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RESEARCH PAPER

Strong influence of dietary intake and physical activity on body fatness in elderly Japanese men: age-associated loss of polygenic resistance against obesity

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Abstract Genome-wide association studies identified single nucleotide polymorphisms (SNPs) associated with body mass index (BMI) in middle-aged populations; however, it is unclear whether these SNPs are associated with body fatness in elderly people. We examined the association between genetic risk score (GRS) from BMI-associated SNPs and body fatness in elderly Japanese men. We also examined the contribution of GRS, dietary macronutrient intake, and physical activity to body fatness by different age groups. GRS was calculated from 10 BMI-associated SNPs in 84 middle-aged (30–64 years) and 97 elderly (65–79 years) Japanese men; subjects were divided into low, middle, and high GRS groups. Dietary macronutrient intake was assessed using a questionnaire, and physical activity was evaluated using both a questionnaire and an accelerometer. The middle-aged individuals with a high GRS had greater BMI; waist circumference; and total abdominal fat, visceral fat, and subcutaneous fat areas than the middle-aged individuals with low GRS, whereas the indicators were not different between the GRS groups in elderly individuals. Multiple linear regression analysis showed that GRS was the strongest predictor of BMI, total abdominal fat, and visceral fat in the middle-aged group, whereas fat, alcohol, and protein intakes or vigorous-intensity physical activity were more strongly associated with these indicators than was GRS in the elderly group. These results suggest that GRS from BMI-associated SNPs is not predictive of body fatness in elderly Japanese men. The stronger contribution of dietary macronutrient intake and physical activity to body fatness may attenuate the genetic predisposition in elderly men.

Keywords Body fatness · Aging · SNP · Genetic risk score · Dietary macronutrient intake · Physical activity

Introduction

The prevalence of obesity in elderly populations is increasing worldwide, including in Asian countries (Popkin and Doak 1998). Obesity and abdominal adiposity increases the risk of cardiometabolic diseases, sarcopenic obesity, and functional disability even in the elderly Asian individuals who generally have a lower body mass index (BMI) than European people (Kim et al. 2009; Ochi et al. 2010; WHO Expert Consultation 2004). Therefore, identifying the determinants of obesity in elderly Asian individuals is important to prevent obesity and to reduce the burden of health care in a rapidly aging society in Asia.

Genetic variation is an important determinant of susceptibility to obesity. Recent genome-wide association studies (GWASs) identified single nucleotide polymorphisms (SNPs) at several genetic loci that are associated with BMI in European and Asian populations (Thorleifsson et al. 2009;

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Wen et al. 2012; Willer et al. 2009). Several studies calculated the genetic risk score (GRS) from the number of risk alleles of GWAS-derived SNPs to examine the polygenic effect of these variants and demonstrated that the GRS is strongly associated with BMI (Cheung et al. 2010; Peterson et al. 2011; Renstrom et al. 2009). However, most of these BMI-associated SNPs were identified in the cohorts consisting of mainly middle-aged individuals; therefore, it is unclear whether these SNPs and GRS are also associated with BMI and indices of adiposity in elderly people.

Interestingly, a recent study reported that the SNPs previously associated with BMI in middle-aged populations and GRS constructed from these variants were not associated with body weight or body fatness in the older European and African-American populations (Murphy et al. 2013). In that study, Murphy et al. further suggested that an increase in body weight from midlife to old age might underlie the weak associations between SNPs and body fatness. However, in contrast to European and African individuals, Asian people generally maintain their body weight from midlife to later life (Funatogawa et al. 2009). Therefore, BMI-associated SNPs identified in middle-aged populations may be associated with BMI and other indicators of body fatness in the elderly Asian populations.

Moreover, not only genetic factors, but also environmental factors including lifestyle, such as dietary intake and physical activity, are associated with obesity (Donnelly et al. 2009; Mozaffarian et al. 2011); however, Murphy et al. did not examine the association of SNPs with body weight in relation to environmental factors. Twin studies demonstrated that the contribution of genetic factors to body weight might decrease with advancing age (Carmichael and Mcgue 1995; Korkeila et al. 1991). Alternatively, environmental factors may have stronger effects on body weight because the genetic influence lessens when people become older. Therefore, it should be examined whether the contribution of environmental factors to body fatness is different between middle-aged and elderly individuals.

In the present study, we calculated GRS on the basis of BMI-associated SNPs previously identified in middle-aged Asian populations. We examined whether GRS is associated with indicators of body fatness in middle-aged and elderly Japanese men, respectively. We also examined whether the contribution of GRS, dietary macronutrient intake, and physical activity to body fatness differ by age groups.

Materials and Methods

Subjects

Eighty-four middle-aged (30–64 years) and 97 elderly (65–79 years) Japanese men participated in this study. All subjects were free from endocrine disorders that might affect their body weight (e.g., Cushing disease, hypothyroidism, hypothyroidism). Subjects also did not take any medications that might affect energy expenditure (e.g., steroids, thyroid hormones). Diabetes status was defined in accordance with World Health Organization criteria (Alberti et al. 1998); 11 subjects (6.1 %) had type 2 diabetes. Current/former smoking status was assessed with a questionnaire. All subjects provided written informed consent before enrollment in the study, which was approved by the Ethical Committee of Waseda University. The study was conducted in accordance with the Declaration of Helsinki.

Anthropometric characteristics

Body weight and body fat percentages (assessed by bioelectrical impedance analysis) were measured using an electronic scale (InnerScan BC-600, Tanita Inc., Tokyo, Japan), whereas height was measured with a stadiometer (YL-65, YAGAMI Inc., Nagoya, Japan). BMI was calculated from measurements of body weight and height. Waist circumference was measured at the umbilical region with an inelastic measuring tape. The total abdominal fat, visceral fat, and subcutaneous fat areas were measured using magnetic resonance imaging (Signa 1.5 T, General Electric Inc., Milwaukee, WI, USA). The imaging conditions included a T1-weighted spin-echo and axial-plane sequence with a slice thickness of 10 mm, a repetition time of 140 ms, and an echo time of 12.3 ms (Usui et al. 2010). Cross-sectional images were scanned at the umbilical region. During the scan, the subjects were asked to hold their breath for approximately 30 s after inhalation to reduce respiratory motion artifacts. The magnetic resonance images were transferred to a personal computer in the Digital Imaging and Communications in Medicine file format, and the cross-sectional area of the visceral fat at the umbilical region was determined using image-analysis software (sliceOmatic 4.3 for Windows, TomoVision, Montreal, Quebec, Canada). To minimize interobserver variation, the same investigator performed all analyses; the coefficient of variation was 0.4 % for the cross-sectional areas of the umbilical region.

