# Biomechanical assessment of botulinum toxin effects in Pisa syndrome disease

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***Abstract*— Pisa syndrome is defined as a postural deviation that could occur among patients with Parkinson's disease, and it is described by a lateral flexion of the trunk (greater than 10° respect to the vertical alignment). The pathophysiology of Pisa syndrome is still not clear but different hypothesis, based on the investigation of altered posture, have been proposed involving the hyperactivity of spinal and abdominal muscles and the description of the relationship between postural control and vertical perception deficit. Different clinical solutions have been adopted and tested with experimental studies. Among them, the treatment with botulinum toxin of paraspinal muscles contributed to the reduction of muscles hyperactivity, bending angles and subjective evaluation of pain. The current research deals with the analysis of botulinum toxin effects on 13 Pisa syndrome patients. A standardized botulinum toxin treatment protocol was applied to all subjects. Subjects performed standing posture in natural and self-corrected conditions before and 1 month after the treatment. Spine kinematics, body weight distribution and muscles activations have been considered as objective biomechanical parameters for the analysis. Two healthy subjects participated to the test as control group. Results highlighted significant differences in body weight distribution for both natural (p-value=0.02) and correct (p-value=0.008) posture, with an improved symmetry after the treatment. Moreover, a significant reduction (p-value=0.002) of the modification in the contralateral muscle pattern was pointed out when assuming a correct posture. Despite the differences in kinematic posture do not highlight significant results, the investigation of several biomechanical features indicated a positive effects of botulinum treatment with potential clinical implications.**

***Keywords—Pisa syndrome, botulinum toxin, standing posture, vertical perception, kinematic spine model, EMG, biomechanics, Parkinson's disease***

## I. Introduction

Several motor and cognitive complications could occur among people with Parkinson's disease (PD), causing negative effects on patients' quality of life. These dysfunctions progressively involve speech, posture, balance and gait, causing the degradation of daily functions and movements [1]. These impairments are not always associated and regulated by the same central and peripheral mechanisms. For these reasons, gait, balance and postural disturbances may differently respond to treatments and interventions [1]. Recent studies focused on the analysis of the pathogenesis and pathophysiology of PD postural alterations [2]–[4].

Pisa syndrome (PS) is defined as a postural deformity in the coronal plane, described by a lateral flexion of the trunk greater than 10° with respect to the vertical alignment [2]. The deformity could increase during dynamic motions such as gait, but it could be sensibly reduced with passive mobilization or supine posture [5]. In some cases, the lateral bending could be associated with rotations in sagittal and transverse planes. The pathophysiology of PS is still not clear and several hypothesis have been proposed, mainly divided in central and peripheral mechanisms [5], [6]. PS might be described as a form of trunk dystonia, involving the hyperactivity of both ipsilateral and contralateral muscles, often combined with degeneration of soft tissues.

Several experimental studies on patients with PS focused on the evaluation of paraspinal lumbar (L2–L4) and thoracic (T8–T10) muscles in standing posture. Di Matteo et al. explored the pattern of muscular activation in PD patients with lateral flexion of the trunk [7]. Results depicted two main different patterns: a typical dystonic activation of ipsilateral muscles and a continuous activity in contralateral muscles. Comparable results have been obtained by Tinazzi on 13 PS patients [8]. These studies represented the first attempt of description and classification of PS pathophysiology. Moreover, these results suggest that a dystonic activity could play a crucial role in causing the bending ipsilaterally to PS and that the contralateral excessive muscle activity corresponds to a compensatory mechanism. Considering the abdominal muscles, Tassorelli et al. registered a tonic hyperactivity in abdominal oblique muscles on the homolateral side with respect to trunk flexion [9], whereas Tinazzi et al. rarely observed this occurrence [8]. Frazzitta and colleagues described the patterns of paraspinal and abdominal muscles of 60 PS patients [10]. In contrast with previous studies, results highlighted a significant hyperactivity of external oblique muscle and a symmetrical activation of paraspinal muscles. The identified differences in outcomes may be a consequence of the high variability of muscle activation across patients.

