Statistical Analysis Plan (SAP)

The Influence of Joint Hypermobility on Lumbar Biomechanical Changes in Back Pain Patients: A Weight-Bearing MRI Study

Study group:

Ingrid Thorseth, BSc.med, Cecilie Lerche Nordberg, BSc.med* Mikael Boesen†, PhD, Henning Bliddal, DMSc*, Philip Hansen, PhD†, Bjarke Brandt Hansen, PhD**

Author Information

From *The Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Denmark. †Department of Radiology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Denmark**

Corresponding author: Ingrid Thorseth, BSc.med, The Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Nordre Fasanvej 57, DK-2000 F, Denmark, E-mail: thorseth@hotmail.com; Phone: +45 5130 2505

Purpose of the statistical analysis plan (SAP)

The SAP is proposed to bring the team together on the same page, and it adds another layer of specificity to the project. The analysis plan will be available on the homepage of The Parker Institute, http://www.parkerinst.dk, after the data was collected, and before analyses will be conducted. The plan includes procedures for executing the statistical analyses of primary and secondary outcomes and other data.

Introduction

Generalised joint hypermobility is a common condition with a prevalence ranging from 2-57 %, depending on sex, age, and race [1]. Previously, joint hypermobility has been associated with arthralgia [2–5], excessive lumbar segmental motion [3], and degenerative MRI findings such as cervical disc degeneration and lumbar disc herniation [6, 7]. Also negative associations between joint hypermobility and MRI findings like spondylolisthesis and disc degeneration have been reported [8, 9]. An increased incidence of injuries has been reported in people with generalised joint hypermobility [2, 10]. This may be the same issue in the lumbar spine and may explain why degenerative changes may be more common in the lumbar spine [10, 11]. It is well-known that lumbar extension affects degenerative pathologies in the upright position [12]. Therefore, it is of interest how joint hypermobility affects dynamic changes in lumbar lordosis and sacral angle between recumbent and upright standing position. These dynamic changes can be visualised by standing, weight-bearing, magnetic resonance imaging (MRI) systems. We suspect that patients with generalised joint hypermobility and low back pain may increase significantly more in lumbar lordosis and sacral angle in the standing position, and hereby facilitate more changes in degenerative pathologies.

Objective

The objective of this study is to investigate the influence of generalised joint hypermobility, defined as a Beighton's score above 4, on biomechanical changes in the lumbar spine between supine and standing position in patients with low back pain. Our primary hypothesis is that low back pain patients with generalised joint hypermobility present a greater increase in lumbar lordosis angle and in sacral angle from supine to standing position compared to back pain patients without generalised joint hypermobility. Due to this expected increase in lumbar lordosis, our secondary hypothesis is that generalised joint hypermobility is associated with higher frequency and increased severity of 1. spondylolisthesis, 2. spinal stenosis, 3. disc herniation during standing weight-bearing MRI.

Data source

This study is based on patients recruited from the outpatient clinic of the Department of Rheumatology, Frederiksberg Hospital, Denmark and private spine surgery/rheumatology clinics in the area of Copenhagen. Patients were referred for standing weight-bearing MRI due to low back pain. Eligibility criteria were age > 18 years and low back pain with or without sciatica. Exclusion criteria were clinical scoliosis, previous spine surgery, "red flag symptoms", and risk of adverse events during weight-bearing MRI. All patients in this study were assessed for generalised joint hypermobility by Beighton's test. The study aims to test low back pain patients with generalised joint hypermobility which we define as a score ≥ 4 on Beighton's test [13–15]. These patients will be compared to low back pain patients with a Beighton score < 4.

Variables

Se tables below

Endpoints and covariates

Se tables below

Statistical Analysis

Data will be reported as descriptive statistics. For categorical data, characteristics of the participants will be described presenting binary outcomes as numbers with corresponding percentages. For continuous outcomes, data will be presented as means with corresponding standard deviations (SD), and for continuous outcomes that are not normally distributed data will be reported as medians with corresponding interquartile range (IQR).

