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Anterior cruciate ligament innervation in primary knee osteoarthritis

Adrián Guerra-González[1], Carmen da Casa[2], Íñigo Crespo[1,2], David Pescador[1,2], Lorena Benito-Garzón[3] and Juan F Blanco[1,2,3]

[1]Orthopaedic Surgery, University Hospital of Salamanca, [2]Biomedical Research Institute of Salamanca (IBSAL) and [3]University of Salamanca (USAL), Salamanca, Spain

Summary. Objective. To relate the Anterior Cruciate Ligament (ACL) innervation and histologic degeneration status to the knee osteoarthritis radiologic and functional status.

Design. Prospective observational study including 30 consecutive patients affected by primary knee osteoarthritis undergoing Total Knee Arthroplasty (TKA). All patients suffering secondary knee osteoarthritis, an antecedent of an infectious process, malignant process, autoimmune disorder, or previous knee surgery were excluded. We recorded biodemographic, clinical, and radiologic variables of all participants previous to the TKA procedure. ACL tissue was harvested during TKA standard procedure and the obtained sample was fixed in 4% formalin and paraffin-embedded. ACL cross-sections were stained by haematoxylin-eosin and Gallego staining for elastic and collagen fibers, and Sevier-Munger silver staining for nervous tissue.

Results. ACL samples histologic degeneration classification reported 15.4% normal, 23.1% slight, 26.9% mild, 11.5% moderate and 23.1% marked. We noted 46.2% large nervous fascicles, 15.4% medium fascicles, 3.8% small fascicles, and no nerve fibers were found in 34.6% ACL samples. No significant correlation was found between the histologic degeneration and the nervous fiber quantification ($p>0.05$, in all cases). We noted a significant histologic degeneration inverse correlation with the VAS scale ($p=0.016$), and nervous fiber quantification correlation with Lequesne maximum distance walked punctuation ($p=0.043$). We also noted greater nervous fiber quantification with minor radiological knee osteoarthritis (Kellgren-Lawrence grade II).

Conclusions. ACL degeneration and innervation deficit may play a role in primary knee osteoarthritis onset, but the lack of a defining relationship among the different parameters assessed justifies further research in greater populations.

Key words: Anterior cruciate ligament, Histology, Knee osteoarthritis, Radiology, Innervation

Corresponding Author: Prof. Juan F Blanco, MD PhD, Cirugía Ortopédica y Traumatología Hospital Universitario de Salamanca, Paseo de la Transición Española, s/n – Salamanca, Spain. e-mail: jfblanco@usal.es

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Introduction

Knee osteoarthritis is a very frequent degenerative pathology that causes pain and dysfunction. Generally, there is articular cartilage and subchondral bone damage that accompany knee osteoarthritis. Some reported risk factors for knee osteoarthritis are directly related to age (Neogi, 2013), with a striking increase in prevalence from 60 onwards, and also to an increase in Body Mass Index (BMI) (Sellam and Berenbaum, 2013). However, the etiology of primary knee osteoarthritis has not been well clarified and is described as a multifactorial process (Johnson and Hunter, 2014).

Among the suspected etiological factors for knee osteoarthritis, those related to Anterior Cruciate Ligament (ACL) status have been pointed out. The ACL plays a crucial role in the biomechanical knee function. The ACL provides stability to the knee and also intervenes in the proprioception processes that contribute to protective mechanism establishment, quadriceps stabilization (Schultz et al., 1984; Halata and Haus, 1989; Nyland et al., 1994; Nematollahi et al., 2017).

When an ACL rupture occurs, knee instability arises and there is a deficit of the neuromuscular protective reflexes of its afferent sensory gateway (Nagelli et al., 2017). The lack of proprioception by a neuromuscular deficit of the knee has been related to the pathogenesis of knee osteoarthritis (Corrigan et al., 1992). This nervous dysfunction related to ACL rupture cannot be fully restored with reconstruction techniques (Krogsgaard et al., 2011). Diverse authors have shown that ACL injury can lead to knee osteoarthritis

development (Lohmander et al. , 2004, 2007; Palmieri-Smith and Thomas, 2009; Nordenvall et al., 2014; Lin et al., 2017).

