を照射し続けて，R8–PMBN/PLA/QDが細胞に取り込まれる様子を同一視野内の細胞で調べた．PMBN/PLA/QDは蛍光強度が減少することなく，R8によりエンドソーム内に取り込まれる様子を継続的に観察することが可能であった．低温での細胞への取り込みの検討や阻害剤を添加した際の取り込みの検討から，R8–PMBN/PLA/QDの取り込みはclathrin依存エンドサイトシスではなく，マクロピノサイトシスであることが明らかとなった．

PMBN/PLA/QD表面に結合させるオリゴペプチドが細胞取り込みに与える効果を調べると，カチオン性のアミノ酸残基が効果的であり，一方，その他のオリゴペプチドを結合してもPMBN/PLA/QDが細胞内に取り込まれないことがわかった．

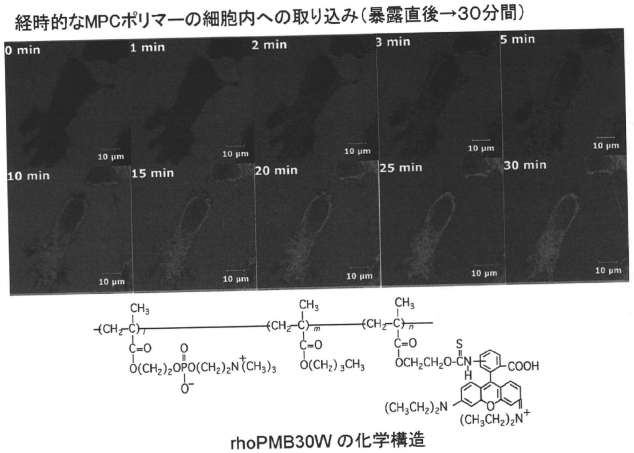

Fig. 5　Time course of cellular uptake of water–soluble amphiphilic MPC polymer having pendant rodamine 6G group.

5. 細胞内に拡散する細胞膜模倣ポリマーマテリアル

特異的なリガンドを持たないPMBN/PLA/QDは細胞に対して認識されない．このナノ粒子と細胞との相互作用を検討する上で，水溶性両親媒性MPCポリマー（溶解状態）と細胞との相互作用の情報は極めて重要である．そこで，Poly(MPC–*co*–BMA)（PMB）系に微量の蛍光色素を側鎖に有する（2－メタクリロイルオキシエチルチオカルバモイルローダミンB（MTR））を組み込んだポリマー（rhoPMB 30W）を合成した[16]．rhoPMB30Wを細胞と共培養したところ，経時的に細胞質内の蛍光強度の増加が観察できた（Fig. 5）．その後，洗浄し，培地に置き換え48時間培養したところ，細胞質内から抜け出ていることが確認された．また，ミトコンドリアマーカーを用いて，rhoPMB30Wとの共局在性を調べてみた結果，rhoPMB30Wはミトコンドリアに集積していることが明らかになった．rhoPMB30Wは曝露後わずか数分間以内に細胞内に侵入していることがわかる．通常エンドサイトシスは早くても細胞内侵入まで30分間から1時間は要すること，細胞内からの逆移行が観察されたことから，rhoPMB30Wの細胞内への移行は分子拡散によると推測される．これまで両親媒性分子で表面を修飾した金ナノ粒子のエネルギー非依存型細胞膜透過（拡散機構）についての報告がなされているが[17]，合成ポリマーでの報告例は全くない．PMB30Wで認められた細胞膜内への可逆的分子拡散は，極めて特異的な現象である．さらに，PMB30Wを溶解材として難水溶性薬物であるパクリタキセルを可溶化した製剤を体内に投入すると，組織への拡散性が高まり，血管から離れた部位まで到達することが認められた．これもPMB30Wの細胞移行の効果によると考えられる[18]．

