Title: Identifying muscle function-based phenotypes associated with radiographic progression of secondary hip osteoarthritis: A prospective cohort study

Abstract

Objective: The purposes of our study were to (1) identify muscle function-based clinical phenotypes in patients with hip osteoarthritis (OA) and (2) determine the association between those phenotypes and radiographic progression of hip OA.

Design: Prospective cohort study.

Setting: Clinical biomechanics laboratory of a university.

Participants: Fifty female patients with mild-to-moderate secondary hip OA were recruited from the orthopaedic department of a single institution.

Interventions: Not applicable.

Main Outcome Measures: Two-step cluster analyses were performed to classify the patients, using hip flexion, extension, abduction, and external/internal rotation muscle strength (cluster analysis 1); relative hip muscle strength to total hip strength (i.e., hip muscle strength balance; cluster analysis 2); and both hip muscle strength and muscle strength balance (cluster analysis 3) as variables. The association between the phenotype and hip OA progression over 12 months (indicated by joint space width [JSW] >0.5mm) was investigated by logistic regression analyses. Hip joint morphology, hip pain, gait speed, physical activity, Harris hip score, and SF-36 scores were compared between the phenotypes.

Results: Radiographic progression of hip OA was observed in 42% of the patients. The patients were classified into two phenotypes in each of the three cluster analyses. The solution in cluster analyses 1 and 3 was similar, and high-function and low-function phenotypes were identified; however, no association was found between the phenotypes and hip OA progression. The phenotype 2-1 (high-risk phenotype) extracted in cluster analysis 2, which had relative muscle weakness in hip flexion and internal rotation, was associated with subsequent hip OA progression, even after adjusting for age and minimum JSW at baseline (adjusted odds ratio [95% confidence interval], 3.60 [1.07–12.05]; $p = 0.039$).

Conclusion: As preliminary findings, the phenotype based on hip muscle strength balance, rather than hip muscle strength, may be associated with hip OA progression.
(297 words)

Keywords: Osteoarthritis, Muscle Strength, Phenotype, Cluster analysis, Disease Progression

List of abbreviations:

AHI; acetabular head index

ARO; acetabular roof obliquity

BMI; body mass index

CE; center edge

HHS; Harris hip score

ICC; intraclass correlation

JSW; joint space width

MDC_{95}; minimal detectable change at 95% confidence level

OA; osteoarthritis

SEM; standard error of the measurement

Introduction

Joint stability is achieved by a combination of static and dynamic stabilizers[1], and muscle force plays a leading role as a dynamic stabilizer[2,3]. Muscle weakness causes a decrease in the muscle force available for joint stability during weight-bearing activities, subsequently, leading to a limp, such as Trendelenburg gait[4]. Furthermore, because muscle forces provide compression of the femoral head into the acetabular concavity, a decrease in hip muscle forces can cause microinstability of the hip joint[3]. Muscle strength is more important in patients with acetabular dysplasia or borderline dysplasia, a precursor to hip osteoarthritis (OA), who are susceptible to microinstability due to insufficient static stabilizers and bone deformation[5,6].

Muscle weakness is major impairment in patients with hip OA, along with joint pain and limited range of joint motion. Hip muscle strength is reduced by about 20% in patients with hip OA on the affected side compared to healthy individuals or the contralateral side[7]. Even patients with mild-to-moderate hip OA and acetabular dysplasia have been reported to have reduced hip muscle strength, especially in flexion, extension, and abduction[8,9]. Hip muscle weakness in such patients, who depend more on dynamic than static stabilizers, may cause worsening joint instability and, therefore, progression of hip OA.

While muscle weakness is common in patients with hip OA, heterogeneity of muscle weakness is also known[7]. This heterogeneity includes individual differences among patients and differences in hip muscle strength in different directions in the same patient. This evidence suggests that clinical phenotypes in hip OA based on muscle function exist; for instance, patients who have overall decreased hip muscle strength and patients who have decreased specific muscle strength, such as in hip flexion and abduction. Given that the force of each hip muscle can affect the magnitude and direction of the hip contact force[10,11] and contributes to the stability of the femoral head against the acetabulum[2,3], imbalance of the hip muscle forces may exacerbate hip microinstability and hip OA. Standing posture, gait-related kinematic/kinetic features, and spinal flexibility have been reported as modifiable risk factors for the progression of hip OA[12–14].

However, no study has demonstrated the phenotypes based on muscle function, and their association with radiographic progression of hip OA, despite hip muscle strength being recommended as a core domain for clinical assessment and clinical trials in patients with hip OA[15,16]. Since muscle strength is generally measured and readily assessed by clinicians, it is clinically important to clarify the muscle function-related risk factors that lead to hip OA progression. Understanding the potentially-modifiable variables associated with hip OA progression could inform future options for targeted rehabilitation.

The aims of our study were to (1) identify muscle function-based clinical phenotypes in patients with hip OA and (2) determine the association between those phenotypes and radiographic progression of hip OA. We hypothesized that phenotypes based on muscle strength balance are more strongly associated with hip OA progression than phenotypes based on muscle strength.

Methods

Participants

Patients were recruited continuously from April 2013 to March 2015 from the orthopaedic department of a single institution. The inclusion criteria were as follows: (1) diagnosis of pre-osteoarthritis (acetabular dysplasia defined by hip pain, a lateral center edge (CE) angle <25°, and a Sharp angle >45° with no other abnormal radiographic findings), early hip OA (slight joint space narrowing and abnormal subchondral sclerosis), or advanced hip OA (marked joint space narrowing with or without cysts or sclerosis); and (2) ability to walk without any assistive device. The exclusion criteria were as follows: (1) baseline joint space width (JSW) <0.5 mm (a reduction in JSW >0.5 mm was defined as disease progression); (2) previous hip surgery; and (3) other conditions such as orthopedic diseases of joints other than the hip joint or neurological diseases that affect activities of daily living. In patients with bilateral hip OA, the side on which the radiographic OA change was more severe was used as the affected side for analysis. The candidate pool was

sex-biased (males, 7.1%), similar to previous studies[17–19]. Only female patients were included in the study due to the difficulty of considering the effect of sex in subsequent analyses. The analysis in this study was performed using the same cohort as in a previous study[12]. All participants provided informed consent, and the study protocol was approved by the institutional ethics committee.

Radiographic assessment of hip OA progression and hip morphology

Hip OA progression was assessed by changes in JSW on digital supine anteroposterior pelvic radiographs taken at baseline and 12 months later. A single experienced examiner measured JSW, using Centricity Enterprise Web, version 3.0[a]. In addition to blinding the patient's name on the radiograph, the radiographs at baseline and 12 months later were randomly arranged for each patient to blind the sequence, according to blinding radiographs recommendations, to determine the structural progression[20]. Minimum JSW was defined as the lowest JSW value of the three or four measurements (see Appendix 1)[21], and radiographic progression of hip OA was defined as JSW reduction >0.5 mm at any of the locations[20,22].

Hip morphology, Sharp angle, CE angle, acetabular head index (AHI), and acetabular roof obliquity (ARO) were measured on the same image on which JSW was measured at baseline (see Appendix 1).