The relation between joint hypermobility score and numerical variables will be analysed using comparative statistics e.g. t-test, while categorical variables will be analysed using chi squared test or Fischer´s exact test, if appropriate. Continuous outcomes that are not normally distributed will be analysed by Mann-Whitney *U* test. For quantitative outcomes, we will calculate reliability by inter class coefficient (ICC) with 95 % confidence interval (CI) using a two-way mixed model. Statistical significance will be set at probability values < 0,05. Data will be analysed using SPSS.

Proposed manuscript outline

Table 1: Baseline Characteristics and Patient Reported Outcomes

	Patients with GJH n =	Patients without GJH n =	Difference Between Groups (95 % CI)			*P*
Patient characteristics						
Females, No						
Age, years						
BMI, kg/m^2						
Beighton's score, points						
Modified Schober, cm						
Back pain characterisation						
Pain, current, NRS						
Pain, average last 14 days, NRS						
Pain, days/week						
Analgesic medication, unspecified, No						
Analgesic medication, opioids, No						
Self-assed risk for chronification of current back pain, NRS						
Belief: Physical activity						

aggravates my pain, No						
Belief: Physical activity might harm my back, No						
Questionnaires						
PainDETECT-Q, points						
Oswestry Disability Index, points						
Work status						
Employed/studying, No						
Sick leave, last 3 months, No						
Current social claim for compensation for back pain, No						
Self-assessed chance for being employed in 6 months, NRS						
Bio-psychosocial aspects						
General feeling of sadness, depression, or hopelessness, NRS						
Anxiety, NRS						
Loneliness, NRS						

GJH is defined by a Beighton score > 4.

BMI: Body Mass Index, CI: Confidence Interval, GJH: Generalised Joint Hypermobility, LDD: Lumbar Disc Degeneration, MD: Mean Difference, MRI: Magnetic Resonance Imaging, No: Number, NRS: Numeric Rating Scale (0-10), OR: Odds Ratio, PainDETECT -Q: PainDETECT Questionnaire, SD: Standard Deviation.

Table 2: Qualitative Data

	Patients with GJH n =	Patients without GJH n =	Difference Between Groups (95 % CI)			*P*
Transitional lumbar vertebrae, no						
Spinal stenosis, no						
Disc herniation, by Fardon*						
Protrusion						
Extrusion						
Lumbar disc degeneration (LDD) by Pfirrmann						
L1 degeneration						
L2 degeneration						
L3 degeneration						
L4 degeneration						
L5 degeneration						
LDD score						

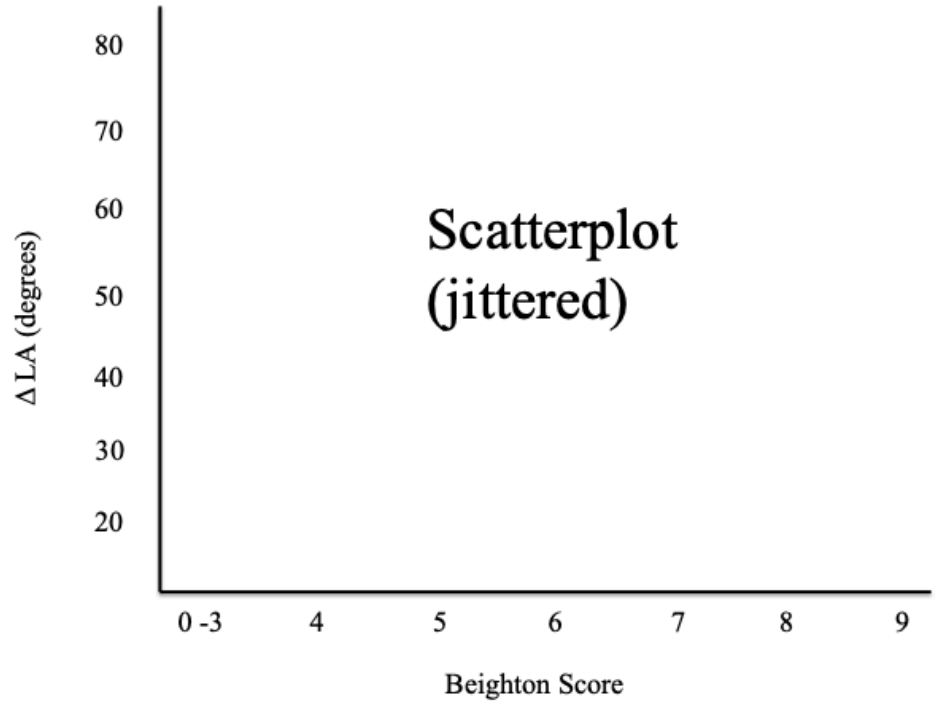
GJH is defined by a Beighton Score > 4.
* Will be based on measurements of the lumbar spine from L2/3 to L5/S1.

