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A cumulative analogue joint involvement scale (CAJIS) for fibrodysplasia ossificans progressiva (FOP)

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ABSTRACT

Background: Fibrodysplasia ossificans progressiva (FOP) is a catastrophic genetic disorder of progressive heterotopic ossification (HO). Assessment of functional mobility in FOP will be essential to support clinical trials of investigational agents.
Results: Of necessity, we developed a simple, rapidly-administered, cumulative analogue joint involvement scale (CAJIS) for FOP based on assessments in 144 individuals worldwide with classic FOP.
Conclusions: CAJIS scores correlated with patient age, activities of daily living, and ambulatory function with excellent inter-rater variability. We show here that the CAJIS score provides an accurate and reproducible snapshot of total body and regional mobility burden in FOP.

1. Introduction

Fibrodysplasia ossificans progressiva (FOP: MIM 135100) is a rare heritable disorder of connective tissue characterized by congenital skeletal malformations and progressive, disabling heterotopic ossification (HO) in characteristic anatomic patterns [1–7].

FOP progresses most notably during flare-ups, but nearly 50% of FOP patients report that progressive mobility restriction occurs in the absence of discrete flare-ups, suggesting the possibility of progressive subclinical HO and/or early progressive degenerative arthropathy [8]. Regardless of the mode of progression, disability is cumulative [1–7].

Wide variability in the rate of disease progression, even among identical twins, attests to the importance of post-natal environmental factors on disease progression [9]. Factors such as soft tissue trauma, surgical biopsies, intramuscular injections, overstretching of the jaw, muscle fatigue, and viral illnesses may trigger HO locally or systemically [2,4,5].

All patients with classic FOP have malformed great toes [1,7]. Variable joint malformations are noted on screening skeletal surveys [7]. Subtle mobility restriction may be noted in infancy due to the presence of congenital malformations of the cervical spine even before appearance of heterotopic ossification [10]. Nevertheless, most infants with FOP have remarkably normal mobility and few, if any, have notable functional restrictions [1,8].

FOP is caused by heterozygous gain-of-function mutations in Activin receptor A type I (ACVR1), a bone morphogenetic protein (BMP) type I receptor in all affected individuals [11,12]. Loss of autoinhibition of the mutant receptor (mACVR1) results in dysregulated BMP pathway signaling and provides a molecular basis for understanding the developmental anomalies, progressive arthropathy and altered threshold for disabling post-natal HO that is a hallmark of the disease as well as providing a robust molecular target for therapy [13–15].

Functional mobility assessment of FOP will be essential to support clinical trials of investigational agents. In order to address this rapidly emerging need, we developed a simple, reproducible, rapidly-administered cumulative analogue joint involvement scale (CAJIS) for FOP that can be readily adapted to any clinical venue. This functional scale could be used independently or in conjunction with measurements of individual joint function and radiographic analysis to assess the status of FOP.

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Here, we present a functionally-validated CAJIS for FOP based on 144 individuals worldwide with classic FOP. CAJIS scores correlated with age, as well as activities of daily living (ADL) and ambulatory status with excellent inter-rater variability. Importantly, we show that the CAJIS provides a rapid, accurate and reproducible snapshot of total body and regional mobility burden of FOP that correlates with age and functional status and can be adapted to any clinical setting.

2. Materials and methods

2.1. Patients

The study included all patients with classic FOP seen by the investigators between 2012 and 2015. All patients had classic FOP defined by confirmation of the canonical ACVR1/ALK2 (R206H) mutation. All assessments were part of routine patient evaluations and were approved by the Investigational Review Board of the Perelman School of Medicine of the University of Pennsylvania.

2.2. Cumulative analogue joint involvement scale (CAJIS)

We developed a CAJIS that reflects gross mobility limitations for individuals with FOP. This scale is based upon a simple analogue assessment of mobility restriction that has been noted in most of the 800 FOP patients seen by us over the past 25 years [1,8]. The CAJIS also notes gross assistance needs with activities of daily living as well as ambulatory status. The CAJIS was designed to assess mobility limitation at 15 anatomic locations in less than two minutes and can be adapted to any clinical setting.