ACL is innervated by nervous fibers coming from the tibial nerve, which presents nerve endings that perforate the posterior capsule and run along the ligamentous path next to the synovial membrane and vessels, until reaching the anterior area of the infrapatellar fat, and thence, accessing the anterior cruciate ligament (Kennedy et al., 1982). The presence of nerve tissue in the ACL, which may represent up to 1% of the total area of the ligament (Schutte et al., 1987), could itself be involved in knee osteoarthritis development (Nagelli et al., 2017).

Some authors have also reported that the osteoarthritis process can lead to ACL histological degeneration changes (Hasegawa et al., 2012).

The aim of this study was to analyze the ACL innervation status in primary knee osteoarthritis patients, in order to relate the ACL innervation and histologic degeneration status to the knee osteoarthritis radiologic and functional status.

Materials and methods

Study design and setting

We performed a prospective observational study including 30 consecutive patients affected by primary knee osteoarthritis at a single tertiary teaching hospital.

Inclusion criteria included patients aged 60 to 80, with no traumatic antecedent affecting the knee. All patients suffering secondary knee osteoarthritis, an antecedent of an infectious process, malignant process, autoimmune disorder, or previous knee surgery were excluded. All participants signed an informed consent previous to their inclusion in the study.

In all cases, surgery was performed unilaterally, so that a right or left total knee arthroplasty was implanted according to the inclusion criteria. Bilateral knee osteoarthritis was present at the time of surgery for 86.67% of patients, and 6.67% had a contralateral knee prosthesis already implanted.

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (CEIm Area de Salud de Salamanca, ref. code: 202002436) and with the Helsinki Declaration of 1975, as revised in 2000.

Participant records

Clinical evaluation

Biodemographic variables were collected regarding gender, age, body mass index (BMI), and laterality. Participants were also evaluated on the following scales previous to surgical treatment: Visual Analogue Scale (VAS) for pain assessment, Lequesne and WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) indexes for knee functional status assessment (Lequesne et al., 1987; Lequesne, 1997; Escobar et al., 2002). The Lequesne score was analyzed globally and in each of its subdomains: pain, maximum walking distance, and use of technical walking aids.

Radiological evaluation

A plain x-ray was taken on both anteroposterior and lateral views of the affected knee. Radiological images were stratified according to the Kellgren-Lawrence classification (Kellgren and Lawrence, 1957).

Surgical procedure and ACL sample

A total knee arthroplasty (TKA) was performed in all cases by parapatellar medial approach. Neuraxial anaesthesia and a pneumatic tourniquet for preventive ischemia were used. All patients received antibiotic prophylaxis with cefazolin (2g i.v.). For skin preparation, chlorhexidine was used in all cases.

Identified ACLs were stratified (as normal, abnormal, or ruptured) according to their macroscopic appearance following Allain et al. (2001). ACL tissue was harvested and the obtained sample was fixed in 4% formalin phosphate-buffered saline (PBS) and paraffin-embedded by the routine procedure.

Histologic study

Multiple longitudinal and transverse four-micron-thick tissue sections were cut. Samples were stained by haematoxylin-eosin (H-E) and Gallego staining for elastic and collagen fibers, and Sevier-Munger silver staining for nervous tissue.

All ACL samples underwent the complete histologic study, longitudinal sections were selected for further analysis as they allowed a more homogeneous and comparable assessment among all the samples. The most relevant findings are presented in the Results section.

Findings on histologic degeneration were classified (as normal, slight, mild, moderate, or marked) according to Kleinbart et al. (1996) (Fig. 1). Gallego staining allowed to assess the degenerative state of the ligament, and in cases with marked degeneration, Gallego stain revealed the developed mucoid tissue, in agreement with the results obtained with H-E stain.

