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ORIGINAL PAPER

Influences of treadmill speed and incline angle on the kinematics of the normal, osteoarthritic and prosthetic human knee

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Abstract

The objective of this paper is to measure and to study the influence of the treadmill speed and incline angle on the kinematics of flexion–extension angles of the human knee joints during 23 tests of walking overground and on plane and inclined treadmill performed by a sample of 14 healthy subjects and during of seven tests performed by a sample of five patients suffering of knee osteoarthritis (KOA), before and three months after the total knee replacement (TKR) surgery. The medium cycles computed and plotted for all experimental tests performed by the healthy subjects' sample and for the osteoarthritic (OA) patients' sample before and after TKR surgery are compared and conclusions are formulated.

Keywords: osteoarthritic knee, prosthetic knee, plane and inclined treadmill, experimental walking tests, average cycle.

Introduction

The importance of biomechanical assessments of human gait has increased in recent times, with the development of data acquisition and processing systems. In medicine, knowledge of gait parameters, permanent and continuous objective tracking of changes in human behavior provides important quantitative biomechanical data on normal and pathological gait, as well as the occurrence, evolution and diagnosis of diseases that affect gait directly or indirectly [1–3]. The techniques of objective monitoring of human gait take into account various devices and equipment used for the acquisition and processing of experimental data targeting a wide range of gait parameters [2]. Numerous scientific papers have highlighted the main advantages wearable sensors systems that can be worn by the subject to measure and analyze various parameters of normal or pathological human walking [1–10]. Using portable sensors, it is possible to monitor the disorders of the pathological gait, as well as the improvement of gait during the rehabilitation period [1, 6, 11]. Research papers studied healthy subjects [7, 9] or evaluated aspects related to the rehabilitation of joint movements after surgery, in prosthetic or orthotic patients [12–17], to evaluate the gait stability [18–25] or to identify movement kinematic differences in patient populations, such as patients with osteoarthritis [11, 13, 20, 24, 25], patients with multiple sclerosis disease [11], with Parkinson's disease [3] or affected by stroke [26], compared to healthy subjects. Biomechanical studies of temporo-spatial and joint kinematics of normal or pathological human locomotion that studied the influence of gait speed on the gait variability were considered a set of walking speeds measured on overground [8] but also, on plane and inclined treadmills [27–30].

Knee osteoarthritis (KOA) involves a degenerative process of femoral and tibial cartilages, associated with pain, the main causes being overweight, physical activity made in excess, joint trauma, immobilization or hypermobility. KOA is associated with less static and dynamic stability and the possibility of falling during daily activities because of the joint laxity [18–25, 31–52]. A high level of gait variability has been associated with a big risk of falling in elderly subjects. Human gait analysis is very important in order to use it for designing bio-inspired robotic structures, as humanoid robots or medical robots [53–56], or rehabilitation devices, as orthotic systems or exoskeletons [57–61]. As a result, the gait analysis is an important tool for diagnosis and treatment of musculoskeletal and neurological diseases.

Aim

The aim of our paper consists into the measurement of the flexion–extension angle of the knee during 23 tests of walking overground and on plane and inclined treadmill performed by a sample of 14 healthy subjects and during of seven tests performed by a sample of five patients suffering of KOA, before and three months after the total knee replacement (TKR) surgery. The average walking cycles and the maximum values were obtained for each experimental test for both knees of the healthy subjects' sample, as well as of osteoarthritic (OA) patients' sample before and after TKR surgery and a comparison of them were performed.

Materials and Methods

Data acquisition systems

Biometrics system [4] is an integrated equipment for complex three-dimensional (3D) analysis of human gait, which allows simultaneous collection of kinematic and dynamic biomechanical data through electrogoniometers, accelerometers, force platforms, electromyography (EMG) sensors, contact pressure sensors and other types of sensors or equipment. A total of 24 synchronized biomechanical datasets can be purchased simultaneously through analog and digital data channels. The Biometrics system is provided with a wide range of robust, lightweight and flexible goniometers and torsometers, which are recommended for simple, fast accurate and synchronized gait measurement across multiple planes, as, *e.g.*, the sagittal plane and the frontal plane [4]. A set of flexible goniometers are shown in Figure 1b. The goniometers consist of two separate output connectors, each of them measuring one different angle variation: the flexion–extension angle, measured in sagittal plane and, respectively, the rotation angle in frontal plane. When used to measure only one axis, only one channel is used, the other being simply unused. Their main characteristics are [4]:

- Accuracy: ±2º for a measured interval of at least 90º.
- Repeatability: 1º for a measurement interval of at least 90º.
- Measuring temperature: from 10ºC to 40ºC.

DataLOG MWX8, shown in Figure 1, is a portable, lightweight (129 g) device that can be attached to the body without interfering with data collection. The DataLOG data acquisition unit allows the collection of both analog and digital data, from a maximum number of 24 sensors simultaneously with frequencies up to 20 kHz. The sampling frequency range on the analog channel is (1, 2, 5, 10, 20, 50, 100, 200, 500, 1000, 1250, 2000, 2500, 5000, 10000, 20000) Hz. Data transfer is performed in real time to a PC using Bluetooth®, providing real-time data transfer and display, but in the absence of a computer, data can be stored in a memory card attached to the device [4].