Hip muscle strength assessment

Isometric muscle strength for hip flexion, extension, abduction, external rotation, and internal rotation was measured at baseline using a handheld dynamometer[b] based on previous studies[23,24]. These five muscle strengths were selected because they are required to exert muscle force during daily activities[25–27] and these muscle weaknesses have been shown in patients with hip OA[7]. Hip muscle strength assessment details are reported in Appendix 2. Hip muscle strength balance was expressed as a percentage of the sum of all hip muscle strength values after each muscle strength value was converted to T-value.

88

89 Hip pain and physical function

90

91 Hip pain at baseline during daily life was assessed using a 100-mm visual analog scale. Gait speed
92 (meters/second) was measured three times during natural walking at the patient's preferred speed
93 on a 7-m walkway, and the mean value was used. The daily physical activity was recorded using a
94 pedometer[c] with validated accuracy[28,29] for seven consecutive days at baseline, the participants
95 returned their records by mail. The mean value of 7 days was used for subsequent analysis. Harris
96 Hip Score (HHS) was recorded to assess the functional status of the patients with hip OA[30]. HHS
97 includes pain, function, absence of deformity, and range of motion items and has a maximum of
98 100 points (best possible outcome). In addition, the physical component summary scale and mental
99 component summary scale scores of SF-36 were used as generic measurement tools to assess health
100 status[31]. These scores were calculated as deviation scores (national standard score: 50), with higher
101 scores representing better health. At baseline measurements, participants were instructed to
102 continue with their current lifestyle and physical activity, and when interviewed after 12 months, no
103 significant changes in lifestyle and physical activity were observed in any of the participants.

104

105 Statistical analysis

106

107 Two-step cluster analysis was used to determine the optimum number of clusters. This clustering
108 method has some advantages over more traditional clustering methods, especially in terms of
109 statistically determining the number of clusters based on a predefined criterion, and is a highly
110 reliable solution[32,33]. Euclidean distance measure was used for distance measurement and Akaike's
111 information criterion was used to identify the optimal number of clusters. The clustering procedure
112 was conducted separately for three datasets: muscle strength variables (cluster analysis 1), muscle
113 strength balance variables (cluster analysis 2), and muscle strength and muscle strength balance
114 variables (cluster analysis 3). The overall goodness of fit of the clustering solution was evaluated
115 using a Silhouette measure. Silhouette measure <0.20 indicated poor solution quality; a measure
116 0.20–0.50, a fair solution; and a measure >0.50, a good solution[32].

To test the stability of the given solution, additional cluster analyses were performed using the following two methods[32]. First, a two-step cluster analysis was repeated using 10 different datasets with random case order. Second, other clustering procedures –hierarchical agglomerative clustering with Ward's method and Euclidean distance measure and k-means clustering with Euclidean distance measure– were performed on the same dataset.

To assess the association between identified phenotypes and the likelihood hip OA progression, univariable logistic regression analysis was performed with radiographic progression (yes/no) as the dependent variable and phenotypes as independent variables. Multivariable logistic regression adjusted for age and minimum JSW at baseline, which can be confounders[34,35], was also performed. We performed a series of Student's *t-tests* on all measurement variables to understand the differences in the profiles of each phenotype. The bootstrap method with 1,000 replicates was employed for logistic regression analysis and comparison of variables between phenotypes. *P* value <0.05 was considered statistically significant. SPSS version 26.0[d] and XLSTAT (Microsoft Excel add-in) [e] were used for statistical analysis.

Results

General profile of the study cohort

The flowchart of this cohort study is shown in Figure 1. Follow-up data were not available for three participants due to scheduling conflicts. The 50 participants' profiles are listed in Table 1. The ages of the patients ranged from 22 to 65 years. Twenty-one patients (42.0%) demonstrated hip OA progression on radiographic evaluation 12 months later.

Phenotype identification and profiles of each phenotype

Cluster analysis 1

The solution of the cluster analysis 1, which included only the muscle strength variables, showed two phenotypes (phenotypes 1-1 and 1-2). The silhouette coefficient was 0.5, which represented fair solution quality, and was considered acceptable clustering[32]. As shown in Figure 2, the importance of the variables related to model estimation tended to decrease from external rotation to internal rotation. Repeated cluster analysis of 10 datasets with different case orders and other clustering procedures retained the same solution, thus ensuring the stability of the solution.

In the univariable and multivariable logistic regression analyses, there was no association between the phenotypes and risk of hip OA progression (Table 2). Compared with phenotype 1-2, phenotype 1-1 showed weaker hip muscle strength (Figure 3), higher body mass index (BMI), worse hip pain, slower gait speed, less physical activity, and lower HHS (Table 3); thus, phenotype 1-1 and 1-2 were characterized as "low-function" and "high-function" phenotypes, respectively.

Cluster analysis 2

The patients were classified into two phenotypes (phenotypes 2-1 and 2-2). The silhouette coefficient was 0.5. The solution remained unchanged after 10 additional clustering on 10 datasets with different case orders, and the other clustering procedures also produced a similar solution for the characteristics of the clustering variables in each cluster (hierarchical clustering, size ratio = 1.38 [29/21]; k-means clustering, size ratio = 1.17 [27/23]). Because each phenotype profile and size ratio were similar in other clustering methods, clustering stability was ensured.

The phenotype 2-1 was associated with radiographic progression of hip OA, and the association remained even after adjustment for age and minimum JSW at baseline (Table 2); thus, phenotype 2-1 was characterized as a "high-risk" phenotype for hip OA progression. Phenotype 2-1 showed muscle strength balance with relatively lower hip flexion and internal rotation (Figure 3), as well as stronger hip abduction muscle strength than phenotype 2-2 (Table 3).

Cluster analysis 3

Cluster analysis 3 also presented a solution with two phenotypes (phenotypes 3-1 and 3-2). The silhouette coefficient was 0.3. The relative importance of the variables for model estimation was generally higher for muscle strength variables than that for muscle strength balance variables (Figure 2). In the stability test, 10 additional two-step cluster analyses remained in the same solution. Since the size ratios were slightly different in the other clustering procedures (hierarchical clustering, size ratio = 1.00 [25/25]; k-means clustering, size ratio = 1.63 [31/19]), cluster analysis 3 might be interpreted as slightly less stable than cluster analyses 1 and 2.

No association was found between the phenotypes and the risk of hip OA progression (Table 2). Similar to the results of cluster analysis 1, compared with phenotype 3-2 (high-function phenotype), phenotype 3-1 (low-function phenotype) showed weaker hip muscle strength (Figure 3), higher BMI, worse hip pain, slower gait speed, and lower HHS (Table 3).

Discussion

This study aimed to identify muscle function-based clinical phenotypes in patients with hip OA and to determine their association with the radiographic progression of the disease. Consistent with our hypothesis, we found that a phenotype based on muscle strength balance, rather than muscle strength, was associated with radiographic progression of hip OA over 12 months. This study showed that relative muscle weakness of hip flexion and internal rotation can be a risk factor for hip OA progression.