ACL innervation status was evaluated by the quantification of nervous fibers and fascicles. Nervous fascicles were classified as large (>six nervous fibers), medium (two to five nervous fibers), or small (one single nervous fiber) following Ehrle et al. (2017). Some ACLs were noted as no nervous tissue was found (Fig. 2).

Statistical analysis

Statistical analysis was performed using IBM® SPSS® Statistics package v.23. Qualitative variables are expressed by percentages and quantitative variables by

their mean and standard deviation. Bootstrapping techniques were used for increasing the statistical power previous to statistical analysis. Qualitative variables were compared by contingency tables (Chi-Square test and Fisher's correction) and quantitative variables by non-parametric correlations (Kendal Tau for ordinal variables, Spearman's Rho for linear correlations abnormally distributed). Qualitative vs. quantitative variables were compared by ANOVA or Student-T test when normally distributed and Kruskal-Wallis or Mann-Whitney U test when abnormally distributed (Shapiro-Wilk $p<0.05$). Post-hoc Bonferroni tests were also performed. A p-value <0.05 was considered statistically significant in all cases.

Results

Thirty consecutive primary knee osteoarthritis patients following TKA were included in the study. The mean age of the study population was 71.7±4.4 and up to 73.3% were women. Detailed characteristics of the population are described in Table 1.

Patients reported a mean VAS of 7.96±2.0 (43.3% VAS 9-10), a mean Lequesne of 17.52±3.4 (83.3% Lequesne >14), and a mean WOMAC of 64.03±16.2. Radiologic knee osteoarthritis Kellgren-Lawrence classification resulted in 20.0% patients grade II, 53.33% grade III, and 26.67% grade IV. Table 2 shows patients' clinical variables distribution on Kellgren-Lawrence classification.

Regarding the analysis of patients' ACL samples, we noted 60.0% were macroscopically normal, 26.67% abnormal and 6.67% ruptured or very degenerated in appearance. In two cases (6.67%), an absence of the ACL during the surgical procedure was noted. In very

Table 1. Biodemographic characteristics of the studied primary knee osteoarthritis population.

Gender	Women	73.33%
Age (years)	Mean ± SD	71.53±4.4
BMI	Mean ± SD	30.83±4.1
Laterality	Right	56.67%

Table 2. Clinical variables distribution among Kellgren-Lawrence knee osteoarthritis radiologic classification.

	Kellgren-Laurence classification			Statistical
	II (n=6)	III (n=16)	IV (n=8)	significance (p-value)
Gender (women)	66.7%	68.8%	87.5%	0.569
Age (years)	71.9±2.8	71.7±4.2	71.3±5.9	0.962
BMI	30.9±3.8	29.5±3.0	34.0±5.1	**0.036**
VAS	8.2±1.9	7.4±2.1	7.8±1.6	0.755
Lequesne	21.2±1.7	16.6±3.2	17.1±3.5	**0.014**[a]
WOMAC	74.5±13.6	59.6±13.6	65.0±19.6	0.146

[a]Post-hoc Bonferroni indicates significant differences between K-L II and III (Mean difference 4.54 (0.82-8.25), p=0.013).

