Moving out of the lab

Moving out the lab

Movement analyses in patients with osteoarthritis of the knee

Design: Mixed Art Myrthe Boymans (Cover); Mario Paiano (DankDiagram)
Layout: Tiny Wouters
Printed by: www.proefschriftmaken.nl

ISBN: 978-94-6423-062-8

Financial support for the publication of this thesis was provided by: Maastricht University, Maastricht University Medical Center (MUMC+), Nederlandse Orthopaedische Vereniging (NOV), Stichting Kliniek en Wetenschap Orthopedie MUMC+, Anna Fonds, Penders Voetzorg, Orthopaedie 2000 and Smeets Loopcomfort.

The research presented in this thesis was conducted at CAPHRI Public Health Research Institute, Department. CAPHRI participates in the Netherlands School of Public Health and Care Research CaRe.

Moving out the lab

Movement analyses in patients with osteoarthritis of the knee

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
op gezag van de Rector Magnificus, Prof.dr. Rianne M. Letschert
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
op vrijdag 22 januari 2021 om 12.00 uur

door

Loek Verlaan
Geboren op 24 juni 1978, te Ubach over Worms, Nederland

Promotores
Prof. dr. L.W. van Rhijn
Dr. K. Meijer

Copromotor
Dr. P.J. Emans

Beoordelingscommissie
Prof. dr. M. Poeze (voorzitter)
Prof. dr. S.K. Bulstra, Rijksuniversiteit Groningen
Prof. dr. A.F. Lenssen
Dr. G. Plasqui
Prof. dr. S.B. Vos, Technische Universiteit Eindhoven

Table of contents

Chapter 1

General introduction

Prevalence of osteoarthritis and its relation to obesity

Osteoarthritis (OA) of the knee is one of the leading causes of global disability[1] and the most common reason for pain in older adults with a significant individual and economic burden.[2,3] It is estimated that between 20% and 30% of adults and elderly suffer from this condition[4], but most likely this is an underestimation, given that not everybody suffering from this condition will consult a doctor. The cumulative costs of OA for society are calculated to be around 0.5% of Gross National Product (GNP).[2]
Besides OA, obesity is also becoming an increasing problem in public health. For example, in the Netherlands 19% of the women above 65 years have a BMI>30 kg/m^2.[5] Predictive numbers will even rise. Research has shown that obese subjects have almost four times the risk of developing knee OA when compared with non-obese subjects. This may possibly be explained by the increased loads the knee experiences in obese subjects.[6,7] Following the current rise in obesity and concomitant increase in life expectancy, prevalence of OA is expected to grow.[8] This poses OA as an enhancing future health problem. Besides age and weight, further risk factors for OA include female gender, genetics, poor diet, joint overuse, trauma, muscle weakness, physical inactivity, and poor habitual movement patterns.[9,10]
The clinical presentation of knee OA is characterized by pain, limitation of movement, tenderness and local inflammation.[11] Those problems often manifest at the medial tibiofemoral compartment, as a result of varus malalignments.[12]

Pathophysiology of osteoarthritis

While the exact pathophysiology of OA remains to be elucidated, it is currently believed that altered joint loading and cartilage metabolism are both key factors in cartilage degradation and subsequent OA development.[13] In persons with healthy cartilage, walking results in a repetitive load, distributed over the medial and lateral condyles. Furthermore, healthy cartilage can maintain homeostasis by adjusting cartilage thickness in those regions with higher loads.[14] Andriacchi et al. hypothesised that an alteration of joint mechanics, for example due to trauma, results in a shift of loading to a region at the medial compartment (Figure 1.1). If the cartilage is not adapted to the increased load, it can result in a degenerative cartilage response.[14] Being the largest weight-bearing joint, the knee is most affected.[15,16]

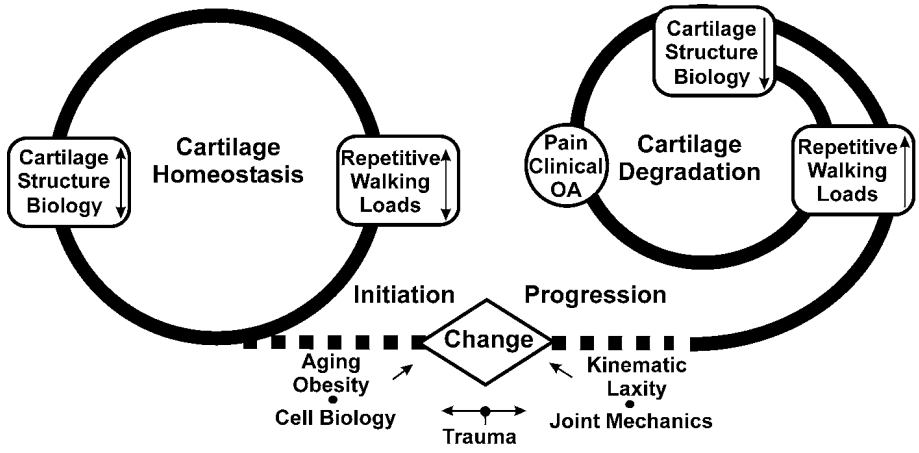

Figure 1.1 Healthy cartilage homeostasis is maintained by the magnitude of the repetitive cyclic loads during walking, and cartilage is thicker in regions with higher loads during walking. The initiation of OA is associated with a change (due to aging, obesity, trauma) in the normal balance between the mechanics of walking and the cartilage biology or structure. Once cartilage starts to degrade, it responds negatively to load and the rate of progression of OA increases with loading.[14]

Biomechanics of osteoarthritis

For some time now, the knee adduction moment (KAM) is considered to be an important indicator of future knee pain and OA.[17,18] KAM is dependent of the magnitude of the ground reaction force (GRF) and its moment arm relative to the knee joint centre (Figure 1.2).[19]

For example, during gait, the GRF is directed medial of the knee. Consequently, an increased medial component of the GRF may lead to a higher KAM.[20,21]

In most knee OA patients, the medial side is affected[12] and the KAM will further increase (Figure 1.2). Due to lateral laxity and varus alignment of the knee joint, the medial compartment transfers substantially higher loads compared to the lateral compartment.[22] Considering that the medial compartment is not adapted to extreme loads, cartilage may deteriorate when the knee is repeatedly exposed to high joint forces during locomotor activities.[23] Especially during walking, the medial compartment of the knee is repeatedly exposed to high joint contact forces. Therefore, the evaluation of knee mechanics during walking is of importance to understand the development of knee OA.[23] Several studies have examined KAM in patients with knee OA.[24-27] For instance, a high KAM is related to the onset and progression of knee OA.[17,23] Especially

the peak load in early stance and the cumulative load of a full gait cycle are strong predictors of the presence, severity and rate of progression of medial compartment knee OA.[28,29]

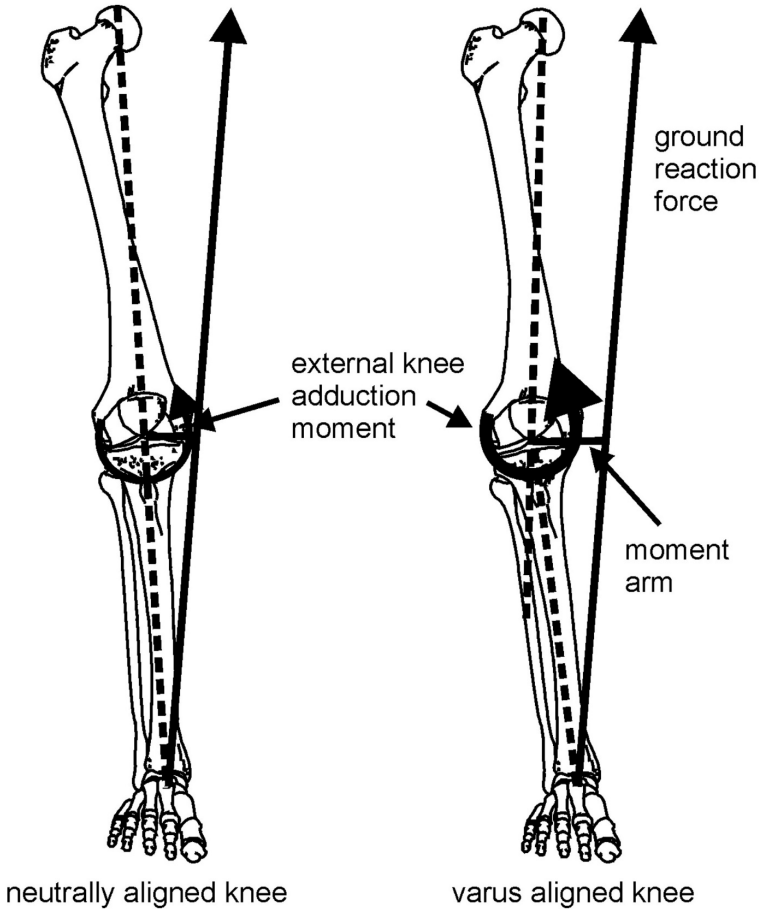

Figure 1.2 The knee adduction moment tends to be greater in varus aligned knees (right) compared to neutrally aligned knees (left) due to a greater moment arm of the ground reaction force about the knee joint center.[20]

While KAM has been thoroughly investigated during gait, little is known about KAM during stair negotiation[30], during which knee loads are higher compared to (level) walking.[31] Furthermore, stair climbing is one the first encountered problems in knee OA patients and is often used to evaluate safety of hospital discharge.[32] In addition, a large

number of falls in the elderly population may be attributed to misstepping on stairs, especially during stair descent.[33]

Although literature on KAM during stair negotiation in knee OA patients is scarce, several factors, including mechanical alignment, lateral trunk lean, foot progression angle (FPA), step width, and stair climbing velocity have been suggested to modify KAM during stair negotiation.[34-36] Those movement adaptations should thus be taken into consideration when evaluating KAM. Furthermore, it is important to discriminate between lean and obese knee OA patients. In previous research, KAM was shown to be dependent on body weight.[37] Increased loads of approximately 20% of total body weight increase KAM in healthy subjects during both stair ascent and descent.[38]

In patients with knee OA compensatory strategies are also seen during STS movements, to avoid pain and overcome movement limitations. STS movement is characterised by the transition from a wide base of support (BoS) – provided by the feet, thighs, and buttocks – to a small BoS, provided by the feet alone. Moreover, high knee and hip extensor moments are required to lift the centre of mass (CoM) against gravity.[39] Especially in certain pathologies, such as knee OA, where pain, joint stiffness, and loss of quadriceps strength are present, performing STS may be challenging.

From previous research it is known that knee OA patients show increased weight-bearing asymmetry[40-42], less flexion of the affected knee[40,41], increased trunk lean towards the unaffected side[43], and more flexion of the trunk[39,40,43] during STS movement. Furthermore, lower knee extension moments are observed[39,44], which is associated with lower quadriceps strength.[41] The observed movement alterations are also linked with earlier and increased activation of the biceps femoris.[40,44] Overall, those movement alterations lead to an increased time to perform STS movement, indicating a decrease in performance.[39,45] However, performing STS at a slower speed may also be a deliberate strategy to reduce accelerations and minimize both joint forces and joint pain.[46] As a result of compensatory movement patterns, in particular asymmetrical loading strategies, the contralateral joint may become more prone to develop OA.[47] This underlines the importance of proper quantification of biomechanics during STS, which may lead to the prevention of further disease progression.

Measurement of physical function in osteoarthritis

Several approaches can be used for assessment of physical function and alterations in movement patterns. In laboratory settings, advanced motion capture systems like force platforms and 3D optical motion capture systems allow the derivation of spatio-temporal (e.g. cadence, stride length), kinematic (e.g. joint angle) and kinetic

parameters (e.g. ground reaction forces, and joint torques).[48-50] These methods employ sophisticated biomechanical analysis and produce detailed functional parameters for clinical research. Disadvantages are that they are time-consuming and require dedicated motion analysis laboratories.

In daily practice, knee OA patients adopt compensatory strategies to avoid pain and overcome movement limitations. The ability to perform activities effectively is essential with respect to independency and participation in society. In previous studies, alterations in movement patterns have already been described in patients with knee OA during activities of daily life, including gait[24,28,51], stair climbing[33,52,53], and sit-to-stand (STS) tasks.[39-44] Most of these studies fail to distinguish between effects of knee OA itself and effects of high body mass index (BMI), which is closely associated with knee OA. As obesity itself may modulate movement patterns during gait, stair climbing and STS tasks, it should not be neglected in biomechanical analyses.[54] Furthermore, obesity is one of that factors that may contribute to OA progression.[55] In this thesis we focus on biomechanical analysis in knee OA patients to derive spatio-temporal, kinematic and kinetic parameters during gait, stair climbing and STS movement in healthy controls and lean and obese knee osteoarthritis patients. We especially focus on the knee adduction moment (KAM). In addition, we investigated different kinds of employed compensatory strategies to perform these activities.

Physical activity

Physical activity monitoring primarily refers to the quantitative analysis of activities performed in the habitual environment over various days.[56] Physical activity is an important determinant of general health and is negatively affected by many chronic degenerative diseases.[57,58] The increased mortality documented for untreated hip OA is attributed to reduced physical activity.[59] Knee OA will have the same results. To understand the association between physical activity and diseases, and to determine the effectiveness of interventions, it is crucial for clinicians and researchers to assess and monitor physical activity during daily life circumstances.[60] Developments in ambulant motion sensor technologies have recently provided more feasible alternatives for objective assessment of actual free-living physical activity.[58,61] Accelerometry has demonstrated its potential to provide an estimation of activity quantity[32], to provide qualitative assessment of physical activity such as spatiotemporal gait analysis[62] and activity intensity measures.[61] Furthermore, accelerometer-based physical activity monitoring permits to differentiate between different activities of daily

living (ADL) such as walking or sitting[63,64] and could select only those activities that are challenging and clinically relevant for specific patient populations.
Most studies monitor activity over a relatively short period of time, from a few minutes[65,66] to a couple of hours[67,68], with the goal to detect motion parameters capable of discriminating between healthy and pathological gaits[69,70] or to directly compare performance of the relatively cheap and easy to use wearable technology over tedious and expensive gait laboratories.[71] Studies on gait of healthy subjects have shown great potential of detailed motion analyses, proficient in discerning a number of different action categories[72] and determining the smoothness and rhythm[73], stability[74], harmony[75] and naturalness of locomotion.[76] To have a good understanding of subtle and small changes in behavior requires long-term and continuous monitoring of movement in a daily setting using accelerometers or motion-capturing systems.
As mentioned before, the exact pathophysiology of OA is still unclear. Physical activity is both a risk factor and a protective factor in the etiology and prognosis of OA of the hip or the knee, depending on the type and intensity of physical activity. Regarding etiology, physical activity may be a risk for developing OA due to mechanically induced degeneration of cartilage.[77-79] In the prognosis of OA of the hip or knee, physical activity, such as walking or bicycling, protects against functional decline[80-83], but physical activity involving heavy loading or a high number of load cycles per year during walking may also be a risk factor for poor prognosis.[84]
Thus, the impact of physical activity on etiology and prognosis of OA seems to depend on the type, intensity and components (e.g. mechanical strain) of physical activity. Detailed assessment and evaluation of physical activity in OA patients may contribute to a better understanding of the disease process and clinical outcomes.[84] In conclusion, either measuring biomechanical load and physical activity in patients with knee OA, is important to get a better understanding in the etiology and prognosis of this disease.

Aims thesis

The primary aim of this thesis is to evaluate the effect of knee OA on spatio-temporal, kinematic and kinetic parameters during gait, stair climbing and STS movement in healthy controls and lean and obese knee OA patients. Secondary, to evaluate physical activity and kinematic signatures distinctive for knee OA.
This results into the following research objectives:

- To investigate the effect of knee OA on KAM during gait (Chapter 2) and during stair negotiation (Chapter 3) in patients with and without obesity

- To investigate the differences in knee and hip kinetics during sit-to-stand movement (Chapter 4).
- To investigate whether a stair climbing test with accelerometer derived motion parameters is clinically feasible and capable to identify differences between demographic groups of healthy subjects (Chapter 5).
- To investigate the potential of ambulant accelerometer-based physical activity monitoring to objectively assess physical activity during daily life circumstances in healthy and patients with advanced knee OA, compared with self-reported levels of physical activity (Chapter 6).
- To investigate kinematic signatures and activity patterns distinctive for knee OA and to discriminate in a number of different action categories and determining the smoothness and rhythm, stability, harmony and naturalness of locomotion (Chapter 7).

Chapters 2 and 3 investigate the first research objective: “the effect of knee OA on KAM during gait and during stair negotiation in patients with and without obesity”. In **chapter 2** a case-control study is presented, including obese and lean patients with knee osteoarthritis and lean, healthy controls. All participants performed gait trials at self-selected and a standardised walking speed. Standard gait analysis was used to calculate three-dimensional lower extremity joint kinematics and kinetics. The same study design is used in **chapter 3**. Instead of performing gait, all subjects ascended and descended a three-step staircase at a self-selected, comfortable speed. Three-dimensional motion analysis was performed to evaluate the external knee adduction moment during stair negotiation. The differences in knee and hip kinetics during sit-to-stand movement are investigated in **chapter 4**. All subjects, including obese and lean patients with knee osteoarthritis and lean, healthy controls, were instructed to perform sit-to-stand transfers at self-selected, comfortable speed. A three-dimensional movement analysis was performed to investigate compensatory mechanisms and knee and hip kinetics during sit-to-stand movement.

Chapter 5 described the first accelerometric study: “Accelerometer based stair climbing in healthy subjects: reference data and demographic differences”. The purpose of this study was to investigate whether a stair climbing test with accelerometer derived motion parameters in a group of healthy subjects is clinically feasible and valid to distinguish between demographic differences. 100 healthy subjects, divided in two age groups, ascended and descended five stairs at preferred, comfortable speed with a triaxial accelerometer attached to the sacrum. Several motion parameters were derived for acceleration peak detection algorithms. **Chapter 6** evaluates the following research objective: “To investigate the potential of ambulant accelerometer-based physical

activity monitoring to objectively assess physical activity during daily life circumstances in healthy and patients with advanced knee OA, compared with self-reported levels of physical activity". Patients with end-stage knee OA and age-matched healthy subjects were measured. An ambulant tri-axial accelerometer was placed onto the lateral side of the upper leg. Physical activity was measured during four consecutive days. Using algorithm-based peak detection methods in Matlab, parameters covering the four FITT (Frequency, Intensity, Time and Type) components were assessed. Self-reported physical activity was assessed using the Short questionnaire to assess health enhancing physical activity (SQUASH). The last research objective will be discussed in **chapter 7**. We set out to investigate kinematic signatures and activity patterns distinctive for knee OA, measured continuously for the duration of a full week under unconstrained daily conditions. This was done by attaching triaxial accelerometers, capable of detecting positional displacement in three spatial orthogonal axes, on the non-affected femur of patients suffering from knee OA as assessed clinically and radiological compared with healthy volunteers. Given the modulatory effect of weight we also included a group of obese knee OA patients. The rationale was that a meticulous description of potential distinctive signatures in knee OA could then be used in future studies and clinical practice to detect early-OA in healthy subjects allowing the rapid initiation of adequate preventive treatments.

Finally, the results of the above described studies and recommendations for future research are discussed in **chapter 8**.

References

1. Bijlsma JW, Berenbaum F,& Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. Lancet. 2011;377:2115-26..
2. Britton R. The economic burden of osteoarthritis. Am J Manag Care. 2009;15:230-5.
3. Felson DT. Clinical practice. Osteoarthritis of the knee. N Engl J Med. 200;354:841-8.
4. Yoshimura N, Muraki S, Nakamura K, Tanaka S. Epidemiology of the locomotive syndrome: The research on osteoarthritis/osteoporosis against disability study 2005-2015. Mod Rheumatol. 2017;27: 1-7.
5. https://www.volksgezondheidenzorg.info/onderwerp/overgewicht/cijfers-context/samenvatting#bronverantwoording
6. Wearing SC, Hennig EM, Byrne NM, Steele JR, Hills AP. Musculoskeletal disorders associated with obesity: a biomechanical perspective. Obes Rev. 2006;7(3):239-50.
7. Coggon D, Reading I, Croft P, McLaren M, Barrett D, Cooper C. Knee osteoarthritis and obesity. Int J Obes Relat Metab Disord. 2001;25(5):622-7.
8. Marshall DA, Vanderby S, Barnabe C, MacDonald KV, Maxwell C, Mosher D, et al. Estimating the Burden of Osteoarthritis to Plan for the Future. Arthritis Care Res. 2015;67(10):1379-86.
9. Palazzo C, Nguyen C, Lefevre-Colau M-M, Rannou F, Poiraudeau S. Risk factors and burden of osteoarthritis. Ann Phys Rehabil Med. 2016;59(3):134-8.
10. Ashkavand Z, Malekinejad H, Vishwanath BS. The pathophysiology of osteoarthritis. J Pharmacy Res. 2013;7(1):132-8.
11. Kraus VB, Blanco FJ, Englund M, Karsdal MA, Lohmander LS. Call for Standardized Definitions of Osteoarthritis and Risk Stratification for Clinical Trials and Clinical Use. Osteoarthritis Cartilage. 2015; 23(8):1233-41.
12. Cicuttini F, Wluka A, Hankin J, Wang Y. Longitudinal study of the relationship between knee angle and tibiofemoral cartilage volume in subjects with knee osteoarthritis. Rheumatology (Oxford). 2004;43(3):321-4.
13. Guilak F. Biomechanical factors in osteoarthritis. Best Pract Res Clin Rheumatol. 2011;25(6):815-23.
14. Andriacchi TP, Koo S, Scanlan SF. Gait mechanics influence healthy cartilage morphology and osteoarthritis of the knee. J Bone Joint Surg Am. 2009;91 Suppl 1:95-101
15. Verhaar JAN. Aandoeningen van de knie in Leerboek Orthopedie (eds. Verhaar & van Mourik) 381-407 (Bohn Stafleu van Loghum, 2008).
16. Fowler-Brown A, et al. The mediating effect of leptin on the relationship between body weight and knee osteoarthritis in older adults. Arthritis Rheumatol. 2015;67,169-75.
17. Miyazaki T, Wada M, Kawahara H, et al. 2002. Dynamic load at baseline can predict radiographic disease progression in medial compartment knee osteoarthritis. Ann Rheum Dis. 2002;61:617-22.
18. Amin S, Luepongsak N, McGibbon CA, et al. Knee adduction moment and development of chronic knee pain in elders. Arthritis Rheum. 2004;51:371-6.
19. Foroughi N, Smith R, Vanwanseele B. The association of external knee adduction moment with biomechanical variables in osteoarthritis: A systematic review. Knee. 2009;16(5):303-9.
20. Mundermann A, Dyrby CO, Andriacchi TP. A comparison of measuring mechanical axis alignment using three-dimensional position capture with skin markers and radiographic measurements in patients with bilateral medial compartment knee osteoarthritis. Knee. 2008;15:480-5.
21. Kutzner I, Trepczynski A, Heller MO, Bergmann G. Knee Adduction Moment and Medial Contact Force – Facts about Their Correlation during Gait. PLoS One. 2013;8(12):e81036.
22. Schipplein OD, Andriacchi TP. Interaction between active and passive knee stabilizers during level walking. J Orthop Res 1991;9:113-9
23. Andriacchi TP, Mundermann A, Smith RL, et al. A framework for the in vivo pathomechanics of osteoarthritis at the knee. Ann Biomed Eng. 2004; 32:447-57.
24. Baliunas AJ, Hurwitz DE, Ryals AB, Karrar A, Case JP, Block JA, et al. Increased knee joint loads during walking are present in subjects with knee osteoarthritis. Osteoarthritis Cartilage. 2002;10(7):573-9.
25. Kaufman KR, Hughes C, Morrey BF, et al. Gait characteristics of patients with knee osteoarthritis. J Biomech 2001;34:907-15.

26. Landry SC, McKean KA, Hubley-Kozey CL, et al. Knee biomechanics of moderate OA patients measured during gait at a self-selected and fast walking speed. J Biomech. 2007;40:1754-61.
27. Sharma L, Hurwitz DE, Thonar EJ, et al. Knee adduction moment, serum hyaluronan level, and disease severity in medial tibiofemoral osteoarthritis. Arthritis Rheum. 1998;41:1233-40.
28. Mundermann A, Dyrby CO, Andriacchi TP. Secondary gait changes in patients with medial compartment knee osteoarthritis: increased load at the ankle, knee, and hip during walking. Arthritis Rheum. 2005; 52(9):2835-44.
29. Thorp LE, Sumner DR, Block JA, et al. Knee joint loading differs in individuals with mild compared with moderate medial knee osteoarthritis. Arthritis Rheum. 2006;54:3842-9.
30. Iijima H, Shimoura K, Aoyama T, Takahashi M. Biomechanical characteristics of stair ambulation in patients with knee OA: A systematic review with meta-analysis toward a better definition of clinical hallmarks. Gait Posture. 2018;62:191-201.
31. Kutzner I, Heinlein B, Graichen F, Bender A, Rohlmann A, Halder A, et al. Loading of the knee joint during activities of daily living measured in vivo in five subjects. J Biomech. 2010;43(11):2164-73.
32. Plasqui G, Joosen AM, Kester AD, Goris AH, Westerterp KR. Measuring free-living energy expenditure and physical activity with triaxial accelerometry. Obes. Res. 2005;13:1363-9.
33. Hicks-Little CA, Peindl RD, Hubbard TJ, Scannell BP, Springer BD, Odum SM, et al. Lower extremity joint kinematics during stair climbing in knee osteoarthritis. Med Sci Sports Exerc. 2011;43(3):516-24.
34. Lewis J, Freisinger G, Pan X, Siston R, Schmitt L, Chaudhari A. Changes in Lower Extremity Peak Angles, Moments and Muscle Activations during Stair Climbing at Different Speeds. J Electromyogr Kinesiol. 2015;25(6):982-9.
35. Guo M, Axe MJ, Manal K. The influence of foot progression angle on the knee adduction moment during walking and stair climbing in pain free individuals with knee osteoarthritis. Gait Posture. 2007;26(3): 436-41.
36. Paquette MR, Klipple G, Zhang S. Greater Step Widths Reduce Internal Knee Abduction Moments in Medial Compartment Knee Osteoarthritis Patients During Stair Ascent. J Appl Biomech. 2015;31(4): 229-36.
37. Browning RC, Kram R. Effects of obesity on the biomechanics of walking at different speeds. Med Sci Sports Exerc. 2007;39(9):1632-41.
38. Hall M, Boyer ER, Gillette JC, Mirka GA. Medial knee joint loading during stair ambulation and walking while carrying loads. Gait Posture. 2013;37(3):460-2.
39. Anan M, Shinkoda K, Suzuki K, Yagi M, Ibara T, Kito N. Do patients with knee osteoarthritis perform sit-to-stand motion efficiently? Gait Posture. 2015;41(2):488-92.
40. Bouchouras G, Patsika G, Hatzitaki V, Kellis E. Kinematics and knee muscle activation during sit-to-stand movement in women with knee osteoarthritis. Clin Biomech. 2015;30(6):599-607.
41. Christiansen CL, Stevens-Lapsley JE. Weight-bearing asymmetry in relation to measures of impairment and functional mobility for people with knee osteoarthritis. Arch Phys Med Rehabil. 2010;91(10):1524-8.
42. Boonstra MC, Schwering PJ, De Waal Malefijt MC, Verdonschot N. Sit-to-stand movement as a performance-based measure for patients with total knee arthroplasty. Phys Ther. 2010;90(2):149-56.
43. Turcot K, Armand S, Fritschy D, Hoffmeyer P, Suva D. Sit-to-stand alterations in advanced knee osteoarthritis. Gait Posture. 2012;36(1):68-72.
44. Patsika G, Kellis E, Amiridis IG. Neuromuscular efficiency during sit to stand movement in women with knee osteoarthritis. J Electromyogr Kinesiol. 2011;21(5):689-94.
45. Su FC, Lai KA, Hong WH. Rising from chair after total knee arthroplasty. Clin Biomech. 1998;13(3): 176-81.
46. Yoshioka S, Nagano A, Hay DC, Fukashiro S. Biomechanical analysis of the relation between movement time and joint moment development during a sit-to-stand task. Biomed Eng Online. 2009;8:27.
47. Shakoor N, Hurwitz DE, Block JA, Shott S, Case JP. Asymmetric knee loading in advanced unilateral hip osteoarthritis. Arthritis Rheum. 2003;48(6):1556-61.
48. Wolf SI, Braatz F, Metaxiotis D, et al. Gait analysis may help to distinguish hereditary spastic paraplegia from cerebral palsy. Gait Posture 2011;22(4):556-64.

