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Gait as predictor of physical function in axial spondyloarthritis: the prospective longitudinal FOLOMI (Function, Locomotion, Measurement, Inflammation) study protocol

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Abstract

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disease affecting predominantly sacroiliac joints and axial skeleton. axSpA progression being irregular and hardly predictable, identifying functional decline is particularly important in patient with axSpA to allow delivery of timely and targeted interventions. Pain, reduced range of motion or altered posture can have adverse consequences on gait. Although gait has previously been used as a sensitive measure of physical outcomes in elderly and pathological populations, to the best of our knowledge, no study has used gait as a predictor of physical function in patients with axSpA. The objective of our study is hence to determine if gait parameters measured in patients with axSpA could predict the evaluation at 18 months of physical function as assessed by the Bath Ankylosing Spondylitis Functional Index (BASFI). This is a prospective and longitudinal study. Sixty patients with axSpA and 30 healthy age- and sex-matched controls will be included. Patients should be aged 18–65 years at time of their first evaluation, followed at Grenoble Alpes University Hospital for axSpA or ankylosing spondylitis, able to walk 180 m without technical help and with stable treatment for at least 12 months. Clinical characteristics, BASFI, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), clinical and laboratory measurements of gait will be assessed during four visits (at baseline and at months 6, 12, and 18). Similar assessments will be performed once for the healthy control group. A linear mixed model at 6, 12 and 18 months will be constructed to answer to the first objective, with the BASFI as dependent variable and gait parameters as explanatory variables. The data collection started in August 2018 and will be completed with the inclusion and follow-up of all the participants. We believe that the combination of clinical and laboratory measurements of gait in patients with axSpA could strengthen the capacity to monitor disease's evolution and to predict changes in patients' physical function. Results of the present study could ultimately allow delivering targeted, timely, personalized interventions and treatment in patients with axSpA.

Trial registration: The study was approved by local ethic committee (CPP Ile De France 1, RCB: 2017-A03468-45, date of agreement: July 17th, last version: V4.0, 2018, March 5th, 2019) and is retrospectively registered in Clinical trials (NCT03761212).

Keywords Ankylosing spondylitis · Axial spondyloarthritis · Spondylarthritis · Walking · Wearable sensors · 6-Minute Walk Test · Timed Up and Go · 10-Meter Walk Test · Instrumented gait

Abbreviations

10MWT	10-Meter Walk Test
AS	Ankylosing spondylitis
BASFI	Bath Ankylosing Spondylitis Functional Index
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
GPAQ	Global Physical Activity Questionnaire
iTUG	Instrumented Timed Up and Go
i6MWT	Instrumented 6-Minute Walk Test
IPAQ	International Physical Activity Questionnaire
SF-36	Short Form 36

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Introduction

Spondyloarthritis (SpA) is a category of inflammatory rheumatic disease with common pathophysiological features [1]. According to the Assessment of SpondyloArthritis international Society (ASAS) criteria, SpA is categorized as axial Spa (axSpA) with predominant involvement of axial skeleton, or peripheral Spa with peripheral or extra-articular manifestations such as enthesitis, uveitis, psoriasis or inflammatory bowel disease [2–4]. Radiologic [i.e., ankylosing spondylitis (AS)] and non-radiologic forms of axSpA are classically described and share common clinical and pathophysiological features [5–10]. Main clinical manifestations of axSpA can include inflammatory back pain, spinal stiffness [11, 12], with adverse consequences on work ability and productivity, quality of life and psychological well-being [13].

axSpA is marked by alternative periods of stable disease activity and flares, which contribute to the unpredictability of the disease [14]. The presence of syndesmophytes [15] or extended active sacroiliitis on MRI images [16, 17], HLA-B27 gene [16], male gender [18], elevated C-reactive protein levels [15, 19] and smoking [15] are seen as predictors of the advancement of the disease to the radiographic stage [20]. However, the natural evolution of axSpA is not fully understood [21].