PMB30Wの分子拡散機序については明確ではないが，以下のように推測できる．両親媒性のMPCポリマーは，MPCユニットにより親水性の外殻を形成するような分子会合体を形成し，細胞膜表面近傍に接触する．この会合体は約20 nmでありPMBN/PLA/QDと同程度である．次いで，疎水性のBMAユニットが外側に配向するように，会合体の構造が変化し細胞膜内の疎水部位を拡散し，さらに内水相で再び構造変化を起こすと考えられる．この構造変化が高分子量のポリマーを細胞膜透過させる役割を担っている．ポリマー粒子のように，コアとなる疎水性ポリマーがポリマー分子の運動性を抑制する場合には，そのままでは拡散することができない．細胞質内でのポリマーの指向性は，結合させる蛍光ユニットの構造に依存していた．

新しい機序による細胞内への分子拡散は，細胞へのバイオ分子の選択導入や，細胞内からのシグナル伝達部位の確定など，細胞内デバイスとして応用可能と考えられる．MPCポリマーは細胞障害性もなく，

この応用には好適である.

6. おわりに

細胞膜模倣ポリマーマテリアルであるMPCポリマーは,医療デバイスの表面処理として実用化され多くの臨床実績がある.この特異的な性質を新たにナノバイオ分野に展開することで,細胞内イメージング,細胞内輸送などを実現できるデバイス創製が可能である.組織再生医療,分子診断・治療,新規創薬など先端バイオ分野の革新的発展に貢献できれば幸いである.

文 献

1) 石原一彦:「ポリマーバイオマテリアル−先端医療のための分子設計−」,コロナ社 (2009)
2) Ishihara K, Ueda T, Nakabayashi N : *Polym. J.*, **22**, 355 (1990)
3) 石原一彦:高分子, **58**(4), 199 (2009)
4) Sugiyama K, Aoki H : *Polym. J.*, **26**, 561 (1994)
5) Lewis AL : *Colloid Surf. B Biointerfaces*, **18**, 261 (2000)
6) Lu DR, Lee SJ, Park K : *J. Biomater. Sci. Polymer Edn*, **3**, 127 (1991)
7) Ishihara K, Nomura H, Mihara T, Kurita K, Iwasaki Y, Nakabayashi N : *J. Biomed. Mater. Res.*, **39**, 323 (1998)
8) 井上祐貴, 石原一彦:表面, **47**(11), 388 (2009)
9) 北野博巳, 井出 誠:高分子, **52**(3), 28 (2003)
10) Ishihara K, Takai M : *J. R. Soc. Interfaces*, **6**, S279 (2009)
11) Goto Y, Matsuno R, Konno T, Takai M, Ishihara K : *Biomacromolecules*, **9**, 828 (2008)
12) Chan WCW, Nie SM : *Science*, **281**, 2016 (1998)
13) Dubertret B, Skourides P, Norris DJ, Noireaux V, Brivanlou AH, Libchanber A : *Science*, **298**, 1759 (2002)
14) Goto Y, Matsuno R, Konno T, Takai M, Ishihara K : *Biomacromolecules*, **9**, 3252 (2008)
15) Rinne J, Albarran B, Jylhava J, Ihalainen TO, Kankaanpaa P, Hytonen VP, Stayton PS, Kulomaa MS, Vihinen-Ranta M : *BMC Biotechnol.*, **7**, 1 (2007)
16) Goda T, Goto Y, Ishihara K : *Biomaterials*, **31**, 2380 (2010)
17) Verma A, Uzun O, Hu Y, Han H-S, Watson N : *Nat. Mater.*, **7**, 588 (2008)
18) Soma D, Kitayama J, Konno T, Ishihara K, Yamada J, Kamei T, Ishigami H, Kaisaki S, Nagawa H : *Cancer Sci.*, **100**, 1979 (2009)

(Received 1 July 2010;
Accepted 12 July 2010)

著者略歴

石原 一彦(いしはら かずひこ)

1984年3月 早稲田大学大学院理工学研究科博士課程修了(工学博士)
1984年4月 (財)相模中央化学研究所 博士研究員
1987年1月 東京医科歯科大学医用器材研究所 助手
1991年1月 東京医科歯科大学医用器材研究所 助教授
1998年4月 東京大学大学院工学系研究科 助教授
2000年6月 東京大学大学院工学系研究科 教授
現在に至る