The equipment used during the tests consists of the following components:

- Two DataLOG devices (Figure 1a).
- Six electrogoniometers (Figure 1b): two of SG 110 type, mounted on both ankle joints, with the purpose of measuring the flexion–extension and eversion–inversion angles of the ankle joint from the lower limbs and four SG 150 electrogoniometers, mounted on both knees and both hip joints, with the purpose of measuring flexion–extension in sagittal plane and rotation angles in frontal plane for both knees and hips.

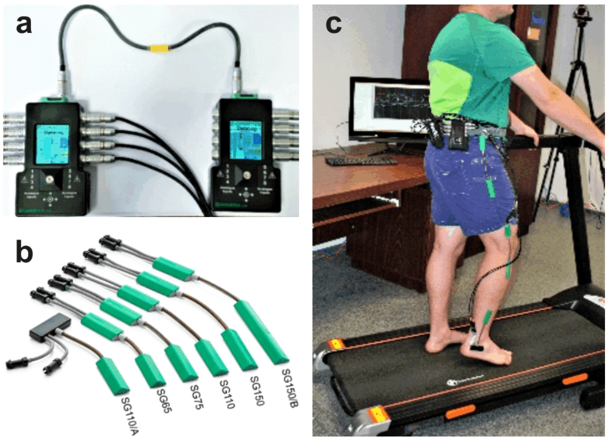

Figure 1 – ***(a) The DataLOG MWX8 equipment; (b) SG goniometer series; (c) The mounted system on a subject during experimental test.***

Subjects and patients

For the experimental study were selected 19 persons grouped in two samples:

- Healthy subjects sample: 14 subjects (eight males and six females). The subjects had no pain, no clinical or historical evidence of arthritic disease or surgical recordings on their lower limbs. The Human Ethics Research Committee of the University of Craiova, Romania, approved the study on human subjects.
- Patient sample: five patients with KOA, of which two female patients and three male patients. During the collection of the data needed for the study, the patients were hospitalized at the Department of Orthopedics, at Emergency County Hospital of Craiova, in order to be prepared for TKR surgery. For all patients, OA knee is the right knee.

In Table 1, the anthropometric data of the subjects and patients samples are presented.

Table 1 – ***Anthropometric data of subjects and patients samples***

		Age [years]	Weight [kg]	Height [cm]	Lower limb length [cm]	Length hip–knee [cm]	Length knee–ankle [cm]
Subjects	Average (StdDev)	26.86 (1.46)	67.29 (6.65)	174.29 (8.27)	79.93 (9.52)	40.93 (4.83)	39 (4.72)
Patients		62.46 (2.37)	74.00 (2.65)	169.33 (2.08)	77.45 (2.18)	39.33 (1.38)	38.12 (1.87)

Experimental tests

The experimental tests were performed using the Biometrics system.

Healthy subjects performed 23 different walking tests on ground and on plane and inclined treadmill, of which three tests were performed on ground with three different speeds and 20 tests were performed on treadmill with different speeds and slopes. In Table 2, the tests performed by healthy subjects on the treadmill in the Laboratory of Biomechanics are presented. The 23 tests (T) are:

- Test 1 (T1): walking on the ground on a platform with a slow speed of approximately 0.5 m/s (1.8 km/h).
- Test 2 (T2): walking on the ground on platforms with a normal speed of approximately 0.69 m/s (2.5 km/h).
- Test 3 (T3): walking on the ground on a platform with a fast speed of approximately 1 m/s (3.6 km/h).

Table 2 – ***Tests run by healthy subjects on the treadmill***

Slope [degrees] / Speed [km/h]	0°	3°	7°	11°	15°
2.5	T4	T5	T6	T7	T8
5	T9	T10	T11	T12	T13
7.5	T14	T15	T16	T17	T18
10	T19	T20	T32	T22	T23

Because of the pain, the patients with advanced osteoarthritis could not pass all the tests on the treadmill. They performed only T1, T2, T3, T4, T5, T6 and T10 tests, at the Emergency County Hospital of Craiova, the day before and three months after the TKR surgery, respectively.

Collection and processing of experimental data

The biomechanical data are collected by electrogoniometers as files data, and transmitted to DataLOG devices, which convert and send them in real time to the computer, *via* Bluetooth®. The block schema of the process of the data acquisition can be seen in Figure 2.

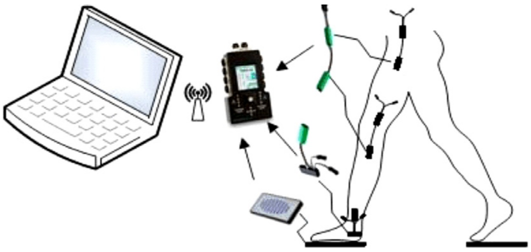

Figure 2 – ***The block schema of the data acquisition process.***

Data received from the PC is converted by the Biometrics software into angles diagrams for the hip, knee and ankle joints.

In this study, the knee flexion–extension is of particular interest. As a result, the presented results will correspond to this joint. A number of 23 tests × 14 subjects × 2 knees = 644 files collected from the 14 healthy subjects and a number of 7 tests × 5 patients × 2 knees × 2 periods (before and after TKR surgery) = 140 files collected from the five patients were processed. The SimiMotion software was used. In order to import the experimental data files collected, and the average normalized cycles of flexion–extension corresponding to each, processed data file were obtained.

