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OA phenotypes, rather than disease stage, drive structural progression – identification of structural progressors from 2 phase III randomized clinical studies with symptomatic knee OA

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SUMMARY

Background/Purpose: The aim of this study was to identify key characteristics of disease progression through investigation of the association of radiographic progression over two years with baseline Joint Space Width (JSW), Kellgren—Lawrence (KL) grade, Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain, Joint Space Narrowing (JSN), and BMI.

Methods: Data from 2206 subjects (4390 knees) were combined for this *post-hoc* analysis of two randomized, double-blind, multi-center, placebo-controlled phase III trials (NCT00486434 and NCT00704847) that evaluated the efficacy and safety of 2-years treatment with oral salmon calcitonin of subjects with painful knee osteoarthritis (OA).

Results: There was a clear positive and significant correlation between KL grade and WOMAC pain and total WOMAC, albeit the variance in pain measures was from min-to-max for all KL categories, emphasizing the heterogeneity of this patient population and pain perception. 32% of target knees did not progress, and only 51% had changes over minimum significant change (MSC). BMI, KL-Score and WOMAC pain was diagnostic, but only KL-score and pain had prognostic value, albeit pain in a non-linear manner.

Conclusion: These data clearly describe significant associations between KL grade, JSW, pain and BMI in patients with symptomatic knee OA. KL grade, BMI and WOMAC pain were diagnostically associated with OA based on JSW but only KL-score and pain in a non-linier fashion was prognostic. 50% of patients did not progress more than MSC, highlighting the importance for identification of structural progressors and the phenotypes associated with these. These results suggest that disease phenotypes, rather than disease status, are responsible for disease progression.

Introduction

Osteoarthritis (OA) is the most common form of arthritis[1–3], One of the most pressing concerns in medical science is the need to treat the right patients with the right medicine. However, in light of the current absence of structure modifying treatments for OA, an even more pressing concern is the need to identify the optimal patient population in which to test a given treatment.

The exact etiology of OA is still relatively unknown, but factors known to be involved include risk factors such as age[4], obesity[4–7], genetic predisposition[4,8], joint mal-alignment[9], acute joint injury[4,10] and reduced gender hormone levels in relation to menopause[2]. These multi-factorial disease etiologies present a challenge to instituting Personalized Health Care (PHC) in OA[11], namely the prospect of providing the right patient with the right drug; the multi-factorial nature of the disease also presents a challenge regarding selection of patient subtypes for targeted drug

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development. It is believed that the ability to segregate patient subtypes would greatly facilitate the development of structure modifying treatments; however, this supposition needs to be tested.

Prediction of OA progression is one of the most important topics in the OA field. As reported from the Osteoarthritis Initiative (OAI), only 4% of OA patients without symptomatic OA and up to 14% with incident OA progress over a 1 year period[12]. This suggests that OA disease activity may vary between periods of inertia and periods of faster progression. Consequently, it is essential to identify the drivers of disease progression in order to develop effective interventions.

OA may have different phenotypes[13]. The field in particular has focused on the articular cartilage phenotype[14] and more recently, a bone driven cartilage progression phenotype[15]. However, a degree of inflammation is now recognized as being a central part of the OA pathology[16,17]. While inflammation may not be the initiator of disease, it may at some point be the driver of disease progression[18]. As multiple tissues are affected, it seems quite unlikely that all OA patients would be effectively treated with the exact same interventions. It is plausible that the failure, in part, of numerous phase II/III OA clinical trial failures, such as; iNOS[19], bisphosphonates[20], and calcitonin[15,21] and the partial failure of strontium ranelate[22], has been due to the failure to identify patient subpopulations which matched the pharmaco-dynamics of the drug[11].

Oral salmon calcitonin (sCT), recently failed to meet study endpoints in two randomized phase III trials[21,23]. The combined information of the two phase III clinical studies of sCT may provide needed insights into the means of identifying subpopulations of OA patients who would be ideally suited for particular interventions. The aim of this *post-hoc* analysis to study baseline characteristics, such as Joint Space Width (JSW), Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain and function scores, of patients with knee OA from two randomized, multicenter, placebo-controlled phase III trials, to identify different phenotypes associated with progression.

Methods

Subjects and methods

This is the first *post-hoc* analysis and was performed using pooled baseline data from 2206 patients participating in two randomized, multicenter, placebo-controlled phase III trials evaluating efficacy and safety of an oral formulation of sCT vs placebo in patients with painful OA of the knee (www.clinicaltrials.gov registration number NCT00486434 and NCT00704847)[49]. The main inclusion criteria for the target knee were 1: American College of Rheumatology (ACR) OA criteria[24], 2: Kellgren–Lawrence (KL) Index: Grades 2 or 3 of the medial tibio-femoral joint, 3: American Rheumatism Association (ARA) functional class I, II, or III[25], 4: a JSW of $\geq$2.0 mm of the medial tibio-femoral joint (measured from knee radiographs), and 5: significant pain, defined as a WOMAC subscale (five questions) result of $\geq$150 mm. In CSMC021C2301, patients with pain <150 mm but with a WOMAC function score of $\geq$510 mm were allowed inclusion. For this analysis, data from both the target knee and the contra-lateral knee were included for all patients, yielding data from 4390 knees. As stated, this population was originally selected to have painful OA in the target knee however; present data includes baseline data from both the target knee and the contra-lateral knee, thus enriching the selected population with a wider range of knee phenotypes.