Three axial sites include: the neck, jaw, and thoraco-lumbar spine. Six upper limb sites include shoulders, elbows, and wrists. Six lower limb sites include: hips, knees, and ankles. At each site, the examiner assesses whether active movement or function was normal (<10% deficit; score of 0), partially impaired (10%–90% deficit; score of 1), or functionally ankylosed (>90% deficit; score of 2) [Table 1]. CAJIS scores were tabulated for the entire body (out of 30) and for individual regions [axial (out of 6), upper limbs (out of 12), lower limbs (out of 12)]. The template shown in Table 2 was used to record all assessments.

Table 1
Cumulative analogue joint involvement scale (CAJIS) for FOP.

The examiner should evaluate the following:
Neck – flexion/extension; rotation; lateral bending [0–2]
Thoraco-lumbar spine – forward flexion; chest expansion with deep breathing [0–2]
Jaw – mouth opening [0–2]
Shoulders – abduction [0–2 for each shoulder]
Elbows – flexion/extension [0–2 for each elbow]
Wrists – dorsiflexion/volarflexion [0–2 for each wrist]
Hips – flexion (standing, sitting, or supine) [0–2 for each hip]
Knees – flexion/extension [0–2 for each knee]
Ankles – dorsiflexion/plantarflexion [0–2 for each ankle]
Scores for each assessed area:
0 = normal to <10% deficit
1 = 10%–90% deficit
2≥ 90% deficit
Possible scores:
Axial = 0–6
Upper limbs = 0–12
Lower limbs = 0–12
Total = 0–30
The examiner MUST also note and record if the patient:
• Can walk [yes/no]
• Uses a wheelchair [yes/no]
• Needs SOME help with activities of daily living [yes/no]
• Needs COMPLETE help with activities of daily living [yes/no]

Forearm rotation (pronation/supination), subtalar motion, and finger/toe motion are not assessed. The CAJIS for each region is based on the greatest limitation in ANY aspect of assessed function. For example, if forward flexion of the thoracic and lumbar spine is not possible but chest expansion is only minimally affected (or vice versa) then the score for the thoracic and lumbar spine would be a 2 (maximal).

2.3. Inter-rater variation in CAJIS

A subset of 23 patients was assessed by two physicians (FSK and RJP) in order to determine the inter-rater variation in CAJIS assessment.

2.4. Data analysis

Descriptive statistics were performed using Microsoft Excel software. Linear regression was used to calculate correlations between total CAJIS score and age. One-way analysis of variance (ANOVA) was performed to examine if there was a difference in mean age, ADL status, and ambulatory status based on regional CAJIS scores. The Tukey post-hoc analysis was used to determine differences in age of individuals with an affected joint (i.e., CAJIS score of 1 or 2) compared to the age of individuals with an unaffected joint at the same location (i.e., CAJIS score of 0), or differences in function (ADL or ambulation) compared to independent status. A chi-square test of independence was performed to examine the relationship between activities of daily living (ADL) status (i.e., independent, some help with ADLs, complete help with ADLs) and CAJIS score [low (0–6) or high (7–12)] of the upper limbs. A chi-square test of independence was also performed to examine the relationship between ambulation status (i.e., ambulatory, as needed wheelchair use, exclusive wheelchair use) and CAJIS score [low (0–6) or high (7–12)] of the lower limbs. All non-descriptive statistical tests were performed using the VassarStats website for statistical computation (http://vassarstats.net). Statistical significance was set to $p < 0.05$.

3. Results

3.1. Total CAJIS score correlates with age

We evaluated the total CAJIS score as a function of age in 144 individuals with classic FOP (74 females, 70 males). The age range of patients in this study was 0.42 to 59 years, represented by the following distribution: 0–9 years (n = 40), 10–19 (n = 43), 20–29 (n = 33), 30–39 (n = 19), 40–49 (n = 4), 50–59 (n = 5). Fig. 1 shows that total CAJIS score is correlated with age based on a presumptive linear relationship and is similar between males and females [R^2 (females) = 0.576; R^2 (males) = 0.654].

