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Novel approach to estimate Osteoarthritis progression – use of the reliable change index in the evaluation of joint space loss

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CP, AJ and HI were involved in the design of the study, the statistical analysis and interpretation of the results. OB, FPD, RC, J-YR and CC all assisted in production of the manuscript. All authors read and approved the manuscript.

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Conflict of interest

Andrew Judge has received consultancy fees, lecture fees and honoraria from Servier, UK Renal Registry, Oxford Craniofacial Unit, IDIAP Jordi Gol and Freshfields Bruckhaus Deringer, is a member of the Data Safety and Monitoring Board (which involved receipt of fees) from Anthera Pharmaceuticals, Inc., and received consortium research grants from Roche.

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Abstract

Objective:

Osteoarthritis-related changes in joint space measurements over time are small and sensitive to measurement error. The Reliable Change (RC) index determines whether the magnitude of change observed in an individual can be attributed to true change. This study aimed to examine the RC index as a novel approach to estimating osteoarthritis progression.

Methods:

Data from 167 men and 392 women with knee osteoarthritis (diagnosed using the ACR criteria) randomised to the placebo arm of the 3-year Strontium Ranelate Efficacy in Knee Osteoarthritis triAl (SEKOIA) and assessed annually. The RC index was used to determine whether the magnitude of change in joint space width (JSW) on radiographs between study years was likely to be true or due to measurement error.

Results:

Between consecutive years, 57 to 69% of participants had an apparent (change less than 0) decrease in JSW, while 31% to 43% of participants had annual changes indicating improvement in JSW. The RC index identified decreases in JSW in only 6.0% between baseline and year 1 and 4.5% between the remaining study years. The apparent increases in JSW were almost eliminated between baseline and year 1, and between years 1 and 2 only 1.3% had a statistically significant increase, dropping to 0.9% between years 2 and 3.

Conclusion:

The RC index provides a method to identify change in JSW, removing many apparent changes that are likely to be due to measurement error. This method appears to be useful for assessing change in JSW in clinical and research settings from radiographs.

Significance and Innovations:

- The aim of this research was to assess the effectiveness of the reliable change index as a novel approach to estimating OA progression, to date no studies have been identified that apply the RC index methodology within musculoskeletal research.

- Interestingly, the reliable change index provides a useful method to identify change in joint space width, removing many of the apparent changes that are likely to be due to measurement error. When compared to crude differences in joint space width measurements, implementation of the reliable change index dramatically reduced the proportions of study participants that were identified as having statically reliable change.

- This method appears to be useful for assessing change in JSW clinical and research settings from radiographs, and may have wider applications to other imaging modalities.

Introduction

Osteoarthritis (OA) is one of the most widespread musculoskeletal disorders worldwide (1, 2), and the knee is a commonly affected joint (3). During natural disease progression the joint affected will have dramatic structural changes, which lead to increasing levels of pain and disability for the sufferer.

Although pain is the most commonly reported manifestation of knee OA (5), it is important to be able to quantify structural disease progression to aid in understanding the risk factors for OA progression and to evaluate non-pharmacological and pharmacological treatments. In epidemiological studies of knee OA, monitoring of structural disease progression has conventionally been based on a radiographic definition of knee OA (6), and knee joint space width (JSW), as a continuous measure, is currently the only Food and Drug Administration (FDA) approved endpoint for clinical trials assessing potential disease-modifying OA drugs (7). JSW refers to measurement of the minimum medial tibiofemoral interbone distance and is assessed in a standard metric scale of millimetres. Knee JSW measurements are small, and in knees from healthy individuals, maximum values are around 8mm (8). However it has also been estimated that joint space measurements could be in error by up to 1mm (9), making it difficult to distinguish real deterioration in disease from measurement error. Previous studies have demonstrated that both the technique used to read the radiograph and positioning of the knee during the radiograph can have a substantial influence on measured JSW (10, 11).