Radiographic evaluation

Radiographs by X-rays were performed to assess KL grade and to measure JSW, using a standardized, quality-controlled method. The X-ray images were read centrally by the same radiologist.

Pain evaluation

Knee OA pain was evaluated using the WOMAC index pain subscale. Patients answered each of the five questions on a 100 mm scale where 0 is no pain at all, and 100 mm is the worst imaginable pain. The total score is the sum of all five results. In the trials that used for this scale, a total WOMAC-assessed pain of $\geq$150 mm was an inclusion criterion, however in CSMC021C2301, patients with pain <150 mm but with a WOMAC function score of $\geq$510 mm were also included.

Statistical methods

The WOMAC pain sub-score, stiffness subs-core, and function sub-score consisted of the sum of the five pain questions, two stiffness questions, and 17 function questions, respectively. Joint space narrowing (JSN) over the 2-year study period was calculated as the difference between the JSW at baseline minus the JSW at month 24. In the assessment of predictors for JSW or the 2-year JSN, quartile group of BMI at baseline (Q1: below 25.6 kg/m^2; Q2: 25.6–28.4 kg/m^2; Q3: 28.4–31.8 kg/m^2; Q4: 31.8 kg/m^2 or above) and quartile group of WOMAC pain (Q1: 184 mm or below, Q2: 185–231 mm, Q3: 232–289 mm, Q4: 290 or above) in target knee at baseline was calculated. The lowest WOMAC pain quartile group was additionally divided into two groups of WOMAC pain from 0 to 149 mm (Q1a) and 150–184 mm (Q1b) in order to take the inclusion criteria of pain of target knee into account when including both target and contra-lateral knee in the model analysis. A random effect mixed model was used for assessment of predictors of the JSW at baseline and the 2-year JSN. The initial mixed model of JSW included JSW as the dependent variable, and the independent variables of KL grade (KL 0, 1, 2, 3, and 4), knee (target, contra-lateral knee), gender, age group (65 years, $\geq$65 years), BMI in quartiles (Q1, Q2, Q3, and Q4), WOMAC pain in quartiles (quartile Q1a, Q1b, Q2, Q3, and Q4), and study as fixed effects as well as all pair-wise interaction terms. Subject was included as a random effect to take the clustering effect into account that each subject contributed with two knees. The mixed model was stepwise reduced by excluding the least significant term until all remaining terms were significant. A similar initial mixed model was used for modeling of JSN. This model included data from the placebo group with JSW change as the dependent variable, and the independent variables of KL grade (KL 1, 2 and 3), baseline JSW group (1–2 mm, 2 mm or above), knee (target, contra-lateral knee), gender, age group (<65 years, $\geq$65 years), BMI in quartiles, WOMAC pain (0–149 mm, 150–184 mm, 185–231 mm, 232–289 mm, 290–500 mm), and study as fixed effects as well as all pair-wise interaction terms. Subject was included as a random effect, and the mixed model was stepwise reduced as described above. A term in the models was considered significant if the *P*-value was less than 5%. All statistical calculations were performed using the SAS software package.

Results

Baseline patient characteristics

Baseline patient demographics are shown in Table I.