The data-driven cluster analysis extracted two distinct clinical phenotypes. Although previous studies have investigated the clustering of patients with hip OA based on various variables–such as genes and biochemical markers[36–39], systemic predisposition to

chondrocalcinosis[40], proximal femoral canal shape[41], JSW narrowing trajectory[42], radiographic grade and measures of mental health[43], motive profiles[44], movement behavior[45], gait kinematics[46], and comorbid symptoms[47]–the relationship between phenotypes and the risk of hip OA progression has not been investigated. Regarding the relative importance in the cluster analysis (Figure 2), cluster analysis 1 –using muscle strength– and cluster analysis 3 –using both muscle strength and muscle strength balance– presented nearly identical solutions because the classification was mainly based on muscle strength in cluster analysis 3. The patients with hip OA could be divided into the low-function phenotype (phenotypes 1-1 and 3-1) and the high-function phenotype (phenotypes 1-2 and 3-2). The "low-function" phenotype had lower general hip muscle strength with higher BMI and worse hip pain, resulting in less physical function. These findings support the reported heterogeneity of muscle function in patients with hip OA[7]. More importantly, clustering based on muscle strength balance (cluster analysis 2) identified a high-risk phenotype (phenotype 2-1) associated with hip OA progression although the confidence interval was wide and its lower bound was close to 1, suggesting a weak association. This finding indicates that impaired muscle strength balance is more important than overall and homogeneous muscle weakness in the context of the risk of hip OA progression. The high-risk phenotype in cluster analysis 2, which had relatively weaker hip flexion and internal rotation and relatively stronger hip extension and abduction, was more likely to develop hip OA than phenotype 2-2 with an odds ratio of 3.60. Since the relative changes in individual hip muscle strength can have a significant impact on changes in the magnitude and direction of hip contact force[10,11], consideration of hip muscle strength balance is important in assessing the risk of and preventing hip OA progression.

The association between high-risk phenotype (phenotype 2-1) with muscle strength imbalance and radiographic progression of hip OA may be due to the structural features of the hip joint and the microinstability's direction. The anterior hip joint has a smaller coverage with the acetabulum than the posterior, and displacement of the femoral head tends to increase anteriorly and inferiorly, as in acetabular dysplasia and tears of labrum and capsular ligament[48–50]. Musculoskeletal modeling simulation has revealed that a reduced force of the iliopsoas muscle, which is a main hip flexor, increases the anterior and resultant hip contact force during hip flexion[51].

Furthermore, the combined role of static and dynamic stabilizers, that is, joint stabilization through adhesion between the muscle and capsular ligament, has been presumed[52]. The anterior part of the gluteus minimus, iliocapsularis, and reflected head of the rectus femoris partially adhere to the capsular ligament, and this unique structure may contribute to anterior hip stabilization by increasing the tension of the anterior capsular ligament due to contraction of these muscles[52]. Their muscle weakness and the associated muscle imbalance around the hip joint may result in inadequate functioning of the stabilization mechanisms, and subsequently, progression of hip OA. Isometric muscle strength, which was measured in this study, is the most clinically available measure of muscle function. Based on our results, larger, longer-term longitudinal and intervention studies, are needed to clarify the relationship between muscle function and disease progression in patients with hip OA. Subsequently, this evidence may contribute to prevention of disease progression.

Study limitations

Several limitations should be considered. The small number of participants, consisting only of female patients with mild to moderate hip OA who are relatively well functioning, could limit the generalizability of our findings. The muscle strength measured was the sum of the exerted forces of some muscles; therefore, the muscle force of each muscle was not measured. Some specific hip muscles, such as the gluteus minimum, have been reported to be atrophied in unilateral hip OA; however, there is also heterogeneity in the changes in individual muscle sizes[53]. Further research is required to investigate the relationship between individual muscle forces and hip OA progression. Muscle strength was measured using isometric contraction. Different clustering solutions can be obtained using muscle strength values obtained by concentric or eccentric contraction. However, such differences in measurement protocols may not have a discernible effect on the findings[7]. Isometric muscle strength is easily assessable in clinical settings; thus, the findings of this study will be useful for clinicians to develop strategies for the prevention of hip OA progression. We calculated the odds ratio in the logistic regression analysis; however, odds ratio can under- or overestimate the relative risk if the modeled event is not rare[54]. Finally, a relatively

short follow-up duration was employed, although the 12-month follow-up met the minimum requirements for generating valid and informative prognostic variables for hip OA[55]. A longer follow-up may establish a stronger relationship between hip muscle function and hip OA progression.

Conclusions

The cluster analysis 1 and 3, which included only hip muscle strength and hip muscle strength and muscle strength balance, respectively, classified low-function and high-function phenotypes. Moreover, as preliminary findings, we identified a high-risk phenotype associated with radiographic progression of hip OA in cluster analysis 2, which based on muscle strength balance alone. The high-risk phenotype had relatively weaker hip flexion and internal rotation and relatively greater hip extension and abduction than the other phenotype. Hip muscle strength balance should therefore be considered in clinical evaluation and treatment strategy development for the prevention of hip OA progression.

(2997 words)

Suppliers:

a, GE Health care, Nightingales Lane, Chalfont Street Giles, Buckinghamshire, HP8 4SP, England