Results

The amplitudes of flexion–extension angle were obtained for each test as data files. In Figure 3, a sequence of the consecutive cycles of experimental angles in sagittal plane and in frontal plane for the three joints of the right leg of Subject 1 in respect with time [s], collected and processed by Biometrics system, are presented.

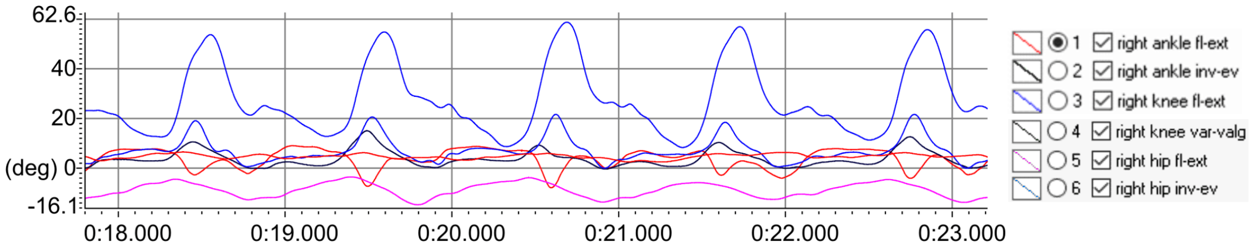

Figure 3 – ***Graphs of consecutive cycles of leg joints movements plotted by the software based on experimental data.***

Healthy subjects' results

The main kinematic parameters obtained from the collection of data corresponding to tests 1–3, for all healthy subjects and for the patient sample, are found in Table 3.

In order to obtain accurate results and considering the natural biological variability, a number of nine consecutive walking cycles were selected for each data file after cutting a number of four cycles on both sides of the walking sequence. Human gait variability imposes the normalization of gait cycles. For this process, the SimiMotion software was used to import the experimental data files collected with Biometrics system and to normalize them. Through all the steps of processing the data obtained from the measurements, the average cycles for the six lower limb joints were obtained for all healthy subjects. In Figure 4, the mean cycles of flexion–extension angles for all joints of Subject 1 corresponding to the T8 test are presented. For each test, using the same algorithm, similar diagrams were computed.

In Figures 5 and 6, the comparative diagrams of the average cycles of the knee flexion–extension angles of healthy sample, function of treadmill incline angle and of treadmill speed are presented.

The shape of the average cycle curve for speeds of 5 km/h, 7.5 km/h and 10 km/h, respectively, was changed by the progressive increase of the maximum values reaching from 47° and 78% of the cycle for the speed of 2.5 km/h to 79° and 75% of the cycle for a speed of 10 km/h (Figures 5 and 6). The second extreme point, the one at the beginning of the running cycle, changes its amplitude reaching a maximum of 32° and 18% of the cycle for the speed of 10 km/h. The shape of the curve of the average cycles changes, the end point of the cycle increasing with the increase of the incline angle of the treadmill from 51° and 77% of the cycle for 0° inclination and up to 58° and 79% of the cycle for 15° inclination.

Table 3 – ***Kinematic parameters corresponding to T1, T2 and T3 tests – healthy sample and patient sample***

		Time [s]	Distance [m]	No. of steps	Rhythm [No. of steps/s]	Frequency [s/No. of steps]
Average (StDev) *Subjects*	T1	31.71 (0.83)	10.71 (0.73)	18.07 (1.00)	0.57 (0.04)	1.76 (0.11)
	T2	18.79 (0.58)	10.36 (0.50)	17.64 (0.93)	0.94 (0.04)	1.07 (0.05)
	T3	14.86 (0.77)	10.00 (0.78)	14.14 (0.86)	0.95 (0.03)	1.05 (0.03)
Average (StDev) *Patients*	T1	24.67 (0.58)	7.33 (0.58)	10.67 (0.58)	0.43 (0.01)	2.32 (0.07)
	T2	18.00 (1.00)	7.00 (0.00)	11.00 (1.00)	0.61 (0.02)	1.64 (0.06)
	T3	13.33 (0.58)	7.00 (0.00)	10.33 (0.58)	0.77 (0.01)	1.29 (0.02)

