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Osteoarthritis induces gender-related changes in the knee range of motion

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Abstract

In time, osteoarthritis (OA) generates the misalignment of the affected joint structures. However, due to the nature of bipedal gait, OA in the lower limb can also cause pathological gait patterns, which can generate instability and falls, with great consequence, especially in the aged population. With goniometry used to evaluate the range of motion (ROM) of joints, we wanted to evaluate how gender impacts gait dynamics in OA patients. For this study, we have compared 106 OA patients (74 females and 32 males) to age matched controls. All participants had their right leg as dominant. Video recording of normal gait was analyzed with a digital goniometry tool phone application, and the knee's ROM was measured in midstance and midswing moment of the gait. During midstance, significant extension and flexion of the knee excursion have been observed in both males and females. During midswing, knee OA presents more differences, whereas subjects with hip and knee OA present changes on the dominant knee. Midstance changes suggest that the knee's joint degenerative changes, such as synovitis, can be linked to hip OA secondary changes. Midswing changes in lower limb OA suggest a connection to the activities of daily life. Gender differences generated by OA must furthermore be studied in both lower limbs so that the best therapeutic approach can be chosen.

Keywords: Angles App, goniometry, range of motion, assessment, joint examination.

Introduction

Osteoarthritis (OA) affects millions in Europe alone [1, 2]. The classical approach in evaluating the gravity of OA is to perform a goniometry exam during the clinical objective examination. This generates range of motion (ROM) information that is obtained from a static measurement [3, 4]. For dynamic measurements, however, a more reliable and accurate software has been developed for these measurements to be standardized. As such, physicians can now use smartphone technology and applications that are able to provide cheap, objective, and detailed goniometry evaluations of gait [5, 6]. With its help, two major gait stages can be analyzed: stance (subdivided into loading response, midstance, and terminal stance) and swing (subdivided into initial swing, midswing, and terminal swing) [7, 8].

Aim

Furthermore, we wanted to identify and use new methods of gait analysis so that falls caused by pathological gait can be prevented. The aim of this study was to investigate if gender plays a role in the midstance and midswing of knee's ROM in patients suffering from OA of the hip, knee or both since some gender-related changes have already been proven to exist in lower limb alignment and ROM in elderly [9], in sportsmen [10], or even in simple single-leg drop jumps [11].

Patients, Materials and Methods

Study design

For this study, we have initially enrolled 124 patients (November 2019 to March 2021) suffering from lower limb OA. They were examined in the Department of Physical and Rehabilitation Medicine, Filantropia Municipal Hospital, Craiova, Romania. At the beginning, no clinical or functional difference between left and right was observed. The inclusion criteria were hip and/or knee pain, Kellgren & Lawrence radiological assessment of lower limb OA, stages 1–3. The exclusion criteria were the inability of walking without

the help of an assistive device as a cane or walking frame due to stage 4 OA (hip, knee, or both – hip and knee), history of joint replacement, stroke or neurological lesions, history of lumbar herniated disc, or severe balance problems.

Depending on the localization of the OA lesion, the remaining 106 subjects (74 females and 32 males) were divided into three OA groups: primary hip bilateral arthritis (42), primary knee bilateral arthritis (25), primary hip and knee bilateral OA (39). A control group of 30 participants was also selected. All subjects have the right lower limb as dominant limb. All subjects in the study were volunteers, with ages between 65 and 83 years old and body mass indexes (BMIs) between 26.32 and 40.06 kg/m^2.

All participants in the study have given their Informed Consent according to the principles outlined in the Declaration of Helsinki. Additionally, the study was approved by the Ethics and Academic and Scientific Deontology Committee of the University of Medicine and Pharmacy of Craiova (Approval No. 111/21.10.2019).

Patient assessment

All enrolled patients underwent objective examination, functional evaluation through the visual analog function scale (VAS), followed by the Western Ontario and McMaster Universities Arthritis Index (WOMAC), followed by video-assisted goniometry measurements, as well as paraclinical examinations, such as X-rays confirming the presence of OA and joint ultrasound (US) confirming the presence of synovitis and/or effusion (Figure 1). The paraclinical investigation performed through US examination was done with the help of Philips HD11 XE Ultrasound System, 12.5 MHz linear sound.

Following the US, a biopsy was also performed on the patients with knee OA, and a histopathological (HP) diagnosis of synovitis was confirmed (Figures 2–17). The biological material prevailed from the synovial membrane was processed in the Clinic of Pathology, Emergency County Hospital, Craiova, through a fixation of the tissues in 10% neutral buffered formalin, at room temperature. After the fixation, the specimens were washed in tap water for an hour, after which they were passed through successive alcohols: 70% (left overnight), 90%, 96%, 100% (each concentration contained the specimens for one hour). Whereupon three incubations in xylene were carried out (3×1 hour), paraffin impregnation (at 56°C, left overnight) and paraffin embedding as blocks was conducted during the subsequent day. The cuts were made to a thickness of 4 μm, with the help of a HMB350 rotary microtome (ThermoScientific). The microtome was set with a system for water section transfer. The specimens in the obtained sections were subsequently applied to slides treated with poly-L-lysine for a better adhesion to be acquired and then placed in the thermostat so that they will dry for 24 hours at 37°C. Furthermore, the protocol for classical histological Hematoxylin–Eosin (HE) staining was initiated.