Other fundamental aspects are the cognitive processes and dysfunctions related to PS, as altered visual-spatial functions and vertical perception deficit. Several previous studies tried to investigate the relationship between postural control and cognition in PD patients [11]–[13]. Scocco and colleagues [14] tested the association of trunk inclination to an modified perception of the subjective visual vertical (SVV). Results highlighted that both PD and PS patients showed SVV deviations compared to healthy control. Nevertheless, no significant difference has been showed by

the comparison between PD and PS patients. In 2018, Huh and colleagues investigated the SVV in PS patients by monitoring of additional variables such as muscles hyperactivity and low back pain [15]. The results highlighted the independent pathogenic role of verticality misperception to PS. However, in 2019, Artusi and colleagues confirmed the presence of specific neuropsychological alterations and highlighted a correlation between PS and individual cortical cognitive deficits [16]. Due to the controversial literature results, the analysis and comprehension of the correlation between cognitive processes and the postural abnormity is still an open challenge.

In the last years, different clinical treatments have been proposed as possible solutions for PS patients, as physiotherapy, deep brain stimulation, pharmacological therapy, orthotics and botulinum toxin [6], [17]–[19]. Treatment with botulinum toxin (BT) has been proposed to reduce the excessive muscular hyperactivity. Due to the different outcomes about electromyography (EMG) of trunk muscles, previous investigations suggested the treatment of different spinal and abdominal muscles. Tassorelli et. al demonstrated the positive effects of BT treatment associated with a rehabilitation program in the improvement of static postural alignment and in the reduction of pain [9]. Patients received different BT treatment based on the preliminary measure of muscular hyperactivity. More recently, Artusi et al. combined Magnetic Resonance Imaging-, Ultrasonography- and EMG-guided approach to treat PS patients with BT [20] and observed a significant improvement in 85% of patients, with 40% average reduction in lateral flexion and 52% enhancement at the Visual Analog Score .

Although the botulinum toxin revealed to be a valid treatment, comprehensive deductions yet cannot be reported due to the lack of clarity on predictive outcomes and the heterogeneity both of muscle selection and injection technique [5]. Moreover, despite the numerous attempts of measuring and describing PS pathophysiology, a standardized biomechanical method to classify it, based on specific objective parameters, needs to be defined.

The principal aim of the current study deals with the biomechanical and objective assessment of botulinum toxin effects during standing posture in patients affected by Pisa syndrome. PS patients performed experimental tests before the treatment and after one month. Standard muscle selection and injection technique were defined and applied to all patients. In order to test the perception of lateral bending and the active contribution of patients in the correction of posture, two different conditions of standing posture (natural and self-correct) have been measured and compared. Biomechanical variables as spine kinematics, ground reaction forces and EMG activities of trunk muscles were investigated.

## II. Materials & Methods

### A. Subjects

Patients were recruited for the study based on the following inclusion criteria: diagnosed idiopathic Parkinson's disease and Pisa syndrome, absence of orthopedic comorbidity and dementia, ability of walking without any type of support. 13 subjects (8 male and 5 female) participated in the experiment after giving informed consent. Mean and standard deviation (SD) values of subjects' anthropometric and clinical data are reported in Table 1. Due to the presence of several spinal deviations between different vertebral segments, based on the principal physiological role, these lateral flexions were classified in primary and compensatory deviations. 10 patients presented the primary spinal lateral deviation on the right side and 3 patients on the left side. In addition, 9 patients presented the starting point of the primary lateral deviation at the lumbar zone (L2-L4) and 4 patients at the end of the thoracic zone (T10-T12).

Two healthy subjects (1 male: 28 years, 1.80 m, 71 kg and 1 female: 32 years, 1.70 m, 68 kg) were involved in the test to obtain reference data of biomechanical parameters.

The biomechanical investigation and the clinical treatment were performed in the so-called 'daily-On' therapeutic condition. Patients maintained their usual therapeutic scheme. The study was approved by the Local Institutional Review Board and all procedures were conformed to the Helsinki Declaration.

### B. Protocol

Tests were performed in the specialized Movement Disorders Center of "Unità Spinale Unipolare – Città della Salute e della Scienza" in Turin, Italy.