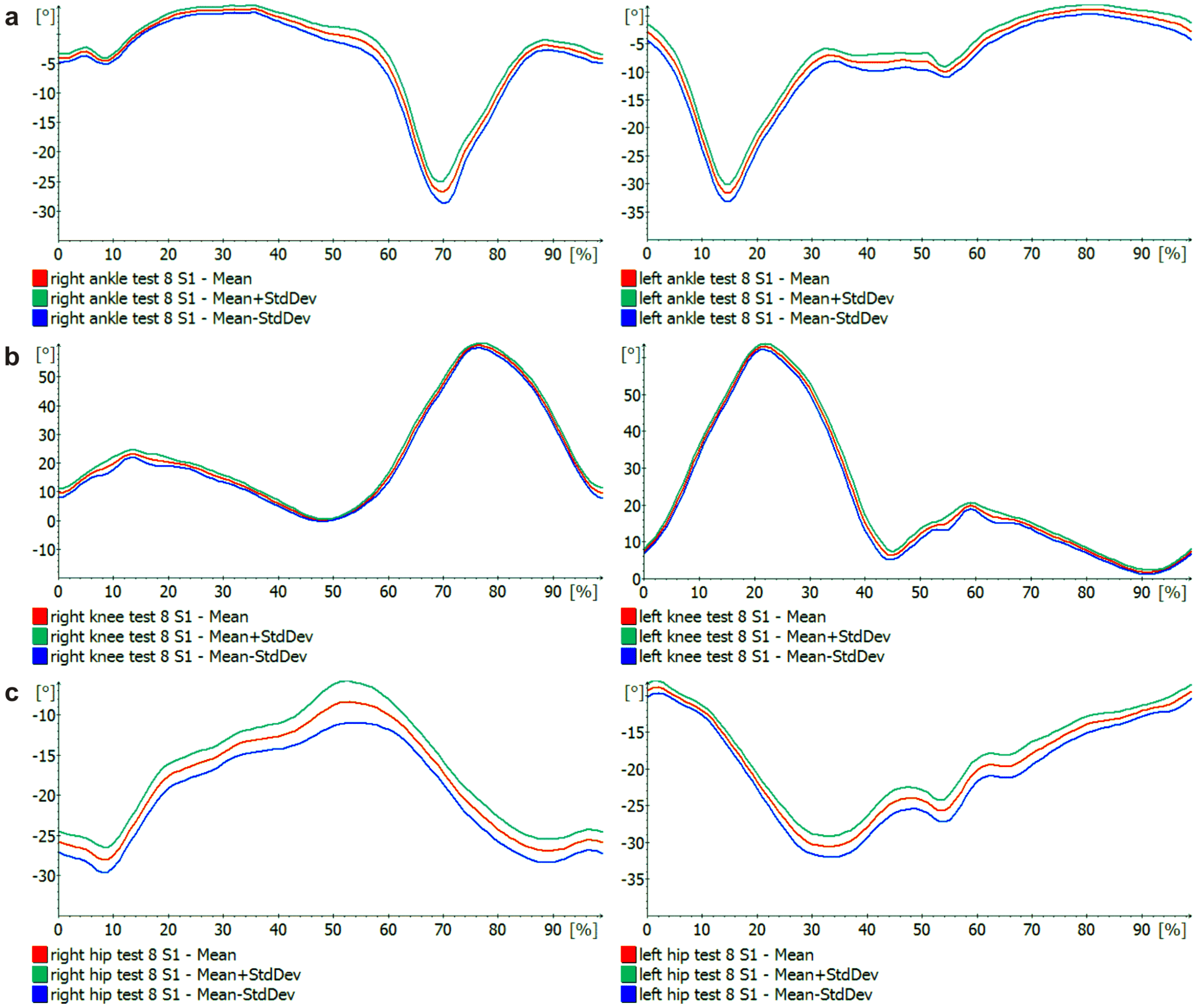

Figure 4 – *Mean cycle, mean cycle + StdDev, mean cycle – StdDev cycle for: (a) Ankle joint, (b) Knee joint, and (c) Right and left lower right hip joint. Subject 1 (S1) – Test 8 (T8). StdDev: Standard deviation.*

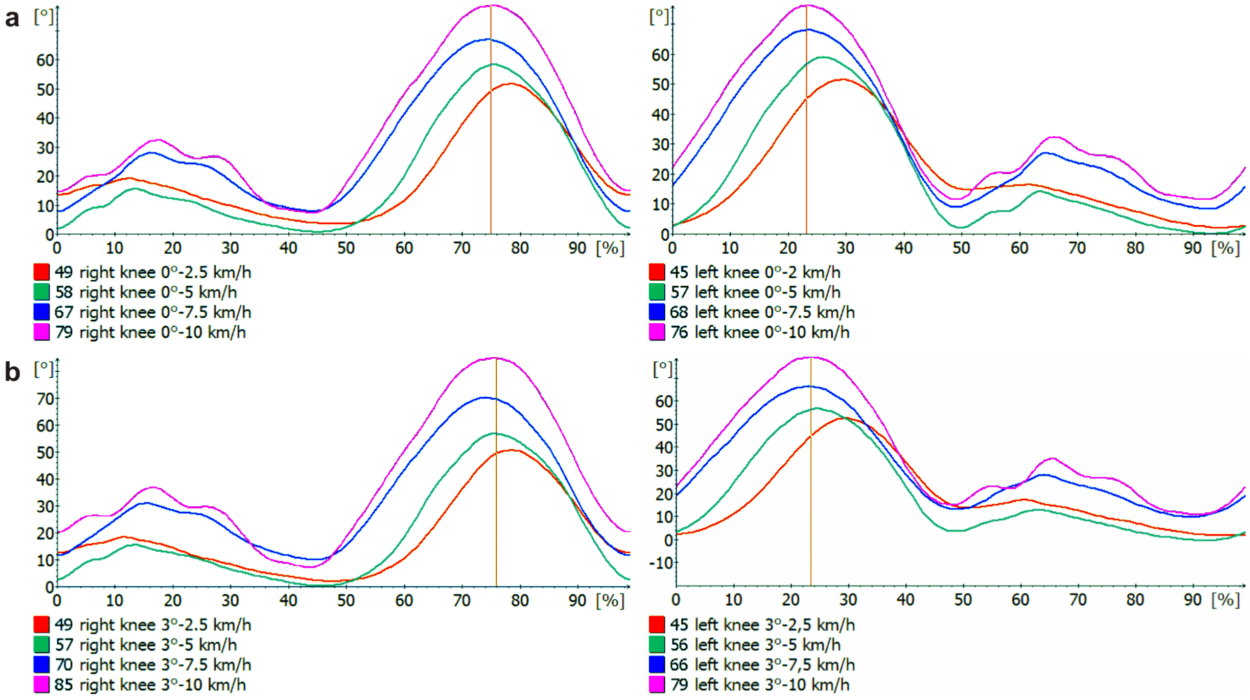

Figure 5 – *Compared diagrams of mean cycles of the healthy subjects' right and left knee joints for the same incline angle, and four different speeds of the treadmill: (a) T4, T9, T14, T19; (b) T5, T10, T15, T20.*

