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Original experimental

Relating clinical measures of pain with experimentally assessed pain mechanisms in patients with knee osteoarthritis

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HIGHLIGHTS

- A model that can predict pain intensity in knee osteoarthritis (KOA) is proposed.
- 55% of the variability in pain can be explained by two pain measures in KOA.
- The pain measures reflect spreading sensitisation and temporal summation.
- This underlines the importance of central pain mechanisms in KOA pain management.

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ABSTRACT

Background: Peripheral and central sensitisation is prominent in knee osteoarthritis (KOA) and could be important for the reduced efficacy in some cases after as well surgery as pharmacological interventions. Although sensitisation is important in KOA it is not known to what degree it contributes to the overall clinical pain problem. The aim was therefore to investigate how much a combination of quantitative pain measures assessing various pain mechanisms (local and spreading hyperalgesia, temporal and spatial summation, descending inhibition) could predict peak pain intensity in patients with KOA.
Methods: While resting in a comfortable recumbent position the pressure pain thresholds (PPT) in the peripatellar region (eight locations) and at the tibialis anterior muscle (TA) were assessed by handheld pressure algometry, computer-controlled pressure algometry and cuff-algometry in the affected leg of 17 KOA patients without pain or sensory dysfunctions in other regions than the knee. Cuff-algometry was used to detect spatial pain summation of the lower leg. Temporal pain summation was assessed by repeated pressure stimulation on the TA muscle. The conditioning pain modulation (CPM) was evaluated by conditioning tonic arm pain and by PPT from the peripatellar region. The participants rated their peak pain intensity in the previous 24 h using on a 10 cm visual analogue scale.
Results: A multiple-regression model based on TA pressure pain sensitivity (spreading sensitisation) and temporal pain summation on the lower leg accounted for 55% of the variance in peak pain intensity experienced by the patients ($P = 0.001$). Significant correlations ($P < 0.05$) were found between PPTs assessed by handheld pressure algometry in the peripatellar region and at TA ($R = 0.94$), PPTs assessed by computer-controlled pressure algometry and handheld pressure algometry in the peripatellar region ($R = 0.71$), PPTs assessed by computer-controlled pressure algometry in the peripatellar region and handheld pressure algometry at TA ($R = 0.71$) and temporal summation at the knee and at TA ($R = 0.73$).
Conclusion: Based on the multiple regression model 55% variance of the perceived maximal pain intensity in painful KOA could be explained by the quantitative experimental pain measures reflecting central pain mechanisms (spreading sensitisation, temporal summation). The lack of other correlations between the methods used in assessing pain mechanisms in this study highlights the importance of applying different tests and different pain modalities when assessing the sensitised pain system as different methods add complementary information.

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Implications: Clinical pain intensity can be explained by influences of different central pain mechanisms in KOA. This has implications for pain management in KOA where treatment addressing central pain components may be more important than previously acknowledged.

1. Introduction

Knee osteoarthritis (KOA) is a prevalent degenerative disease associated with pain, reduced functional level, and impaired quality of life [1–3] with significant socio-economic impact [4,5]. Total knee arthroplasty (TKA) is a treatment modality [6,7] which in some studies have shown that most patients get pain relief [8], while other studies have shown that 15–30% of the patients do not obtain adequate pain relief [9,10]. Furthermore a meta-analysis has shown small and time limited effects of pharmacological interventions on pain in the treatment of KOA [11]. It has been speculated that sensitisation in KOA could be important for the somewhat poor outcome after as well surgery as pharmacological interventions [12].

Peripheral as well as central sensitisation is prominent in OA [13–16]. Previous studies have found that patients with painful KOA have lower pressure pain thresholds (PPT) than controls for both the affected knee and heterotopic body areas, and that higher clinical pain ratings of longer durations cause more sensitisation [14,16]. Furthermore KOA patients show a significant facilitation of temporal summation from both the knee and the tibialis anterior muscle (TA) and have less efficient descending conditioning pain modulation (CPM) as compared to matched controls [14]. A previous study has indicated that cuff-algometry could be useful in assessing pain sensitisation in KOA, and at the same time it enables the option to study spatial summation as a central mechanism [17].

Although sensitisation is important in KOA it is not know to what degree it contributes to the overall clinical pain problem.