49. Ro DH, Kim JK, Lee DW, et al. Residual varus alignment after total knee arthroplasty increases knee adduction moment without improving patient function: A propensity score-matched cohort study. Knee 2019;26(3):737-44.
50. Nha KW, Shon OJ, Kong BS, et al. Gait comparison of unicompartmental knee arthroplasty and total knee arthroplasty during level walking. PLoS One 2018;13(8):e0203310.
51. Kumar D, Manal KT, Rudolph KS. Knee joint loading during gait in healthy controls and individuals with knee osteoarthritis. Osteoarthritis Cartilage. 2013;21(2):298-305.
52. Asay JL, Mundermann A, Andriacchi TP. Adaptive patterns of movement during stair climbing in patients with knee osteoarthritis. J Orthop Res. 2009;27(3):325-9.
53. Gonçalves GH, Selistre LFA, Petrella M, Mattiello SM. Kinematic alterations of the lower limbs and pelvis during an ascending stairs task are associated with the degree of knee osteoarthritis severity. Knee. 2017;24(2):295-304.
54. Sibella F, Galli M, Romei M, Montesano A, Crivellini M. Biomechanical analysis of sit-to-stand movement in normal and obese subjects. Clin Biomech 2003;18(8):745-50.
55. Sowers MR, Karvonen-Gutierrez CA. The evolving role of obsity in knee osteoarthritis. Curr Opin Rheumatol 2010;22(5):533-7.
56. Grimm B, Bolink S. Evaluating physical function and activity in the elderly patient using wearable motion sensors. EFFORT Open Rev 2017;13;1(5):112-120.
57. Westerterp KR. Reliable assessment of physical activity in disease: an update on activity monitors. Curr. Opin. Clin. Nutr. Metab. Care. 2014;17:401-6.
58. Lindemann U, Zijlstra W, Aminian K, Chastin SF, de Bruin ED, Helbostad JL, Bussmann JNJ. Recommendations for standardizing validation procedures assessing physical activity of older persons by monitoring body postures and movements. Sensors (Basel). 2013;14:1267-77.
59. Haim A, Rozen N, Dekel S, Halperin N, Wolf A. Control of knee coronal plane moment via modulation of center of pressure: a prospective gait analysis study. J Biomech 2008;41:3010-6.
60. Dobkin BH. Wearable motion sensors to continuously measure real-world physical activities. Curr Opin Neurol 2013;26:602-8.
61. Tobias JH, Gould V, Brunton L, Deere K, Rittweger J, Lipperts M, Grimm B. Physical activity and bone: may the force be with you. Front Endocrinol. (Lausanne). 2014;5:20.
62. White DK, Tudor-Locke C, Felson DT, Gross KD, Niu J, Nevitt M, Lewis CE, Torner J, Neogi T. Walking to meet physical activity guidelines in knee osteoarthritis: is 10,000 steps enough?," Arch. Phys. Med. Rehabil. 2013;94:711-7.
63. Gonzalez-Villanueva L, S. Cagnoni S, Ascari L. Design of a wearable sensing system for human motion monitoring in physical rehabilitation. Sensors (Basel). 2013;13:7735-55.
64. de Groot IB, Bussmann JB, Stam HJ, Verhaar JA. Actual everyday physical activity in patients with end-stage hip or knee osteoarthritis compared with healthy controls. Osteoarthritis Cartilage. 2008;16: 436-42.
65. Taraldsen K, Chastin SF, Riphagen II, Vereijken B, Helbostad JL. Physical activity monitoring by use of accelerometer-based body-worn sensors in older adults: a systematic literature review of current knowledge and applications. Maturitas. 2012;71:13-9.
66. Menz HB, Lord SR, Fitzpatrick RC. Acceleration patterns of the head and pelvis when walking on level and irregular surfaces. Gait Posture. 2003;18:35-46.
67. Hickey A, Del Rin S, Rochester L, Godfrey A. Detecting free-living steps and walking bouts: validating an algorithm for macro gait analysis. Physiol. Meas. 2017;38:1-15.
68. Wagenaar RC, et al. Continuous monitoring of functional activities using wearable, wireless gyroscope and accelerometer technology. Conf. Proc. IEEE Eng. Med. Biol. Soc. 2011;2011:4844-7.
69. Tabak M, et al. Telemonitoring of daily activity and symptom behavior in patients with COPD. Int. J. Telemed. Appl. 2012;438736:1-8.
70. Kirchner M, Schubert P, Liebherr M, Haas CT. Detrended fluctuation analysis and adaptive fractal analysis of stride time data in Parkinson's disease: stitching together short gait trials. PLoS One. 2014;9(1):e85787.

71. Bolink SAAN, et al. Validity of an inertial measurement unit to assess pelvic orientation angles during gait, sit-stand transfers and step-up transfers: Comparison with an optoelectronic motion capture system. Med. Eng. Phys. 2016;38:225-31.
72. Lugade V, Fortune E, Morrow M, Kaufman K. Validity of using tri-axial accelerometers to measure human movement – Part I: Posture and movement detection. Med. Eng. Phys. 2014;36:169-76.
73. Senden R, Grimm B, Meijer K, Savelberg H, Heyligers IC. The importance to including objective functional outcomes in the clinical follow up of total knee arthroplasty patients. Knee. 2011;18:306-11.
74. Doi T, et al. The harmonic ratio of trunk acceleration predicts falling among older people: results of a 1-year prospective study. J. Neuroeng. Rehabil. 2013;10:1-6.
75. Iosa M, et al. Stability and harmony of gait in patients with subacute stroke. J. Med. Biol. Eng. 2016;36: 635-43.
76. Stergiou N, Harbourne R, Cavanaugh J. Optimal movement variability: a new theoretical perspective for neurologic physical therapy. J. Neurol. Phys. Ther. 2006;30:120-9.
77. Brandt KD, Dieppe P, Radin EL. Etiopathogenesis of osteoarthritis. Rheum Dis Clin North Am 2008; 34:531-59.
78. Verweij LM, van Schoor NM, Deeg DJ, et al. Physical activity and incident clinical knee osteoarthritis in older adults. Arthritis Rheum. 2009;61:152-7.
79. Vignon E, Valat JP, Rossignol M, et al. Osteoarthritis of the knee and hip and activity: a systematic international review and synthesis (OASIS). Joint Bone Spine. 2006;73:442-55.
80. Dekker J, van Dijk GM, Veenhof C. Risk factors for functional decline in osteoarthritis of the hip or knee. Curr Opin Rheumatol. 2009;21:520-4.
81. Fransen M, McConnell S, Bell M. Therapeutic exercise for people with osteoarthritis of the hip or knee. A systematic review. J Rheumatol. 2002:29:1737-45.
82. Baar van ME, Assendelft WJJ, Dekker J, et al. Effectiveness of exercise therapy in patients with osteoarthritis of the hip or knee: a systematic review of randomized clinical trials. Arthritis Rheum. 1999;42:1361-9.
83. Dunlop DD, Semanik P, Song J, et al. Risk factors for functional decline in older adults with arthritis. Arthritis Rheum. 2005;52:1274-82.
84. Terwee CB, Bouwmeester W, van Elsland SL, et al. Instruments to assess physical activity in patients with osteoarthritis of the hip or knee: a systematic review of measurement properties. Osteoarthritis Cartilage. 2011;19:620-33.

Chapter 2

Obesity is the main factor in the increased knee adduction moment in female osteoarthritis patients during gait

Verlaan L., Oomen P.W., Schmitz T., Liu W.Y, Peters M.J.M, Emans P.J., van Rhijn L.W., Drost M.R., Meijer K

Submitted

Abstract

Background
Knee osteoarthritis is a common cause of immobility and is characterized by pain and limitation of daily activities. The knee adduction moment is related to the onset and progression of knee osteoarthritis and can be estimated by gait analysis. Furthermore, body weight is an important risk factor for the development of knee osteoarthritis and is also related to the adduction moment. Next to body weight, age and female gender are also important risk factors for knee osteoarthritis.

Research question
What is the relationship of knee osteoarthritis, the incremental effect of obesity and walking speed with the adduction moment.

Methods
This case-control study included 15 obese and 18 lean female patients with knee osteoarthritis and 22 healthy controls. All participants performed gait trials at self-selected and a standardised walking speed (1.5 m/s). Standard gait analysis was used to calculate three-dimensional lower extremity joint kinematics and kinetics.

Results
At self-selected speed obese patients walked slower and adduction moments were significantly increased compared to the lean groups. Standardised speed was faster compared to self-selected speed in all groups and resulted in a larger difference in adduction moments between obese patients and the lean groups. The results of the lean osteoarthritis group showed no statistically significant differences in peak and impulse knee adduction moment compared to the weight-matched controls.

Significance
The results of this study indicate that osteoarthritis has no effect on knee adduction moment but obesity in combination with osteoarthritis has a more prominent effect on knee adduction moment. Patients, especially obese patients, walk slower and implement smaller steps to reduce peak knee loading.

Introduction

Osteoarthritis (OA) is a common musculoskeletal disease, characterized by cartilage degradation and subchondral bone deformations that can occur in any joint.[1] The knee joint is most commonly affected, and it is clinically characterized by pain, limitation of movement, tenderness, and local inflammation.[2] Age, female gender, and weight are known as contributors to the progression of knee OA.[3,4] Prevalence of knee OA increases with age, especially in people aged 50 years and older and this effect is elevated in females.[5] According to the World Health Organization, OA is the fourth leading cause of immobility, with a prevalence of 18% for women and 9.6% for men aged above 60 years.[6] Furthermore, obese subjects with a BMI between 30 and 35 kg/m^2 have almost four times the risk of developing knee OA compared to subjects with a BMI below 25 kg/m^2.[7] Other risk factors for knee OA include muscle weakness[8] and gait abnormalities.[9]

In most knee OA patients, the medial side is affected.[10] Due to lateral laxity and varus alignment of the knee joint, the medial compartment experiences substantially higher loads compared to the lateral compartment.[11] At some point cartilage is unable to adapt to the specific load and starts to deteriorate.[12] Especially during walking, the medial compartment of the knee is repeatedly exposed to high joint contact forces.[13] Therefore, the evaluation of knee mechanics during walking is of importance to understand the development of knee OA.[14] Several studies have examined the knee adduction moment (KAM) parameters in patients with knee OA.[15-18] A high KAM is related to the onset and progression of knee OA.[14] Typically, KAM is calculated as the product of the coronal plane ground reaction force vector and the perpendicular distance from the vector to the knee joint center and is the best predictor of lower extremity alignment.[19] Varus alignment increases the moment arm, which increases KAM. Ro et al found significant higher KAM parameters in females older than 55 years, but no differences in lower extremity alignment between both sexes.[20] Biomechanical explanations for increased knee joint loading and increased rates of knee OA in females are lacking.

According to knee OA, especially the peak load in early stance and the cumulative load of a full gait cycle are strong predictors of the presence, severity and rate of progression of medial compartment knee OA.[21] However, we suggest that these studies might overestimate the relationship of knee OA with the KAM, since groups are not completely comparable for body weight or severity of knee OA. For example, Landry et al., Mundermann et al. and Blazek et al. included groups of patients with unequal body weight or severity of OA.[16,17,21] Body weight is an important factor contributing to joint loading; it has been shown that obese subjects have an increased ground reaction force

compared to normal-weighted controls.[22] Furthermore, systemic factors from adipose tissue could accelerate knee cartilage degeneration in obese subjects.[23]
To investigate the effect of knee OA on KAM, it is of great importance to use accurate diagnostics for measuring the degree of OA. Harding et al.[18] investigated participants with moderate OA. To objectify the degree of OA only X-rays were applied, and no radiological imaging was used for the controls. The current study applied MRI for all participants and X-rays for all participants with knee OA to have an accurate measurement for the degree of knee AO for all participants.
In order to reduce high joint loading, obese participants and knee OA patients demonstrate similar adaptations in their walking pattern.[22] These adaptations are strategies to redirect or decrease the amount of ground reaction force, or to influence alignment of the knee joint. For example, reducing walking speed is a comprehensive strategy to decrease ground reaction force. It has been shown that especially patients with mild knee OA benefit from reducing walking speed in order to reduce the maximal KAM.[24] In addition, obese participants showed decreased joint loading with slower walking speeds.[22] On the other hand, toe-out gait is a strategy to influence the alignment of the knee joint. A toe-out gait is possibly induced by external hip rotation.[25] Previous studies showed that a high toe-out gait was able to decrease KAM during stance.[26] A greater toe-out angle seems to shift the load closer to the centre of the knee joint, resulting in lower KAM values. Therefore, toe-out angle should be taken into account, considering KAM in patients with knee OA.
The purpose of this study was to evaluate the relationship between knee OA and KAM, and the incremental effect of obesity. Therefore, we aim to include three groups of female participants: lean OA patients, weight matched healthy control participants and obese knee OA patients. Our secondary aim is to evaluate the effect of walking speed and toe-out angle that are associated with the KAM.

Materials and methods

Participants

Three groups were included consisting of an obese knee OA group (BMI: 30-40 kg/m^2), a lean knee OA group (BMI: 20-25 kg/m^2) and a healthy control group (BMI: 20-25 kg/m^2). Only women with an age between 50 and 65 years were included, as knee OA prevalence is highest in this group. Furthermore, selecting only females reduced the risk for bias, since cartilage composition and gait mechanics are different between men and women.[20] The upper aged limit was adopted to prevent inclusion of participants at

high risk of having comorbidities (e.g. type II diabetes mellitus, osteoporosis, dementia, cardiovascular disease). OA patients having a Kellgren Lawrence (KL) score between 1 and 3 at the medial tibiofemoral site were included. Knee OA patients were recruited by the 'Artrose Kliniek' Maastricht at the Maastricht University Medical Center (MUMC+). Healthy participants were recruited through the department of Human Movement Sciences, the department of Physical Therapy (MUMC+) and through local physical therapy clinics in Maastricht.

Clinical exclusion criteria were any inflammatory arthritis, trauma, OA at any other joint including tibiofemoral OA on the lateral site, patellofemoral OA, anterior cruciate ligament injury, medial and collateral ligament injury, psychiatric illness (patients are excluded on this point when such a diagnosis is present in the patient's medical file according to the DSM classification criteria for psychiatric illnesses). Healthy participants were included when they were non-obese (BMI: 20-25 kg/m^2), did not have knee OA (according to the American College of Rheumatology classification criteria[27]) and did not meet any of the exclusion criteria.

This case control study (Level of Evidence: III) was approved by the Maastricht University Medical Ethical Committee and all participants gave their informed consent.

Radiological imaging

Roentgenography and MRI of the knee was performed in order to evaluate the knee cartilage. An X-ray was used for screening purpose; patients were included when they had a Kellgren-Lawrence-knee score between 1 and 3 at the medial tibiofemoral site. Two orthopaedic surgeons assessed the x-rays individually.

To more accurately assess cartilage health in all study groups, Magnetic Resonance Imaging (MRI) was performed using a 3T Philips Intera Scanner (*Philips Medical Systems, Best, The Netherlands*). Cartilage health was evaluated based on MRI Osteoarthritis Knee Score (MOAKS).[28] For a more detailed description of imaging procedures, we refer to Verlaan et al..[29]

Measurements

Gait analysis took place at the Motion Laboratory of Maastricht University. A three-dimensional motion capture system (*Vicon Motion Systems, 6 MX3 and 2 T20 cameras, 200Hz, Oxford, UK*) and a force platform (*9081E, 1000Hz, Kistler Instruments AG, Winterthur, Switzerland*) were used simultaneously within the Nexus software. Sixteen retroreflective markers were placed on the subject's lower extremities in order to use the 3D motion capture system according as defined by the plug-in-gait marker placement manual: both sides on the spina iliaca anterior superior, spina iliaca

posterior superior, thigh (the line between the trochantor major and lateral epicondyle of femur), lateral epicondyle of femur, lower leg (the line between the lateral epicondyle of femur and lateral malleolus), lateral malleolus, tuber calcanei and art. metatarsophalangeale II. Inverse dynamics was performed using ground reaction forces and motion analysis, in order to calculate joint moments. Furthermore, anthropometrical data such as height, mass, leg length, knee and ankle width were obtained.

The participants walked barefooted during the gait analysis. Gait analysis was performed at self-selected walking speed and a standardised walking speed of approximately 1.5 m/s (trials were acceptable between 1.4 m/s and 1.6 m/s). Subject were instructed to walk without aiming for the force platform in such a way that the fifth step landed completely on the force platform (the affected leg in the OA groups or dominant leg in the control group) and they continued to walk for at least three steps after hitting the force platform. Walking speed was monitored by two electronic timing gates. Per subject five correct trials per speed condition were obtained.

Data analysis

Three-dimensional ankle, knee, hip and foot progression angles and moments were processed via the dynamic pipeline of VICON Nexus software (*version 1.8.5*). Subsequent data analysis was performed in Microsoft Excel 2013 and IBM SPSS statistics 23 with α=0.05. One-way analysis of variance (ANOVA) was used to detect an overall significant difference between groups. In addition, post hoc Bonferroni tests were performed for multiple comparisons. The kinetic and kinematic data of the fifth step of each trial at both self-selected and standardised speed were normalized in 0-100% of stance phase with intervals of 0.5%. Our primary outcome measure was the magnitude of KAM (Nm). Therefore, the early and late KAM peaks were obtained for each trial. Furthermore, the dip amongst the peaks was determined and the KAM impulse (Nm·s) was calculated by numerical integration. Finally, data are also presented after a correction for body mass (Nm/kg and Nm·s/kg), since body weight is expected to have a major effect on KAM.

Statistics

Mean and standard deviations were calculated for the anthropometric data, significance between groups was calculated using one-way ANOVA. Bonferonni post hoc procedures were used for pair-wise comparisons. Averages over the different trials per subject were calculated for knee, ankle, foot progression, and hip angles all in x-y-z direction, KAM and flexion-extension moment. Statistical differences between groups

and walking conditions (i.e. self-selected and standardized speed) were tested using two-way repeated measures ANOVA. Finally, a linear regression with Pearson correlation were used for toe-out angle and hip rotation angle and their correlation with the first and second peak of KAM and KAM impulse.

Results

Anthropometrical and spatiotemporal characteristics

In total 55 participants were included in three groups. No statistical differences were found for age, height, weight or BMI between the lean OA and control group. The obese OA group was significantly shorter and heavier compared to the lean groups. The Kellgren-Lawrence grade and MOAKS indicated no differences in severity of knee OA between the lean and obese knee OA group (Table 2.1).

Table 2.1 Anthropometric data between groups.

	Healthy subjects	Lean knee OA patients	Obese OA patients
Number	22	18	15
Height (cm)	166 (SD 4.2)	166 (SD 5.4)	161 (SD 5.4)*#
Weight (kg)	62 (SD 5.9)	65 (SD 7.5)	84 (SD 11.7)*#
Age (years)	58 (SD 4.3)	59 (SD 3.0)	58 (SD 5.1)
KL grade† (N)	0:22	1:3;2:10;3:5*	1:0;2:9;3:6*
MOAKS (score/items)	0.50 (SD 0.09)	0.94 (SD 0.19)*	1.03 (SD 0.16)*

Data is displayed as mean (SD standard deviation); *: significant difference compared to Control group (P<0.05); #: significant difference compared to Lean OA group (P<0.05); KL: Kellgren-Lawrence; † Inter observer reliability: R^2 Lean OA: 0.905, R^2 Obese OA: 0.739; MOAKS: MRI Osteoarthritis Knee Score.

At self-selected pace obese OA patients walked on average slower than lean OA and control participants (respectively. 1.11, 1.28, 1.34 m/s). All groups walked slower at self-selected speed compared to standardised walking speed (1.5 m/s). Obese patients walked with significantly shorter strides at both speeds (-0.08 m); and higher stride frequency with 7% at standardised speed compared to healthy participants (Table 2.2).

Table 2.2 Spatiotemporal data between groups.

	Self-selected speed			Standardized speed		
	Healthy subjects	Lean knee OA patients	Obese OA patients	Healthy subjects	Lean knee OA patients	Obese OA patients
Speed (m/s)	1.34 (SD 0.15)	1.28 (SD 0.14)	1.11 (SD 0.14)*#	1.51 (SD 0.05)	1.52 (SD 0.09)	1.48 (SD 0.07)
Cadance (Hz)	1.98 (SD 0.15)	2.00 (SD 0.24)	1.91 (SD 0.19)	2.13 (SD 0.12)	2.18 (SD 0.18)	2.28 (SD 0.14)*
Step Length (m)	0.67 (SD 0.05)	0.64 (SD 0.06)	0.59 (SD 0.06)*#	0.71 (SD 0.05)	0.70 (SD 0.04)	0.65 (SD 0.05)*#
Step Width (mm)	167 (SD 26.3)	169 (SD 27.2)	196 (SD 31.0)*#	171 (SD 27.6)	175 (SD 23.6)	183 (SD 30.8)

Data is displayed as mean (SD standard deviation); *: significant difference compared to Control group (P<0.05); #: significant difference compared to Lean OA group (P<0.05).

KAM between groups

At self-selected speed, the first peak of KAM (Nm) during early stance (non-normalized) was 40% higher for the obese knee OA group compared to healthy controls (P=0.004) (Figure 2.1A). Moreover, no significant differences were found between the lean groups or between OA groups for the first peak of KAM at self-selected speed. The second peak of KAM showed significant differences between the obese OA group compared to the lean OA group and healthy control group (resp. P=0.002 and P<0.001), but no differences were found between the lean groups at self-selected speed. Furthermore, the mean KAM impulse was 59% higher for the obese group compared to the lean OA group at self-selected speed (P<0.001). No statistical differences for KAM impulse were found between the lean groups. The dip of KAM at mid stance between the first and second peak was significant higher for the lean OA group compared to the healthy controls (76%), moreover, a significant incremental effect for the obese OA group was found (75%).

Walking at a faster standardised pace (1.5 m/s) resulted in similar significant differences compared to self-selected speed (non-normalized) (Figure 2.1B). However, at the standardised walking speed we found the first peak of KAM also statistically higher for obese OA compared to the lean OA group (P<0.001)

Normalizing KAM (Nm/kg) for body mass effectively removed the differences in the first peak of KAM between the three groups at both walking speeds (Figure 2.1C and 2.1D). Furthermore, KAM impulse and second peak were not significant different between OA groups after normalization for body mass. KAM impulse at both speeds and the second peak of KAM at self-selected speed remain significant higher after normalization for the obese knee OA group compared to the healthy control group.

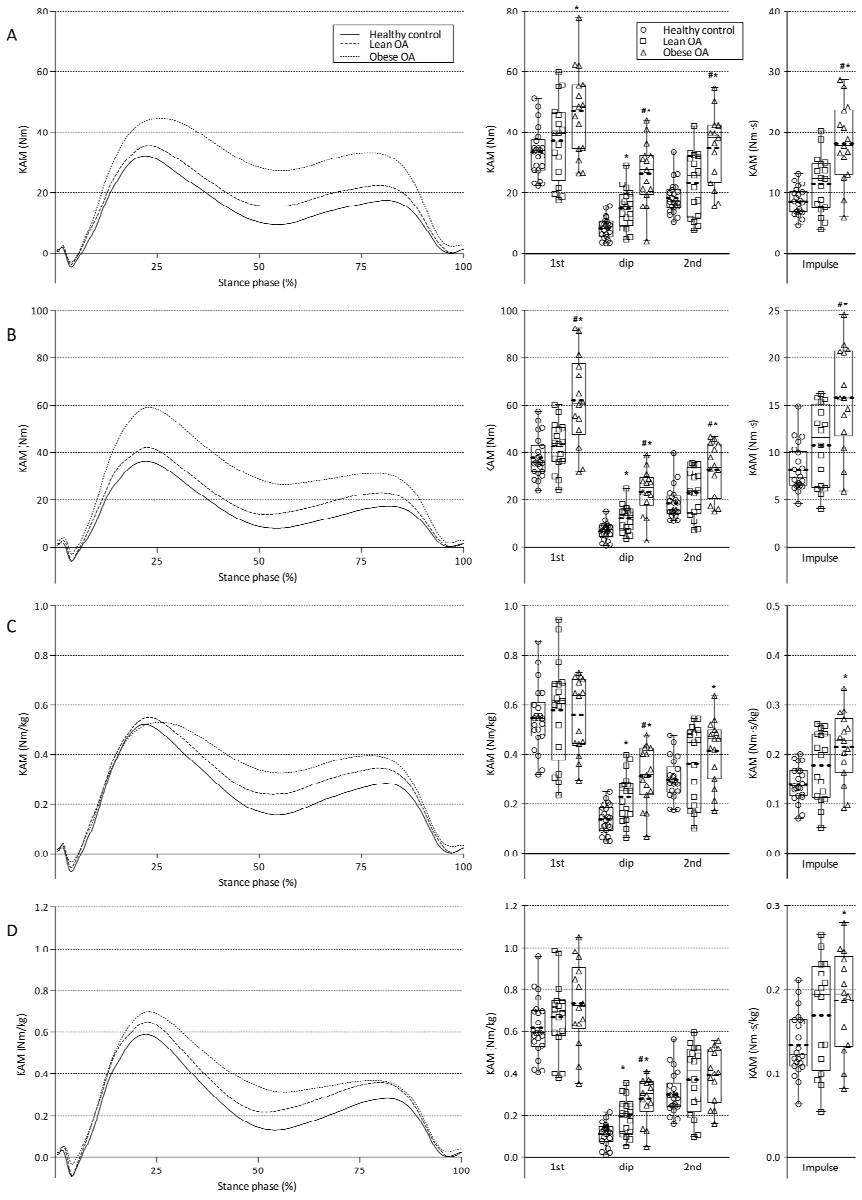

Figure 2.1 Knee adduction moment during 100% of stance phase divided per study groups. Figures show mean curve per group (left); a box plot of first peak, dip and second peak (middle); and a box plot of impulse (right). Raw KAM data is presented in **A**) at self-selected speed; and **B**) at standardised speed (1.5 m/s). KAM data normalized for body mass is presented in **C**) at self-selected speed; and **D**) standardised speed (1.5 m/s). *: significant difference compared to Control group (P<0.05); $^{\#}$: significant difference compared to Lean OA group (P<0.05). Boxplots show quartiles and individual mean, group mean is indicated by dotted line through boxplot.

Correlations of KAM to kinematic parameters

Hip exorotation was related to KAM in the obese knee OA group at standard speed only; 1° hip external rotation decreased KAM impulse by 7.2 Nmm·s/kg R^2=0.33 (*P*=0.029). The other groups did not show correlations between KAM and hip rotation. Furthermore, no correlations were found in any group between toe-out angle and KAM at self-selected or standard speed (*P*>0.1).

Discussion

The primary aim of this study was to evaluate whether knee OA or the incremental effect of obesity has a more prominent role in the magnitude of KAM. Therefore, we evaluated walking mechanics at different speeds between clearly defined groups for age, BMI and severity for knee OA. Our results showed overall significantly higher KAM parameters for obese knee OA patients, normalized and non-normalized for weight, compared to lean knee OA patients and lean healthy controls. At higher walking speeds this difference was even more pronounced. Lean OA patients showed no significant differences in KAM peaks and total impulse compared to weight matched healthy controls. Furthermore, walking speed did not influence KAM significance between weight matched participants. Therefore, we suggest that osteoarthritis has no effect on knee adduction moment but obesity in combination with osteoarthritis has a more prominent effect on knee adduction moment.

An elevated KAM was associated with the onset and progression of knee OA.[12] However, our results show that impulse and peaks of KAM were not found statistically different between knee OA patients and weight matched healthy volunteers. Interestingly, our results on body mass normalized KAM found significant higher KAM impulse and second peaks in obese patients compared to healthy controls. This indicates that obesity remains an important determinant of KAM, even if KAM values were normalized for body mass. Current literature acknowledges the importance of body mass in relation to KAM.[30] On the other hand, most studies included groups of patients with unequal body weight or severity of OA.[16,17,21] Moreover, interventions targeting weight reduction show up to reduce KAM.[18]

Next to weight reduction, it is known that several gait modifications are associated with a reduction of the magnitude of the first peak of the KAM. From electromyography (EMG)-driven modelling studies it is known that muscle forces have a major contribution to knee joint loading.[31] On the other hand, gait modifications seem to have

different effects on muscle activation patterns around the knee.[31] In the recent study we only looked at possible gait modifications.

Spatiotemporal characteristics should be taken into account considering KAM. First, walking speed is an important characteristic that influences KAM; decreasing walking speed can substantially reduce KAM.[24] Our results show a significant decrease of 6.3-7.2% of KAM at self-selected speed compared to standard speed in all groups. Second, obese OA patients implemented significantly smaller step length at both speeds, in order to reduce peak loading at the knee joint. In addition, they have the slowest self-selected pace and increase mainly stride frequency at standardised speed. These smaller steps decrease vertical acceleration, which possibly decreases peak loading of KAM.[32] On the other hand, this strategy increased the dip of KAM during mid stance.

A different strategy to decrease joint loading is to increase toe out angle. However, literature is not conclusive about toe out angle as possible strategy to decrease KAM. Moreover, toe out gait is expected to decrease second peak of KAM for some patients, whilst other patients benefit from a toe in strategy in order to decrease KAM.[17,33] Our results showed no correlation between toe-out angle and KAM. Furthermore, hip exorotation seemed to lower total KAM loading in the obese knee OA group; however, no correlations were found in the other groups. Van der Noort et al suggested an increased KAM in early stance phase caused by hip exorotation, although no beneficial effects over the entire stance phase were found.[33] Another gait strategy which may reduce KAM during gait is medializing the knee during the stance phase (medial thrust). For example, Gerbrands et al reported a significant reduce of the first KAM peak, although, late stance KAM peak and KAM impulse showed no significant differences after correcting for walking speed.[34] More recently, Booij et al showed a reduce of KAM of 43% during medial thrust conditions.[31]

In the present study both patients and healthy volunteers received MRI for MOAKS determination. Hence, healthy cartilage was confirmed in the control group; and obese and lean knee OA patients did not differ in cartilage degeneration. Taking the number of participants into account we were unable to use stratification for severity. Severity of knee OA was shown to be positively correlated to the magnitude of KAM.[21] Interestingly, in the aforementioned study of Mundermann et al. severe OA patients had a higher body mass (+10 kg) compared to the less severe patients.[21] Our results suggest that body mass might contribute to this difference.