Table I
Demographic characteristics

Parameter	CSMC021C2301 N = 1176	CSMC021C2302 N = 1030	All N = 2206
Gender − n (%)			
Male	372 (31.6)	404 (39.2)	776 (35.2)
Female	804 (68.4)	626 (60.8)	1,430 (64.8)
Age (years)			
Mean (SD)	64.5 (6.63)	64.3 (6.93)	64.4 (6.77)
Median (min, max)	64.3 (50, 80)	63.7 (51, 80)	64.2 (50, 80)
Age group (years) − n (%)			
<65	614 (52.2)	580 (56.3)	1194 (54.1)
≥65	562 (47.8)	450 (43.7)	1012 (45.9)
Race − n (%)			
Caucasian	1071 (91.1)	873 (84.8)	1944 (88.1)
Asian	104 (8.8)	144 (14.0)	248 (11.2)
Other	1 (0.1)	13 (1.3)	14 (0.6)
BMI (kg/m^2)			
Mean (SD)	29.0 (4.70)	29.0 (5.21)	29.0 (4.95)
Median (min, max)	28.4 (18.1, 57.7)	28.3 (17.3, 50.3)	28.4 (17.3, 57.7)
KL grade − n (%)			
Target knee			
KL 2	1032 (87.8)	809 (78.5)	1841 (83.5)
KL 3	144 (12.2)	221 (21.5)	365 (16.5)
Contra-lateral knee			
Not applicable	12 (1.0)	10 (1.0)	22 (1.0)
KL 0	36 (3.1)	56 (5.4)	92 (4.2)
KL 1	230 (19.6)	186 (18.1)	416 (18.9)
KL 2	644 (54.8)	458 (44.5)	1102 (50.0)
KL 3	222 (18.9)	293 (28.4)	515 (23.3)
KL 4	32 (2.7)	27 (2.6)	59 (2.7)
JSW (mm)			
Target knee			
Mean (SD)	3.37 (0.96)	3.47 (1.02)	3.42 (0.99)
Median (min, max)	3.3 (1.8, 6.7)	3.5 (1.8, 7.3)	3.4 (1.8, 7.3)
Contra-lateral knee			
Mean (SD)	3.31 (1.37)	3.33 (1.48)	3.32 (1.42)
Median (min, max)	3.5 (0.0, 8.0)	3.5 (0.0, 8.0)	3.5 (0.0, 8.0)
WOMAC pain (mm)			
Target knee			
Mean (SD)	237 (76)	247 (70)	242 (73)
Median (min, max)	229 (40, 500)	235 (117, 495)	232 (40, 500)
Contra-lateral knee			
Mean (SD)	179 (110)	184 (114)	181 (112)
Median (min, max)	173 (0, 500)	183 (0, 500)	178 (0, 500)

Table II
Spearman correlation (Rho) of baseline characteristics and baseline JSW

JSW	KL grade at baseline		BMI	Age	WOMAC pain	KL
Target knee	2−3	Rho	−0.122	−0.06	−0.08	−0.28
		P-value	<0.0001	0.005	0.0004	<0.0001
		n	2206	2206	2205	2206
Contra-lateral knee	0 to 4	Rho	−0.14	−0.11	−0.20	−0.37
		P-value	<0.0001	<0.0001	<0.0001	<0.0001
		n	2184	2184	2094	2184
Contra-lateral knee	0−1	Rho	−0.04	−0.10	−0.06	−
		P-value	0.33	0.03	0.19	
		n	508	508	492	
Contra-lateral knee	2−3	Rho	−0.15	−0.07	−0.20	−
		P-value	<0.0001	0.008	<0.0001	
		n	1617	1617	1550	
Contra-lateral knee	4	Rho	−0.21	−0.20	0.01	−
		P-value	0.12	0.13	0.94	
		n	59	59	52	

function of KL grades is shown in Fig. 1(A); this also shows that the patient disease characteristic of JSW was comparable in the two studies, CSMC021C2301 and CSMC021C2302. As a possible result of the inclusion criteria, for KL grade 3 knees, the mean JSW of the signal knee was significantly higher than that of the non-signal knee [Fig. 1(B)].

Association between KL grade and WOMAC score

The mean impact on pain and function of a KL grade 4 severity of OA (1034 ± 323 mm) was roughly double that of a KL grade 0 knee without radiographic OA (475 ± 390 mm) [Fig. 1(C)]. As observed for both pain and JSW, for all KL grades except KL grade 4 (with a minimum reported function score of 270 mm), there was a high level of variation in function scores ranging from no impairment (0 mm) to nearly the highest possible level of impairment.

Mean baseline WOMAC pain-score (five questions) in all knees (target and contra-lateral) stratified by KL grade is given in Table IV. Mean OA pain was correlated with KL grades in a near-linear fashion (Table IV and Fig. 1(D)). Mean pain ranged from 135 mm (95% confidence interval (CI) of mean 112−157 mm) at KL grade 0, to 285 mm (95% CI of mean: 254−315 mm) in KL grade 4 knees. The level of pain experienced by OA patients, regardless of KL grade, varied greatly as reflected by scores ranging from absolutely pain free (0 mm) to the worst imaginable pain (500 mm) for all KL grades, except for the KL 4 group wherein the lowest reported value was 40 mm (Table IV). Although the mean level of pain in the target knees was similar for KL grades 2 and 3, the KL grade 2 target knees were associated with more pain than contra-lateral knees, whereas the KL grade 3 target knees had similar mean pain scores to KL grade 3 contra-lateral knees [Fig. 1(C)].

Diagnostic correlations − burden of disease

Baseline JSW was significantly correlated with BMI, age, WOMAC pain and KL grade (Table II) for both the target and contra-lateral knees. Interestingly, these correlations were only significant in the subset of contra-lateral knees that were KL grades 2−3, which represented the largest subgroup by severity grade.