A standardized treatment with Onabotulinum toxin (2ml saline dilution) was defined and applied to all patients based on previous studies and analyses [20]. The muscles involved in the treatment were to the side of trunk deviation. Experimental tests were conducted in two different sessions: before the treatment (T0) and one month (32 ± 5 days) after the treatment (T1).

The patients were required to assume a standing posture, with each foot positioned on a separate force platform. Data were recorded during two different conditions, one trial each: 'natural' condition, in which the patient was asked to assume a posture that he perceived as comfortable and natural, and 'self-correct' condition, in which the patient was asked to voluntarily straighten the spine in a vertical posture. Each trial lasted from three to five seconds.

The healthy subjects were measured only one time. Four different trials were performed for simulating the several postural deformities: natural standing posture, standing with a trunk flexion (80°), standing with right lateral bending (45°) and standing with left lateral bending (45°).

### C. Instrumentation and kinematic model

A motion capture system based on stereophotogrammetry was used for the experimental analysis and data registration. It was composed by:

- 2 cameras Vicon VUE for video recording (1080p, 50 Hz);
- 8 infrared-cameras Vicon Bonita 10 for infrared capture (1024x1024 resolution, 100 Hz);
- 2 Kistler force plates (1000 Hz) for the detection of ground reaction forces;
- 8 wireless Pico EMG COMETA (1000 Hz) for the surface acquisition of spinal muscles activation.
- 15 passive reflective markers (diameter 14 mm) for the customized human spine kinematic model.

Passive markers were positioned on anatomical landmarks of the subject (Fig. 1A). The multi-segment spinal kinematic model was previously developed and validated on healthy subjects [21], then used in a preliminary analysis on PS patients [22].

TABLE I. PATIENTS' ANTHROPOMETRIC AND CLINICAL DATA

Mean (SD)

| *Age (years)* | *Height (m)* | *Mass (kg)* | *PD duration (years)* | *PS duration (years)* |
|---|---|---|---|---|
| 70 (9) | 1.69 (0.11) | 66 (13.99) | 10 (5) | 4 (5) |

The model divides the human spine in different rigid segments (Fig. 1B) and the evaluation of relative angles with the YXZ Euler convention. An explanation of the model development, characteristics and validation has been reported in previous studies [21], [22]. Because the healthy subjects did not present any postural deviation of the trunk, the kinematic measure was implemented only for the PS patients.

Electromyographic (EMG) probes have been positioned (Fig. 1C) on the human spine, in correspondence of the thoracic and lumbar portions of the longissimus and iliocostalis muscles, based on anatomical landmarks [23] and by palpation. Both right and left sides have been considered. These muscles have been selected because of their role in the lateral deviation of the trunk and their involvement in the treatment with botulinum toxin.

### *D. Data analysis*

Three objective parameters were considered: trunk angular kinematics, ground reaction forces and EMG signals.

Vicon Nexus pipelines were used for the markers post-processing (trajectory reconstruction and filling gaps). A customized Procalc pipeline was developed to estimate the frontal and sagittal relative angles between spinal segments [21]. Mean values were reported for each subject separately. A paired t-test (level of significance $\alpha$=0.05) was implemented to compare relative angles between T0 and T1 and between natural and correct postures.

Ground reaction forces (GRFs) on each foot were acquired and analyzed separately, to consider the different weight distribution on homolateral and contralateral sides. Inter-subjects mean and standard errors values were obtained for each side (homolateral, contralateral) and each condition (natural, correct). Differences between homolateral and contralateral sides have been obtained at T0 and T1. The normality of data distribution has been verified with the Shapiro-Wilk test ($\alpha$=0.05). A paired t-test (significance $\alpha$=0.05) was implemented to test the differences between T0 and T1, but also between natural and correct condition (p-value $\leq$ 0.05). Considering the healthy subjects, the GRFs were monitored in the three conditions to verify the symmetrical distribution of weight and any variation due to the assumed bending posture.