3.2. Regional CAJIS scores correlate with age

Higher CAJIS score was associated with significantly greater average age in the axial skeletal regions (Fig. 2), right upper extremity (Fig. 3) and right lower extremity (Fig. 4). There were no differences in CAJIS scores between right and left extremities (data not shown). Post-hoc analysis of all joint locations, and of all locations except the neck and thoraco-lumbar spine, revealed that a CAJIS score of 2 or 1 was associated with significantly greater age, respectively, compared to CAJIS score of 0.

3.3. Upper extremity CAJIS predicts ADL status

Fig. 5 shows the relationship between ADL status and CAJIS score of the upper extremities. Individuals who required some or complete help with ADLs had significantly higher CAJIS scores compared to those who were independent for ADLs. By Chi-square analysis, individuals with a low CAJIS score were likely to be independent for ADLs and those with a high CAJIS score were likely to require some or complete help with ADLs [χ^2 (2, N = 144) = 59.72, $p < 0.001$].

Table 2
CAJIS recording template.

CAJIS Recording Template

Name:_____

DOB:_____ **Age:** _____

Date: _____

Disability: Walks: _____
Uses wheelchair: _____
Needs **some** assistance with activities of daily living:_____
Needs **complete assistance** with activities of daily living:_____

	Affected (1)	Functionally ankylosed (2)	
Neck			
Thoracic & lumbar spine			
Jaw			
R shoulder			
L shoulder			
R elbow			
L elbow			
R wrist			
L wrist			
R hip			
L hip			
R knee			
L knee			
R ankle			
L ankle			
TOTAL			
			SUMMATION

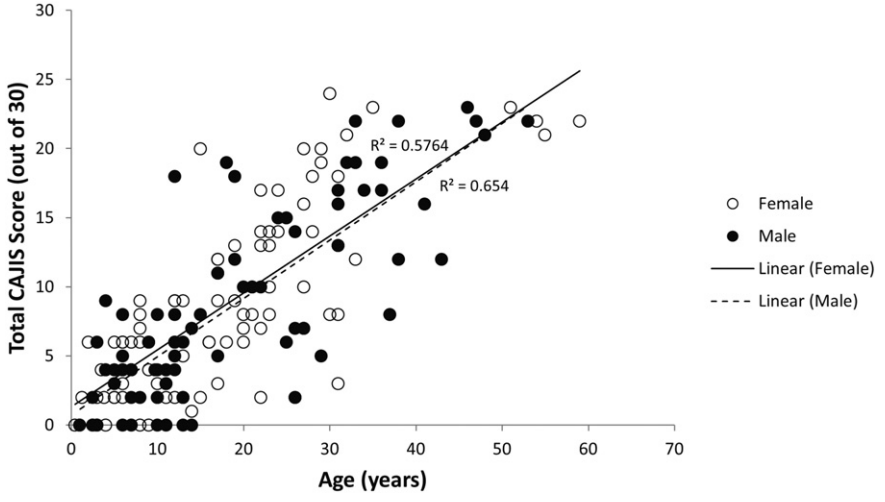

Fig. 1. CAJIS scores are correlated with age and similar between males and females. N = 144 assessments. R^2 (males) = 0.654, R^2 (females) = 0.576, coefficients of determination.

