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Quantitative assessment of gait deviation: contribution to the objective measurement of disability

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Abstract

Three biomechanical parameters based on force plate measurements were defined as indicators of gait deviation. Symmetry was specified as the relative difference in stance time and vertical impulse loading between both feet, constancy as the mean S.D. of the force curves for one subject under a specified gait condition and discrepancy as the average difference between the individual gait pattern and the expected force curves, normalised by the value of the S.D. in a control group. One hundred and forty four patients with osteoarthritis (OA) of the lower extremity and 144 control subjects were studied. There were 45 patients with OA of the hip, 54 of the knee and 45 of the ankle and their function was determined using the Harris Hip score, the hospital for special surgery knee score and the Mazur ankle score, respectively. The temporal asymmetry indicator was more sensitive to unilateral joint affliction, whereas the discrepancy indicators were sensitive to the presence of OA. Both correlated with the patient's function as measured by the relevant clinical score. A significant increase of gait discrepancy was detected in the arthritis group when patients were asked to walk at faster speeds; whilst walking barefoot led to an unexpected reduction of intra-subject kinetic variability. Our results confirm the validity and usefulness of the gait deviation concept in patients with OA. © 2000 Elsevier Science B.V. All rights reserved.

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1. Introduction

Rehabilitation can be regarded as a typical problem of feedback control [1] and measurement of function is an essential component of rehabilitation. There are several problems with functional assessment (FA). The first is the subjectivity that governs most disability-oriented measurement tools, the second is the restriction to a specific pathology and the third is the low sensitivity to change. Biomechanical instrumentation is precise and reliable enough to analyse gait [2]. The main problem does not lie in obtaining objective data, but in defining objective and reliable criteria to analyse data appropriately. Functional Assessment can be defined as the measurement of the ability of a subject to carry out a task in a 'normal' way [3]. Most clinical investigations have focused on the analysis of biomechanical alter-

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ations to describe typical gait patterns or to study methods of improving associated disorders. Nevertheless, such 'impairment-oriented' perspective does not usually permit measuring the extent of the physical disability.

Two principles for defining a 'disability-oriented' FA can be devised: empirical, inductive methods or theoretical, deductive approaches. The inductive approach provides a 'black-box' model linking observations with pre-assigned functional classifications. A training algorithm learns to associate input patterns into output classes. The advantage is that no model of correct function is required, but two limitations exist: it requires a very high number of training samples, that must be classified by an expert beforehand and functional classification is only sustained by statistical criteria [4]. Typical examples of these techniques are statistical classifiers and neural networks [5]. On the other hand, a deductive approach relies on reference data for normal function for example, clinical assessment scales or functional battery tests [6]. However,

new models of FA are needed which make use of data delivered by biomechanical instrumentation that are applicable independently of the specific pathologies. The principal benefits are twofold: objectivity is introduced during evaluation and FA is founded on solid clinical and biomechanical knowledge.

In this paper, the complex task of FA is split into simple components, which can be considered independently from an integrated assessment of function. Deviation from normality is hypothesised as one of these components of altered gait. The aim of this study is to determine an objective, reliable and simple method for measuring gait deviation as one possible indicator of disability.

2. Patients and methods

2.1. Subjects and patients

One hundred and forty four control subjects and 144 patients suffering from lower limb osteoarthritis (OA) were studied at our gait laboratory. Selection criteria for the control subjects were: age range between 18 and 70 years old and no known history of neuro-musculoskeletal diseases which might affect walking. The patients were within the same age range as the control group and could walk unassisted for at least 1 km and preference was given to a unilateral, monoarticular OA. There were 45 patients with OA of the hip, 54 of the knee and 45 of the ankle and their function was determined using the Harris hip score [7], the hospital for special surgery knee score [8] and the Mazur ankle score [9], respectively (Fig. 1). Ankle and knee OA was found more commonly in females, whereas hip OA was distributed evenly between males and females. Osteoarthritis of the knee was often seen bilaterally whereas OA of the ankle was usually unilateral. In cases of multiple joint involvement, the patients were assigned to the group depending on their dominant joint pathology. Eighty five percent of patients experi-



Clinical functional index

Fig. 1. Average scores in the clinical functional assessment scales Mazur (ankle), HSS (knee) and Harris (hip).

enced discomfort or pain when walking and 67% had functional limitations when walking or climbing steps. All were able to follow the experimental procedure. Some overlap between the older controls and patients was inevitable due to natural ageing.