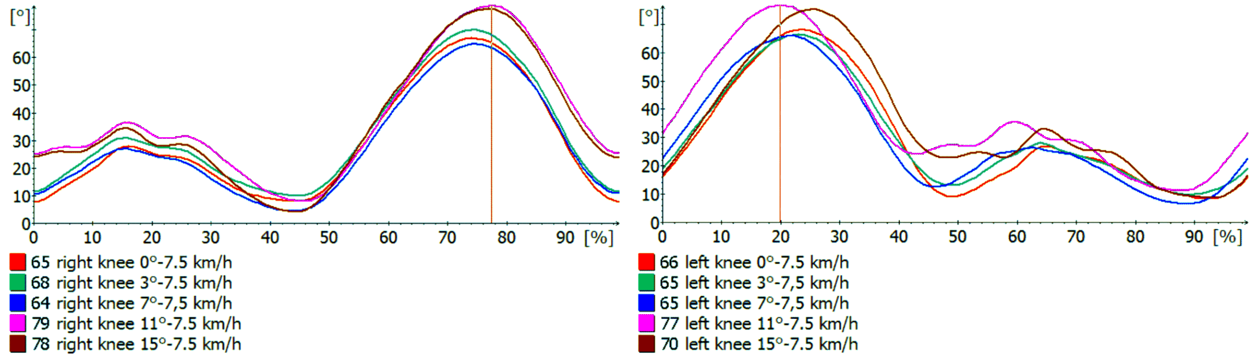

Figure 6 – *Compared diagrams of mean cycles of the healthy subjects' right and left knee joints for the same speed, 7.5 km/h, and the treadmill incline: 0°, 3°, 7°, 11°, and 15° – T14, T15, T16, T17, and T18.*

In Table 4, the average values of the flexion–extension amplitude of right and left knee for healthy subjects sample are shown, while in Figure 7, these values corresponding to each of 23 experimental tests are plotted.

Table 4 – *Average value of flexion–extension amplitude for right and left knee of subjects' sample*

Test	Left knee [°]	Right knee [°]
T1	51.16	51.96
T2	56.97	57.77
T3	59.61	60.41
T4	45.01	50.93
T5	45.46	49.53
T6	50.69	54.09
T7	53.16	55.36
T8	59.37	58.77
T9	56.86	60.10
T10	58.23	61.03
T11	58.33	62.23
T12	63.34	63.69
T13	65.91	64.76
T14	63.97	68.79
T15	70.41	72.91
T16	70.63	75.73
T17	79.23	82.03
T18	81.82	84.59
T19	78.06	79.21
T20	78.86	86.72
T21	82.47	87.04
T22	86.59	91.61
T23	92.63	92.74

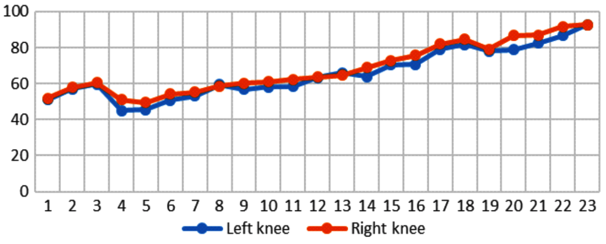

Figure 7 – *The average values of flexion–extension amplitude [°] for right and left knee, for each of the T1–T23 tests.*

In Figures 8 and 9, the variation of the right knee flexion–extension angle can be observed depending on the treadmill incline angle and, respectively, depending on the walking speed.

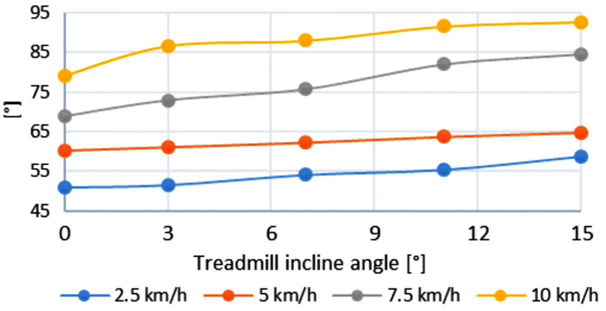

Figure 8 – *Variation of flexion–extension angle depending on the treadmill incline angle for the right knee.*

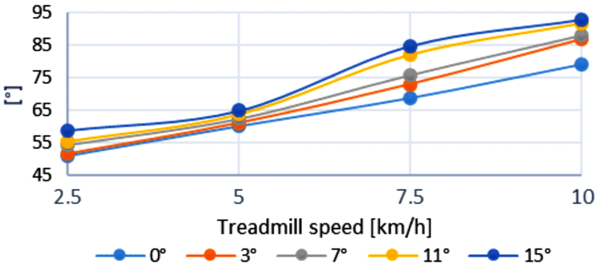

Figure 9 – *Variation of flexion–extension angle depending on the treadmill speed for the right knee.*

In Figure 8, the diagrams show that, for the same incline angle, the right flexion–extension angle increases by approximately 24–35°, with the increase of the walking speed from 2.5 km/h to 10 km/h. The diagrams show that at 0° inclination of the treadmill, for the right knee the maximum values vary from 50.93° to 80.87°, while, for 0° inclination of the treadmill, the maximum values vary from 58.77° to 92.74°, increasing with the increase of treadmill speed.