To date, no single gold standard statistical method is recommended in epidemiological studies that focus on disease progression through monitoring JSW measurements. When JSW measurements have been shown to be normally distributed, OA disease progression has been compared between groups using the simple method of calculating the mean difference between measurements, and then testing whether group differences are significant using such statistical techniques as paired t-tests (12). Non-parametric rank comparisons have also been used to compare structural change if JSW measurements have a skewed distribution (13). However, such statistical techniques will only reveal differences in means between groups or indicate whether a population mean joint space has changed over time; such methods give no information on changes within individuals. An individual's change is the observed difference between two measurements taken at different times, and this may be dominated by measurement error in either or both measurements. In addition to obscuring disease deterioration, measurement error may lead to an apparent increase in joint space being observed. Due to the pathological process associated with OA i.e. cartilage volume loss, with ultimate involvement of underlying bone, it can be hypothesized that any significant observed increase in JSW arises as a result of measurement error. Therefore it is important, in both research and clinical settings, to minimise the effect of measurement error to identify differences that are more likely to be due to real change in disease. In research, it is important to ensure that the effects of any treatment or behavioural factors that are being related to disease progression are correctly identified. In a clinical setting, identification of rapid radiological progression may inform clinical management.

The Reliable Change (RC) index is a statistical method for identifying whether an observed change within an individual is meaningful in the presence of measurement error (14). The RC index provides a method of determining whether an individual's observed change is likely to

be true or whether it is attributable to measurement error; the greater the error in the measurement under investigation, the lower the likelihood that an observed change can be attributed to deterioration.

To date, the RC index has been mainly used in health psychology, and little is known about its value outside this setting (15). We therefore assessed the use of the RC index in a clinical research setting by implementing the index as a novel approach to estimate OA progression. We considered measurements of knee JSW taken at yearly intervals, within the control arm of an international, multicentre, randomised controlled trial of therapy for knee OA RC index results were compared with crude differences, and the well-recognised cut-points of 0.5 and 0.8mm in joint space narrowing (JSN) (16).

Methods

Study design

This study uses data from patients randomised to the placebo arm of the 3-year Strontium Ranelate Efficacy in Knee OsteoarthrItis triAl (SEKOIA) (17). This was an international trial established to assess the effect of a drug treatment, strontium ranelate, on radiological and clinical progression of OA in the knee joint. Patients were recruited into the trial between 2006 and 2008 from 98 study centres across 18 different countries and were randomised to either a drug regime of strontium ranelate 1g/day, strontium ranelate 2 g/day, or a placebo treatment. Participants were recruited from secondary care establishments where they were already receiving outpatient care for knee OA. To be eligible for entry into SEKOIA, ambulatory

Caucasian men and women aged over 50 years had to have a primary diagnosis of knee OA as defined by the clinical criteria of the American College of Rheumatology (ACR) (18). On radiograph, patients had to have knee K&L grade 2 or 3 (19); and JSW between 2.5mm and 5mm at an inclusion screen and predominant OA of the medial tibiofemoral compartment. The SEKOIA study conformed to the principles of the Declaration of Helsinki and the trial is registered (ISRCTN41323372).

Radiographs were performed at the time of selection and then annually on the target knee, using a standardised technique described elsewhere (20). The radiographer recorded a fixed flexion posterioanterior view (fixed angle 10°), using a SynaFlexer^{TM} positioning frame (BioClinica (formerly Synarc), San Francisco, USA) (21). All radiographs were measured centrally (INSERM UMR 1033, Lyon, France) by a single reader blinded to treatment allocation and participant identity. Minimal JSW (mm) at the medial tibiofemoral compartment was measured using a standardised computer-assisted method (22). Radiological progressors were defined as those whose joint space changed by more than 0.5mm or 0.8mm over the 3 year duration of SEKOIA, as per the definition developed by Bruyere et al in 2005(16) (23) .