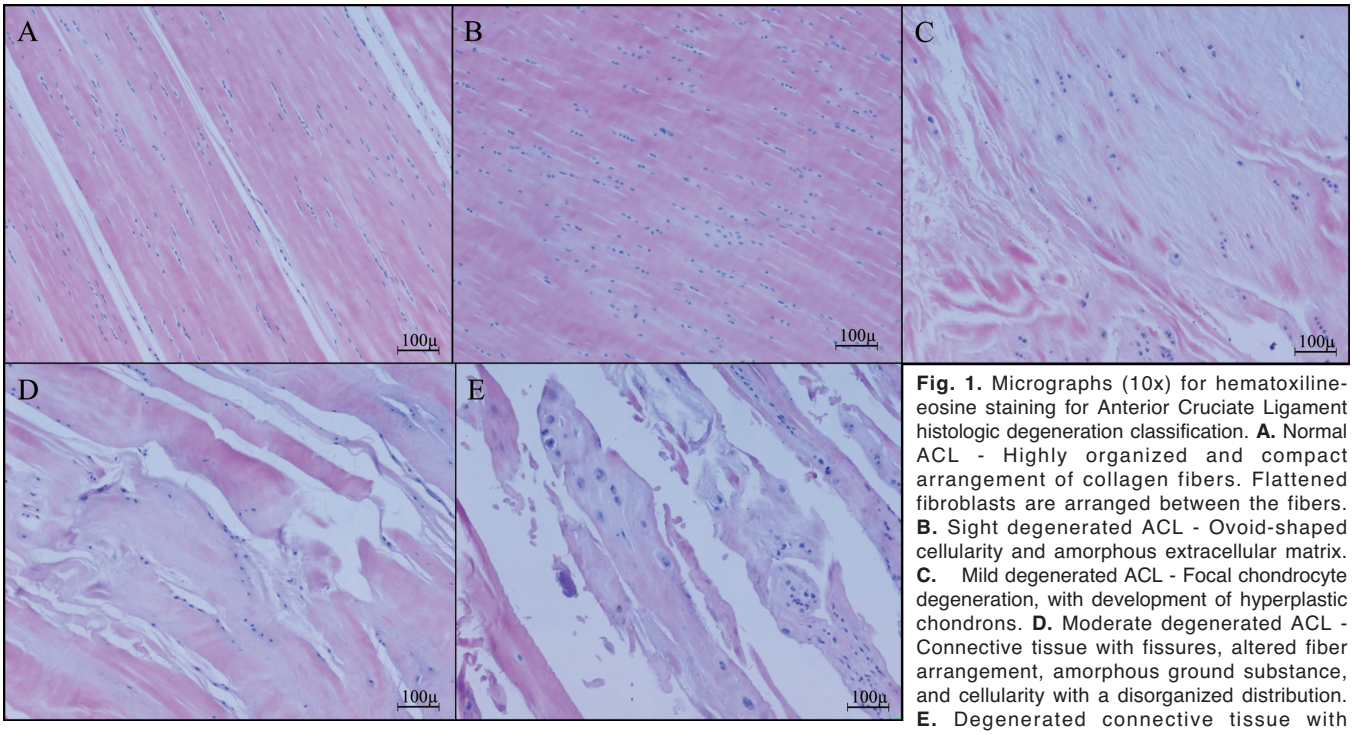

Fig. 1. Micrographs (10x) for hematoxiline-eosine staining for Anterior Cruciate Ligament histologic degeneration classification. **A.** Normal ACL - Highly organized and compact arrangement of collagen fibers. Flattened fibroblasts are arranged between the fibers. **B.** Sight degenerated ACL - Ovoid-shaped cellularity and amorphous extracellular matrix. **C.** Mild degenerated ACL - Focal chondrocyte degeneration, with development of hyperplastic chondrons. **D.** Moderate degenerated ACL - Connective tissue with fissures, altered fiber arrangement, amorphous ground substance, and cellularity with a disorganized distribution. **E.** Degenerated connective tissue with disruption of collagen fibers, a predominance of amorphous ground substance, and disorganized cellularity. Scale bar: 100μm.

severe cases, no ACL sample could be obtained. The remaining 26 ACL samples were further analyzed. Histologic degeneration classification (Fig. 1) reported 15.4% normal ACL, 23.1% slightly degenerated ACL, 26.9% mildly degenerated ACL, 11.5% moderate degenerated ACL, and 23.1% markedly degenerated ACL.

Concerning innervation status, measured by nervous fiber quantification, we noted 46.2% large nervous fascicles, 15.4% medium fascicles, 3.8% small fascicles, and an absence of fibers in 34.6% ACL samples. No significant correlation was found between the histologic degeneration and the nervous fiber quantification ($p>0.05$, in all cases).

