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Original article

Secondary hyperalgesia occurs regardless of unilateral or bilateral knee osteoarthritis involvement in individuals with mild or moderate level

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ABSTRACT

Background: Secondary hyperalgesia in individuals with less severe levels of knee osteoarthritis remains unclear. The objective of this study was to measure the pressure pain threshold of individuals with mild or moderate knee osteoarthritis and compare with no osteoarthritis.

Methods: Ten healthy controls and 30 individuals with mild or moderate knee osteoarthritis divided into two groups (unilateral and bilateral involvement) were included. Dermatomes in lumbar levels (L1, L2, L3, L4 and L5) and sacral level (S1 and S2), myotomes (vastus medialis, vastus lateralis, rectus femoris, adductor longus, tibialis anterior, peroneus longus, iliacus, quadratus lumborum, and popliteus muscles), and sclerotomes in lumbar levels (L1-L2, L2-L3, L3-L4, L4-L5 supraspinous ligaments), over the L5-S1 and S1-S2 sacral areas, pes anserinus bursae, and at the patellar tendon pressure pain threshold were assessed and compared between individuals with and without knee osteoarthritis.

Results: Knee osteoarthritis groups (unilateral and bilateral) reported lower pressure pain threshold compared to the control group in most areas (dermatomes, myotomes, and sclerotomes). There were no between group differences in the supra-spinous ligaments and over the L5-S1 and S1-S2 sacral areas of the sclerotomes. No difference was seen between knee osteoarthritis.

Conclusion: These findings suggest that individuals with mild to moderate knee osteoarthritis had primary and secondary hyperalgesia, independent of unilateral or bilateral involvement. These results suggest that the pain have to be an assertive focus in the clinical practice, independent of the level of severity or involvement of knee osteoarthritis.

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A hiperalgesia secundária ocorre independentemente do envolvimento unilateral ou bilateral da osteoartrite de joelho em indivíduos com doença leve ou moderada

Palavras-chave:
Osteoartrite de joelho
Dor
Limiar de dor à pressão
Hiperalgesia secundária

RESUMO

Introdução: A ocorrência de hiperalgesia secundária em indivíduos com níveis menos graves de osteoartrite de joelho ainda é incerta. O objetivo deste estudo foi medir o limiar de dor à pressão de indivíduos com osteoartrite de joelho leve ou moderada e comparar com indivíduos sem osteoartrite.
Métodos: Foram incluídos 10 controles saudáveis e 30 indivíduos com osteoartrite de joelho leve ou moderada, divididos em dois grupos (envolvimento unilateral e bilateral). Foi avaliado e comparado o limiar de dor à pressão em dermátomos nos níveis lombares (L1, L2, L3, L4, L5) e níveis sacrais (S1 e S2), miótomos (músculos vasto medial, vasto lateral, reto femoral, adutor longo, tibial anterior, fibular longo, ilíaco, quadrado do lombo e poplíteo) e esclerótomos nos níveis lombares (ligamentos supraespinais L1-L2, L2-L3, L3-L4, L4-L5), sobre as áreas sacrais L5-S1 e S1-S2, bolsa anserina e tendão patelar entre os indivíduos com e sem osteoartrite de joelho.
Resultados: Os grupos osteoartrite de joelho (unilateral e bilateral) relataram menor limiar de dor à pressão em comparação com o grupo controle na maior parte das áreas (dermátomos, miótomos e esclerótomos). Não houve diferenças entre os grupos nos ligamentos supraespinais e ao longo das áreas sacrais L5-S1 e S1-S2 dos esclerótomos. Não foi observada qualquer diferença entre os indivíduos com osteoartrite de joelho.
Conclusão: Esses achados sugerem que os indivíduos com osteoartrite de joelho leve a moderada tinham hiperalgesia primária e secundária, independentemente do acometimento unilateral ou bilateral. Esses resultados sugerem que a dor precisa serum foco assertivo na prática clínica, independentemente do grau de gravidade ou envolvimento da osteoartrite de joelho.