Written consent was obtained for the study. The following measurements were taken: height, weight, shoulder width, hip width and foot length. Controls underwent a free walking test, a stability test of one min without losing standing balance (Romberg test) and a 2 m tandem-walk (one foot behind the other on an imaginary line) to exclude gait pathology.

2.2. Gait analysis

A 12 m gait corridor was used as a walkway and two extensometric 60×40 cm force plates (DINASCAN[®]), that were not visible to the subjects. In addition, two photoelectric barriers were used to calculate the average progression velocity and a chronograph determined cadence from the duration of ten consecutive steps. The experimental design involved two controllable factors: cadence and shod/barefoot walking condition. Gait analysis was performed at three different but self-selected velocities: a normal free-selected speed and two imposed cadences whose rhythms were suggested to the patient/subject by asking him/her to walk slightly faster and slightly slower than usual. The patient/subject was analysed first while wearing his/her street shoes and then walking barefoot.

An analysis was only accepted after verifying that the subjects' feet had landed correctly on the force plate and in the given sequence (right-left). Quality control of the force signals was performed by a trained technician studying the trajectory of the centre of progression (COP) just after the measurement. Three to five trials were taken thus giving six different experimental conditions.

2.3. Data analysis

The force records were normalised in time by the stance phase duration T and in amplitude by the subject's body weight M. Each force plate was considered independently, so that for each subject two force trajectories were available. The individual force pattern was calculated per subject and experimental condition as the mean of the measured 3-5 gait records. To reduce variability, subjects were subdivided into two groups: those younger than 45 years of age and those older.

Normalised force curves were grouped into 24 combinations dependent on: sex (male/female), age range ($<45/ \ge 45$), shod/barefoot condition and induced walking speed (normal/fast/slow). For each of these 24 combinations, the mean vertical force FZ,ref(*t*), mean antero-posterior force FX,ref(*t*) and mean medio-lat(1)

eral force FY,ref(t) were computed for each limb independently, together with the corresponding S.D. bands DZ,ref(t), DX,ref(t), y DY,ref(t), as shown in Eq. (1)

$$\begin{split} \mathbf{\underline{F}}_{ref}(t) &= \frac{1}{N} \cdot \begin{pmatrix} \sum_{j=1}^{N} F_{Z,j}(t) \\ \sum_{j=1}^{N} F_{X,j}(t) \\ \sum_{j=1}^{N} F_{Y,j}(t) \end{pmatrix} ; \\ \mathbf{\underline{\Theta}}_{ref}(t) &= \begin{pmatrix} \sqrt{\frac{1}{N-1} \cdot \sum_{j=1}^{N} (F_{Z,j}(t) - F_{Z,ref}(t))^2} \\ \sqrt{\frac{1}{N-1} \cdot \sum_{j=1}^{N} (F_{X,j}(t) - F_{X,ref}(t))^2} \\ \sqrt{\frac{1}{N-1} \cdot \sum_{j=1}^{N} (F_{Y,j}(t) - F_{Y,ref}(t))^2} \\ \sqrt{\frac{1}{N-1} \cdot \sum_{j=1}^{N} (F_{Y,j}(t) - F_{Y,ref}(t))^2} \end{pmatrix} ; \\ T_{ref} &= \frac{1}{N} \cdot \sum_{j=1}^{N} \cdot T_j \quad ; 0 \le t \le T_{ref} \end{split}$$

In Eq. (1) and the next equations, the following terms were used: N: number of samples. t: time. Fref(t); Dref(t): reference force vector and S.D. band vector. Tref: average stance duration of the reference population. FX(t); FY(t); FZ(t): horizontal, lateral and vertical force curves.

Hence, the reference force pattern was defined by a mean force vector Fref(t) and a S.D. vector Dref(t), which are shown in its three components in Fig. 2 for an illustrative factor combination.