To assess the cells in the synovial inflammatory infiltrate, an immunohistochemical (IHC) study was performed, in which we used the following antibodies: anti-cluster of differentiation (CD) 3 (monoclonal mouse anti-human CD3, clone F7.2.38, 1/25 dilution, Dako) for highlighting T-lymphocytes; anti-CD20 (monoclonal mouse anti-human CD20cy, clone L26, 1/50 dilution, Dako) for highlighting B-lymphocytes; anti-CD68 (monoclonal anti-human CD68, clone KP1, 1/100 dilution, Dako) for the study of macrophages; anti-tryptase (monoclonal mouse anti-human mast cell tryptase, clone AA1, 1/500 dilution, Dako) for highlighting mast cells; anti-CD34 (monoclonal mouse anti-human CD34 Class II, clone QBEnd 10, 1/50 dilution, Dako) for marking vascular endothelial cells.

Video-assisted goniometry measurements and statistics

To determine the knee's ROM, patients were recorded while walking at their normal gait speed for 3 m. The recording was made during a second gait cycle, in a sagittal plane and the left and right sides were separately recorded. We used a fixed camera, placed 1 m from the ground.

The videos were uploaded into Angles video goniometry App (a smartphone app funded by Duquesne University, Pennsylvania, USA, generated for the improvement of motor skills in pediatric physical therapy) [12, 13]. Within the 3-m distance, the patients reach the midstance and midswing position 2–3 times. The measure was made on the second midstance and midswing, as the first one was discarded as being too close to the start position and the third was usually towards the end of the distance and the gait was visible distorted by the patients. Using the second midstance and midswing of the gait, the ROM measurement was done manually marking the great trochanter, lateral condyle and lateral ankle generating the posterior angle of the knee (Figures 3 and 4).

After data acquisition, a two-way analysis of variance (ANOVA) test (Šídák's multiple comparisons test) was performed. The statistical significance was set at $p<0.05$. All figures display mean value and standard deviation (SD), and the statistical significance was displayed as follows: *: $p\leq0.05$, **: $p\leq0.01$, ***: $p\leq0.001$, and ****: $p\leq0.0001$.

Results

Clinical assessment

All patients were investigated upon the admission from a clinical and paraclinical point of view. The subjects presenting advanced OA and higher scores at the function VAS scale and WOMAC Index in the clinical examination exhibited synovitis and/or effusion in the OA joints at the US examination (Figure 1).

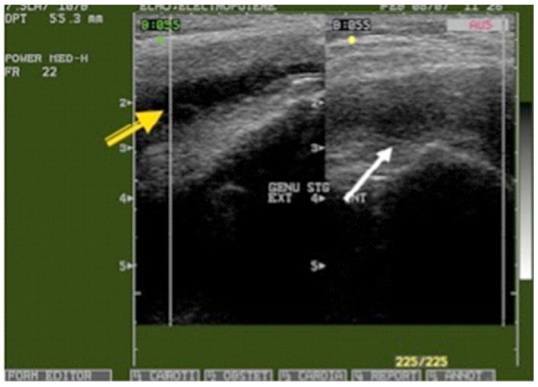

Figure 1 – ***Two knee joint US images. In the right image, synovitis is shown in the knee joint (white arrow), while on the left US image, signs of fluid collection in the synovial sac of the knee can be noticed (yellow arrow). US: Ultrasound.***

The knee's ROM changes based on the gender during midstance of OA patients

During midstance, the knee's ROM in men and women changed depending on the joint affected by OA and the side of the lesion. As such, in men suffering from left hip OA, the ROM of the knee increased compared to controls (170.5° compared to 162.8°, p=0.0117) (Figure 2B), generating a higher knee extension. No difference could be seen in men suffering from hip OA in the right leg (Figure 2A). In contrast, female subjects suffering from hip OA of the dominant leg, adapted by increasing the knee's ROM compared to controls (159.740° in control groups compared to 168.758°, p<0.0001), while women with hip OA had no impact in the knee's ROM of the non-dominant lower limb (160.793° compared to 164.234°, p>0.05) (Figure 2B).

Interestingly, the only difference we found when analyzing the knee's ROM in patients with knee OA, in midstance, was in the dominant leg of males (166.057° compared to 156.58°, p<0.0001) (Figure 2F), with females maintaining a close to normal ROM even in the presence of OA (Figure 2E).

When investigating the ROM in patients with OA in both hip and knee, the difference observed was basically a summation of hip and knee changes seen in the individual patients' groups. As such, the non-dominant leg was affected in males with a higher knee excursion than the control (162.843° in controls compared to 170.677° in OA patients, p=0.0140) (Figure 2C), with both females and males exhibiting adaptive changes in the knee ROM of the dominant leg (control male group 166.057° compared to 160.547°, control female group 159.740° compared to hip and knee female group 164.245°) (Figure 2D).