Physical function of patients with axSpA is usually assessed in clinical setting with the same scale as patients with AS, namely the Bath Ankylosing Spondylitis Functional Index (BASFI) [22]. Most of patients with axSpA have impaired physical function, as assessed by a high score on the BASFI [23]. In patients with AS, physical function can be predicted with age, smoking status, or social support [24]. However, prediction of physical function in patients with axSpA still needs to be deepened, especially as it appears to be related to work productivity loss and absenteeism [25], health-related quality of life [26], or depression in patients with axSpA [27] and constitutes a major predictor of total medical costs of patients with AS [28].

Previous works have also reported altered physical function in patients with AS [24, 29], that was related to an altered gait [30–33], with more cautious pattern, more variability and decreased range of motion at hip and knee joints observed in patients with AS compared to healthy controls [31, 33, 34]. However, gait in patients with axSpA has been poorly assessed [35], without comparison of gait to an healthy control group.

We hypothesize that gait could represent a valuable marker of axSpA evolution. Besides, there is growing interest in applying gait measurement to predict physical outcomes in elderly [36–38]. For instance, gait has previously been shown to predict lower extremity limitations [37], or disability [38] in older adults. However, to the best of our knowledge, no study has used gait parameters as predictors of physical function in patients with axSpA.

Methods

Aims

The primary objective of FOLOMI (Function, Locomotion, Measurement and Inflammation) study is to determine if gait parameters measured in patients with axSpA could predict the evaluation of physical function at 18 months.

The secondary objectives are fourfold:

1. To study the relationship between gait parameters measured at baseline (T0) and the physical function as assessed by the BASFI at T0 in patients with axSpA.
2. To study the relationship between gait parameters at T0 and the disease activity score evaluated by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at T0 in patients with axSpA.
3. To assess general state of health of patients with axSpA and its evolution by appreciating: level of physical activity, state of fatigue, diurnal sleepiness and quality of life.
4. To compare gait parameters between patients with axSpA and healthy controls.

Study design

The study is a prospective and longitudinal cohort, taking place in Grenoble Alpes University Hospital, France. This study was approved by local ethics committee (CPP IDF1, RCB: 2017-A03468-45, date of agreement: July 17th, 2018) and is registered in Clinical Trials (NCT03761212). Inclusion of patients with axSpA started in August 2018 and planned to finish in August 2021. 60 patients with axSpA will be included and followed during 18 months. A healthy control group of 30 participants will be included, and age and sex matched to the 30 first patients with axSpA.

Participants

Inclusion and exclusion criteria for patients and healthy controls are displayed in Table 1.

When participants will be included, the exclusion criteria will be

- Participants who revoke his consent to the study.
- Medical state that is not compatible for the further study.
- Pregnant women.
- Protocol violation.
- Conduct of the study that is not respected.

Table 1 Inclusion and exclusion criteria for participants

Inclusion criteria	Non-inclusion criteria
Patients with axial spondyloarthritis	
Aged 18–65 years at the time of their first evaluation	Musculo-skeletal, cardio-respiratory or neurologic disease that could affect gait
axSpA (based on ASAS criteria) or AS (based on modified New York Criteria)	Hip or knee arthroplasty done or planned in the following 18 months
Able to walk 180 m without technical help	Not able to speak French
With stable treatment for 12 months	Desire of pregnancy in the following 18 months
With a public health insurance (French social security)	Adults protected by laws (Article L1121-5)
Healthy controls	
Aged 18–65 years at the time of evaluation	Musculo-skeletal, cardio-respiratory or neurologic disease that could affect gait
Able to walk 180 m without technical help	Hip or knee arthroplasty done
With a public health insurance (French social security)	Not able to speak French
	Desire of pregnancy in the following 18 months
	Adults protected by laws (Article L1121-5)

Data collected before exclusion of the participant will be used in data analysis, unless objected by the participant.

Data collection and measurements

Patients with axSpA

Patients with axSpA will be recruited by rheumatologists in consultations or day-care programs and be oriented to the physiotherapist.

After explaining the study protocol and checking inclusion and non-inclusion criteria, the physiotherapist will collect written informed consent from the patients with axSpA. Unless otherwise specified, clinical characteristics, BASFI, BASDAI, clinical and laboratory measurements of gait will be collected at study enrolment (baseline) and every 6 months during an 18-month follow-up. In other words, four sessions, T0, T6, T12 and T18, of assessment will be performed (Table 2, following SPIRIT figure).

