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SYNOVITIS DETECTED BY ULTRASONOGRAPHY PREDICT THE RISK OF DEVELOPING KNEE OSTEOARTHRITIS IN EARLY KNEE OSTEOARTHRITIS FROM THE IWAKI COHORT STUDY

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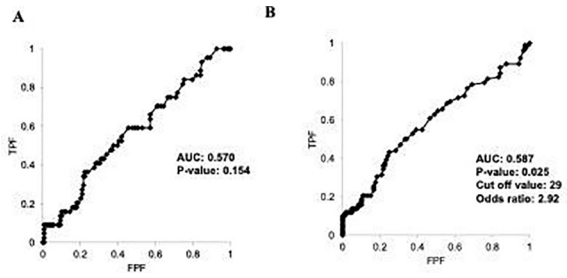
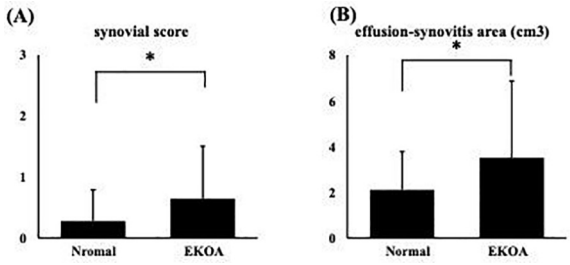
Purpose: Early diagnosis and intervention for knee osteoarthritis (OA) are important. The prevalence of abnormalities detected on magnetic resonance imaging (MRI), such as bone marrow lesions, meniscal lesions, and synovitis, were higher in the knees with early knee OA (EKOA) than those with normal knees. Among these abnormalities, synovitis has been reported to be a trigger of cartilage degeneration. The purpose of this study was to investigate the influence of synovitis on progression of knee OA in participants without radiographic abnormalities. It was hypothesized that the presence of synovitis would be demonstrated in knees with EKOA, and that synovitis would be correlate with progression of knee OA.

Methods: Subjects were voluntary participants from the Iwaki Health Promotion Project of 2016 and 2019. We excluded participants whose radiograph showed radiographic knee OA (KL grade $\geq$ 2) at baseline, whose ultrasonography (US) data was incomplete. Finally, a total of 404 participants were included in this analysis. EKOA was defined according to the international criteria based on the knee injury and OA outcome scales (KOOS), joint line tenderness, and crepitation. Participants were classified into non-OA (i.e. without EKOA) and EKOA group. Furthermore, to investigate an influence of obesity on progression of knee OA, participants with overweight was defined as those with a BMI of 25 or higher. Synovitis was quantified by the effusion area (mm^2) at the echo-free space of the suprapatellar pouch detected by US. At 3-year follow-up, we defined knees with KL grade of 0 or 1 as the non-progressors, and knees with radiographic knee OA as the progressors. In addition, we assessed the effusion volume (cm^3) using MRI to confirm the US data. 255 womenwithout radiographic abnormalities were randomly enrolled and performed MRI. Receiver operating characteristic (ROC) analysis and logistic regression analysis were performed to investigate the influence of the effusion area on progression of knee OA.

Results: Fifty-five of 404 participants (14%) were classified into the EKOA group at baseline, and its prevalence were 10% in men and 21% in women. The overall mean age was 50.7 ± 13.3 years, and the mean BMI was 22.7 ± 3.1 kg/m^2 at baseline. The mean values of the effusion area detected by ultrasonography in the non-OA and EKOA groups were 39.9 ± 34.2 and 54.6 ± 39.5 mm^2 in men (p=0.048), and 31.2 ± 30.8 and 50.9 ± 48.1 mm^2 in women (p=0.002), respectively.ROC analysis showed that the optimal effusion area cut-off value to diagnose EKOA was 29 mm^2 (AUC = 0.587; odds ratio: 2.92; p = 0.025) in women.



The sensitivity was 63%, and specificity was 63%. We could not detect the optimal cut-off value of effusion area in men (p=0.154). In MRI analysis, the effusion volume and synovitis showed higher in the EKOA group than those in the Non-OA group.



The number of non-progressors and progressors were shown in Table 2.

The fraction of progressors was significantly higher in the EKOA groups than those in the Non-OA groups (p=0.003). Next, we compared the effusion area between non-progressors and progressors in the Non-OA and EKOA groups. Progressors tended to show greater effusion area, but there was only significant difference between progressors in the female EKOA and non-progressors in the female Non-OA groups (p=0.006)

	Male			Female		
	Non-OA	EKOA	p-value	Non-OA	EKOA	p-value
Age	50.6±13.9	55.7±14.1	0.118	49.8±13.1	53.7±10.8	0.039
BMI	23.5±2.8	24.6±2.3	0.092	21.7±2.8	23.4±4.6	0.027
KOOS						
Symptom	96.2±4.7	73.9±16.2	<0.001	95.5±5.1	78.5±14.2	0.001
Pain	97.9±4.3	75.8±11.8	<0.001	97.8±4.0	75.4±14.	0.001
Function	99.5±1.3	87.9±17.4	<0.001	99.3±1.8	88.1±12.4	0.001
QOL	94.5±9.1	55.9±17.4	<0.001	90.7±13.1	57.9±15.7	0.001
KLG 0, n (%)	130 (78)	14 (82)	0.725	135 (73	25 (66)	0.343
Effusion- area (mm2)	39.9±34.2	54.6±39.5	0.048	31.2±30.8	50.9±48.1	0.002