b, μ-TAS F-1, Anima Co., Ltd, Tokyo, Japan

c, EX-500, Yamasa Tokei Co., Ltd, 2-4-9, Kaminoge, Setagaya-ku, Tokyo, Japan

d, IBM Japan Ltd, 19-21, Nihonbashi, Hakozaki-cho, Chuo-ku, Tokyo, Japan

e, Mindware Inc, 1-4, Ekimotomachi, Kita-ku, Okayama, Japan

References

1. Domb BG, Philippon MJ, Giordano BD. Arthroscopic capsulotomy, capsular repair, and capsular plication of the hip: Relation to traumatic instability. Arthroscopy 2013;29:162–73. https://doi.org/10.1016/j.arthro.2012.04.057
2. Bolia I, Chahla J, Locks R, Briggs K, Philippon MJ. Microinstability of the hip: A previous unrecognized pathology. Muscles Ligamants Tendons J 2016;6:354–60. https://doi: 10.11138/mltj/2016.6.3.354
3. Safran MR. Microinstability of the hip. Gaining acceptance. J Am Acad Orthop Surg 2019;27:12–22. https://doi.org/10.5435/JAAOS-D-17-00664
4. Trendelenburg F. Trendelenburg's test: 1895. Clin Orthop Relat Res 1998;355:3–7.
5. Woodward RM, Vesey RM, Bacon CJ, White SG, Brick MJ, Blankenbaker DG. Microinstability of the hip: A systematic review of the imaging findings. Skeletal Radiol 2020;49:1903–19. https://doi.org/10.1016/j.otsr.2016.09.002
6. Curtis DM, Murray IR, Money AJ, Pullen WM, Safran MR. Hip microinstability: Understanding a newly defined hip pathology in young athletes. Arthroscopy 2022;38:211–3. https://doi.org/10.1016/j.arthro.2021.12.001
7. Loureiro A, Mills PM, Barrett RS. Muscle weakness in hip osteoarthritis: A systematic review. Arthritis Care Res 2013;65:340–52. https://doi.org/10.1002/acr.21806
8. Loureiro A, Constantinou M, Diamond LE, Beck B, Barrett R. Individuals with mild-to-moderate hip osteoarthritis have lower limb muscle strength and volume deficits. BMC Muscloskeletal Disord 2018;19:303. https://doi.org/10.1186/s12891-018-2230-4
9. Jacobsen JS, Jacobsen SS, Søballe K, Hölmich P, Thorborg K. Isometric hip strength impairments in patients with hip dysplasia are improved but not normalized 1 year after preiacetabular osteotomy: A cohort study of 82 patients. Acta Orthop 2021;92:285–91. https://doi.org/10.1080/17453674.2020.1864911
10. Correa TA, Crossley KM, Kim HJ, Pandy MG. Contributions of individual muscles to hip joint contact force in normal walking. J Biomech 2010;43:1618–22. https://doi.org/10.1016/j.jbiomech.2010.06.036
11. Skalshøi O, Iversen CH, Nielsen DB, Jacobsen J, Mechlenburg I, Søballe K, et al. Walking patterns and hip contact forces in patients with hip dysplasia. Gait Posture 2015;42:529–33.

https://doi.org/10.1016/j.gaitpost.2015.08.008
12. Tateuchi H, Koyama Y, Akiyama H, Goto K, So K, Kuroda Y, et al. Daily cumulative hip moment is associated with radiographic progression of secondary hip osteoarthritis. Osteoarthritis Cartilage 2017;25:1291–8. https://doi.org/10.1016/j.joca.2017.02.796
13. Kumar D, Wyatt C, Lee S, Okazaki N, Chiba K, Link TM, et al. Sagittal plane walking patterns are related to MRI changes over 18-months in people with and without mild-moderate hip osteoarthritis. J Orthop Res 2018;36(5):1472e7. https://doi.org/10.1002/jor.23763
14. Tateuchi H, Akiyama H, Goto K, So K, Kuroda Y, Ichihashi N. Sagittal alignment and mobility of the thoracolumbar spine are associated with radiographic progression of secondary hip osteoarthritis. Osteoarthritis Cartilage 2018;26:397–404. https://doi.org/10.1016/j.joca.2017.12.005
15. Dobson F, Choi YM, Hall M, Hinman RS. Clinimetric properties of observer-assessed impairment tests used to evaluate hip and groin impairments: A systematic review. Arthritis Care Res 2012;64:1565–75. https://doi.org/10.1002/acr.21707
16. Smith TO, Hawker GA, Hunter DJ, March LM, Boers M, Shea BJ, et al. The OMERACT-OARSI core domain set for measurement in clinical trials of hip and/or knee osteoarthritis. J Rheumatol 2019;46:981–9. https://doi.org/10.3899/jrheum.181194
17. Aoki H, Nagao Y, Ishii S, Masuda T, Beppu M. Acetabular and proximal femoral alignment in patients with osteoarthritis of the dysplasic hip and its influence on the progression of disease. J Bone Joint Surg Br 2010;92-B:1703–9. https://doi.org/10.1302/0301-620X.92B12.23446
18. Nakamura J, Oinuma K, Ohtori S, Watanabe A, Shigemura T, Sasho T, et al. Distribution of hip pain in osteoarthritis patients secondary to developmental dysplasia of the hip. Mod Rheumatol 2013;23:119–24. https://doi.org/10.1007/s10165-012-0638-5
19. Okano K, Takaki M, Okazaki N, Shindo H. Bilateral incidence and severity of acetabular dysplasia of the hip. J Orthop Sci 2008;13:401–4. https://doi.org/10.1007/s00776-008-1252-4
20. Altman RD, Bloch DA, Dougados M, Hochberg M, Lohmander S, Pavelka K, et al. Measurement of structural progression in osteoarthritis of the hip: the Barcelona consensus group. Osteoarthritis Cartilage 2004;12:512–24. https://doi.org/10.1016/j.joca.2004.04.004
21. Jacobsen S, Sonne-Holm S. Hip dysplasia: a significant risk factor for the development of hip

osteoarthritis. A cross-sectional survey. Rheumatology 2005;44:211–8. https://doi.org/10.1093/rheumtology/keh436

22. Ornetti P, Brand K, Hellio-Le Graverand MP, Hochberg M, Hunter DJ, Kloppenburg M, et al. OARSI-OMERACT definition of relevant radiological progression in hip/knee osteoarthritis. Osteoarthritis Cartilage 2009;17:856–63. https://doi.org/10.1016/j.joca.2009.01.007
23. Pua YH, Wrigley TW, Cowan SM, Bennell KL. Intrarater test-retest reliability of hip range of motion and hip muscle strength measurements in person with hip osteoarthritis. Arch Phys Med Rehabil 2008;89:1146–54. https://doi.org/10.1016/j.apmr.2007.10.028
24. Bieler T, Magnusson SP, Kjaer M, Beyer N. Intra-rater reliability and agreement of muscle strength, power and functional performance measures in patients with hip osteoarthritis. J Rehabil Med 2014;46:997–1005. https://doi.org/10.2340/16501977-1864
25. Eitzen I, Fernandes L, Nordsletten L, Snyder-Mackler L, Risberg MA. Weight-bearing asymmetries during sit-to-stand in patients with mild-to-moderate hip osteoarthritis. Gait Posture 2014;39:683–8. https://doi.org/10.1016/j.gaitpost.2013.09.010
26. Zeni J Jr, Pozzi F, Abujaber S, Miller L. Relationship between physical impairments and movement patterns during gait in patients with end-stage hip osteoarthritis. J Orthop Res 2015;33:382–9. https://doi.org/10.1002/jor.22772
27. Meyer CA, Corten K, Fieuws S, Deschamps K, Monari D, Wesseling M, et al. Evaluation of stair motion contributions to new insights into hip osteoarthritis-related motion pathomechanics. J Orthop Res 2016;34:187–96. https://doi.org/10.1002/jor.22990
28. Crouter SE, Schneider PL, Karabulut M, Bassett Jr DR. Validity of 10 electronic pedometers for measuring steps, distance, and energy cost. Med Sci Sports Exerc 2003;35:1455–60. https://doi.org/10.1249/01.MSS.0000078932.61440.A2
29. Schneider PL, Crouter SE, Bassett Jr DR. Pedometer measures of free-living physical activity: comparison of 13 models. Med Sci Sports Exerc 2004;36:331–5. https://doi.org/10.1249/01.MSS.0000113486.60548.E9
30. Harris WH. Traumatic arthritis of the hip after dislocation and acetabular fractures: treatment by mold arthroplasty. An end-result study using a new method of result evaluation. J Bone Joint Surg Am 1969;51:737–55.

31. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473–83.
32. Mooi E, Sarstedt M. Cluster analysis. A concise guide to market research. Springer, Berlin, 2011.
33. Benassi M, Garofalo S, Ambrosini F, et al. Using two-step cluster analysis and latent class cluster analysis to classify the cognitive heterogeneity of cross-diagnostic psychiatric inpatients. Front Psychol 2020;11:1085. https://doi.org/10.3389/fpsyg.2020.01085
34. Bierma-Zeinstra SM, Koes BW. Risk factors and prognostic factors of hip and knee osteoarthritis. Nat Clin Pract Rheumatol 2007;3:78–85. https://doi.org/10.1038/ncprheum0423
35. Zacharias A, Pizzari T, English DJ, Kapakoulakis T, Green RA. Hip abductor muscle volume in hip osteoarthritis and matched controls. Osteoarthritis Cartilage 2016;24:1727–35. https://doi.org/10.1016/j.joca.2016.05.002
36. van Spil WE, Jansen NWD, Bijlsma JWJ, Reijman M, DeGroot J, Welsing PMJ, et al. Cluster within a wide spectrum of biochemical markers for osteoarthritis: data from VHECK, a large cohort of individuals with very early symptomatic osteoarthritis. Osteoarthritis Cartilage 2012;20:745–54. https://doi.org/10.1016/j.joca.2012.04.004
37. Juchtmans N, Dhollander AA, Coudenys J, Audenaert EA, Pattyn C, Lambrecht S, et al. Distinct dysregulation of the small leucine-rich repeat protein family in osteoarthritic acetabular labrum compared to articular cartilage. Arthritis Rheum 2015;67:435–41. https://doi.org/10.1002/art.38930
38. Coutinho de Almeida R, Mahfouz A, Mei H, Houtman E, den Hollander W, Soul J, et al. Identification and characterization of two consistent osteoarthritis subtypes by transcriptome and clinical data integration. Rheumatol 2021;60:1166–75. https://doi.org/10.1093/rheumatology/keaa391
39. Tuerlings M, van Hoolwerff M, Houtman E, Suchiman EHED, Lakenberg N, Mei H, et al. RNA Sequencing Reveals Interacting Key Determinants of Osteoarthritis Acting in Subchondral Bone and Articular Cartilage: Identification of IL11 and CHADL as Attractive Treatment Targets. Arthritis Rheum 2021;73:789–99. https://doi.org/10.1002/art.41600
40. Abhishek A, Doherty S, Maciewicz R, Muir K, Zhang W, Doherty M. Evidence of a systemic

predisposition to chondrocalcinosis and association between chondrocalcinosis and osteoarthritis at distant joints: a cross-sectional study. Arthritis Care Res 2013;65:1052–8. https://doi.org/10.1002/acr.21952

41. Merle C, Waldstein W, Gregory JS, Goodyear SR, Aspden RM, Aldinger PR, et al. How many different types of femora are there in primary hip osteoarthritis? An active shape modeling study. J Orthop Res 2014;32:413–22. https://doi.org/10.1002/jor.22518
42. Nelson AE, Smith JA, Alvarez C, Arbeeva L, Renner JB, Murphy LB, et al. Associations between baseline and longitudinal semi-automated quantitative joint space width at the hip and incident hip osteoarthritis: Data from a community-based cohort. Arthritis Care Res 2021, online ahead of print. https://doi.org/10.1002/acr.24742
43. Crijns TJ, Brinkman N, Ramtin S, Ring D, Doornberg J, Jutte P, et al. Are There Distinct Statistical Groupings of Mental Health Factors and Pathophysiology Severity Among People with Hip and Knee Osteoarthritis Presenting for Specialty Care? Clin Orthop Relat Res 2022;480:298–309. https://doi.org/10.1097/CORR.0000000000002052
44. Krauss I, Katzmarek U, Rieger MA, Sudeck G. Motives for physical exercise participation as a basis for the development of patient-oriented exercise interventions in osteoarthritis: a cross-sectional study. Eur J Phys Rehabil Med 2017;53:590–602. https://doi.org/10.23736/S1973-9087.17.04482-3
45. de Hoop AMS, Kloek CJJ, Pisters MF, Veenhof C. Movement behaviour patterns in patients with hip and/or knee osteoarthritis in the physical therapy setting: a cross-sectional study. BMC Musculoskeletal Disord 2020;21:651. https://doi.org/10.1186/s12891-020-03644-0
46. van Drongelen S, Stetter BJ, Böhm H, Stief F, Stein T, Meurer A. Identification of Patients with Similar Gait Compensating Strategies Due to Unilateral Hip Osteoarthritis and the Effect of Total Hip Replacement: A Secondary Analysis. J Clin Med 2021;10:2167. https://doi.org/10.3390/jcm10102167
47. Murphy SL, Lyden AK, Phillips K, Clauw DJ, Williams DA. Subgroups of older adults with osteoarthritis based upon differing comorbid symptom presentations and potential underlying pain mechanisms. Arthritis Res Ther 2011;13:R135. https://doi.org/10.1186/ar3449
48. Akiyama K, Sakai T, Koyanagi J, Yoshikawa H, Sugamoto K. Evaluation of translation in the

normal and dysplastic hip using three-dimensional magnetic resonance imaging and voxel-based registration. Osteoarthritis Cartilage 2011;19:700–10. https://doi.org/10.1016/j.joca.2011.01.017

49. Myers CA, Register BC, Lertwanich P, Ejnisman L, Pennington WW, Giphart JE, et al. Role of the acetabular labrum and the iliofemoral ligament in hip stability: an in vitro biplane fluoroscopy study. Am J Sports Med 2011;39:85S–91S. https://doi.org/10.1177/0363546511412161
50. Han S, Alexander JW, Thomas VS, Choi J, Harris JD, Doherty DB, et al. Does Capsular Laxity Lead to Microinstability of the Native Hip? Am J Sports Med 2018;46:1315–23. https://doi.org/10.1177/0363546518755717
51. Lewis CL, Sahrmann SA, Moran DW. Effect of position and alteration in synergist muscle force contribution on hip forces when performing hip strengthening exercises. Clin Biomech 2009;24:35–42. https://doi.org/10.1016/j.clinbiomech.2008.09.006
52. Walters BL, Cooper JH, Rodriguez JA. New findings in hip capsular anatomy: dimensions of capsular thickness and pericapsular contributions. Arthriscopy 2014;30:1235–45. https://doi.org/10.1016/j.arthro.2014.05.012
53. Lawrenson PR, Crossley KM, Vicenzino BT, Hodges PW, James G, Croft KJ, et al. Muscle size and composition in people with articular hip pathology: a systematic review with meta-analysis. Osteoarthritis Cartilage 2019;27:181–95. https://doi.org/10.1016/j.joca.2018.10.008
54. Davies HTO, Crombie IK, Tavakoli M. Who can odds ratios mislead? BMJ 1998;316:989–91. https://doi.org/10.1136/bmj.316.7136.989
55. Wright AA, Cook C, Abbott JH. Variables associated with the progression of hip osteoarthritis: a systematic review. Arthritis Rheum 2009;61:925–36. https://doi.org/10.1002/art.24641

Figure legends

Fig 1 Flowchart of participants in cohort study

Data from 50 participants were analyzed in this study.

