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Responsiveness of qualitative and quantitative MRI measures over 2.7 years

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Disclosures: JPP and JMP are consultants for and shareholders in ArthroLab; the other authors declare no competing interests.

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Introduction

- There are currently no approved disease-modifying osteoarthritis drugs (DMOADs) available which modify structural progression in OA.
- Radiography remains the only approved method by regulatory authorities to assess structural change in clinical OA trials of DMOADs.
- In order to have MRI accepted as a measurement tool in clinical trials, responsive outcome measures for structural rate of change using MRI are needed.

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Objective

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- The aim of this study was to compare the responsiveness of MRI-derived measures over 2.7 years.

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Methods: TASOAC

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Tasmanian Older Adult Cohort Study (TASOAC)

- Prospective population-based study of community-dwelling older adults
- 1,099 men and women between the ages of 50 and 80 yrs (mean 62 yrs, 51% female)
- Current study: N = 430 who had an MRI at baseline and follow-up (approx. 2.7 years later)

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Methods: MRI

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- 1.5T MRI scan of the right knee at both time points
- Sequences included:
  - T1-weighted fat-suppressed (3D) gradient-recalled acquisition in the steady state
  - T2-weighted fat-suppressed 2D fast spin-echo

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Methods: Cartilage volume

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- Cartilage volume: Cartilage volume was calculated by manually drawing contours around the cartilage boundaries on a section by section basis (mm^3), CV 2.0 – 2.2%
- 4 sites: medial tibial, medial femoral, lateral tibial, lateral femoral
- Total tibiofemoral (mm^3) = MT + MF + LT + LF

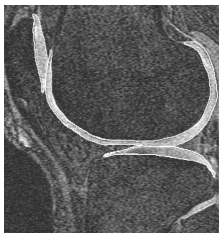

Figure: Cartilage volume segmentation

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Methods: Cartilage defects

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Cartilage defect grading system	
Grade 0	Normal cartilage
Grade 1	Focal blistering and low-signal intensity area with intact surface/bottom
Grade 2	Irregularities on surface/bottom, loss of thickness of less than 50%
Grade 3	Deep ulceration with loss of thickness > 50%
Grade 4	Full-thickness chondral wear with exposure of subchondral bone

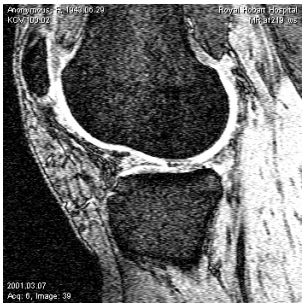

Fig. Cartilage defect

- ICC 0.80 – 0.95
- 4 sites: medial tibial, medial femoral, lateral tibial, lateral femoral
- Total tibiofemoral (possible range 0 – 16) = MT + MF + LT + LF

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Methods: Bone marrow lesions

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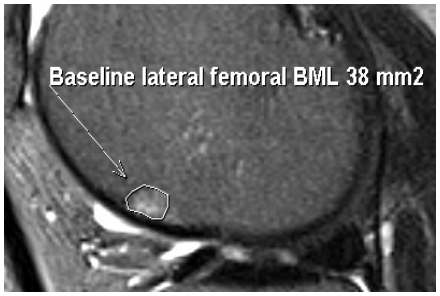
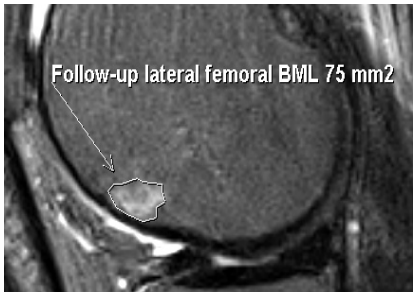
- Maximum area (mm^2) of the lesion at baseline and follow-up
- 4 sites: medial tibial, medial femoral, lateral tibial, lateral femoral
- Total tibiofemoral (mm^2) = MT + MF + LT + LF





ICC 0.97

Doré *et al*, ART 2010.12:R223

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Methods: Bone marrow lesions

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BML ordinal scale at all four sites:

0: Normal

1: Mild, <25% of the region

2: Moderate, 25 – 50% of the region

3: Severe, >50% of the region

Total tibiofemoral (possible range 0 – 12) = MT + MF + LT + LF

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Methods: Meniscal pathology

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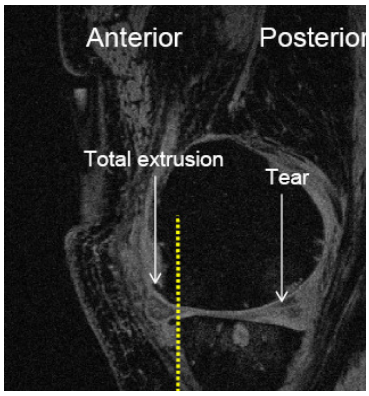
- Proportion of the menisci affected by a tear, partial or full extrusion was scored separately (yes/no) at the anterior, middle, and posterior horns (medially/laterally)
  - 0 – 6 for tears
  - 0 – 6 for partial extrusions
  - 0 – 6 for full extrusion
- Total meniscal pathology score (possible range from 0 – 18) = tears + partial + full extrusion



ICC 0.86 to 0.96 (tear)
ICC 0.85 to 0.92 (extrusion)

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Methods: Tibial bone area

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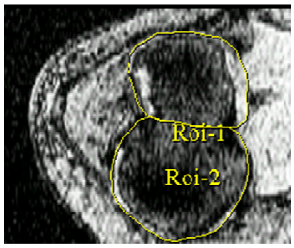
- Cross-sectional surface area of the tibial plateau
- Area was measured on 3 slices closest to the tibial cartilage and the mean of all three areas was used as an estimate of tibial plateau bone area (mm^2)
- CV 2.2–2.6%