We wished to match individual patient records with the corresponding reference force patterns and this was possible for the factors sex, age and shod/barefoot condition, but was uncertain for cadence, because no individual gait pattern could match accurately the cadence of the reference patterns. Since reference patterns were stored together with their average stance duration, Tref, it was decided to use a linear interpolation scheme between the two nearest reference patterns: one above and one below the actual individual stance phase duration T. Being $F_{\rm ref}^-$ (t) the nearest reference pattern slower and $F_{\rm ref}^+$ (t) the nearest reference pattern faster than the individual pattern, Eq. (2) displays the interpolation method

$$\underline{\mathbf{F}}_{ref}(t) = \underline{\mathbf{F}}_{ref}^{-}(t) + K \cdot (\underline{\mathbf{F}}_{ref}^{+}(t) - \underline{\mathbf{F}}_{ref}^{-}(t))$$

$$K = \frac{T_{ref}^{-} - T}{T_{ref}^{-} - T_{ref}^{+}} \quad ; \quad T_{ref}^{+} \le \bar{T} \le T_{ref}^{-} \quad ; \quad \bar{T} = \frac{T_{1} + T_{2}}{2}$$
(2)

Reference patterns were defined as a function of stance duration. Reference patterns of individual records whose stance duration lay outside the threshold of the three reference force patterns, were equalled to the nearest reference pattern.

2.4. Definition of gait indicators

We assumed that normal gait is symmetrical and that deviation from a reference pattern is a sign of disability. We determined three types of indicators for gait deviation: symmetry, constancy and discrepancy indicators.

The temporal asymmetry indicator (TAI) was defined as the relative difference in stance time (T1 and T2)between both limbs, as seen in Eq. (3)

$$TAI = \frac{T_1 - T_2}{T_1 + T_2}$$
(3)

The load asymmetry indicator (LAI) was calculated as the relative difference in vertical impulse loading (II)and I2 between both extremities (Eq. (4)):

$$LAI = \frac{I_1 - I_2}{I_1 + I_2} \quad ; \quad I = \int^T F_Z(t) \cdot dt \quad ; \quad 0 \le t \le T$$
 (4)

The force variability indicator (*FVI*) was postulated as the average S.D. of the individual force curves DZ, DX and DY obtained from the 3–5 trial repetitions, where the coefficients φZ , φX and φY are weights associated to the corresponding vertical, horizontal or lateral component (Eq. (5)):

$$FVI = \varphi_Z FVI_Z + \varphi_X FVI_X + \varphi_Y FVI_Y$$

$$FVI_Z = \frac{1}{T} \cdot \int_0^T \Theta_Z(t) \cdot dt; \quad 0 \le t \le T$$
 (5)

Force discrepancy was defined as the average difference between the individual gait pattern and the expected force curves for the same subject, normalised at each time instant by the value of the S.D. in the control group. The continuous force discrepancy index (*CFDI*) was defined by Eq. (6):

$$CFDI = \varphi_Z \ CFDI_Z + \varphi_X \ CFDI_X + \varphi_Y \ CFDI_Y$$

$$CFDI_Z = \sqrt{\frac{1}{T} \cdot \int_0^T \left(\frac{F_Z(t) - F_{Z,ref}(t)}{\Theta_{Z,ref}(t)}\right)^2 \cdot dt} \quad ; \quad 0 \le t \le T$$
(6)

Assuming a Gaussian distribution around each data point of the reference pattern Fref(t), extreme discrepancy occurred when the individual pattern exceeds the 95% CI for any data point. According to statistical inference, this occurs when these differences exceed 1.96 times the value of the S.D. at this time instant. The extreme force discrepancy index (*EFDI*) is zero when the individual force curve is contained within the normal boundaries and is proportional to the amount of deviation at extremes (Eq. (7))

$$EFDI = \varphi_Z EFDI_Z + \varphi_X EFDI_X + \varphi_Y EFDI_Y$$

Table 1					
Subject	distribution	in	the	validation	groups

Original popula- tion	Number of female subjects (>45 years) walking barefoot	Number of female subjects compared at free and faster cadences	Number of female subjects compared shod/barefoot
Control	27	11	20
Ankle os- teoarthritis	11	3	-
Knee os- teoarthritis	34	8	16
Hip os- teoarthritis	7	3	-

$$EFDI_{Z} = \begin{cases} 0 & ; \frac{F_{Z}(t) - F_{Z,ref}(t)}{\Theta_{Z,ref}(t)} \le 1.96 \\ \sqrt{\frac{1}{T}} \cdot \int_{0}^{T} \left(\frac{F_{Z}(t) - F_{Z,ref}(t)}{\Theta_{Z,ref}(t)} - 1.96\right)^{2} \cdot dt & ; \frac{F_{Z}(t) - F_{Z,ref}(t)}{\Theta_{Z,ref}(t)} \ge 1.96 \end{cases} \leq 1.96 \quad (7)$$