When comparing ACL innervation and degeneration status to the clinical variables previously noted, we revealed a homogeneous distribution of ACL innervation and histologic status with aging, gender, and BMI ($p>0.005$, in all cases).

According to the preoperative VAS scale referred by patients, we observed a discrete negative correlation between the histologic degeneration and 2-point grouped VAS scale (Kendall Tau=-0.366, $p=0.016$). We did not find a statistically significant relationship between the overall Lequesne score and ligament innervation, but we noted a slight significant positive correlation between Lequesne's maximum distance walked punctuation and nervous fiber quantification in ACL samples (Spearman $\varrho=0.372$, $p=0.043$). We also noted a significant relationship between reported WOMAC and ACL histologic degeneration ($p=0.010$), but no significant linearity could be addressed ($p>0.05$).

Finally, we evaluated the relationship of ACL innervation status to Kellgren-Lawrence radiological

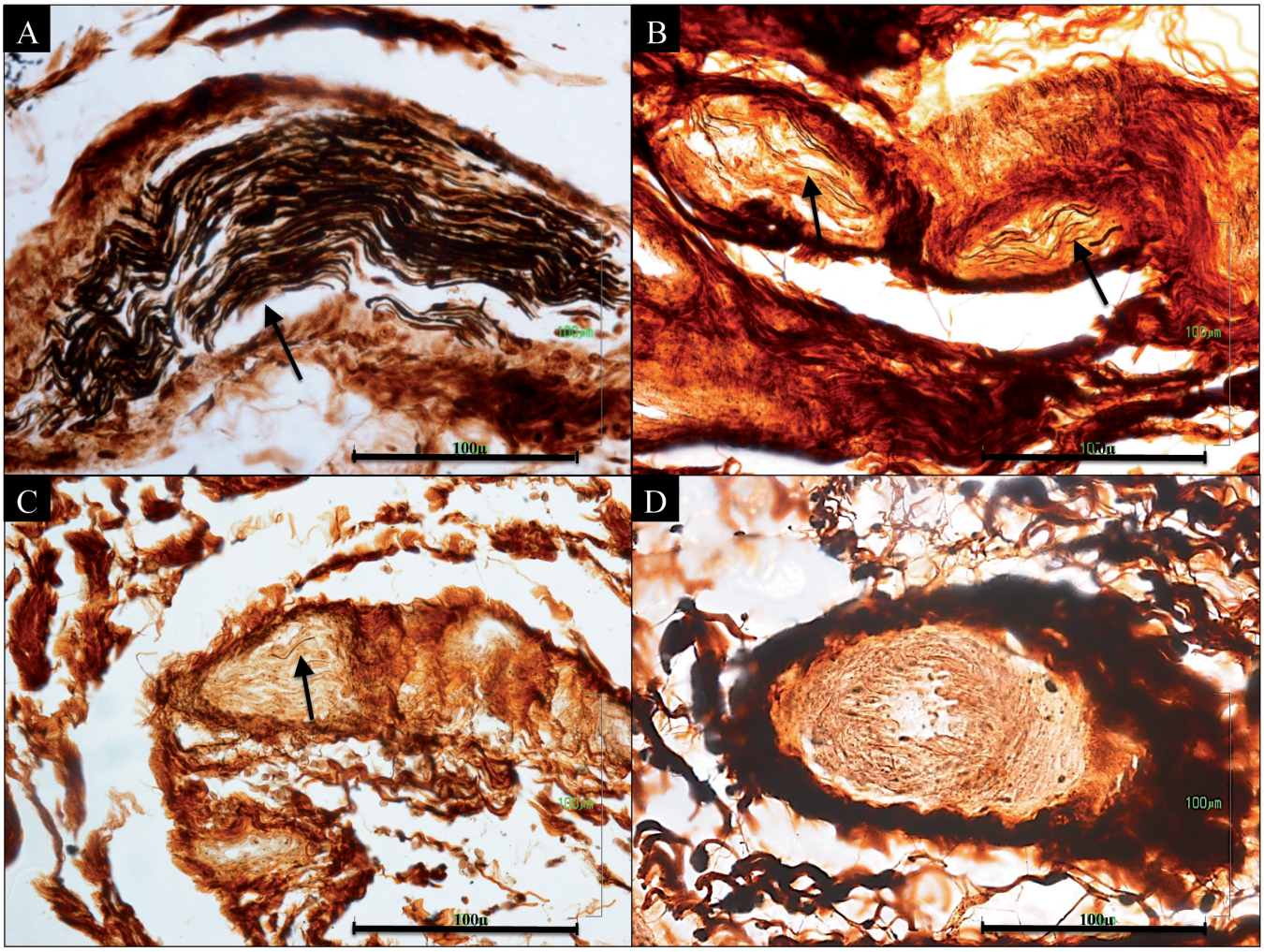

Fig. 2. Micrographs (Axial cut, 40x) for Sevier-Munger silver stain for Anterior Cruciate Ligament nervous fascicles classification. Arrows indicate nervous fibers. **A.** Large nerve fascicle – High number of nerve fibers highly compacted. **B.** Two medium-type nerve fascicles with a small number of nerve fibers. **C.** Detail of a small type nerve fascicle where only one nerve fiber is visible. **D.** Nerve fascicle with the absence of nerve fibers. Scale bars: 100 μm.

knee osteoarthritis grade. We noted the innervation status determining a mean number of nervous fibers of 6.17±7.4 for patients classified with minor radiological knee osteoarthritis (Kellgren-Lawrence II), 3.36±4.1 for Kellgren-Lawrence III patients, and 3.50±3.5 for Kellgren-Lawrence IV patients. No statistical significance was achieved for the cited results (Fig. 3, $p>0.05$, in all cases), or for Kellgren-Lawrence potential correlation to ACL histologic degeneration ($p>0.05$).