EMG signals were acquired at 1000 Hz. Raw signals were rectified, Butterworth low-pass filtered (2nd order, 2 Hz cutoff) and the 50 Hz component and its 4 harmonics were Notch filtered. The elaborated data were averaged along each acquisition and reported for each subject separately. Setting on each axis of an orthogonal space, the activation of one of the recorded muscles, leads to the definition of a geometrical muscle space whose dimensionality is equal to the number of recorded muscles, and each muscle vector represents the activation recorded at a particular sample time [24]. A vector, representing the mean activity of the muscles, was calculated from data collected during each trial from muscles on both homolateral and contralateral sides. The angles between the muscle vectors calculated during the natural and the correct conditions, which indicated the variation in the muscle activation of one side required to reduce the bending, were calculated at T0 and T1. The normality of their distribution has been rejected with the Shapiro-Wilk test ($\alpha$<0.05) and therefore a paired Wilcoxon signed rank test (significance $\alpha$=0.05) was implemented to test the differences between T0 and T1.

Customized Matlab® routines were developed to analyse the EMGs and GRFs signals, to obtain descriptive statistics of variables and to implement the statistical comparison.

## III. RESULTS

Results are described and discussed separating the three objective variables of investigation.

*a) Kinematics:* Fig. 2 reports the spinal kinematic results, collected from one PS patient, both in sagittal (Fig. 2A) and in coronal (Fig. 2B) planes. Angles describe the relative orientation of adiacent segments. Dark colours refer to results at T0, light colour at T1. Both natural and correct postures are depicted. No statistical significance (p-value>0.05) was pointed out by the inter-subjects comparison between T0 and T1, and between natural and correct postures.

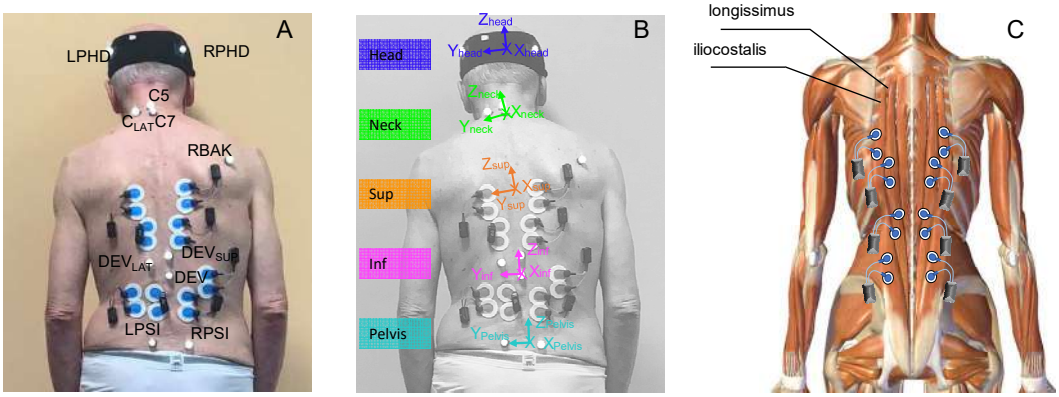



Fig. 1. (A) Markers positioning for the development of the customized multi-segments spinal model, (B) Segmentation of the trunk and head in five regions and correspondent local coordinate systems, (C) Positioning of surface EMG probes in correspondence of longissimus and iliocostalis muscles at thoracic and lumbar zones, on the right and left sides.