Physical activity

Physical activity was measured using a uniaxial accelerometer (Kenz Lifecorder EX, SUZUKEN Co Ltd., Nagoya, Japan). Instructions for the accelerometer were given to the subjects before the test period; they were told to continuously wear it on their belt or waistband at the right midline of the thigh for 10 days, except when sleeping or bathing. Moderate-intensity physical activity (MPA) and vigorous-

intensity physical activity (VPA) were used as the indices of physical activity. On a scale with the points 0, 0.5, and 1–9, the Lifecorder system determined the level of physical activity intensity every 4 s. As described previously (Kumahara et al. 2004), the amount of time spent at intensity levels 4–6 and 7–9 were used as the amount of time spent in MPA and VPA, respectively. We also calculated the time spent in moderate- and vigorous-intensity physical activity (MVPA) from MPA and VPA. Subjects recorded leisure time physical activities performed during 10 days in a questionnaire, because several types of activity such as swimming, cycling, and rowing cannot be assessed by an accelerometer. We calculated self-reported time spent in MPA and VPA based on the metabolic equivalents (METs) of each activity (Ainsworth et al. 2000); MPA was defined as 3.0–5.9 METs and VPA as ≥6.0 METs. When an accelerometer indicated intensity levels 0 or 0.5 at the periods that subjects reported as being engaged in MPA or VPA in the questionnaire, we added the time spent in MPA and VPA to the accelerometer-measured MPA and VPA. Total energy expenditure was also assessed through a combination of an accelerometer and a questionnaire such as a MPA and VPA assessment. Valid physical activity data were obtained from 79 (94.0 %) middle-aged and 94 (96.9 %) elderly subjects and analyzed.

Dietary assessment

Dietary intake was assessed using a brief self-administered diet history questionnaire (BDHQ). The BDHQ is a 4-page questionnaire that yields information on consumption frequency of selected foods to estimate the dietary intake of 58 food and beverage items (Kobayashi et al. 2011). The validity of the nutrient intake data assessed with the BDHQ was confirmed using semi-weighed 16-day dietary records as a reference (Kobayashi et al. 2012). On the basis of the total daily energy intake and dietary macronutrient intake assessed using the BDHQ, we calculated the percentage of energy intake from carbohydrates, fat, protein, and alcohol.

Collection and analysis of blood samples

Blood samples were collected between 8:30 and 11:00 a.m. after a 12-h overnight fast and then centrifuged at 3,000×*g* for 15 min at 4 °C. Serum and plasma were stored at −80 °C until the time of analysis. Concentrations of HDL cholesterol, LDL cholesterol, triglycerides, and fasting glucose were determined using standard enzymatic techniques (BML, Inc., Tokyo, Japan). Glycated hemoglobin (HbA1c) levels were determined using the latex coagulation method (BML, Inc.).

SNP selection

Ten BMI-associated SNPs were selected for this study. All selected SNPs met the following criteria: (1) a significant genome-wide association ($p < 5.0 \times 10^{-8}$) in any GWAS of European-descent populations (Thorleifsson et al. 2009; Willer et al. 2009), (2) a suggestive association ($p < 1.0 \times 10^{-4}$) in the meta-analysis in Asian populations (Wen et al. 2012), and (3) the minor allele frequency (MAF) in the Japanese population was ≥0.05. *SEC16B* rs574367, *TMEM18* rs11127485, *TFAP2B* rs4715210, and *MC4R* rs6567160 were not included in the SNP array in the present study; these were replaced with rs543874, rs2867125, rs987237, and rs10871777, all of which are in strong linkage disequilibrium with the original SNPs, respectively ($D' = 1.0$, $r^2 > 0.7$, in HapMap JPN). All of the SNPs were in Hardy–Weinberg equilibrium ($p > 0.001$) and their MAF was ≥0.05 in our study population (Table 1).

SNP genotyping

Nuclear DNA was extracted from peripheral blood using the QIAamp DNA Mini kit (QIAGEN, Hilden, Germany); DNA quality was evaluated using agarose gel electrophoresis and spectrophotometry. We confirmed that none of the DNA samples was fragmented and that the A260/A280 ratio was 1.8–2.0. SNP genotyping was performed by using the Infinium HumanExome BeadChip version 1.1 (Illumina, Inc., San Diego, CA, USA) according to the manufacturer's protocol. Genotype calling was performed using the GenTrain clustering algorithm (version 1.0) in the GenomeStudio (ver. 2011.1; Illumina, Inc.). Cluster boundaries were determined using the standard cluster files provided by Illumina. The SNP call rate was at least 98.7 % for all samples.

Calculation of GRS

We calculated GRS according to the 10 selected SNPs. We assumed that each SNP acts in an additive manner, and the GRS was calculated using a weighted method (Cheung et al. 2010; Renstrom et al. 2009; Tanisawa et al. 2014). Each SNP was weighted by its effect size per allele on BMI (in percentage of the SD) derived from a meta-analysis in Asian populations (Wen et al. 2012). The weighted scores for each SNP were calculated by multiplying each effect size by the number of corresponding risk alleles. These scores were totaled to obtain a GRS for each subject. We divided subjects into the low, middle, and high GRS groups according to the tertile of a GRS. The range for each GRS group was as follows: low: 10–30; middle: 31–38; and high: 39–67.

Table 1 SNPs selected to calculate GRS

SNP	Gene symbol	Chromosome	Base pair position (GRCh37.p10)	Allele (M/m)	Risk allele	MAF	β*	HWE *p*
rs543874	*SEC16B*	1	177889480	A/G	G	0.22	6.57	0.662
rs2867125	*TMEM18*	2	622827	C/T	C	0.08	5.05	0.614
rs713586	*ADCY3*	2	25158008	T/C	C	0.46	2.94	0.457
rs10938397	*GNPDA2*	4	45182527	A/G	G	0.33	3.71	0.091
rs987237	*TFAP2B*	6	50803050	A/G	G	0.25	3.84	0.847
rs6265	*BDNF*	11	27679916	T/C	C	0.40	4.53	0.537
rs2241423	*MAP2K5*	15	68086838	A/G	G	0.33	3.10	1.000
rs17817449	*FTO*	16	53813367	T/G	G	0.19	8.46	0.144
rs10871777	*MC4R*	18	57851763	A/G	G	0.24	5.64	0.223
rs3810291	*TMEM160*	19	47569003	A/G	A	0.23	3.48	0.003