The midswing of OA patients generates less gender-specific changes in the knee's ROM

During midswing, female groups presented the most interesting changes, regardless of the joint where the OA lesion was noted (Figure 3, B, D and F). In all these cases, we observed an increase in the knee ROM of women with OA. In hip OA groups, the only gender specific change of knee ROM was in the dominant leg of women with an increase of the knee's ROM (137.967° compared to 147.325°, p=0.0020) (Figure 3B), generating a knee extension.

Interestingly, the non-dominant knee ROM decreased for both males and females with knee OA (140.583° in control group comparing to 135.997° in females with knee OA, p=0.0306 and 148.173° in control compared to 131.570° in males with knee OA, p<0.0001) (Figure 3E), while, on the dominant side, only women presented significant increasing differences (137.967° compared to 151.928°, p=0.0024) (Figure 3F), exhibiting a knee extension, as opposed to the non-dominant side. In the dominant leg of patients with both hip and knee OA, the knee's ROM was different both for males and females (137.967° compared to 144.208°, p=0.0006 for females and 150.280° compared to 141.423°, p=0.0003 for males) (Figure 3D). However, the nature of change was different between genders. If for women the ROM had decreasing values comparing to the control group, for males the ROM increased (Figure 3D), while on the non-dominant side, the values were not significant (Figure 3C).

HP and IHC study

Following the US, the diagnosis was confirmed through the HP examination of the biological material, underlining in HE staining the presence of synovial connective tissue with an abundant chronic inflammatory infiltrate and vascular congestion, rich in lymphocytes and plasma cells. In the IHC study, labeled with anti-CD3, anti-CD20, anti-CD68, anti-tryptase, and anti-CD34 antibodies, diffuse or focal T- and B-lymphocytes, angiogenesis signs and disseminated macrophages were highlighted, all providing us with a diagnosis of synovitis (Figures 4–18).

Discussions

In this study, we were able to show, using objective goniometry measurements, differences between the knee's ROM of men and women suffering from lower limb OA, confirming our initial hypothesis. This calls for the need of a detailed investigation of such patients so that the best therapeutic option can be correctly implemented furthermore.

With the progression of degenerative processes accompanying OA, gait adaptation is inevitable [14, 15]. Additional synovial inflammation (synovitis) has been proven to commonly appear in OA [16], even before visible cartilage degeneration. Due to synovial inflammation, angiogenesis will be stimulated, hence a vascular invasion is induced by chondrocytes, generating new bone formation. Because of endochondral ossification present in the growth plate and the bone formation, the joint cartilage gets smaller dimensions, so the articular cartilage will be thinner. Furthermore, the new vessels hereby present in high numbers due to local inflammation will generate bone extension from the subchondral structures [17]. Figures 4–18 can best emphasize the modifications present in the joint at a cellular level. As we can see in Figure 5, areas of synovial necrosis can be detected even in different stages of OA. Be that as it may, a biopsy of each OA patients generates high costs, so, other diagnosis methods must be found beginning with early stages of OA.

Thus, the clinical early detection of gait disturbances can be difficult [18]. The disease has thus the potential to generate disability either by itself (the alignment of bone and joint structures are impacted) or because of the higher falling rate of OA patients [19]. Ultimately, OA affects mobility and, in time, the gait of patients, making the correct diagnosis and treatment to be essential to ensure an active life for OA patients.

With OA affecting gait in different ways, some pathological gait cycles could be observed starting with a simple antalgic or coxalgic gait, all the way to Trendelenburg gait [20, 21]. Although such changes are frequently described in literature, OA adaptive changes between OA genders are not that well investigated, even though differences between normal gait are also frequently cited [22]. With more and more people needing hip or knee replacement surgery [23], the prevention of these late stages through correct physical therapy seems like a cheaper and more beneficial approach for OA patients [24]. If left untreated, OA can lead to great disability and even death in elderly, secondary to fractures from falling during a pathological gait cycle [25]. Also, while the speed of gait is visible impacted in OA patients, the ROM of the knee is less investigated in literature.