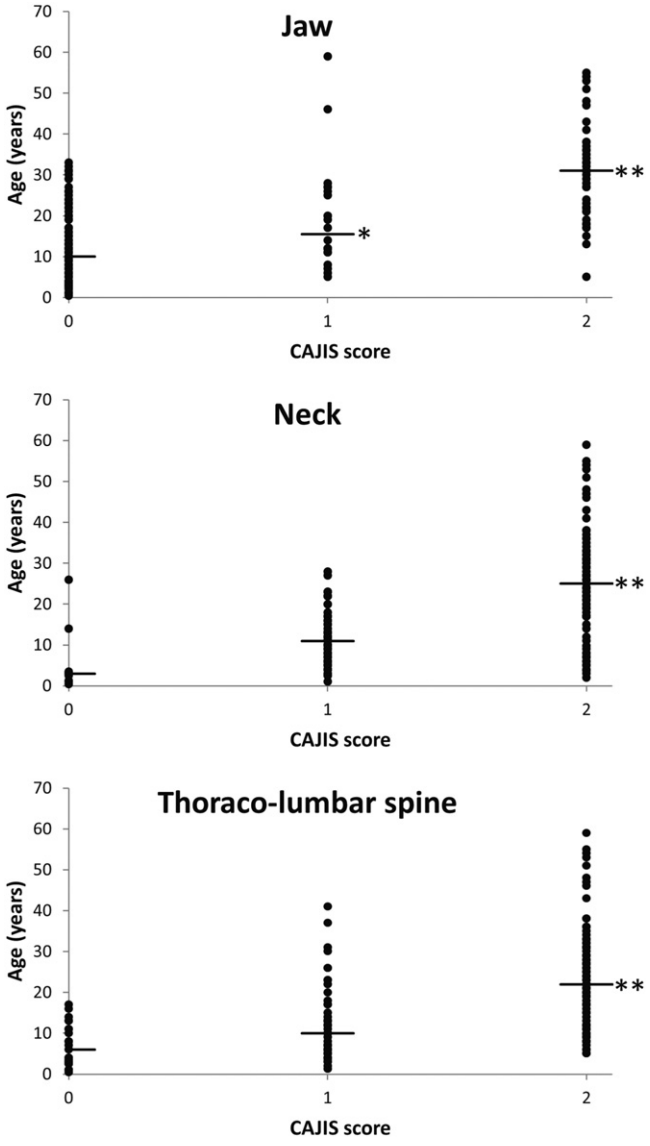

Fig. 2. CAJIS scores are significantly related to age in axial skeletal regions by 1-way ANOVA ($p < 0.0001$for each site). Post-hoc analysis (compared to CAJIS score of 0): **, $p < 0.01$; *, $p < 0.05$. Cross bars indicate medians. N = 144 assessments.