Fig 2 Relative importance of predictors in clustering

This graph shows the relative importance of each variable in each cluster analysis, which is a measure of the importance of the contribution of each attribute in estimating the cluster. Hip muscle strength balance was calculated as the percentage of each muscle strength to the total T-valued muscle strength.

Fig 3 Muscle function profiles of each phenotype

Radar charts represent the differences in muscle strength and muscle strength balance between phenotypes. Muscle strength was plotted using T-score. Cluster analyses 1, 2, and 3 included muscle strength variables, muscle strength balance variables, and both muscle strength and muscle strength balance variables, respectively.

Table 1 Demographic, radiographic, physical, and hip function characteristics of the participants

	All patients (n = 50)
Age, years	47.4 ± 10.7
Body mass index	22.4 ± 4.1
Radiographic	
Progression of hip OA, n (%)	Progressors, 21 (42.0%) Non-progressors, 29 (58.0%)
Minimum JSW, mm	3.33 ± 1.44
Sharp angle, degrees	45.0 ± 6.5
CE angle, degrees	23.4 ± 11.5
AHI, degrees	73.8 ± 11.0
ARO, degrees	22.4 ± 7.9
Pain (VAS), mm	42.0 ± 27.5
Gait speed, m/sec.	1.1 ± 0.2
Physical activity, steps	6,596 ± 2,551
Harris Hip Score	86.9 ± 9.9
SF-36	
PCS	49.4 ± 8.6
MCS	48.4 ± 11.8
Muscle strength, Nm/kg	
Flexion	0.87 ± 0.25
Extension	1.46 ± 0.57
Abduction	0.75 ± 0.21
External rotation	0.36 ± 0.12
Internal rotation	0.32 ± 0.12

(Footnotes for Table 1)

Values are mean ± standard deviation.

Abbreviations: JSW, joint space width; CE center edge; AHI, acetabular head index; ARO, acetabular roof obliquity; VAS, visual analogue scale; PCS, physical component summary scale score; MCS, mental component summary scale score.

Table 2 Univariable and multivariable logistic regression exploring the association between phenotypes and likelihood of progression of hip osteoarthritis

	No progression, n	**Progression, n**	**Total, n**	**Crude OR** (95% CI)	***p***	**Adjusted OR*** (95% CI)	***p***
Cluster analysis 1 (Muscle strength)							
Phenotype 1	16	15	31	2.03 (0.61–6.72)	0.241	2.18 (0.64–7.40)	0.227
Phenotype 2	13	6	19				
Total	29	21	50				
Cluster analysis 2 (Muscle strength balance)							
Phenotype 1	12	15	27	3.54 (1.07–11.77)	**0.025**	3.60 (1.07–12.05)	**0.039**
Phenotype 2	17	6	23				
Total	29	21	50				
Cluster analysis 3 (Muscle strength + Muscle strength balance)							
Phenotype 1	14	12	26	1.43 (0.46–4.42)	0.534	1.44 (0.46–4.49)	0.563
Phenotype 2	15	9	24				
Total	29	21	50				

(Footnotes for Table 2)

Reference group is phenotype 2 in all cluster analyses.

Bold of *P* value indicates statistically significant.

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval

* Adjusted for age and minimum joint space width at baseline.

Table 3 Profile of phenotypes for each of the three-cluster analyses

	Cluster analysis 1 (Muscle strength)				**Cluster analysis 2** (Muscle strength balance)				**Cluster analysis 3** (Muscle strength + muscle strength balance)			
	Phenotype 1 (n = 31)	**Phenotype 2 (n = 19)**	***p*** (95% CI)*	***d*†**	**Phenotype 1** (n = 27)	**Phenotype 2** (n = 23)	***p*** (95% CI)*	***d*†**	**Phenotype 1** (n = 26)	**Phenotype 2** (n = 24)	***p*** (95% CI)*	***d*†**
Age, years	46.6 ± 9.4	48.1 ± 12.9	0.661 (-8.03, 5.77)	0.14	47.3 ± 12.3	47.0 ± 8.6	0.926 (-5.66, 6.59)	0.03	47.5 ± 8.9	46.8 ± 12.6	0.835 (-6.01, 6.64)	0.06
Body mass index	23.8 ± 4.3	20.1 ± 2.6	**< 0.001 (1.89, 5.62)**	0.99	22.6 ± 4.2	22.3 ± 4.2	0.802 (-2.13, 2.66)	0.07	24.6 ± 4.3	20.1 ± 2.4	**< 0.001 (2.56, 6.37)**	1.28
Radiographic												
Minimum JSW, mm	3.15 ± 1.52	3.51 ± 1.21	0.355 (-1.13, 4.22)	0.26	3.08 ± 1.43	3.55 ± 1.38	0.253 (-1.26, 0.40)	0.33	3.04 ± 1.61	3.55 ± 1.14	0.198 (-1.27, 0.27)	0.36
Sharp angle, degrees	45.5 ± 7.2	43.9 ± 5.5	0.419 (-1.95, 5.36)	0.24	44.4 ± 6.1	45.6 ± 7.2	0.539 (-5.08, 2.72)	0.18	45.0 ± 7.3	44.8 ± 5.9	0.923 (-3.48, 4.08)	0.03
CE angle, degrees	22.0 ± 11.9	25.9 ± 10.7	0.259 (-10.78, 2.59)	0.34	24.5 ± 12.7	22.1 ± 9.9	0.469 (-4.27, 8.60)	0.21	21.7 ± 11.8	25.3 ± 11.2	0.272 (-10.10, 3.15)	0.31
AHI, degrees	72.7 ± 10.8	75.6 ± 11.8	0.388 (-9.41, 4.01)	0.26	74.0 ± 11.8	73.5 ± 10.4	0.875 (-5.90, 7.22)	0.04	72.5 ± 10.9	75.2 ± 11.5	0.387 (-8.96, 3.32)	0.24
ARO, degrees	23.1 ± 6.9	20.8 ± 9.6	0.371 (-2.52, 7.32)	0.29	22.5 ± 8.6	22.0 ± 7.3	0.827 (-4.03, 5.19)	0.06	23.5 ± 6.1	20.9 ± 9.6	0.294 (-1.84, 7.25)	0.33
Pain (VAS), mm	50.2 ± 26.3	30.0 ± 25.6	**0.014 (4.95, 35.56)**	0.78	43.5 ± 26.9	41.2 ± 29.3	0.781 (-14.69, 18.71)	0.08	51.4 ± 27.6	32.8 ± 25.0	**0.018 (4.36, 32.02)**	0.70
Gait speed, m/sec.	1.09 ± 0.16	1.21 ± 0.14	**0.006 (-0.22, -0.04)**	0.79	1.16 ± 0.15	1.10 ± 0.18	0.202 (-0.03, 0.16)	0.36	1.07 ± 0.16	1.21 ± 0.15	**0.002 (-0.22, -0.06)**	0.90
Physical activity, steps	5,937 ± 2,374	7,557 ± 2,688	**0.044 (-3167.29, -90.93)**	0.65	6,528 ± 2,498	6,566 ± 2,771	0.960 (-1496.85, 1409.42)	0.01	5,853 ± 2,499	7,296 ± 2,531	0.053 (-2891.14, -39.01)	0.57
Harris Hip Score	83.6 ± 10.5	91.4 ± 6.5	**0.003 (-13.06, -3.61)**	0.85	86.7 ± 11.0	86.7 ± 8.8	0.980 (-5.57, 5.19)	0.00	82.4 ± 10.1	91.4 ± 7.7	**0.001 (-13.92, -4.01)**	1.00
SF-36												
PCS	35.5 ± 11.9	40.0 ± 8.3	0.140 (-9.97, 1.33)	0.42	37.1 ± 11.7	37.3 ± 9.9	0.941 (-6.12, 6.33)	0.02	35.0 ± 12.9	39.6 ± 7.7	0.137 (-10.27, 1.31)	0.43
MCS	50.5 ± 8.3	47.4 ± 9.2	0.266 (-2.05, 8.68)	0.36	49.3 ± 6.7	49.3 ± 10.9	0.990 (-5.18, 5.38)	0.00	50.2 ± 8.7	48.4 ± 8.7	0.475 (-3.27, 6.79)	0.21
Muscle strength, Nm/kg												
Flexion	0.73 ± 0.15	1.10 ± 0.23	**< 0.001 (-0.49, -0.26)**	2.01	0.83 ± 0.27	0.92 ± 0.24	0.228 (-0.24, 0.05)	0.35	0.69 ± 0.13	1.07 ± 0.21	**< 0.001 (-0.48, -0.28)**	2.20
Extension	1.13 ± 0.32	2.04 ± 0.48	**< 0.001 (-1.18, -0.66)**	2.35	1.61 ± 0.61	1.29 ± 0.50	0.058 (0.00, 0.62)	0.57	1.05 ± 0.28	1.93 ± 0.47	**< 0.001 (-1.11, -0.68)**	2.30

