

## Article

# Modified gait parameters at the knee joint during midstance in patients with osteoarthritis

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**Abstract:** *Background and Objectives:* Sports medicine, orthopaedic and rehabilitation physicians use gait analysis and goniometry to evaluate and diagnose patients with neuro-musculo-skeletal diseases. Goniometry is a measuring method that shows the joint's range of motion. Three-dimensional goniometry has been used in order to assess the patients in a kinematic manner, but they are not affordable, so, phone apps come handy to any orthopaedic or rehabilitation physician so we can have a clear image of the progress made by the patient after the rehabilitation program or should something happen and the patient cannot come to the facility, such as the Covid-19 pandemic, when some orthopaedic and most of the rehabilitation facilities have been temporarily closed. Midstance has been chosen as the moment of the gait evaluation in this paper since it has an important role in stability. The objective of this paper is to figure out if the measurements taken during midstance at the knee joint of the subjects can be statistically significant and used during usual examinations. *Materials and Methods:* Four groups of subjects: patients suffering from hip, knee, hip and knee osteoarthritis and a control group volunteered their participation, being asked to normally walk while their gait was recorded and uploaded into Angles App – a phone based videogoniometer. *Results:* Patients suffering from hip osteoarthritis have a higher knee angle on the right side than the ones suffering from knee osteoarthritis, hip and knee osteoarthritis and the control group. Female patients suffering from hip osteoarthritis also presented a more flexed knee than the ones suffering from knee osteoarthritis and the ones in the control group, the knee flexion presenting itself as a compensation mechanism. *Conclusion:* Video goniometry can help us make an orthopaedic, rehabilitation or neurology database for each assessment with constant updates of the evolution of the osteoarthritis patient's treatment.

**Keywords:** angles app, goniometry, range of motion, assessment, telemedicine, joint examination.

## 1. Introduction

Gait analysis has been used for many years as a diagnostic method for different types of diseases (neurological, musculoskeletal) [1–3] in patients coming in the orthopaedic or rehabilitation clinic. During the clinical examination both gait and goniometric assessment are crucial for the outcome of the rehabilitation program, thus making the physician look for easier ways to assess a patient and have an easy and accessible data base where one can add visual representation of each patient that comes into the clinic and try to make yearly or every few months comparisons through each patient's measurements taken in time and documenting the benefits and evolution of the rehabilitation and note how much one can postpone knee surgery. Gait is divided into two big moments [3]: stance (subdivided into: loading response, midstance, terminal stance) and swing (subdivided into: initial swing, midswing and terminal swing). The moment we are going to focus our attention on in this research paper is midstance.

Midstance has been chosen because this is the first part of the single-leg support period and stability is a major concern in osteoarthritis (OA) patients, as the base of support decreases significantly, and the center of gravity moves to its highest point through leg extension furthermore in the gait cycle. The most important function of the lower limb is stability, so it is our job to prevent falls [4,5].

Goniometry is a tool mostly used in order for the clinicians to measure the joint's range of motion (ROM). Classic goniometry has been used until now with live measurements and the physician examining the static patient has full control of joints, but since the examiner can sometimes miss important details, nowadays the ubiquity of smartphone technology and applications (apps) [6–12] provides us with many more options. Thus, many goniometer apps have been proven to have a high validity and reliability in measuring more than gait, running, but also, spine flexion or extension, the knee range of motion (ROM) in young adults [8,13–16] and even the rib hump in scoliosis [17]. Measurements have also been done with the help of three-dimensional motion analysis, and many studies have focused their attention on plantar pressure plates and electromyography (EMG) analysis [18,19], too, but their cost and dimensions makes it difficult for them to be present in every sports medicine, neurology, orthopaedics or rehabilitation practice [2,6,20–22]. The Angles Video Goniometer app (Angles app) offered on an iOS software for smart devices such as iPhones has proven its validity versus both the mechanical goniometer and Kinovea (two-dimensional motion analysis software used in research settings) [7]. The multiple types of measurements for gait analysis are no longer an issue nowadays, equipment wise, since our purpose is using the information gathered in order for it to be used in our patients' benefit as good as possible and in the shortest amount of time, without the necessity of laborious interpretation or a special gait lab [23].