The aim of the present study was therefore to combine quantitative pain measures assessing peripheral and central sensitisation and investigate how much they could predict maximal pain intensity in patients with KOA.

2. Materials and methods

2.1. Material

Patients diagnosed with radiological and symptomatic KOA in 2007–2009 ($n = 48$) drawn from the Hospital patient files were contacted by telephone and asked if they were willing to undergo a pain assessment session. Seventeen still reporting pain (pain duration range 24–468 months) in their knee agreed to participate of whom eight had meanwhile undergone a TKA (24–48 months prior to the current study). Participants that had undergone TKA and participants that had not undergone TKA had similar clinical pain characteristics. The participants were not allowed to have pain or sensory dysfunctions in any other region than the knee and they should be able to collaborate. Furthermore they were asked to refrain from the use of any pain medication 24 h before the experiment. Demographics are shown in Table 1. This study was approved by the local ethics committee of the North Denmark Region (N-20100050) and conducted in accordance with the Helsinki Declaration. Before the study, oral and written information were provided to the participants, and written consent was obtained from all of the participants.

2.2. Clinical pain

Before the pain assessment session the participants were asked to rate their peak pain intensity in the previous 24 h using a 10 cm (0–10) VAS with the left end (0) marked as 'no pain' and the right end (10) by 'worst pain possible' (VAS max).

Table 1
Demographics of participants ($n = 17$).

Demographic variable	Fractions or mean ± SD
Age (years)	65.1 ± 7.9
Gender (women/men)	4/13
Body Mass Index (kg/m^2)	29.7 ± 5.6
Affected knee (unilateral/bilateral)	12/5
TKA (yes/no)	8/9
Duration of pain (months)	115.1 ± 124.4
Peak pain in previous 24 h (cm)	3.6 ± 2.8
Pain at rest (cm)	1.8 ± 1.8
Pain during physical activity (cm)	3.7 ± 3.2
WOMAC total (arbitrary unit)	32.2 ± 21.5

2.3. Protocol

The participants rested in a comfortable recumbent position during the pain assessment session. The pressure pain sensitivity in the peripatellar region and at TA of the affected leg was assessed by handheld pressure algometry and temporal summation of pressure pain was assessed using a computer-controlled pressure algometer. The pressure pain sensitivity of the lower leg was further evaluated by cuff-algometry including assessment of temporal and spatial summation. The conditioning pain modulation was evaluated by experimental tonic pain induced in the arm by cuff pressure stimulation (conditioning stimulation) and assessment of pressure pain thresholds (test stimulus) in the peripatellar region.

2.3.1. Assessment sites

Eight test sites in the peripatellar region and one site at TA (5 cm distal to the tibial tuberosity) were located in relation to bony landmarks and marked. Site 1) 2 cm distal to the inferior medial edge of patella; site 2) 2 cm distal to the inferior lateral edge of patella; site 3) 3 cm lateral to the midpoint on the lateral edge of patella; site 4) 2 cm proximal to the superior lateral edge of patella; site 5) 2 cm proximal to the superior edge of patella; site 6) 2 cm proximal to the superior medial edge of patella; site 7) 3 cm medial to the midpoint on the medial edge of patella; and site 8) at centre of patella (Fig. 1).

2.3.2. Handheld pressure algometry

A hand-held pressure algometer (Algometer Type II, Somedic AB, Sweden) was used for the PPT measurements. The probe (1 cm^2) was placed perpendicular to the skin and pressure was applied (30 kPa/s) until the participant defined the pressure as pain and pressed a button, which stored the pressure applied in the given moment. The PPT was measured twice on each site and the average of the two measurements from all eight sites for the peripatellar region (handheld PPT knee) and TA (handheld PPT TA) was used in the statistical analysis [14].