Reliable change index

The RC index was first developed in 1991 by Jacobson and Truax (14). The principle behind the index is to determine whether the magnitude of change observed in a study participant can be attributed to true change, i.e. the change observed is more than could be explained by the unreliability of the measure. Several variations of the RC index have been proposed (24), however all variations of the index identify the extent to which study participants' current

measurements differ from their previous measurements. All variations of the RC index follow the same fundamental expression:

$$RC\ index = \frac{Y - Y'}{SE};$$

where Y is the study participant's measurement at the latter time point, Y' represents the predicted measurement for the study participant at the latter time point of interest and SE is the standard error of the score. The different approaches to the RC index vary in how they determine the different elements of the RC index. The version of the RC index that will be explored within this study was developed by Christensen and Mendoza (25). The RC index formula for each study participant, which produces a standardised score (RC index) is:

$$RC\ index = \frac{X_2 - X_1}{\sqrt{S_1^2 + S_2^2 - 2S_1S_2r_{xy}}}$$

The predicted score is represented by the study participant's measurement time point 1, X_1, and the same study participant's actual measurement at time point 2 is X_2. The standard error is derived using $S_1^2$and S_2^2 which are the variances of the measurements at time point 1 and 2 respectively, S_1 and S_2 are the standard deviations of the measurements at time point 1 and 2 respectively and r_{xy} is the Pearson's correlation coefficient between the measurements at the two time points. Using this version of the RC index does not require the assumption of equal variance in measurements between time points.

The RC index calculation yields a standardised z-score (i.e. the scores have a mean of 0 and a standard deviation of 1). Following the convention of using 5% level of statistical significance an RC index score of ±1.96 or larger in magnitude denotes a statistically significant difference,

indicating that the change observed reflects more than the fluctuations in the measurement procedure. Each study participant's RC index score can be categorised into one of three categories: an increase (RC index > 1.96), a decrease (RC index<-1.96) or stable (RC index between -1.96 and 1.96). A magnitude of change threshold can be calculated from the standard error derived during the calculation of the RC index, with a level of change in JSW that can be considered statistically reliable being calculated as $1.96*\sqrt{S_1^2 + S_2^2 - 2S_1S_2r_{xy}}$.

Statistical analysis

Study participants' continuous characteristics were checked for normality and summarised using means and standard deviations (SD). Crude differences in JSW were calculated between each SEKOIA study visit to provide a change in JSW in millimetres per year between each study year. The RC index was calculated between each SEKOIA study visit as described above for all study participants. All analyses were undertaken using STATA 13 [StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP].

Results

In the SEKOIA study, 559 patients were randomised to the placebo arm; demographic characteristics of these participants are presented in Table 1. On entry, participants had a median disease duration of just over 4 years, with men having suffered from knee OA longer than women. The majority of participants (63%) had Kellgren and Lawrence grade 2 at baseline, and proportions were similar in men and women. Participants' mean (SD) age was

62.8 (7.5) years, with the mean for men being greater than for women, at 63.8 (7.8) and 62.3 (7.3) years respectively. The mean (SD) JSW at baseline was 3.51 (0.83) mm, which reduced to 3.15 (1.00) mm by the end of the study. The minimum JSW at baseline was 0.65mm, reducing to 0.38mm during the duration of the study and the largest individual reduction in JSW over the study was 3.34mm.

The 472 intention-to-treat placebo population were used here to assess change in JSW; table 2 and table 3 present the crude changes and RC index results across all SEKOIA study years.

Of the 465 study participants who had knee JSW measurement at baseline and year 1, nearly 70% had either no change or an apparent decrease in joint space width over the year when assessing using crude change, and this figure was nearly 60% between the remaining study years (Table 2). An RC index value was calculated for the differences in measurements between each SEKOIA study visit for each study participant. The SD at baseline for all JSW measurements was 0.82 and therefore the variance of JSW measurements at baseline was 0.67, while for all JSW measurements at year 1 the SD was 0.92 and the variance 0.84. The correlation between the two time points was 0.84. As an example, a participant with a baseline JSW of 4.841mm, and a JSW at year 1 of 3.981mm, the RC index value would be:

$$\frac{3.981 - 4.841}{\sqrt{0.67 + 0.84 - 2 * 0.82 * 0.92 * 0.84}} = -1.75$$

Thus the RC index for the study participant indicates that no statistically significant change in JSW has occurred. Performing this calculation for each study participant between baseline and year 1 indicated that 28 (6.0%) study participants had an RC index less than -1.96 when assessing the observed difference. Thus it is only in these 28 study participants that a

statistically reliable decrease in JSW was observed that was larger than would be expected through fluctuation in the joint space measurements or measurement error. A similar pattern was observed between year 1 and year 2, and between year 2 and year 3, with 4.5% and 4.0% respectively having a statistically significant reliable decrease in knee joint space measurements between these years.