Discussion

Our work has been aimed at establishing the possible correlation between the degree of knee osteoarthritis (both clinical and radiological) and the ACL innervation and histological degeneration status. We noted a significant relationship between the knee clinical functional status (VAS, Lequesne, and WOMAC) and the ACL degeneration status.

Previous studies already related knee osteoarthritis with ACL histologic degeneration (Allain et al., 2001; Kleinbart et al., 1996), and even correlated radiologic knee osteoarthritis to ACL and PCL histologic degeneration (Mullaji et al., 2008), based on their own measurement scales. However, no previous clinical functional assessment could be added to the ACL degeneration assessment.

Several mechanisms have been described to find an explanation for knee osteoarthritis produced secondary to ACL injury. Among these, the biomechanical alteration of the knee joint has been studied (Andriacchi and Dyrby, 2005; Chaudhari et al., 2008), as well as damage to the articular cartilage associated with ACL lesions (Fleming et al., 2010) and to a lesser extent neuromuscular deficits (Palmieri-Smith and Thomas, 2009).

Our work presents a methodological difference from previous studies: we evaluated the ACL innervation status by excluding patients with previous knee surgery but on established and symptomatic knee osteoarthritis patients, carrying out an objective and reproducible quantitative analysis.

Some studies have described a link between the pathogenesis of knee osteoarthritis with the ACL innervation deficit. Pioneering studies (Finsterbush and Friedman, 1975; O'Connor et al., 1985) showed how an inadequate innervation of the knee joint can promote degenerative changes in the articular cartilage and thus explains the phenomenon of articular degeneration, but also ACL degeneration may precede articular cartilage changes, and relate the ACL degeneration to already cartilage-damaged knees (Hasegawa et al., 2012).