Medial and lateral tibial bone area

Total tibial (mm^2) = medial + lateral

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Data analysis

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- Responsiveness is the sensitivity to change or the ability to detect change using a particular instrument.
- The standardized response mean (SRM) is one of several available effect size indices used to gauge the responsiveness of scales to clinical change.

$$SRM = \frac{mean\ of\ change}{SD\ of\ change}$$

- 0.2 small, 0.5 moderate, 0.8 large (Husted *et al*, J Clin Epidemiol 2000. 53(5))

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Results: Study characteristics

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Table 1. Characteristics of participants at baseline (n=430)	
	Mean (SD, range) except for %'s
Age (years)	63.0 (7.2, 51 – 79)
Male sex (%)	49
BMI (kg/m^2)	27.6 (4.4, 19 – 46)
ROA present (%)	57
MRI measures	
Total tibiofemoral cartilage volume (mm^3)	13,417 (3,267, 7167 – 25401)
Cartilage defects present† (%)	32
Total meniscal pathology score	5.6 (1.3, 0 – 10)
Total tibial bone area (mm^2)	3384 (472, 2405 – 4696)
Bone marrow lesion (BML) present (%)	43
Mean total BML size (mm^2)	101 (115, 5 – 727)
Mean total ordinal score	2.3 (1.6, 1 – 10)

†Defined as grade 2 or higher.

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Results: SRM for cartilage

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Table 2. Change (SD) and SRM values for cartilage measures over 2.7 years		
	Mean change (SD of change)	SRM
Cartilage volume		
Medial tibial (mm^3)	-185 (342)	-0.54
Lateral tibial (mm^3)	-151 (298)	-0.51
Medial femoral (mm^3)	-126 (234)	-0.54
Lateral femoral (mm^3)	-110 (231)	-0.48
Total tibiofemoral (mm^3)	-538 (669)	-0.80
Cartilage defects		
Medial tibial (0 – 4)	0.2 (0.5)	0.35
Lateral tibial (0 – 4)	0.2 (0.5)	0.33
Medial femoral (0 – 4)	0.3 (0.5)	0.49
Lateral tibial (0 – 4)	0.2 (0.5)	0.35
Total tibiofemoral (0 – 16)	0.7 (1.2)	0.62

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Results: SRM for BMLs

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Table 3. Change (SD) and SRM values for bone marrow lesion measures over 2.7 years

	Mean change (SD of change)	SRM
Bone marrow lesion (areal)		
Medial tibial (mm^2)	3 (49)	0.06
Lateral tibial (mm^2)	5 (45)	0.11
Medial femoral (mm^2)	0.2 (33)	0.01
Lateral femoral (mm^2)	6 (63)	0.09
Total tibiofemoral (mm^2)	14 (112)	0.12
Bone marrow lesion (ordinal)		
Medial tibial (0 – 3)	0.10 (0.5)	0.11
Lateral tibial (0 – 3)	0.05 (0.5)	0.09
Medial femoral (0 – 3)	0.02 (0.5)	0.03
Lateral tibial (0 – 3)	0.06 (0.5)	0.13
Total tibiofemoral (0 – 12)	0.20 (1.1)	0.17

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Results: SRM for meniscal pathology and tibial bone area

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Table 4. Change (SD) and SRM values for meniscal pathology and tibial bone area over 2.7 years

	Mean change (SD of change)	SRM
Meniscal pathology		
Tears (0 – 6)	0.4 (1.0)	0.39
Partial extrusion (0 – 6)	0.003 (0.35)	0.01
Full extrusion (0 – 6)	0.02 (0.16)	0.12
Total meniscal pathology score (0 – 18)	0.04 (1.1)	0.39
Total summary score increase (0 – 1)	0.26 (0.44)	0.59
Tibial bone area		
Medial tibial (mm^2)	-24 (112)	-0.22
Lateral tibial (mm^2)	12 (85)	0.14
Total tibial (mm^2)	-12 (141)	-0.09

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Results: SRM for meniscal pathology and tibial bone area

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Results: Summary

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- Best sensitivity to change seen with summary scores rather than compartmental based scores

- Tibiofemoral cartilage volume: -0.80
- Tibiofemoral cartilage defects: 0.62
- Tibiofemoral BML size (areal measure): 0.12
- Tibiofemoral BML grade (ordinal measure): 0.17
- Total meniscal pathology score: 0.59
- Tibial bone area: -0.09

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Discussion

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ARD Online First, published on February 21, 2012 as 10.1136/annrheumdis-2011-200970
Clinical and epidemiological research

EXTENDED REPORT

Zoledronic acid reduces knee pain and bone marrow lesions over 1 year: a randomised controlled trial

Laura Louise Laslett,[1] Dawn A Doré,[1] Stephen J Quinn,[2] Philippa Boon,[1] Emma Ryan,[1] Tania Maree Winzenberg,[1] Graeme Jones[1]

- Zoledronic acid treatment significantly reduced areal BML size (despite **very low** SRM values for this measure)
- Primarily due to a large effect (around 40% in the treatment group improved)
- When cartilage volume is used as an outcome in clinical trials, studies have powered on an expected 1 – 2% reduction in cartilage volume loss.

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Conclusion

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- Higher SRMs provide advantages with regards to adequately powering studies.
- Using summary scores in clinical trials will enhance the power with which the effect of a therapeutic intervention can be seen.
- However, although one can optimize trial efficiency by finding more responsive endpoints, magnitude of effect appears <u>at least</u> equally important in selecting outcome measures.

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Thank you, any questions?