Introduction

The knee is the most common joint affected by osteoarthritis, and the prevalence increases with aging.[1] Pain is the main symptom of knee osteoarthritis (KOA), and its presence and severity are important determinants of decreased functional capacity.[2,3] Primary hyperalgesia has been defined as increased activity of primary afferent nociceptors at the site of a determined injured tissue, while secondary hyperalgesia is defined as presence of pain in areas beyond the original injured area.[4] Primary and secondary hyperalgesia may occur in KOA and result in modulation of nociceptors and spinal horn neurons, respectively.[5]

The pressure pain threshold (PPT) has been considered the most reliable parameter to classify inflammation in osteoarthritis,[6,7] and has been used to detect the presence of secondary hyperalgesia in dermatomes, myotomes, and sclerotomes.[2,5] PPT seems to have different levels between individuals with and without osteoarthritis,[2,8] however, current evidence does not answer if PPT levels are different between the different severities (e.g., mild or moderate) of KOA.[2,9,10] In the past, Gerecz-Simon et al.[11] evaluated individuals with knee OA, but just pain was mild and moderate. Also, they used only two points in lower limb. Recently, it has been demonstrated that individuals with moderate KOA present localized pain and not contralateral hyperalgesia,[12] however, in this study, although not mentioned, the characteristics of the participants suggests that individuals had unilateral KOA. Therefore, assessing PPT in multiples points might bring meaningful information about the pain, as well as contribute to clinical approach. As joint damage occurs gradually in osteoarthritis (i.e., with progressive function loss of tissue stabilizers),[13] secondary hyperalgesia would be expected to occur in the development process of osteoarthritis, and unilateral or bilateral involvement might play a role on this,[14] resulting in different painful points. Thus, this study aimed to measure the PPT levels in mild or moderate KOA individuals with unilateral and bilateral involvement and compare to individuals without KOA. We hypothesized that some level of secondary hyperalgesia would be present in individuals with mild and moderate KOA and would be effect of unilateral or bilateral involvement.

Materials and methods

Participants

After the University Research Ethics Committee approval (No. 0012/2010) and conforms the Helsinki Declaration of 1975, the study recruitment was carried out in the Rheumatology Clinic of the university hospital and TV regional news. Four hundred-thirty individuals with KOA were contacted via telephone. Sixty individuals attended the personal evaluation to confirm their adjustment in the criteria for inclusion/exclusion.

Table 1 – Characteristics of knee osteoarthritis (KOA) and healthy control individuals.

Individuals	Age (mean ± SD)	Gender	I/MI knee	Severity KOA	Medications
Control ($n = 10$)	57.8 ± 6.22	Females ($n = 6$)	–	–	–
		Males ($n = 4$)	–	–	–
KOA					
Unilateral ($n = 15$)	59.86 ± 7.61	Females ($n = 11$) Males ($n = 4$)	Right knee ($n = 11$) Left knee ($n = 4$)	Mild ($n = 7$) Moderate ($n = 8$)	$n = 8$
Bilateral ($n = 15$)	64 ± 10.06	Females ($n = 7$) Males ($n = 8$)	Right knee ($n = 9$) Left knee ($n = 6$)	Mild ($n = 4$) Moderate ($n = 11$)	$n = 7$

SD, standard deviation; I, involved knee in unilateral KOA; MI, more involved knee in bilateral KOA.

For inclusion, individuals should be 50-years-old or more, have diagnosed KOA in the evaluation (unilateral or bilateral), and pain for at least 6 months. The diagnosis of KOA was based on the classification of the American College of Rheumatology,[15] accompanied by radiological evidence of osteoarthritis affecting one or more compartments, according to the radiological criteria of Kellgren and Lawrence.[16] Individuals were excluded if they had any of the following: other musculoskeletal disorders; chronic diffuse pain (fibromyalgia), chronic inflammatory conditions, such as autoimmune diseases (rheumatoid arthritis, lupus, gout); diabetes mellitus; neuromuscular disorders, such as Parkinson's disease; vertigo or other conditions that could affect the sensory capabilities and control of movement. Individuals who used central control of pain medications, such as antidepressants also were excluded, but individuals who used oral nonsteroidal anti-inflammatory drugs, it was allowed to continue its use.