GRS genetic risk score, *HWE* Hardy–Weinberg equilibrium, *M* major allele, *m* minor allele, *MAF* minor allele frequency, *SNP* single nucleotide polymorphism

* Effect of SNPs per allele on BMI (in percentage of the SD) derived from the meta-analysis (Wen et al. 2012)

Statistical analysis

All statistical analyses were performed with SPSS, version 21.0 (SPSS, Inc., Chicago, IL, USA), or PLINK, version 1.07 (Massachusetts General Hospital, Boston, MA, USA). The allelic frequencies of the selected SNPs were calculated using a gene-counting method, and the Hardy–Weinberg equilibrium and linkage disequilibrium for each SNP were assessed by the Chi-square test. Student's *t* test (for normally distributed variables), Mann–Whitney *U* test (for non-normally distributed variables), or the Chi-square test (for categorical variables) was used to evaluate the differences between the middle-aged and elderly groups. The differences in the indicators of body fatness among age groups and GRS groups were assessed by two-way analysis of covariance (ANCOVA) adjusted for age, current/former smoking status, and type 2 diabetes. A post hoc test with Bonferroni correction was used to identify significant differences among mean values if a significant main effect or interaction was identified. Multiple linear regression analysis was performed to examine the associations of GRS, dietary macronutrient intake, and physical activity with indicators of body fatness in the middle-aged and elderly groups, respectively. All measurements and calculated values are presented as mean ± SD (for normally distributed variables) or medians (interquartile range) (for non-normally distributed variables). The level of significance was set at $p < 0.05$.

Results

Subject characteristics

The characteristics of the study subjects are shown in Table 2. Height, body weight, and total energy expenditure were lower in the elderly group than in the middle-aged group ($p < 0.05$). Fasting glucose and HbA1c levels were higher in the elderly group than in the middle-aged group ($p < 0.05$).

Association among age groups, GRS groups, and indicators of body fatness

We compared the indicators of body fatness among different age groups and GRS groups. Two-way ANCOVA adjusted for age, current/former smoking status, and type 2 diabetes detected a significant interaction effect between age groups and GRS groups on body weight, BMI, waist circumference, total abdominal fat, visceral fat, and subcutaneous fat. BMI and waist circumference were significantly higher in the high and middle GRS groups than in the low GRS group only among the middle-aged group (Fig. 1a; Table 3, $p < 0.05$), whereas no significant difference was observed in BMI and waist circumference among different GRS groups in the elderly group. Furthermore, the middle-aged individuals with a high GRS had higher body weight, total abdominal fat, visceral fat, and subcutaneous fat than middle-aged individuals with a low GRS (Fig. 1b; Table 3, $p < 0.05$); however, these values were not different between the GRS group in the elderly group.

Contribution of GRS, physical activity, and dietary macronutrient intake to body fatness in middle-aged and elderly men

Because the relationship of GRS groups with indicators of body fatness differed by age groups, we performed multiple linear regression analysis to examine the strength of contributions of GRS, physical activity, and dietary macronutrient intake to body fatness in the middle-aged and elderly groups (Table 4). We selected GRS, VPA, fat intake, protein intake, and alcohol intake as independent variables, and BMI, total abdominal fat, and visceral fat as dependent variables. When we entered carbohydrate

Table 2 Characteristics of the subjects ($n = 181$)

	Middle-aged	Elderly	p^*
n	84	97	
Age (year)	53.4 ± 11.4	70.0 ± 3.9	**<0.001**
Height (cm)	171.1 ± 5.8	168.5 ± 7.1	**0.007**
Body weight (kg)	70.2 ± 9.5	66.7 ± 9.0	**0.012**
BMI (kg/m^2)	23.9 ± 2.7	23.4 ± 2.3	0.172
Body fat (%)	20.0 ± 4.8	21.0 ± 4.3	0.145
Waist circumference (cm)	84.0 ± 8.2	85.1 ± 6.7	0.325
Total abdominal fat (cm^2)	223.2 ± 93.0	230.0 ± 73.6	0.592
Visceral fat (cm^2)	106.0 ± 49.4	116.9 ± 47.6	0.131
Subcutaneous fat (cm^2)	117.2 ± 54.6	113.1 ± 39.5	0.561
HDL cholesterol (mg/dL)	57.0 (50.0–68.0)	61.0 (51.3–68.0)	0.376
LDL cholesterol (mg/dL)	121.5 ± 30	122.7 ± 28.3	0.784
Triglycerides (mg/dL)	95.0 (67.0–127.0)	83.5 (65.0–116.0)	0.253
Fasting glucose (mg/dL)	95.0 (88.0–101.0)	98.0 (93.0–105.0)	**0.002**
HbA1c (%)	4.9 (4.8–5.0)	4.9 (5.0–5.2)	**0.006**
Total energy expenditure (kcal/day)†	2342 ± 244	2121 ± 263	**<0.001**
MPA (min/day)†	40.0 (27.0–55.0)	41.0 (21.5–55.0)	0.786
VPA (min/day)†	6.0 (1.0–13.0)	2.0 (0.0–11.0)	0.081
MVPA (min/day)†	51.0 (34.0–68.0)	50.5 (27.8–68.3)	0.778
Total energy intake (kcal/day)	2150 ± 653	2213 ± 627	0.509
Carbohydrate intake (% energy)	51.0 ± 7.7	50.9 ± 8.4	0.870
Fat intake (% energy)	25.6 ± 5.1	24.6 ± 5.6	0.204
Protein intake (% energy)	15.1 ± 2.7	15.0 ± 2.6	0.956
Alcohol intake (% energy)	5.7 (2.3–13.7)	7.8 (2.4–13.4)	0.583
Current/former smoking status (%)	42.9	51.5	0.243
Type 2 diabetes (%)	2.4	9.3	0.053

Data are mean ± SD or median (interquartile range) values. Data were analyzed using Student's *t* test (for normally distributed variables), Mann–Whitney *U* test (for non-normally distributed variables), or Chi-square test (for categorical variables)

BMI body mass index, *HbA1c* glycated hemoglobin, *MPA* moderate-intensity physical activity, *MVPA* moderate- and vigorous-intensity physical activity, *VPA* vigorous-intensity physical activity

Boldface indicates significance ($p < 0.05$)

* Middle-aged vs. elderly

† Middle-aged: $n = 79$; elderly: $n = 94$

intake, fat intake, and alcohol intake into the models simultaneously, the variance inflation factors exceeded 10; therefore, we excluded carbohydrate intake from the models. In the middle-aged group, GRS was the strongest predictor of BMI ($p < 0.001$), total abdominal fat ($p = 0.001$), and visceral fat ($p = 0.003$). On the other hand, other dietary macronutrient intake and VPA were not associated with any indicators of body fatness, although alcohol intake was associated with visceral fat ($p = 0.024$). In contrast to the middle-aged group, high fat intake was the strongest predictor of increased BMI ($p = 0.037$), total abdominal fat ($p = 0.001$), and visceral fat ($p < 0.001$) in the elderly group; however, GRS was not associated with any indicators. Additionally, both low VPA and high alcohol intake were associated with increased total abdominal fat and visceral fat ($p < 0.05$, respectively); low protein intake was also associated with increased visceral fat ($p = 0.037$). We also entered MVPA into the models instead of VPA; however, MVPA was not associated with indicators of body fatness in either the middle-aged or the elderly group.