Given the Covid-19 pandemic context, one can also take into account a telemedicine approach, thus we can assess from afar the patients' improvement or changes in the joints' range of motion without them actually having to come into the facility [24–28], unless it is an emergency.

Osteoarthritis (OA) is a whole organ disease that affects people worldwide, about 40 million people only in Europe [29], because of the lack of mobility it gives to the affected joints. It is caused by cell stress and the degradation of the extracellular matrix initially formed because of the macro- and microinjuries happening during life, activating thus

responses that cause maladaptive repairs, such as pro-inflammatory pathways to innate immunity. In the beginning, there are only cellular and molecular transformations, followed, in time, by misalignments of the bone and joint structure (the degradation of the cartilage, bone remodeling, osteophyte formation, inflammation of the joint and, throughout the years, loss of the normal joint function), that can become pathological [30,31] and will need, in time, a surgical approach with a better outcome [32–34]. Gait analysis in OA has been taken into account as an early diagnosis method for hip and knee OA [35], but, because of the small groups of patients that have been studied until now, the kinematic parameters have been considered insufficient in order for them to be quantifiable measures in OA [2,36].

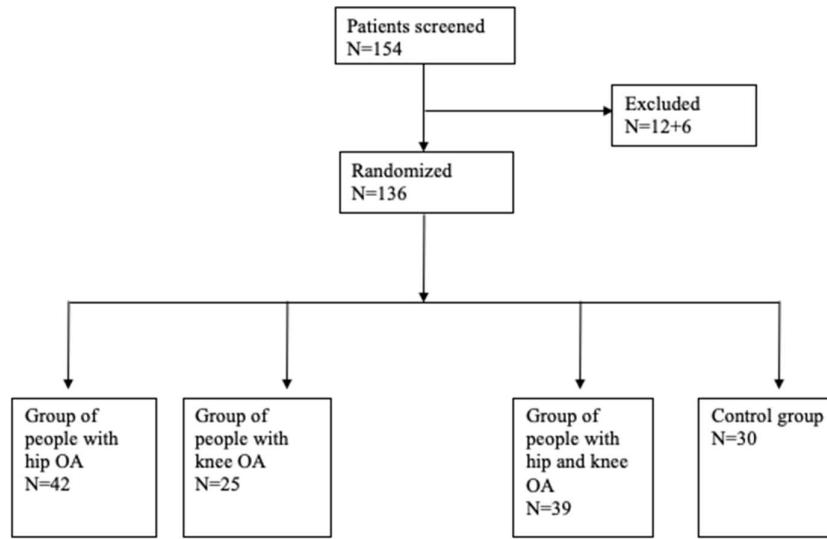
The purpose of this paper is to observe the differences of the knee joint angle during the midstance moment of each subject's gait, to outline the statistically different results between the groups of subjects and prove the fact that we can start more research on videogoniometry, helping us include phone goniometry apps in the classical, thorough clinical examination.

## 2. Materials and Methods

### *Participants*

In this single-blinded randomized trial we have initially examined 154 patients suffering from osteoarthritis (OA) at the lower limbs without clinical and functional differences between left and right side and with the right arm and leg as a dominant limb. The exclusion criteria were: 12 of them have been excluded because they were stage 4 osteoarthritis (hip, knee or hip and knee) and were only able to walk with the help of an assistive device as a cane or walking frame, six of them had suffered a stroke and had neurological lesions. Subjects were recruited based on volunteering. The remaining 136 patients are aged between 42 and 83 years old and have been divided into 4 groups of subjects: people suffering from hip primary bilateral arthritis, patients with primary bilateral knee arthritis, people suffering from both hip and knee primary bilateral OA and a control group. All participants in the study have given their Informed Consent according to the principles outlined in the Declaration of Helsinki and an ethical approval of the research project has been released by the Committee of Ethics and Academic and Scientific Deontology of the University of Medicine and Pharmacy of Craiova (no. 111/21.10.2019).