Our work agrees with these statements, as we already noted degenerated ACLs in primary knee osteoarthritis patients, but also non-degenerated ACL were found. We noted that most cases showed a macroscopically intact ACL, as recently pointed out by Roussi et al. (2021), although a macroscopically normal appearance was not exempt from microscopical degeneration in all cases (Trompeter et al., 2009). The fact that intact ACLs (both macroscopically and microscopically) were found in knee osteoarthritis patients, leads us to think that the pathogenesis of osteoarthritis might not be solely due to the ACL degeneration. Surgeons should consider bi-cruciate retaining total knee arthroplasty in some cases. Indeed, it seems to be a dual mechanism in which diverse factors that may lead to the onset of osteoarthritis also lead to ACL damage (Hasegawa et al., 2012), but also, ACL primary injury might also imply the onset of osteoarthritis (Hill et al., 2005; Fleming et al., 2010).

Our work described the ACL innervation status on primary knee osteoarthritis patients. A previous study with limited numbers of cadaveric samples (Amir et al., 1995) showed an increase in nerve tissue in patients with knee osteoarthritis and supported the regenerative capacity of unmyelinated nerve fibers in response to injury. It should be noted that there is no information available as to whether these were cases of primary knee osteoarthritis or whether they underwent previous ACL reconstruction or pharmacological treatment.

We could not relate the ACL innervation level to the ACL histologic degeneration level, but we noted a better functional ability to walk measured by the Lequesne index with the higher nerve fiber quantification. This could be interpreted to suggest that patients with better innervation will have better proprioception which would allow them the greater functional capacity. Besides, we also noted lower patient-reported values on the VAS scale with the greater histological ACL degeneration. This finding suggests that the greater architectural alteration of the ACL may affect the nociceptors in the ACL, causing the patient to feel less pain than those with histologically intact ligaments. Previous work by Kwee et al. (2018) found ACL mucoid degeneration was not related to patient-reported pain by WOMAC pain subscale.

Our study is not exempt from limitations. As we

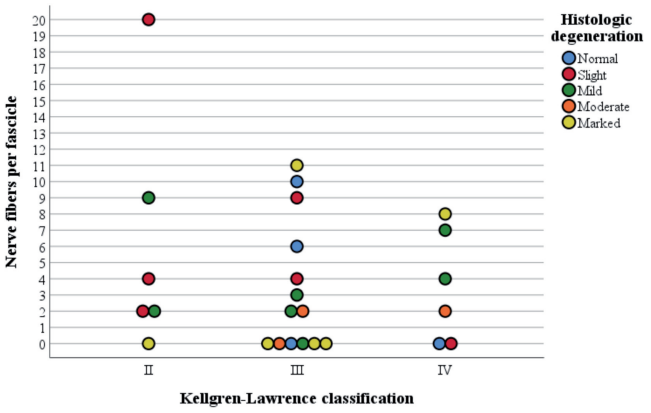

Fig. 3. Plot graph representing ACL nerve fibers quantification regarding Kellgren-Lawrence knee osteoarthritis radiologic classification. Color legend for ACL histologic degeneration.

noted for other studies, a report on previous pharmacological treatment that could affect the ACL degeneration status is missing. Also, the analysis of ligaments in patients undergoing total knee arthroplasty might create a selection bias by not evaluating patients who were not candidates for joint replacement.

In view of the heterogeneity of the results founds in previous studies, our work reported detailed ACL innervation status relative to knee osteoarthritis. ACL degeneration or innervation deficit may play a role in knee osteoarthritis onset, but the lack of a defining relationship among the different parameters assessed justifies further research in greater populations.

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Author contributions. Conception and design: ICC, DP, JFB; Provision of study materials or patients: AG, ICC, DP, JFB; Collection and assembly of data: AG, LB; Analysis and interpretation of the data: AG, LB, CdaC, JFB; Statistical expertise: CdaC; Drafting of the article: CdaC, JFB; Final approval of the article: All authors.

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Conflict of interest. All authors declare no conflict of interest.

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