Discussion

The main finding of the present study is that GRS from BMI-associated SNPs previously identified in the middle-aged populations is not associated with any indicator of body fatness in elderly Japanese men, even though it is a strong predictor of body fatness in middle-aged Japanese men. We also demonstrated that the strength of the contributions of dietary macronutrient intake and physical activity to body fatness differed by the age group, which may explain in part the dissociation of the genetic influence on body fatness in the elderly individuals.

In accordance with our finding, a study recently reported that the SNPs previously associated with BMI in the middle-aged populations were not associated with body weight and adiposity in older European and African-American populations (Murphy et al. 2013). In the subjects participating in the longitudinal study, an average weight gain from midlife to old age was about 5 %, and only one-third of the subjects maintained body weight within 5 % (Murphy et al. 2013). It was also reported that age-related

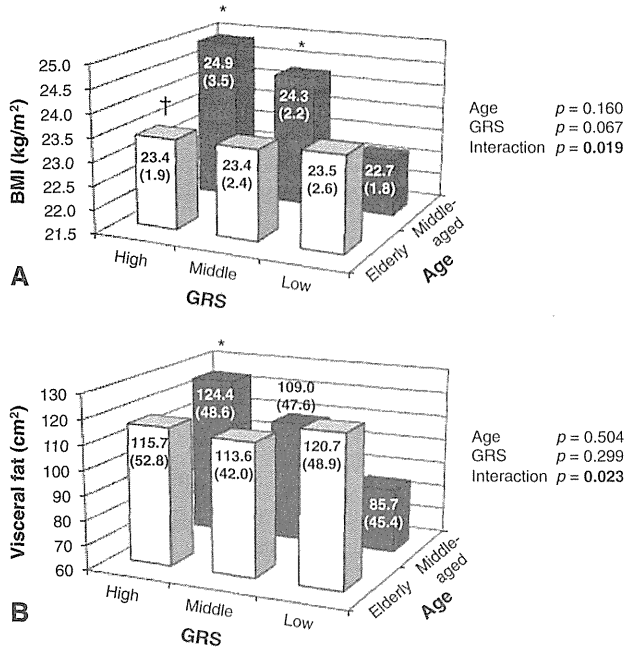

Fig. 1 BMI (**a**) and Visceral fat (**b**) among age groups and GRS groups. Data are presented as mean (SD) values. Data were analyzed using two-way ANCOVA adjusted for age, current/former smoking status, and type 2 diabetes. *$p < 0.05$ versus the low GRS group within the same age group. †$p < 0.05$ versus the middle-aged group within the same GRS group. *Boldface* indicates significance ($p < 0.05$). *BMI* body mass index, *GRS* genetic risk score

body composition and fat distribution changes occur even in weight-stable elderly individuals (Zamboni et al. 2003). These age-related anthropometric changes were suggested to account for the dissociation between BMI-associated SNPs with adiposity in elderly individuals. However, the indicators of body fatness including BMI, body fat percentage, waist circumference, total abdominal fat, visceral fat, and subcutaneous fat were not statistically different between the middle-aged and elderly Japanese individuals in the present study. This suggests that null associations of BMI-associated SNPs with indicators of body fatness may not be explained by changes in body weight and body composition from midlife to old age and are likely common phenomena among various ethnic populations.

Our data have demonstrated that dietary macronutrient intake and physical activity are more strongly associated with body fatness in the elderly than in the middle-aged, suggesting that the relative contributions of genetic and environmental factors to body fatness differ by age groups. Among the dietary factors, fat intake was the most robustly associated with BMI, total abdominal fat, and visceral fat in elderly individuals. Many studies reported that the percentage of energy intake from fat is strongly associated with obesity in Western countries (Bray and Popkin 1998; Dreon et al. 1988). In contrast, no relationship between fat intake and BMI was observed in young Japanese women or

Table 3 Association among age groups, GRS groups, and indicators of body fatness ($n = 181$)

Age group	Middle-aged (30–64 years)			Elderly (65–79 years)			Age	GRS	Interaction
GRS	Low	Middle	High	Low	Middle	High	*p*	*p*	*p*
n	30	25	29	37	31	29			
Age (year)	52.5 ± 11.8	54.0 ± 11.9	53.7 ± 10.8	69.0 ± 3.5	70.0 ± 3.9	71.3 ± 3.9	**<0.001**	0.473	0.881
Body weight (kg)	66.3 ± 5.9	72.0 ± 8.3	72.7 ± 12.2*	67.4 ± 9.7	65.4 ± 8.2	67.1 ± 9.1	0.282	0.152	**0.047**
BMI (kg/m²)	22.7 ± 1.8	24.3 ± 2.2*	24.9 ± 3.5*	23.5 ± 2.6	23.4 ± 2.4	23.4 ± 1.9†	0.160	0.067	**0.019**
Body fat (%)	18.5 ± 4.2	20.4 ± 4.8	21.1 ± 5.1	21.5 ± 4.9	20.7 ± 4.7	20.6 ± 3.1	0.715	0.722	0.059
Waist circumference (cm)	80.2 ± 6.8	85.9 ± 7.0*	86.3 ± 9.1*	85.6 ± 7.2	84.3 ± 6.5	85.3 ± 6.3	0.310	0.125	**0.010**
Total abdominal fat (cm²)	183.0 ± 79.9	231.9 ± 85.7	257.4 ± 98.5*	239.6 ± 80.3†	226.8 ± 70.5	221.2 ± 68.8	0.782	0.234	**0.005**
Visceral fat (cm²)	85.7 ± 45.4	109.0 ± 47.6	124.4 ± 48.6*	120.7 ± 48.9	113.6 ± 42.0	115.7 ± 52.8	0.504	0.299	**0.023**
Subcutaneous fat (cm²)	97.4 ± 40.3	122.9 ± 53.6	133.0 ± 63.0*	118.9 ± 45.4†	113.2 ± 41.3	105.5 ± 27.8	0.847	0.332	**0.012**