2.3.3. Computer-controlled pressure algometry

For computer-controlled recordings of the pain threshold the pressure was increased with 1 kg until the participant defined the pressure as pain. The PPT was measured twice on the most sensitive of the eight sites on the knee (computer PPT knee) and at TA

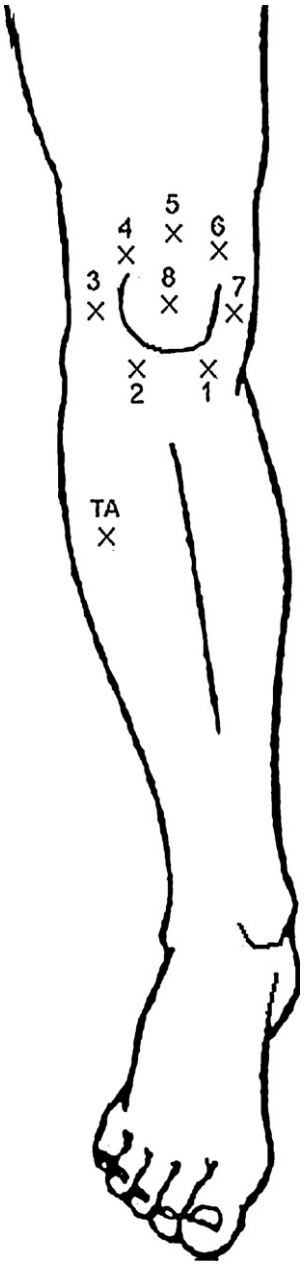

Fig. 1. PPT measurement sites.

(computer PPT TA) and the average of the two measurements was applied in the statistics.

2.3.4. Temporal summation of pressure pain

Temporal summation was assessed using a computer-controlled pressure algometer (Aalborg University, Aalborg, Denmark). The mechanical pressure stimuli were applied perpendicular to the skin surface [18]. A circular aluminium footplate with a 1 cm^2 padded contact surface was fixed to the tip of the piston. The pressure stimulation was feedback controlled via recordings of the actual force. The sequential stimulation consisted of ten pressure stimuli (1 s duration and 1 s interstimulus interval) at the level of the pressure pain threshold recorded with the computer-controlled pressure algometer [19]. The computer-controlled recordings of the PPT were also used for the sequential stimulation, which was applied to the most sensitive site and to TA, respectively. Skin contact between the individual pressure stimuli was kept by applying a constant force of 0.1 kg. The contact force of 0.1 kg between two stimuli did not evoke pain. The participants rated their pain intensity continuously during the sequential stimulation on an electronic visual analogue scale (VAS) where '0' indicated 'no pain', and '10 cm' indicated "maximal pain" (Aalborg University, Aalborg, Denmark). The VAS signal for each stimulus was sampled by a computer at 200 Hz. The mean VAS scores during 1 s after each stimulus were extracted, normalised by subtraction of the mean VAS score from the first stimulation, and the accumulated VAS score (VAS sum) over the ten stimuli was extracted. Two series of stimulations in the peripatellar region (VAS sum knee) and at TA (VAS sum TA) were performed and the mean of VAS sum were used in the further analysis.

2.3.5. Cuff algometry

The deep-tissue pain sensitivity was further evaluated by recordings of pain thresholds to cuff pressure stimulations using a computer-controlled cuff-algometer (Aalborg University, Aalborg, Denmark) [17]. The test setup consisted of a 13-cm wide cuff with an equal-sized proximal and distal chamber, the electronic VAS and a pressure release button, which the participants used to rate their pain intensity and release the pressure, respectively. The cuff was wrapped around the middle of the leg at the level of the heads of the m. gastrocnemius. The pressure was increased with a rate of 0.5 kPa/s. The maximal pressure limit was 100 kPa. The participant was instructed to rate the cuff pain intensity continuously on the VAS from the point where the pressure was defined as pain (Cuff PPT) and to press the pressure release button when the pain was intolerable (Pain Tolerance Threshold; PTT). The test was performed by inflating both chambers twice and a mean of parameters were applied in the analysis.

The cuff pain sensitivity was also assessed by inflating the proximal and the distal chambers alone. To assess spatial summation the cuff PPT from both chambers was divided by the mean of cuff PPT from the proximal and the distal chamber (spatial sum ratio); lower ratios indicate a higher spatial summation. Temporal summation to cuff pain stimulation was assessed by sequential stimulation consisting of ten cuff pressure stimuli (1 s duration and 1 s interstimulus interval) with both chambers at an intensity equivalent to the mean of cuff PPT and cuff PTT. A constant non-painful force of 5 kPa was kept between the individual pressures ensuring that the pressure was applied at the same place for all ten stimulations. The participants rated their pain intensity continuously during the sequential stimulation on an electronic VAS. The mean VAS scores during 1 s after each stimulus were extracted, normalised by subtraction of the mean VAS score from the first stimulation, and the accumulated VAS score (cuff VAS sum) over the ten stimuli was extracted. Two series of stimulations at were performed and the mean of VAS sum were used in the further analysis.