井上 祐貴(いのうえ ゆうき)

2005年3月 東京大学大学院工学系研究科マテリアル工学専攻博士課程修了 博士(工学)
2005年4月 京都大学再生医科学研究所 産学官連携研究員
2008年4月 東京大学大学院工学系研究科 特任研究員
2010年4月 東京大学大学院工学系研究科 助教(マテリアル工学専攻)
現在に至る

松野 亮介(まつの りょうすけ)

2006年3月 九州大学大学院工学府物質創造工学専攻博士後期課程修了 博士(工学)
2006年4月 東京大学ナノバイオ・インテグレーション研究拠点 特任助手
2007年4月 東京大学ナノバイオ・インテグレーション研究拠点 特任助教
2010年4月 東京大学大学院工学系研究科 特任研究員
現在に至る

生体の構造・機能模倣がもたらす長寿命人工関節

京　本　政　之*

JJSB

Bio-mimicking, structure and function confer high durability to joint replacement

Joint replacement is an effective treatment for patients with severe arthritis whose number has been increasing due to the expansion of the elderly population. As a result, the quality (durability) of all artificial joints is becoming increasingly important. Therefore, I can see that the durable and natural joint-like artificial joint replacements i.e., MPC-grafted cross-linked polyethylene bearing material will be necessary for all next generation artificial joints. The suggested approaches for bio-mimicking are surely novel in the field of orthopaedic biomaterials science. I think that the important research goal for future prospects is a creation of ultimate artificial joint interface mimicking the natural joint cartilage.

高齢化が進む現在，人工関節の果たす役割は大きく，その長寿命化が期待されている．その寿命を制限する人工関節の弛みを阻止し，完全に再置換術をなくすバイオマテリアルの方向性についてまとめた．MPC処理架橋ポリエチレンは，ポリエチレン摩耗粉の発生を抑制することで，人工関節の弛みを阻止する次世代の人工関節用バイオマテリアルとして非常に期待されているが，その生体の機能模倣という研究展開は今後より重要になってくると考えられる．

*Masayuki Kyomoto**

Key words：人工関節，摺動材料，長寿命

"50 active years after 50: increasing the quality of our second half-century" とは，昨年，イギリスでの人工関節への取組みについてBBC放送より紹介されたキャッチフレーズである．外傷や疾患により関節がその機能を発揮できなくなったとき，具合がわるくなった関節を切除し，人工の関節をその代替として手術する人工関節置換術は患者の痛みをとり除く治療としてすでに確立している．人工関節の耐用年数(寿命)は患者の状態にもよるが約15～20年といわれており，人工関節置換術を受けた患者は人工関節の入れ換え(再置換術)の潜在的な対象である．

再置換術は，患者やその家族に大きな負担を強いることになるため，従来，60歳以上の比較的高齢の患者を対象としてきた．しかし，最近では患者の価値観や生活の質が尊重されるようになり，50歳代でも，より快適な生活をおくるための一手段として人工関節置換術を選択する患者も少なくない．冒頭の"50 active years after 50"はこの流れを汲んだものであり，活動性が高く充実した生活を実現するための人工関節の果たす役割は大きく，その長寿命化が期待されている．

一般に，ポリエチレン(PE)と金属またはセラミックスを組み合わせた摺動システムが，人工関節の関節運動を担っている．しかし，PEの摩耗粉が引き起こすインプラント周囲の骨吸収と弛みは再置換術に至る主因の一つで，人工関節置換術における深刻な問題である．従来，摺動面の組み合わせや素材自体の改良などのさまざまな試みが行われているが，"PE摩耗粉の減少"が主題の研究開発は引きつづき望まれると考えられる．筆者らは，2-メタクリロイルオキシエチルホスホリルコリン(MPC)ポリマーを架橋PE(CLPE)表面にナノグラフト処理した革新的な人工関節用(PMPC処理CLPE)カップを開発した．