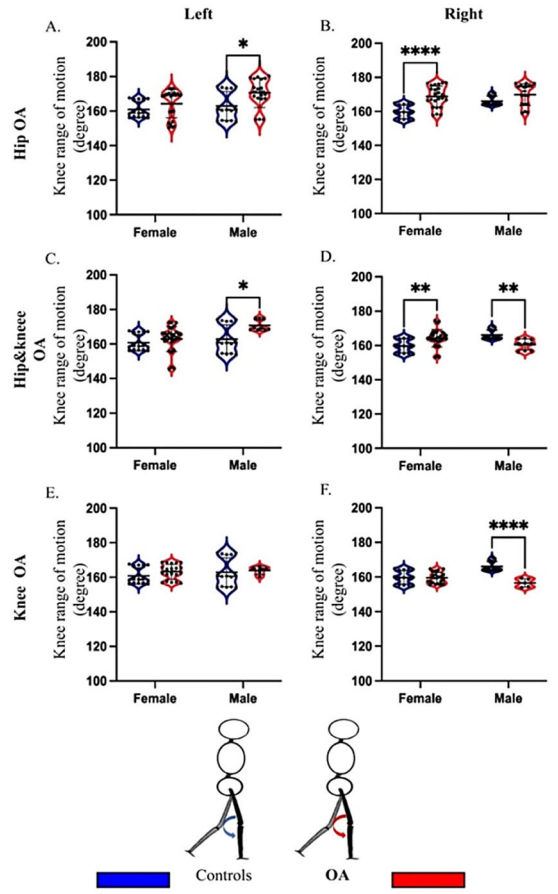

Figure 2 – ***Knee's ROM in patients suffering from lower limb joint OA during midstance. While hip OA increased the knee's ROM of the left leg in men (A), in females this could only be noticed on the right leg (B). In contrast with hip OA, knee OA in women suggested the fact that they suffer no measurable consequences in both legs (C), compared to the right knee's ROM during midstance in men (D). In males suffering from both hip and knee OA, both left (E) and right (F) knees presented significant differences, while in women with hip and knee OA, results were underlined only in the right knee's ROM (F). The statistical significance is displayed as follows: *: p≤0.05, **: p≤0.01, ***: p≤0.001, and ****: p≤0.0001. OA: Osteoarthritis; ROM: Range of motion.***

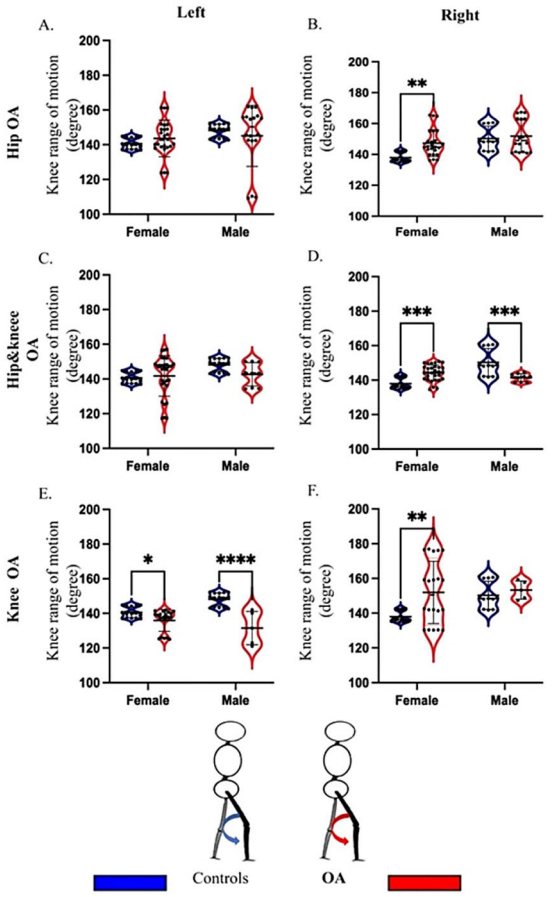

Figure 3 – ***Knee's ROM in patients suffering from lower limb joint OA during midswing. While hip OA exhibited no significant results in the knee's ROM of the left (A) nor right (B) leg in men, females only exhibited present significant results in the right knee's ROM group with hip OA (B). In males and females suffering from both hip and knee OA, no significant results were presented in the left knee ROM (C), whereas on the right knee important differences in both genders were underlined (D). Knee OA affected no females nor males, measurable consequences on the left side being absent (E), compared to the right knee's ROM during midswing in men and women (F). The statistical significance is displayed as follows: *: p≤0.05, **: p≤0.01, ***: p≤0.001, and ****: p≤0.0001.***

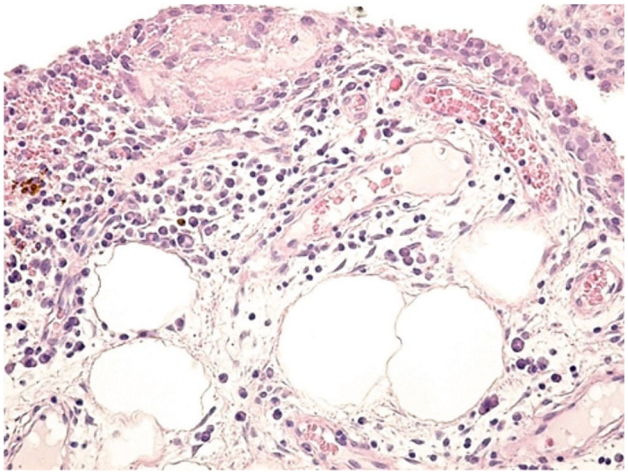

Figure 4 – ***Synovial image with moderate inflammatory infiltrate and vascular congestion in patients with knee osteoarthritis after biopsy of the knee. HE staining, ×200. HE: Hematoxylin–Eosin.***