Association between KL grade and mean JSW

Mean baseline JSW in all knees (target and contra-lateral) stratified by KL grade is shown in Table III. The mean JSW did not differ greatly between KL grades 0 to 2 knees, but was markedly reduced in KL 3 knees and further reduced in KL 4 knees. There was high inter-patient variation, but a highly statistical correlation between KL grade and JSW, in the target knee −0.29 P < 0.0001 and contra-lateral knee −0.39, P < 0.0001. In the KL 2 group of 2943 knees, a mean JSW of 3.60 mm with a standard deviation of ±0.98 mm was observed, while the mean JSW of KL grade 3 knees was 2.42 mm ± 1.48 mm (Table III). The distribution of JSW as a

Table III
JSW (mm) in KL grade groups

KL grade	N (knees)	Mean JSW	STD	SEM	Range of JSW
All	4390	3.37	1.22	0.018	0−8.0
KL 0	92	3.92	0.82	0.086	2.4−6.4
KL 1	416	3.74	0.83	0.041	1.1−6.6
KL 2	2943	3.60	0.98	0.018	0−7.7
KL 3	880	2.49	1.48	0.050	0−7.9
KL 4	59	1.49	2.52	0.328	0−8.0
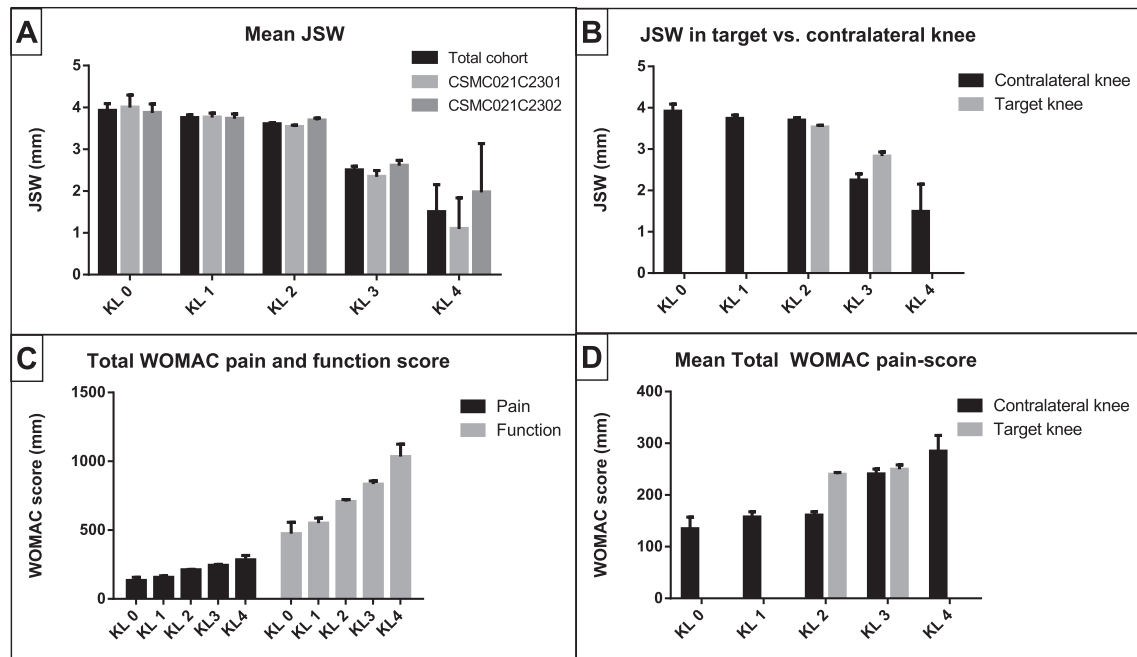
Fig. 1. Baseline JSW, pain and function, stratified by KL Grade. A) Mean JSW in osteoarthritic knees graded KL 0–4 in the total cohort ($N = 4390$), and the two individual trials, CSMC021C2301 ($N = 2352$) and CSMC021C2302 ($N = 2060$). B) JSW in the target ($N = 2206$) vs the contra-lateral contra-lateral knees ($N = 2184$) C) Mean WOMAC pain ($N = 4299$) and function ($N = 4278$) scores in the total cohort. D) Mean total WOMAC pain in the target ($N = 2205$) and contra-lateral ($N = 2094$). Error bars are 95% confidence limit of mean.

Association between JSW and KL grade as a function of study, knee, gender and WOMAC pain

The assessment of JSW measured at baseline revealed a statistically highly significant correlation of JSW and KL-score ($P < 0.0001$, Fig. 2). This effect was different between the two studies ($P = 0.05$, Fig. 2(A)), target knee and contra-lateral knee ($P < 0.0001$, Fig. 2(B)), gender-dependent ($P = 0.004$, Fig. 2(C)), and dependent on WOMAC pain group ($P < 0.001$, Fig. 2(D)).

Overall only a minor decrease in JSW was observed in knees with KL 1 and KL 2 as compared to KL 0, whereas a major decrease in JSW was observed in KL 3 knees of 1.57 mm (95% CI: 1.20–1.93 mm) and 1.27 mm (95% CI: 0.93–1.61 mm) in CSMC021C2301 and CSMC021C0212302; and KL grade 4 knees of 2.08 mm (95% CI: 1.52–2.64 mm) and 1.84 mm (95% CI: 1.22–2.46 mm) [Fig. 2(A)].