The coefficients φz , $\varphi z \varphi x$ and φy were chosen according to the relative importance and the reliability of the corresponding ground reaction force component. We decided to omit medio-lateral forces, because of their low signal-to-noise ratio [10]. We also decided to consider the vertical force component alone as the variable determining the proposed gait indicators because of its much higher magnitude and to simplify the mathematical model. Hence, these coefficients were set to: $\varphi z = 1$ and $\varphi x = \varphi y = 0$.

2.5. Validation

The test procedure was designed to check the validity and sensitivity of the postulated gait indicators within the control and OA populations. We validated the following three assumptions

- 1. Sensitivity to the presence of OA. OA should limit walking ability depending on the joints affected.
- 2. Sensitivity to changes in experimental conditions. Patients' should change when asked to walk barefoot or at a higher velocity. However, control subjects should not be significantly affected.
- 3. Correlation with clinical functional scales. Changes in function should be reflected by changes in the functional scores.

The following statistical methods were used:

One-way ANOVA (P = 0.05) for assessing differences between the control and the arthritis groups. And a post-hoc analysis for significant differences among each pair of pathological groups using the Bonferroni test.

Student *t*-test was used to detect significant differences before and after altering the gait conditions (P = 0.05). The Pearson correlation coefficient was used to compare control and OA populations by calculating it between gait indicators and the Mazur, HSS and Harris scores.

To reduce potential noise sources, results were calculated only for a subgroup of female patients who agreed to walk shod and at a free selected cadence and also barefoot at a faster cadence (Table 1).

3. Results

3.1. Sensitivity to the presence of OA

Table 2 shows the sensitivity of the proposed indicators to the presence of OA. Mean stance time has been included as an indirect measure of gait speed. Temporal asymmetry (*TAI*) was higher for hip patients and significantly higher for ankle patients compared to control subjects (P = 0.019), but very similar for the control and the knee subgroups. Significant differences were also found in the *TAI* between knee and ankle patients (P = 0.008). Load asymmetry (*LAI*) showed no statistically significant differences, although ankle patients tended to exert a higher vertical impulse on their sound leg. There were no differences in the constancy indicators.

A statistically significant difference between the discrepancy indicators of the control and the OA population as a whole was demonstrated (P = 0.004). Knee patients showed the least discrepancy, whereas hip patients evidenced the highest discrepancy levels in the OA group (Fig. 2). Ankle and knee patients tended to spend more time per cycle in stance than hip patients and controls who had a 5% reduction in stance duration.

3.2. Sensitivity to change in experimental conditions

Table 3 shows the effect of changing cadence and walking barefoot or shod in the controls and patients. Although not statistically significant with this sample size, an opposite trend between control subjects and

Original population TAI LAI FVI CFDI EFDI NT/sec 0.91% S.D. 0.6% 1.78%S.D. 0.9% 3.45% S.D. 1.2% 5.07% S.D. 2.3% 0.23% S.D. 0.7% 0.610 S.D. 0.060 Control (C) 38 Ankle osteoarthritis (A) 10 1.81% S.D. 1.7% 2.23% S.D. 1.4% 3.70% S.D. 1.0% 6.42% S.D. 1.7% 0.36% S.D. 0.6% 0.650 S.D. 0.038 0.639 S.D. 0.056 Knee osteoarthritis (K) 41 0.84% S.D. 0.6% 1.83% S.D. 1.2% 3.51% S.D. 1.0% 5.87% S.D. 1.6% 0.29% S.D. 0.5% Hip osteoarthritis (H) 7.71% S.D. 2.2% 1.01% S.D. 1.1% 14 1.50% S.D. 1.6% 1.62% S.D. 1.2% 2.88% S.D. 1.7% 0.612 S.D. 0.052 ANOVA C-Arthritis (P < 0.05) F = 1.36 P = 0.25F = 0.18F = 0 P = 1.0F = 8.79 (*) F = 1.80 P = 0.18F = 5.66 (*) _ P = 0.004P = 0.68P = 0.019Paired Bonferroni test (P<0.05) C-A (*) p = 0.019C-H (*) C-H (*) P = 0.007_ _ _ KA (*) P = 0.008P = 0.001K-H (*) P = 0.014