2.3.6. Conditioning pain modulation

Ischemic compression of the left arm was used as heterotopic noxious conditioning stimulation for evoking CPM. A 7.5 cm wide tourniquet cuff (VBM, Germany) was wrapped around the left arm. The lower rim of the tourniquet cuff was placed 3 cm proximal to the cubital fossa. The cuff control unit (Aalborg University, Denmark) was programmed to maintain the pressure at 36 kPa (which is above the systolic pressure). The participant was asked to repeat hand grip for ten times or more until he or she rated the pain as 4 cm on the electronic VAS. When the target VAS of 4 cm was reached, PPTs at all peripatellar sites and TA were re-assessed. The cuff was released after PPT assessments were finished. The potency of CPM was evaluated as a mean of two measurements of PPT during the tonic cuff pain divided by the mean of two measurements of PPT before the tonic pain for the peripatellar region

Table 2
Correlation coefficients between pain assessment parameters. The presented *P*-values are Bonferroni corrected. 'Handheld PPT': PPT measured using a handheld algometer. 'Computer PPT': PPT measured using a computer-controlled pressure algometer. 'VAS sum': The accumulated VAS score over the ten stimuli as a measure of temporal summation. 'CPM': Conditioning Pain Modulation. 'Cuff PPT': PPT measured using a cuff algometer. 'Spatial sum ratio': Cuff PPT from both chambers divided by the mean of cuff PPT from the proximal and the distal chamber as a measure of spatial summation.

Pain assessment parameters	Mean ± SD	Correlation	Handheld PPT knee	Handheld PPT TA	Computer PPT knee	Computer PPT TA	VAS sum knee	VAS sum TA	CPM knee	CPM TA	Cuff PPT	Spatial sum ratio
Handheld PPT knee (kPa)	469 ± 349	*R*										
		P-value										
Handheld PPT TA (kPa)	419 ± 252	*R*	0.94									
		P-value	<0.001									
Computer PPT knee (kg)	5.59 ± 3.20	*R*	0.71	0.82								
		P-value	<0.001	<0.001								
Computer PPT TA (kg)	5.29 ± 2.39	*R*	0.17	0.32	0.70							
		P-value	NS	NS	NS							
VAS sum knee	19.8 ± 14.3	*R*	0.03	−0.05	−0.18	−0.40						
		P-value	NS	NS	NS	NS						
VAS sum TA	19.9 ± 13.3	*R*	0.05	−0.09	−0.31	−0.69	0.73					
		P-value	NS	NS	NS	NS	<0.001					
CPM knee	1.21 ± 0.22	*R*	−0.47	−0.40	−0.24	<0.01	0.21	0.11				
		P-value	NS	NS	NS	NS	NS	NS				
CPM TA	1.23 ± 0.32	*R*	−0.31	−0.45	−0.33	−0.05	0.14	0.04	0.59			
		P-value	NS	NS	NS	NS	NS	NS	NS			
Cuff PPT (kPa)	8.92 ± 4.68	*R*	0.65	0.51	0.35	−0.07	0.10	0.03	−0.66	−0.19		
		P-value	NS	NS	NS	NS	NS	NS	NS	NS		
Spatial sum ratio	0.86 ± 0.18	*R*	−0.17	−0.27	−0.28	−0.09	0.29	0.20	0.52	0.61	−0.29	
		P-value	NS	NS	NS	NS	NS	NS	NS	NS	NS	
Cuff VAS sum	16.4 ± 14.8	*R*	−0.17	−0.07	−0.03	−0.05	0.18	0.27	0.27	−0.12	−0.24	0.14
		P-value	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