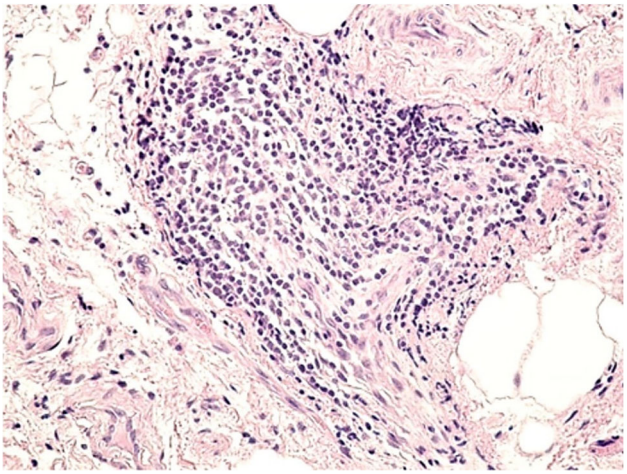

Figure 5 – ***Image of synovial connective tissue with an abundant chronic inflammatory infiltrate, with a focal appearance, rich in lymphocytes and plasma cells. HE staining, ×200.***

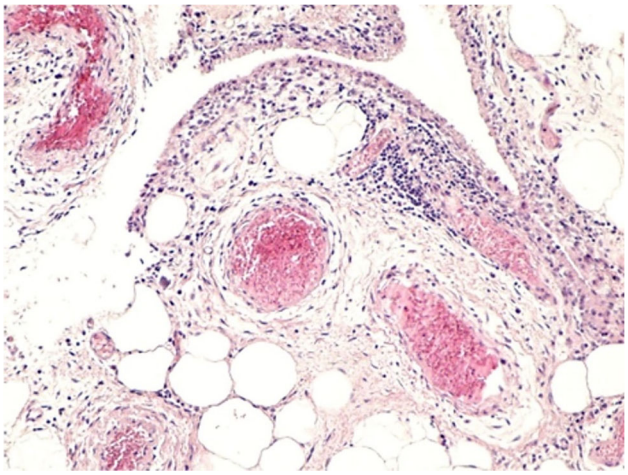

Figure 6 – ***Synovial area with intense vascular congestion and moderate inflammatory infiltrate. HE***

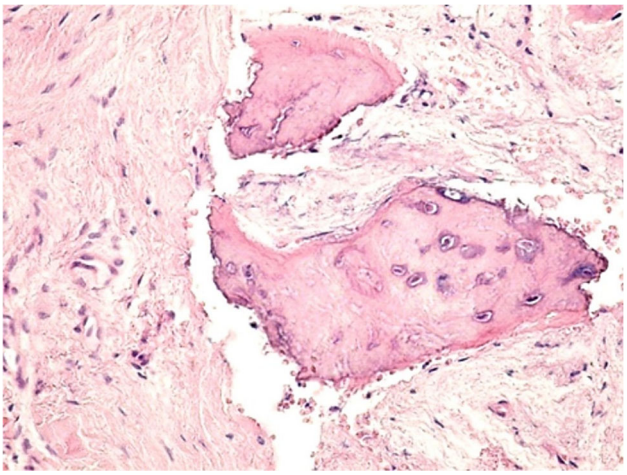

Figure 7 – ***Synovial membrane with areas of ectopic ossification. HE staining, ×200.***

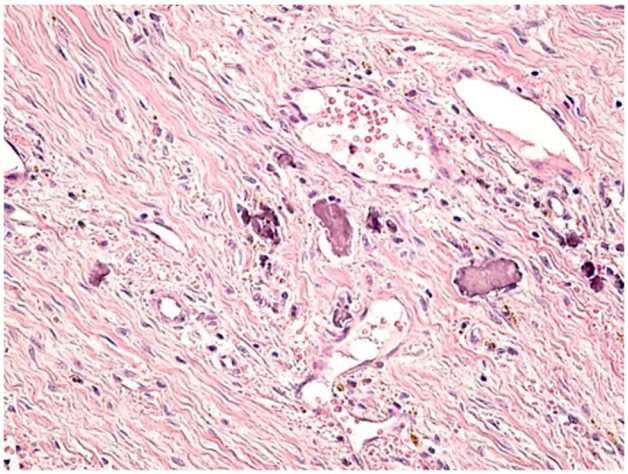

Figure 8 – ***Synovial membrane with vascular congestion. Collagen fibrosis and deposition of calcium salts. HE staining, ×200.***

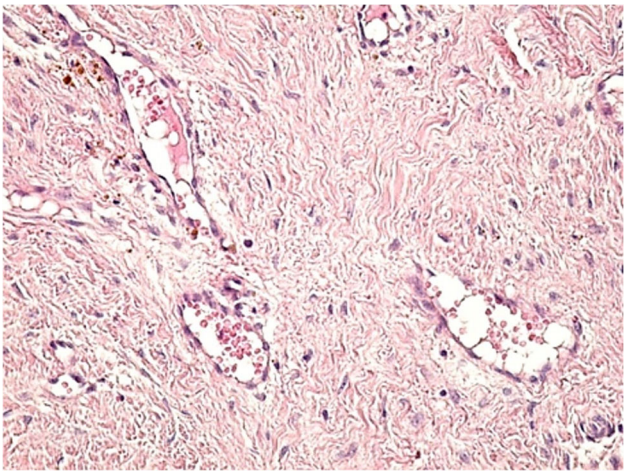

Figure 9 – ***Peripheral synovial area with pronounced fibrosis and numerous capillary-type vessels. HE staining, ×200.***