Abduction	0.63 ± 0.14	0.95 ± 0.18	**< 0.001 (-0.41, -0.22)**	2.05	0.82 ± 0.23	0.67 ± 0.17	**0.021 (0.02, 0.26)**	0.73	0.60 ± 0.11	0.92 ± 0.17	**< 0.001 (-0.40, -0.24)**	2.25
External rotation	0.28 ± 0.07	0.49 ± 0.09	**< 0.001 (-0.25, -0.16)**	2.69	0.35 ± 0.12	0.38 ± 0.13	0.431 (-0.10, 0.04)	0.24	0.29 ± 0.07	0.44 ± 0.12	**< 0.001 (-0.22, -0.10)**	1.54
Internal rotation	0.26 ± 0.07	0.42 ± 0.12	**< 0.001 (-0.23, -0.10)**	1.74	0.30 ± 0.11	0.35 ± 0.13	0.150 (-0.12, 0.01)	0.42	0.25 ± 0.07	0.40 ± 0.12	**< 0.001 (-0.20, -0.09)**	1.54
Muscle strength balance††, %												
Flexion	20.1 ± 2.0	19.9 ± 2.1	0.760 (-1.03, 1.37)	0.10	19.3 ± 1.9	20.9 ± 1.7	**0.003 (-2.75, -0.56)**	0.88	19.9 ± 2.1	20.2 ± 1.9	0.605 (-1.39, 0.84)	0.15
Extension	20.0 ± 1.5	20.2 ± 1.8	0.577 (-1.23, 0.67)	0.12	21.0 ± 1.3	18.9 ± 1.1	**< 0.001 (1.39, 2.73)**	1.73	19.8 ± 1.6	20.3 ± 1.6	0.260 (-1.40, 0.34)	0.31
Abduction	20.0 ± 2.0	20.0 ± 2.6	0.946 (-1.39, 1.35)	0.00	21.1 ± 2.0	18.6 ± 1.6	**< 0.001 (1.51, 3.50)**	1.37	19.8 ± 2.0	20.3 ± 2.4	0.422 (-1.77, 0.78)	0.23
External rotation	20.0 ± 2.3	20.3 ± 1.8	0.341 (-1.63, 0.57)	0.14	19.5 ± 2.2	20.6 ± 1.8	0.092 (-2.14, 0.20)	0.54	20.3 ± 2.1	19.7 ± 2.1	0.344 (-0.64, 1.81)	0.29
Internal rotation	20.2 ± 1.6	19.5 ± 2.0	0.231 (-0.42, 1.80)	0.40	19.1 ± 1.5	21.0 ± 1.6	**< 0.001 (-2.76, -1.07)**	1.23	20.3 ± 1.7	19.6 ± 1.8	0.139 (-0.22, 1.73)	0.40

(Footnotes for Table 3)

Values are mean ± standard deviation. Bold indicates statistically significant.

Abbreviations: JSW, joint space width; CE center edge; AHI, acetabular head index; ARO, acetabular roof obliquity; VAS, visual analogue scale; PCS, physical component summary scale score; MCS, mental component summary scale score; CI, confidence interval.

* Independent-sample *t* test.

† Cohen's *d*.

†† Percentage of each muscle strength value converted into T-score.

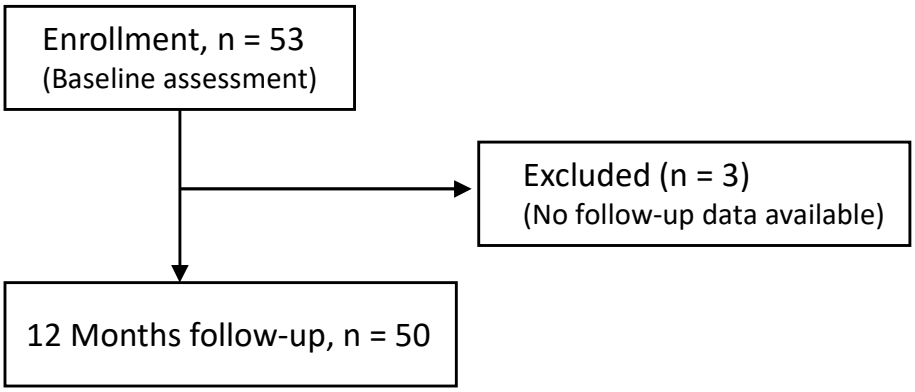
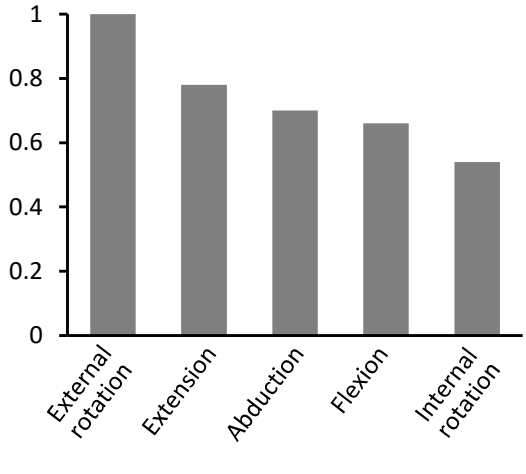
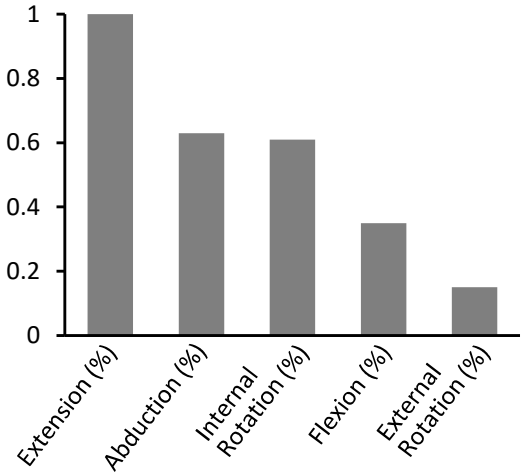