After selection, 30 individuals with KOA were included. Ten individuals older than 50 years who had no history of injury, surgery, and pain in the lower extremities were selected by convenience to compose the control group. All included participants signed the informed participation consent, and were divided into three groups: bilateral KOA ($n = 15$), unilateral KOA ($n = 15$) and control ($n = 10$). Table 1 shows the participants' characteristics.

Pain assessment

A digital force gauge (Force TEN™ FDX, Wagner Instruments, Greenwich, CT, USA) and with a flat ½ inch diameter head were used for mechanical quantification of hyperalgesia and allodynia resulting from peripheral or central nociceptive sensitization. The measurements were performed bilaterally in the dermatomes at levels L1, L2, L3, L4, L5, S1 and S2, using the pinch and roll maneuver described by Imamura et al.[5] The same was taken for myotomes, at nine predetermined locations (vastus medialis, vastus lateralis, rectus femoris, adductor longus, tibialis anterior, peroneus longus, iliacus, quadratus lumborum, and popliteus muscles). Finally, the sclerotomes were evaluated in the L1–L2, L2–L3, L3–L4, L4–L5 supraspinous ligaments, over the L5–S1 and S1–S2 sacral areas, pes anserinus bursae, and at the patellar tendon (Fig. 1). Two experienced researchers collected all the data, using strict criteria for the location of the points. The PPT was expressed in kg/cm^2, with the highest values denoting less severe symptoms.

Statistical analysis

In many situations it is necessary to check whether there is a significant difference in mean treatment k ($k > 2$). One solution would be the F test through the analysis of variance (ANOVA), which allows us to jointly test the means of k treatments. However, in some situations the model assumptions (normality and homogeneity independence of residuals) are not satisfied. Therefore we recommend the use of non-parametric tests, i.e., a non-parametric inference. In this work we applied the Kruskal–Wallis test consisting of a non-parametric ANOVA because the assumptions of parametric ANOVA were not met.[17]

Results

Significant difference in the mean values of the PPT was found between control and KOA unilateral and bilateral groups ($p < 0.03$), while no difference was found between KOA unilateral and bilateral groups. The KOA groups had a lower pain threshold in most areas of the dermatomes (Table 2), myotomes (Table 3), and sclerotomes (only the pes anserinus bursae and patellar tendon; Table 4). However, there was no difference in the mean values of the PPT ($p > 0.05$) in the sclerotomes of the supraspinous ligaments, over the L5-S1 and S1-S2 sacral areas (Table 4).

Discussion

The aim of this study was to measure the PPT of individuals with mild and moderate KOA (with unilateral and bilateral involvement) and compare with those without KOA. The results showed that compared to controls, individuals with mild and moderate KOA had lower PPTs in most areas, while