Data are mean ± SD values. Data were analyzed by two-way ANCOVA adjusted for age, current/former smoking status, and type 2 diabetes

BMI body mass index, *GRS* genetic risk score

Boldface indicates significance ($p < 0.05$)

* $p < 0.05$ versus the low GRS group within the same age group

† $p < 0.05$ versus middle-aged group within the same GRS group

Table 4 Multiple linear regression analysis with BMI, total abdominal fat, and visceral fat as dependent variables ($n = 173$)

	BMI		Total abdominal fat		Visceral fat	
	β	*p*	β	*p*	β	*p*
Middle-aged ($n = 79$)						
GRS	**0.491**	**<0.001**	**0.382**	**0.001**	**0.321**	**0.003**
VPA (min/day)	0.003	0.973	−0.048	0.653	−0.061	0.554
Fat intake (% energy)	0.119	0.341	0.152	0.245	0.107	0.399
Protein intake (% energy)	0.180	0.130	0.174	0.160	0.176	0.144
Alcohol intake (% energy)	0.084	0.455	0.115	0.328	**0.262**	**0.024**
Model r^2	**0.301**	**0.001**	**0.235**	**0.008**	**0.276**	**0.001**
Elderly ($n = 94$)						
GRS	0.035	0.752	−0.049	0.633	0.004	0.968
VPA (min/day)	−0.166	0.124	**−0.232**	**0.024**	**−0.198**	**0.046**
Fat intake (% energy)	**0.303**	**0.037**	**0.460**	**0.001**	**0.520**	**<0.001**
Protein intake (% energy)	−0.103	0.457	−0.243	0.063	**−0.267**	**0.037**
Alcohol intake (% energy)	0.103	0.404	**0.231**	**0.048**	**0.399**	**0.001**
Model r^2	0.082	0.453	**0.187**	**0.016**	**0.231**	**0.002**

All models were adjusted for age, current/former smoking status and type 2 diabetes

Boldface indicates significance ($p < 0.05$)

β standardized coefficient, *BMI* body mass index, *GRS* genetic risk score, *VPA* vigorous-intensity physical activity

young and middle-aged Chinese populations in which fat intake was relatively low (mean 29.4 and 24.8 %, respectively) (Sasaki et al. 2003; Stookey 2001). Although several lines of evidence is available regarding the effect of fat intake on body fatness in elderly people, reduced fat oxidation is suggested to explain susceptibility to fat accumulation in this group (Levadoux et al. 2001; Rising et al. 1996). This age-related change in energy metabolism may contribute to the strong association between fat intake and body fatness only in elderly individuals despite a relatively low percentage of energy intake from fat. Moreover, high protein intake was also associated with low visceral fat only in elderly individuals. Several studies demonstrated that adequate protein intake prevents age-related muscle loss (Genaro and Martini 2010; Houston et al. 2008). Decline in muscle mass is closely related to visceral adiposity in elderly people (Song et al. 2004; Yamada et al. 2014), which may explain the relationship between high protein intake and low visceral fat in the present study.

Furthermore, a high level of VPA was associated with low total abdominal fat and visceral fat in elderly individuals. Total energy expenditure of physical activity seems to be important for body weight control; however, the benefit of VPA independent from the total volume of activity was documented in several studies. For example, it was demonstrated that high-intensity exercise training induced a greater decrease in subcutaneous skinfolds than low-intensity exercise training, even though training-induced energy expenditure was about half that in low-intensity exercise training (Tremblay et al. 1994). High-intensity exercise is associated with increased energy expenditure and fat oxidation at a resting state (Treuth et al. 1995, 1996); therefore, VPA may strongly influence body fatness, especially in elderly people with a decreased metabolic rate.

Nevertheless, the total coefficient of determination (model r^2) for BMI was not significant in the elderly, even though model r^2 for total abdominal fat and visceral fat was comparable between the middle-aged and elderly groups. It suggests that dissociation between GRS and BMI cannot be explained by dietary macronutrient intake and physical activity only. Although BMI is widely used as an indicator of body fatness, it is also associated with total muscle mass in older people (Iannuzzi-Sucich et al. 2002; Kanehisa and Fukunaga 2013). Therefore, genetic factors associated with muscle mass may greatly contribute to individual variations in BMI in the elderly. We should also consider environmental factors in early life. The elderly individuals participating in the present study were born around World War II when Japan faced serious food shortage. Fetal and early childhood malnutrition has been shown to increase the risk of obesity in adulthood (Black et al. 2013; Oken and Gillman 2003); therefore, nutritional status in early life may diminish the association of BMI-associated SNPs with BMI in the elderly Japanese.

The present study has several limitations. First, the sample size was relatively small, which might have led to a type 2 error. Second, although current body weight is influenced by dietary intake and physical activity during the several preceding months, we cross-sectionally examined the association of these values. Prospective studies will provide the more accurate relationship of genetic factors, dietary macronutrient intake, and physical activity with body fatness in elderly individuals. Third, our study included only male subjects. Several twin studies reported that the heritability of BMI differs by sex to a certain

degree (Korkeila et al. 1991). Last, the majority of the participants in this study were in the normal BMI range (73.5 % of the subjects with a BMI < 25). Our findings should be confirmed by studies with a larger population and a wide range of BMIs and indices of adiposity. In the future, prospective studies will conclude whether aging alters the relationship between GRS from BMI-associated SNPs and body fatness independently of the cohort effect. If the genetic effect gradually decreases throughout life, it is worth examining whether GRS more strongly predicts obesity in a younger population. In addition, identifying the underlying molecular mechanisms, such as by analyzing an age-related change in the epigenetic profiles in BMI-associated genes, will make our findings more persuasive.

In conclusion, the present study revealed that GRS from BMI-associated SNPs previously identified in middle-aged populations is not associated with body fatness in elderly Japanese men. The strong contribution of dietary macronutrient intake and physical activity to body fatness may attenuate the genetic predisposition to obesity in elderly individuals. Our findings suggest that balanced dietary intake and increased physical activity can reduce the risk of obesity in later life, even in individuals with high genetic susceptibility to obesity in midlife. Alternatively, genetic resistance to obesity is lost in an age-dependent manner; therefore, genetically lean middle-aged individuals should sustain a healthy lifestyle to maintain a proper body weight in later life.