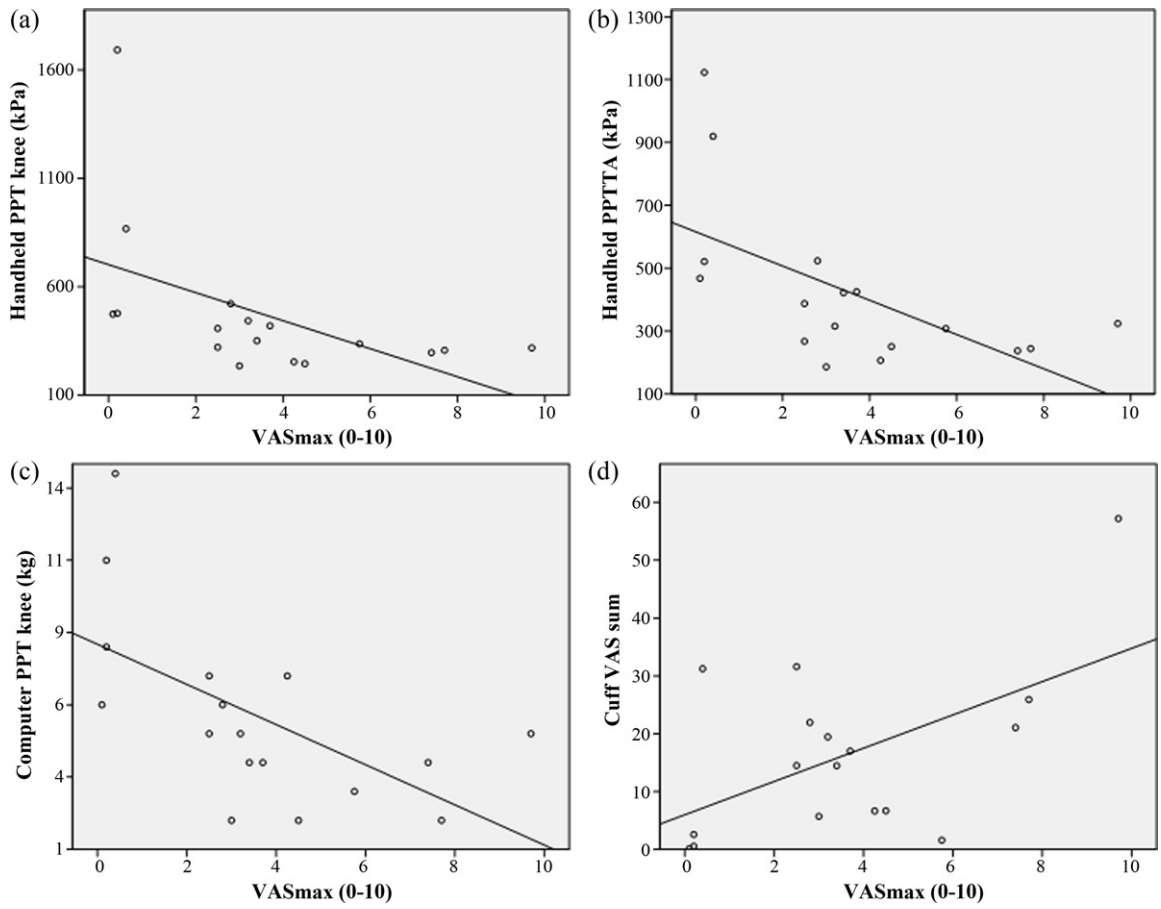

Fig. 2. Scatter plots illustrating the relationship between VAS max and (a) handheld PPT knee, (b) handheld PPT TA, (c) computer PPT knee and (d) cuff VAS sum. See Table 2 for explanation of abbreviations.

(CPM knee) and TA (CPM TA); a higher number indicating a more potent CPM.

2.4. Statistical analysis

Data are presented as mean values and standard deviations (SD). Data were normally distributed, confirmed by visual inspection of *Q*–*Q* plots. Pearsons Product Moment Correlations were assessed between the pain assessment parameters. To correct for multiple correlations *P*-values were Bonferroni corrected. The pain assessment parameters were set as independent variables in a multiple regression model where VAS max (Table 1) was set as the dependent variable. VAS max was chosen as the dependent variable since the intensity of the ongoing pain is related to the sensitisation in patients with KOA [14,16] and other chronic pain conditions [20]. Variables with a *P*-value of less than 0.20 in the univariate analysis were included in the multivariate regression. The construction of the multiple regression model followed the construction proposed by Hosmer et al. [21]. Variables in the final model with a *P*-value above 0.05 were only kept in the model if it caused more than 20% change in the estimate of the other variables. The assumptions of normality and constant variance of the model were verified using a normal probability plot of residuals and a plot of standardised residuals against standardised predicted value. Tolerance level was used to test for colinearity. Any variable that has a tolerance level of less than 0.01 were excluded from the model. Beta values were used as a measure of how much each independent variable affected the dependent variable. *P*-values less than 0.05 were considered to be significant. All analyses were done using IBM SPSS Statistics (Version 19).