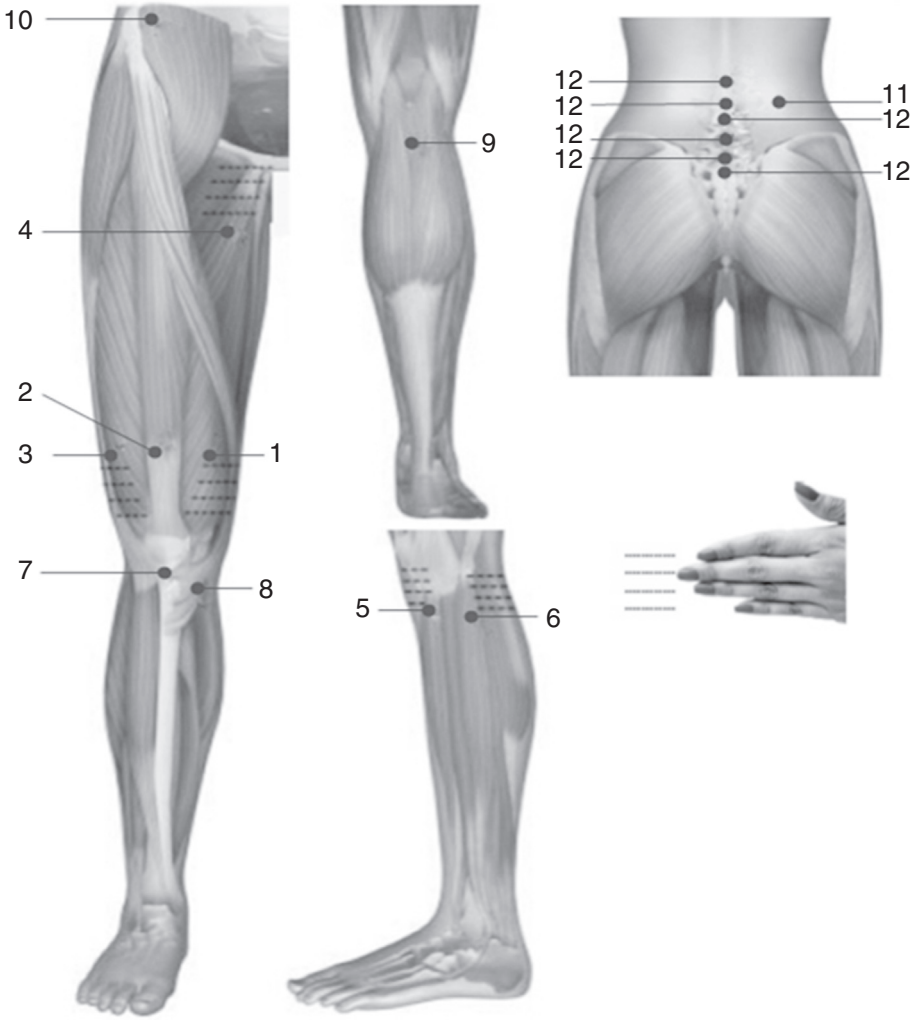

Fig. 1 – The anatomic sites used in the evaluation of the pressure pain threshold (PPT) of the muscles, patellar tendon, and pes anserinus busae in the anterior, posterior, and lateral views. (1) Vastus medialis muscle; (2) rectus femoris muscle; (3) vastus lateralis muscle; (4) adductor longus muscle; (5) anterior tibialis muscle; (6) peroneus longus muscle; (7) patellar tendon; (8) pes anserinus bursae; (9) popliteal muscle; (10) iliac muscle; (11) quadratus lumborum muscle; (12) supraspinous ligaments and sacral areas between L5-S1 and S1-S2. Figure adapted from Imamura et al.[5]

no difference occurred between unilateral or bilateral KOA involvement.

According Courtney et al.,[18] primary hyperalgesia seems to be based on sensitization of peripheral C-fiber nociceptors of deep somatic tissues when a stimulus is applied at the location of the inflammation. This process progresses if the nociceptive stimulation persists. In such cases, the nerve endings of the central nervous system may be altered because of the increase in the receptive field, making them more sensitive to stimuli.[5] The increase in synaptic excitability increases the response to both noxious and non-noxious stimuli, leading to allodynia and secondary hyperalgesia. In secondary hyperalgesia, a stimulus out of the lesion area causes pain in the individual.[18]