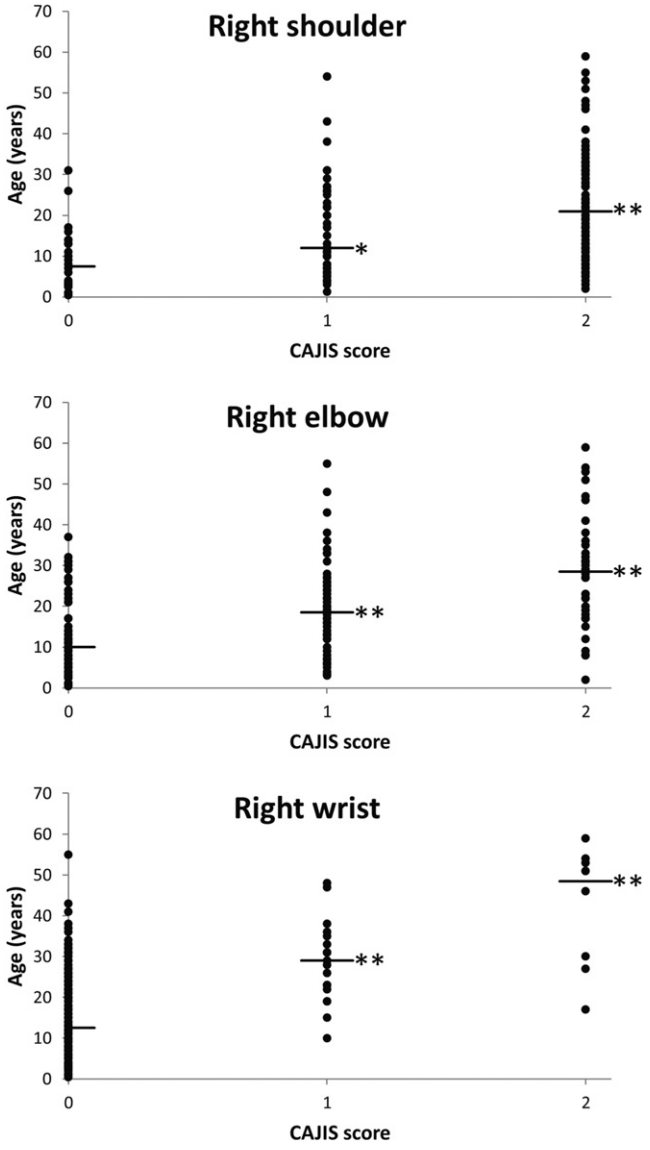

Fig. 3. CAJIS scores are significantly related to age in the right upper extremity by 1-way ANOVA ($p < 0.0001$ for each site). Post-hoc analysis (compared to CAJIS score of 0): **, $p < 0.01$; *, $p < 0.05$. Cross bars indicate medians. N = 144 assessments.

3.4. Lower extremity CAJIS predicts ambulatory status

Fig. 6 shows the relationship between ambulatory status and CAJIS score of the lower extremities. Individuals who required the use of a wheelchair, either as needed or exclusively, had significantly higher CAJIS scores compared to those who were exclusively ambulatory. By Chi-square analysis, individuals with a low CAJIS score were likely to be ambulatory and those with a high CAJIS score were more likely to require a wheelchair [χ^2 (2, N = 144) = 81.85, $p < 0.0001$].

3.5. Inter-rater reliability with CAJIS is very high

The inter-rater difference in CAJIS scores was 0.96 (out of 30) and the median difference was 1. The inter-rater correlation in the application of the CAJIS is very high (Fig. 7, $R^2 = 0.971$).

4. Discussion

Functional mobility assessment of FOP will be essential to support clinical trials of investigational agents. We therefore developed a simple, rapidly-administered, clinically-applicable CAJIS for FOP that could be adapted to any clinical venue. We show here that CAJIS scores provide an accurate and reproducible snapshot of total body and regional mobility burden of FOP that correlates with age and functional status.

There are several limitations of the CAJIS. First, each major joint is weighted equally except for the hands and feet which are minimally involved with HO and are excluded from the analysis. The functional implications of joint immobility vary between individuals and may be related to handedness, sequence of joint involvement, or final position of an ankylosed joint. Detailed position and ankylosis diagrams could be rendered for each individual but would be cumbersome and have limited inter-patient utility.

Second, axial involvement is less heavily weighted in the CAJIS than appendicular involvement, but is designed to reflect that functional mobility is affected regionally in the neck and back rather than in specific intervertebral joints. Third, the scale does not assess incremental loss of joint function that can result from aborted flare-ups or disease activity between flare-ups. In fact, CAJIS score is not necessarily linked with flare-up frequency or disease severity associated solely with previous flare-ups. The reasons for this are that the CAJIS is a measure of global