In Figures 10 and 11, the variation of the left knee flexion–extension angle depending on the treadmill incline angle and, respectively, depending on the walking speed are shown.

The maximum value of flexion–extension angle of left knee varies from 45.01°, related to the speed of 2.5 km/h until 78.6°, value related to the speed of 10 km/h (Figure 10). In this diagram, it can be observed the increase of the maximum value of the flexion–extension angle with the increase of the treadmill incline [6]. Thus, the maximum value of the flexion–extension angle increases by 10–12° from 0° inclination to 15° inclination in the case of speed of 2.5 km/h and 5 km/h and increases by 15–20° for the tests performed at 7 km/h and 10 km/h, respectively.

From diagrams in Figures 10 and 11, it can be seen that the knee angle increases more pronounced in function of increasing walking speed than in the case of increasing the incline angle of the treadmill.

Patients' results

In Figures 12 and 13, the diagrams of the normalized mean cycle corresponding to the T1, T2 and T3 tests performed by the patients' sample are presented. Similar diagrams were obtained for the other tests.

Compared with the measurements made on healthy subjects, changes in values can be observed in the angle graphs for patients affected by KOA (Figures 12 and 13). For all walking tests analyzed, the difference between the maximum mean knee flexion angle values for the healthy subjects sample and the mean knee flexion angle for the OA knee corresponding to the patient sample before the surgery is about 12.5°–20°, depending on the test performed. Improvement of gait is evident after the TKR surgery, when the amplitude of the average flexion cycle of the prosthetic knee increased by 5°–9°. The cycles' allure of the knee affected by OA presents much more pronounced changes, compared to those of the knees of healthy subjects, highlighting the degree of wear and laxity in the KOA. Because of the influence of the pain in KOA and on the tendency of the human body in maintaining its stability, the range of motion of OA patients was smaller than of the healthy subjects, the knees of OA patients being on average less flexed than the knees of the healthy subjects.

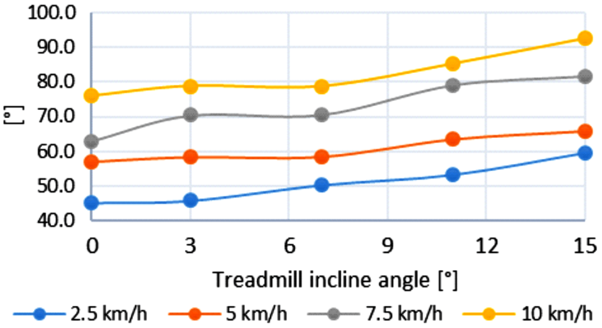

Figure 10 – ***Variation of flexion–extension angle depending on the treadmill incline angle for the left knee.***

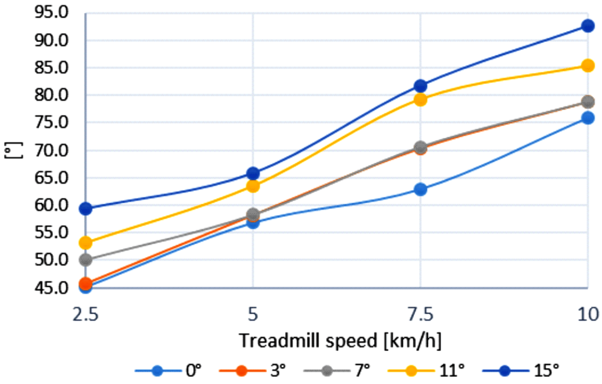

Figure 11 – ***Flexion–extension angle variation depending on the treadmill speed for the left knee.***

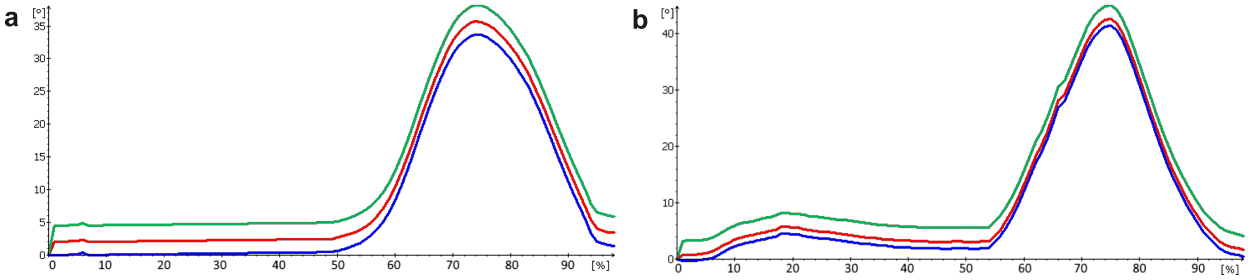

Figure 12 – ***Diagram of the mean cycle (red color), mean cycle + StdDev (green color) and mean cycle – StdDev (blue color) of the right knee for T1 test – entire sample of patients: (a) Before TKR surgery; (b) Three months after TKR surgery. StdDev: Standard deviation; TKR: Total knee replacement.***