Although the process of degeneration in KOA is not clear, the results of this study revealed that the individuals with mild to moderate KOA had primary and secondary hyperalgesia, whereas the healthy controls did not. Comparing the data from this study with those of Imamura et al.,[5] it is suggested that when KOA progresses, secondary hyperalgesia also increases. Imamura et al.[5] also reported the presence of secondary hyperalgesia in distant regions of the knee, including the lumbar region, in severe KOA individuals. In contrast, in the present study, the individuals with mild to moderate KOA showed no alterations in the lumbar region. However, there were changes in the pain threshold of distant parts of the knee that exhibited secondary hyperalgesia (Tables 2 and 3). Therefore, our results suggest the secondary hyperalgesia would occur along the degeneration process and would not be a feature present only in the severe level of KOA. Similar results were showed by Rakel et al.,[12] however, the PPT points were only in one point each primary and secondary hyperalgesia, and the way to determinate of the mild KOA was considered a limitation of the study by authors. The present study used the classification of the American College of Rheumatology,[15] and therefore, it confirms the results of Rakel et al.,[12] adding the sensitivity to mechanical stimulus in dermatomes, myotomes, and sclerotomes.

Table 2 – Results Kruskal–Wallis test for pressure pain threshold on dermatomes.

Dermatomal	χ^2[a]	p-Value	Groups		Mean of the ranks[b,c]	
L1	18.7044	0.0022	Control	Right knee	61.55	a
				Left knee	57.85	a
			Unilateral	Involved knee	34.97	b
				Noninvolved knee	34.97	b
			Bilateral	More involved knee	35.00	b
				Less involved knee	31.40	b
L2	13.9418	0.0159	Control	Right knee	58.05	a
				Left knee	55.70	a
			Unilateral	Involved knee	31.97	b
				Noninvolved knee	34.33	b
			Bilateral	More involved knee	35.20	b
				Less involved knee	38.67	b
L3	23.2273	0.0003	Control	Right knee	61.70	a
				Left knee	62.20	a
			Unilateral	Involved knee	33.87	b
				Noninvolved knee	34.23	b
			Bilateral	More involved knee	35.47	b
				Less involved knee	29.83	b
L4	22.0370	0.0005	Control	Right knee	62.15	a
				Left knee	59.8	a
			Unilateral	Involved knee	31.67	b
				Noninvolved knee	39.20	b
			Bilateral	More involved knee	30.30	b
				Less involved knee	33.53	b
L5	19.7702	0.0014	Control	Right knee	59.60	a
				Left knee	61.15	a
			Unilateral	Involved knee	32.10	b
				Noninvolved knee	35.70	b
			Bilateral	More involved knee	34.83	b
				Less involved knee	32.87	b
S1	22.3136	0.0005	Control	Right knee	60.60	a
				Left knee	61.50	a
			Unilateral	Involved knee	33.63	b
				Noninvolved knee	35.90	b
			Bilateral	More involved knee	27.77	b
				Less involved knee	37.30	b
S2	14.9281	0.0107	Control	Right knee	58.45	a
				Left knee	57.25	a
			Unilateral	Involved knee	33.73	b
				Noninvolved knee	34.73	b
			Bilateral	More involved knee	34.73	b
				Less involved knee	35.00	b

[a] χ^2 statistical value with one-tailed probability α.
[b] The mean ranks derive the means of PPT collected and was represented by lowercase letters.
[c] Different lowercase letters in the column, the means of the ranks of the PPT differ by Kruskal–Wallis test at 5% significance level.

Hassan et al.[3] noted that drugs could act on peripheral and/or central pain mechanisms. However, in the present study, part of the participants ($n = 15$; Table 1) were using, but this seems to not interfere in PPT, since most of the PPT points were more sensitive compared with control group. These results reinforce the evidence that drugs usually have limited action in chronic pain, and unsatisfactory in pain relief.[19] Taylor et al.[20] reported that both physicians and patients (51% of respondents) are unhappy with the inadequate control of KOA provided by traditional anti-inflammatory non-steroidal therapy. Their study included patients with mild (31%) and moderate or severe KOA (60%). In addition, these results suggest that for secondary hyperalgesia treatment and control of pain in KOA, central pain drugs could be useful, since NSAIDs act only on peripheral pain mechanisms.[21]

Riddle and Stratford[14] found pain influence about the side of involvement (unilateral or bilateral) measured by self-report, but our results showed that pain not influenced the side of involvement and not supported the results of the Riddle and Stratford.[14] Despite of important difference of size sample between these studies, we should considerate that an objective mechanism of pain mensuration (PPT) could be different of the self-report measure. Riddle and Stratford[14] also suggested that difference observed in function between unilateral and bilateral pain could be a reflection of differences in pain severity. The pain measured by self-report was associated

Table 3 – Results Kruskal–Wallis test for pressure pain threshold on myotomes.