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壮・中年期のロコモ対策

Locomotive syndrome among middle aged population

緒方　徹*
Ogata Toru

抄録▶ロコモという言葉は高齢者の介護予防の場面だけでなく，健康日本21でロコモとメタボの関連についても触れられるなど，若年層においても使われるようになってきた．ロコモ度テストでは若年層から高齢者まで一つの尺度体系で運動器を捉えることが目指されている．今後，このテストを共通尺度として活用することで運動器の健康維持や，メタボを中心とする他の疾患との関連性についてのエビデンスが蓄積していくことが期待される．

Key Words　ロコモ度テスト，メタボリックシンドローム，検診

*国立障害者リハビリテーションセンター

はじめに

ロコモティブシンドロームの提唱と対策は運動器の健康からみた介護予防として認知度があがり，すでに多くの地方自治体で取り組みが始まっている．実際に要支援や要介護の認定を受ける人は75～84歳で29％（平成23年高齢社会白書）であることからも，高齢者あるいは後期高齢者において，運動器疾患により移動機能が低下していく状態を評価し，介入によって改善に導くことがロコモ対策の方向性になろうとしている．その一方で，いわゆる壮年期（30～44歳）や中年期（45～64歳）の運動器はどのように捉えるべきであろうか．この世代においても運動器に問題を持つ人は少なからずいるものの，そのほとんどは自立した生活を送っており，将来的に運動器が原因で介護が必要になるとしても10年以上先のことである．したがって，どの程度の運動機能から注意が必要なのか，その設定は高齢者の場合と異なる考え方が必要となる．

壮・中年期のロコモにおける標準値の意味

高齢者におけるロコモの評価に関してはさまざまな運動機能テストや質問票が試みられているが，この分野でのエビデンスを構築する過程ではロコモの診断基準が厳密に議論されることが予想される．すなわち，多くの疾患で実施されるように，「……検査の値が……以上，かつ（または），……スコアが……以上」といったように，特定の検査の基準値が診断基準に盛り込まれる可能性が高い．基準値の設定には高齢者層の縦断調査による，介護認定のリスク因子分析などが参考とされるのではないか．

一方，50歳の人にとって上記のような基準値を設定することは可能だろうか．縦断調査を行っても実際に介護認定となるのはほとんどのケースで70歳以降，20年先である．この期間を追跡調査することは現状では困難であるし，なによりも基準値を設定できるのが20年後となってしまう．

そこで考えられる方法が年齢別基準値という考え方である．一般的に運動機能は年齢ととも

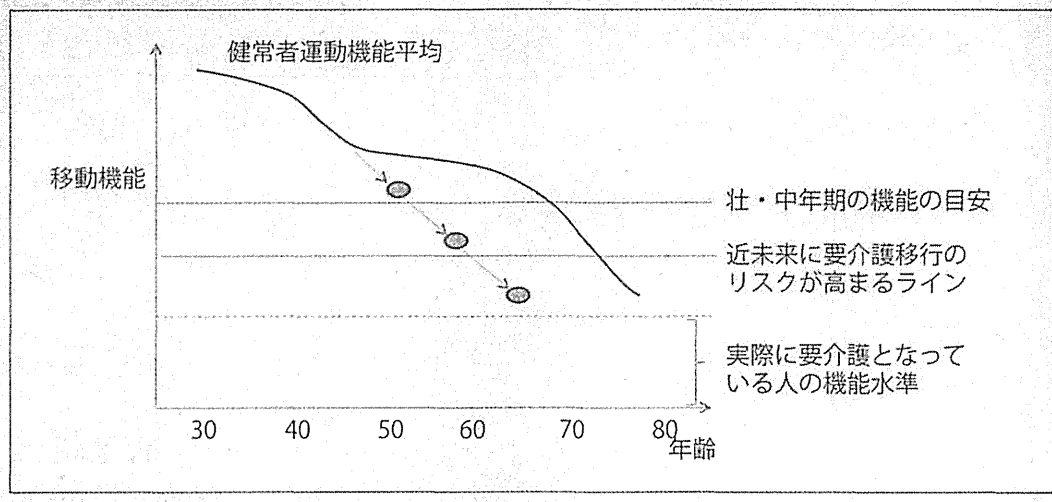

図1　ロコモに至るまでの経過

ロコモは高齢になって急にリスクが上がるものではなく，年齢とともに段階的にロコモのリスクラインに近づいていくものと考えられる．

に低下傾向を示す．その一般的な変化パターンからどの程度逸脱しているかによって運動器の健康度を知るという方法である．おそらくこの手法が広く認識されているのが骨密度の分野であろう．骨密度検査をする際に描かれる標準値曲線は，20歳台で骨量がピークに達し，その後漸減するカーブを描く．40歳で骨密度を測定することは稀であろうが，仮に若年平均の80％を超えていたとしても年代別平均から逸脱していればなんらかの病態を考えるきっかけとなる．

標準的な運動機能の年齢推移については，文部科学省が実施する新体力テストに報告があるほか，われわれが行った健常成人755名を対象とした調査においても20歳台が最も機能が高く，男女とも年齢とともに漸減する傾向が観察されている[1]．したがって，ロコモの基準値のイメージ図としては図1のように，年齢に応じた標準域と危険域の設定が考えられる．壮・中年期のロコモとは年齢標準値から逸脱し，危険域に近づいていくプロセスと捉えるとわかりやすい．

壮・中年のロコモを捉えるさまざまな手法

成人の体力を考える目安として用いられる一つの指標が文部科学省が実施している新体力テストのデータである．新体力テストは以下の項目を測定し，各項目に加点して総点を算出する方式を採択している[2]．

成人(20～64歳)：握力，上体起こし，長座体前屈，反復横とび，急歩，20 mシャトルラン，立ち幅とび

高齢者(65～79歳)：ADL，握力，上体起こし，長座体前屈，開眼片足立ち，10 m障害物歩行，6分間歩行

これらの運動機能テストにはさまざまな要素が含まれており，文字通り体力を総合的に評価することを意図している．一方でロコモは「運動器疾患による」，「移動機能の障害」に焦点を絞った概念であることから主として歩行機能と(下肢)筋力および自覚的運動器の状態を評価の対象としている．これは日本国内で実施された大規模コホート調査ROAD Studyにおいて，高齢者が4年以内に介護申請をするに至るリスク因子として，歩行機能，立ち上がり機能，筋力といった要素が有意なものとして見いだされたことを背景としている[3]．ロコモはあくまでも運動器疾患を背景とした機能障害を評価の対象にしているので，体力テストとは視点が異なることに留意したい．