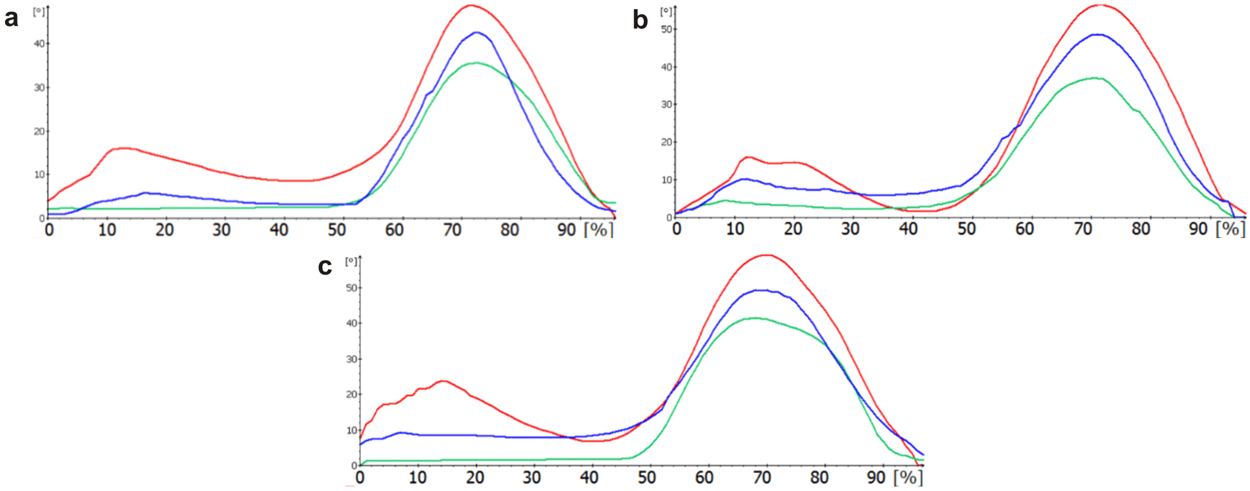

Figure 13 – ***Compared mean cycles of the sample of healthy subjects (red color), sample of patients before TKR surgery (green color) and sample of patients after TKR surgery (blue color) for the tests: (a) T1; (b) T2; (c) T3. TKR: Total knee replacement.***

In Table 5, the average value of flexion–extension amplitude for the right and left knees of the patients are shown, while in Figure 14, these values are plotted for the healthy subjects and OA patients.

Table 5 – ***Average value of flexion–extension amplitude for right and left knee of patients***

Tests \ Values	Knee before TKR		Knee after TKR	
	R	*L*	*R*	*L*
T1	37.3	40.5	42.5	45.3
T2	38.1	42.9	46.1	51.7
T3	41.2	44.1	50.2	53.5
T4	38.5	41.8	43.7	46.8
T5	39.4	42.3	44.5	47.6
T6	40.8	43.7	46.1	48.3
T10	43.7	45.1	47.6	49.8

TKR: Total knee replacement; R: Right; L: Left.

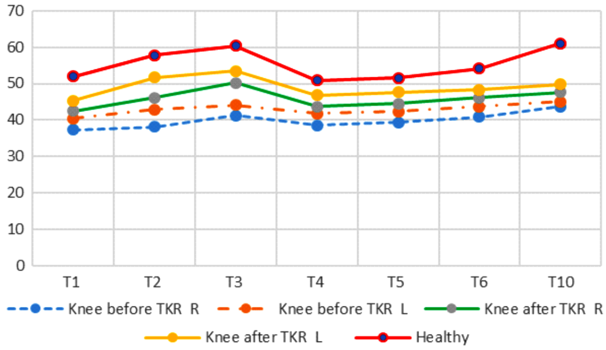

Figure 14 – ***Compared diagrams of average flexion–extension amplitude of right (R) and left (L) knees for healthy subjects and patients before and after TKR. TKR: Total knee replacement.***

Differences between the two groups of patients (before and three months after TKR surgery, respectively) were assessed using analysis of variance (ANOVA) test. To compare the differences between the sample of healthy subjects and that of patients before and after TKR, the Student's *t*-test was used, considering a $p=0.05$ value for the level of statistically significant difference. The maximum values of the flexion angle for the healthy knees and for the OA knees determined during the performed trials were compared and tested. There was a significant improvement of the flexion angle after TKR surgery ($p<0.05$) in the patients' sample for all experimental tests. The maximum flexion angles were significantly different ($t_{calc}>t_{cr}$ and $p<0.05$) for the healthy knees and OA knees before TKR surgery. In addition, the maximum flexion angles were significantly different ($t_{calc}>t_{cr}=2.228$ and $p=0.0352<0.05$) for the OA knees before and after TKR surgery. The maximum flexion angles were not significantly different ($t_{calc}<t_{cr}=2.31$ and $p=0.0563>0.05$) for the prosthetic knees and the knees of healthy subjects.