Myotomal	χ^2[a]	*p*-Value	Groups		Mean of the ranks[b,c]	
ILIO	12.1881	0.0323	Control	Right knee	55.10	a
				Left knee	56.20	a
			Unilateral	Involved knee	38.37	b
				Noninvolved knee	31.00	b
			Bilateral	More involved knee	35.63	b
				Less involved knee	36.80	b
AL	17.8989	0.0031	Control	Right knee	62.95	a
				Left knee	55.10	a
			Unilateral	Involved knee	32.90	b
				Noninvolved knee	32.47	b
			Bilateral	More involved knee	34.83	b
				Less involved knee	37.10	b
RF	24.3074	0.0002	Control	Right knee	64.00	a
				Left knee	61.10	a
			Unilateral	Involved knee	32.83	b
				Noninvolved knee	31.00	b
			Bilateral	More involved knee	34.53	b
				Less involved knee	34.23	b
VM	21.1307	0.0008	Control	Right knee	59.15	a
				Left knee	62.55	a
			Unilateral	Involved knee	31.03	b
				Noninvolved knee	34.03	b
			Bilateral	More involved knee	37.17	b
				Less involved knee	32.63	b
VL	18.8512	0.0020	Control	Right knee	62.30	a
				Left knee	57.10	a
			Unilateral	Involved knee	35.33	b
				Noninvolved knee	31.20	b
			Bilateral	More involved knee	33.73	b
				Less involved knee	36.13	b
TA	24.7054	0.0002	Control	Right knee	61.20	a
				Left knee	64.20	a
			Unilateral	Involved knee	34.87	b
				Noninvolved knee	34.37	b
			Bilateral	More involved knee	32.17	b
				Less involved knee	31.00	b
FL	21.5347	0.0006	Control	Right knee	63.10	a
				Left knee	59.10	a
			Unilateral	Involved knee	30.30	b
				Noninvolved knee	34.17	b
			Bilateral	More involved knee	34.87	b
				Less involved knee	35.20	b
QL	24.6522	0.0002	Control	Right knee	59.35	a
				Left knee	65.70	a
			Unilateral	Involved knee	31.47	b
				Noninvolved knee	33.10	b
			Bilateral	More involved knee	32.17	b
				Less involved knee	35.90	b
POP	26.3413	<0.000	Control	Right knee	62.35	a
				Left knee	64.45	a
			Unilateral	Involved knee	31.20	b
				Noninvolved knee	34.70	b
			Bilateral	More involved knee	30.77	b
				Less involved knee	34.80	b

ILIO, iliacus muscle; AL, adductor longus muscle; RF, rectus femoris muscle; VM, vastus medialis muscle; VL, vastus lateralis muscle; TA, tibialis anterior muscle; FL, peroneus longus muscle; QL, quadratus lumborum muscle; POP, popliteus muscle.

[a] χ^2 statistical value with one-tailed probability α.

[b] The mean ranks derive the means of PPT collected and was represented by lowercase letters.

[c] Different lowercase letters in the column, the means of the ranks of the PPT differ by Kruskal–Wallis test at 5% significance level.

Table 4 – Results Kruskal–Wallis test for pressure pain threshold on sclerotomes.