Comparison of JSW in target knee vs contra-lateral knee showed that the JSW was comparable in knees with KL grade 2, but the target knees with KL grade 3 had a higher JSW of 0.48 mm (95% CI: 0.36–0.61 mm; $P < 0.001$) in comparison with the contra-lateral knee [Fig. 2(B)]. In general females seemed to have slightly lower JSW of 0.10 mm–0.67 mm than males as observed in KL grade groups of KL0, KL1, KL2, and KL4 [Fig. 2(C)].

There was a significant association between WOMAC pain and JSW ($P < 0.0001$) and this effect was KL-score dependent ($P = 0.001$). In KL grade 0, 1, and 2 knees there seemed to be no

association between JSW and WOMAC pain score. In KL grade 3 knees there was a gradual decrease in JSW with increasing WOMAC pain with a difference of 0.37 mm (95% CI: 0.14 to 0.61; $P = 0.002$) between those with highest pain as compared to those with lowest pain. A more dramatic effect was observed for the KL grade 4 knees [Fig. 2(D)].

There was statistically highly significant effect of BMI with a decrease in JSW with increasing BMI ($P < 0.0001$). The effect size in difference in JSW between subjects in the highest quartile (Q4) having BMI of 31.8 kg/m^2 or above in comparison with subjects in the lowest quartile (Q1) having a BMI below 25.6 kg/m^2 was a decrease of 0.31 mm (95% CI: 0.21–0.42 mm; $P < 0.0001$) [Fig. 2(E)].

Age in the age groups of below 65 years as compared with 65 years or above did not in itself contribute statistically significant to JSW ($P = 0.23$).

Association between KL grade, WOMAC and progression (JSN)

Table VI shows the distribution of subjects classified according to their degree of JSN at the 2-year end point. The classification of minimum statistically significant JSN of 0.26 mm is based on an estimation of the imprecision of a single JSW reading of 2.8%[26] and an overall mean JSW of 3.3–3.4 mm at study start. The number of progressors knees was similar in the target and contra-lateral knees. Only 32% of total knees in the target knee progressed measured as delta JSN <0, and only 49% progressed above the minimal significant change (Table V).

Overall, including all knees of the placebo group, the mean JSN progression (mean ± SEM) was 0.286 ± 0.016 mm during the 2-year trial period. Further sub-group analysis showed that over the 2 years, mean ± SEM knee JSN progression was 0.320 ± 0.024 mm for the target knees in comparison with 0.250 ± 0.022 mm for the contra-lateral knees ($P < 0.01$). The correlations between BMI, WOMAC pain, JSW, KL grade and JSN after 2 years are given in Table VI. KL grade was significantly associated with JSN progression ($P < 0.05$) in the target, but not the contra-lateral knee.

Table IV
WOMAC pain (mm) in KL grade groups

KL grade	N (knees)	Mean pain score	STD	SEM	Range pain scores
All	4316	212	99	1.5	0–500
KL 0	88	135	105	11.2	0–410
KL 1	404	157	104	5.2	0–430
KL 2	2904	211	94	1.7	0–500
KL 3	851	245	94	3.2	0–500
KL 4	52	285	109	15.2	40–463
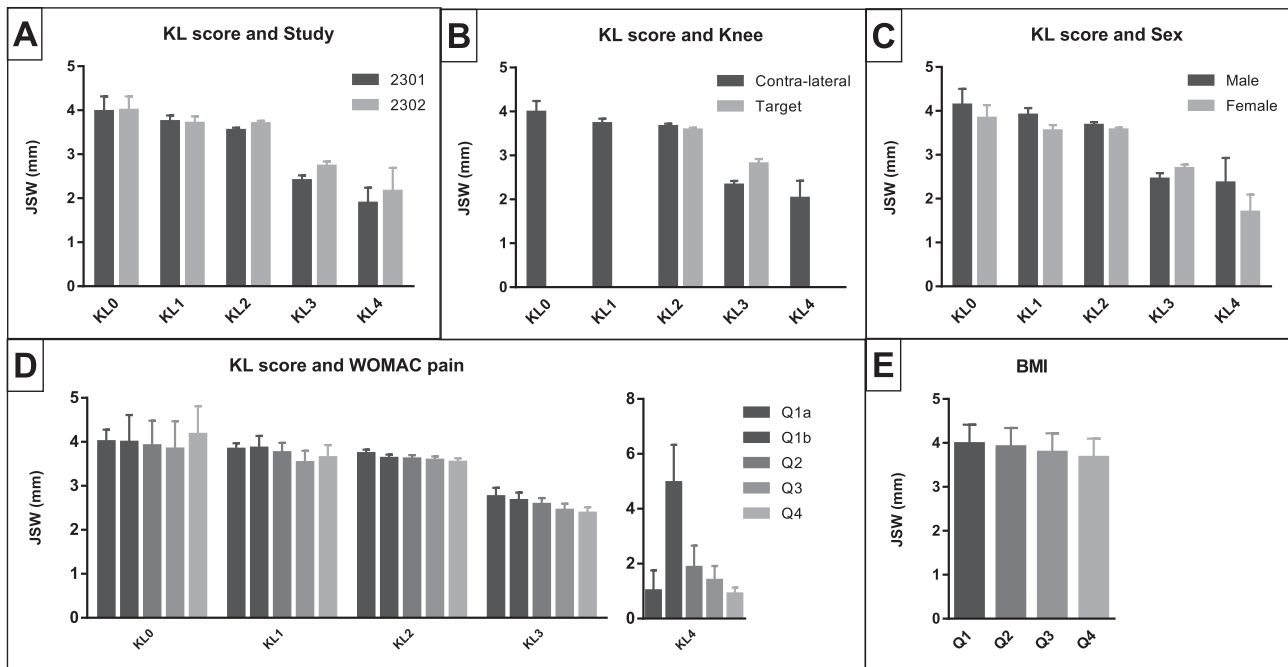
Fig. 2. Baseline JSW from mixed model analysis showing the JSW (LS means ± 95% CI) according to KL-score and study (A), KL grade and target knee (B), KL-score and gender (C), BMI in quartiles (E), and KL-score and WOMAC pain (D). Totally 4299 knees had complete data and were included in the model.