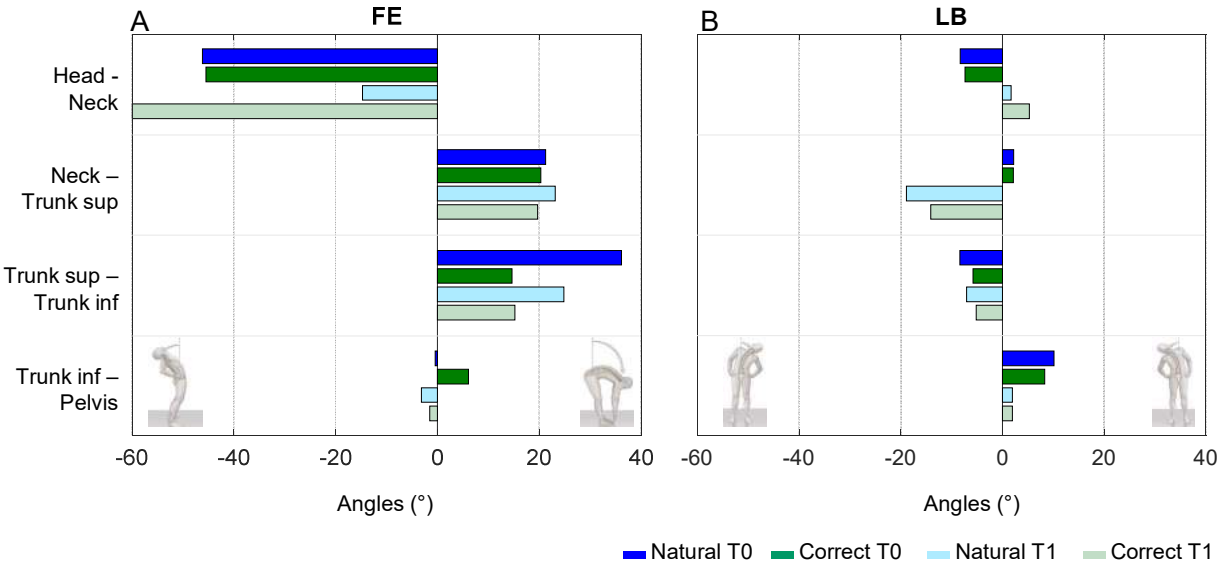
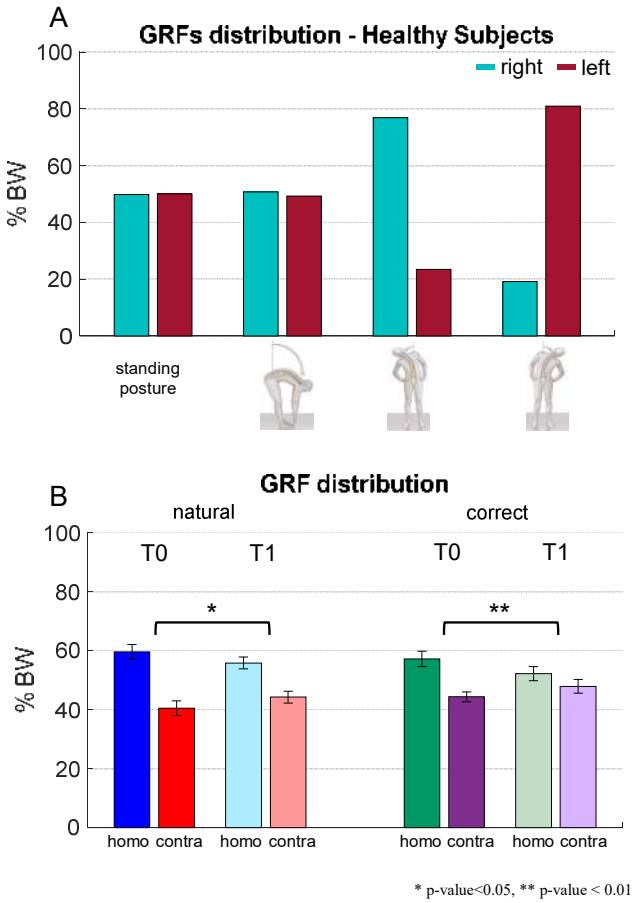



Fig. 2. Example of kinematic results of one PS patient along the sagittal (A) and coronal (B) planes during natural (blue) and corrected (green) postures at T0 (dark colors) and T1 (light colors). Relative angles have been calculated between adiacent spinal segments.