A limitation to our study design is the lack of a fourth group of weight matched obese control participants. Literature already provided evidence that body weight without knee OA contributed significantly to a high KAM magnitude.[22] Nevertheless, our results should be taken carefully when interested in the sole effect of obesity on KAM. A

second limitation is that we included female participants only. Study results are hard to generalize to male patients, since female patients demonstrate no difference in alignment, but an increased KAM compared to male patients.[20] A final limitation is that we measured lower extremities only. Hence, we were unable to determine trunk sway. Literature has shown that trunk sway was able to decrease KAM up to 65%.[35] Future studies should take trunk sway into account in order to find possible gait adaptations.

Conclusions

In conclusion, this study included clearly defined groups in order to evaluate the effect of knee OA, obesity and walking speed on KAM. The results show that obesity combined with knee OA had more effect than knee OA pathology alone on KAM peaks and impulse. Moreover, differences in KAM were primarily found between the obese knee OA group and the lean groups and secondarily between knee OA patients and weight matched healthy participants, which implies that knee OA pathology alone is not the major determinant of KAM. The toe-out angle, hip endo/exorotation and speed did not correlate with KAM in any group. Finally, in the evaluation of KAM, spatiotemporal characteristics (e.g. walking speed and step length) should be taken into account.

References

1. Allen KD, Golightly YM. Epidemiology of osteoarthritis: state of the evidence. Curr Opin Rheumatol. 2015;27(3):276-83.
2. Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, et al. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis. 2003;62(12):1145-55.
3. Zhang W, Doherty M, Peat G, Bierma-Zeinstra MA, Arden NK, Bresnihan B, et al. EULAR evidence-based recommendations for the diagnosis of knee osteoarthritis. Ann Rheum Dis. 2010;69(3):483-9.
4. Wei J, Gross D, Lane NE, Lu N, Wang M, Zeng C, et al. Risk factor heterogeneity for medial and lateral compartment knee osteoarthritis: analysis of two prospective cohorts. Osteoarthritis Cartilage. 2019;27:603-10.
5. Arden N, Nevitt MC. Osteoarthritis: epidemiology. Best Pract Res Clin Rheumatol. 2006;20(1):3-25.
6. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. Bull World Health Organ. 2003;81:646-56.
7. Anderson JJ, Felson DT. Factors associated with osteoarthritis of the knee in the first national Health and Nutrition Examination Survey (HANES I). Evidence for an association with overweight, race, and physical demands of work. Am J Epidemiol. 1988;128(1):179-89.
8. Segal NA, Glass NA, Torner J, et al. Quadriceps weakness predicts risk for knee joint space narrowing in women in the MOST cohort. Osteoarthritis Cartilage. 2010;18(6):769-75.
9. Al-Zahrani KS, Bakheit AM. A study of the gait characteristics of patients with chronic osteoarthritis of the knee. Disabil Rehabil. 2002;24(5):275-80.
10. Lu N, Niu J, Choi H, Zhang Y. Difference in Risk Factor Profile Between Medial and Lateral Compartment Involvement in Tibiofemoral Knee Osteoarthritis [abstract]. Arthritis Rheumatol. 2016; 68 (suppl 10).
11. Schipplein OD, Andriacchi TP. Interaction between active and passive knee stabilizers during level walking. J Orthop Res. 1991;9(1):113-9.
12. Andriacchi TP, Koo S, Scanlan SF. Gait mechanics influence healthy cartilage morphology and osteoarthritis of the knee. J Bone Joint Surg Am. 2009;91 Suppl 1:95-101.
13. Andriacchi TP. Dynamics of knee malalignment. Orthop Clin North Am. 1994;25(3):395-403.
14. Andriacchi TP, Mundermann A, Smith RL, Alexander EJ, Dyrby CO, Koo S. A framework for the in vivo pathomechanics of osteoarthritis at the knee. Ann Biomed Eng. 2004;32(3):447-57.
15. Baliunas AJ, Hurwitz DE, Ryals AB, Karrar A, Case JP, Andriacchi TP. Increased knee joint loads during walking are present in subjects with knee osteoarthritis. Osteoarthritis Cartilage. 2002;10(7):573-9.
16. Landry SC, McKean KA, Hubley-Kozey CL, Stanish WD, Deluzio KJ. Knee biomechanics of moderate OA patients measured during gait at a self-selected and fast walking speed. J Biomech. 2007;40(8):1754-61.
17. Blazek K, Asay JL, Erhart-Hledik J, Andriacchi T. Adduction moment increases with age in healthy obese individuals. J Orthop Res. 2013;31(9):1414-22.
18. Harding GT, Hubley-Kozey CL, Dunbar MJ, Stanish WD, Astephen Wilson JL. Body mass index affects knee joint mechanics during gait differently with and without moderate knee osteoarthritis. Osteoarthritis Cartilage. 2012;20(11):1234-42.
19. Schmitz A, Noehren B. What predicts the first peak of the knee adduction moment? Knee. 2014;21:1077-83.
20. Ro DH, Lee DY, Moon G, Lee S, Seo SG, Kim SH, et al. Sex differences in knee joint loading: Cross-sectional study in geriatric population. J Orthop Res. 2017;35(6):1283-9.
21. Mundermann A, Dyrby CO, Andriacchi TP. Secondary gait changes in patients with medial compartment knee osteoarthritis: increased load at the ankle, knee, and hip during walking. Arthritis Rheum. 2005;52(9):2835-44.
22. Browning RC, Kram R. Effects of obesity on the biomechanics of walking at different speeds. Med Sci Sports Exerc. 2007;39(9):1632-41.
23. Bao JP, Jiang LF, Chen WP, Hu PF, Wu LD. Expression of vaspin in the joint and the levels in the serum and synovial fluid of patients with osteoarthritis. Int J Clin Exp Med. 2014;7(10):3447-53.

24. Mundermann A, Dyrby CO, Hurwitz DE, Sharma L, Andriacchi TP. Potential strategies to reduce medial compartment loading in patients with knee osteoarthritis of varying severity: reduced walking speed. Arthritis Rheum. 2004;50(4):1172-8.
25. Svenningsen S, Terjesen T, Auflem M, Berg V. Hip rotation and in-toeing gait. A study of normal subjects from four years until adult age. Clin Orthop Relat Res. 1990;(251):177-82.
26. Ogaya S, Naito H, Iwata A, Higuchi Y, Fuchioka S, Tanaka M. Toe-Out Gait Decreases the Second Peak of the Medial Knee Contact Force. J Appl Biomech. 2015;31(4):275-80.
27. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum. 1986;29(8): 1039-49.
28. Hunter DJ. Guermazi A, Lo GH, Grainger AJ, Conaghan PG, Boudreau RM, et al. Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). Osteoarthritis Cartilage. 2011;19(8):990-1002.
29. Verlaan L, Boekesteijn RJ, Oomen PW, Liu W-Y, Peters MJM, Witlox MA, et al. Biomechanical Alterations during Sit-to-Stand Transfer Are Caused by a Synergy between Knee Osteoarthritis and Obesity. BioMed Research International. 2018;2018:7.
30. Messier SP, Pater M, Beavers DP, Legault C, Loeser RF, Hunter DJ, et al. Influences of alignment and obesity on knee joint loading in osteoarthritic gait. Osteoarthritis Cartilage. 2014;22(7):912-7.
31. Booij MJ, Richards R, Harlaar J, van den Noort JC. Effect of walking with a modified gait on activation patterns of the knee spanning muscles in people with medial knee osteoarthritis. Knee. 2020;27: 198-206.
32. Gerbrands TA, Pisters MF, Vanwanseele B. Individual selection of gait retraining strategies is essential to optimally reduce medial knee load during gait. Clin Biomech (Bristol, Avon). 2014;29(7):828-34.
33. van den Noort JC, Schaffers I, Snijders J, Harlaar J. The effectiveness of voluntary modifications of gait pattern to reduce the knee adduction moment. Hum Mov Sci. 2013;32(3):412-24.
34. Gerbrands TA, Pisters MF, Theeven PJR, Verschueren S, Vanwanseele B. Lateral trunk lean and medializing the knee as gait strategies for knee osteoarthritis. Gait Posture. 2017;51:247-53.
35. Mundermann A, Asay JL, Mundermann L, Andriacchi TP. Implications of increased medio-lateral trunk sway for ambulatory mechanics. J Biomech. 2008;41(1):165-70.

Chapter 3

Knee adduction moments are not increased in obese knee osteoarthritis patients during stair negotiation

Verlaan L., Boekesteijn R.J., Oomen P.W., Liu W.Y., Peters M.J.M., Emans P.J., van Rhijn L.W., Meijer K.

Gait & Posture. 2019;73:154-160

Abstract

Background
Negotiating stairs is an important activity of daily living that is also associated with large loads on the knee joint. In medial compartment knee osteoarthritis, the knee adduction moment during level walking is considered a marker for disease severity. It could be argued that the discriminative capability of this parameter is even better if tested in a strenuous stair negotiation task.

Research question
What is the relation with knee osteoarthritis on the knee adduction moment during the stance phase of both stair ascent and descent in patients with and without obesity?

Methods
This case control study included 22 lean controls, 16 lean knee osteoarthritis patients, and 14 obese knee osteoarthritis patients. All subjects ascended and descended a two-step staircase at a self-selected, comfortable speed. Three-dimensional motion analysis was performed to evaluate the knee adduction moment during stair negotiation.

Results
Obese knee osteoarthritis patients show a prolonged stance time together with a more flattened knee adduction moment curve during stair ascent. Normalized knee adduction moment impulse, as well as the first and second peaks were not different between groups. During stair descent, a similar increase in stance time was found for both osteoarthritis groups.

Significance
The absence of a significant effect of groups on the normalized knee adduction moment during stair negotiation may be explained by a lower ambulatory speed in the obese knee osteoarthritis group, that effectively lowers vertical ground reaction force. Decreasing ambulatory speed may be an effective strategy to lower knee adduction moment during stair negotiation.

Introduction

Osteoarthritis (OA) is a common musculoskeletal disease, characterized by cartilage degradation and subchondral bone deformations that can occur in any joint.[1] Most commonly, OA manifests at the knee joint where it locally causes pain, movement limitations, tenderness, and inflammation.[2] According to the World Health Organization, OA is the fourth leading cause of immobility, with a prevalence of 18% for women and 9.6% for men aged above 60 years.[3] Prevalence of knee OA increases with age, especially above 50 years. This age-related increase in prevalence is further amplified by the female gender.[4] Another important risk factor for knee OA is obesity. Research has shown that obese subjects have almost four times the risk of developing knee OA when compared with non-obese subjects, which may be explained by both an increased knee loading as well as chronic low-grade inflammation.[5,6]

In most patients, knee OA is localized at the medial compartment.[7] Medial knee loads may be increased due to lateral laxity and varus alignment.[8] Considering that the medial compartment is not adapted to extreme loads, cartilage may deteriorate when the knee is repeatedly exposed to high joint forces during locomotor activities. Currently, it is believed that particularly high knee adduction moments (KAM) correlates with cartilage loss in the knee.[9] Several studies have already examined the KAM in patients with knee OA during level walking.[10-12] Here, especially the first KAM peak together with the cumulative load, determined from the impulse, are shown to be discriminative for the presence, severity and rate of progression of medial compartment knee OA.[9,13] In addition, obesity has been reported to augment KAM during level walking.[14] However, after removal of the direct contributions of body weight, KAM parameters may be different due to obesity-related level walking adaptations to limit knee loading.[14,15]

KAM is dependent of the magnitude of the ground reaction force (GRF) and its moment arm relative to the knee joint centre.[16] During level walking, the GRF vector usually passes medially of the knee. While KAM has been thoroughly investigated during level walking, little is known about KAM during stair negotiation[17], during which knee loads are higher compared to level walking.[18] Second, stair climbing is one the first encountered problems in knee OA patients and is often used to evaluate safety of hospital discharge.[19]

Although literature on KAM during stair negotiation in knee OA patients is scarce, several factors, including mechanical alignment, lateral trunk lean, toe-out gait, step width, and stair climbing velocity have been suggested to modify KAM during stair negotiation.[20-22] Those movement adaptations should thus be taken into consideration when evaluating KAM. Furthermore, it is important to discriminate between lean and

obese knee OA patients.[23] The aim of the current study is therefore to compare normalized KAM during the stance phase of stair negotiation between lean knee OA patients, obese knee OA patients, and healthy controls. As a secondary aim we also sought to explore select characteristics that could impact KAM such as ground reaction force, spatiotemporal parameters and toe-out angle. At last we want to investigate the relationship between normalized KAM during stair negotiation and level walking.

Methods

Study population

This cross-sectional study included three groups: obese knee OA (body mass index (BMI): 30-40 $kg \cdot m^{-2}$), lean knee OA (BMI: 20-25 $kg \cdot m^{-2}$) and healthy controls (BMI: 20-25 $kg \cdot m^{-2}$). Only women aged between 50 and 65 years were included in study, as knee OA prevalence is highest in this group. The upper aged limit was adopted to prevent inclusion of participants at high risk of having comorbidities (e.g. type II diabetes mellitus, osteoporosis, dementia, cardiovascular disease). OA patients having a Kellgren Lawrence (KL) score between 1 and 3 at the medial tibiofemoral site were included in this study. Recruitment of knee OA patients occurred via the 'Artrose Kliniek' at the Maastricht University Medical Center (MUMC+), The Netherlands. Healthy controls were recruited by the department of Nutrition and Movement Sciences, the department of Physical Therapy (MUMC+), and local physical therapy clinics in Maastricht, The Netherlands.

Exclusion criteria were any inflammatory arthritis, trauma, OA at any other joint in the lower extremities including patellofemoral OA and tibiofemoral OA on the lateral site, anterior cruciate ligament injury, medial and collateral ligament injury, and psychiatric illness according to the Diagnostic and Statistical Manual of Mental Disorders classification criteria for psychiatric illnesses (patients were excluded when diagnoses were present in their medical files). Healthy women were non-obese, did not meet the exclusion criteria, and did not have knee OA according to the American College of Rheumatology classification criteria.[24]

All subjects gave informed consent before participating in this study. This study was ethically approved by the METC aZM/UM.

Radiographic imaging

Radiographic imaging was used to evaluate knee cartilage and knee OA status. Presence of knee OA was assessed from X-ray images by the Kellgren-Lawrence knee score.[25] The X-ray images were evaluated double blind by two independent orthopaedic surgeons.
To more accurately assess cartilage health in all study groups, Magnetic Resonance Imaging (MRI) was performed using a 3T Philips Intera Scanner *(Philips Medical Systems, Best, The Netherlands)*. Cartilage health was evaluated based on the MRI Osteoarthritis Knee Score (MOAKS).[26] For a more detailed description of imaging procedures, we refer to Verlaan et al.[27]

Instrumentation

Motion analysis was performed with an eight camera, three-dimensional (3D) motion capture system *(Vicon, MX3, Oxford Metric, United Kingdom)* together with Nexus software V1.8. Kinetic data were obtained by one force platform *(9281A, Kistler instruments AG, Winethur, Switzerland)* which was incorporated in the first step of a two-step staircase. For reliable assessment of point of application of the GRF, the height of the stairs was taken into account. Sixteen reflective markers were placed on the lower extremities according to the Vicon Plug in Gait model in order to use the 3D motion capture system. In the obese knee OA group, however, there were occasional deviations from the model when the abdominal fat depot limited visibility of the markers on the spina iliaca anterior superior. In accordance with the Vicon Plug-in Gait Reference Guide, makers were then placed more dorsal and/or lateral. Correction for these deviations occurred by manually inserting the true distance between the left and right spina iliaca anterior superior into the system.

Procedure

Subjects were asked to ascend and descend the stairs barefooted at a self-selected, comfortable speed. The staircase consisted of one step (height=20 cm, length=30 cm; width=80 cm) which contained an embedded force plate, and a platform (height=20 cm, length=60 cm, width=80 cm). For safety reasons a railing was added to the staircase (Figure 3.1). Only one foot was placed at the step containing the force plate, corresponding to a step-over-step stair negotiation pattern. As a way of standardization, healthy subjects used their dominant leg, while knee OA patients used their affected leg to land on the step containing the force plate. Test trials were allowed for movement familiarization. Measurements were repeated with 10 seconds of resting intervals, until at least five successful trials were recorded.

During level walking analysis, subjects were asked to walk barefooted at self-selected walking speed. They were instructed to walk without aiming for the force platform in such a way that the fifth step landed completely on the force platform (i.e. the dominant leg for healthy subjects and the affected leg for OA patients).

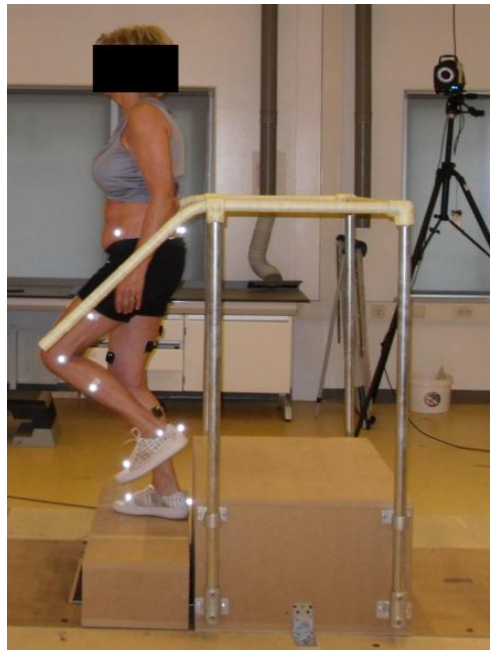

Figure 3.1 Staircase used in the experimental set-up. The staircase consisted of one step, containing the embedded force plate and one platform. Note that this picture was obtained during a pilot-session and that no footwear was worn during the actual measurements.

Data analysis

Data were processed via a dedicated MATLAB routine. Stair ascent and descent were analyzed separately to generate the biomechanical parameters of study. Those parameters included: stance phase duration, toe-out angle, KAM peaks, KAM dip, KAM impulse, and vertical (GRFz) and medio-lateral (GRFx) ground reaction forces. Positive values of the GRFz and GRFx correspond to the vertical and medial directed GRFs respectively. KAM impulse was obtained via numerical integration, using the trapezoid method, of the KAM-stance time curve. The toe-out angle was defined as the angle between the foot vector and sagittal laboratory axis. All parameters were normalized to the stance phase with intervals of 0.5%. Stance phase was defined as the time from heel strike till toe-off, which was based on GRF. Further, joint moments and the vertical

ground reaction force were normalized for body mass to remove the direct effects of body mass on KAM parameters.

Statistical analysis

Variables were tested for normality using the Shapiro-Wilk test. Accordingly, group differences were analysed with one-way ANOVA and non-parametric Kruskal-Wallis tests. Post-hoc analyses were performed using LSD and pairwise comparisons with Bonferroni adjustments respectively. A Chi-Square test was performed to test differences in the distribution of KL scores between groups. Data are presented as mean with standard deviation in brackets. A Pearson's correlation was performed to investigate the relation between toe-out angle and KAM impulse. In addition, the KAM parameters from the current study were correlated with the KAM parameters for the same subjects during level walking at preferred speed. Level of significance was set at $\alpha<0.05$. All statistical analyses were performed with SPSS statistics version 24 *(IBM, New York, United States of America).*

Results

Subject characteristics

Fifty subjects were included in this study (Table 3.1). There were no significant differences in age and height between groups. However, weight and BMI were higher in the obese knee OA group compared to both the controls and lean knee OA group. Radiographic analysis confirmed presence of knee OA in both groups. Distribution of the KL scores was not different between the two knee OA groups for both raters (P=0.263 and P=0.456). For the KL scoring, agreement between both orthopaedic surgeons was substantial (κ=0.656). Absence of meaningful knee OA in the control group was evidenced by MOAKS scoring, which was significantly lower in the control group, compared to both lean (P=0.005) and obese knee OA groups (P=0.002).

Ground reaction force

In absolute numbers both vertical and medial GRFs were increased in obese knee OA patients (P <0.050) (Table 3.2). After normalization for body mass, the first peak of the GRFz was reduced in obese knee OA patients compared to healthy controls and lean knee OA patients during stair ascent (P<0.001). During stair descent, only obese knee OA patients showed a lower first peak GRFz compared to healthy controls (P=0.005).

The GRFx was only increased in the obese knee OA group during stair ascent, when compared with healthy controls and lean OA patients. During stair descent, the dip of the GRFx during mid-stance was higher in the obese knee OA group compared to both the controls and lean knee OA group.

Table 3.1 Patient characteristics of the study groups, presented as mean (SD).

Demographics	Group		
	Control (n=20)	Lean knee OA (n=14)	Obese knee OA (n=16)
Age (years)	58.5 (4.7)	60.1 (3.4)	58.8 (4.6)
Height (m)	1.66 (0.04)	1.67 (0.05)	1.62 (0.07)
Weight (kg)	62.9 (6.2)	66.1 (7.3)	86.7 (13.1)[1,2]
BMI (kg/m²)	22.7 (1.8)	23.8 (2.2)	32.7 (3.2)[1,2]
KL-score (1; 2; 3)*	-	Rater A: 2; 6; 6	Rater A: 0; 8; 6
	-	Rater B: 3; 6; 5	Rater B: 3; 4; 7
MOAKS (score/items)	0.53 (0.43)	0.96 (0.68)[1]	1.15 (0.60)[1]

BMI = body mass index, KL = Kellgren Lawrence, MOAKS = MRI osteoarthritis knee score, OA = osteoarthritis. 1 = significantly different from control, 2 = significantly different from lean knee OA. ***** = for two obese knee OA patients no X-ray has been obtained, however, presence of OA was here confirmed by MRI.

KAM during stair negotiation

Before normalization, KAM parameters were increased in obese knee OA patients during both stair ascent and descent (P<0.050) (Table 3.2). However, after normalization obese knee OA patients show a more flattened KAM curve during both stair ascent and stair descent (Figure 3.2). During stair ascent, this pattern in obese knee OA patients was characterized by an increased KAM at the dip compared to both healthy controls (P=0.003) and lean knee OA patients (P=0.038). Both obese (P<0.001) and lean knee OA patients (P=0.019) showed a similar increase of the KAM dip during stair descent, when compared to healthy controls. After normalization, KAM impulse, first KAM peak, and the second KAM peak were not different between groups during stair ascent (P>0.050). Despite high between-subject variability (Figure 3.2), KAM impulse was found 45% higher in the obese knee OA group during stair descent, when compared to healthy controls (P=0.012).

Spatiotemporal parameters

During stair ascent obese knee OA patients showed a 15.7% longer stance phase than healthy controls (P<0.001) and 8.4 % longer stance phase compared to lean knee OA patients (P=0.033). Both lean and obese knee OA patients also showed increased stance times during stair descent, when compared to healthy controls. For the obese knee OA group this was an increase of 15.7% (P=0.001), whereas this was 10.7% for the lean knee OA group (P=0.019) (Table 3.2).

Table 3.2 Biomechanical parameters during stair negotiation. Data are presented as mean (SD).

	Stair Ascent			Stair Descent		
Biomechanical parameter	Control (n=20)	Lean knee OA (n=14)	Obese knee OA (n=16)	Control (n=20)	Lean knee OA (n=14)	Obese knee OA (n=16)
Stance phase duration (s)	0.89 (0.10)	0.95 (0.09)	1.03 (0.11)[1,2]	0.75 (0.08)	0.83 (0.07)[1]	0.87 (0.13)[1]
Toe-out angle (°)	6.5 (9.3)	0.7 (9.7)	3.6 (11.6)	16.1 (6.5)	9.9 (9.3)	15.2 (10.3)
KAM (Nm)						
1st peak	46.3 (9.6)	40.6 (16.7)	51.2 (11.4)	32.5 (10.2)	35.2 (7.0)	46.3 (18.5)[1,2]
Dip	7.6 (5.9)	10.0 (8.2)	20.8 (10.3)[1,2]	9.0 (4.0)	15.1 (6.0)[1]	25.9 (11.8)[1,2]
2nd peak	17.3 (8.6)	19.7 (13.5)	33.0 (15.4)[1,2]	38.8 (14.1)	41.9 (15.5)	56.4 (23.0)[1,2]
KAM impulse (Nm*s)	16.1 (5.3)	17.0 (8.1)	28.3 (8.8)[1,2]	13.8 (4.7)	19.1 (5.9)	27.6 (12.5)[1,2]
KAM (Nm/kg)						
1st peak	0.74 (0.16)	0.61 (0.24)	0.60 (0.17)	0.52 (0.18)	0.54 (0.12)	0.56 (0.22)
Dip	0.12 (0.09)	0.15 (0.12)	0.24 (0.11)[1,2]	0.16 (0.07)	0.23 (0.09)[1]	0.29 (0.14)[1]
2nd peak	0.28 (0.14)	0.30 (0.19)	0.39 (0.19)	0.62 (0.23)	0.64 (0.24)	0.66 (0.30)
KAM impulse (Nm*s/kg)	0.26 (0.08)	0.26 (0.12)	0.31 (0.11)	0.22 (0.08)	0.29 (0.10)	0.32 (0.15)[1]
Medial GRF (N)						
1st peak	24.5 (10.0)	24.7 (7.56)	39.2 (11.2)[1,2]	40.8 (10.4)	43.9 (17.2)	62.2 (15.4)[1,2]
Dip	3.22 (4.9)	5.56 (5.6)	11.8 (9.2)[1,2]	5.1 (5.7)	7.8 (6.9)	19.8 (12.5)[1,2]
2nd peak	20.7 (8.33)	20.0 (8.9)	35.2 (14.8)[1,2]	25.7 (5.6)	28.2 (8.9)	43.0 (15.3)[1]
Medial GRF (N/kg)						
1st peak	0.39 (0.15)	0.38 (0.11)	0.45 (0.11)	0.65 (0.17)	0.66 (0.22)	0.71 (0.15)
Dip	0.05 (0.08)	0.08 (0.09)	0.13 (0.10)[1]	0.08 (0.09)	0.12 (0.10)	0.22 (0.12)[1,2]
2nd peak	0.33 (0.13)	0.30 (0.13)	0.40 (0.15)	0.41 (0.09)	0.43 (0.13)	0.49 (0.13)
Vertical GRF (N)						
1st peak	625.5 (65.8)	675.4 (83.6)	836.9 (119.9)[1,2]	951.7 (104.0)	942.4 (169.8)	1171.1 (184.4)[1,2]
Dip	432.1 (63.8)	497.9 (61.1)[1]	654.0 (114.1)[1,2]	456.8 (65.5)	510.9 (59.0)	672.5 (126.9)[1,2]
2nd peak	773.8 (85.1)	759.2 (82.0)	976.2 (146.0)[1,2]	583.4 (63.3)	643.8 (68.1)	825.4 (125.9)[1,2]
Vertical GRF (BW)						
1st peak	1.06 (0.04)	1.04 (0.04)	0.99 (0.04)[1,2]	1.53 (0.13)	1.45 (0.17)	1.38 (0.16)[1]
Dip	0.70 (0.07)	0.77 (0.05)[1]	0.77 (0.06)[1]	0.74 (0.06)	0.79 (0.04)[1]	0.79 (0.09)[1]
2nd peak	1.26 (0.08)	1.17 (0.07)[1]	1.15 (0.12)[1]	0.95 (0.06)	1.00 (0.05)	0.97 (0.07)

OA = osteoarthritis, KAM = knee adduction moment, GRF = ground reaction force, BW = body weight. 1 = significantly different from control, 2 = significantly different from lean knee OA.

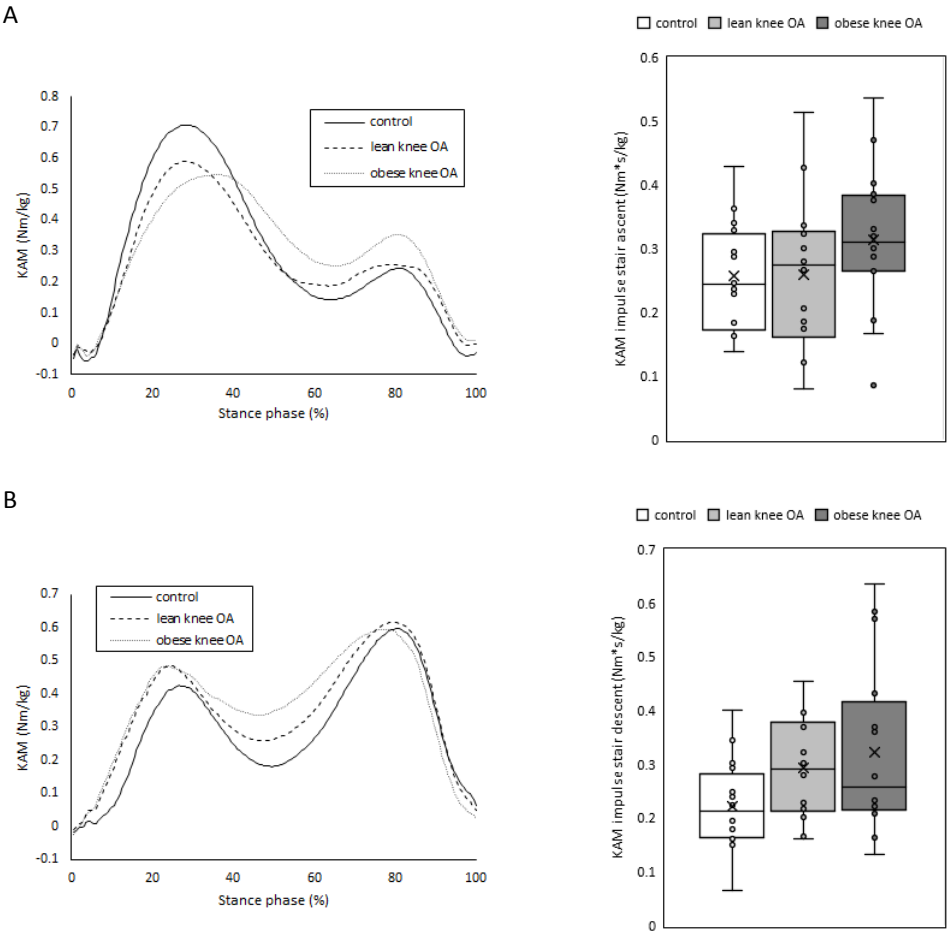

Figure 3.2 KAM vs stance phase curve and KAM impulse during stair ascent (A) and descent (B). In the boxplot; circles represent the individual datapoints, cross indicates the group mean value. Upper and lower quartiles are indicated by the whiskers, the boxes represent the interquartile range.