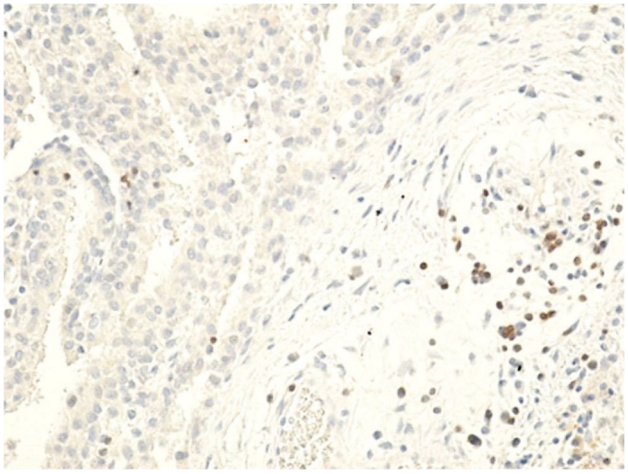

Figure 10 – ***Image of synovial membrane with numerous diffusely disseminated T-lymphocytes. Immunolabeling with anti-CD3 antibodies, ×200. CD3: Cluster of differentiation 3.***

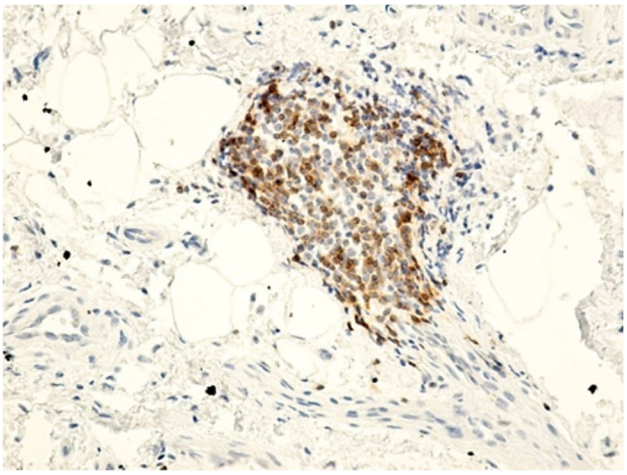

Figure 11 – ***Synovial membrane image with focally distributed T-lymphocytes. Immunolabeling with anti-CD3 antibodies, ×200.***

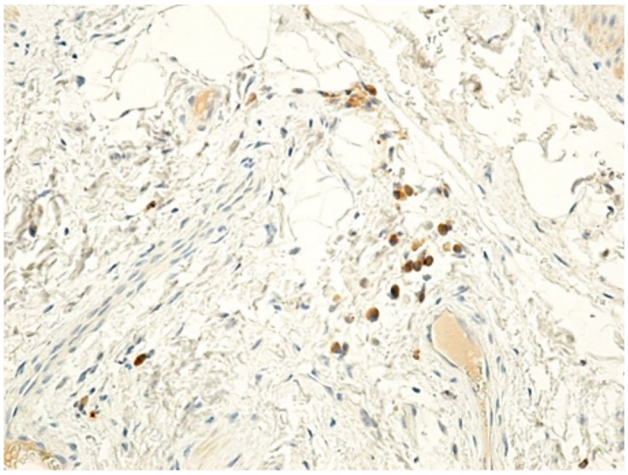

Figure 12 – ***Synovial membrane image with rare diffusely disseminated B-lymphocytes. Immunolabeling with anti-CD20 antibodies, ×200. CD20: Cluster of differentiation 20.***

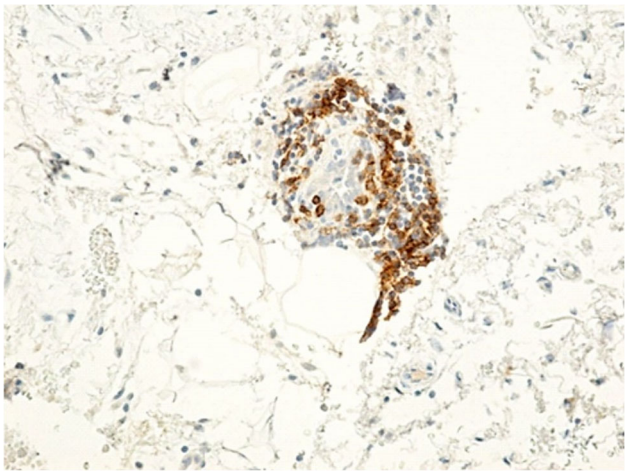

Figure 13 – ***Synovial membrane image with focally distributed B-lymphocytes. Immunolabeling with anti-CD20 antibodies, ×200.***