Healthy controls

Healthy control participants will be recruited by investigators and scientific collaborators. Assessments will be conducted once. The physiotherapist will explain the study protocol, check inclusion and non-inclusion criteria and collect

Table 2 Patient assessments based on SPIRIT guidelines

Time points	Study period			
	Baseline T0 (inclusion)	6 months T6 ± 3 weeks	12 months T12 ± 3 weeks	18 months T18 ± 3 weeks
Enrolment				
Eligibility screen	X			
Information letter and written consent form	X			
Assessments				
Clinical characteristics (height, weight, medical history, treatment, disease duration and HLA-B27 status)	X	X	X	X
Disease duration and treatment	X	X	X	X
BASFI [22, 39]	X	X	X	X
BASDAI [40, 41]	X	X	X	X
Pain intensity [42] and location [43]	X	X	X	X
Gait assessments (cf Table 3)	X	X	X	X
Lower limb range of motion [44], sacroiliac pain tests [45], hand to ground distance, Schöber indexes [46]	X			X
Self-assessment questionnaires: IPAQ [47], SF-36 [48], Epworth [49] and Pichot [50], foot function index [51, 52], smoking status [53], working activity with GPAQ [54] and WPAI [55], social support [56]	X			X
Adverse events	X	X	X	X

BASFI Bath Ankylosing Spondylitis Functional Index, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *10MWT* 10-Meter Walk Test, *iTUG* instrumented Timed Up and Go, *i6MWT* instrumented 6-Minute Walk Test

Table 3 Gait assessments for patients and healthy controls

Tests	Description
1. A 10-Meter Walk Test (10MWT)	Performed at comfortable walking speed [57], in single- and dual-task conditions (three trials per condition). In the dual-task condition, participants will have to carry a full cup of water in their dominant hand with the following instruction: "perform both tasks as well as possible" [58, 59]. The physiotherapist will note whether there is any spillage of water [59]
2. An instrumented Timed Up and Go (iTUG)	Participants will be asked to stand up from a chair without the use of the arms, walk 7 m, turn around a plot, walk back and sit down on the chair without the use of the arms, as fast as possible (three trials) [60, 61]. iTUG will be performed in standardized conditions with standard chair height, their knee flexed at 100° and their feet placed symmetrically [62]
3. An instrumented 6-Minute Walk Test (i6MWT)	Performed following American Thoracic Society guidelines [63]. Participants will have to walk back and forth during 6 min, along a flat straight enclosed 30-m corridor turning around cones. Instructions given to the participants will be to "walk as far as possible for 6 min, i.e., walk the longest distance, so as fast as possible for 6 min" [63]. Every minute, standard sentences of encouragement will be provided. Number of turns will be counted to estimate the covered distance. At the beginning and the end of the i6MWT, dyspnoea, fatigue and potential other symptoms will be collected

written informed consent. The physiotherapist will collect healthy controls' clinical characteristics. As for patients with axSpA, healthy controls will have to complete gait assessments and eight self-assessment questionnaires—IPAQ, SF-36, Epworth and Pichot scales, foot function index, smoking and work status, and social support.

Gait assessments will be performed, wearing walking shoes, using six inertial measurement units with tri-axial accelerometers and gyroscopes. These wearable sensors will be placed on feet, wrists, lower back and sternum to compute gait parameters.

Sample size and power calculations

The sample size calculation was computed using the NQuery Advisor® software. Sixty subjects are necessary to detect a multiple linear relation, with a determination coefficient R^2 of 0.21 or more (low to high intensity), and a power of 80%, with alpha risk of 5% and three covariates (gait speed, stride time and stride length). To study this relationship at three different times (6, 12 and 18 months), an adjustment of alpha risk with Bonferroni correction was taken into account ($\alpha' = \alpha/3 = 0.017$).