細胞膜を構成するリン脂質分子に着目し分子設計

* Research Department, Japan Medical Materials Corporation　日本メディカルマテリアル株式会社研究部
[略歴]　2001年 奈良先端科学技術大学院大学物質創成科学研究科博士前期課程修了．同年 京セラ株式会社バイオセラム事業部入社．2004年 日本メディカルマテリアル株式会社研究部出向．2005年 東京大学大学院工学系研究科　共同研究員．2007年 日本メディカルマテリアル株式会社研究部転籍．2008年 東京大学大学院医学系研究科客員研究員．2009年 博士(工学)(東京大学)現在に至る．専門：生体材料工学．趣味：テニス，ドライブ

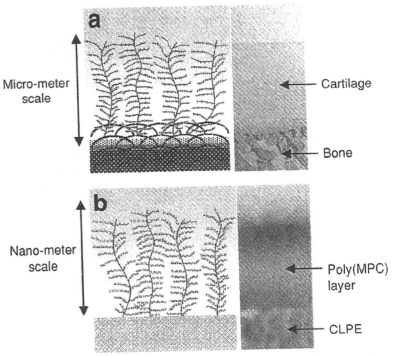

図1 Schematic models and microscopic images of poly (MPC)(PMPC)-grafted CLPE surface mimicking cartilage
a：Cartilage．b：PMPC-grafted CLPE

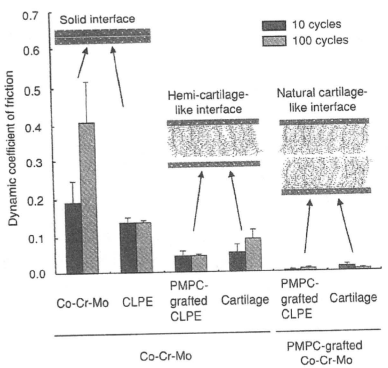

図2 Dynamic coefficient of friction for the various interface: solid, hemi-cartilage-like, and natural cartilage-like interfaces
（Kyomoto M et al., 2009[1]より一部改変）

された MPC を用いて基材表面を処理すると，容易に人工細胞膜構造を構築できる．この表面はすぐれた生体親和性，抗血栓性を発揮するとともに，親水性であることから水の薄膜層を形成する．生体関節軟骨表面にはナノスケールのリン脂質層が存在し，この層が関節面の保護と潤滑作用に寄与していることが知られている．すなわち，MPC ポリマーの導入にて CLPE 表面にナノスケールのリン脂質層の構築が可能となる PMPC 処理 CLPE 表面の構造および作用メカニズムは，生体関節軟骨表面のそれらを模倣していると考えられる（図1）．PMPC 処理 CLPE は，PE 摩耗粉の発生の抑制により，人工関節の弛みを阻止する次世代の人工関節用バイオマテリアルとして非常に期待されており，その生体の機能模倣という研究展開は，より重要になると考えられる．

また，PMPC 処理 CLPE のように生体関節軟骨“表面”を模倣するだけでなく，生体関節“界面”としての機能を模倣する PMPC 処理 CLPE と PMPC 処理金属の組み合わせ（図2）[1]や，関節液（または体液）中のタンパク質，リン脂質がその界面で果たす機能を積極的に取り入れた人工関節など，バイオマテリアルのみでなくバイオデバイスコンポーネントというトータルパッケージのデザインも，今後の方向性として重要であろう．さらには，生体関節界面の機能模倣にとどまらず，人工関節摺動面での軟骨再生，生体関節そのものの再構築が可能となる人工関節が，きたるべき再生医療へ“つながる”未来型人工関節バイオマテリアルの将来像ではないかと想像する．

現在，PMPC 処理 CLPE だけでなく，材料劣化の抑止を目的としたビタミン E 添加 PE など，世界に先駆けて日本より創製されたバイオマテリアルが，人工関節の長寿命化に大きく貢献しようとしている．人工関節の長寿命化は，高齢化が進むに伴って増えつづける人工関節の再置換術を減らすとともに，これまで手術の適応が困難であった若年患者への治療法の選択肢が広がるなど多くの可能性を有する．

一方，技術の進歩とともに発生する新たな課題に対して，医工，産学官の間の“つながり”を再構築，強化し，その研究開発を緊密に連携させながら進めることが引きつづき必要である．筆者も，領域や技術のつながりを意識し，革新的な技術で人工関節の弛みを阻止し，完全に再置換術をなくす研究を継続し，未来のバイオマテリアルへとつなげていきたい．

文　献

1）Kyomoto M, Moro T, Iwasaki Y, Miyaji F, Kawaguchi H et al.: Superlubricious surface mimicking articular cartilage by grafting poly(2-methacryloyloxyethyl phosphorylcholine) on orthopaedic metal bearings. J Biomed Mater Res A　2009, 91: 730-741.