The assessment of predictors for JSN at the 2 year endpoint included the target knees and contra-lateral knees with KL grades of 1, 2, and 3 and a minimum JSW at baseline of 1 mm or above comprising in total 1475 knees. It was found that KL grade at baseline was a statistically significant predictor for JSN ($P = 0.03$) with highest JSN in KL grade group 3 and almost comparable JSN in KL grade group 1 and 2 (Fig. 3). As compared with KL grade 1, a KL grade of 2 was associated with an increased JSN of 0.02 mm (95% CI: −0.09−0.14 mm) and a KL grade of 3 was associated with an increased JSN of 0.14 mm (95% CI: 0.00−0.28 mm).

WOMAC pain was statistically significantly ($P = 0.02$) associated with JSN with the pattern of relationship showing an inverted U-shape pattern (Fig. 3). The highest JSN was observed in the WOMAC pain quartiles of Q2 and Q3 and lowest JSN in Q1a and Q4. As compared with Q1a (low pain ranging from 0 to 149) mm, moderate pain in Q2 (185−231 mm) and Q3 (232−289 mm) was associated with an increased JSN of 0.13 mm (95% CI: 0.03−0.23 mm) and 0.15 mm (95% CI: 0.05−0.25 mm) whereas higher pain in Q4 of 290 mm or above was associated with an increase of 0.05 mm (95% CI: −0.05−0.16 mm) only.

There was a statistically significant minor difference between studies of 0.08 mm (95% CI. 0.00−0.16 mm; $P = 0.04$) lower JSN in CSMC021C2301 as compared with CSMC021C2302. The lower JSN in CSMC021C2301 was caused by lower JSN in females than males in CSMC021C2301 ($P < 0.0001$). There was no significant difference in JSN between genders in CSMC0212302 ($P = 0.82$), and the parameters of baseline JSW group (1−2 mm, 2 mm or above), knee (target, contra-lateral knee), and age group (<65 years, ≥65 years) were not statistically significant associated with JSN. Also BMI in quartiles was not significantly associated with JSN ($P = 0.23$) although there might be a trend of higher JSN the higher the BMI quartile (Fig. 3).

Discussion

To the best of our knowledge, these combined data represent the largest randomized clinical trial (RCT) dataset available for *post*

hoc analysis of symptomatic knee OA patients at risk of progression. The main findings were;

1. 51% of patients in the target, and 55% of the contra-lateral knee did not progress above the calculated minimum significant change (MSC). 32% and 36% respectively, did not progress, JSN change more <0 mm. This clearly suggests that selection criteria can be further refined to better enrich for progressors.
2. Progression in relation to pain was non-linear. The Q2−Q3 quartile progressed faster than the Q1 and Q4 quartiles. This suggests that OA symptoms are a risk factor for progression, however that severe pain does not necessarily confer greater risk of progression and that different phenotypes of pain/progressors may exist.
3. Pain scores correlated better with JSW in contra-lateral vs target knees, suggesting different pain reporting or perception in target vs contra-lateral.
4. BMI, Age and WOMAC pain were diagnostically strongly associated with a diagnosis of OA based on JSW, but only KL grade and WOMAC pain were prognostic, i.e., for predicting JSN.
5. The risk of progression was associated with baseline radiographic status − such as KL grade; a stronger association was observed for progression when an OA clinical descriptive phenotype included pain, and KL grade in combination.