Relation between toe-out gait and KAM

There were no differences in toe-out gait during stair negotiation between the different groups. During stair descent, however, for all subjects, toe-out angle correlated with KAM impulse (r=-0.391; P=0.005). Overall, a 1° increase of toe-out gait was related with a decrease in KAM impulse of 5.3 x 10^{-3} Nm*s/kg. Within groups, however, foot progression angle did not correlate with KAM impulse.

Correlations between level walking and stair negotiation

Irrespective of the study group, KAM patterns were comparable between level walking and stair negotiation (Figure 3.2). Especially the dip (r=0.846; P<0.001) and the second peak (r=0.770; P<0.001) of KAM during stair ascent showed high correlations with KAM during level walking. First peak KAM during stair ascent correlated with the first peak during level walking (r=0.310; P=0.041). When considering stair descent, the dip of KAM correlated with KAM dip during level walking (r=0.618; P<0.001). Additionally, the first peak correlated with the first peak during level walking (r=0.419; P=0.004).

Discussion

In the current study, obese knee OA subjects show a more flattened KAM curve during stair ascent. During stair descent, both OA groups show a similar increase in KAM dip at mid-stance, compared to healthy controls. This corresponds with increases in medial and vertical GRF during mid-stance in the obese knee OA group, which may relate with increased stance times of obese knee OA patients during both stair ascent and stair descent. Lastly, KAM parameters were related when compared between level walking and stair negotiation, indicating task similarities.

Previous studies on stair negotiation in knee OA patients showed no significant effect of knee OA on normalized KAM peaks in obese knee OA patients during stair climbing[11,22], as also found in this study. Without normalization, KAM parameters were significantly increased in obese knee OA patients, which is caused by the direct contribution of body mass to KAM. The absence of statistical significance of the normalized KAM peaks does however not indicate that KAM is not an important parameter for stair negotiation.[17] Flattened KAM curves, characterized by a less pronounced dip at mid-stance, have previously been recognized in obese and severe knee OA patients during level walking.[28] Therefore, cumulative load (i.e. KAM impulse) was proposed as more accurate indicator for differences between the study groups, as the impulse is not restricted to a certain timepoint.[29,30] No significant differences in normalized KAM impulse were found between the different groups during stair ascent, whereas obese knee OA patients have an increased impulse during stair descent. We suggest that the absence of statistical significance for the KAM parameters may be explained by compensatory movement strategies, such as ambulatory velocity. Increases in stance time were found in obese knee OA patients, implying a decrease in ambulatory velocity. A decrease in vertical acceleration lowers the vertical GRF and thus may lead to a reduction in KAM.[31] Indeed, both peaks of the vertical GRF were decreased during stair

ascent in both the obese and lean knee OA group, when compared with healthy controls. Furthermore, a decrease in ambulatory velocity is accompanied by an increase in vertical GRF at mid stance. Besides the KAM peaks and dip, ambulatory velocity directly affects KAM impulse as this is the integral of KAM over the stance duration. Despite the increased stance time in the obese knee OA group, KAM impulse did not differ between groups during stair ascent.

Reasons for this may include the high observed heterogeneity in KAM in both obese and lean knee OA patients (Figure 3.2). This between-subject variability may indicate differential use of compensatory mechanisms that could reduce KAM and thus underlie the non-significance found during stair ascent. For example, the present study showed that only obese knee OA patients tend to prolong their stance phase during stair ascent, whereas both obese and lean OA have prolonged stance phases during stair descent. In addition, a significant correlation between toe-out gait and KAM impulse was found during stair descent. By increasing the toe-out angle the knee joint axis is rotated externally. As a result, the GRF will pass more posterior and less medial of the knee joint centre, which leads to conversion of KAM into a knee flexion moment.[28] Increased toe-out gait also causes a shift of the centre of pressure during late stance, resulting in a GRF vector with a lower lever arm which lowers the second KAM peak.[21] Although we found a correlation between toe-out gait and KAM impulse, there were no indications for differential use of toe-out gait between groups. Therefore, we believe that, besides lowering ambulatory speed, increased toe-out gait during stair negotiation may further benefit obese knee OA patients.

Furthermore, similarities in KAM patterns were found between level walking and stair negotiation (Figure 3.3). This suggests that movement strategies are not altered between different activities of daily living. In other words, those who successfully reduce KAM during level walking, seem to be able to adequately reduce KAM during stair negotiation as well. Clinically, this would imply that focus could be intensified on reducing KAM for only one activity of daily living and the reductions in the other may follow. Furthermore, it implies that there may be similarities in biomechanical models underlying level walking and stair negotiation.

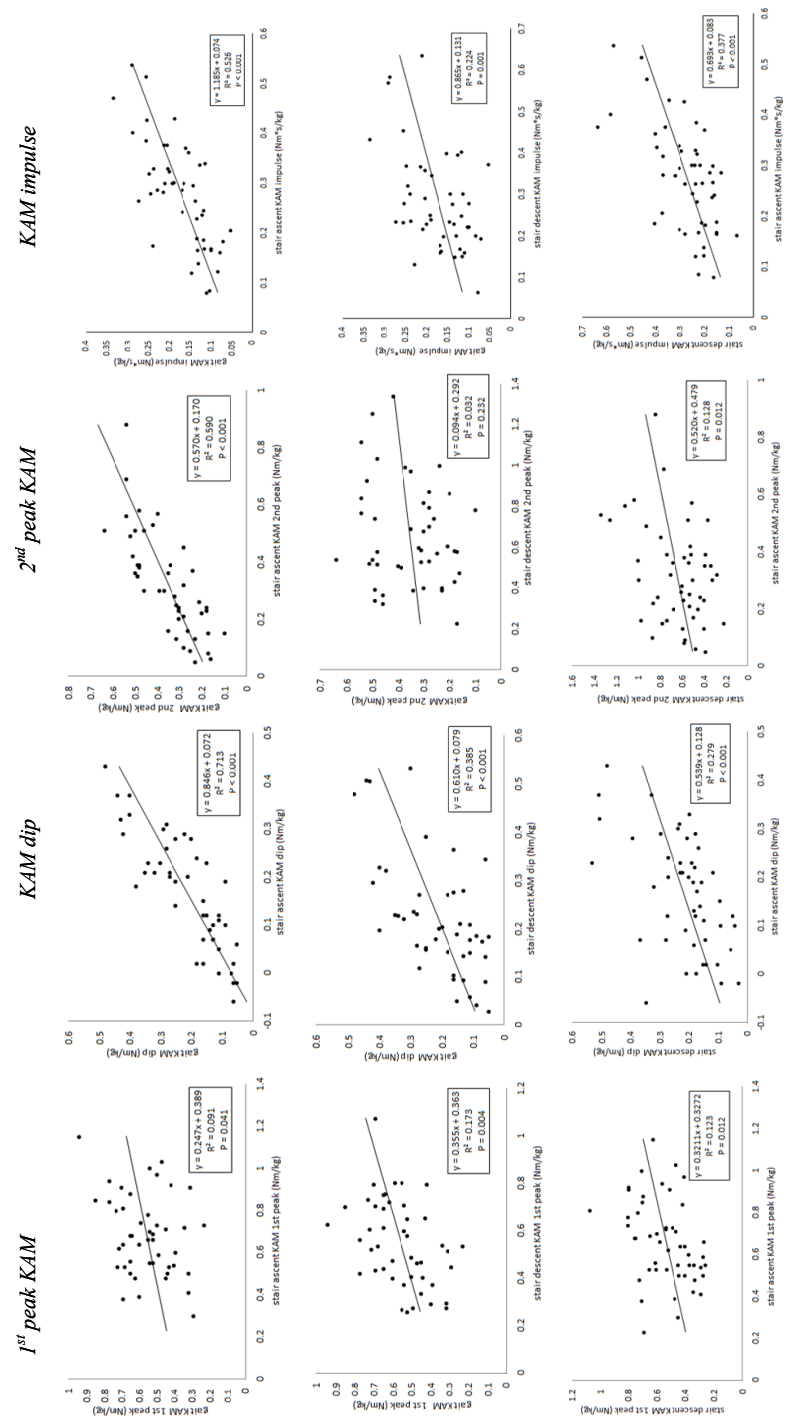

Figure 3.3 Correlations of KAM parameters between gait and stair negotiation for all subjects.

The present study design allowed investigation to compare KAM between knee OA in absence and presence of obesity. However, there were some limitations. Although we tried to optimize marker placement, markers did not exactly coincide with the anatomical landmarks, which could be a small source of error. Furthermore, soft tissue artifacts are expected to be more prominent in the obese population, introducing additional variability. However, given the fact that variability of KAM parameters is comparable between the lean and obese knee OA group, we believe the contribution of soft tissue artifacts is not disparate between groups. Nevertheless, the overall high variability in KAM parameters might also be attributed to inaccuracies of the Plug-in-Gait model in the frontal plane. The lack of a fourth control group, being weight matched obese control subjects, limits our interpretations of the individual effect of obesity on KAM. Due to the fact trunk biomechanics were not investigated, effects of lateral trunk lean on KAM cannot be excluded. Future studies should therefore investigate lateral trunk lean in relation to KAM in lean and obese knee OA patients, with the addition of a fourth control group.

Conclusions

The current study showed that, after removing the direct effects of body mass, there are no significant differences between the study groups in the first and second KAM peaks during stair negotiation. Possible reasons for this may include increased stance times for obese knee OA patients that lower vertical GRF and thus KAM. As a side effect, KAM dip at mid-stance was increased in obese knee OA patients. Increased toe-out gait may also lower KAM. However, there were no indications for differential use of this compensatory strategy between study groups. Furthermore, significant correlations between KAM parameters were found during stair negotiation and level walking.

References

1. Allen KD, Golightly YM. Epidemiology of osteoarthritis: state of the evidence. Curr Opin Rheumatol. 2015;27(3):276-83.
2. Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, et al. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis. 2003;62(12):1145-55.
3. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. Bull World Health Organ. 2003;81(9):646-56.
4. Arden N, Nevitt MC. Osteoarthritis: epidemiology. Best Pract Res Clin Rheumatol. 2006;20(1):3-25.
5. Coggon D, Reading I, Croft P, McLaren M, Barrett D, Cooper C. Knee osteoarthritis and obesity. Int J Obes Relat Metab Disord. 2001;25(5):622-7.
6. Robinson WH, Lepus CM, Wang Q, Raghu H, Mao R, Lindstrom TM, et al. Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis. Nat Rev Rheumatol. 2016;12(10):580-92.
7. Cicuttini F, Wluka A, Hankin J, Wang Y. Longitudinal study of the relationship between knee angle and tibiofemoral cartilage volume in subjects with knee osteoarthritis. Rheumatology (Oxford). 2004;43(3):321-4.
8. Sharma L, Song J, Felson DT, Cahue S, Shamiyeh E, Dunlop DD. The role of knee alignment in disease progression and functional decline in knee osteoarthritis. JAMA. 2001;286(2):188-95.
9. Sharma L, Hurwitz DE, Thonar EJ, Sum JA, Lenz ME, Dunlop DD, et al. Knee adduction moment, serum hyaluronan level, and disease severity in medial tibiofemoral osteoarthritis. Arthritis Rheum. 1998;41(7):1233-40.
10. Baliunas AJ, Hurwitz DE, Ryals AB, Karrar A, Case JP, Block JA, et al. Increased knee joint loads during walking are present in subjects with knee osteoarthritis. Osteoarthritis Cartilage. 2002;10(7):573-9.
11. Kaufman KR, Hughes C, Morrey BF, Morrey M, An KN. Gait characteristics of patients with knee osteoarthritis. J Biomech. 2001;34(7):907-15.
12. Landry SC, McKean KA, Hubley-Kozey CL, Stanish WD, Deluzio KJ. Knee biomechanics of moderate OA patients measured during gait at a self-selected and fast walking speed. J Biomech. 2007;40(8):1754-61.
13. Thorp LE, Sumner DR, Wimmer MA, Block JA. Relationship between pain and medial knee joint loading in mild radiographic knee osteoarthritis. Arthritis Rheum. 2007;57(7):1254-60.
14. Segal NA, Yack HJ, Khole P. Weight, rather than obesity distribution, explains peak external knee adduction moment during level gait. Am J Phys Med Rehabil. 2009;88(3):180-246.
15. Harding GT, Hubley-Kozey CL, Dunbar MJ, Stanish WD, Astephen Wilson JL. Body mass index affects knee joint mechanics during gait differently with and without moderate knee osteoarthritis. Osteoarthritis Cartilage. 2012;20(11):1234-42.
16. Foroughi N, Smith R, Vanwanseele B. The association of external knee adduction moment with biomechanical variables in osteoarthritis: A systematic review. Knee. 2009;16(5):303-9.
17. Iijima H, Shimoura K, Aoyama T, Takahashi M. Biomechanical characteristics of stair ambulation in patients with knee OA: A systematic review with meta-analysis toward a better definition of clinical hallmarks. Gait Posture. 2018;62:191-201.
18. Kutzner I, Heinlein B, Graichen F, Bender A, Rohlmann A, Halder A, et al. Loading of the knee joint during activities of daily living measured in vivo in five subjects. J Biomech. 2010;43(11):2164-73.
19. Costigan PA, Deluzio KJ, Wyss UP. Knee and hip kinetics during normal stair climbing. Gait Posture. 2002;16(1):31-7.
20. Lewis J, Freisinger G, Pan X, Siston R, Schmitt L, Chaudhari A. Changes in Lower Extremity Peak Angles, Moments and Muscle Activations during Stair Climbing at Different Speeds. J Electromyogr Kinesiology. 2015;25(6):982-9.
21. Guo M, Axe MJ, Manal K. The influence of foot progression angle on the knee adduction moment during walking and stair climbing in pain free individuals with knee osteoarthritis. Gait Posture. 2007;26(3):436-41.

22. Paquette MR, Klipple G, Zhang S. Greater Step Widths Reduce Internal Knee Abduction Moments in Medial Compartment Knee Osteoarthritis Patients During Stair Ascent. J Appl Biomech. 2015;31(4): 229-36.
23. Browning RC, Kram R. Effects of obesity on the biomechanics of walking at different speeds. Med Sci Sports Exerc. 2007;39(9):1632-41.
24. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum. 1986;29(8):1039-49.
25. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis. 1957;16(4): 494-502.
26. Hunter DJ, Guermazi A, Lo GH, Grainger AJ, Conaghan PG, Boudreau RM, et al. Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). Osteoarthritis Cartilage. 2011;19(8):990-1002.
27. Verlaan L, Boekesteijn RJ, Oomen PW, Liu W-Y, Peters MJM, Witlox MA, et al. Biomechanical Alterations during Sit-to-Stand Transfer Are Caused by a Synergy between Knee Osteoarthritis and Obesity. Biomed Res Int. 2018;2018:7.
28. Reeves ND, Bowling FL. Conservative biomechanical strategies for knee osteoarthritis. Nat Rev Rheumatol. 2011;7(2):113-22.
29. Rutherford DJ, Hubley-Kozey CL, Deluzio KJ, Stanish WD, Dunbar M. Foot progression angle and the knee adduction moment: a cross-sectional investigation in knee osteoarthritis. Osteoarthritis Cartilage. 2008;16(8):883-9.
30. Thorp LE, Sumner DR, Block JA, Moisio KC, Shott S, Wimmer MA. Knee joint loading differs in individuals with mild compared with moderate medial knee osteoarthritis. Arthritis Rheum. 2006;54(12):3842-9.
31. Protopapadaki A, Drechsler WI, Cramp MC, Coutts FJ, Scott OM. Hip, knee, ankle kinematics and kinetics during stair ascent and descent in healthy young individuals. Clin Biomech (Bristol, Avon). 2007;22(2):203-10.

Chapter 4

Biomechanical alterations during sit-to-stand transfer are caused by a synergy between knee osteoarthritis and obesity

Verlaan L., Boekesteijn R.J., Oomen P.W., Liu W.Y., Peters M.J.M., Witlox M.A., Emans P.J., van Rhijn L.W., Meijer K.

Biomed Res Int. 2018:3519498

Abstract

Osteoarthritis (OA) is one of the major causes of immobility and its current prevalence in elderly (>60 years) is 18% in women and 9.6% in men. Patients with osteoarthritis display altered movement patterns to avoid pain and overcome movement limitations in activities of daily life, such as sit-to-stand transfers. Currently, there is a lack of evidence that distinguishes effects of knee osteoarthritis on sit-to-stand performance in patients with and without obesity**.** The purpose of this study was therefore to investigate differences in knee and hip kinetics during sit-to-stand movement between healthy controls and lean and obese knee osteoarthritis patients. Fifty-five subjects were included in this study, distributed over three groups: healthy controls (n=22), lean knee osteoarthritis (n=14) and obese knee OA patients (n=18). All subjects were instructed to perform sit-to-stand transfers at self-selected, comfortable speed. A three-dimensional movement analysis was performed to investigate compensatory mechanisms and knee and hip kinetics during sit-to-stand movement. No difference in sit-to-stand speed were found between lean knee OA patients and healthy controls. Obese knee osteoarthritis patients, however, have reduced hip and knee range of motion, which is associated with reduced peak hip and knee moments. Reduced vertical ground reaction force in terms of body weight and increased medial ground reaction forces indicate use of compensatory mechanisms to unload the affected knee in the obese knee osteoarthritis patients. We believe that an interplay between obesity and knee osteoarthritis leads to altered biomechanics during sit-to-stand movement, rather than knee osteoarthritis alone. From this perspective, obesity might be an important target to restore healthy sit-to-stand biomechanics in obese knee OA patients.

Introduction

Osteoarthritis (OA) is one of the world's leading causes of immobility and is defined by degeneration of subchondral bone and articular cartilage in joint spaces.[1] Most commonly, OA affects weight-bearing joints such as the knee, which leads to severe alterations in biomechanics during activities of daily life.[2] According to the World Health Organisation, the prevalence of OA is 18% in elderly women, whereas this is 9.6 % in elderly men.[3] Following the current rise in obesity and concomitant increase in life expectancy, prevalence of OA is expected to increase.[4] This poses OA as an increasing future health problem. Besides age and weight, further risk factors for OA include female gender, genetics, poor diet, joint overuse, trauma, muscle weakness, physical inactivity, and poor habitual movement patterns.[5,6] While the exact pathophysiology of OA remains to be elucidated, it is currently believed that altered joint loading and cartilage metabolism are both key factors in cartilage degradation and subsequent OA development.[7]

The clinical presentation of knee OA is characterized by pain, limitation of movement, tenderness and local inflammation.[8] Those problems often manifest at the medial tibiofemoral compartment, as a result of varus malalignments.[9] To avoid pain and overcome movement limitations, knee OA patients adopt compensatory strategies in their daily routine. In previous studies, such alterations in movement patterns have already been described in patients with knee OA during activities of daily life, including gait[10-12], stair climbing[13-15], and sit-to-stand (STS) tasks.[16-21] The ability to perform those activities effectively is essential with respect to independency and participation in society.

In this study, we will specifically investigate STS movement, which is characterised by the transition from a wide base of support (BoS) – provided by the feet, thighs, and buttocks – to a small BoS, provided by the feet alone. Moreover, high knee and hip extensor moments are required to lift the centre of mass (CoM) against gravity.[20] Especially in certain pathologies, such as knee OA, where pain, joint stiffness, and loss of quadriceps strength are present, performing STS may be challenging.

From previous research it is known that knee OA patients show increased weight-bearing asymmetry[17,18,21], less flexion of the affected knee[16,18], increased trunk lean towards the unaffected side[17], and more flexion of the trunk[16,17,20] during STS movement. Furthermore, lower knee extension moments are observed[19,20], which is associated with lower quadriceps strength.[18] The observed movement alterations are also linked with earlier and increased activation of the biceps femoris.[16,19] Overall, those movement alterations lead to an increased time to perform STS movement, indicating a decrease in performance.[20,22] However, performing STS at a slower speed

may also be a deliberate strategy to reduce accelerations and minimize both joint forces and joint pain.[23] As a result of compensatory movement patterns, in particular asymmetrical loading strategies, the contralateral joint may become more prone to develop OA.[24] This underlines the importance of proper quantification of biomechanics during STS, which may lead to the prevention of further disease progression.
Although there are quite some studies that have investigated the effects of knee OA on STS movements, most of those studies fail to distinguish between effects of OA itself and effects of high body mass index (BMI), which is closely associated with OA. As obesity itself may modulate movement patterns during STS, it should not be neglected in biomechanical analyses.[25] Furthermore, obesity is one of that factors that may contribute to OA progression.[26] Therefore, we investigated the differences in knee and hip kinetics during STS movement between healthy controls and lean and obese knee osteoarthritis patients. In addition, we investigated different kinds of employed compensatory strategies to perform STS movements. We hypothesize that the combination of obesity and knee osteoarthritis is responsible for altered knee and hip kinetics and an increase in time during STS transfer, rather than knee osteoarthritis alone. To overcome joint pain, we expect that obese knee OA patients will increase loading of the unaffected leg, which increases their time to rise from a chair.

Materials and methods

Study population

In this case-control study three groups were studied: healthy controls (BMI=20-25 kg/m^2), lean knee OA patients (BMI=20-25 kg/m^2), and obese knee OA patients (BMI=30-40 kg/m^2). Subjects having a Kellgren Lawrence (KL) score between 1 and 3 at the medial tibiofemoral site were included in the OA groups.[27] The specific focus on medial knee OA is related to its prevalence and relation with increased external knee adduction moments during locomotion.[28] Only women aged between 50 and 65 years were included, as knee OA prevalence is the highest in this group. The upper age limit was adopted to prevent inclusion of participants that are at high risk of having comorbidities. Recruitment of knee OA patients occurred via the 'Artrose Kliniek' at the Maastricht University Medical Center (MUMC+). Healthy controls were recruited by the department of Nutrition and Movement Sciences, the department of Physical Therapy (MUMC+), and local physical therapy clinics in Maastricht.
Exclusion criteria were any inflammatory arthritis, trauma, OA at any other joint, and moderate to severe OA in the ipsilateral patellofemoral OA and/or lateral tibiofemoral

OA, anterior cruciate ligament injury, medial and collateral ligament injury, and psychiatric illness according to the Diagnostic and Statistical Manual of Mental Disorders classification criteria for psychiatric illnesses (patients were excluded when diagnoses were present in their medical files). Healthy women were non-obese, did not meet the exclusion criteria, and did not have knee OA according to the American College of Rheumatology classification criteria.[29] Absence of knee OA in the control group was also ensured by Magnetic Resonance Imaging (MRI).
All subjects were informed on the purpose of the study and gave informed consent before participating in this study. This study was ethically approved by the METC aZM/UM.

Radiographic analysis

Radiographic imaging was used to evaluate knee cartilage health and knee OA status. Presence of knee OA was assessed from X-ray images by the KL knee score.[27] The X-ray images were evaluated double blind by two independent orthopaedic surgeons.
To more accurately assess cartilage health in all study groups, MRI was performed using a 3T Philips Intera Scanner *(Philips Medical Systems, Best, The Netherlands)*. Scanning sequences included fat saturated proton density-weighted turbo spin echo and fat saturated T2 weighted sequences. Cartilage health in the knee was evaluated based on the MRI Osteoarthritis Knee Score (MOAKS).[30] In this semi-quantitative scoring system, the knee is subdivided into 14 regions which are scored on seven features. The 14 sub-regions include different sites at the patella, femur and tibia: the medial and lateral patella; the medial and lateral trochlea, the medial and lateral central femur, and the medial and lateral posterior femur; the medial and lateral anterior tibia, the medial and lateral central tibia, and the medial and lateral posterior tibia. In the present study, only the articular cartilage feature of the MOAKS was scored. The articular cartilage score provides separate scores for the size and depth of cartilage damage in each of the sub-regions. The size of any cartilage loss (partial and full-thickness loss) as well as the size of full-thickness cartilage loss was scored as a % of surface area as related to the size of each individual region as either 0 (none), 1 (<10% of region of cartilage surface area), 2 (10-75% of region of cartilage surface area), 3 (>75% of region of cartilage surface area) or N (no score possible). To correct for cases where scoring was not possible, the total MOAKS score was divided by the number of items scored.

Instrumentation

Movement analysis was performed with an eight camera, three-dimensional (3D) motion capture system *(Vicon, MX3, Oxford Metric, UK)* together with Nexus software.

Kinetic data were obtained by one force platform *(9281A, Kistler instruments AG, Winethur, Switzerland)* which measured ground reaction force in order to calculate joint torques and forces. Sixteen reflective markers were placed on the lower extremities according the Vicon Plug in Gait model in order to use the 3D motion capture system. In the obese knee OA group, however, it was sometimes necessary to deviate from the model, as the abdominal fat depot limited visibility of the spina iliaca anterior superior. In those cases, markers were placed more lateral and/or dorsal, according to the Vicon Plug in Gait Marker Placement Manual.

Sit-to-stand task

Subjects were asked to rise from a chair on a self-selected, comfortable speed. The chair had no arm and backrests and height was adjusted to knee and hip angles of 90 degrees. Use of the arms was prohibited, which was ensured by positioning each hand on the contralateral shoulder. Further, trials were performed barefoot and feet were placed parallel and in line with the shoulders. The dominant (control group) or affected (knee OA groups) leg was placed on the force platform. Leg dominance was assessed by asking the subject which leg would be used to kick a ball. After completion of the STS transfer, subjects were asked to sit again from the obtained standing position. Two test trials were performed to get familiar with the movement. Measurements were repeated seven times with 10 seconds of resting intervals.

Data analysis

Data were processed via MATLAB to generate the variables of study. Parameters of interest were: total time, sub-phase duration, ankle/knee/hip ROM in the sagittal plane, ankle/knee/hip extension moments, knee adduction moments, and the vectors of the ground reaction forces: anterior-posterior (GRFy), vertical (GRFz), and mediolateral (GRFx). Joint moments and GRFz were corrected for body weight (BW). Trials were normalized to 100% of the STS task with intervals of 0.5%. The start of the trial was defined by the first moment the GRFz exceeded 20% of the maximal GRFz, with a threshold of 40 N. End of the trial was defined by the moment when the GRFz was lower than 20% of the maximal GRFz. Trials were subdivided into three phases based on joint kinematic events. Those phases included the leaning phase (start – maximal hip flexion), momentum phase (maximal hip flexion – maximum ankle dorsiflexion), and extension phase (maximum ankle dorsiflexion – end of trial).[31]

Statistical analysis

Normality of data was tested with the Shapiro-Wilk test. Averages were calculated over the different trials for the following parameters: STS time, sub-phase duration, GRF (all vectors), ankle/knee/hip sagittal ROM, ankle/knee/hip sagittal moments, and frontal knee moments. Reliability of the kinetic data for the knee and hip was tested using the intra class correlation (ICC).[32] Group differences for STS parameters were analysed with one-way ANOVA using LSD post-hoc analysis and non-parametric Kruskal Wallis tests using pairwise comparisons with Bonferroni adjustments. Data are presented as mean ± standard deviation (SD). The level of agreement for the Kellgren-Lawrence scoring was tested with Cohen's kappa. The relations between knee OA severity and BMI, and knee OA severity and time to perform the STS were tested with Pearson correlations. Significance level was set at $\alpha<0.05$. All statistical analysis was performed with IBM SPSS statistics 24.

Results

Subject characteristics

Fifty-five subjects were included in this study (Table 4.1). No significant differences in age were found between the three groups. The obese group had a higher body mass and was shorter than both the controls and lean knee OA group. Consequently, BMI was significantly higher in the obese knee OA group. Radiographic analysis indicated that both knee OA groups show average KL scores between two and three, confirming the presence of knee OA. Concordance between both orthopaedic surgeons was substantial ($\kappa=0.639$). The sum of MOAKS, corrected for the number of items scored, further demonstrated absence of meaningful knee OA in the control group, as it differed significantly from both the lean knee OA group ($P=0.027$) and obese knee OA group ($P<0.001$). Furthermore, there was no significant difference in MOAKS between the two OA groups.

STS time

No significant differences between groups were observed in the duration of the STS task. (Table 4.2). The relative contribution of all sub-phases was not significantly different between groups. In all groups, duration of the extension phase was relatively the longest (64.1%–68.7%), while duration of the leaning phase (17.8%-21.2%) and momentum phase (12.1%-16.0%) contributed less to STS duration. However, time to

perform the first trial was significantly higher than the last trial in the knee OA group (*P*=0.025), pointing towards a learning effect.