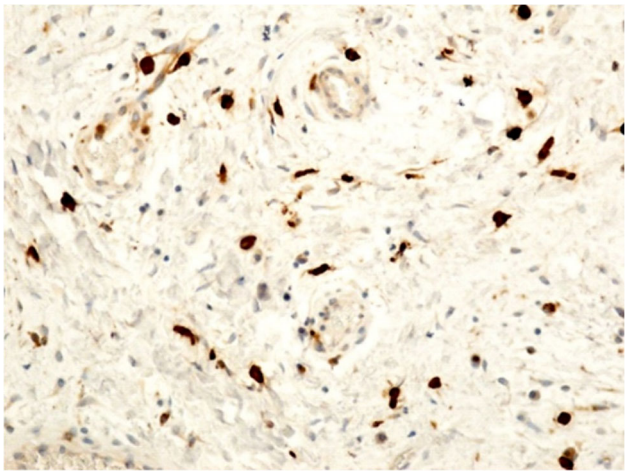

Figure 14 – ***Synovial membrane with numerous diffusely disseminated macrophages. Immunolabeling with anti-CD68 antibodies, ×200. CD68: Cluster of differentiation 68.***

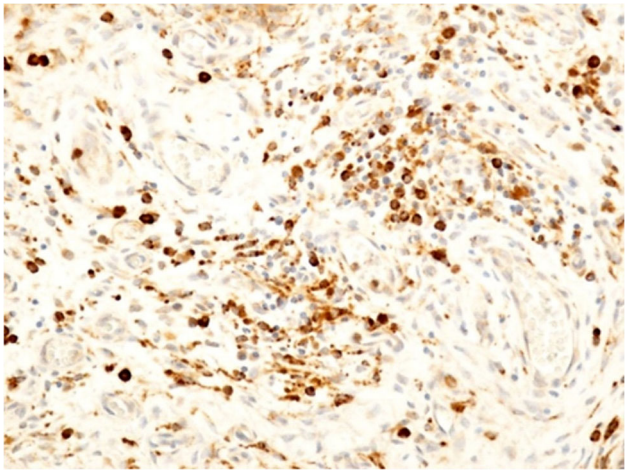

Figure 15 – ***Abundant inflammatory infiltrate composed of macrophages. Immunolabeling with anti-CD68 antibodies, ×200.***

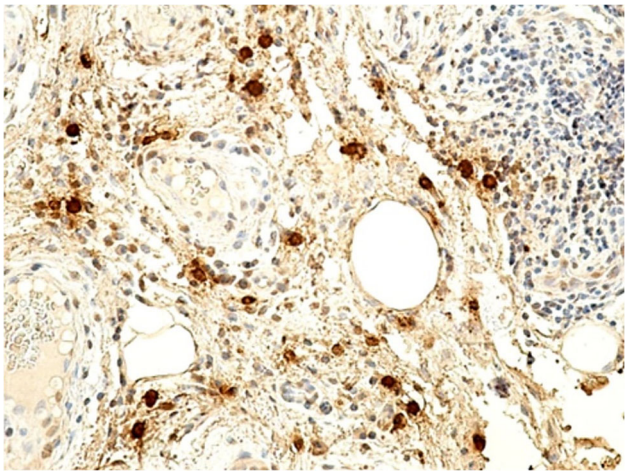

Figure 16 – ***The area of the synovial membrane heavily infiltrated with mast cells. Immunolabeling with anti-tryptase antibodies, ×200.***

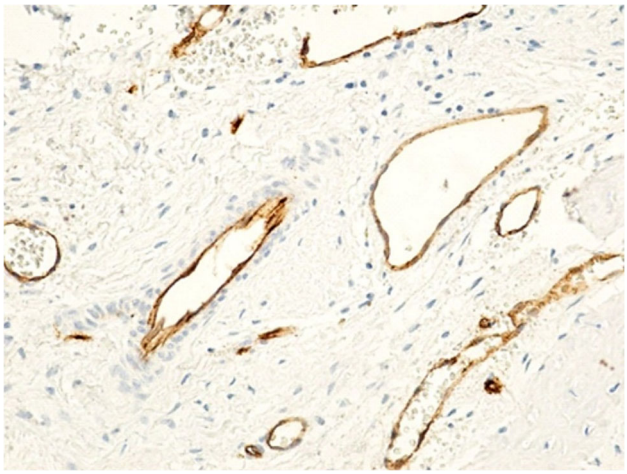

Figure 17 – ***Synovial membrane with numerous vessels of medium caliber. Immunolabeling with anti-CD34 antibodies, ×200. CD34: Cluster of differentiation 34.***

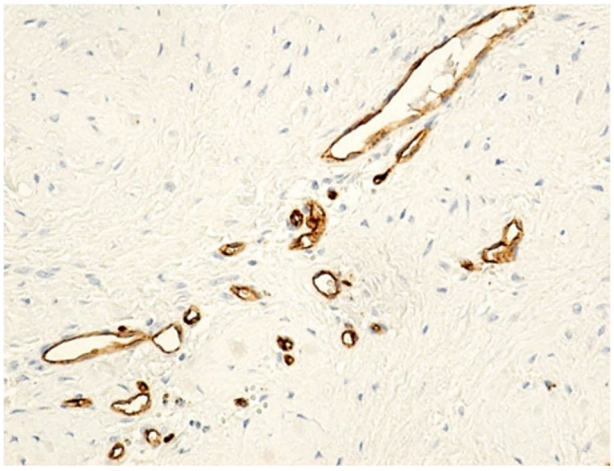

Figure 18 – ***Synovial membrane with angiogenesis. Immunolabeling with anti-CD34 antibodies, ×200.***