Conversely, around 30% of study participants were identified as having an increase in crude JSW measurement between baseline and year 1, and approximately 42% of study participants were identified as having a crude increase between year 1 and year 2, or between year 2 and year 3. Using the RC index calculation, 5 study participants (1.1%) had an RC index greater than 1.96 when the observed differences between baseline and year 1 were assessed. These 5 study participants are of note as they appear to have had an increase in JSW greater than can be explained by the fluctuations of an imprecise measurement procedure. Use of the RC index for measurements between year 1 and year 2, and between year 2 and year 3 indicated that only 5 (1.3%) and 3 (0.9%) study participants respectively had an increase in JSW during those time periods. No study participants were found to be consistently identified as having a statistically significant reliable increase or decrease across all the following time periods: between baseline and year 1, between year 1 and year 2, and between year 2 and year 3.

Of the 336 study participants with measurements at baseline and year 3, 78% had crude decreases in JSW over the 3-year duration, with nearly 36% having had a decrease in JSW more than 0.5mm and 18.5% having had JSN of 0.8mm or more. This measure of progression also identified a greater number of study participants with a decrease in knee JSW than the 11% identified using the RC index score (Table 3). When considering those study participants

who were identified as having a crude increase in JSW between baseline and year 3 (74 study participants) only 1 (0.3%) study participant was still identified as having an increase when using the RC index score.

All RC index values were normally distributed, and a magnitude of change in millimetres (threshold) was calculated by transforming the RC index results to give a change in JSW above which it can be said that statistically reliable change occurred. When calculating the magnitude of change in millimetres using the RC index the magnitude varied between 0.85mm to 1.23mm for the different study periods under consideration.

Very similar patterns were seen when RC index scores were calculated for men and women, and by K&L grade separately.

Discussion

The aim of this study was to assess the effectiveness of the RC index as a novel approach to estimating OA progression, through assessment of knee JSW at yearly intervals. Although it is highly unlikely individual disease progression would be classified using the crude difference alone, if the measurements of the crude differences were taken in isolation it would lead to the conclusion that, between baseline and year 1, 70% of those study participants under observation had a worsening of their knee OA. However use of the RC index indicates that only 6.0% (28) of study participants had a statistically reliable decrease in observed JSW that was larger than would be expected through measurement error in joint space measurements between baseline and year 1. Therefore considerably fewer study participants than initially highlighted through

simple differences can reliably be considered to have had a decrease in joint space. Similar patterns were observed between years 1 and 2, and between years 2 and 3. Considerably more study participants, 10.7% (36), had a statistically reliable decrease in observed change in JSW across the total duration of the SEKOIA trial indicating that reliable change becomes easier to detect when longer time periods exist between joint space measurements. This in part may be explained by there having been greater time for disease progression to have occurred, allowing for potentially greater deterioration, which can be more easily distinguished from the measurement error that is still present.

Conversely, around 31% of study participants from between baseline and year 1, and approximately 42% of study participants between year 1 and year 2, or between year 2 and year 3 were identified as having an absolute increase in JSW. As real increases are extremely unlikely, this shows the impact of measurement error; if crude differences are assessed, without taking any account of measurement error, over a third of study participants would appear to have had some improvement in their knee OA condition. Use of the RC index identified a markedly lower number of 5 participants (1.1%) between baseline and year 1, 5 (1.3 %) between years 1 and 2, and only 3 (0.9%) between years 2 and 3 having an increase in JSW.