Table 4.1 Patient characteristics of the three different study groups, presented as mean (± SD).

Demographics	Group		
	Control (n=22)	Lean knee OA (n=14)	Obese knee OA (n=19)
Age (years)	58.7 (4.4)	60.1 (3.5)	59.0 (5.1)
Height (m)	1.66 (0.04)	1.67 (0.05)	1.62 (0.07)[1,2]
Weight (kg)	62.9 (6.1)	66.1 (7.3)	86.4 (12.3)[1,2]
BMI (kg/m²)	22.5 (2.0)	23.7 (2.3)	32.4 (3.4)[1,2]
KL-score	-	2.21 (0.74)	2.38 (0.70)
MOAKS (score/items)	0.50 (0.42)	1.01 (0.69)[1]	1.22 (0.66)[1]

BMI = body mass index, KL = Kellgren Lawrence, MOAKS = MRI osteoarthritis knee score, OA = osteoarthritis. 1 = significantly different from control; 2 = significantly different from lean knee OA

Table 4.2 STS-parameters for all different groups. Data are presented as mean (±SD.).

STS-parameter	Group		
	Control (n=22)	Lean knee OA (n=14)	Obese knee OA (n=19)
STS time (s)			
Total	0.99 (0.21)	1.11 (0.28)	1.17 (0.43)
Sub-phase duration (%)			
Leaning phase	17.8 (6.1)	19.2 (6.2)	21.2 (9.6)
Momentum phase	16.0 (6.0)	12.1 (4.7)	14.7 (5.1)
Extension phase	66.2 (7.0)	68.7 (5.1)	64.1 (7.8)
Joint ROM (º)			
Ankle (sagittal)	18.8 (6.6)	18.9 (6.1)	14.2 (6.5)
Knee (sagittal)	85.5 (11.4)	85.8 (8.2)	75.9 (10.3)[1,2]
Hip (sagittal)	79.7 (7.4)	81.7 (5.4)	73.1 (12.3)[1,2]
Maximum joint moment (Nm/kg)			
Ankle (sagittal)	0.32 (0.12)	0.32 (0.09)	0.29 (0.08)
Knee (sagittal)	0.89 (0.20)	0.83 (0.16)	0.70 (0.18)[1]
Knee (frontal)	0.30 (0.22)	0.26 (0.21)	0.27 (0.18)
Hip (sagittal)	0.87 (0.19)	0.79 (0.15)	0.67 (0.16)[1]
Ground reaction force (BW)			
GRFz max	0.62 (0.06)	0.58 (0.05)	0.54 (0.08)[1]
Ground reaction force (N)			
GRFz max	374.6 (48.8)	376.2 (52.9)	459.0 (89.4)[1,2]
GRFx max	33.9 (8.22)	37.1 (10.2)	45.9 (16.5)[1,2]
GRFy max	37.4 (12.2)	34.9 (12.4)	47.7 (12.6)[1,2]

STS = sit-to-stand, ROM = range of motion, BW = bodyweight, GRFz = vertical ground reaction force, GRFx = medio-lateral ground reaction force, GRFy= anterior-posterior ground reaction force, OA = osteoarthritis. 1 = significantly different from control; 2 = significantly different from lean knee OA.

Kinetics and kinematics

Kinetic data for the knee and hip in the sagittal plane showed high repeatability with an ICC of 0.970 and 0.917 respectively. Knee ROM in the sagittal plane was significantly lower in the obese knee OA group compared to both healthy controls (*P*=0.007) and lean knee OA patients (*P*=0.009). Similarly, hip ROM was significantly lower in the obese knee OA group, compared to healthy controls (*P*=0.023) and lean knee OA patients (*P*=0.009). The reductions in knee and hip ROM corresponded with lower maximal knee (*P*=0.002) and hip extension moments (*P*=0.001) in the obese knee OA group compared to the control group (Figure 4.1). For the ankle, no significant differences in ROM and joint moments were found between groups. Maximal knee adduction moments did not differ between groups.

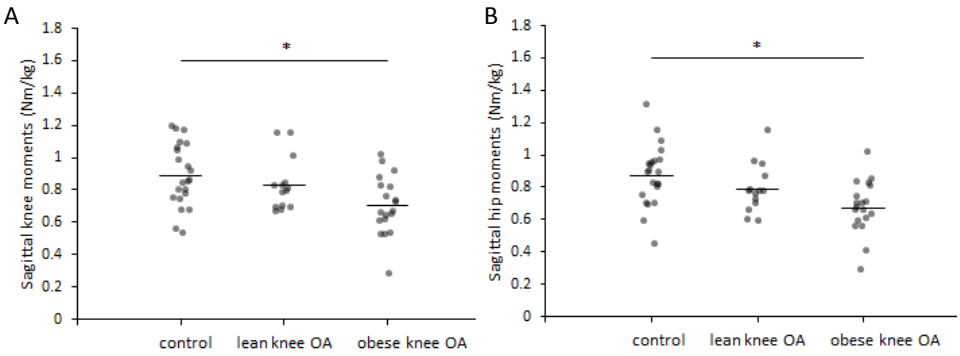

Figure 4.1 Sagittal joint moment during STS transfer for the three different groups for knee (A) and hip (B). The horizontal lines indicate the mean group values. *P<0.050

Ground reaction force

The maximum of GRFz, after correction for bodyweight, was lower in the obese knee OA group, when compared to healthy controls (*P*=0.001). No differences in GRFz were found between the lean knee OA group and the controls. GRFx was higher in the obese knee OA group compared to both lean knee OA (*P*=0.045) and controls (*P*=0.003). Similarly, GRFy was higher in the obese knee OA group compared to both the lean knee OA patients (*P*=0.005) and healthy controls (*P*=0.010).

Correlations

A significant correlation between knee OA severity – defined by the sum of the MOAKS score divided by the number of items scored – and time to perform the STS transfer was found (r=0.338; *P*=0.020).

Discussion

The aim of the current study was to investigate differences in knee and hip kinetics during STS movement between healthy controls and lean and obese knee OA patients. Second, use of compensatory strategies was investigated in the different study groups. We were able to show reduced knee and hip ROM, accompanied by reduced peak hip and knee moments in the obese knee OA group. In addition, GRFz corrected for bodyweight was lower in the obese knee OA group compared to the control group. Obese subjects also showed a greater GRFx than both other groups, indicating the use of compensatory mechanisms to unload the affected knee. Total time to perform STS was not different between groups. Furthermore, none of the investigated STS parameters was different between the lean knee OA group and controls.

In previous research it has been show that knee OA patients show alterations in STS movement.[16-22] To our knowledge, none of those studies distinguishes between effects of high body mass and effects of knee OA in this impairment. Strikingly, lean subjects with knee OA did not show any signs of movement alterations during STS. Contrarily, we showed that only obese knee OA patients have different STS movement patterns. In line with others, we were able to show reductions in ROM for the knee and hip in the sagittal plane for obese knee OA patients.[16,18] Bouchouras et al. speculate that this reduction may be caused by greater agonist-antagonist co-activation. By early recruitment of the biceps femoris compared to the vastus lateralis, the affected joint would be protected from extreme excursions and pain could be avoided. Furthermore, co-contraction could increase joint stiffness and limit joint range of motion.[16] Unfortunately, electromyographic data in this study was not included. Therefore, it was not possible to substantiate mechanisms of altered co-contraction and co-activation in the obese knee OA population. Nevertheless, pain avoidance is considered as a reasonable explanation for the reduced ROM. Considering the correlation between BMI and knee OA severity, it seems plausible that obese knee OA patients experience more pain than lean knee OA patients and thus avoid extreme joint excursions. However, future studies should first establish the relation between pain and obesity in knee OA patients.

Adequate hip and knee extension forces are also essential for efficient STS performance.[20] During STS movement, obese knee OA patients display lower peak extension moments for both knee and hip. According to Sibella et al. obese subjects without knee OA tend to unload their lower back by transferring the load to their knees.[25] We provide evidence that this statement is not applicable to obese subjects with knee OA, as knee extension moments are decreased in obese knee OA patients. Compensatory strategies, such as weight bearing asymmetry and lateral trunk lean, are proposed to reduce sagittal joint moments at the affected side of knee OA patients with pain alleviation as primary goal.[17,18] Although we did not measure trunk biomechanics, our results show a decreased GRFz after correction for body weight and an increased GRFx in the obese knee OA group only. Apparently, obese knee OA subjects tend to unload their affected leg by displacing the body towards the unaffected side, whereas lean knee OA patients do not show this adaptation. We therefore suggest that the compensatory strategies previously reported in literature, including weight bearing asymmetry, only occur when both obesity and knee OA are present.[17,18]

Generally, STS performance is quantified by the total time to perform the task. Although we did expect to find differences in STS duration, total time was not significantly different between groups, which is in contrast with studies of Su et al. and Turcot et al.[17,22] In their studies, the increase of time was attributed to use of compensatory strategies. Differences in knee OA severity may possibly underly this discrepancy in findings, as our results show a positive correlation between knee OA severity and STS time. The current study included only mild to moderate medial knee OA patients (KL score=2-3) with unilateral involvement, whereas the study of Turcot included obese end-stage knee OA patients (KL score=4) and Su et al. included both unilateral and bilateral knee OA patients with unknown BMI. We therefore conclude that there is no increase in STS time in both lean and obese patients with mild to moderate OA. It might have occurred that knee OA severity was not high enough to find a significant increase in time in the obese knee OA group.

In short, alterations in lower limb biomechanics seem to be only apparent in presence of both obesity and knee OA during STS movement. Within this group, compensatory mechanisms might be necessary to avoid pain and to preserve the ability to perform the task. Although our current study design allowed to distinguish between effects of knee OA and obesity, there were some limitations. We could not explain the occurrence of compensatory mechanisms by pain avoidance, as pain was not measured in this study. Besides, no markers were placed on the trunk to investigate its role in movement adaptations. Furthermore, muscle activity was not measured. Future studies on STS movement should be performed with a similar study design that includes

electromyographic data, trunk biomechanics, and pain measurements. Finally to investigate the exact influence of BMI, our suggestion would be to include a second control non-OA obese group.

Conclusion

Our study shows that the biomechanical alterations during sit to stand movement are the result of an interplay between high body mass and knee OA, rather than knee OA alone. The combination of obesity and knee OA leads to reduced ROM in the knee and hip of the affected leg. Similarly, peak extension moments are decreased in both joints. This might be explained by asymmetrical loading, characterized by a lower GRFz, corrected for bodyweight, and higher GRFx of the affected leg. Since only obese knee OA patients show movement alterations, losing weight could restore sit-to-stand biomechanics to a healthy pattern. Future studies should examine the differences in muscle activity and trunk biomechanics between the different study groups for more insight in employed compensatory strategies.

References

1. Allen KD, Golightly YM. Epidemiology of osteoarthritis: state of the evidence. Curr Opin Rheumatol. 2015;27(3):276-83.
2. Vincent KR, Conrad BP, Fregly BJ, Vincent HK. The Pathophysiology of Osteoarthritis: A Mechanical Perspective on the Knee Joint. PM & R. 2012;4(5 0):S3-S9.
3. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. Bull World Health Organ. 2003;81(9):646-56.
4. Marshall DA, Vanderby S, Barnabe C, MacDonald KV, Maxwell C, Mosher D, et al. Estimating the Burden of Osteoarthritis to Plan for the Future. Arthritis Care Res. 2015;67(10):1379-86.
5. Palazzo C, Nguyen C, Lefevre-Colau M-M, Rannou F, Poiraudeau S. Risk factors and burden of osteoarthritis. Ann Phys Rehabil Med. 2016;59(3):134-8.
6. Ashkavand Z, Malekinejad H, Vishwanath BS. The pathophysiology of osteoarthritis. J Pharmacy Res. 2013;7(1):132-8.
7. Guilak F. Biomechanical factors in osteoarthritis. Best Pract Res Clin Rheumatol. 2011;25(6):815-23.
8. Kraus VB, Blanco FJ, Englund M, Karsdal MA, Lohmander LS. Call for Standardized Definitions of Osteoarthritis and Risk Stratification for Clinical Trials and Clinical Use. Osteoarthritis Cartilage. 2015;23(8):1233-41.
9. Cicuttini F, Wluka A, Hankin J, Wang Y. Longitudinal study of the relationship between knee angle and tibiofemoral cartilage volume in subjects with knee osteoarthritis. Rheumatology (Oxford). 2004;43(3):321-4.
10. Baliunas AJ, Hurwitz DE, Ryals AB, Karrar A, Case JP, Block JA, et al. Increased knee joint loads during walking are present in subjects with knee osteoarthritis. Osteoarthritis Cartilage. 2002;10(7):573-9.
11. Mundermann A, Dyrby CO, Andriacchi TP. Secondary gait changes in patients with medial compartment knee osteoarthritis: increased load at the ankle, knee, and hip during walking. Arthritis Rheum. 2005;52(9):2835-44.
12. Kumar D, Manal KT, Rudolph KS. Knee joint loading during gait in healthy controls and individuals with knee osteoarthritis. Osteoarthritis Cartilage. 2013;21(2):298-305.
13. Asay JL, Mundermann A, Andriacchi TP. Adaptive patterns of movement during stair climbing in patients with knee osteoarthritis. J Orthop Res. 2009;27(3):325-9.
14. Hicks-Little CA, Peindl RD, Hubbard TJ, Scannell BP, Springer BD, Odum SM, et al. Lower extremity joint kinematics during stair climbing in knee osteoarthritis. Med Sci Sports Exerc. 2011;43(3):516-24.
15. Gonçalves GH, Selistre LFA, Petrella M, Mattiello SM. Kinematic alterations of the lower limbs and pelvis during an ascending stairs task are associated with the degree of knee osteoarthritis severity. Knee. 2017;24(2):295-304.
16. Bouchouras G, Patsika G, Hatzitaki V, Kellis E. Kinematics and knee muscle activation during sit-to-stand movement in women with knee osteoarthritis. Clin Biomech (Bristol, Avon). 2015;30(6):599-607.
17. Turcot K, Armand S, Fritschy D, Hoffmeyer P, Suva D. Sit-to-stand alterations in advanced knee osteoarthritis. Gait Posture. 2012;36(1):68-72.
18. Christiansen CL, Stevens-Lapsley JE. Weight-bearing asymmetry in relation to measures of impairment and functional mobility for people with knee osteoarthritis. Arch Phys Med Rehabil. 2010;91(10): 1524-8.
19. Patsika G, Kellis E, Amiridis IG. Neuromuscular efficiency during sit to stand movement in women with knee osteoarthritis. J Electromyogr Kinesiol. 2011;21(5):689-94.
20. Anan M, Shinkoda K, Suzuki K, Yagi M, Ibara T, Kito N. Do patients with knee osteoarthritis perform sit-to-stand motion efficiently? Gait Posture. 2015;41(2):488-92.
21. Boonstra MC, Schwering PJ, De Waal Malefijt MC, Verdonschot N. Sit-to-stand movement as a performance-based measure for patients with total knee arthroplasty. Phys Ther. 2010;90(2):149-56.
22. Su FC, Lai KA, Hong WH. Rising from chair after total knee arthroplasty. Clin Biomech (Bristol, Avon). 1998;13(3):176-81.
23. Yoshioka S, Nagano A, Hay DC, Fukashiro S. Biomechanical analysis of the relation between movement time and joint moment development during a sit-to-stand task. Biomed Eng Online. 2009;8:27.

24. Shakoor N, Hurwitz DE, Block JA, Shott S, Case JP. Asymmetric knee loading in advanced unilateral hip osteoarthritis. Arthritis Rheum. 2003;48(6):1556-61.
25. Sibella F, Galli M, Romei M, Montesano A, Crivellini M. Biomechanical analysis of sit-to-stand movement in normal and obese subjects. Clin Biomech (Bristol, Avon). 2003;18(8):745-50.
26. Sowers MR, Karvonen-Gutierrez CA. The evolving role of obesity in knee osteoarthritis. Curr Opin Rheumatol. 2010;22(5):533-7.
27. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis. 1957;16(4):494-502.
28. Sharma L, Hurwitz DE, Thonar EJ, Sum JA, Lenz ME, Dunlop DD, et al. Knee adduction moment, serum hyaluronan level, and disease severity in medial tibiofemoral osteoarthritis. Arthritis Rheum. 1998;41(7):1233-40.
29. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum. 1986;29(8):1039-49.
30. Hunter DJ, Guermazi A, Lo GH, Grainger AJ, Conaghan PG, Boudreau RM, et al. Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). Osteoarthritis Cartilage. 2011;19(8):990-1002.
31. Schenkman M, Berger RA, Riley PO, Mann RW, Hodge WA. Whole-body movements during rising to standing from sitting. Phys Ther. 1990;70(10):638-48; discussion 48-51.
32. McGinley JL, Baker R, Wolfe R, Morris ME. The reliability of three-dimensional kinematic gait measurements: a systematic review. Gait Posture. 2009;29(3):360-9.

Chapter 5

Accelerometer based stair climbing in healthy subjects: reference data and demographic differences

Verlaan L., Storken G., Heiligers I.C., Grimm B.

Juniper Online Journal of Cases Studies. 2019;9(5) Article ID 555771

Abstract

Background

Accelerometers facilitate analysis outside traditional gait laboratories. Before using these devices on a larger scale and in clinical settings, a thorough assessment of their performance in diverse populations is required. The goal of this study was to present an acceleration-based reference database for stair climbing in healthy subjects. The effect of age was studied with different parameters, such as step time up and down, asymmetry and irregularity.

Methods

Our study included 100 healthy subjects, which were divided in two age groups. The group of younger adults consisted of 54 subjects with a mean age of 26 years and the group of older adults consisted of 46 subjects with a mean age of 65 years.

Findings

Average step times were slightly higher ascending compared to descending. Step time difference, between ascending and descending, was significant between the young and elderly group. Irregularity and asymmetry did not diverge between the age groups. In addition, effects of age on gait parameters were found to be consistent with those reported in studies using other methodologies.

Interpretation

Stair climbing based findings together with all the advantages of the device support the application of accelerometer-based gait analysis for routine clinical use and in daily life.

Introduction

Over the years, patient expectations regarding the outcome of orthopaedic surgery have changed significantly. At this moment a high functional improvement (e.g. sport) is expected, while previously patients were satisfied when having less pain and an increased mobility. Next to this there is a demand for shorter hospitalization, for which faster rehabilitation and higher mobility levels are required.[1]

To diagnose and postoperatively monitor these ever more demanding orthopaedic patients, it becomes increasingly important to objectively measure function. At present function and mobility of patients are clinically evaluated by questionnaires and visual assessment, producing mainly subjective and mostly pain related functional results.[2,3] Objective and more accurate techniques such as video-based gait analysis, force platforms and EMG, are mainly used in research settings only. Unfortunately, these techniques are less suitable for routine clinical application because of high costs and complexity demanding designated space, personnel and long set-up times. Furthermore, a lot of studies take place in laboratory settings creating an unusual situation.[4,5]

Motion analysis using body-fixed accelerometers is less capacious but its relative simplicity, its low cost and ease of operation make it suitable for routine clinical application. The less rich data output with few basic parameters may even be seen as an advantage in clinical practice where it aims to be used as a complementary scale for outcome scoring instead of a sophisticated motion analysis requiring expert interpretation. Accelerometer derived motion parameters were clinically validated for normal gait in healthy subjects.[6] Lately accelerometer-based gait analysis has come forward as a potential partial alternative for conventional gait analysis because of its high reliability in analyzing gait parameters and lower limb motion.[7,8] Various clinically relevant gait parameters, such as cadence and walking variability, can simultaneously be obtained from acceleration signals by autocorrelations or peak detection algorithms.[9-11] However, gait was identified as not demanding enough to distinguish finer functional differences. Then again stair climbing is an important and common functional activity that may be a more informative clinical evaluation procedure than level walking for patients with disorders of the lower extremity.[12] Consequently, stair climbing may produce more sensitive motion parameters with accelerometer-based motion analysis. To make inertia-based motion analysis with accelerometers applicable for clinical evaluation a reference database for healthy stair climbing is required. Another complementary aspect regarding to questionnaires is the possibility of testing functional improvement more accurately. Whereas a questionnaire has a maximum score, the accelerometer can measure functional improvement without reaching a

ceiling effect. This makes them perfectly applicable for routine orthopaedic follow-up. A standard hospital stair with normal surroundings, without intimidating equipment etc, provides a more natural environment to measure stair climbing than the usual laboratory setting. To conduct a single stair test, including setup, measurement and analysis, may take as little as 10 min, permitting the examination of several subjects in a relatively short time period. In addition, accelerometer-based gait analysis can be used for quick analysis of multiple steps, which allows us to test fluctuations in gait pattern during stair climbing resulting in the measurement of different variables such as symmetry and regularity.
This study a.) investigates whether a stair climbing test with accelerometer derived motion parameters is clinically feasible, b.) investigates whether this test is capable to identify differences between demographic groups of healthy subjects and c.) documents a reference database for stair climbing in healthy subjects.

Materials and methods

Subjects

Only healthy subjects were recruited into the study so that reference data for normal stair climbing could be collected. The health status was assessed in a standardised way using a self-made questionnaire investigating the absence of any pathologies possibly affecting movements considered as normal. Excluding criteria were the presence of a musculoskeletal or neurological disorder, or any previous surgical intervention that could affect physical activity. Ascending and descending of stairs was measured in 100 volunteer subjects (64 females, 36 males) with a mean age of 44 years old (SD 21; range 17-81). The study group was divided in two age groups: a young group and an old group. The young group (*n:* 54: 34 females, 20 males) had a mean age of 26 years (SD 17; range 17-49) and the old group (*n:* 46: 30 females, 16 males) had a mean age of 65 years (SD 10; range 50-81) (Table 5.1). Other values recorded were height, weight, BMI and dominant side. Ethical approval and informed consent were obtained for all subjects.

Table 5.1 Demographics of subjects categorized by decade of age (averages and standard deviations).

	F : M	Age [yrs]	Height [cm]	Weight [kg]	BMI [kg/m^2]	Dominant side (right : left)
Total *n:* 100	64 : 36	44 (±21)	171 (±9.8)	70 (±12)	24 (±3.3)	87 : 13
Young *n:* 54	34 : 20	26 (±17)	175 (±21)	69 (±22)	22 (±5.9)	46 : 8
Old *n:* 46	30 : 16	65 (±8.0)	167 (±9.2)	72 (±13)	26 (±3.4)	41 : 5

Equipment

During the measurements the lower trunk accelerations were measured by a light weight triaxial accelerometer (size 62x41x18 mm, weight 53 g, f=100Hz, range: 2 g, McRoberts BV, The Hague, The Netherlands.[9] The accelerometer was attached tightly with a belt to the sacrum, which produced the most reliable accelerometer signals.[13-15] Data was stored on a local memory card (256 MB). The unit was powered by two AAA1.5V batteries.

Protocol

Subjects ascended and descended five stairs two times at preferred, comfortable speed and were not allowed to use the handrails during stair climbing. The stairs consisted of 10 stairs with step dimensions of 18 cm (riser height) by 29 cm (tread). Subjects were requested to wear shoes with flat soles. We started with ascending five stairs, followed with a rest of 3 seconds. Next the five ascending stairs were completed. The last ascending stair was finished with standing feet together and a rest period of 3 seconds, followed by turning around, standing feet together and again a rest period of 3 seconds. Descending stairs was measured according to the same procedure as ascending the stairs. A whole measurement had a maximum duration of 30 seconds.
For the reproducibility and inter-rater reliability, the measurement was repeated one week later with another observer under the same circumstances.

Data analysis

Raw data was downloaded to a PC using specific software (Mira 1.9 Beta, McRoberts BV, The Hague, The Netherlands.[9] Based on the principles to detect steps of level walking[11], several motion parameters were derived for acceleration peak detection algorithms in Matlab 7.1 (Mathworks, USA): first the average step time up and down (t_{up}, t_{down}) defined as the time per step up and the time per step down in msec. Second, the difference between the average step time up and down (t_{up}-t_{down}). Third, irregularity up and down (irr_{up}, irr_{down}) defined as the difference between maximum and minimum step times. Fourth, the asymmetry up and down ($asym_{up}$, $asym_{down}$) described as the difference between the step times of the dominant and non-dominant leg. Taken into account that the first and the last step were part of the start and ending phase, and that they did not occur in a fluent motion, only data of the second, third and fourth step per five-step flight were analysed. Moreover, stair test parameters were compared for age differences, and correlated to subject demographics such as gender and BMI.

Statistical analysis

Inter-rater reliability was evaluated for each parameter using Intra Class Correlation coefficients (ICC). ICCs >0.75, between 0.40-0.75, and <0.40 were interpreted respectively as an excellent, fair-to-good and poor reliabilitity.[9] Age group comparison were performed using independent samples t-test and subject demographics correlations were examined using Pearson's R (P<0.05). All statistics was performed using SPSS version 15.0.

Results

Reliability and reproducibility

Average values for most stair test parameters were similar across two sessions. T-tests showed no significant differences (P<0.05) in any of the stair parameters between both measurement days, indicating that climbing stairs was similar over time. Inter-rater reliability was very good for Tup, Tdown and Tup-down, respectively 0.94, 0.97 and 0.81 and fairly good for irregularity up (0.61) and down (0.73).

Step time up and down

In all subjects combined, average step times, mean 604ms (SD 106), were slightly higher ascending, mean t_{up} 613 ms (SD 71), compared to descending, mean t_{down} 594 ms (SD 114), P<0.05, Table 5.2. This difference was visible for most individuals (76/100). The step time difference between ascending and descending was 19 ms (SD 65), with a significant difference (P<0.01) between the young (t_{up}-t_{down}=49 ms) and elderly group taking on average more time to descend (-16 ms). All subjects with descending times at least 20 ms slower than ascending (19/100) were found in the elderly group (P<0.01, Figure 5.1). Furthermore, correlations between step times and demographic parameters gender and BMI were calculated. Step time up (P<0.05) and step time down (P<0.01) correlated significantly with BMI while no correlations were found between gender and step times. Additional t-tests illustrated that subject with a higher BMI (>25) showed significantly higher step times down (P<0.01) and almost significantly step times up (P=0.06).

Table 5.2 Stair climbing parameters [ms] overall and per age group (*P<0.01).

[ms]	Avg	SD	Min	Max	Young	Old
t_{up}	613	71	470	888	592	638*
t_{down}	594	114	428	1172	543	654*
Δt_{up}-t_{down}	19	65	-287	103	49	-16*
Irr_{up}	121	49	40	260	123	119
Irr_{down}	123	48	50	250	118	129
$Asym_{up}$	49	35	2	138	50	40
$Asym_{down}$	39	29	0	113	30	50

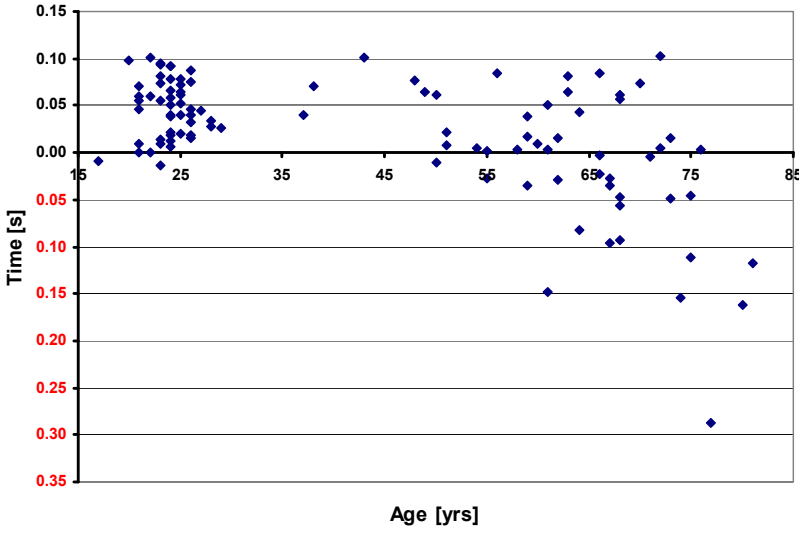

Figure 5.1 Average difference step time up minus down vs. age. Dotted line is threshold t_{up}-t_{down}= -0.02s.

Irregularity and asymmetry

Irregularity was nearly equal for ascending, mean 121 ms (SD 49), and descending, mean 123 ms (SD 48). Between age groups no differences were found in irregularity for ascending, young mean 123 ms (SD 107); old mean 119 ms (SD 47), and descending, young mean 118 ms (SD 96); old mean 129ms (SD 48). Next to this, asymmetry did not show large differences between stepping up, mean 49 ms (SD 35), and stepping down mean 39 ms (SD 29). Furthermore, no differences were found between age groups in asymmetry (ascending, young vs. old: 50 vs. 40 ms and descending, young vs. old: 30 vs. 50 ms). However, asymmetry revealed that steps with the dominant leg were of equal or faster speed than the non-dominant leg in 43/46 cases ascending and 39/46 cases

descending. Moreover, no correlation was found between irregularity and the demographic parameters gender and BMI.

Discussion

The purpose of this study was to investigate whether a stair climbing test with accelerometer derived motion parameters in a group of healthy subjects is clinically feasible and valid to distinguish between demographic differences. Our findings confirmed that the accelerometer is able to provide good and reproducible measurement of temporal stair climbing parameters in healthy subjects in daily life, non-laboratory situations.