Discussions

The aim of the present study was to investigate the effect of different walking inclinations and speeds on knee flexion angle of healthy subjects and patients with KOA. This study examined the kinematic changes of the OA knees, compared with a healthy control group, depending on walking speed and incline. Several gait changes with KOA have been reported [20–29, 31–33]. A decreased range of motion is usually reported as a response to the pain and functional alterations associated with KOA disease [32, 34] and decreased range of motion at all joints of lower limbs has been reported [35]. Because the OA sample was tested before TKR, these alterations could be considered as a compensatory gait response to pain and disability [31].

The patients evaluated in the present study suffer of severe OA disease, similar to that reported by patients in papers [36, 37]. The difference between the OA sample and the healthy sample reveals that KOA are subjected to higher levels of disability. In moderate KOA, the differences registered for kinematical parameters are similar to those of healthy subjects, with similar appearance of gait [38]. Within the knee OA literature, the knee flexion angles are varied, some studies reporting greater knee flexion [34], some studies finding greater knee extension [39] and others finding no difference [40, 41] in OA patients compared to controls. Important decreasing in KOA flexion range of motion has been reported in several clinical evaluations of OA patients [34, 40, 42]. Some possible reasons for this disagreement could be the use of different measurement tools, not using treadmill and not control. These findings suggest that knee range of motion is related to OA grade, incline and walking speed, these factors being a cause for differences in knee kinematics between groups. According to the findings of Anbarian *et al.* [43] and Stief *et al.* [44], patients with *varus* knee malalignment and an installed OA degenerative process, use more muscular activity in order to stabilize the joint during the stance phase of walking. As inclination increases, knee joint has more flexion at the moment of heel contact as compared to normal walking, that is, at the moment of heel contact, knee joint extension will be greater as compared to walking on a non-inclined surface [45]. As the treadmill incline angle increases, the stride mechanism changes and the joint approaches loose-packed position, and consequently, the value of *varus* misalignment decreases, as the results obtained by [46]. These findings are similar with the results of Lange *et al.* [47] and Haggerty *et al.* [48], where the authors had studied the influence of incline walking on healthy individuals and indicate that as walking inclination increases, the adduction moment applied to the medial compartment of the knee joint decreases. The main changes in the dynamics of the knee depending on incline angles and treadmill speed are studied. Differences in biomechanical parameters were significant between subject and between condition [47, 48]. Knee flexion at heel strike increased with increasing angle walking up, conclusions similar with those presented by Rowe *et al.* [49]. Gait changes in OA patients can be explained as a possible strategy of gait compensation used by them to reduce the moment arm of the ground reaction force during stance. A faster progression of existing OA and an initiation of OA at the other joints of lower limb are influenced by a rapidly increasing of joint forces. Mündermann *et al.* [39] showed the importance and the effects on the biomechanics of all lower limbs joints of interventions conducted to slowing the rate of progression of OA.

Severe changes in gait variables were found, similar with those found by Asthepen *et al.* [31], while reduced ranges of motion for all joints of lower limbs and reduced values of maximum knee flexion angles were found, similar with those reported by Dingwell & Marin [21], Jordan *et al.* [22] and England & Granata [23]. All changes in KOA gait are consistent with previous studies [31, 33, 50]. The maximum values of knee angles were smaller in the severe KOA patients' group than in the TKR patients group and, respectively, those in TKR group were smaller than those obtained in the healthy group.

In the present study, we used electrogoniometry, an accurate and effective method to evaluate the knee biomechanics and the range of motion of human joints, in laboratory as well as in other places like home (daily activities), sports halls (to monitor the performance) or clinics (to diagnose and monitor different diseases). The advantages of electrogoniometry are that it is non-invasive, it is well accepted by the participants in experimental tests and no dangerous effects on the human body are registered [1–6]. The surveys concerning the patient satisfaction following TKR surgery suggest that the ability of more knee flexion influences a patient's view of the outcome, similar with the results presented in [51].

At three months after TKR, all patients recorded an improvement in knee biomechanics as the physical evaluation demonstrated. However, a better knee function and an immediate improvement in range of motion measured during experimental tests, increased with about 6–9° after TKR, are effects of improved mobility due to pain relief.

One of Watt *et al.* [52] conclusions shows that KOA disease is a process that involves many interrelated factors that interact to determine biomechanical changes during its evolution. The present study investigated the influences of the treadmill speed and incline angle on the biomechanical changes associated with KOA.

For future work, an increased number of patients will be considered for the biomechanical evaluation as well as other parameters, like body mass index (BMI), walking surface structure or age will be taken into consideration in order to identify multifactorial changes in gait biomechanics associated with KOA.

Conclusions

In this paper, the influences of treadmill speed and incline angle on the variation of flexion–extension angles of the human knee joints during 23 tests of walking overground and on plane and inclined treadmill performed by a sample of 14 healthy subjects and during of seven tests performed by a sample of five patients suffering of KOA, before and three months after the TKR surgery. A comparison between the average cycles of each test obtained for the healthy subjects' sample and for the OA patients' sample before and after TKR surgery is made and conclusions are formulated. The increase of the incline of the treadmill leads to the increase of the maximum value of the flexion–extension angle. The knee flexion–extension angle has a more pronounced increase with increasing walking speed than in the case of increasing the incline angle of the treadmill. The present study revealed that, due of the influence of the OA knees pain and of body tendency of maintaining its stability, the KOA were on average less flexed than the knees of healthy subjects and, respectively, the healthy knees of the patients were on average less flexed than those of the healthy subjects.

Conflict of interests

The authors have stated explicitly that there is no conflict of interests connected to this article.

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