3. Results

Significant correlations (Table 2) were found between handheld PPT in the peripatellar region and at TA ($R = 0.94$), computer PPT in the peripatellar region and handheld PPT in the peripatellar region ($R = 0.71$), computer PPT in the peripatellar region and handheld PPT at TA ($R = 0.82$) and VAS sum at the knee and VAS sum at TA ($R = 0.73$).

Univariate regression analysis showed significant associations between the perceived maximal VAS scores (pain intensity) and handheld PPT knee (Beta = −0.515), handheld PPT TA (Beta = −0.600), computer PPT knee (Beta = −0.603) and cuff VAS sum (Beta = 0.540) (Table 3 and Fig. 2). No systematic differences were found between participants that had undergone TKA and participants that had not undergone TKA in the univariate analysis of associations between pain intensity and experimental pain measures.

The multiple regression model consisting of the handheld PPT from TA and cuff VAS sum ($F_{2,14} = 10.84$, $P = 0.001$; $R^2 = 0.61$, Adjusted $R^2 = 0.55$) accounted for 55% of the variance in the dependent variable. Beta-values and *P*-values are presented in Table 3. The correlation between the independent variables were low and acceptable ($R < 0.08$) and the tolerance were high (>0.99) indicating that the independent variables in the model do not depend linearly on each other.

4. Discussion

Based on the multiple regression model 55% variance of the perceived maximal pain intensity in painful KOA could be

Table 3
Results of the univariate and multivariate analysis. Beta values are only indicated when significant. *P*-values less than 0.05 were considered to be significant. See Table 2 for explanation of abbreviations.

Independent variables	Univariate analysis		Multivariate analysis	
	Beta	*P*-value	Beta	*P*-value
Handheld PPT knee	−0.515	0.034*	–	–
Handheld PPT TA	−0.600	0.011*	−0.563	0.005*
Computer PPT knee	−0.603	0.010*	–	–
Computer PPT TA	–	0.228	–	–
VAS sum knee	–	0.427	–	–
VAS sum TA	–	0.261	–	–
CPM knee	–	0.567	–	–
CPM TA	–	0.405	–	–
Cuff PPT	–	0.282	–	–
Cuff VAS sum	0.540	0.025*	0.499	0.010*
Spatial sum ratio	–	0.116	–	–

explained by the quantitative experimental pain measures reflecting central pain mechanisms (spreading sensitisation, temporal summation).

In addition significant positive correlations between various pressure pain threshold measures and temporal summation from the knee (local sensitisation) and tibialis anterior (spreading sensitisation) were found.

The important role of central mechanisms in OA has recently been further substantiated as treating OA patients with pregabalin peri-operatively resulted in the important finding that none of the patients developed chronic post-operative pain after TKA [22].

4.1. Model predicting maximal clinical pain intensity in KOA

In the univariate analysis a significant negative association was found between the peak pain intensity in the previous 24 h (VAS max) and pressure pain thresholds assessed manually in the peripatellar region and at TA and computer-controlled pressure algometer in the peripatellar region. This is consistent with previous studies on osteoarthritis where reduced pressure pain thresholds were related to higher pain intensity [14,16,23]. Furthermore a significant positive relation was found between the peak pain intensity and the degree of temporal summation assessed by cuff algometry. This is also supported by previous studies on KOA and temporal summation [14]. Some care should be taken in the interpretation of the association between the peak pain intensity and the pain sensitivity parameters, since ten variables were applied in the univariate analysis, which could lead to a false positive error. However, as presented, the findings are in agreement with previous studies [14,16,23].