Table 2 Sensitivity analysis of the proposed gait indicators to the presence of osteoarthritis



Fig. 2. Right limb force pattern for healthy females, barefoot, over 45, walking at their self-selected cadsence. Mean stance duration is 0.645 s.

patients could be discerned in the symmetry indicators. In the patients, *TAI* decreased and simultaneously *LAI* increased by 10–25%, when both experimental conditions were made harder, whereas only minor changes were found in the control group. A significant decrease in mean stance time occurred for all subjects/patients following each change, which would indicate an increase in cadence. This difference was more pronounced in the OA group reaching about 10% when barefoot (P < 0.001). Augmenting walking pace led to a dramatic but inconsistent increase of kinetic discrepancy in the control group (P > 0.05), though a 21% significant increase (P < 0.01) could be established for the patients. No significant modifications of the CFDI were found when subjects walked unshod.

3.3. Correlation with clinical functional scales

Table 4 shows the Pearson correlation coefficients (r)



Fig. 3. Dispersion plot and linear regression curve for the assosiation of *CFDI* and the clinical functional scales (Mazur, MSS and Harris).

when comparing the proposed gait indicators and the clinical functional scales. Fig. 3 shows the dispersion plot of the most correlated parameter (CFDI) with controls. The force discrepancy indicators (CFDI and EFDI) showed a moderate but very significant indirect proportionality (r = -0.456, P < 0.001) with respect to the clinical indices, especially when all subjects/patients were considered. Severe OA, resulting in a lower clinical score, was correlated with a higher discrepancy value. Symmetry gain in stance phase duration (expressed by TAI) was significantly correlated with an increase in the clinical score (r = -0.457), particularly when only patients were considered. TAI appeared therefore, to capture one dimension correlating with the functional ability of the OA patients. However, no significant relationships were detected for the rest of the indicators.

Table 3

Sensitivity analysis of the proposed gait indicators to changes in the experimental conditions

Population	Free/faster cadence $n = 11$	Shod/barefoot $n = 20$
Control (differences and Student <i>t</i> -test)	$\Delta TAI = -7.85\% (t = 0.301; P = 0.77)$ $\Delta LAI = -2.0\% (t = 0.16; P = 0.88)$ $\Delta FVI = +22.3\% (t = -1.37; P = 0.20)$ $\Delta CFDI = +43.7\% (t = -1.80; P = 0.10)$ $\Delta EFDI = +495\% (t = -1.18; P = 0.27)$ $\Delta T = -6.5\% (*) (t = 2.65; P = 0.02)$ n = 14	$\Delta TAI = +15.4\% (t = -0.75; P = 0.46)$ $\Delta LAI = -3.0\% (t = 0.30; P = 0.77)$ $\Delta FVI = -84.9\% (*) (t = 9.81; P < 0.001)$ $\Delta CFDI = -2.3\% (t = 0.43; P = 0.67)$ $\Delta EFDI = +40.3\% (t = -0.52; P = 0.61)$ $\Delta T = -4.9\% (*) (t = 2.91; P = 0.01)$ n = 16
Osteoarthritis (differences and Student <i>t</i> -test)	$\Delta TAI = -24.5\% (t = 0.84; P = 0.42)$ $\Delta LAI = +27.1\% (t = 1.12; P = 0.28)$ $\Delta FVI = +0.82\% (t = -0.05; P = 0.96)$ $\Delta CFDI = +21.1\% (*) (t = -3.21; P < 0.01)$ $\Delta EFDI = +82.4\% (t = -1.90; P = 0.08)$ $\Delta T = -8.3\% (*) (t = 4.79; P < 0.001)$	$ \begin{aligned} \Delta TAI &= -20.0\% \ (t = 1.33; \ P = 0.20) \\ \Delta LAI &= +10.3\% \ (t = -0.71; \ P = 0.49) \\ \Delta FVI &= -81.5\% \ (*) \ (t = 9.40; \ P < 0.001) \\ \Delta CFDI &= +3.8\% \ (t = -0.69; \ P = 0.50) \\ \Delta EFDI &= +130\% \ (t = -1.25; \ P = 0.23) \\ \Delta T &= -9.6\% \ (*) \ (t = 6.80; \ P < 0.001) \end{aligned} $