Therefore, automatic gait analysis can prove beneficial for different types of patients [26]. In state-of-the-art gait labs, three-dimensional motion analysis can be obtained. This can include, but is not restricted to, plantar pressure plates and electromyography analysis [27]. Unfortunately, the running cost and sheer size of such labs make it impractical to have them outside regional hospitals [28]. Therefore, video-assisted goniometry applications look like a viable alternative, proving their validity *versus* both mechanical goniometer and a two-dimensional motion analysis software used in research settings for static and gait analysis [8]. As such, reliable goniometry is made simpler.

With two independent processes taking place at the same time: age-related changes in the knee's ROM, during midstance and OA affecting stability [29], early correction of midstance and midswing posture becomes essential to the treatment program [30].

With midstance being an important factor of stability in gait, of note is the presence of changes in the knee's ROM in patients with hip OA, with females being susceptible to dominant leg changes, while males to non-dominant ones (Figure 2, A and B). It is unclear if our observations are secondary due to hip joint's abnormalities, however, their existence needs to be closely investigated and corrected.

During the same gait time point, male subjects with OA affecting both hip and knee joints tend to have a more flexed dominant knee during midstance (Figure 2, C and D), with similar findings in knee's ROM in literature [31, 32]. To continue, only the dominant leg of males' patients suffering from knee OA seem to suffer changes in the knee ROM (Figure 2F).

During the midswing stage of gait, the only two gender difference are indicated in female in the dominant leg (Figure 3, B and D). It remains unclear whether these alterations are solely caused by the joint degeneration and the subsequent gait adaptation, or the differences can be caused by other factors like pregnancy [33], or even social dress-codes that impacts females' gait [34, 35]. With midswing changes having been reported only in female and not male dancers, we were able to show that females suffer knee ROM changes only in the dominant lower leg (Figure 3, B and D). Nevertheless, it leads us to speculate that lower limb OA alterations during midstance and midswing can be linked to the activities of daily life, without minimizing the need to correct it in these patients.

Not many data were exhibited differentiating midstance or midswing phases in knee's ROM in females with knee OA during midswing (Figure 3, E and F) even though other studies exhibited decreased knee ROM angles across the gait cycle [36, 37]. Different results presented between midstance and midswing phases of this study can be caused by important variances in the study design and methods used.

Our observations made on men during midswing with hip and knee OA and men with knee OA (Figure 3, D and E) may lead us to think that since the hamstring muscles are biarticular muscles they cannot control the subject's extension in both joints without causing any pain. Hence, a reduction of the pain will be present through a modified knee angle during midswing [38].

A more interesting fact to be underlined in patients suffering from lower limb OA with knee abnormalities comparable to our results is the importance of BMI in one's OA formation. A close relationship amongst OA joint degradation, along with progressive muscle loss (such as sarcopenia) and metabolic syndromes such as obesity has been proven in both male and female subjects [39]. It is highly important to underline since it was shown that men that lose weight tend to have a decreased opportunity of developing OA in their elderly years, but not so many findings emphasize which are the differences between the dominant and non-dominant lower limbs [40, 41].

To continue, another discussion point that needs to be brought into light is the correlations between OA, sarcopenia, and the presence of synovitis in OA patients. Sarcopenia is defined as progressive muscle loss and has been proven to be linked to OA, although not entirely known if it is a consequence or a cause of it [42, 43]. When the deterioration of the muscle happens in geriatric patients, the ROM is be also affected. Since magnetic resonance imaging (MRI)-detected infrapatellar synovitis has been proven to correlate with the clinical progression of knee OA [44], synovitis is an important ROM modifying factor to be also considered in significant gait disturbances.

Females with hip OA (with or without knee OA) present important changes on the dominant limb, even though in literature it has been tried to see whether the dominance of the limb generates OA joint degenerations, or it is the disease that may cause differences between limbs, but a longitudinal examination is needed approaching as well [45].

Conclusions

Bipedal gait consists in being one of the most important function of humans, alongside with speech abilities. Goniometry has been and still is one of the best methods of diagnostics used in lower limb pathologies. Even though this method has its limitations, our findings have, overall, comparable outcomes with previous studies. Gait disorders increase with age; hence, it is highly important to know what roles gender play during the stages of midstance and midswing of the knee in patients with hip OA, knee OA, or hip and knee OA. The causality of OA remains not completely known, but correlations with patient's history

and activities of daily living give us important insight so that a complete personalized rehabilitation program through exercises can be initiated as a cautious measure and prevent arthroplasty.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

An ethical approval of the research project has been released by the Committee of Ethics and Academic and Scientific Deontology (Institutional Review Board) of the University of Medicine and Pharmacy of Craiova (Approval No. 111/21.10.2019).

Patient consent for publication

Informed consent was obtained from all subjects involved in the study.

Competing interests

The authors declare no conflict of interests.

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