**Figure 1: Flowchart explaining the assignment of the participants in the study.**



### Measures

The patients were asked to walk at their normal gait speed and were filmed 3 times from a sagittal plane, on each side, with the help of an iPhone camera (the first two videos on each side were taken in order for the patient to get accustomed to what he/she has to do). The camera was set at 1 m from the ground, being fixed on a tripod, giving us the ability of not moving during the examination, but also to visualize the entire patient's body.

### Design and Procedures

Furthermore, the videos were uploaded into Angles video goniometry App [37]. In this paper only the measurements taken during midstance of the hip joint will be discussed. Once we have uploaded the video, we fast forwarded until each midstance moment of the gait where each joint angle of the inferior limb was measured (hip, knee and ankle angle).

### Statistical analysis

We have performed the comparison of the groups with the use of standardized methods [38] the ordinary one-way ANOVA test for this observational study [29] with the help of statistics package from a personal computer (GraphPad Software, Prism 9.0, macOS X). We set the statistical significance at  $p<0.05$ . Before the tests were performed, the Anderson-Darling, D'Agostino & Pearson and the Shapiro-Wilk tests were checked in order to see the normality and lognormality of each group. Data for statistical analysis were calculated as means  $\pm$  95% CIs.

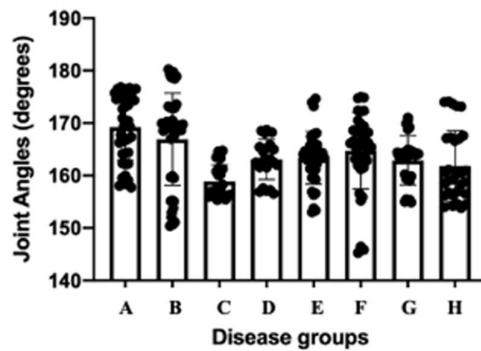
## 3. Results

### 3.1. Statistically significant results

It can be noticed in Table 1 that the patients suffering from hip OA present on the right side an angle higher with a mean of 10.33 degrees at the knee joint during midstance than the ones suffering from knee OA, higher with a mean of 5.838 degrees than the group of patients with hip and knee OA and an angle with a mean of 6.331 degrees higher than the control group, meaning that the hip arthritis group has a more extended knee during

midstance than all groups. All other comparisons on the right side have been proven to be not significant statistically. The measurements on the left side are only statistically significant between the group of patients with hip OA versus the control group on the left side with the mean difference of 5.112 degrees. Figure 2 presents each group's distribution of the knee joint's range of motion right limb (dominant) versus left limb (non-dominant).

**Figure 2. Knee joint angle measurements during midstance. Changes between disease groups. Left vs Right. Normal gait speed.**



A – Group with hip osteoarthritis – right knee; B – Group with hip osteoarthritis – left knee; C – Group with knee osteoarthritis – right knee; D – Group with knee osteoarthritis – left knee; E – Group with hip and knee osteoarthritis – right knee; F – Group with hip and knee osteoarthritis – left knee; G – Control group – right knee; H – Control group – left knee;

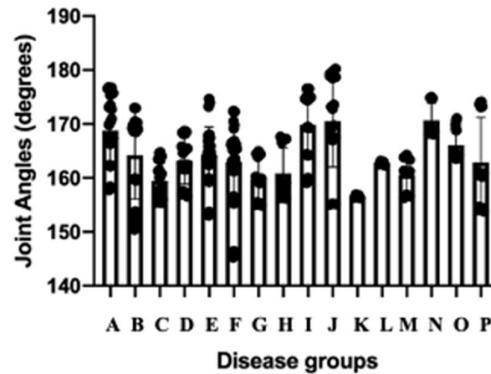
**Table 1. Knee joint angle during midstance. Changes between disease groups. Left vs Right. Normal gait speed. One way ANOVA.**