Enrollment, n = 53
(Baseline assessment)
Excluded (n = 3)
(No follow-up data available)
12 Months follow-up, n = 50

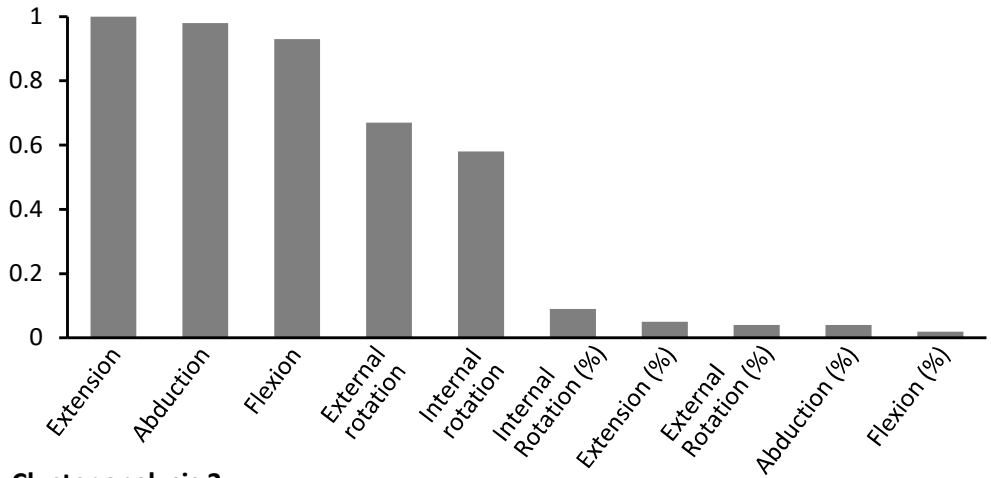
Fig 1



Cluster analysis 1



Cluster analysis 2



Cluster analysis 3

Fig 2

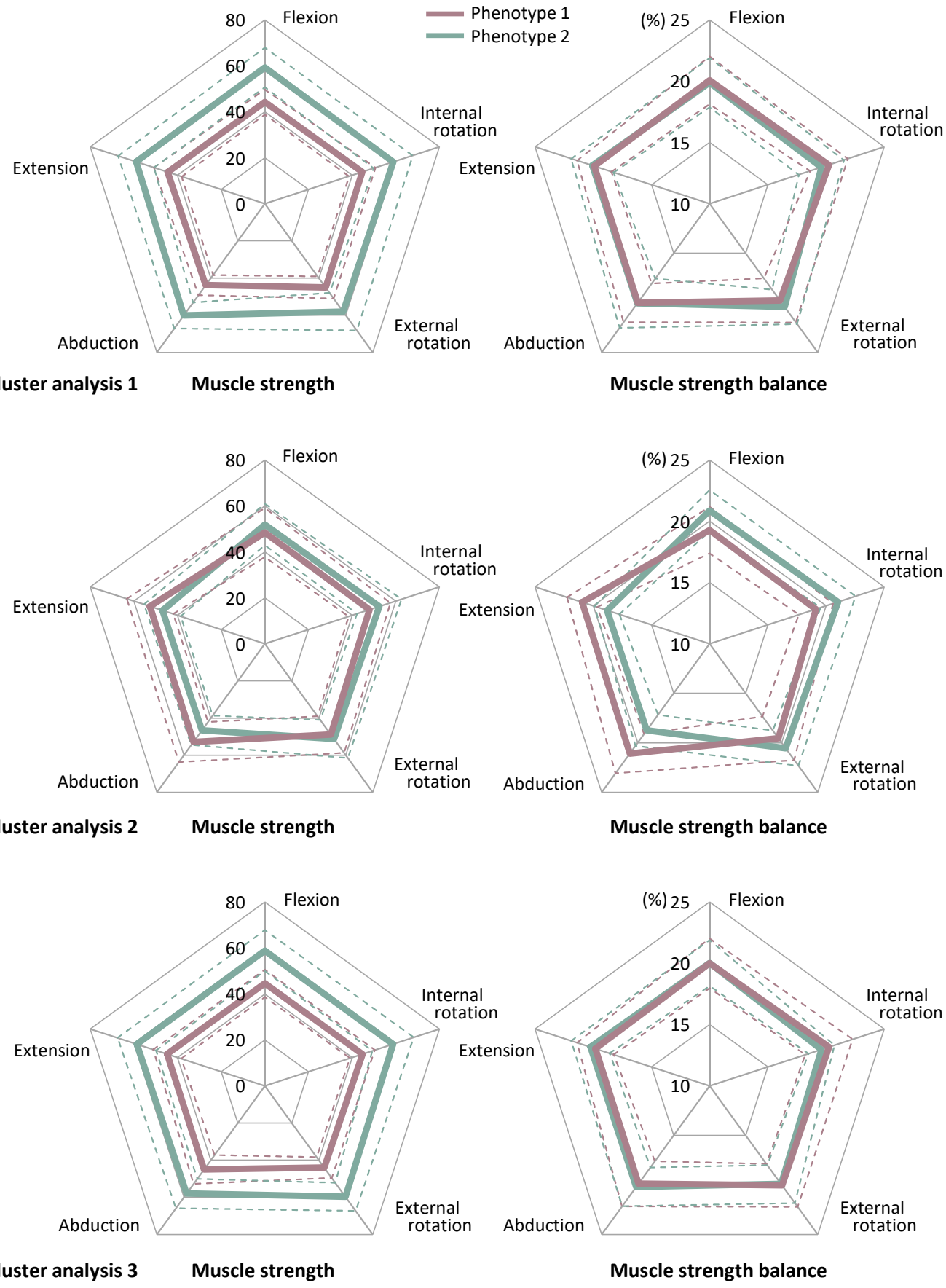

Phenotype 1
Phenotype 2
80
60
40
20
0
(%) 25
20
15
10
Flexion
Internal rotation
External rotation
Abduction
Extension
Cluster analysis 1
Muscle strength
Muscle strength balance
Cluster analysis 2
Muscle strength
Muscle strength balance
Cluster analysis 3
Muscle strength
Muscle strength balance

Fig 3