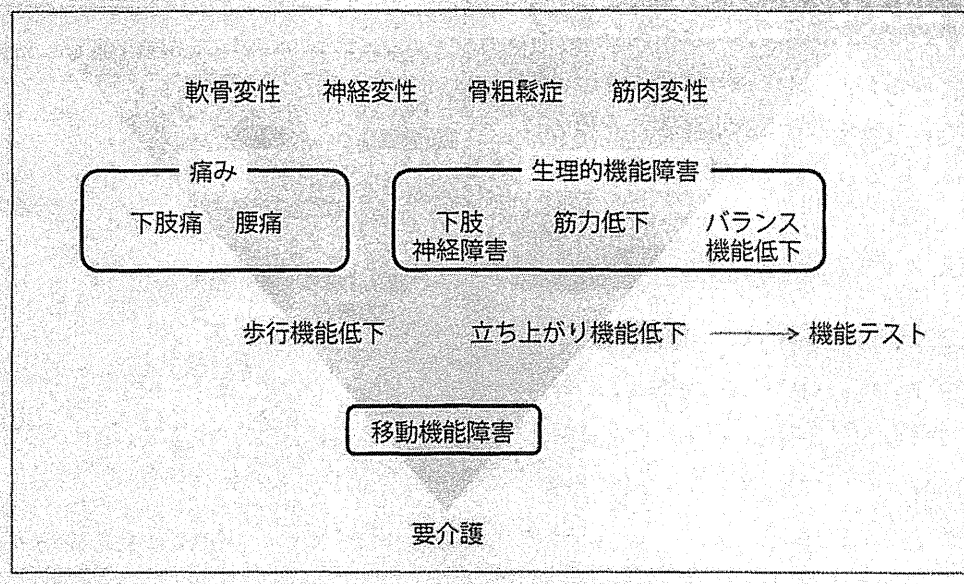

図2　ロコモの概念と機能テスト
2ステップテスト，立ち上がりテストで計測される機能低下の背景には病態およびそれによって引き起こされる生理的機能障害や痛みが存在する．

「ロコモ度テスト」の概要とそのデータ

ロコモの視点から青壮年期から老年期に至る広い年齢層で運動器を評価するツールとして2013年に日本整形外科学会から発表されたのが「ロコモ度テスト」である．これは2ステップテスト，立ち上がりテスト，自記式質問票ロコモ25の3つから構成されている．詳細は別項で取り上げられているが，ここでは3つの指標が何を評価しているか，また評価した結果をどのように活用すべきかに触れる．

2ステップテストは最大歩行速度と高い相関を示すことが報告されており，また，立ち上がりテストは膝伸展力との相関が高い[4]．最大歩行速度や膝伸展力の測定は一般の健診や外来診療中には計測が困難であるのに対し，ロコモ度テストの2つの運動機能テストは簡便に実施可能な点が特徴である．歩行機能と下肢筋力は一見身体機能の同じ面を見ているようだが，歩行は筋力だけでなく，姿勢，バランス制御，柔軟性を含む複合的動作である(図2)．実際に立ちあがりテストの結果と2ステップテストの値を年齢補正をしたうえで比較すると，両者の偏相関係数はむしろ低値である(筆者ら未発表データ)．

ロコモ度テストの3つの指標を明らかな運動器疾患を持たない人を対象に計測すると，20歳台に最も高い運動機能を示し，年齢とともに漸減していく傾向がいずれの指標でも観察された．さらに40～60歳台は比較的横這い推移を示し，70歳台以降で低下が顕著になる傾向がみられる[1]．

「ロコモ度テスト」の活用方法

ロコモ度テストの大きな特徴は，簡便に実施できるスクリーニング・ツールであることと，全世代に対して同じテストを実施できることである．年代別の標準値が確定するにはまだサンプル数が少ないと考えられ，今後さらなる調査によって各年代の標準値が設定されることが期待される．またそれと同時に，高齢者においては縦断コホート調査などから得られるデータに基づいて，数年内に要介護移行に至るリスク因子とそのカットオフ値が示されることになるだろう．

こうした値の設定を受けて，ロコモ度テスト

は「年齢相応の標準的運動機能から逸脱し」「要介護のリスクを持つラインに近づいていく」というロコモの経過を把握する尺度になっていくと期待される.

壮・中年期のロコモ対策の実際

1. 啓発活動と自己診断によるアプローチ

壮・中年期の特徴の一つが，状態が悪くならない限り，運動機能低下が受診行動につながらないという点である．ロコモ度テストの中で，立ち上がりテストの40 cm片足立ちは一般のイスとほぼ同じ高さであることから自分でも容易にチェックすることができる．2ステップテストは一定の記録機材がないと測れないが，例えば自分にとっての2ステップ値1.3が何cmになるかを計算し，床に印をつけておけばそれを2歩で超えられるかでチェックが可能である．ロコモ25は日整会ロコモチャレンジのWebサイトで実施可能なほか，携帯サイトのアプリでも記録できるものがある.

こうした自己診断はあくまできっかけであり，その後の行動変容に結び付くことがロコモ対策の重要な点である．筋力の衰えや体重増加によって年代別標準値から離れていった場合には，それを自覚して生活・運動習慣を変えるきっかけになることが望ましい．また，痛みが原因で機能が低下した場合には病院を受診してその背景病態を明らかにし，適切な治療を受けることが期待される.

2. 検診の中での活用

高齢者に対しては今後自治体が開催する検診事業によるロコモ対策が進むことが予想される．壮・中年期においてもメタボ健診などのなんらかの検診に組み合わせる形での実施が現実的であろう．自己診断と異なり，検診の場ではそれぞれの運動機能テストについて正確な数値を得ることができる．このことは経年変化を把握することを可能にするため，その変化に基づいた指導あるいは本人の自覚につながるのではないか．もちろん，その中で適切な病院受診指導が必要なことはいうまでもない.

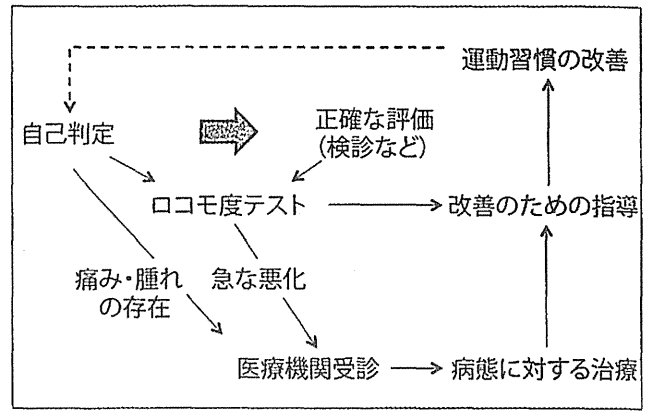

図3　壮・中年期のロコモ対策

自己判定または検診などの場におけるロコモ度テストの活用により，自分の運動器の健康状態を知り，適切な指導を得ることで運動習慣の改善・維持につなげる．医療機関の果たす役割は病態への治療介入によって運動習慣改善のサイクルを支援することと位置付けられる.