Šídák's multiple comparisons test	Mean Diff	95,00% CI of diff
Group of patients with hip arthritis – right knee vs. Group of patients with hip arthritis – left knee	2,299	-1,865 to 6,463
Group of patients with hip arthritis – right knee vs. Group of patients with knee arthritis – right knee	10,33	5,505 to 15,14
<i>p&lt;0,0001</i>		
Group of patients with hip arthritis – right knee vs. Group of patients with hip and knee arthritis – right knee	5,838	1,595 to 10,08
<i>p=0,0009</i>		
Group of patients with hip arthritis – right knee vs. Control group – right knee	6,331	1,770 to 10,89
<i>p=0,0008</i>		
Group of patients with hip arthritis – left knee vs. Group of patients with knee arthritis – left knee	3,846	-0,9738 to 8,666
Group of patients with hip arthritis – left knee vs. Group of patients with hip and knee arthritis – left knee	2,219	-2,024 to 6,462
Group of patients with hip arthritis – left knee vs. Control group – left knee	5,112	0,5506 to 9,673

p=0,0162		
Group of patients with knee arthritis – right knee vs. Group of patients with knee arthritis – left knee	-4,18	-9,577 to 1,217
Group of patients with knee arthritis – right knee vs. Group of patients with hip and knee arthritis – right knee	-4,488	-9,376 to 0,4009
Group of patients with knee arthritis – right knee vs. Control group – right knee	-3,994	-9,161 to 1,173
Group of patients with knee arthritis – left knee vs. Group of patients with hip and knee arthritis – left knee	-1,627	-6,515 to 3,262
Group of patients with knee arthritis – left knee vs. Control group – left knee	1,266	-3,901 to 6,433
Group of patients with hip and knee arthritis – right knee vs. Group of patients with hip and knee arthritis – left knee	-1,319	-5,640 to 3,002
Group of patients with hip and knee arthritis – right knee vs. Control group – right knee	0,4932	-4,140 to 5,127
Group of patients with hip and knee arthritis – left knee vs. Control group – left knee	2,892	-1,741 to 7,526
Control group – right knee vs. Control group – left knee	1,08	-3,846 to 6,006

In table 2, the significant difference of the means was between the group of women suffering from hip OA and the group of women suffering from knee OA. The measurements were made on the right side and it was a difference of 9.273 degrees between their means. Also, the women's group with hip OA also has a 9.018 degrees difference at the knee joint during midstance, on the right side, comparing to the control group of patients. Furthermore, significant differences are shown between groups of men, while developing a normal speed gait and it is revealed that the group of men suffering from hip OA present a mean of 13.28 degrees higher as ROM at the knee joint comparing to the group suffering from knee OA, a 9.311 degrees difference from the group suffering from both hip and knee OA, whilst the group suffering from hip OA compared to the control group on left side shows a 7.682 degree higher. Patients suffering from both hip and knee OA showed 10.13 degrees more flexion on the right knee than on the left knee. Figure 3 consists in the distribution of the ROM for each knee joint in both male and female groups of subjects.

**Figure 3. Knee joint angles measurements during midstance. Changes between disease groups. Male. Female. Normal gait speed.**



A – Group with hip osteoarthritis – right knee – female group; B – Group with hip osteoarthritis – left knee female group; C – Group with knee osteoarthritis – right knee – female group; D – Group with knee osteoarthritis – left knee – female group; E – Group with hip and knee osteoarthritis – right knee – female group; F – Group with hip and knee osteoarthritis – left knee – female group; G – Control group – right knee – female group; H – Control group – left knee – female group; I – Group with hip osteoarthritis – right knee – male group; J – Group with hip osteoarthritis – left knee – male group; K – Group with knee osteoarthritis – right knee – male group; L – Group with knee osteoarthritis – left knee – male group; M – Group with hip and knee osteoarthritis – right knee – male group; N – Group with hip and knee osteoarthritis – left knee – male group; O – Control group – right knee – male group; P – Control group – left knee – male group.

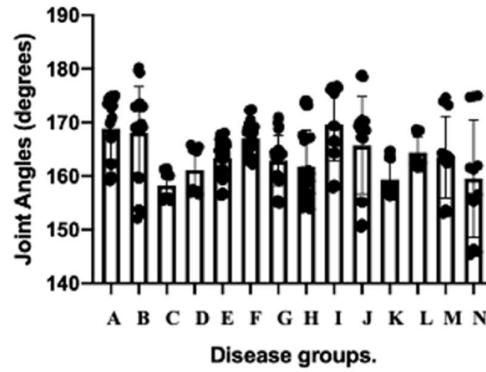
**Table 2. Knee joint angle during midstance. Changes between disease groups. Women. Men. Normal gait speed. One way ANOVA.**