Sclerotomal	χ^2[a]	*p*-Value	Groups		Mean of the ranks[b,c]	
TP	24.5637	0.0002	Control	Right knee	63.60	a
				Left knee	61.30	a
			Unilateral	Involved knee	34.43	b
				Noninvolved knee	33.53	b
			Bilateral	More involved knee	29.00	b
				Less involved knee	35.77	b
PG	19.6622	0.0014	Control	Right knee	59.80	a
				Left knee	59.95	a
			Unilateral	Involved knee	33.67	b
				Noninvolved knee	39.33	b
			Bilateral	More involved knee	31.77	b
				Less involved knee	31.40	b
L1-L2	3.9834	0.1364	Control	Right knee	48.00	a
				Left knee	43.20	a
			Unilateral	Involved knee	43.27	a
				Noninvolved knee	39.83	a
			Bilateral	More involved knee	41.63	a
				Less involved knee	30.47	a
L2-L3	2.3155	0.3142	Control	Right knee	37.22	a
				Left knee	–	
			Unilateral	Involved knee	37.58	a
				Noninvolved knee	–	
			Bilateral	More involved knee	45.60	a
				Less involved knee	–	
L3-L4	4.4425	0.1085	Control	Right knee	37.62	a
				Left knee	–	
			Unilateral	Involved knee	47.48	a
				Noninvolved knee	–	
			Bilateral	More involved knee	35.43	a
				Less involved knee	–	
L4-L5	1.5373	0.4636	Control	Right knee	40.30	a
				Left knee	–	
			Unilateral	Involved knee	36.85	a
				Noninvolved knee	–	
			Bilateral	More involved knee	44.28	a
				Less involved knee	–	
L5-S1	3.3315	0.1890	Control	Right knee	47.45	a
				Left knee	–	
			Unilateral	Involved knee	41.10	a
				Noninvolved knee	–	
			Bilateral	More involved knee	35.27	a
				Less involved knee	–	
S1-S2	0.3497	0.8396	Control	Right knee	39.30	a
				Left knee	–	
			Unilateral	Involved knee	39.32	a
				Noninvolved knee	–	
			Bilateral	More involved knee	42.48	a
				Less involved knee	–	

PT, patella tendon; PG, pes anserinus bursae; L1-L2, L1-L2 supraspinous ligament; L2-L3, L2-L3 supraspinous ligament; L3-L4, L3-L4 supraspinous ligament; L4-L5, L4-L5 supraspinous ligament; L5-S1, L5-S1 sacral area; S1-S2, S1-S2 sacral area.

[a] χ^2 statistical value with one-tailed probability α.

[b] The mean ranks derive the means of PPT collected and was represented by lowercase letters.

[c] Different lowercase letters in the column, the means of the ranks of the PPT differ by Kruskal–Wallis test at 5% significance level.

with psychological state according to Wise et al.,[22] which could have influenced the results of Riddle and Stratford.[14]

Finally, in this study two researchers made the collection of the data and we did not assess the inter-rater reliability, what can be considered a limitation of the study, since there could be a slight difference in the locations of the anatomical points. However, they were both experienced and used strict criteria for the location of the points. As reported by Fisher,[6] the individual described by the PPT is well correlated between different researchers and local analysis.

Taking all together, individuals with mild to moderate KOA had primary and secondary hyperalgesia, independent of unilateral or bilateral involvement. These results suggest that the pain have to be an assertive focus in the clinical practice, independent of the level of severity or involvement of KOA.

Conflicts of interest

The authors declare no conflicts of interest.