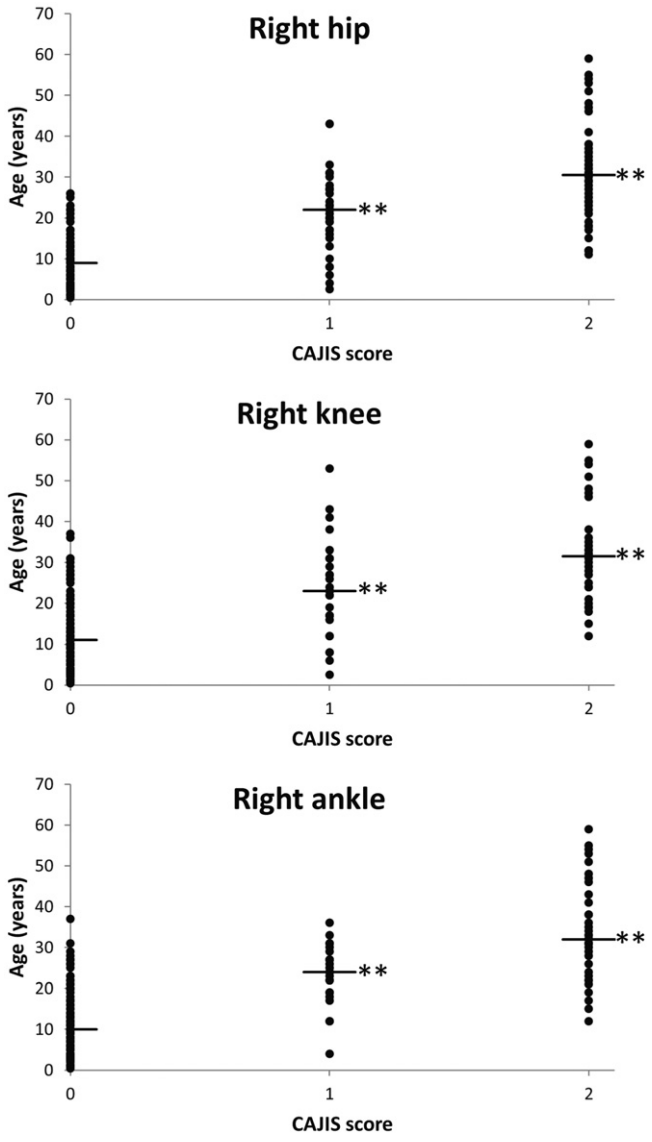

Fig. 4. CAJIS scores are significantly related to age in the right lower extremity by 1-way ANOVA ($p < 0.0001$ for each site). Post-hoc analysis (compared to CAJIS score of 0): **, $p < 0.01$; *, $p < 0.05$. Cross bars indicate medians. N = 144 assessments.

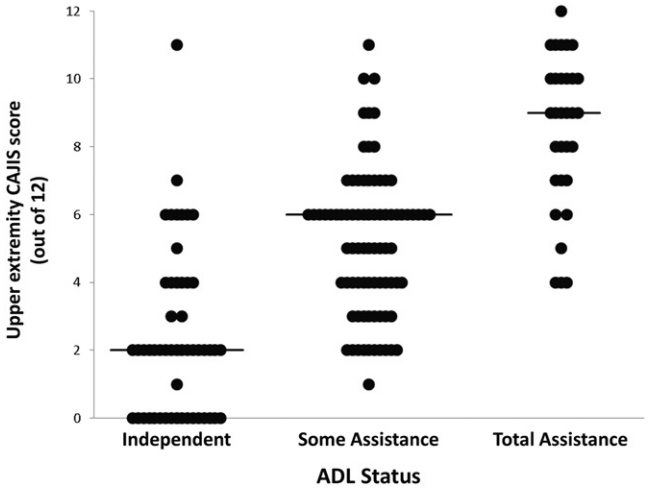

Fig. 5. Upper extremity CAJIS score predicts ADL status. One-way ANOVA, $p < 0.05$; Tukey post-hoc analysis Independent versus Some Assistance, $p = 0.001$; Independent versus Total Assistance, $p = 0.001$. Cross bars indicate medians. N = 144 assessments.

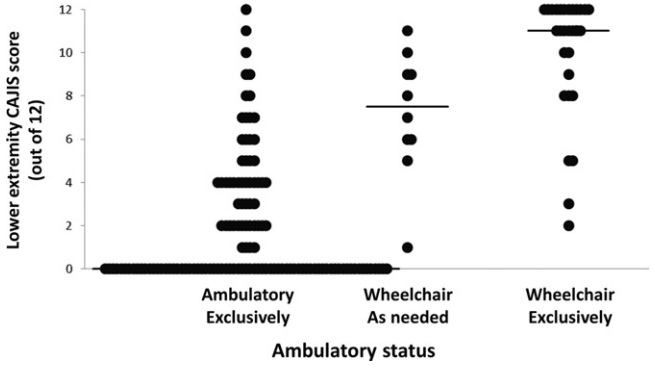

Fig. 6. Lower extremity CAJIS score predicts ambulatory status. One-way ANOVA, $p < 0.05$; Tukey post-hoc analysis Ambulatory Exclusively versus Wheelchair As Needed, $p = 0.001$; Ambulatory Exclusively versus Wheelchair Exclusively, $p = 0.001$. Cross bars indicate medians. N = 144 assessments.