Clin Orthop Relat Res
DOI 10.1007/s11999-010-1718-5

SYMPOSIUM: UHMWPE FOR ARTHROPLASTY: FROM POWDER TO DEBRIS

Cartilage-mimicking, High-density Brush Structure Improves Wear Resistance of Crosslinked Polyethylene

A Pilot Study

Masayuki Kyomoto PhD, Toru Moro MD, Yoshio Takatori MD, Hiroshi Kawaguchi MD, Kazuhiko Ishihara PhD

Abstract

Background In natural synovial joints under physiologic conditions, fluid thin-film lubrication by a hydrated layer of the cartilage is essential for the smooth motion of the joints. The considerably less efficient lubrication of artificial joints of polyethylene is prone to wear, leading to osteolysis and aseptic loosening and limiting the longevity of THA. A nanometer-scale layer of poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC) with cartilage-mimicking brushlike structures on a crosslinked polyethylene (CLPE) surface may provide hydrophilicity and lubricity resembling the physiologic joint surface.

Questions/purposes We asked whether the photoirradiation time during graft polymerization would affect the density and stability of the PMPC layer and the PMPC-grafted surface would enhance the durability of artificial joints. We investigated the effect of photoirradiation time and the resultant characteristics of the PMPC layer on the durability of the CLPE.

Methods For each of the PMPC-grafted CLPE surfaces with various photoirradiation times (six groups: 0 [untreated CLPE], 11, 23, 45, 90, and 180 minutes), 18 sample pieces (total of 108 samples) were evaluated in surface analyses, and four cups (total of 24 samples) were evaluated in a hip simulator test.

Results The density of the PMPC layer increased with an increase in the photoirradiation time. The hip simulator test confirmed the PMPC-grafted CLPE with a high density of the PMPC layer exhibited minimal wear as compared with the untreated CLPE. High-density PMPC grafting appears essential for maintaining the high wear resistance of the PMPC-grafted CLPE. To obtain a high-density PMPC layer, the photoirradiation time must be greater than 45 minutes.

Conclusions The cartilage-mimicking, density brushlike structure of the PMPC-grafted CLPE could extend high durability to acetabular cups in THA.

Clinical Relevance Our in vitro findings suggest the wear performance of CLPE acetabular cups in THA can be improved by this approach.

One or more of the authors (YT) have received funding from a Health and Welfare Research Grant for Translational Research (H17-005) and Research on Medical Devices for Improving Impaired QOL (H20-004) from the Japanese Ministry of Health, Labour and Welfare. This work was performed at The University of Tokyo, Tokyo, Japan.

M. Kyomoto (✉)
Research Department, Japan Medical Materials Corp, 3-3-31, Miyahara, Yodogawa-ku, Osaka 532-0003, Japan
e-mail: kyomotom@jmmc.jp

M. Kyomoto, K. Ishihara
Department of Materials Engineering, The University of Tokyo, Tokyo, Japan

M. Kyomoto, T. Moro, Y. Takatori
Division of Science for Joint Reconstruction, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

T. Moro, Y. Takatori, H. Kawaguchi
Sensory & Motor System Medicine, Faculty of Medicine, The University of Tokyo, Tokyo, Japan

Published online: 04 December 2010

Introduction

The number of artificial hips used for primary and revised hip arthroplasty is increasing every year worldwide [20]. Thus, durability of artificial hips has become increasingly important. The most commonly used artificial hip system is a bearing couple composed of polyethylene (PE) and a cobalt-chromium-molybdenum (Co-Cr-Mo) alloy. However,