The high inter-rater reliability shows that there is acceptable consistency between different stair walks of individual subjects and between different observers taking the test, a common scenario in routine clinical outcome assessment. Inter-observer variability may come from sensor placement, patient instruction and data analysis all of which still have improvement potential such as using even smaller sensors with direct to skin fixation, to use a standard instruction video or perform fully automated signal analysis. Furthermore, our study (N=100) contained a much larger sample size, than comparable studies of Stacoff et al.[16] (N=20) and of Riener et al.[5] (N=10).

Average step times up were higher than step times down as expected by the difference in energy expenditure. Individuals with slower step times down were all elderly indicating that a loss of balance, coordination, strength, proprioception or fear of falling compensates the benefits of an energetically less demanding movement. Moreover, fear of falling plays an important factor in stair climbing because the largest proportion of falls in elderly people was reported to occur on stairs.[17] Especially in descending stairs, accidents occur about three times more frequently while descending stairs than ascending stairs.[18] Hsu et al., found that older adults developed different strategies for stair descent than younger adults.[19] One of the strategies included an increased support time at the push-off phase, which suggested that the step time down for elderly will increase in comparison with younger people. This was mentioned by Stacoff et al.[16] that older people compared with younger people walked with significant lower speed during stair climbing. No differences were found between age groups in ascending and descending the stairs, which could be due to the small number of subjects per age group (20 subjects divided over three groups. Above that, they concluded that age seems to be a factor which should be taken in consideration. This matches with our findings, which demonstrated a strong significant difference in descending the stairs between age groups.

In addition, Stacoff et al.[16] found in twenty healthy subjects longer step times for ascending, increasing from 692 ms to 741 ms with increasing step height with riser heights: 13.3 cm (flat), 17.1 cm (standard) to 20.0 cm (steep). Descending step times varied from 612 ms to 644 ms. They found longer step times for ascending, varying from 692 ms for flat up to 741 ms for steep up, then step times for descending, varying from 612 ms for flat down to 644 ms for steep down. The differences with our step times results are small, with slightly faster times determined for both ascending and descending. Besides different subject demographics and health status in comparison to our study, this may be an effect of different step heights and depths used as well as differences in the instructions with regards to the speed. The comparison of age groups in their study revealed that in general subjects of the young group (mean age: 33.7 yrs) were faster in all test conditions step heights, both up and down, than those of the old group (mean age: 76.5 yrs), except for the standard stair ascent and the steep stair descend.[16] Riser height used in our study is comparable with standard height used in the study of Stacoff et al.[16] (18.0 cm vs 17.1 cm).

Although not the focus of this study, the relation between step times and BMI seem to reflect that adults with an increased BMI become slower on stair walking.[20] These findings may suggest an association between increased BMI and mobility disability. This latter association was described for older adults in a recent review.[21]

In the contrary to step times, overall asymmetry and irregularity during stair ascending and descending did not change between young and old. This can be an effect of testing healthy people without pathologies. Testing 'unhealthy' subjects, especially with unilateral pathologies such as meniscal tear, would be likely to show difference between asymmetry and irregularity.

However, steps taken with the dominant leg tend to be faster than with the non-dominant leg in most of the cases, no difference in gait asymmetry was proven, as mentioned earlier. In the past only one study confirmed that asymmetry during stair climbing increases in stair descending[16], where others could not.[22] The functional asymmetry during gait does not necessarily appear to be the consequence of abnormality, but rather relates to the different tasks of limbs, i.e. limb dominance.[22] At the same time, asymmetry clearly identified the strength of the dominant leg indicating its potential as a powerful parameter to detect and monitor unilateral pathologies such as meniscal tear. Unfortunately, results of the asymmetry were only registered in the first 46 subjects.

For normal gait Senden et al.[6] already validated the accelerometer in healthy subjects. They found significant effects of gender on step time and speed. However, contrarily to our study, no significant differences were observed between age groups. Compared to normal gait, stair climbing requires a larger effort, which can explain the difference in

step time during stair climbing between young and old. In elderly, fatigue could be a factor of influence when using a standard stair instead of a shorter staircase.
Although step times and step time-based parameters such as asymmetry and irregularity have been proven as reliable and valuable motion parameters which are easy to measure, they provide limited information. In future we aim to extend the analysis of the acceleration signal to other non-temporal stair climbing parameters (e.g. dynamic sway) or use 3D gyrometers for a richer signal.

Conclusion

With a test duration of <30 s and reproducible, sensitive parameters, the acceleration- and step time-based stair test is a functional assessment suitable for routine clinical follow-up and to complement classic questionnaire-based scores. The test can distinguish stair climbing performance between young and old healthy subjects, which extends previous comparable studies on normal gait. Furthermore, the test can detect the dominant leg indicating its diagnostic potential in pathological motion, especially in unilateral pathologies encountered in orthopaedics such as joint replacement. The relatively large number of healthy subjects tested in this study provides reference data for future studies on the test's diagnostic potential to identify specific pathologies, such as for instance meniscal tears.

References

1. Elgar FJ, Worrall G, Knight JC. Functional assessment of elderly clients of a rural community-based long-term care program: A 10-year cohort study. Can J Aging-Revue canadienne du vieillissement. 2002;21: 455-63.
2. Brunnekref JJ, van Uden CJ, van Moorsel, Kooloos JG. (2005) Reliability of videotaped observational gait analysis in patients with orthopaedic impairments. BMC Musculoskelet Disord. 2005;6:17-26.
3. Salch M, Murdoch G. In defence of gait analysis. Observation and measurement in gait assessment. J Bone Joint Surg. 1985;67B:237-41.
4. Reid SM, Graham RB, Costigan PA. Differentiation of young and older adult stair climbing gait using principal component analysis. Gait Posture. 201031:197-203.
5. Riener R, Rabuffetti M, Frigo C. Stair ascent and descent at different inclinations. Gait Posture. 2002;15: 32-44.
6. Senden R, Grimm B, Heyligers IC, Savelberg HHCM, Meijer K. Acceleration-based gait test for healthy subjects: Reliability and reference data. Gait Posture; 2009;30:192-6.
7. Maffiulett NA, Gorelick M, Kramers-de Quervain I, Bizzini M, Munzinger JP, et al. Concurrent validity and intrasession reliability of the IDEEA accelerometry system for the quantification of spatiotemporal gait parameters. Gait Posture. 2008;27:160-3.
8. Mackey AH, Scott NS, Walt SE. Reliability and validity of an activity monitor (IDEEA) in the determination of temporal-spatial gait parameters in individuals with cerebral palsy. Gait Posture. 2008;28:634-9.
9. Brandes M, Zijlstra W, Heikens S, Lummel van R, Rosenbaum D. Accelerometry based assessment of gait parameters in children. Gait Posture. 2006;24:482-6.
10. MoeNilssen R, Helbostad JL. Estimation of gait cycle characteristics by trunk accelerometry. J Biomech. 2004;37:121-6.
11. Zijlstra W, Hof AL. Assessment of spatio-temporal gait parameters from trunk accelerations during human walking. Gait Posture. 2003;18:1-10.
12. Bing Yu, Thomas Kienbacher, Eric S Growney, Marjorie E. Johnson, and Kai-Nan An. Reproducibility of the kinematics and kinetics of the lower extremity during normal stair-climbing. J Orthop Res. 1997;15: 348-52.
13. Moe-Nilssen R. Test-retest reliability of trunk accelerometry durig standing and walking. Arch Phys Med rehabil. 1998;79:1377-85.
14. Hendriksen M, Lund H, Moe Nilssen R, Bliddal H, Danneskiod-Samsoe B. Test-retest reliability of trunk accelerometric gait analysis. Gait Posture. 2004;19:288-97.
15. Menz HB, Lord SR, Fritzpatrick RC. Acceleration patterns of the head and pelvis when walking on level and irregular surfaces. Gait Posture. 2003;18:35-46.
16. Stacoff A, Diezi C, Luder G, Stussi E, Kramers-de Quervain IA. Ground reaction forces on stairs : effects of stair inclination and age. Gait and Posture. 2005;21:24-38.
17. Verghese J, Wang C, Xue X, Holtzer R. Self-reported difficulty in climbing up or down stairs in nondisabled elderly. Arch Phys Rehabil. 2008;89:100-4.
18. Liikavainio T, Isolehto J, Helminen HJ, Perttunen J, Lepola V, et al. Loading an gait symmetry during level and stair walking in asymptomatic subjects with knee osteoarthritis: importance of quadriceps femoris in reducing impact force during heel strike? Knee. 2007;14:231-8.
19. Hsu MJ, Wei SH, Yu YH, Chang YJ. Leg stiffness and electromyography of knee extensors/flexors: comparison between older and younger adults during stair descent. J Rehab Res Dev. 2007;44:429-36.
20. Apovian CM, Frey CM, Wood GC, Rogers JZ, Still CD, et al. Body mass index and physical function in older women. Obes Res. 2002;10:740-7.
21. Vincent HK, Vincent KR, Lamb KM. Obesity and mobility disability in the older adult. Obes Rev. 2010;11:568-79.
22. Bertucco M, Cesari P. Dimensional analysis and ground reaction forces for stair climbing: Effects of age and task difficulty. Gait Posture. 2009;29:326-31.

Chapter 6

Accelerometer-based physical activity monitoring in patients with knee osteoarthritis: Objective and ambulatory assessment of actual physical activity during daily life circumstances

Verlaan L., Bolink S.A.A.N., van Laarhoven S.N., Lipperts M., Heyligers I.C., Grimm B., Senden R.
The Open Biomedical Engineering Journal. 2015;9:157-163

Abstract

Background

It is important to assess physical activity objectively during daily life circumstances, to understand the association between physical activity and diseases and to determine the effectiveness of interventions. Accelerometer-based physical activity monitoring seems a promising method and could potentially capture all four FITT (i.e. Frequency, Intensity, Time, Type) components of physical activity considered by the World Health Organization (WHO).

Aim

To assess the four FITT components of physical activity with an accelerometer during daily life circumstances and compare with self-reported levels of physical activity in patients with knee osteoarthritis (OA) and a healthy control group.

Methods

Patients (n=30) with end-stage knee OA and age-matched healthy subjects (n=30) were measured. An ambulant tri-axial accelerometer was placed onto the lateral side of the upper leg. Physical activity was measured during four consecutive days. Using algorithm-based peak detection methods in Matlab, parameters covering the four FITT components were assessed. Self-reported physical activity was assessed using the Short questionnaire to assess health enhancing physical activity (SQUASH).

Results

Knee OA patients demonstrated fewer walking bouts (154±79 versus 215±65 resp.; *P*=0.002), step counts (4402±2960 steps/day versus 6943±2581 steps/day; *P*=0.001) and sit-to-stand (STS) transfers (37±14 versus 44±12; *P*=0.031) compared to controls. Knee OA patients demonstrated more time sitting (65±15% versus 57±10% resp.; *P*=0.029), less time walking (8±4% versus 11±4% resp.; *P*=0.014) and lower walking cadence (87±11 steps/min versus 99±8 steps/min resp.; *P*<0.001). Accelerometer-based parameters of physical activity were moderately-strong (Pearsons's r=0.28-0.49) correlated to self-reported SQUASH scores.

Conclusion

A single ambulant accelerometer-based physical activity monitor feasibly captures the four FITT components of physical activity and provides more insight into the actual physical activity behavior and limitations of knee OA patients in their daily life.

Introduction

Physical activity is an important determinant of general health and is negatively affected by many chronic degenerative diseases.[1,2] To understand the association between physical activity and diseases, and to determine the effectiveness of interventions, it is crucial for clinicians and researchers to assess and monitor physical activity during daily life circumstances.[3] Various studies have demonstrated that physical activity programs convey general health benefits and improve disease-related symptoms and complications, such as pain, fatigue and functional limitation.[4] Monitoring physical activity to provide individual feedback could therefore be an essential part of a wide spectrum of applications[3,5], including patients with cardiovascular diseases, neurodegenerative diseases (e.g. Parkinson's disease) and knee osteoarthritis (OA).[6] Assessment of physical activity is traditionally employed by self-report questionnaires. These questionnaires are inexpensive and easy to use in clinical practice, however due to subjectivity they are prone to overestimation and may not reflect actual physical activity.[4,7] Moreover, self-report questionnaires do not have the potential to assess all four components of physical activity considered by the World Health Organization (WHO): Frequency, Intensity, Time and Type (abbreviated FITT).[2,8] Current guidelines for physical activity may be realistic and reasonable for self-reported physical activity, however it is not clarified yet what levels of objectively assessed physical activity are reasonable and associated with health benefits. Reports in literature have demonstrated that with self-reported assessment of physical activity, up to 62% of the general population meet the activity intensity guidelines whereas only 9.6% meet these same guidelines when defined from objective physical activity monitoring.[9]

The current gold standard method to objectively assess free-living physical activity is the doubly labeled water method (DLW), which involves the ingestion of water labelled with stable isotopes ^{2}H and ^{18}O.[10] As energy is expended in the body, CO_2 and H_2O are produced, and the differences between the isotope elimination rates are used to calculate total energy expenditure. Although DLW is a very precise and accurate method to assess energy expenditure[11], it is not feasible for routine use and it does not allow assessment of physical activity by the four FITT components. Developments in ambulant motion sensor technologies have recently provided more feasible alternatives for objective assessment of actual free-living physical activity.[2,12] These ambulant activity monitors (AMs) have evolved considerably over the years from simple pedometers to AMs equipped with heart rate monitors, GPS trackers and accelerometers.[3] Validation studies of methods for the assessment of physical activity have shown that accelerometry is superior to self-report questionnaires and heart rate

monitoring compared to DLW.[1,13] Moreover, accelerometry has demonstrated its potential to provide an estimation of activity quantity[13], to provide qualitative assessment of physical activity such as spatiotemporal gait analysis[9] and activity intensity measures.[12] Furthermore, accelerometer-based physical activity monitoring permits to differentiate between different activities of daily living (ADL) such as walking or sitting[5,14] and could select only those activities that are challenging and clinically relevant for specific patient populations. Therefore, accelerometer-based physical activity monitoring is currently the most widely used method to objectively assess physical activity in daily life circumstances and could potentially capture all four FITT components of physical activity.

The primary aim of this study was to investigate the potential of ambulant accelerometer-based physical activity monitoring to objectively assess the four FITT components of physical activity during daily life circumstances. A second aim of the study was to apply accelerometer-based physical activity monitoring in a physically impaired population of patients with advanced knee OA, and to compare their levels of physical activity to an age-matched healthy control group. A third aim of the study was to compare objectively assessed levels of physical activity by an ambulant accelerometer to subjective self-reported levels of physical activity assessed by a questionnaire.

Materials and methods

Participants

Patients (n=30) with end-stage knee OA (Kellgren-Lawrence scale 3-4) that were listed for a total knee replacement (TKR) at the outpatient clinic, were approached and asked to participate. An age-matched healthy control group (n=30) was used for comparison (Table 6.1). All participants were informed about the study prior to participation and oral informed consent was obtained. Ethical approval for testing the participants was obtained by the Medical Ethics Committee (METC) of the Atrium Medical Centre Heerlen, The Netherlands, with METC number: 10-N-72. Healthy participants had no joint pain and no medical history of lower extremity joint surgery. Knee OA patients were excluded when there was a presence of OA in the contralateral knee for which a TKR would be indicated, when they were wheelchair-bound and if they were not living independently. Exclusion criteria for the control group were the presence of a musculoskeletal or neurological disorder, or any previous surgical intervention that

could affect the level of actual physical activity. All participants were asked to behave according to their normal habits during the physical activity monitoring.

Table 6.1 Participants' demographics demonstrating significant differences for body mass and body mass index (BMI) between the knee OA group and control group.

	Knee OA group n=30		Control group n=30	
	Mean ± SD	(range)	Mean ± SD	(range)
Male/female	11/19		16/14	
Age (years)	68.7 ± 6.9	(56 – 81)	67.3 ± 8.4	(56 – 89)
Height (cm)	169.3 ± 12.3	(149 – 191)	171.7 ± 8.0	(156 – 190)
Body mass (kg)	86.6 ± 19.1*	(52 – 125)	74.4 ± 13.2	(50 – 104)
BMI (kg/m^2)	29.6 ± 5.7**	(21 – 42)	24.7 ± 3.4	(19 – 32)

*P<0.01; **P<0.001.

Physical activity monitor (AM)

A commercially available, small (dimensions: 64x25x13 mm) and lightweight (weight 18 g) tri-axial accelerometer (GCdataconcepts, US) was used as activity monitor (AM). Battery life of the AM is sufficient to measure seven consecutive days of activities. The AM was attached onto the lateral side of the non-affected upper leg, using hypo-allergenic double-sided tape (Figure 6.1). Twelve-bit data (range ±2 g) was collected at a sampling rate of 40 Hz and stored on an on-board memory micro-SD card. The raw acceleration signal was analyzed using the inclinometer function of the accelerometer and algorithm-based peak detection methods in Matlab, based on previously published principles.[15,16] Briefly, calibration of the accelerometer's orientation is performed within a period of level walking that is manually selected. Within this walking period, the average magnitudes of the three acceleration vectors and the gait cycle frequency (GCF; Hz) are derived to allow further differentiation between activities. Differentiation between standing periods and sitting periods is based on the direction of the gravitation vector and allows identification of sit-to-stand (STS) transfers. Walking is differentiated from other upright activities (all classified as standing) by application of heuristic rules to the GCF. A walking period is classified when at least 5 consecutive heel strike peaks are detected, with <1.5 seconds between peaks for a GCF>0.6 Hz and <3.0 seconds between peaks for a GCF<0.6 Hz. This algorithm allows activities and postures to be differentiated and counted, to derive frequency measures (# steps/day, # walking bouts/day, # sit-to-stand transfers/day), to determine the time or duration of these activities (expressed as % of the total measured time) and type of activity (sitting, standing, walking) can be identified. Besides quantitative parameters, qualitative parameters can be derived such as walking intensity (cadence (step/min)) and the distribution of activities (e.g. short (<5 min) versus long (>5 min) walking

bouts). These parameters cover all four FITT components (Frequency, Intensity, Time and Type) of physical activity considered by the WHO.
Physical activity was measured during four successive days as previous studies have shown that three to four days of activity monitoring are required to characterize an individual's habitual physical activity pattern.[17,18] The AM was worn only during waking hours with a minimum of 8 hours a day and removed at night.

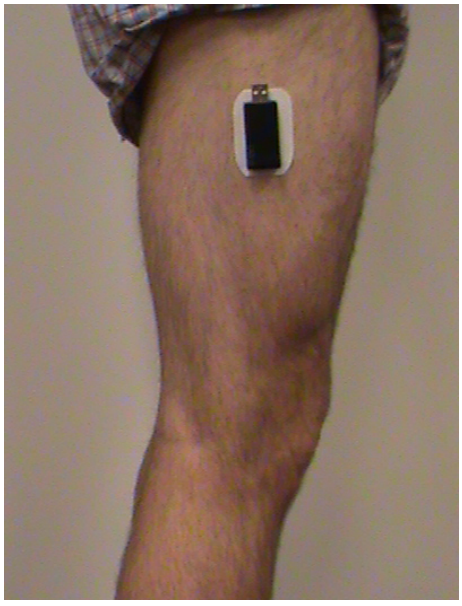

Figure 6.1 AM position.

Self-report questionnaires

Perceived physical activity was measured using the Short questionnaire to assess health enhancing physical activity (SQUASH) which assesses habitual physical activity during a normal week over the past few months.[19,20] Total score is expressed in minutes of physical activity per week.[21]

Statistical analysis

Statistical analyses were performed using IBM SPSS statistics. First data were explored for normal distribution using the Kolmogorov-Smirnov test. Results were presented as

means with standard deviations (SDs) and their range. Differences between the knee OA group and control group were evaluated by an independent-samples T-test. The association between groups' demographic variables and outcomes of AM parameters was investigated with linear regression analysis, demonstrating the level of significance (p-value) and the degree of the association expressed by the partial correlation coefficient. The association between AM parameters and self-reported physical activity score assessed by the SQUASH questionnaire was calculated with Pearson's r correlation coefficient.

Results

The two groups showed no significant differences in age (68.7±6.9yrs vs. 67.3±8.4yrs) and height (169.3±12.3yrs vs. 171.7±8.0yrs), however the knee OA group demonstrated a significantly higher body mass index (BMI; kg/m^2) than the control group (BMI=29.6±5.7 versus 24.7±4.3; $P<0.001$). In the knee OA group, 37% was male whereas in the control group 53% was male (Table 6.1). Linear regression analysis demonstrated that the difference in BMI between groups had a significant influence on the time spent sitting (partial correlation coefficient=0.37; $P=0.017$) and the amount of walking bouts <1 min (partial correlation coefficient=0.34; $P=0.027$).

The knee OA group recorded physical activity during an average of 12.7±1.8 hours/day which was significantly less than the healthy control group recording 13.6±1.3 hours/day ($P=0.03$). Considering the four FITT components of physical activity, the knee OA group was less active than the control group on all components. The frequency of walking bouts (154±79 versus 215±65 resp.; $P=0.002$), step counts (4402±2960 steps/day versus 6943±2581 steps/day; $P=0.001$) and sit-to-stand (STS) transfers (37±14 versus 44±12; $P=0.031$) was significantly less in knee OA patients compared to controls (Table 6.2). Walking intensity was significantly less for knee OA patients compared to controls, considering walking cadence (87±11 steps/min versus 99±8steps/min resp.; $P<0.001$) and considering the duration of walking bouts with a larger percentage of short (<1min and <5 min) walking bouts found in knee OA patients (Table 6.2). Time (i.e. duration) and type of activity distribution demonstrated significantly less time walking for the knee OA group compared to the control group (8±4% versus 11±4% resp.; $P=0.014$) and significantly more time sitting (65±15% versus 57±10% resp.; $P=0.029$). In addition, knee OA patients demonstrated fewer short (<1min) sitting events compared to healthy controls (8±3 versus 13±7 resp.; $P=0.002$) but similar long (>5 min) sitting events (29±13 versus 33±8; $P>0.05$).

Table 6.2 Outcome for accelerometer-based physical activity monitoring, demonstrating mean values per day and comparing results for knee OA patients with a control group.

		Knee OA group (Mean±SD)	Control group (Mean±SD)	P-value
AM - quantitative parameters	# STS Transfers	37 ± 14	44 ± 12	0.031
	range	14 - 92	25 - 62	
	# Walking bouts	154 ± 79	215 ± 65	0.002
	range	28 - 343	122 - 394	
	# Steps counts	4402 ± 2960	6943 ± 2581	0.001
	range	887 - 14449	2742 - 13395	
	% Sitting	65 ± 15	57 ± 10	0.029
	range	33 - 86	37 - 76	
	% Walking	8 ± 4	11 ± 4	0.014
	range	2 - 18	5 - 21	
	% Standing	27 ± 12	31± 8	n.s.
	range	8 - 52	15 - 44	
	Cadence (steps/min)	87 ± 11	99 ± 8	<0.001
	range	64 - 104	82 - 114	
AM – qualitative parameters	# Walking bouts <1min.	148 ± 76	204 ± 61	0.006
	range	25 - 328	119 - 363	
	# Walking bouts 1-5min.	154 ± 79	214 ± 65	0.004
	range	28 - 342	122 - 393	
	# Walking bouts >5min.	0.40 ± 0.76	0.43 ± 0.73	0.046
	range	0 - 3	0 - 3	
	% of walking bouts <1min.	96 ± 3	95± 2	0.007
	range	90 - 104	88 - 98	
	% of walking bouts 1-5min.	5 ± 3	4 ± 2	0.016
	range	2 – 16	1 - 10	
	% of walking bouts > 5min.	0.22 ± 0.42	0.37 ± 147	n.s.
	range	0 – 2	0 -8	
	# short sitting events < 1min.	8 ± 3	13 ± 7	0.002
	range	0-19	3 - 29	
	# long sitting events >1min	29 ± 13	33 ± 8	n.s.
	range	0 - 74	20 - 52	
	SQUASH	3085 ± 2236	5314 ± 2876	0.005
	range	480 - 8410	850 - 10815	

Self-perceived physical activity also demonstrated less physical activity for patients with knee OA compared to the control group. SQUASH scores were significantly lower for knee OA patients (3085±2236min versus 5314±2876min resp.; P=0.005). SQUASH scores demonstrated moderate correlations with quantitative AM parameters: bouts walking (r=0.49; P<0.001), step counts (r=0.36; P=0.008), percentage time sitting (r=-0.44; P=0.001), percentage time walking (r=0.33; P=0.014), percentage time standing (r=0.42; P=0.002) and to the qualitative AM parameters: walking bouts <1 min (r=0.46; P<0.001), walking bouts 1-5min (r=0.45; P=0.001) and amount of short sitting events (r=0.28; P=0.039).

Discussion

This study demonstrates that an ambulant accelerometer-based physical activity monitor allows objective assessment of the four FITT components of physical activity during daily life circumstances. Frequency, Intensity, Time and Type (FITT) of physical activity in patients with advanced knee OA were significantly different to an age-matched healthy control group. Accelerometer-based levels of actual physical activity were moderately (Pearsons's r=0.28-0.49) correlated to self-reported levels of perceived physical activity. This could suggest that both methods partially overlap in the domain of physical activity but also capture different aspects of physical activity. These findings might also explain discrepancies that have been found between self-reported and objectively assessed levels of physical activity required to meet current recommended physical activity guidelines.[4,9,22,23]

Knee osteoarthritis (OA) is a degenerative disease associated with functional impairments and physical activity limitations which deteriorate slowly over time. Patients with knee OA suffer from pain, joint stiffness and reduced muscle strength, and have difficulties in many daily life activities[24], including walking, rising from a chair and stair climbing.[25] Patients with knee OA tend to avoid physical activity in order to prevent pain and may believe physical activity is harmful to their joint[23] whereas this passive coping style is a risk factor for future limitations in activities.[24] Restriction of physical activity reported by patients affects their quality of life and could be indicative for total knee replacement surgery.[14] Findings of this study confirm validity of the avoidance model as explanation for deterioration of physical activity limitations in patients with knee OA, considered by the four FITT components of physical activity.[24] Knee OA patients demonstrated less activity frequency expressed by the amount of STS-transfers, walking bouts and step counts; lower activity intensity expressed by lower walking cadence and fewer long (>5 min) walking bouts; less activity time expressed by the lower percentage of time spent walking; and the distribution of the type of activity demonstrated a more sedentary lifestyle for knee OA patients. Despite lack of physical activity and exercise, a sedentary lifestyle alone has negative effects on health indices.[26] Historically, physical activity was believed to increase risk of knee OA. However, it is now recognized to improve muscle strength, reflex inhibition, proprioception, and range of motion in the knee and decrease the risk of excess weight gain.[22] Therefore, regular exercises and other structured activities have a favorable effect on pain and function and form a safe, multifaceted therapeutic treatment to improve health and many of the factors that lead to disability in the sedentary knee OA patient.[27]

Findings of the current study are in accordance to the few previous published studies that compared levels of physical activity between patients with end-stage knee OA and healthy persons.[4,14,22,28] A study by de Groot et al.[14] compared accelerometer-based physical activity levels in 44 patients with knee OA to healthy controls. They also found a significant higher BMI (32.1±5.8) in knee OA patients compared to the control group (26.8±3.8), which was significantly related to the percentage of movement-related activity. In their study population, knee OA patients demonstrated less STS transfers (46±14 versus 61±23) and spent less time walking (6±3% versus 9±3%). Comparing their outcomes with our results, we found slightly less STS transfers for knee OA patients (37±14) and healthy controls (44±12). Furthermore, knee OA patients (8±4%) spent slightly more time walking compared to healthy controls (11±4%). The rather small differences with our study results might be explained by the methods that were used to assess physical activity. De Groot et al. assessed physical activity with four AMs during 48 consecutive hours whereas in the current study, one AM was used and worn during four consecutive days only during waking hours, resulting in an average assessment time of ±13hours/day. Another study[28] assessing physical activity in 25 patients with end-stage knee OA, using a bi-axial accelerometer armband, found significantly less steps/day compared to a healthy control group (6625±2970 versus 8576±2872) which was negatively influenced by BMI. Besides the use of a different type of AM, physical activity was monitored during 24 h/day which could explain absolute differences for step counts found in the current study. Therefore, a limitation of this study is that participants were allowed to remove the AM during a substantial part of the day. Thus we cannot feasibly compare absolute activity numbers (e.g. step count, STS-transfers, walking bouts) with results from literature and current physical activity guidelines. However, in a study by Farr et al.[22] knee OA patients were also instructed to wear the accelerometer during all waking hours which resulted in a recording time of 13.8±2.2 hours/day, comparable to the recording time of 12.7±1.8 hours/day in the current study. Another issue for concern is the type of AM used and its location. An AM should theoretically be located near the body's centre of mass to reflect movements of the total body.[1] Alternatively, AMs can be attached to locations of the body where they would register the most activity (e.g. the legs during walking) or to a location with a specific clinical interest (e.g. the arm in wheelchair-bound persons). An AM located at the lateral side of the upper leg permits measurement of whole body movement, does not interfere with daily activities, and is the most frequently used site in epidemiological studies.[22] Regarding the type of AM, a review on validity of AMs published between 2000 and 2012 already included 40 different devices.[29] Even a more recent review on the performance of 11 AMs demonstrated a large heterogeneity in

outcome with 8 out of the 11 explaining less than 50% of the variation in activity expenditure compared to the gold standard doubly labelled water method.[1]
Nonetheless, accelerometry seems the most promising method for ambulant and objective assessment of physical activity and has demonstrated its superiority to self-report questionnaires and heart rate monitoring.[1] An accelerometer-based AM allows assessment of physical activity in daily life conditions and could provide real-life feedback to facilitate diagnostics, more compliance and behavioral change to recommend or to advise against certain activities in conservative management of knee OA.[3,27] Furthermore, physical activity has become one of the main determinants of outcome assessment following a total knee replacement (TKR), besides functional capacity tests (e.g. Timed Up and Go test) and self-reported levels of functional outcome and satisfaction (i.e. questionnaires), and could provide personalized feedback for more targeted rehabilitation. Although rehabilitation after TKR aims to improve physical activity[30], still an important minority of patients do not improve postoperatively.[31] Due to difficulty in restoring mobility after surgery, patients in rehabilitation after TKR may explore difficulties to be sufficiently physically active to meet guidelines for healthy persons and to return to living independently.[23,32,33] It is therefore important to use valid and reliable tools to objectively assess levels of physical activity, to capture specific activity impairments patients encounter in daily life and to set new realistic guidelines for objectively assessed levels of physical activity. Furthermore, longitudinal assessment of physical activity in daily life conditions with an accelerometer, has the potential to provide real-life feedback via graphics and text messages by mobile health care services and could facilitate more compliance and personal rehabilitation after an intervention.