3. 病院などでの活用

整形外科外来に通院中の壮・中年期の患者の場合，その多くがなんらかの運動器疾患の診断を受けていると考えられる．注意したいのは新規の半月板損傷などで疼痛や腫脹により運動機能が著しく落ちている場合，仮に介護リスクのカットオフ値を超えていたとしても，それが理由でその人の介護リスクが高まっているとは考えない．あくまで慢性期での評価が前提である．検診での測定と同様，病院においても正確な評価が可能となるため，経年的な変化を捉えることが診療上にも有用と考えられる(図3).

ロコモとメタボ

メタボリックシンドロームが世に定着して10年がたった現在，ロコモとメタボの関係性が壮・中年期の健康の大きな問題になっている．診療の場で肥満とともに膝・腰を中心とする運動器の痛みを目にする機会は少なくない．痛みの改善には体重コントロールが必要だが，そのための運動は痛みがあってできない，といったジレ

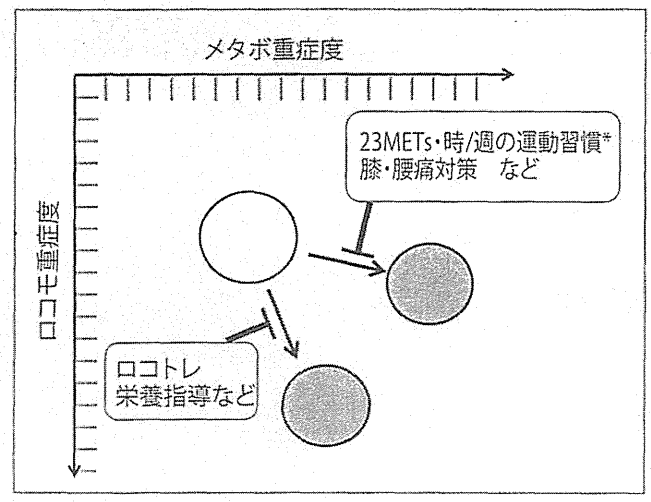

図4　メタボとロコモの相互関係
メタボとロコモが共存する場合，相互に増悪因子となりうる．それぞれの重症度に応じた対策が必要になると予想される．（*厚生労働省　身体活動指針2013）

ンマに陥ることもしばしばである．こうした段階に至るとロコモとメタボが互いの増悪因子になっていることは容易に想像され，実際にいくつかの報告がすでにされている[5,6]．しかし，両者を関連づけて治療する，あるいは生活指導をする方法で確立したものはないのが実情である．

今後，ロコモとメタボを関連づけるさまざまなエビデンスが見いだされることが期待されるが，一番の解決策は早期発見と予防であろう．すなわち，壮・中年期の人がロコモかメタボのいずれかの基準に該当した場合，もう一方の状態がどうなっているかを確認することが重要であると考えられる．すなわち，図4に示すように壮・中年期の健康をロコモとメタボの2つの軸で捉える方法が考えられる．ロコモの悪化度に比べメタボの状態が著しく悪ければそちらをまず解決すべきであるし，その逆もありうる．

現在のところメタボの特定健診で運動器を調べることはないが，一連のロコモの基準が明確になり，ロコモ度テストに含まれるような簡易テストの認知度が高まると，今後ロコモとメタボを関連づけた健診が実施されるようになるかもしれない．

ロコモと痩せすぎ

肥満が運動器にとって大きな増悪因子であると同様に，痩せすぎもまた問題の一つである．高齢者で問題になるサルコペニアに該当しないまでも，不適切なダイエットなどを背景に「痩せすぎ」と思われる壮・中年期の人（特に女性）は少なくない．高齢になってからの運動機能の低下は女性の方が顕著であることを考えると，早い段階で運動機能維持についての自覚を促し，適切な運動習慣と栄養摂取に導くことが予防につながると思われる．

まとめ

壮・中年期のロコモについて，ロコモ度テストを中心に考え方と本人への啓発のアプローチについて述べた．多くの場合，壮・中年期の運動機能低下は病院への受診行動に直結するものではなく，対応策も生活・運動習慣の改善が一番に考えられる．しかし，そうした啓発活動の中で医療機関が果たす役割は大きく，また運動器機能低下の原因として痛みがあればその病態を明らかにし，適切な治療を行うことが求められる．

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学術集会案内

第1回セミナー「Bone Cement IBBC Heritage」

日　時：2014年11月30日（日）14時～12月1日（月）17時
場　所：富永病院 大西啓靖記念人工関節研究センター
〒556-0017 大阪市浪速区湊町 1-4-48
TEL：06-6568-1601（代）FAX：06-6568-1608
趣　旨：骨セメントの基礎，最適な骨母床の作成，そしてセメントテクニックについて学ぶ．
さらに「IBBC」手技の本質を知ってその手技を習得する．
看護師もワークショップで骨セメントの取り扱いについて実践する．
開催日程とプログラムの内容：
1）2014年11月30日（日）14時～17時30分
①講義：骨セメントの基礎，最適な骨母床の作成，セメントテクニック「IBBC」手技の本質
講師：大西啓靖，大橋弘嗣，飯田哲
②骨セメントのハンズオンワークショップ
2）2014年12月1日（月）9時～17時
①手術見学（午前中に2例，各3名まで手術室内で見学，それ以外の方はモニターにて見学）
②討論と症例検討
参加費：10,000円（宿泊は各自でご手配ください）　看護師は無料
募集人数：約20名
応募方法：氏名，勤務先，勤務先住所，TEL，FAX，E-mailをご記入の上，下記FAXまたはE-mailへお申し込みください
申し込み先：富永病院 大西啓靖記念人工関節研究センター
担当　大西宏之（代表　大西啓靖）
FAX：06-6568-1608　E-mail：onishi@tominaga.or.jp
★別途，手術のみの見学希望も随時受け付けております．
手術日　月・火・木曜日　3症例／1日（3カ月以上前に上記FAX，E-mailまで予約してください）