CI: Confidence Interval, GJH: Generalised Joint Hypermobility, LDD: Lumbar Disc Degeneration, MD: Mean Difference, MRI: Magnetic Resonance Imaging, No: Number, OR: Odds Ratio, SD: Standard Deviation.

Table 3: Quantitative Data						
	Patients with GJH n =	Patients without GJH n =	Difference Between Groups (95 % CI)			*P*
Angle measurements						
LLA, standing*						
LLA, supine*						
Δ LLA*						
SA, standing*						
SA, supine*						
Δ SA*						
Spondylolisthesis						
Anterolisthesis, standing						
Anterolisthesis, supine						
Δ Anterolisthesis						
*For LLA and SA, patients with transitional vertebras will not be included in statistic calculations. GJH: Generalised Joint Hypermobility, CI: Confidence Interval, LLA: Lumbar Lordosis Angle, SA: Sacral Angle, SD: Standard Deviation, MD: Mean Difference, No: Number OR: Odds Ratio.						

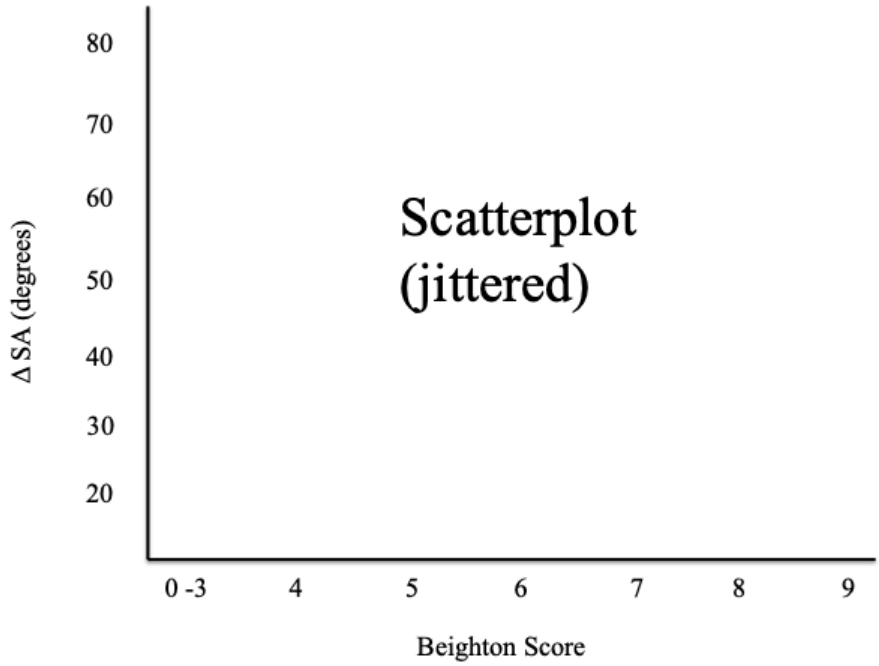
Table 4: Intraobserver Reliability of Lumbar Lordosis Angle and Sacral Angle measuement		
	ICC*	95 % CI
LLA, standing, degree		
LLA, supine degree		
SA, standing degree		
SA, supine degree		
Spondylolisthesis, standing, mm		
Spondylolisthesis, supine, mm		
*ICC using an absolute agreement definition based on 10 randomly selected images. CI: Confidence Interval, ICC: Intraclass correlation coefficients, LLA: Lumbar Lordosis Angle, SA: Sacral Angle		

Figure 1



If appropriate following illustration will be included otherwise it will be reported as supplementary. Other comparative illustrations will be included if relevant.