In the present study, the model consisting of pressure pain thresholds assessed manually at TA and temporal summation assessed using a cuff-algometer, accounted for 55% of the variance in peak pain in previous 24 h (VAS max). The beta values in the final model indicate that the impact of the two independent variables (and thereby hyperalgesia and temporal summation) on peak pain in previous 24 h are almost equivalent. A change of one SD in the independent variable would result in a change of −0.56 (more pain lower PPT) and 0.50 (more pain more summation) SD in pain, respectively. In the final model pressure pain thresholds assessed manually at TA and temporal summation assessed using a cuff-algometer were significant predictors of pain. A previous study developed a similar model combining different PPT-measurements to predict pain intensity in KOA and found a R^2 of 0.61 [16], but the present study is the first to combine different quantitative sensory tests (QSTs) reflecting different peripheral and central pain mechanisms in the prediction of pain in KOA. In a study comparing patients with chronic whiplash-associated disorder to healthy controls the partial least squares regression showed a R^2 of 0.49 when trying to identify which QSTs most powerful differed between the two groups. Furthermore it was found that PPT was one of the most important variables when trying to differentiate the two groups and inter-correlations between pain intensity variables and PPT in the chronic whiplash-associated disorder group in a multivariate context [24]. Hence the model in the present study is fully equivalent to previous studies trying to account for clinical pain measures using experimentally assessed pain mechanism in chronic pain states.

4.2. Association between pain modalities

There were positive correlations between handheld PPT knee and handheld PPT TA, between computer PPT knee and handheld PPT knee, between computer PPT knee and handheld PPT TA and between VAS sum knee and VAS sum TA. An association between these parameters was expected as they all reflects different aspects of sensitisation [12,25]. In addition, previous studies found high correlations within the same pain assessment modality [26,27], but not between modalities [27,28]. We did not have the possibility to perform a full personality or a selected gene phenotyping of the participants. Hence we cannot, as in the presented studies rule out a trait-related general high pain sensitivity. However, assessing the PPT from TA is a way to investigate spreading sensitisation [12], and hence an indicator for central sensitisation as previously shown in KOA [14], unilateral epicondylitis [29], chronic low back pain [30] and whiplash [31]. In the present study we confirmed the previous finding [14] of a relationship between both peripatellar and TA PPTs and the clinical pain intensity. This support the proposition that central sensitisation is an important factor in chronic musculoskeletal pain [32].

The lack of other correlations between the other QST methods highlight the importance of applying different tests and different pain modalities when assessing the reorganised pain system as different methods add complementary information. A similar lack of correlation between different types of QST stimulation have previously been described [26,27,33,34]. One modality is truly insufficient when assessing experimentally the status and complexity of pain and a multimodal and optimally a multi-tissue assessment regime is needed [27,35].

The present study is limited by the sample size, the fact that it does not take differences in pain duration and other characteristics (gender, age, etc.) of the participants or TKA versus no TKA into account. For instance, both pain intensity [20] and duration of the pain [36] affect the degree of widespread muscle hyperalgesia and the area where the patient experiences pain. The inclusion of these aspects in this study would however have made an evaluation of the influence of the different characteristics impossible and at the same time increased the complexity of the model making the interpretation harder. Future studies should evaluate these aspects in relation to the prediction of pain in the future leading to a combined model to predict pain. Furthermore a limitation is the use of only pressure pain stimulation. Cold pain thresholds have for example been found predictive for patients developing chronic pain after a whiplash injury [37]. Different pain modalities represent different specific pathways of the pain and should therefore ideally be combined when assessing pain in an experimental setting [27,33].

However this is the first study to combine different mechanistic experimental pain measures in prediction pain in KOA and may form the basis for selecting a set of pain measures to mechanistically phenotype OA patients. This may be developed to predict high risk sensitised patients prior to surgery or selecting patients for the most optimal treatment.

5. Conclusions

A total of 55% of the variability in maximal clinical pain intensity can be explained by combining a set of mechanism based experimental pain measures in KOA.

Particular the pain measures reflecting central pain mechanisms (spreading sensitisation and temporal summation seems to be very important factors explaining pain in OA. This has implications for pain management in OA where treatment modalities addressing the central pain components may be more important than previously acknowledged.

Author contributions

STS was leading the co-ordination of the trial. STS, TGN, LL, OS, MBL and LAN assisted with the protocol design and procured the project funding. STS wrote this manuscript. All authors participated in the trial design, discussed the results, provided feedback on drafts of this paper and read and approved the final manuscript.

Role of the funding source

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Financial disclosure

None reported.

Conflict of interest

None reported.

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