The discussion is divided into "diagnostic & burden of disease measures" and "prognostic measures", according to the BIPED criteria[27].

Diagnostic and burden of disease measures

At baseline, mean JSW was consistent across the two trials, both overall and comparing subgroups with identical KL grades. WOMAC pain, BMI, age and KL grade were highly associated with JSW (Burden of disease), as diagnostic markers, which corroborates numerous findings[28,29]. As KL grade is partly confounded by JSW assessment this correlation to two measure of burden of disease

Table V
Distribution according to degree of JSN at year 2 in KL grade groups

JSN	<0 mm	0–0.26 mm	0.26–0.5 mm	0.5–1.0 mm	1.0–2.0 mm	>=2 mm
Target knee						
All	32% (256)	19% (152)	16% (130)	19% (147)	11% (86)	3% (20)
KL 2	34% (223)	19% (128)	16% (107)	18% (118)	10% (68)	2% (13)
KL 3	25% (33)	18% (24)	17% (23)	22% (29)	13% (18)	5% (7)
Contra-lateral knee						
All 774	36% (278)	19% (148)	19% (149)	16% (122)	8% (62)	2% (15)
KL 0	35% (9)	19% (5)	27% (7)	15% (4)	4% (1)	0% (0)
KL 1	33% (42)	23% (29)	23% (29)	13% (17)	7% (9)	2% (2)
KL 2	35% (149)	20% (85)	19% (79)	15% (64)	9% (37)	1% (6)
KL 3	37% (68)	15% (28)	17% (32)	18% (33)	8% (15)	4% (7)
KL 4	59% (10)	6% (1)	12% (2)	24% (4)	0% (0)	0% (0)

Table VI
Spearman correlation (Rho) of baseline characteristics and JSW change at year 2

|		BMI	WOMAC pain	JSW	KL grade
JSW change in target knee	Rho	−0.03	0.02	0.04	−0.09
	P-value	0.39	0.57	0.31	0.01
	n	791	791	791	791
JSW change in contra-lateral knee	Rho	−0.01	−0.09	−0.07	−0.03
	P-value	0.71	0.01	0.04	0.36
	n	774	751	774	774

measures was expected. We found that mean JSW was virtually similar in KL grades 0–2 with a sharp drop in JSW in KL 3 and a further drop in KL 4. It is noteworthy that overall, no significant reduction occurred in JSW across KL grade 0–2, indicating minor changes in cartilage thickness at these radiographic severity stages. The significant drop in JSW from KL grade 2 to 3 is expected, and is likely to be a direct reflection of the emphasis on the element of JSN in the classification of KL grades 3 and 4. For KL grade 2, the target knee had a lower JSW compared to the contra-lateral knee (3.32 ± 0.03 mm vs 3.42 ± 0.02 mm, respectively, in alignment with the lower mean pain observed in the contra-lateral knee. For KL grade 3 this was different, which for the major part may be due to the inclusion criteria emphasizing on JSW >2 mm for target knees. Further analysis showed a stronger correlation between JSW and pain levels regardless of KL grade contra-lateral vs target, empha- sizing the large variation between burden of disease and pain levels, and the difference between pain and reporting of pain in target vs contra-lateral knees. The wide ranges and high standard deviations of observed JSW, regardless of KL group, is remarkable, and underscores the heterogeneity of this disease population in

which neither pain, JSW nor KL grade alone seem to be good de- scriptors of disease severity.

Pain and the relation to joint damage is a much debated area in the OA field[30–36], as pain and joint damage are not necessarily correlated. As expected, in relation to the selection criteria, subjects reported less mean (± SEM) WOMAC pain in the contra-lateral knees than in the target knee (181 ± 2.5 mm vs 242 ± 1.6 mm), but interestingly, a slightly lower mean JSW (3.32 ± 0.03 mm vs 3.42 ± 0.02 mm) was observed, possibly due to the inclusion criteria. For knees with KL grade 2, considerably less pain was re- ported in the contra-lateral knees compared to target and for KL grade 3 knees; the pain was similar in the target and contra-lateral knees (161 ± 3.2 vs 240 ± 1.7 mm. This may suggests that pain perception differences in relation to JSW in the target knee compared to the contra-lateral knee, possibly due to active inflammation and over reporting of pain in the target knees.