Šídák's multiple comparisons test	Women		Men	
	Mean	95,00%	Mean	95,00%
	Diff	CI of diff	Diff	CI of diff
Group of patients with hip arthritis – right knee vs. Group of patients with hip arthritis – left knee	4,524	-1,399 to 10,45	-0,6672 to 6,172	-7,507 to 6,172
<b>Group of patients with hip arthritis – right knee vs. Group of patients with knee arthritis – right knee</b>	<b>9,273</b>	<b>3,060 to 15,48</b>	<b>13,28</b>	<b>2,905 to 23,65</b>
	<b>p=0,0001</b>		<b>p=0,0015</b>	
<b>Group of patients with hip arthritis – right knee vs. Group of patients with hip &amp; knee arthritis – right knee</b>	<b>4,512</b>	<b>-1,107 to 10,13</b>	<b>9,311</b>	<b>0,9347 to 17,69</b>
			<b>p=0,014</b>	
<b>Group of patients with hip arthritis – right knee vs. Control group – right knee</b>	<b>9,018</b>	<b>2,264 to 15,77</b>	<b>3,801</b>	<b>-3,372 to 10,97</b>
	<b>p=0,0007</b>			
Group of patients with hip arthritis – left knee vs. Group of patients with knee arthritis – left knee	1,061	-5,151 to 7,273	7,795	-2,577 to 18,17
<b>Group of patients with hip arthritis – left knee vs. Group of patients with hip &amp; knee arthritis – left knee</b>	<b>1,313</b>	<b>-4,306 to 6,932</b>	<b>-0,1517 to 8,225</b>	<b>-8,528 to 8,225</b>

<b>Group of patients with hip arthritis – left knee vs.</b>	3,44	-3,313	<b>7,682</b>	<b>0,5085</b>
<b>Control group – left knee</b>		to 10,19		<b>to 14,85</b>
<b>p=0,0227</b>				
Group of patients with knee arthritis – right knee vs.	-3,688	-10,18	-6,15	-19,13 to
Group of patients with knee arthritis – left knee		to 2,801		6,827
Group of patients with knee arthritis – right knee vs.	-4,76	-10,68	-3,967	-15,41 to
Group of patients with hip & knee arthritis – right knee		to 1,163		7,478
Group of patients with knee arthritis – right knee vs.	-0,255	-7,263	-9,477	-20,07 to
Control group – right knee		to 6,753		1,119
Group of patients with knee arthritis – left knee vs.	0,2515	-5,672	-7,947	-19,39 to
Control group – left knee		to 6,175		3,498
Group of patients with knee arthritis – left knee vs.	2,379	-4,629	-0,1133	-10,71 to
Control group – left knee		to 9,387		10,48
<b>Group of patients with hip &amp; knee arthritis – right knee vs. Group of patients with hip &amp; knee arthritis – left knee</b>	1,324	-3,974	<b>-10,13</b>	<b>-19,80 to</b>
		to 6,622		<b>-0,4577</b>
<b>p=0,0298</b>				
Group of patients with hip & knee arthritis – right knee vs. Control group – right knee	4,505	-1,983	-5,51	-14,16 to
		to 10,99		3,141
Group of patients with hip & knee arthritis – left knee vs. Control group – left knee	2,128	-4,361	7,833	-0,8178
		to 8,616		to 16,48
Control group – right knee vs.	-1,053	-8,545	3,213	-4,279 to
Control group – left knee		to 6,439		10,71

In table 3 it is emphasized the fact that people living in the urban area and suffering from hip OA have a statistically significant mean difference of 10.65 degrees compared to the ones suffering from knee OA and compared to the control group there is a 5.974 degrees difference at the knee's ROM. On the left side, the patients suffering from hip OA present a 6.297 degrees higher ROM at the knee joint than the control group on the left side. No control group is presented in the rural group because there have not been any patients from the rural environment presenting to the doctor's office with minimum symptoms. Be that as it may, the group of patients suffering from hip OA compared with the group of patients suffering from knee arthritis have a right knee flexion with a mean of 10.23 degrees higher, and on the non dominant side compared to the ones with hip and knee arthritis a 6.204 degrees mean difference is noticed. Also, figure 4 underlines the distribution of the measurements made at the knee joint during midstance of the discussed groups.

