

Possibility of synovial TRAP5b as biomarker for bone pain in patients with knee OA

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Disclosures: We do not have COI.

1. Introduction

Pain is a major source of disability and the reason for hospital visits in patients with knee osteoarthritis (OA). Recent our study showed that tartrate resistant acid phosphatase (TRAP) positive osteoclast density in subchondral bone was associated with pain (1), and the osteoclast densities increased in subchondral bone with bone marrow lesion (BML) compared with subchondral bone without BML. Osteoclasts secrete netrin-1 and nerve growth factor (NGF) to induce sensory nerves (1,2). Osteoclasts in subchondral might contribute to OA pain by this generation of chemical factors. This study aims to verify the possibility of synovial TRAP5b as a biomarker for bone pain in patients with knee OA. The hypothesis is that synovial TRAP5b is associated with knee pain and BML size in patients with knee OA.

2. Materials and methods

2.1 Samples: Synovial fluids and blood serum were obtained from 70 patients with knee OA (50 female, 20 male). Six patients had OA with KL-grade 1, 23 with KL-grade 2, 16 with KL-grade 3 and 25 with KL-grade 4. Protocols were approved by Kochi university.

2.2 Synovial fluids and blood serum analysis: Concentrations of TRAP5b, interleukin-6 (IL-6) and matrix metalloproteinase-3 (MMP-3) in synovial fluids and blood serum were analyzed.

2.3 BML scoring: MRI Osteoarthritis Knee Score (MOAKS) was used for BML scoring. In MOAKS, subchondral BMLs were scored in each of the 15 anatomical locations according to percentage of the volume of each BML including volume of any associated cysts as 0 = none, 1 < 33%, 2 = 33–66%, and 3 > 66%.

3. Results

Levels of synovial TRAP5b, IL-6 and MMP-3 were significantly different from the data in blood serum (Table 1). Synovial TRAP5b significantly correlated with pain during walk and BML score in females only (Table 2 and 3). These associations between synovial TRAP5b, and pain during walk and BML score retained significance after adjustment for synovial IL-6, synovial MMP3, age, BMI and KL-grade. There were no correlations of serum TRAP5b, synovial IL-6 and MMP3, and serum IL-6 and MMP3 with pain and BML score (Table 2 and 3).

4. Discussion

In this study, we firstly demonstrated that synovial TRAP5b was significantly associated with walking pain and BML size, independent of synovial IL-6, synovial MMP3, age, BMI and KL-grade in female patients with knee OA. Our results support a role for subchondral osteoclast activity in the generation of OA and synovial TRAP5b may be useful as a biomarker for bone pain in female patients with knee OA.

Previous studies showed that osteoclasts secrete netrin-1 and NGF to induce sensory nerve (1,2). High serum concentrations of TRAP-5b, an indicator of osteoclast number, were shown to be associated with subchondral osteoclast density, OA pain, and worse pain prognosis (3). Studies of osteoclast inhibitors such as bisphosphonates, denosumab, and strontium ranelate show reductions in joint pain in people with knee OA (4,5). Zoledronic acid, a bisphosphonate, reduced knee pain and BML size in OA patients (5), although findings from a meta-analysis of randomized controlled trials did not support analgesic effects of bisphosphonates in knee OA (6). Our data suggest that OA knee pain has multiple sources, and targeting osteoclasts will have clinically important benefits only in females whose osteoclast activity is the predominant driver of pain.

5. Significance

Synovial TRAP5b is significantly associated with walking pain and BML size, independent of synovial IL-6, synovial MMP3, age, BMI and KL-grade in female patients with knee OA.

Table 1: Characteristics of the patient

		Female (50 knees)	Male (20 knees)	P
Age	Mean(SD)	71 ± 9	67 ± 13	0.13
KL-grade	Median(IQR)	3 (2, 4)	3 (1, 3)	0.65
Pain during walk (VAS) (mm)	Median(IQR)	56 (30, 67)	40 (30, 56)	0.38
Pain at rest (VAS) (mm)	Median(IQR)	20 (9, 30)*	4 (0, 10)	0.01
TRAP5b				
Synovial fluid (mU/dL)	Median(IQR)	236 (149, 325)	141 (90, 219)	0.08
Blood serum (mU/dL)	Median(IQR)	437 (273, 566)	354 (274, 430)	0.32
IL-6				
Synovial fluid (pg/mL)	Median(IQR)	180 (61, 429)	111 (48, 300)	0.70
Blood serum (pg/mL)	Median(IQR)	2.4 (1.6, 4.9)	1.7 (1.5, 3.6)	0.24
MMP3				
Synovial fluid (ng/mL)	Median(IQR)	3719 (1838, 7311)	2971 (2185, 9667)	0.74
Blood serum (ng/mL)	Median(IQR)	50 (36, 59)	54 (52, 152)	0.15
MRI				
BML score (0-27)	Median(IQR)	6 (3, 9)	4 (2, 8)	0.31

Unpaired t-test and Mann-Whitney U-test * P<0.05 vs Male

Table 2: Correlation of TRAP5b, IL-6 and MMP with pain

	Female (50 knee)			
	Pain during walk		Pain at rest	
	Spearman's r	p	Spearman's r	p
TRAP5b				
Synovial fluid	0.34*	0.02	0.13	0.16
Blood serum	0.27	0.07	0.16	0.28
IL-6				
Synovial fluid	-0.02	0.85	0.05	0.72
Blood serum	0.18	0.25	0.26	0.07
MMP3				
Synovial fluid	0.15	0.32	0.21	0.17
Blood serum	0.12	0.59	0.36	0.10

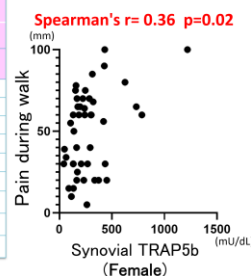
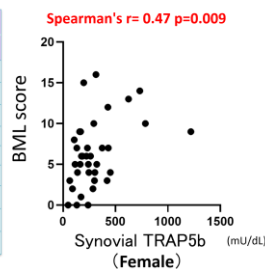


Table 3: Correlation of TRAP5b, IL-6 and MMP with BML score

	Female (50 knee)	
	Spearman's r	p
TRAP5b		
Synovial fluid	0.46	0.003
Blood serum	0.26	0.11
IL-6		
Synovial fluid	0.0001	1.00
Blood serum	0.34	0.05
MMP3		
Synovial fluid	0.08	0.65
Blood serum	0.47	0.05



References; 1) Aso K, et al. Arthritis & Rheumatology 2019. 2) Zhu S et al. J Clin Invest. 2019. 3) Nwosu LN, et al. Osteoarthritis Cartilage 2017. 4) Reginster JY, et al. Ann Rheum Dis 2013. 5) Laslett LL, et al. Ann Rheum Dis 2012. 6) Vaysbrot EE, et al. Osteoarthritis Cartilage 2018.