Statistical methods

Statistics will be conducted with SPSS® software. An intermediate statistical analysis will be conducted when half of the patients will be included. Statistical analysis will be done at T0, T6, T12 and T18. If some data are missing, they will be replaced by the multiple-imputation method. To answer to the first objective, a linear mixed model at 6, 12 and 18 months will be constructed, with the BASFI as dependent variable and gait parameters as explanatory variables.

If normality is assumed, quantitative parameters will be described by mean ± standard deviation and the 95% confidence interval. Pearson correlation coefficients will be calculated between gait parameters and BASFI or BASDAI. Evolution of clinical state and gait pattern in patients with axSpA will be assessed using repeated measured analysis of variance. To compare patients with axSpA and healthy controls, bilateral *t* tests will be conducted.

Discussion

To the best of our knowledge, this prospective longitudinal study is the first to investigate if gait parameters could predict the evaluation of physical function as assessed by BASFI, at 18 months in patients with axSpA.

axSpA evolution is heterogeneous and hardly predictable as disease course is usually made of successive inflammatory flares [14]. Key predictors of axSpA evolution to the radiographic stage are gender, smoking status, or high level of CRP [15, 18, 19]. In patients with AS, better physical function can be related to higher social support, younger age and non-smoker status [24]. However, prediction of physical function still needs to be deepened especially as it appears to be part of health-related quality of life [26], depression [27], and work productivity [25].

In older adults, gait has been reported as a predictor of lower extremity limitations [37], or disability [38]. Considering decreased range of movement, pain, altered posture and feet abnormalities [52, 64, 65], previous studies have reported that AS leads to an altered gait pattern, with shorter stride length or decreased hip and knee ranges of motion compared to healthy controls [31, 33].

To determine specific axSpA consequences on gait pattern, the FOLOMI study will compare gait of patients with axSpA with healthy age- and sex-matched controls. Only few case–control studies on patients with AS have been published [31–33, 66–68] and only one has assessed gait in patients with axSpA [35]. Besides, the strength of the FOLOMI study is to combine clinical and laboratory measurements of gait during an 18-month follow-up, using material and tests applicable to clinical practice. In previous studies on patients with AS, gait was assessed either with clinical tests, i.e., TUG test [67], or 6MWT [66, 67], or with the use of 3D cameras that is hardly applicable to clinical routine [69]. Wearable inertial sensors are also able to capture different phases and features of walking pattern, such as pace, rhythm, variability or asymmetry [70], and do permit to capture gait pattern over an extended space and time, and thus in clinical practice [69, 71].

We believe that the combination of clinical and laboratory measurements of gait in patients with axSpA could strengthen the capacity to monitor disease's evolution and to predict changes in patients' physical function [72]. This could ultimately allow delivering targeted, timely, personalized interventions and/or treatment [73–77] in patients with axSpA.

Author contributions All authors have contributed to the design of this project. JS and NV wrote the manuscript and all authors read and approved this manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no proprietary, financial, professional, or other competing interests regarding this study and the publication of this paper.

Ethics approval and consent to participate The study was approved by local ethic committee (CPP IDF1, RCB: 2017-A03468-45, date of agreement: July 17th, last version: V4.0, 2018, March 5th, 2019). This study protocol is registered on ClinicalTrials.gov, with the following ID: NCT03761212 and follow the SPIRIT checklist. Written informed consent will be obtained from all participants by the physiotherapist or a medical doctor. Any modification to the initial protocol will be presented to the local ethics committee and has to be accepted before application and will be registered on ClinicalTrials.gov.

Data management Data of the participants are anonymized with a participant number. A clinical research associate, mandated by the Grenoble Alpes University Hospital, will monitor the study depending on inclusion rhythm and following a pre-prepared plan. Each monitoring will be associated with a written record. Besides, an audit or an inspection by health authorities can be conducted, independently of the sponsor and promotor, at any time to ensure research quality, result validity, and law respect.

Trial status The data collection started in August 2018 and will be completed with the inclusion and follow-up of all the participants (60 patients with axSpA and 30 healthy controls). We plan the results of this study to be presented at international oriented scientific and clinical conferences and to be published in peer-reviewed scientific journals.

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