**Figure 4. Knee joint angles measurements during midstance. Changes between disease groups. Urban. Rural. Normal gait speed.**



A – Group with hip osteoarthritis – right knee – urban group; B – Group with hip osteoarthritis – left knee – urban group; C – Group with knee osteoarthritis – right knee – urban group; D – Group with knee osteoarthritis – left knee – urban group; E – Group with hip and knee osteoarthritis – right knee – urban group; F – Group with hip and knee osteoarthritis – left knee – urban group; G – Control group – right knee – urban group; H – Control group – left knee – urban group; I – Group with hip osteoarthritis – right knee – rural group; J – Group with hip osteoarthritis – left knee – rural group; K – Group with knee osteoarthritis – right knee – rural group; L – Group with knee osteoarthritis – left knee – rural group; M – Group with hip and knee osteoarthritis – right knee – rural group; N – Group with hip and knee osteoarthritis – left knee – rural group.

**Table 3. Knee joint angle during midstance. Changes between disease groups. Urban. Rural. Normal gait speed. One way ANOVA.**

Šídák's multiple comparisons test	Urban		Rural	
	Mean	95,00%	Mean	95,00%
	Diff	CI of diff	Diff	CI of diff
Group of patients with hip arthritis – right knee vs. Group of patients with hip arthritis – left knee	0,7567	-4,873 to 6,386	3,841	-1,435 to 9,118
<b>Group of patients with hip arthritis – right knee vs. Group of patients with knee arthritis – right knee</b>	<b>10,65</b>	<b>2,672 to 18,62</b>	<b>10,23</b>	<b>3,211 to 17,25</b>
	<b>p=0,0008</b>		<b>p=0,0001</b>	
Group of patients with hip arthritis – right knee vs. Group of patients with hip & knee arthritis – right knee	5,533	-0,5063 to 11,57	6,076	-0,1113 to 12,26
<b>Group of patients with hip arthritis – right knee vs. Control group – right knee</b>	<b>5,974</b>	<b>0,06786 to 11,88</b>	-	-
	<b>p=0,0444</b>			
Group of patients with hip arthritis – left knee vs. Group of patients with knee arthritis – left knee	6,976	-0,9999 to 14,95	1,364	-4,416 to 7,144
<b>Group of patients with hip arthritis – left knee vs. Group of patients with hip &amp; knee arthritis – left knee</b>	<b>1,107</b>	<b>-4,933 to 7,147</b>	<b>6,204</b>	<b>0,01727 to 12,39</b>
	<b>p=0,0489</b>			

<b>Group of patients with hip arthritis – left knee vs.</b>	<b>6,297</b>	<b>0,3912</b>	-	-
<b>Control group – left knee</b>		<b>to 12,20</b>		
<b>p=0,0246</b>				
Group of patients with knee arthritis – right knee vs.	-2,915	-11,07	-5,023	-11,27 to
Group of patients with knee arthritis – left knee		to 5,243		1,220
Group of patients with knee arthritis – right knee vs.	-5,114	-12,80	-4,153	-10,78 to
Group of patients with hip & knee arthritis – right knee		to 2,571		2,468
Group of patients with knee arthritis – right knee vs.	-4,673	-12,25	-	-
Control group – right knee		to 2,907		
Group of patients with knee arthritis – left knee vs.	-5,869	-13,55	4,840	-1,782 to
Group of patients with hip&knee arthritis – left knee		to 1,816		11,46
Group of patients with knee arthritis – left knee vs.	-0,6783	-8,258		-
Control group – left knee		to 6,902		
Group of patients with hip&knee arthritis – right knee vs. Group of patients with hip&knee arthritis – left knee	-3,67	-9,320	3,97	-3,010 to 10,95
Group of patients with hip & knee arthritis – right knee vs. Control group – right knee	0,4406	-5,066	-	-
Group of patients with hip & knee arthritis – left knee vs. Control group – left knee	5,191	-0,3161	-	-
Control group – right knee vs. Control group – left knee	1,08	-4,280	-	-
		to 6,440		

The adjusted p value was underlined in tables 1, 2 and 3 only for the statistically significant data, for the other comparisons p was greater than 0.05.