Table 1

Osteoarthritis and Cartilage

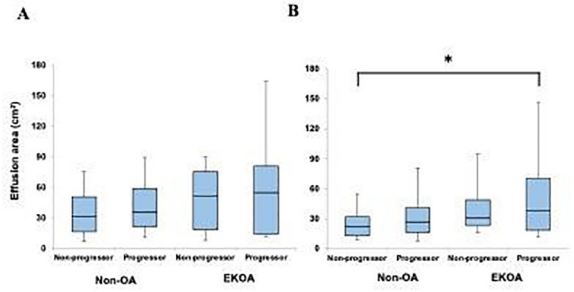
Clinical characteristics of participants

Baseline	Total			Male			Female		
	Non-progressors	Progressors	p-value	Non-OA	EKOA	RKOA	Non-OA	EKOA	RKOA
Non-OA	235 (60%)	114 (40%)	0.003	124 (75%)	4 (2%)	37 (23%)	100 (54%)	7 (4%)	77 (42%)
EKOA	23 (42%)	32 (58%)		7 (41%)	3 (18%)	7 (41%)	11 (29%)	2 (5%)	25 (66%)

Table 2

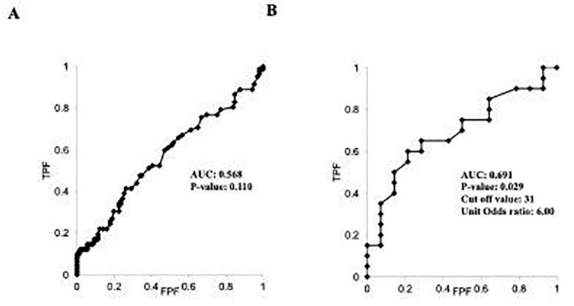
Osteoarthritis and Cartilage

Knee OA in participants by non-OA and EKOA at baseline, and changes over 3 years



Logistic regression analysis showed that women (β=0.60, p<0.001), EKOA (β=0.60, p=0.009), BMI (β=0.10, p=0.002) and effusion area (β=0.01, p=0.008) were significantly correlated with progression of knee OA.

Based on the results of logistic regression analysis, ROC analysis was performed to detect the optimal cut-off value of effusion area to predict the progressors in female participants with and without overweight. The cut-off value of effusion area was 31 mm ^{2} (AUC = 0.691; odds ratio: 6.00; p = 0.029) in women overweight.



Conclusions: Higher effusion area measured by US and higher BMI at baseline were the risk factors for progression of knee OA in those with EKOA patients. Synovitis might be a target for the prevention of knee OA at an early stage.

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OSMOLARITY-INDUCED ALTERED INTRACELLULAR MOLECULAR CROWDING DRIVES OSTEOARTHRITIS PATHOLOGY

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Purpose: Osteoarthritis (OA) is a complex disease of which the underlying mechanisms are yet to be fully understood. Interestingly, although a lower joint osmolarity has long been recognized as a consequence of OA, its role as a potential driving force behind the disease has remained largely uninvestigated. In contrast, for other diseases such as Alzheimer's disease, diabetes, and sickle cell anaemia, a change in osmolarity has been identified as an integral part of the aetiology in recent years. We have observed that the osmolarity of synovial fluid differs between OA (~300 mOsm) and healthy (~400 mOsm) joints. Indeed, culturing chondrocytes in medium with a higher osmolarity (380 - 450 mOsm) associates with superior chondrogenic phenotypes as compared to chondrocytes cultured in commonly used cell culture media, which has an OA-like osmolarity (300 - 330 mOsm). We hypothesized that the osmolarity would regulate the chondrocyte's intracellular molecular crowding. Molecular crowding controls almost every aspect of cell function, yet its potential has remained largely unexplored in the field of cartilage biology. We therefore have investigated the role of osmolarity on chondrocyte behaviour, and demonstrated that it regulates chondrocytes' sensitivity and responsivity to anabolic and catabolic triggers, which is at least in part mediated via altered intracellular molecular crowding.

Methods: We exposed human primary chondrocytes (hPCs) and various cell lines to 330 ± 10 mOsm to mimic OA joints or 400 ± 10 mOsm to mimic healthy joints. Osmolarity was controlled by adjusting the NaCl concentration of the culture medium. Changes in BMP, IL1β and TGFβ

Parameter	Univariate crude				Multivariate adjusted (stepwise)			
		p	OR	95% CI	β	p	OR	95% CI
Female	0.49	<0.001	2.67	0.27 - 0.71	0.60	<0.001	3.36	0.37 - 0.84
BMI	0.05	0.098	3.70	-0.01- 0.12	0.10	0.027	2.15	0.03 - 0.18
Effusion area	0.01	0.012	10.4	0.00 - 0.01	0.01	0.008	3.25	0.00 - 0.02
EKOA	0.52	<0.001	2.86	0.23 - 0.82	0.60	0.009	2.02	0.04 - 0.67

Table 3

Osteoarthritis and Cartilage

Examination of factors related to the progression of knee OA in male participan