joint dysfunction due to all causes (e.g., heterotopic ossification due to flare-ups, accelerated arthritis, impingement of a joint due to osteochondromas, joint dysplasias, and intra-articular synovial osteochondromatosis), flare-ups to do always lead to heterotopic ossification (or heterotopic ossification that impairs joint function), and FOP progression occurs without flare-ups in almost half of patients. Fourth, we limited the initial CAJIS evaluation to those who had classic FOP both phenotypically and genotypically (97% of FOP patients worldwide) in order to preserve the fidelity of analysis [11,16]. However, future CAJIS evaluation of patients with FOP variants is desirable and applicable.

The CAJIS can be used at any age, with the approach to assessment only differing at younger ages where patients may not fully respond to prompting to actively move joints. In these cases, the approach then becomes one of observation of spontaneous movements in the course of normal activities. Very young patients who have not reached certain milestones, such as dressing independently or walking, cannot be evaluated for disabilities associated with activities daily living.

Although the CAJIS is not meant to replace detailed range-of-motion assessment for any particular joint, it is designed to enable a rapid assessment of total body mobility burden in any clinical setting. Its limitations however should not obscure the central value of the CAJIS score for FOP: a rapid, comprehensive, cumulative analogue assessment of joint involvement that is independent of the rate, timing, order, or position of progressive disease activity. Based on the average change in cross-sectional total CAJIS score over time, we estimate that the score increases by about 0.5 per year (across all ages). This suggests that the CAJIS should be assessed at least every two years to detect an increase in the CAJIS of one. However, younger patients can be expected to accumulate joint dysfunction more quickly than older patients, and so annual assessment by CAJIS may be more appropriate. Presently, CAJIS

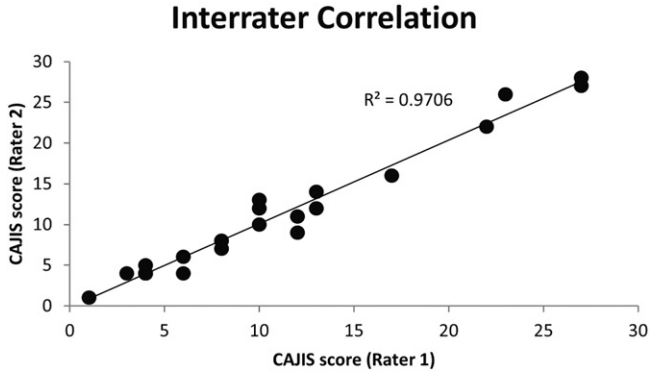

Fig. 7. Inter-rater correlation in the application of the CAJIS is very high. N = 23; $R^2 = 0.971$, coefficient of determination ($p < 0.0001$).

evaluations have been incorporated into the design of two ongoing clinical trials (clinicaltrials.gov/fop).

5. Conclusions

We developed and validated a simple, rapidly-administered, cumulative analogue joint involvement scale (CAJIS) for FOP. CAJIS scores correlated with patient age, ambulatory and ADL status with excellent inter-rater variability. The CAJIS evaluation can be performed rapidly in any clinical setting.

Conflict of interest

The authors declare that they have no competing interests.

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Authors' roles

Conception and design of the work were by FSK and RJP. Collection and/or assembly of data were by FSK and RJP. The manuscript was written by FSK and RJP, with revisions by MA. Data analysis and interpretation were performed by all authors. The manuscript was approved by all authors.

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