#### 4. Discussion

We have chosen midstance since it is known to have a important purpose in giving stability to the human body [4]. For the daily functionality of the body, standing on one or both feet, stability [39] and mobility have a significant purpose. In the rehabilitation programs, stability is one of the priorities of the objectives of the treatment itself [3,4,23,40]. If not succeeded, then one will recommend knee arthroplasty in order for the patient to fully benefit from a complete course of treatment, before [41] and after [42] surgery and notice improvements in a short amount of time [42–45].

It is highly important for us to gather more information on gait adaptation parameters that occur in OA [46–50], since gait is a common functional activity of daily life. The adaptation mechanisms come from the musculoskeletal deformities at the joint sites resulting in a pathological walk.

Subjects with hip OA exhibited significant extension on the knee joint measurements during midstance in most of the groups, whereas the subjects suffering from knee OA present with a more flexed knee joint during midstance. This can be explained through the fact that the hamstring muscles are biarticular muscles [51] and, in patients suffering from

OA the hamstrings cannot control the subject's extension [52] in both joints without causing any pain. Thus, the knee extension in hip OA [53,54] presents itself most likely as a compensation mechanism.

Most of the patients have presented with significant differences on the right side at the right knee joint measurements and it is a normal occurrence in this particular disease [55]. Given the fact that all of the subjects in the study suffer from primary bilateral OA, without clinical and functional differences between right and left, all of them have the right side as the dominant side and their gait tends to begin with the right lower limb, meaning that they are going to unequally load more on the right side rather than on the left. Thus, in our opinion this is an explanation for the fact that the joint angles on the right side tend to be more affected.

Our results can be successfully compared to the ones in literature, by the decrease of the knee flexion during walking in patients with OA [56] compared to healthy subjects [57], but unfortunately, we do not have comparison data on OA patients examined during gait using a phone goniometry app.

This has been the first study in Romania on subjects living in both rural and urban area and suffering from primary bilateral OA. Patients living in the rural area do not usually request medical examinations until the disease is advanced, and this is why the control group from the rural area is missing entirely.

## 5. Conclusions

All in all, this study on electronic goniometry methods using the personal phone is helpful for a physician given the fact that one can monitor the rehabilitation program and the up-and-coming results, store them on a computer and use them as a comparison factor further in the future, when the patient returns for the next round of treatment or when the trip to the facility includes more dangers on the way, taking into consideration events as the Covid-19 pandemic. We, as orthopaedic and rehabilitation physicians, have to complete a thorough analytic, clinical and functional evaluation of the patient, but one must never forget about the kinematic chain of the lower limb at the admission check-up. If all these conditions are not met, a simple, local examination of the knee at the patients suffering from knee and/or hip OA will determine incomplete results for a correct and complete rehabilitation program and an optimal treatment of the gait.

**Author Contribution:** conceptualization: Carmen Stătescu and Andrei Deaconu, methodology: Doru Stoica; software: Bogdan-Ion Gavrilă; validation: Doru Stoica and Bogdan-Ion Gavrilă; formal analysis: Carmen Stătescu; investigation: Carmen Stătescu; resources: Rodica Trăistaru and Tudor-Adrian Bălșeanu; data curation: Bogdan-Ion Gavrilă.; writing—original draft preparation: Carmen Stătescu.; writing—review and editing: Carmen Stătescu, Rodica Trăistaru and Tudor-Adrian Bălșeanu, visualization: Carmen Stătescu and Andrei Deaconu; supervision: Rodica Trăistaru and Tudor-Adrian Bălșeanu; project administration: Rodica Trăistaru and Tudor-Adrian Bălșeanu; funding acquisition: not applicable. All authors have read and agreed to the published version of the manuscript.

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(Institutional Review Board) of the University of Medicine and Pharmacy of Craiova (no. 111/21.10.2019).

**Informed Consent Statement:** All participants in the study have given their written Informed Consent according to the principles outlined in the Declaration of Helsinki in order for this paper to be published.

**Conflicts of Interest:** The authors declare no conflict of interest.

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