Conclusion

This study demonstrates that an ambulant accelerometer-based physical activity monitor provides a clinically feasible method to objectively assess the four FITT components of physical activity during daily life circumstances in patients with advanced knee OA. Our study results suggest that parameters of physical activity derived by one ambulant tri-axial accelerometer can be used as an objective measurement system to supplement self-report questionnaires and provide more insight into the actual physical activity behavior and limitations of knee OA patients in their daily life.

References

1. Westerterp KR., Reliable assessment of physical activity in disease: an update on activity monitors. Curr Opin Clin Nutr Metab Care. 2014;17:401-6.
2. Lindemann U, Zijlstra W, Aminian K, Chastin SF, de Bruin ED, Helbostad JL, et al. Recommendations for standardizing validation procedures assessing physical activity of older persons by monitoring body postures and movements. Sensors (Basel). 2013;14:1267-77.
3. Dobkin BH. Wearable motion sensors to continuously measure real-world physical activities. Curr Opin Neurol. 2013;26:602-8.
4. Dunlop DD, Song J, Semanik PA, Chang RW, Sharma L, Bathon JM, et al. Objective physical activity measurement in the osteoarthritis initiative: Are guidelines being met? Arthritis Rheum. 2011;63: 3372-82.
5. Gonzalez-Villanueva L, Cagnoni S, Ascari L. Design of a wearable sensing system for human motion monitoring in physical rehabilitation. Sensors (Basel). 2013;13:7735-55.
6. Vissers MM, Bussmann JB, de Groot IB, Verhaar JA, Reijman M. Physical functioning four years after total hip and knee arthroplasty. Gait Posture. 2013;38:310-5.
7. Shephard RJ. Limits to the measurement of habitual physical activity by questionnaires. Br J Sports Med. 2003;37:197-206.
8. Cavill JL, Jancey JM, Howat P. Review and recommendations for online physical activity and nutrition programmes targeted at over 40s," Glob Health Promot. 2012;19:44-53.
9. White DK, Tudor-Locke C, Felson DT, Gross KD, Niu J, Nevitt M, et al. Walking to meet physical activity guidelines in knee osteoarthritis: is 10,000 steps enough? Arch Phys Med Rehabil. 2013;94:711-7.
10. Park J, Kazuko IT, Kim E, Kim J, Yoon J. Estimating free-living human energy expenditure: Practical aspects of the doubly labeled water method and its applications.,Nutr Res Pract. 2014;8:241-8.
11. Ravussin E, Harper IT, Rising R, Bogardus C.,"Energy expenditure by doubly labeled water: validation in lean and obese subjects. Am J Physiol. 1991;261:E402-9.
12. Tobias JH, Gould V, Brunton L, Deere K, Rittweger J, Lipperts M, et al. Physical Activity and Bone: May the Force be with You. Front Endocrinol (Lausanne). 2014;5:20.
13. Plasqui G, Joosen AM, Kester AD, Goris AH, Westerterp KR. Measuring free-living energy expenditure and physical activity with triaxial accelerometry. Obes Res. 2005;13:1363-9.
14. de Groot IB, Bussmann JB, Stam HJ, Verhaar JA. Actual everyday physical activity in patients with end-stage hip or knee osteoarthritis compared with healthy controls. Osteoarthritis Cartilage. 2008;16: 436-42.
15. Preece SJ, Goulermas JY, Kenney LP, Howard D, Meijer K, Crompton R. Activity identification using body-mounted sensors--a review of classification techniques. Physiol Meas. 2009;30:R1.
16. Mathie MJ, Celler BG, Lovell NH, Coster AC. Classification of basic daily movements using a triaxial accelerometer. Med Biol Eng Comput. 2004;42:679-87.
17. Masse LC, Fuemmeler BF, Anderson CB, Matthews CE, Trost SG, Catellier DJ, et al,"Accelerometer data reduction: a comparison of four reduction algorithms on select outcome variables. Med Sci Sports Exerc. 2005;37:S544-54.
18. Kang M, Hart PD, Kim Y. Establishing a threshold for the number of missing days using 7 d pedometer data. Physiol Meas. 2012;33:1877-85.
19. Wendel-Vos GC, Schuit AJ, Saris WH, Kromhout D. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. J Clin Epidemiol. 2003;56:1163-9.
20. Wagenmakers R, van den Akker-Scheek I, Groothoff JW, Zijlstra W, Bulstra SK, Kootstra JW, et al. Reliability and validity of the short questionnaire to assess health-enhancing physical activity (SQUASH) in patients after total hip arthroplasty," BMC Musculoskelet Disord. 2008;9:141.
21. Davis AM, Perruccio AV, Canizares M, Hawker GA, Roos EM, Maillefert JF, et al. Comparative, validity and responsiveness of the HOOS-PS and KOOS-PS to the WOMAC physical function subscale in total joint replacement for osteoarthritis. Osteoarthritis Cartilage. 2009;17:843-7.
22. Farr JN, Going SB, Lohman TG, Rankin L, Kasle S, Cornett M, et al. Physical activity levels in patients with early knee osteoarthritis measured by accelerometry. Arthritis Rheum. 2008;59:1229-36.

23. Wallis JA, Webster KE, Levinger P, Taylor NF. What proportion of people with hip and knee osteoarthritis meet physical activity guidelines? A systematic review and meta-analysis. Osteoarthritis Cartilage. 2013;21:1648-59.
24. Pisters MF, Veenhof C, van Dijk GM, Dekker J, CARPA Study Group. Avoidance of activity and limitations in activities in patients with osteoarthritis of the hip or knee: a 5 year follow-up study on the mediating role of reduced muscle strength. Osteoarthritis Cartilage. 2014;22:171-7.
25. Dobson F, Hinman RS, Roos EM, Abbott JH, Stratford P, Davis AM, et al. OARSI recommended performance-based tests to assess physical function in people diagnosed with hip or knee osteoarthritis. Osteoarthritis Cartilage. 2013;21:1042-52.
26. Dowd KP, Harrington DM, Bourke AK, Nelson J, Donnelly AE. The measurement of sedentary patterns and behaviors using the activPAL Professional physical activity monitor. Physiol Meas. 2012;33: 1887-99.
27. Vignon E, Valat JP, Rossignol M, Avouac B, Rozenberg S, Thoumie P, et al. Osteoarthritis of the knee and hip and activity: a systematic international review and synthesis (OASIS). Joint Bone Spine. 2006;73: 442-55.
28. Holsgaard-Larsen A, Roos EM. Objectively measured physical activity in patients with end stage knee or hip osteoarthritis. Eur J Phys Rehabil Med. 2012;48:577-85.
29. Van Remoortel H, Giavedoni S, Raste Y, Burtin C, Louvaris Z, Gimeno-Santos E, et al. Validity of activity monitors in health and chronic disease: a systematic review. Int J Behav Nutr Phys Act. 2012;9:84.
30. Peiris CL, Taylor NF, Shields N. Patients receiving inpatient rehabilitation for lower limb orthopaedic conditions do much less physical activity than recommended in guidelines for healthy older adults: an observational study. J Physiother. 2013;59:39-44.
31. Beswick AD, Wylde V, Gooberman-Hill R, Blom A, Dieppe P. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. BMJ Open. 2012;2:e000435.
32. Groen JW, Stevens M, Kersten RF, Reininga IH, van den Akker-Scheek I. After total knee arthroplasty, many people are not active enough to maintain their health and fitness: an observational study. J Physiother. 2012;58:113-6.
33. Brandes M, Ringling M, Winter C, Hillmann A, Rosenbaum D. Changes in physical activity and health-related quality of life during the first year after total knee arthroplasty. Arthritis Care Res (Hoboken). 2011;63:328-34.

Chapter 7

Signatures of knee osteoarthritis in women in the temporal and fractal dynamics of human gait

Vangeneugden* J., Verlaan* L., Oomen P.W., Liu W.Y., Peters M.J.M.,
Natour N., Emans P.J., Meijer K.
* contributed equally to this paper

Clinical Biomechanics. 2020;76:105016

Abstract

Background

Osteoarthritis of the knee is characterized by progressive cartilage deterioration causing pain and function loss. Symptoms develop late with limited disease-modifying opportunities. Osteoarthritis is a major cause of immobility, with a higher prevalence above 60 years. This age-related increase in prevalence is further amplified by the female gender. Imaging and biochemical analyses for detection of osteoarthritis of the knee are expensive and labor-intensive. Continuous movement tracking could aid in detecting onset and/or worsening of symptoms.

Methods

We used portable technology to investigate kinematic differences in female patients with knee osteoarthritis, weight-matched healthy female volunteers and obese female patients with osteoarthritis of the knee. Knee osteoarthritis was established radiographically and corroborated using magnetic resonance imaging.

Findings

The total amount, type and level of activity did not differ significantly between groups. The temporal activity pattern during the day was however significantly different with a bimodal signature in healthy volunteers only. Sequence analyses revealed more time to recuperate after dynamic activity in both patient groups. Analysis of walking bouts revealed significant differences in stride interval dynamics, indicative of gait naturalness, only in healthy volunteers. Temporal activity, sequence and walking patterns were independent of body weight.

Interpretation

We thus provide for the first-time evidence of temporal specific kinematic signatures in amount and quality of movement also in stride interval dynamics between people with and without osteoarthritis of the knee independent of body weight. These findings could allow early and non-intrusive diagnosis of osteoarthritis enabling concordant treatment.

Introduction

Osteoarthritis of the knee (KNOA; *KNee OsteoArthritis*) is one of the leading causes of global disability[1] and the most common reason for pain in older adults with a significant individual and economic burden.[2,3] It is estimated that between 20% and 30% of adults and elderly suffer from this condition.[4] The demographic change ahead of us, i.e. increasing average age of men and women, and lifestyle habits, i.e. increasing obesity, will only aggravate the impact of this disease.[5] Being the largest weight-bearing joint, the knee is most affected by wear and tear and biomechanical load.[6,7]

Current operative approaches for KNOA have experienced enormous improvements over the last couple of years.[1] However, KNOA is a disease of multifactorial origin, starting as a preclinical condition that can become very advanced before it becomes symptomatic due to the avascular and noninnervated nature of cartilage[8], cf. the pre-osteoarthritis stage. Biochemical analyses[13] and imaging[14-16] to examine this stage are however not conclusive, expensive and invasive. Neuromuscular exercises and proprioceptive training have been successful in preventing or at least slowing down KNOA[9]. Still on a global scale, approximately 1.5 million total knee arthroplasty (TKA) surgeries, the end-stage of KNOA, are performed.[10-12]

The pathomechanics of clinically manifest KNOA is well described under restricted laboratory settings using accelerometers or motion-capturing systems[17-19] however a good understanding of subtle and small changes in behavior requires long-term and continuous monitoring of movement in a daily setting. Activity patterns are typically probed using questionnaires, however questionnaires are very susceptible to subjectivity.[20]

Accelerometers have been used in a number of diverse fields.[21-29] They are less expensive, less complex to use and mimic realistic settings better than gait analysis laboratories, yet they produce more objective and detailed data than subjective interpretation of movement parameters. With regard to KNOA not much is known about kinematic signatures typical for the disease.

Most studies monitor activity with the goal to detect motion parameters capable of discriminating between healthy and pathological gaits.[23,30,31] A lot more information can and should be extracted from these rich and ecologically valid data sets. Studies on the gait of healthy subjects have shown great potential of detailed motion analyses, proficiency in discerning a number of different action categories[32] and the capability to determine the smoothness[33], rhythm[33], stability[34], harmony[35] and naturalness of locomotion.[36] Our goal was to document in great detail the effect of osteoarthritis of the knee on macro- and mesoscale temporal patterns and on complex gait characteristics using unconstrained, continuous and long-term monitoring.

We set out to investigate kinematic signatures and activity patterns distinctive for KNOA, measured continuously for the duration of a full week under unconstrained daily conditions. This was done by attaching triaxial accelerometers, capable of detecting positional displacement in three spatial orthogonal axes, on the non-affected femur of patients suffering from KNOA as assessed clinically and radiological compared with healthy volunteers. Only women aged between 50 and 65 years were included in study, as KNOA prevalence is highest in this group. According to the World Health Organization, OA is the fourth leading cause of immobility, with a prevalence of 18% for women and 9.6% for men aged above 60 years.[37] Prevalence of knee OA increases with age, especially above 50 years. This age-related increase in prevalence is further amplified by the female gender.[38] Given the modulatory effect of weight we also included a group of obese KNOA patients. The rationale was that a meticulous description of potential distinctive signatures in KNOA could then be used in future studies and clinical practice to detect early-OA in healthy subjects allowing the rapid initiation of adequate preventive treatments.
The goal of our study was to examine differences in activity patterns, temporal, sequence and fractal dynamics between patients suffering from osteoarthritis of the knee and matched healthy participants following continuous, long-term (one week) and unconstrained monitoring at home, taking body weight into account.

Methods

Subjects

This study included three groups: healthy controls (BMI: 20-25 kg/m^2), lean KNOA (BMI: 20-25 kg/m^2) and obese KNOA (body mass index (BMI): 30-40 kg/m^2). Only women aged between 50 and 65 years were included, as KNOA prevalence is highest in this group. The upper aged limit was adopted to prevent inclusion of participants at high risk of having comorbidities (e.g. type II diabetes mellitus, osteoporosis, dementia, cardiovascular disease). OA patients having a Kellgren Lawrence (KL) score between 1 and 3 at the medial tibiofemoral site were included.
All subjects participated in a larger study, i.e. the *KNOA study* referring to “Knee Osteoarthritis”, coordinated at the Maastricht University Medical Center (MUMC+). The KNOA study consisted of monitoring physical activity over a longer time span, i.e. one week, while subjects were instructed to engage in regular daily activities. Radiological assessment of KNOA was done by means of the Kellgren and Lawrence classification

system[39] and further corroborated by magnetic resonance imaging using the *MRI Osteoarthritis Knee Score*, i.e. MOAKS.[40]

Table 7.1 Anthropometric measurements and imaging characteristics. An asterisk indicates a significant difference of the variable between the three groups (Kruskal-Wallis test).

Parameter	group 1 healthy volunteers n = 11 mean (SD)	group 2 lean KNOA patients n = 11 mean (SD)	group 3 obese KNOA patients n = 10 mean (SD)	*P*
Age (years)	57.6 (4.5)	60.2 (4.7)	59.9 (4)	0.3
Height (m)	1.67 (0.05)	1.66 0(.06)	1.63 (0.1)	0.34
Weight (kg)	64.1 (5.74)	66.9 (6.3)	84.9 (13.44)	<0.001*
BMI (kg/m^2)	22.83 (1.12)	24.36 (2.16)	31.27 (2.07)	<0.001*
KL (grade)	n.a.	2 (.63)	2.3 (0.67)	0.18
(1; 2; 3)		(2; 7; 2)	(1; 5; 4)	
MOAKS (grade)	0.29 (0.36)	1.01 (0.66)	1.04 (0.75)	0.95

Significant differences between groups, tested with concordant Mann-Whitney U tests, are between groups 1 and 2 with group 3 on weight and BMI, between group 1 and groups 2 and 3 on MOAKS and KL. There was no significant association between KL-grades in the two different OA groups (group 2 and group 3) (Chi-square statistic = 1.29, *P*=0.52).

Exclusion criteria were any inflammatory arthritis, trauma, OA at any other joint in the lower extremities including patellofemoral OA and tibiofemoral OA on the lateral site, anterior cruciate ligament injury, medial and collateral ligament injury, and psychiatric illness according to the Diagnostic and Statistical Manual of Mental Disorders classification criteria for psychiatric illnesses (patients were excluded when diagnoses were present in their medical files). Healthy women were non-obese, did not meet the exclusion criteria, and did not have knee OA according to the American College of Rheumatology classification criteria.[41]

The study was approved by the Medical Ethical Committee Maastricht University Medical Centre and all subjects gave their informed consent. All procedures were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments.

Imaging analyses: radiography and magnetic resonance imaging

Radiographic imaging was used to evaluate knee cartilage and knee OA status. Presence of knee OA was assessed from X-ray images by the Kellgren-Lawrence (KL) knee score.[39] Subjects having a score between 1 and 3 at the medial tibiofemoral site were included in this study. The X-ray images were evaluated double-blind by two independent orthopaedic surgeons.

To more accurately assess cartilage health in all study groups, Magnetic Resonance Imaging (MRI) was performed using a 3T Philips Intera Scanner *(Philips Medical Systems, Best, The Netherlands)*. Cartilage health was evaluated based on the MRI Osteoarthritis Knee Score (MOAKS).[40] For a more detailed description of imaging procedures, we refer to Verlaan et al.[42]

Equipment

Accelerations were measured using a three-dimensional accelerometer (49x40x14 mm; length, width x height; weight: 30 gr), i.e. KXSD9 tri-axis Digital Accelerometer[43] with a Texas Instruments microcontroller capable of monitoring positional displacements expressed in amount of gravitational inertial force (g) in anteroposterior, mediolateral and vertical or cranial-caudal directions.[26] The accelerometer was secured midway between patella and spina iliaca anterior superior using adhesive hypoallergic tape to reduce extraneous movements as much as possible. Data were sampled at 25 Hz and stored on a local internal memory of 2 GB. The unit was powered by a Lithium Ion battery capable of recording approximately two weeks at abovementioned sampling frequency.[26]

Protocol

Accelerometers were positioned and instructions were given at the policlinic of orthopedic surgery. Subjects were instructed to wear the accelerometer at all times during a full week to ten days when a new appointment was made to remove the apparatus. Accelerometers were waterproof and adhesive tape strong enough for the full duration. Importantly, subjects were not primed or influenced in any way to move different than usual. Instructions for correct reattaching the accelerometer when necessary were also provided.

Data analysis

Raw data was downloaded to a PC using commercially available software packages (*IDEEQ* from Maastricht Instruments Inc.). Files were converted to readable .bin files and imported into *Matlab* (Mathworks, Natick, MA, USA) for further processing and analyses. Analyses and algorithms applied were largely in line with previously published work from our laboratory.[22,26] Kinematic traces were converted to conventional coordinates following International Society of Biomechanics (*ISB*) gait guidelines.[44] Parameters of interest were: different levels of activity, i.e. sitting/lying, standing and dynamically active and differentiations of dynamically activity from bottom to top

respectively low, medium and vigorous activity. Average physical activity per subject and per group. Fluctuations of average physical activity during the course of the day. Differences in time to recuperate after activity and complex fluctuations in gait pattern using detrended fluctuation analyses. A detailed description on all procedures and algorithms written in *Matlab* can be found as supplementary material to this paper (Supplementary Methods). All data is made available to the general public and can be obtained by contacting the corresponding author.

Statistical analysis

Non-parametric statistics, i.e. Kruskal-Wallis H tests, equivalent to one-way ANOVAs, with Mann-Whitney U tests, to test for pairwise significance were run on data with only one factor and limited data entries, i.e. when running hypotheses of one variable between groups. N-way ANOVAs were run on hypotheses containing more than one factor, e.g. the temporal signature of average activity over the course of the day between groups. Significant F-statistics were followed up with Bonferonni-corrected pairwise post-hoc tests. All analyses were performed in *Matlab* and custom scripts were made if not available in the library or online repositories. A *P*-value of ≤0.05 was considered significant. Bootstrap analysis was performed on the temporal activity patterns between groups by creating an empirical distribution constructed by drawing 10000 random samples (n=10) with replacement. Bootstrap confidence intervals were set at 95%.

Results

Subjects characteristics

Thirty-two subjects were included in this study, divided over three study groups. The first group consisted of healthy volunteers (n=11), the second group of body weight matched subjects suffering from KNOA with Kellgren-Lawrence (KL) scores ranging from 1 to 3 (n=11; mean KL 2) and the third group of obese subjects with KNOA and Kellgren-Lawrence scores 1 to 3 (n=10; mean KL 2.43; comparison between KL-scores of the two KNOA groups, Mann-Whitney U test, U=1.78, P=0.1826). Furthermore, there was no significant association between KL-grades in the two different OA groups (group 2 and group 3) (Chi-square statistic=1.29, P=0.52). The MOAKS between the healthy volunteers and the two KNOA groups, lean and obese, were also significantly different (mean MOAKS 0.29 (n=8) vs. 1.01 (n=9) and 1.04 (n=9) respectively; Mann-Whitney U tests, both *P's*=0.02), but not between the two patient groups (Mann-Whitney U test,

P=0.95). Obesity thus has no influence on the severity of the osteoarthritis as evidenced by magnetic resonance imaging. Please note that we did not obtain MRI data from all subjects, i.e. group 1=8/11, group 2=9/11 and group 3=9/10. Average BMIs were 22.83, 24.36 and 31.27 kg/m^2 respectively (Kruskal-Wallis test, *H*=20.02, *P*<0.001; post-hoc Mann-Whitney U test showed significant differences between group 3 and other 2 groups only). Groups were also matched according to age (57.6, 60.2 and 59.9 years; Kruskal-Wallis test, *H*=2.43, *P*=0.2966). Full anthropometric measurements can be found in Table 7.1.

Continuous monitoring and classification of kinematics

The accelerometers we employed lasted 7-10 days without recharging and sampling quality was good and stable during the entire duration as evidenced by a randomly chosen epoch of 20 minutes from a random subject (Figure 7.1a). Figure 7.1b represents a 2-minute zoomed-in section from mid-epoch. Action classification results are indicated by the full black line above the kinematic traces. During active episodes we further looked at the intensity of activity, plotted as dots above the classification line.

For each subject we visualized the average activity level per hour in color plots (Figure 7.1c) to discern potential temporal patterns of activity that could discriminate between the three groups. Red colors represent hours with lots of activity, blue colors the opposite. As such, day-night cycli are easily discriminable.[45]

Next, we applied correlation analyses using the 24-h activity patterns to look for potential patterns between all recorded days of all subjects (Figure 7.1d) and between an averaged 24-h curve per subject within or between groups (Figure 7.1e). The average correlation index per day within each group was .39, .38 and .33 respectively (unbalanced one-way ANOVA, *F*=32.94, *P*<0.001) with a significantly lower index for the obese KNOA patients compared to the other two groups (*P*<0.001, Bonferonni-corrected). This points to the fact that within the obese KNOA group larger differences between subjects exist.

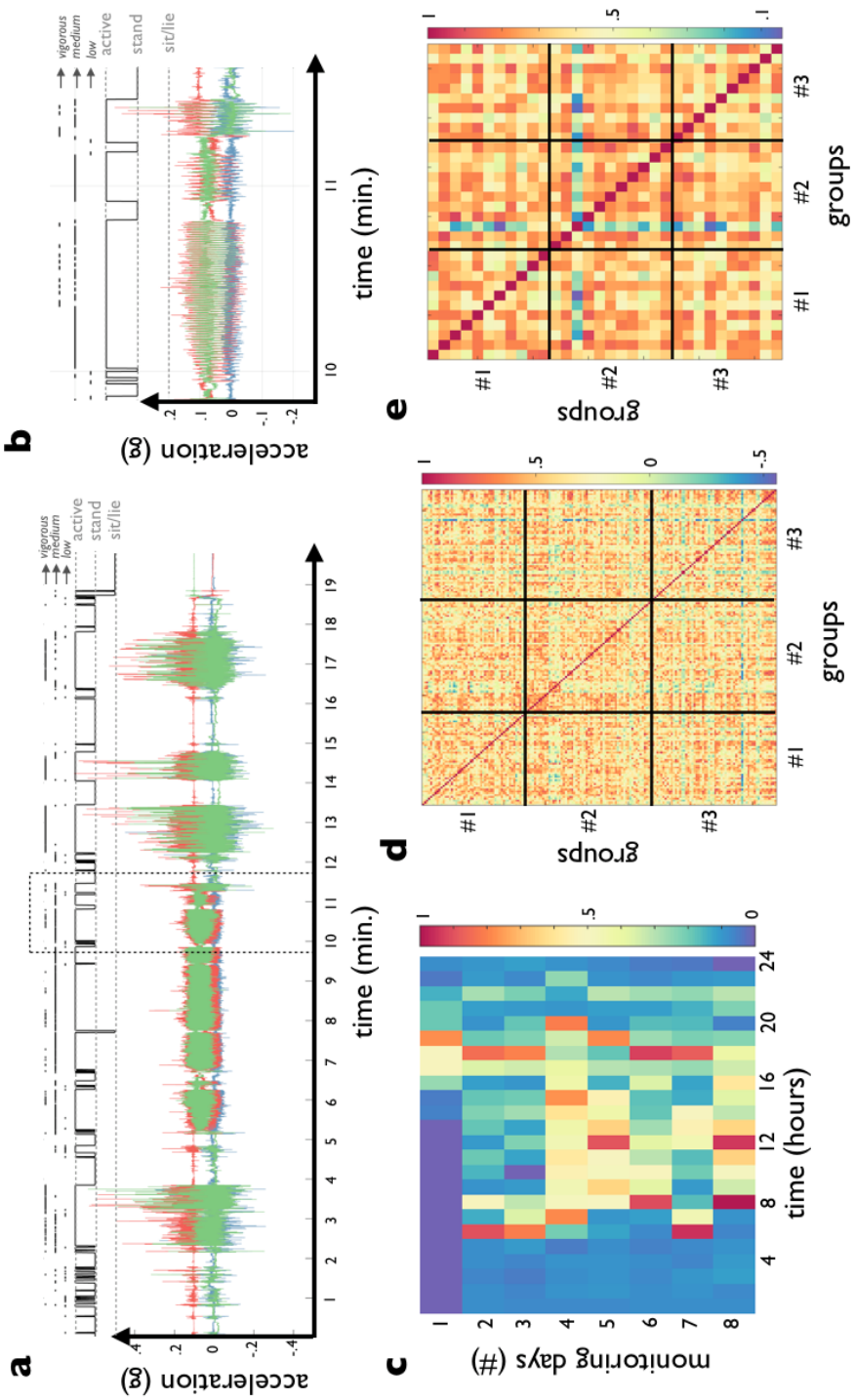
a
b
c
d
e
acceleration (g)
time (min.)
vigorous
medium
low
active
stand
sit/lie
monitoring days (#)
time (hours)
groups
#1
#2
#3

Figure 7.1 Data acquisition and classification under unconstrained conditions.
a. Twenty-minute epoch with raw kinematic XYZ-signals from an accelerometer attached to the left femur represented by red, green and blue colors respectively for anteroposterior, vertical and mediolateral directions. The full line depicts three different levels of activity, i.e. sitting/lying, standing and dynamically active. The black dots represent the level of activity during the latter, with three differentiations from bottom to top respectively low, medium and vigorous activity. Please note that the kinematic traces have not been converted to ISB-coordinates. **b**. Zoomed image on an approximately two-minute section of the kinematic traces from a (box). Vertical raster lines denote minutes. Rest conform a. **c**. Average physical activity per hour for multiple monitoring days for a random subject from group 1. Data were normalized across days but within subject. Please note that during the first 13 hours of day 1 and the last hour of day 8 the accelerometer was not active, i.e. subject was not monitored. Hours per day are represented on the horizontal axis, different monitoring days on the vertical axis. **d**. Matrix representing correlations between the 24h-average activity profiles across all monitoring days within each subject, across subjects and across groups. **e**. Matrix representing correlations between the averaged 24h-activity profile per subject across subjects and across groups. In **d**. and **e**. correlations are color-coded by means of the accompanying color bar. The full black lines demarcate the different groups. No evident pattern is discernable.

OA does not affect total amount, type nor level of activity

Next, we looked at potential differences in temporal signatures of activity patterns between groups. For each subject in each group we obtained one average temporal signature, represented in Figure 7.2a. Two subjects from the first group and one subject from the third group were excluded due to insufficient full monitoring days (<5 days). We either normalized the temporal signatures to the maximum activity pattern of each subject individually (Figure 7.2a upper panels) or to the maximum activity within the whole group (Figure 7.2a lower panels). The former gives an idea on the absolute fluctuations in activity during the day per subject, while the latter gives a more realistic and relative indication of fluctuation patterns over groups. In total there are no differences between groups in activity pattern over days (Figure 7.2b; Kruskal-Wallis test, H=2.1, P>0.05). Subjects in all three groups moved on average equally over days, although healthy subjects tended to move a bit more than lean subjects with KNOA (*SMA* group 1=0.2754 units vs. *SMA* group 2=0.2443 units) who in turn tended to move a bit more than obese subjects with KNOA (*SMA* group 3=0.2277 units), however all effects were not significant. Similar results were obtained when testing the per-subject normalized data.