Prognostic measures

BMI and age were not statistically significant associated with JSN progression; these results are in accord with previous findings, which suggested that subchondral bone texture by fractal signature analysis was the best predictor of radiographic progression[28,29]. Of great interest was the fact that pain[37–41] was associated with pro- gression, albeit not in a linear manner. The Q2–Q3 pain quartile progressed the fastest. Many factors may explain this, possibly due to less physical activity or active inflammation, but more likely to the nature of this different OA population compared to other studies, consisting exclusively of KL grade 2–3 with symptomatic OA pain, who constitute the treatment-population of OA studies. Most likely other parameters of activity may later be assessed by
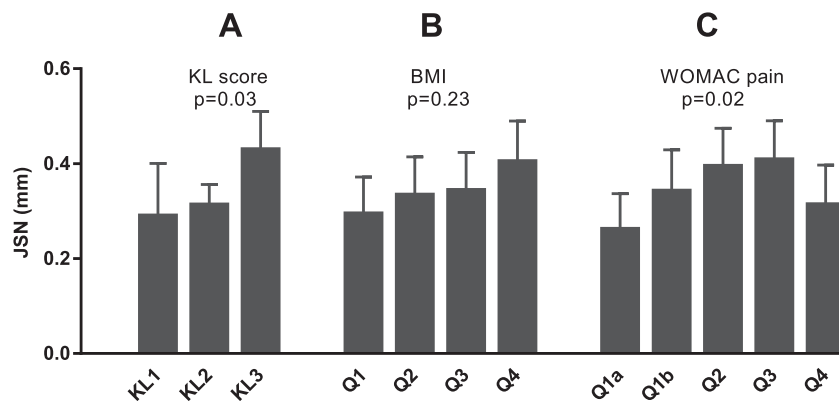
Fig. 3. JSN predictors from mixed model analysis showing the JSN at the 2-year endpoint in the placebo group (LS means ± 95% CI) according to baseline KL-score (A), baseline BMI in quartiles (B; Q1 below 25.6 kg/m^2; Q2 25.6–28.4 kg/m^2, Q3 28.4–31.8 kg/m^2, Q4 31.8 kg/m^2 or above), and baseline WOMAC pain group (C; Q1a 0–149 mm, Q1b 150–184 mm, Q2 185–231 mm, Q3 232–289 mm, Q4 290–500 mm). Totally 1457 knees in KL 1, 2, an 3 had complete data and were included in the model.

serological biomarkers[42] and contribute to the understanding of pain, pathological processes and progression.

BMI was not a risk factor for progression albeit highly diagnostic. This may be consequent to the small effect size of BMI on JSW, and as the follow-time was only 2 years compared to long term demographic studies, the time to research significant was not present, although a trend was observed. Further analysis may focus on the fat distribution which has been shown to be very important in the cardiovascular field for predicting acute myocardial infarction (AMI), as central fat was demonstrated to be a risk factor while peripheral fat was protective[43,44].

The demographic and radiographic data used in the current analysis suggests that a combination of KL grade, with pain and BMI may in part be important together with other modalities for identification of the OA phenotype associated with progression of OA.

General considerations

A randomized clinical study may be different compared to epidemiological studies in many aspects, in particular consequent to stringent inclusion criteria for signal knees. Investigator initiated studies often aim to recruit a high number subjects for investigating prevalence and incidence (an all-comer strategy), whereas clinical trials aim to recruit knee OA patients with specified characteristics which allow for identification of progression and thus enabling identification of treatment efficacy. Examples of large-scale population studies that focus on OA are the OAI[50], CHECK[51], MOST[52], RSI-III[53], Chingford[54] and the JoCo[55] studies. Two additional differences are important to consider (1) Clinical studies focus on specific target joints in contrast to many of the population based studies and (2) clinical trials tend to include older patients with overweight of women (60−70%)[19,20,22]. Consequently to these considerations, this largest combined RCT for prevalent symptomatic OA population is clearly different from the large epidemiologic cohort studies, and may be used as a database for improved design of future OA RCTs. The average JSN progression of 0.159 mm/year in the current study was comparable to the progression in the prevalent OA patient population reported for CHECK, OAI and the JoCoOA[37,45−47].

Conclusion

There is an urgent medical need to further identify disease phenotypes, preferably by simple technologies, to allow for patient selection of bone, cartilage and inflammation driven OA phenotypes and matching the best intervention to each individual phenotype[11]. Hopefully, our results, together with lessons learned from other fields in which PHC long has been debated such has RA[48], may assist in PHC for OA by enabling better designs for tailoring clinical studies in the future.

Author contributions

MK, CC, ACBJ and BJR made the first draft of the manuscript. JRA, MK, BJR and CC designed the protocols. PA performed parts of the study, and wrote sections of the manuscript. IB and ACBJ performed all statistical analyses. CL and MM participated in data analysis and writing of sections. VK participated in all parts of the manuscript. AB and JRA reviewed all data and study protocols. All authors critically reviewed the last version of the manuscript and participated in the entire process.

Conflicts of interest

All authors but Peter Alexandersen, Martin Michael, Christopher Ladel and Virginia Kraus are employees of Nordic Bioscience, a company engaged in biomarker research and development of treatments for OA. Peter Alexandersen is an employee of CCBR, a company engaged in biomarker research and development of treatments for OA. Novartis and Nordic Bioscience co-sponsored the studies. Novartis provided the medications for the study. Martin Michaels, Christopher Ladel are full time employees of Merck-Serono a company engaged in the development of treatments for OA.

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