Figure 2



References

1. Remvig L, Jensen D V., Ward RC (2007) Epidemiology of general joint hypermobility and basis for the proposed criteria for benign joint hypermobility syndrome: Review of the literature. J Rheumatol 34:804–809. doi: 20557901

2. Murray KJ (2006) Hypermobility disorders in children and adolescents. Best Pract Res Clin Rheumatol 20:329–351. doi: 10.1016/j.berh.2005.12.003

3. Kim H-J, Yeom JS, Lee D-B, et al (2013) Association of Benign Joint Hypermobility With Spinal Segmental Motion and Its Clinical Implication in Active Young Males. Spine (Phila Pa 1976) 38:E1013–E1019. doi: 10.1097/BRS.0b013e31828ffa15

4. Scheper MC, De Vries JE, Verbunt J, Engelbert RHH (2015) Chronic pain in hypermobility syndrome and ehlers-danlos syndrome (Hypermobility type): It is a challenge. J Pain Res 8:591–601. doi: 10.2147/JPR.S64251

5. Sohrbeck-Nøhr O, Kristensen JH, Boyle E, et al (2014) Generalized joint hypermobility in

childhood is a possible risk for the development of joint pain in adolescence: a cohort study. BMC Pediatr 14:302. doi: 10.1186/s12887-014-0302-7

6. Lee SM, Oh SC, Yeom JS, et al (2016) The impact of generalized joint laxity (GJL) on the posterior neck pain, cervical disc herniation, and cervical disc degeneration in the cervical spine. Spine J 16:1453–1458. doi: 10.1016/j.spinee.2016.08.009
7. Han WJ, Kim H-B, Lee GW, et al (2015) Generalized Joint Laxity is Associated with Primary Occurrence and Treatment Outcome of Lumbar Disc Herniation. Korean J Fam Med 36:141–5. doi: 10.4082/kjfm.2015.36.3.141
8. Kim T-H, Lee H-M, Moon S-H, et al (2013) Joint Laxity Negatively Correlates With Lumbar Disc Degeneration in Young Adults. Spine (Phila Pa 1976) 38:E1541–E1547. doi: 10.1097/BRS.0b013e3182a595f3
9. Bird HA, Eastmond CJ, Hudson A, Wright V (1980) Is generalized joint laxity a factor in spondylolisthesis? Scand J Rheumatol 9:203–205. doi: 10.3109/03009748009112347
10. Pacey V, Nicholson L, Adams R, et al (2010) A Systematic Review With Meta-Analysis: Generalized Joint Hypermobility and Risk of Lower Limb Joint Injury During Sport. Am J Sport Med 38:1487–1497. doi: 10.1177/0363546510364838
11. Kirkaldy-Willis WH, Farfan H. (1982) Instability of the Lumbar Spine. Clin Orthop relatied Res 165:110–123.
12. Hansen BB, Bendix T, Grindsted J, et al (2015) Effect of Lumbar Disc Degeneration and Low-Back Pain on the Lumbar Lordosis in Supine and Standing. Spine (Phila Pa 1976) 40:1690–1696. doi: 10.1097/BRS.0000000000001120
13. Beighton P, Solomon L, Soskolne CL (1973) Articular mobility in an African population. Ann Rheum Dis 32:413–418. doi: 10.1136/ard.32.5.413
14. Grahame R, Bird HA, Child AH (2000) The Revised (Brighton 1998) Criteria for the

diagnosis of Benign Joint Hypermobility Syndrome (BJHS).pdf. J Reum 27:1777–9.

15. Juul-Kristensen B, Røgind H, Jensen D V., Remvig L (2007) Inter-examiner reproducibility of tests and criteria for generalized joint hypermobility and benign joint hypermobility syndrome. Rheumatology 46:1835–1841. doi: 10.1093/rheumatology/kem290