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Calculation modus	п	TAI	LAI	FVI	CFDI	EFDI	Т
With control subjects	79	-0.380 (*) P = 0.001	-0.064 P = 0.58	-0.009 P = 0.94	-0.456 (*) P < 0.001	-0.371 (*) P = 0.001	-0.179 P = 0.115
Without control sub- jects	52	-0.457 (*) P = 0.001	-0.045 P = 0.75	0.093 P = 0.51	-0.285 (*) P = 0.041	-0.324 (*) P = 0.019	-0.135 P = 0.34

Table 4 Pearson correlation coeficients when comparing the proposed gait indicators and the clinical functional scales (Mazur, HSS and Harris

4. Discussion

Three indicators, symmetry, discrepancy and constancy, have been developed to express gait deviation in a population of patients with OA. We used data from force plates as they are a convenient and non invasive method of measurement. We studied a mixed population of OA patients to test the sensitivity of our gait indicators and assumed that they were more disabled than the control group. Future studies could benefit from classifications based on functional criteria, rather than on specific locomotor disabilities.

The asymmetry indicators were higher for patients with more pronounced unilateral OA (ankle and hip groups), whereas force discrepancy seemed to depend on the severity of the arthritis (higher for hip and lower for knee patients). Significant differences were found between control subjects and ankle or hip patients in temporal asymmetry and could be explained by the fact that most knee patients were bilaterally affected, whereas the ankle and hip patients were mostly unilaterally affected. Ankle and knee patients tended to spend more time per cycle in stance than hip patients and control subjects. Several authors have demonstrated that free walking velocity is a consistent indicator of overall functional status [11,12] and our results are compatible with this hypothesis. Discrepancy indicators were seen between the control and the OA group as a whole. Neither load asymmetry, nor constancy indicators showed consistent disparities. No differences could be ascertained in the constancy indicators, denoting a comparable stability in the gait pattern for all subjects measured. An opposite finding (very high FVI values) would have been expected for patients with a specific gait alteration and would benefit from further investigation.

We noticed a trend of increasing load asymmetry but reducing temporal asymmetry when patients were asked to walk faster or barefoot. Walking barefoot or at a higher pace may exacerbate pain in the OA population. In addition, force discrepancy increased in all subjects, but only significantly in the patients when they walked faster. A very significant decrease in mean stance time was seen in all subjects following each change, which would indicate an increase in cadence. This difference was more pronounced in the arthritis group reaching about 10% when barefoot (P < 0.001). Additional measurement of step length and progression speed would be required, to study the compensations taking place. Increasing cadence led to a dramatic but inconsistent increase of kinetic discrepancy in the control group (P > 0.05), though a 21% significant increase (P < 0.01)was seen in the patients. No significant modifications of the CFDI were found when subjects walked unshod. Asking the patient to walk faster may, therefore, amplify the discrepancy between his/her gait pattern and the one expected from a healthy subject more than when walking barefoot. One possible explanation for the irregular behaviour of the discrepancy indicators in control subjects, could be the method of interpolating the reference patterns, especially when the individual stance time exceeded the interpolation limits (Eq. (2)). We unexpectedly noticed a dramatic and significant decrease of the kinetic variability (FVI) of about 80% in both groups when walking barefoot (P < 0.001) which could only be attributed to a more consistent gait pattern. There may be two possible explanations for this observation: firstly many female patients wore high-heeled shoes that made their gait pattern more variable and secondly as a consequence of acclimatisation to the laboratory conditions.

We observed a significant correlation between the functional scores and the biomechanically derived gait indicators *TAI* and *CFDI*. Improved temporal symmetry and a decrease in force discrepancy were negatively correlated with OA. The correlation between clinical scores and *TAI* and *CFDI* confirms their potential usefulness as biomechanical indices of gait deviation.

A similar approach to the one proposed by ourselves has been reported by Santambrogio [13], who defined a quantitative method to measure gait deviation using statistically derived reference bands from ground reaction forces. Other authors have specified their own symmetry [14] and/or energy efficiency indicators [15] in attempting to assess gait in several different pathologies. However, our investigation focused not only on the definition of indicators but also validated the method in a control and OA population to test its potential clinical applicability.

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