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REFERENCES

1. Shakoor N, Furmanov S, Nelson DE, Li Y, Block JA. Pain and its relationship with muscle strength and proprioception in knee OA: results of an 8-week home exercise pilot study. J Musculoskelet Neuronal Interact. 2008;8:35–42.
2. Arendt-Nielsen L, Nie H, Laursen MB, Laursen BS, Madeleine P, Simonsen OH, et al. Sensitization in patients with painful knee osteoarthritis. Pain. 2010;149:573–81.
3. Hassan BS, Doherty SA, Mockett S, Doherty M. Effect of pain reduction on postural sway, proprioception, and quadriceps strength in subjects with knee osteoarthritis. Ann Rheum Dis. 2002;61:422–8.
4. Hunter DJ, McDougall JJ, Keefe FJ. The symptoms of osteoarthritis and the genesis of pain. Med Clin North Am. 2009;93:83–100.
5. Imamura M, Imamura ST, Kaziyama HHS, Targino RA, Hsing WT, de Souza LPM, et al. Impact of nervous system hyperalgesia on pain, disability, and quality of life in patients with knee osteoarthritis: a controlled analysis. Arthritis Rheum. 2008;59:1424–31.
6. Fischer AA. Pressure algometry over normal muscles. Standard values, validity and reproducibility of pressure threshold. Pain. 1987;30:115–26.
7. Suokas AK, Walsh DA, McWilliams DF, Condon L, Moreton B, Wylde V, et al. Quantitative sensory testing in painful osteoarthritis: a systematic review and meta-analysis. Osteoarthritis Cartilage. 2012;20:1075–85.
8. Lee YC, Lu B, Bathon JM, Haythornthwaite JA, Smith MT, Page GG, et al. Pain sensitivity and pain reactivity in osteoarthritis. Arthritis Care Res. 2011;63:320–7.
9. Graven-Nielsen T, Wodehouse T, Langford RM, Arendt-Nielsen L, Kidd BL. Normalization of widespread hyperesthesia and facilitated spatial summation of deep-tissue pain in knee osteoarthritis patients after knee replacement. Arthritis Rheum. 2012;64:2907–16.
10. Stubhaug A, Breivik H. Knee osteoarthritis patients with intact pain modulating systems may have low risk of persistent pain after knee joint replacement. Scand J Pain. 2015;6:41–2.
11. Gerecz-Simon EM, Tunks ER, Heale J-A, Kean WF, Buchanan WW. Measurement of pain threshold in patients with rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and healthy controls. Clin Rheumatol. 1989;8:467–74.
12. Rakel B, Vance C, Zimmerman MB, Petsas-Blodgett N, Amendola A, Sluka KA. Mechanical hyperalgesia and reduced quality of life occur in people with mild knee osteoarthritis pain. Clin J Pain. 2015;31:315–22.
13. Heijink A, Gomoll AH, Madry H, Drobnic M, Filardo G, Espregueira-Mendes J, et al. Biomechanical considerations in the pathogenesis of osteoarthritis of the knee. Knee Surg Sports Traumatol Arthrosc. 2012;20:423–35.
14. Riddle DL, Stratford PW. Unilateral vs bilateral symptomatic knee osteoarthritis: associations between pain intensity and function. Rheumatology. 2013;52:2229–37.
15. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. Arthritis Rheum. 1986;29:1039–49.
16. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis. 1957;16:494–502.
17. Conover WJ. Practical nonparametric statistics. 3rd ed. New York: Wiley; 1999.
18. Courtney CA, Kavchak AE, Lowry CD, O'Hearn MA. Interpreting joint pain: quantitative sensory testing in musculoskeletal management. J Orthop Sports Phys Ther. 2010;40:818–25.
19. Ambrose KR, Golightly YM. Physical exercise as non-pharmacological treatment of chronic pain: why and when. Best Pract Res Clin Rheumatol. 2015;29:120–30.
20. Taylor SD, Everett SV, Taylor TN, Watson DJ, Taylor-Stokes G. A measure of treatment response: patient and physician satisfaction with traditional NSAIDs for osteoarthritis control. Open Access Rheumatol Res Rev. 2013:69–76.
21. Batlouni M. Anti-inflamatórios não esteroides: efeitos cardiovasculares, cérebro-vasculares e renais. Arq Bras Cardiol. 2010;94:556–63.
22. Wise BL, Niu J, Zhang Y, Wang N, Jordan JM, Choy E, et al. Psychological factors and their relation to osteoarthritis pain. Osteoarthritis Cartilage. 2010;18:883–7.