*b) Ground Reaction Forces:* Fig. 3 depicts the results of weight distribution in healthy (A) and pathological subjects (B) expressed as percentage of total body weight. Fig. 3A shows the averaged values of the two healthy subjects during the several postural tasks: standing, flexion, lateral bending on the right and left side. Green bars refer to the right foot, red bars to the left foot. The graph reveals a symmetrical distribution of weight in normal and flexed posture, while stresses the asymmetry in case of right and left side bending. Fig. 3B depicts the inter-subjects mean and standard error values separating homolateral and contralateral feet respect to the side of trunk deviation. Dark colours refer to the results at time T0, light colours to the results at time T1, both during natural and correct standing posture. The paired t-test comparing the T0 and T1 values of the differences between homo and contralateral weight distribution reveals statistical significance both in normal (p-value=0.02) and correct (p-value=0.008) positions. Nevertheless, no statistical significance was pointed out for the comparison between natural and correct positions before (p-value=0.18) and after (p-value=0.08) BT treatment.

*c) EMGs:* Fig. 4 depicts the results of angles between the muscle vectors, calculated in pathological subjects, during the normal and the correct conditions at time T0 and T1. Mean and standard error values are reported separating homolateral and contralateral muscles. Dark colours refer to T0, light colour to T1. The Wilcoxon paired signed rank test revealed a significant reduction of the modification in the muscle pattern between T0 and T1 when assuming a straighter posture from a normal posture, but only for contralateral muscles (p-value=0.002) and not for homolateral ones (p-value>0.05). These results are in line with data acquired from the healthy participants that showed an increase of the activity of the contralateral muscles (+21,2%), but not in homolateral muscles (-0.5%), during the voluntary lateral flexion with respect to the vertical standing posture.




* p-value<0.05, ** p-value < 0.01

Fig. 3. GRFs distribution: A) averaged results of GRFs in healthy subjects performing different movements (standing, flexion posture, lateral bending on the right and lateral bending on the left). B) Mean and standard errors values of GRFs distribution in PS patients separating homolateral and contralateral foot. Results are reported as % of the total body weight.

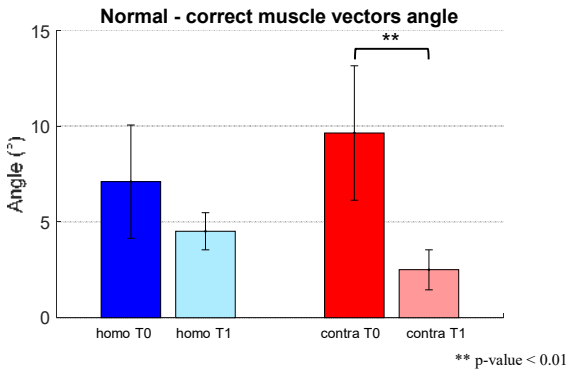



Fig. 4. EMG signals analysis represented by muscles vectors angle. Mean and standard error values are depicted with the separation between homolateral and contralateral muscles.

## IV. Discussion

The current research aimed to assess the effects of the administration of botulinum toxin in patients with Pisa syndrome by measuring biomechanical parameters before and after one month from the treatment. Patients performed standing posture in two conditions to point out any differences in vertical alignment perception and active correction of posture. Three objective parameters have been considered for the comparison and statistical analysis.

The first expected improvement is the alignment of the spine with the vertical direction, as stressed by previous literature [25]. However, the simplification of the spine as a single segment and the monitoring of angle only in the coronal plane could introduce some limitations. For this reason, a customized multi-segment model of the spine has been development, validated and tested [21], [22]. The adopted model allows to evaluate and relate the position of several upper body segments, from the head to the pelvis ones. The example reported in Fig. 2 demonstrates the reduction of anterior flexion between trunk sup and trunk inf, both in the difference between natural and correct posture (reduced flexion of 21° at T0, 10° at T1), both in the difference between T0 and T1 (reduced flexion of 11° in natural posture, negligible differences in correct posture). Considering the coronal plane and comparing results from T0 and T1, the graph shows a negligible reduction in lateral flexion between trunk superior and trunk inferior (around 1° both in natural and correct postures), greater between trunk inferior and pelvis (around 8° both in natural and correct postures). Inter-subject results reported some differences in all relative angles, but without significance. The main reason could be identified in the heterogeneity of the population. Indeed, patients presented different starting point of the lateral deviation, different contribution of rotation in sagittal and transverse planes and different progression of the PS disease. Moreover, the results pointed out a different response to BT, that could interest both the alignment between trunk superior and trunk inferior, both the alignment between trunk inferior and pelvis, and finally a different contribution from other segments for postural adjustment. For these reasons, the monitoring of only kinematics seems to be restricted.