To date, no studies have been identified that apply the RC index methodology within musculoskeletal research, not only to monitor joint space measurements but also assess disease deterioration. The RC index has, however, been successfully applied within psychological and neurological research. For example Ferguson et al used the RC index to determine clinically significant change between pre- and post-intervention SF-36 scores that provide a continuous measure of patient health. Ferguson highlighted that the use of the RC index is an important

technique, as assessing crude differences alone does not provide reliable information about whether an intervention has had clinically meaningful effects (26, 27). However an assumption of the RC index is stability measurements between time points and so this method has not been previously applied to assess deterioration. The natural disease progression of OA is a slow process, often taking many years. Therefore the assumption would be that on an annual basis little or no change in JSW in a study participant would have occurred, and so in this new and novel application of the RC index the assumption of stability was upheld.

There are other statistical techniques and metrics currently used within musculoskeletal research to identify whether change has been significant, such as the standard error of the measurement (SEM) or standardized response mean (SRM). However neither of these techniques are appropriate for assessment at the individual level rather the population level. Therefore an advantage of using the RC index is that reliability of an individual study participant's change can be determined, and additionally the estimate of the standard error used within the RC index calculation can be used to quantify the JSW change above which change could be considered statistically reliable. Although the RC index has its merits, there has also been much debate and criticism of the technique (24, 28). One of the major criticisms is that, although all variations of the calculation can be simplified to the same fundamental expression, each approach differs slightly in how the elements of the RC index are calculated. For example, the original definition of the RC index developed by Jacobson and Traux(14) requires an externally-derived test-retest reliability coefficient to be able to calculate the standard error and assumes equal variance in the measurements at both time points. Hinton-Bayre has made a comparison of the different RC variations but there is currently no consensus as to which RC index should be used (24).

A further criticism of the RC index is that the index is specific but not very sensitive, but this is partly due to the magnitude of measurement error within longitudinal studies. Within this study the conventional 5% level of significance was followed, meaning that the cut-point for RC index scores was ±1.96, but this is an arbitrary cut-point and to increase the sensitivity of the RC index a less strict cut-off could be used.

The RC index aims to distinguish true progression of JSN in those with knee OA from measurement error. Although use of JSW longitudinally is the current gold standard for monitoring disease progression, previous studies have shown that inconsistent knee positioning during radiographs can cause a systematic shift in JSW (10) and so change in JSW may be due to change in positioning of the knee during radiograph rather than disease progression. However, previous studies have shown that the use of the inter-margin distance is optimal in reducing variation in JSW due to knee positioning (29). The minimal JSW (mm) at the medial tibiofemoral compartment, the inter-margin distance, was measured in SEKOIA annually from radiographs obtained under strict study protocol (20, 23). Therefore the data in this study were collected with all the associated safeguards around methodology and training, and all radiographs were assessed by one reader, thus reducing measurement error. It is thus likely that the joint space measurements collected during the SEKOIA study contain less measurement error than routine clinical measurements. As there are different radiographic techniques that can be used to obtain knee radiographs it would be important to assess the use of the RC index in data where other methods have been used, particularly in routine clinical practice. However, it is important to remember that the RC index only indicates statistically reliable change and does not provide information about the reason for change. The RC index is thus unable to

distinguish changes in JSW due to variability in the radiographic positioning from disease progression.

As there is no 'gold standard' method for assessing statistically significant change in JSW when assessing OA disease progression, there is no comparator for the RC index. However, the use of this novel approach does take account of measurement error, unlike calculation of crude differences. The formula is also simple enough that summary statistics derived from the study population enable assessment of individual study participants' reliable change

Despite its simplicity, a conceptual problem with the RC index is that no account is taken within the calculation of the duration between the study visits. However application of the RC index informs of thresholds which can be used to further explore change, particularly in a clinical trial setting. It can help with determining study duration and assist in sample size determination. It is also possible that once calculated, the RC index groupings and individual scores could also be used in further statistical analysis to investigate characteristics and phenotypes which may be associated with disease progression, after accounting for the presence of measurement error.

There are some limitations to this study. The study participants already had established OA when recruited into SEKOIA and it would be of value to assess the performance of the RC index in a population with wider variability in JSW. It is notable that the RC index did not remove all apparent increases in JSW. No measure is entirely reliable and there is always a balance between the sensitivity and specificity of the cut points chosen. To eliminate all apparent increases, a higher level of statistical significance could be used within the RC index

calculation, though this would reduce the number of decreases identified. Alternatively, if the concern was about missing true deterioration, a lower level could be used.