More evident results have been pointed out by the analysis of weight distribution and EMG signals. Indeed, both outcomes show a significant difference between T0 and T1. PS patients register an asymmetrical distribution of weight during the standing posture, with greater % on the homolateral side. This result is coherent with the simulation of lateral bending performed by healthy subjects (Fig. 3A) and with previous preliminary investigation [22]. After the BT treatment, all patients revealed a significant reduction of asymmetry both in natural and corrected posture. Indeed, at T0, the difference between homolateral and contralateral sides was 20% in the natural position, 13% in the correct position. At T1, the asymmetry was of 12% in the natural and 4% in the correct position. No statistical difference was pointed out in the comparison between natural and correct conditions. However, the different values confirm the ability of patients to actively participate in the correction of vertical alignment. The reduction of asymmetrical weight distribution could positively contribute to balance, in the maintenance of standing posture for longer time and in the distribution of intersegmental joint loads at the lower limbs. This finding could also have a relevant clinical implication since it could be associated result with reduced risk of fall.

Comparable results could be highlighted from the EMG analysis. The EMG signals of spinal muscles confirm the hyperactivity already presented in previous studies [7], [8]. On the contralateral side, a significant difference was pointed out in the comparison between T0 and T1 of the required muscular activation to vertically align the spinal posture (from natural to correct posture). Moreover, the smaller standard error at T1 respect to T0 reveals a reduction of variability between patients. The absence of statistical difference in homolateral side demonstrates the negligible role of those muscles in posture correction and confirms the effect of BT treatment in reducing the muscular activity. These results are in line with data from healthy participants, which showed an increase of the muscle activity of the only contralateral muscles, with respect to a vertical standing posture.

All the biomechanical outcomes highlight altered values compared to physiological ones and depict a change after the BT treatment. Despite the standardized clinical and experimental protocols, a crucial variability in spinal posture among subjects was pointed out. Nevertheless, the benefits of BT treatment have been assessed in weight distribution and muscular activation in all the patients. The obtained results highlight the importance of measuring and relating several biomechanical variables, also in case of no variation or even worsening in the kinematic evaluation.

## V. Conclusion

In this study, the BT effects were tested in PD patients with PS receiving the same standardized treatment to iliocostalis and longissimus muscles homolaterally to the side of trunk deviation. Experimental tests were not limited to a single biomechanical variable, but different variables were taken into account to acquire a wider knowledge on the pathophysiology of PS and the effects of BT for PS.

Despite the inter-patient variability might prevent to assess the effects of the BT in terms of kinematic parameters, the other biomechanical parameters confirmed the positive outcome of the treatment. In fact, after one month from the BT administration, patients revealed a significant reduction in the asymmetry of weight

distribution and in the activity of contralateral muscles required to correct the vertical alignment, suggesting a beneficial effect of the BT treatment in reducing the pathological altered posture. Therefore, results highlighted the importance of investigating different biomechanical parameters in addition to the kinematic measure of spine alignment.

Some limitations should be pointed out. Since data and results highlighted a huge variability among subjects, a larger population should be enrolled in the study, which may lead to significant results also in terms of kinematic parameters. Moreover, only the static posture was performed by the patients. Additional dynamic movements such as gait or other daily activities could be experimentally investigated. Finally, the experimental tests have been repeated only one time after the BT treatment, assuming that the greatest effect of BT could be detected after one month. The evaluation of the biomechanical posture and dynamic movements at different time intervals might highlight different progression of BT effects. The knowledge of the patient-specific evolution after a standardized BT administration, would allow to design a more effective and long-term treatment plan for PS patients.

Future investigations will be extended to a larger population of PS patients, but also of healthy subjects for the comparison with a control group. Different static, dynamic and cognitive tasks will be performed by the subjects. Additional biomechanical and clinical parameters will be considered for more complete and transversal analysis.

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