Few studies have assessed long-term reduction of joint space in a population of patients with OA of the knee. Applying the RC index within knee OA disease progression studies should enable a greater understanding of the progression of JSN. If the value of RC indices is confirmed in other populations it may aid research, lead to better management of patients with the disease, and assist in improving and/or maintaining quality of life for a patient with knee OA.

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Table 1 Participants characteristics

	Men *(n = 167)*		**Women** *(n = 392)*		**All** *(n=559)*	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (years)	63.8	7.8	62.3	7.3	62.8	7.5
BMI (Kg/m^2)	29.8	4.1	29.8	5.5	29.8	5.1
Severity of knee osteoarthritis						
Joint space width at baseline (mm)	3.65	0.85	3.44	0.82	3.51	0.83
Joint space width at 36m (mm)	3.20	1.06	3.12	0.98	3.15	1.00
Joint space narrowing over 36m study duration (mm)	-0.44	0.68	-0.40	0.60	-0.41	0.63
	Minimum	**Maximum**	**Minimum**	**Maximum**	**Minimum**	**Maximum**
Joint space width at baseline (mm)	0.99	5.43	0.65	6.11	0.65	6.11
Joint space width at 36m (mm)	0.38	5.47	0.58	5.50	0.38	5.50
Joint space narrowing over 36m study duration (mm)	-2.25	1.59	-3.34	0.70	-3.34	1.59
	Median	**Range**	**Median**	**Range**	**Median**	**Range**
Disease duration (months)	58	0 - 502	49	0 - 457	51	0 - 502
	n	**%**	**n**	**%**	**n**	**%**
Kellgren and Lawrence Grade						
2	103	61.7	247	63.0	350	62.6
3	64	38.3	145	37.0	209	37.4

Table 2 Crude changes and Reliable Change Index results

	Baseline to year 1		Year 1 to year 2		Year 2 to year 3	
	N		**N**		**N**	
Total in study	465		400		329	
	N	**%**	**N**	**%**	**N**	**%**
Crude increase	146	31.4	171	42.8	138	41.9
Crude decrease	319	68.6	229	57.3	191	58.1
RCI increase	5	1.1	5	1.3	3	0.9
RCI decrease	28	6.0	18	4.5	13	4.0
Progression threshold (mm)	0.91		0.82		0.88	

Table 3 Crude changes, radiological progressors and Reliable Change Index results

	Baseline to year 3 (total study duration)	
	N	
Total in study	336	
	N	**%**
Crude increase	74	22.0
Crude decrease	262	78.0
Radiological progressor (JSN of 0.5mm)	120	35.7
Radiological progressor (JSN of 0.8mm)	62	18.5
RCI increase	1	0.3
RCI decrease	36	10.7
Progression threshold (mm)	1.23	

Appendix 1

Executive Committee

J-Y Reginster (Chairman), C Cooper (International Coordinator), C Christiansen, P Delmas (deceased July 2008), R Chapurlat (from 2008 onward), H Genant, J Zacher, N Bellamy.

Steering Committee

C Cooper (International Coordination, Chair), National Coordinators (see below), and representatives from the Central Reading Centres.

Safety Committee

C Speirs, G Bréart, O Meyer.

Central Reading Centre (Lyon)

D Gensburger, M Arlot, J-P Roux, R Chapurlat

Central Reading Centre (Liege)

R Deroisy, O Bruyère, J-Y Reginster.

National Coordinators

P Sambrook (Australia), B Leeb (Austria), A Verbruggen (Belgium), W Bensen (Canada), T Hala (Czech Republic), M Holm-Bentzen (Denmark), I Valter (Estonia), X Chevalier (France), B Swoboda (Germany), S Adami (Italy), M Kloppenburg (The Netherlands), E Grazuleviciute (Lithuania), J Badurski (Poland), J Branco (Portugal), E Nasonov (Russia), F Navarro (Spain), T Spector (UK).

Investigators

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