The average amount of time (proportions) spent sitting or lying, standing or being dynamically active during waking hours (Figure 7.2c left panel) did not reveal significant differences between groups (respective scores group 1: 0.6, 0.34 and 0.06; group 2: 0.55, 0.38 and 0.07; group 3: 0.6, 0.35 and 0.05; unbalanced two-way ANOVA, F=0.21, P=0.99). The level of dynamic activity, expressed as frequencies, was also not significantly different (respective scores group 1: 2.02, 19.15 and 0.87; group 2: 2.04,

18.54 and 1.2; group 3: 3.15, 17 and 0.79; unbalanced two-way ANOVA, *F*=0.39, *P*=0.68; see Figure 7.2c right panel; notice that proportions do not add up to 1 given that during some hours subjects did not express any physical activity, e.g. sitting at a desk for longer than one hour).

Based on these analyses it is clear that KNOA, in our sample, does not affect the total amount of physical activity, type of activity, nor the level of activity.

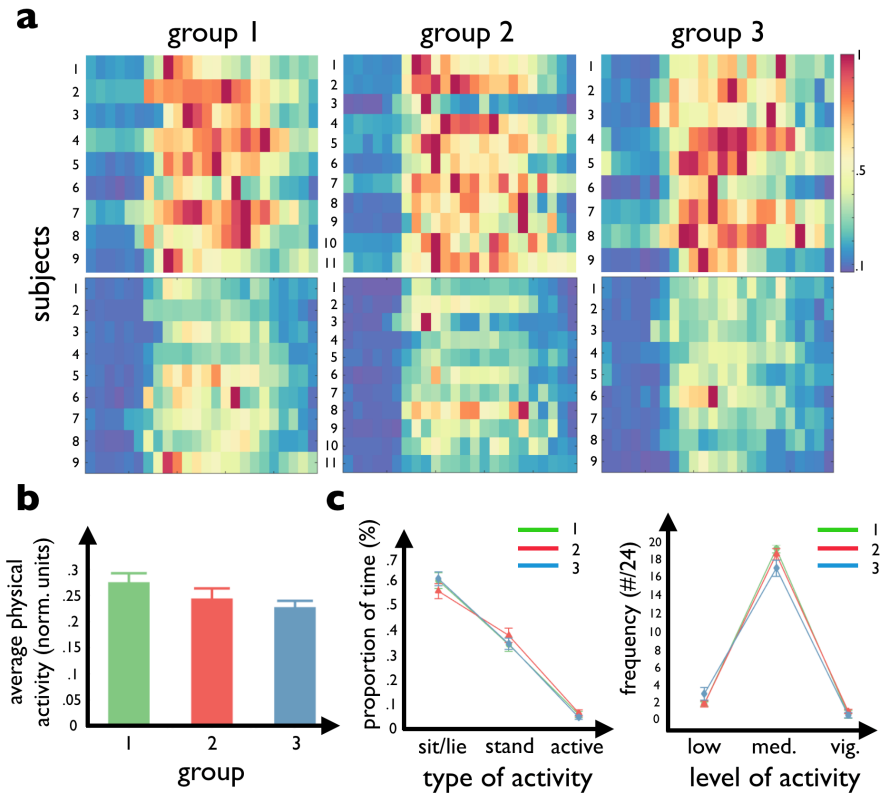

Figure 7.2 OA does not affect total amount, type nor level of activity.
a. Average physical activity per subject and per group. Upper panels represent data normalized to the maximum physical activity per hour per subject. Lower panels represent data normalized to the maximum hourly physical activity profile within each group. Only data from subjects containing at least 7 days of full-day monitoring were used to calculate day-averages per subject. Horizontal axis depicts hours per day, vertical axis the number of subjects with full 7-day monitoring data, i.e. 9, 11 and 9 subjects respectively. **b**. Average full-day activity levels between groups are comparable (Kruskal-Wallis test, H=2.1, *P*>0.05), calculated on the traces normalized per subject (lower panels in a.). **c**. Left, average time (%) spent performing the different classified actions (sitting/lying, standing and dynamically active) for the three groups during the active day. i.e. from waking up until going to bed. Right, average frequencies of activity level (low, middle or vigorous) performed most within each hour calculated only for dynamically active epochs. Values in b and c are SD standard error of the mean.

Lack of bimodal activity patterns during the course of the day in OA

However, eyeballing the color plots in Figure 7.2a, qualitative differences between groups seem to be present. To get a better idea on temporal fluctuations, we plotted and directly compared the temporal signatures of the three groups (Figure 7.3). Temporal patterns over days differed significantly (two-way unbalanced ANOVA, F=18.56, P<0.001) with lower levels of activity in the afternoon from 3 to 5 P.M. for the KNOA patients, independent of body weight. Also, temporal activity patterns in the morning, at 12 A.M. for the obese patients and from 11 A.M. to 1 P.M. for the lean KNOA group differed with the healthy subjects. All post-hoc pairwise tests were performed using Bonferonni correction. Notwithstanding the lack of a general significant effect in physical activity over days (Figure 7.2b), examining temporal signatures in more detail reveals group-specific patterns with a more bimodal type of activity-level in the healthy group. Results were corroborated by bootstrap analysis with significantly lower levels of activity for the KNOA patients in the afternoon, from 3 to 5 P.M., and vice versa for the healthy subjects (all P's<0.05). Furthermore, the increased activity levels at 12 A.M. was significant for the healthy subjects and significantly lowered in the lean (both P's<0.05), but not the obese patients. However, the differences at 11 A.M. and 1 P.M. were not significant between groups. Thus, the main finding of increased temporal activity patterns in healthy subjects as compared to subjects suffering from osteoarthritis in the early afternoon, i.e. from 3 to 5 P.M., was not due to small sample sizes.

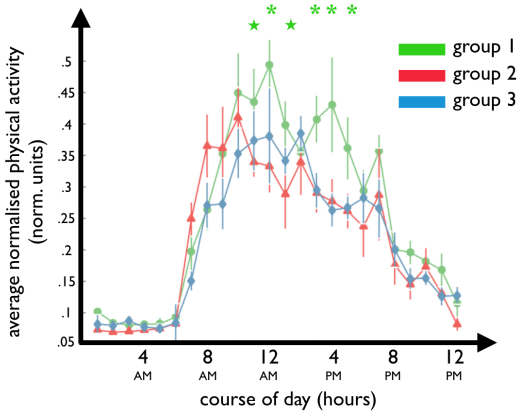

Figure 7.3 Different temporal activity patterns between groups. Fluctuations of average physical activity during the course of the day are different for the three groups. Calculated on 9, 11 and 9 subjects respectively. A bimodal signature is present in activity patterns of healthy subjects (group 1) with significant peak activities in late morning and late afternoon. Values are SD standard error of the mean. Green asterisks and stars represent significant pairwise comparison at P's<0.01 between group 1 and group 2 + 3 and group 1 and group 2 respectively.

Increased time to recuperate in OA following locomotion but not standing

We were interested in potential differences in time to recuperate after such events. Instead of looking at large spans of time, i.e. 1-hour epochs, we divided the temporal kinematic traces in bouts of 5 minutes and subjected it to our action classification algorithm. Following a standing epoch, no significant differences were observed within the 30-minute interval between groups (repeated measures two-factor ANOVA, F=1, P=0.37) (Figure 7.4a). Following an active epoch, significant differences between groups were observed (repeated measures two-factor ANOVA, F=5.18, P<0.01), albeit without any significant pairwise comparison (Figure 7.4b). There thus seems to exist a general trend for more rest, i.e. sitting or standing, after an active period in patients with KNOA as compared to healthy subjects.

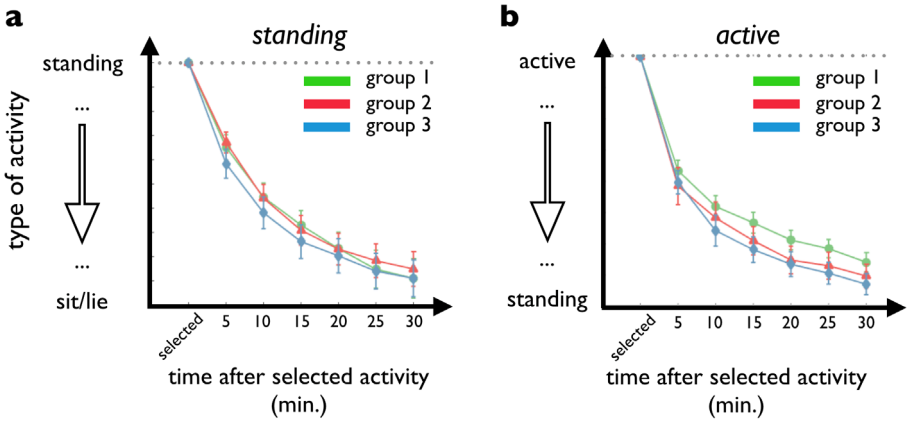

Figure 7.4 Increased time to recuperate in OA following locomotion but not standing.
Sequential consequences after standing (**a**) or being dynamically active (**b**) for at least 5 minutes on the activity type in the subsequent 30 minutes, divided in 5 minutes sections. Values range from 1 to 3, i.e. 1=sitting/lying, 2=standing and 3=dynamic activity. Two-way ANOVAs not significant in a, but factor 'group' was significant in b (P<0.01).

Reduced stride-to-stride fluctuations in OA

An important yet subtle observation in the analysis of gait dynamics has provided insight into pathological alterations in the physiology of gait.[46,47] Close examination of gait revealed complex fluctuations in gait pattern and more specifically in stride-to-stride fluctuations previously considered to be mere noise. Short- and long-term autocorrelations of these non-stationary signals can be unraveled using detrended

fluctuation analyses (DFA), a fractal analysis technique, in line with extensive research in cardiology.[48]

Following the extraction of walking bouts[22], a previously validated algorithm based on the filtered anteroposterior acceleration signal using integration processes and peak detection algorithms[49] was applied to detect left and right steps. Based on these left-right steps we were able to look at a number of walking parameters influenced by osteoarthritis or obesity between the three groups.

Mean step time (medians 607 ms, 637 ms and 697 ms respectively; Kruskal-Wallis test, *H*=1.32, *P*=0.5165; Figure 7.5a), average of mean stride time left and right (medians 1.0145 s, 1.0752 s and 1.1932 s respectively; Kruskal-Wallis test, *H*=1.29, *P*=0.5165; Figure 7.5b) and harmonic ratios, indicative of the smoothness and rhythm of gait (anteroposterior direction: medians 2.1869, 1.8506 and 2.2793 respectively; Kruskal-Wallis test, *H*=0.19, *P*=0.9114; vertical direction: medians 2.5486, 2.1427 and 2.5075 respectively; Kruskal-Wallis test, *H*=0.18, *P*=0.9129; lateromedial direction: medians 0.5627, 0.5194 and 0.4218 respectively; Kruskal-Wallis test, *H*=1.46, *P*=0.4808; Figure 7.5c; all harmonic ratios expressed in amplitudes), were similar across the three groups. However, the DFA index, a parameter of locomotor function looking at stride-to-stride time fluctuations as an indicator for naturalness or good health of gait, was significantly different between groups (medians of slope α 0.8138, 0.6695 and 0.6424 respectively; Kruskal-Wallis test, *H*=7.58, *P*<0.05), with significant differences between the group of healthy subjects and both patients groups with KNOA, but independent of BMI (Mann-Whitney U test, *Us* 2.07, 2.85 and 0.04 between group 1 & 2, group 1 & 3 and group 2 & 3; *P*<0.05, *P*<0.05 and *P*=0.9719 respectively).

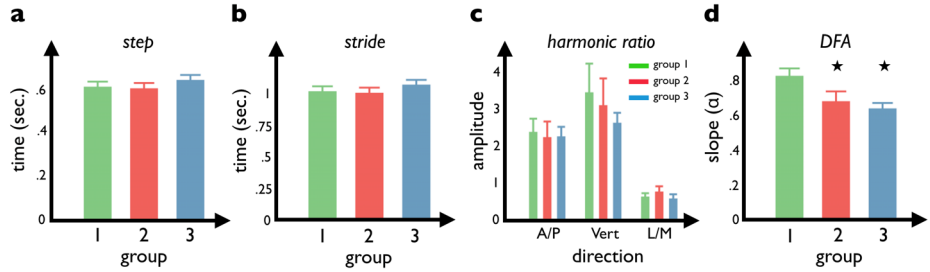

Figure 7.5 Reduced stride-to-stride time interval fluctuations in OA. Different walking parameters calculated on left and right step detection based on automatic selection of walking traces from concatenated kinematic traces: **a**. mean step time, **b**. mean stride time, **c**. harmonic ratios for anteroposterior, vertical and mediolateral accelerations and **d**. detrended fluctuation analysis (DFA). Black stars denote significant p-values (*P*'s<0.05).

Discussion

To the best of our knowledge this study is the first in its kind to document in great detail the effect of osteoarthritis of the knee on macro- and mesoscale temporal patterns and on complex gait characteristics using unconstrained, continuous and long-term monitoring.

Within the domain of KNOA only a handful of studies have been carried out previously using accelerometers, yet this study differed notably from these studies in a number of ways. A first study by Liu and colleagues[50] looked into the effect of KNOA on physical activity and symptoms change over the course of a year. This study however lacked a control group of matched healthy volunteers. BMI as potential confounder for OA[51] was not considered in their design and motion analyses only allowed discriminating light from moderate-to-vigorous activity.

A second study by Staab and colleagues[52] investigated gait parameters more in detail using spectral analyses and a combination of accelerometry and motion capturing by an optoelectronic system. This study did contain a control group of osteoarthritis-free subjects although not matched according to age or weight. According to our results the latter non-matched variable should not resort too much effect, yet the former variable can have serious implications on detailed gait parameters.[45] Moreover, we only found a significant difference in the presence of more long-range stride-to-stride time interval correlations (DFA) in healthy subjects compared to patients. Staab and colleagues[52] did find differences in gait velocity, cadence and symmetry, possibly pointing to the fact that their groups were more diverse than our groups. The fact that we only found a specific and well-defined difference between patients with and without KNOA in the domain of naturalness of gait and not on any other gait parameter could provide evidence for a more defined demarcation of KNOA in our study.

Recently, both Alkjaer and colleagues[17] and Clermont and Barden[19] did not find significant differences in DFA between patients with and without KNOA. The DFA for subjects from our healthy group was in range of previously reported DFA values from their and other studies (our DFA: 0.81 vs. DFAs from other studies: 0.72, 0.77, 0.88 and 0.76, the former two DFAs from the abovementioned studies, the latter two from [53] and[54] respectively). The DFA values of our KNOA patients were lower than reported by Alkjaer et al.[17] and Clermont and Barden[19], i.e. 0.67 and 0.64 vs. 0.80 and 0.77 respectively. This could be due to a number of reasons. Firstly, we used longer kinematic traces for our stride-to-stride calculations (on average 40 min. vs. 10 min. in both studies). Secondly and more importantly we monitored subjects under unconstrained and natural conditions, thus being less susceptible to experiment-desired outcomes, e.g. *forced* locomotion during the monitoring phase in a laboratory

setting.[55] The variety in severity of KNOA as measured by the Kellgren and Lawrence scale was similar and is unlikely to account for the observed differences.[56] We do not think that the nature of the concatenated signal used in our analyses could account for these discrepancies.[30]

Another important addition to these studies is the fluctuating activity pattern during the course of the day in healthy volunteers but not KNOA patients. This finding is completely new within the field of KNOA but has been observed before in COPD patients[23] and could also provide opportunities for early detection and initiation of neuromuscular and proprioceptive training programs.[9] However, we were not able to relate this difference in temporal activity pattern to the severity of the underlying cartilage damage (KL-scores) due to the low number of subjects in our study. Nor were we able to relate this finding to the level of experienced pain since we did not collect these data.

Furthermore, our sequence analyses pointing to more time needed for recuperation in KNOA patients after being active, but not standing still, is also completely new and could also be used as a tool in early detection. We must however emphasize that pairwise post-hoc tests did reveal trends, but not significance, between healthy volunteers and KNOA patients. A more extensive study with more subjects in all groups could potentially yield significant results when analyzing kinematic data to detect sequence effects.

We are mindful of the fact that we only had a limited amount of subjects in our three groups. Moreover, we only included females. It is known that KNOA increases with age, especially in people above 50 years and that this increment is amplified in women.[38] Although our subjects were within this age range, we do not think our data could not be extrapolated to the other gender or other age groups. A more extensive study with more subjects (including males), longer and more monitoring periods could strengthen our results.

More importantly, we realize that our study did not incorporate experienced pain as predictor or moderator to manifest behavior. Fukutani and colleagues[57] have recently shown that patients with late KNOA (KL-scale 3 and 4) ascend and descend stairs less and avoid sit-to-stand transitions more than patients with early KNOA (KL-scale 1 and 2), a finding associated with experienced pain. To account for these observations, we recently recorded detailed motion data via an optoelectronic motion capturing system, of the same subjects included in this study performing the actions investigated by Fukutani and colleagues[57], i.e. walking on a flat surface (Verlaan et al., submitted), ascending and descending stairs[58] and sit-to-stand[42] and vice versa.

Conclusion

This study systematically examined differences in activity patterns, temporal, sequence and fractal dynamics between patients suffering from osteoarthritis of the knee and matched healthy participants following continuous, long-term (one week minimum) and unconstrained monitoring at home, taking body weight into account.

In sum, the results highlight the importance of continuous monitoring of movement patterns in daily settings in order to discriminate at the behavioral level patients with and without KNOA. As such, these subtle yet significant differences in temporal dynamics, i.e. temporary decrease in activity in early afternoon and more time needed to recuperate after physical activity, and fractal dynamics, i.e. with reduced naturalness of gait, between patients with knee osteoarthritis and healthy controls could be used as behavioral markers for early detection and/or worsening of symptoms in KNOA.[8,12] These behavioral markers are measured easily, rapidly and non-invasively and can operate in concert with biomarkers and (non)-invasive imaging techniques to signal potential underlying structural damage in subjects prone to development of OA, i.e. presence of risk factors.[8]

References

1. Bijlsma JW, Berenbaum,F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. Lancet. 2011;377:2115-26.
2. Britton R. The economic burden of osteoarthritis. Am J Manag Care. 2009;15:230-5.
3. Felson DT. Clinical practice. Osteoarthritis of the knee. N Engl J Med. 2006;354:841-8.
4. Yoshimura N, Muraki S, Nakamura K, Tanaka S. Epidemiology of the locomotive syndrome: The research on osteoarthritis/osteoporosis against disability study 2005-2015. Mod Rheumatol. 2017;27:1-7.
5. Richmond SA, et al. Are joint injury, sport activity, physical activity, obesity, or occupational activities predictors for osteoarthritis? A systematic review. J Orthop Sports Phys Ther. 2013;43:515-9.
6. Verhaar JAN. Aandoeningen van de knie in Leerboek Orthopedie (eds. Verhaar & van Mourik) 381-407 (Bohn Stafleu van Loghum) 2008.
7. Fowler-Brown A, et al. The mediating effect of leptin on the relationship between body weight and knee osteoarthritis in older adults. Arthritis Rheumatol. 2015;67:169-75.
8. Ryd L, et al. Pre-osteoarthritis: Definition and diagnosis of an elusive clinical entity. Cartilage. 2015;6: 156-65.
9. Roos EW, Arden NK. Strategies for the prevention of knee osteoarthritis. Nat Rev Rheumatol. 2016;12: 92-101.
10. Singh JA. Epidemiology of knee and hip arthroplasty: A systematic review. Open Orthop. 2011;5:80-5.
11. Leta TH, Lygre SH, Skredderstuen A, Hallan G, Furnes O. Failure of aseptic revision total knee arthroplasties. Acta Orthop. 2015;86:48-57.
12. Chu CR, Williams AA, Coyle CH, Bowers ME. Early diagnosis to enable early treatment of pre-osteoarthritis. Arthritis Res Ther. 2012;14:212-22.
13. Heinegard D, Saxne T. The role of the cartilage matrix in osteoarthritis. Nat Rev Rheumatol. 2011;7: 50-6.
14. Eckstein F, et al. Clinical, radiographic, molecular and MRI-based predictors of cartilage loss in knee osteoarthritis. Ann Rheum Dis. 2011;70:1223-30.
15. Kokkonen HT, et al. Delayed computed tomography arthrography of human knee cartilage in vivo. Cartilage. 2012;3:334-41.
16. Huang YP, Wang SZ, Saarakkala S, Zheng YP. Quantification of stiffness change in degenerated articular cartilage using optical coherence tomography-based air-ject indentation. Connect. Tissue Res. 2011;52: 433-43.
17. Alkjaer T, et al. Gait variability and motor control in people with knee osteoarthritis. Gait Posture. 2015; 42:479-84.
18. Cho Y, Kim M, Lee W. Effect of proprioceptive training on foot posture, lower limb alignment, and knee adduction moment in patients with degenerative knee osteoarthritis: a randomized controlled trial. J Phys Ther Sci. 2015;27:371-4.
19. Clermont CA, Barden JM. Accelerometer-based determination of gait variability in older adults with knee osteoarthritis. Gait Posture. 2016;50:126-30.
20. Skender S, et al. Accelerometry and physical activity questionnaires – a systematic review. BMC Public Health. 2016;16:515-25.
21. Noorkoiv M, Rodgers H, Price CI. Accelerometer measurement of upper extremity movement after stroke: a systematic review of clinical studies. J Neuroeng Rehabil. 2014;11:144-55.
22. Annegarn J, et al. Differences in walking pattern during 6-min walk test between patients with COPD and healthy subjects. PLoS One. 2012;7:e37329.
23. Tabak M, et al. Telemonitoring of daily activity and symptom behavior in patients with COPD. Int J Telemed Appl. 2012;438736:1-8.
24. Baskerville R, Ricci-Cabello I, Roberts N, Farmer A. Impact of accelerometer and pedometer use on physical activity and glycaemic control in people with type 2 diabetes: a systematic review and meta-analysis. Diabet Med. 2017;34:612-20.

25. Taraldsen K, Chastin SF, Riphagen II, Vereijken B, Helbostad JL. Physical activity monitoring by use of accelerometer-based body-worn sensors in older adults: a systematic literature review of current knowledge and applications. Maturitas. 2012;71:13-9.
26. Senden R, Grimm B, Meijer K, Savelberg H, Heyligers IC. The importance to including objective functional outcomes in the clinical follow up of total knee arthroplasty patients. Knee. 2011;18:306-11.
27. Lipperts M, van Laarhoven S, Senden R, Heyligers I, Grimm B. Clinical validation of a body-fixed 3D accelerometer and algorithm for activity monitoring in orthopaedic patients. J Orthop Trans. 2017;11: 19-29.
28. Scheer JK, et al. Initial experience with real-time continuous physical activity monitoring in patients undergoing spine surgery. Clin Spine Surg. 2017;30:1434-43.
29. Cain KL, Sallis JF, Conway TL, Van Dyck D, Calhoon L. Using accelerometers in youth physical activity studies: a review of methods. J Phys Act Health. 2013;10:437-50.
30. Kirchner M, Schubert P, Liebherr M, Haas CT. Detrended fluctuation analysis and adaptive fractal analysis of stride time data in Parkinson's disease: stitching together short gait trials. PLoS One. 2014;e85787:1-6.
31. Bolink SAAN, et al. Validity of an inertial measurement unit to assess pelvic orientation angles during gait, sit-stand transfers and step-up transfers: Comparison with an optoelectronic motion capture system. Med Eng Phys. 2016;38:225-31.
32. Lugade V, Fortune E, Morrow M, Kaufman K. Validity of using tri-axial accelerometers to measure human movement – Part I: Posture and movement detection. Med Eng Phys. 2014;36:169-76.
33. Menz HB, Lord SR, Fitzpatrick RC. Acceleration patterns of the head and pelvis when walking on level and irregular surfaces. Gait Posture. 2003;18:35-46.
34. Doi T, et al. The harmonic ratio of trunk acceleration predicts falling among older people: results of a 1-year prospective study. J Neuroeng Rehabil. 2013;10:1-6.
35. Iosa M, et al. Stability and harmony of gait in patients with subacute stroke. J Med Biol Eng. 2016;36: 635-43.
36. Stergiou N, Harbourne R, Cavanaugh J. Optimal movement variability: a new theoretical perspective for neurologic physical therapy. J Neurol Phys Ther. 2006;30:120-9.
37. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. Bull World Health Organ. 2003;81: 646-56.
38. Arden N, Nevitt MC. Osteoarthritis: epidemiology. Best Pract Res Clin Rheumatol. 2006;20:3-25.
39. Kellgren JH, Lawrence JS. Radiological assessment of rheumatoid arthritis. Ann Rheum Dis. 1957;16: 485-93.
40. Hunter DJ, et al. Evolution of semi-quantative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). Osteoarthritis Cartilage. 2011;19:990-1002.
41. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum. 1986;29: 1039-49.
42. Verlaan L, Boekesteijn RJ, Oomen PW, Liu W-Y, Peters MJM, Witlox MA, et al. Biomechanical Alterations during Sit-to-Stand Transfer Are Caused by a Synergy between Knee Osteoarthritis and Obesity. BioMed Research International. 2018;2018:7.
43. http://www.microelectronicos.com/datasheets/KXSD9-2050.pdf
44. Wu G, et al. ISB recommendation on definitions of joint coordinate systems of various joints for the reporting of human joint motion – Part II: shoulder, elbow, wrist and hand. J Biomech. 2005;38: 981-92.
45. Tracy DJ, et al. Separating bedtime rest from activity using waist or wrist-worn accelerometers in youth. PLoS One. 2014;9:1-9.
46. Hausdorff JM, Edelberg HK, Mitchell SL, Goldberger AL, Wei JY. Increased gait unsteadiness in community-dwelling elderly fallers. Arch Phys Med Rehabil. 1997;78:278-83.
47. Hausdorff JM. Gait dynamics, fractals and falls: finding meaning in the stride-to-stride fluctuations of human walking. Hum Mov Sci. 2007;26:555-89.
48. Goldberger AL, et al. Fractal dynamics in physiology: alterations with disease and aging. Proc Natl Acad Sci USA. 2002;99:2466-72.

49. Zijlstra W, Hof AL. Assessment of spatio-temporal gait parameters from trunk accelerations during human walking. Gait Posture. 2003;18:1-10.
50. Liu SH, et al. Objectively measured physical activity and symptoms change in knee osteoarthritis. Am J Med. 2016;129:497-505.
51. Zheng H, Chen C. Body mass index and risk of knee osteoarthritis: systematic review and meta-analysis of prospective studies. BMJ Open. 2015;5:1-8.
52. Staab W, et al. Accelerometer and gyroscope based gait analysis using spectral analysis of patients with osteoarthritis of the knee. J Phys Ther Sci. 2014;26:997-1002.
53. Gates DH, Su JL, Dingwell JB. Possible biomechanical origins of the long-range correlations in stride intervals of walking. Physica A. 2007;380:259-70.
54. Kobsar D, Olson C, Paranjape R, Barden JM. The validity of gait variability and fractal dynamics obtained from a single, body-fixed triaxial accelerometer. J Appl Biomech. 2014;30:343-7.
55. Dingwell JB, Cusumano JP. Re-interpreting detrended fluctuation analyses of stride-to-stride variability in human walking. Gait Posture. 2010;32:348-53.
56. Kiss RM. Effect of severity of knee osteoarthritis on the variability of gait parameters. J Electromyogr Kinesiol. 2011;21:695-703.
57. Fukutani N, et al. Knee pain during activities of daily living and its relationship with physical activity in patients with early and severe knee osteoarthritis. Clin Rheumatol. 2016;35:2307-16.
58. Verlaan L, Boekesteijn R, Oomen PW, Liu WY, Peters MJM, Emans PJ, van Rhijn LW, Meijer K. Knee adduction moments are not increased in obese knee osteoarthritis patients during stair negotiation. Gait Posture. 2019;73:154-60.

Chapter 8

General discussion

General discussion

Osteoarthritis (OA) is thought to be the most prevalent chronic joint disease. The incidence of osteoarthritis is rising because of an ageing population and the epidemic of obesity.[1] The knee joint is most commonly affected and clinically characterized by pain, limitation of movement, tenderness, and local inflammation.[2] Normal activities of daily living, such as walking, stair negotiation and sit-to-stand (STS) transfer become painful or rather impossible in patients with knee OA. To avoid pain and to overcome movement limitations, knee OA patients adopt compensatory strategies in their daily routine. How to implement these findings and measurement technologies in clinical practice remains of interest.

The primary aim of this thesis was to evaluate kinematic and kinetic changes in patients with knee OA with and without obesity, during daily physical activities using three-dimensional motion analysis. Secondary, we evaluated if physical activity and kinematic signatures were distinctive for knee OA.

The main findings, recommendations for future studies, and potential use for clinical purposes will be discussed. Finally, a general conclusion is provided.

Kinematic and kinetic changes during gait, stair negotiation and sit-to-stand transfer in patients with knee OA with and without obesity

In **chapter 2, 3 and 4** we focused on the effect of knee OA on knee adduction moment (KAM) during gait, stair negotiation and sit-to-stand (STS) transfer in knee OA patients with and without obesity. During gait, the ground reaction force (GRF) is directed medially to the knee.[3] An increased medial component of the GRF will lead to a higher KAM which in turn relates to the onset and progression of knee OA.[3] In most knee OA patients, the medial side is affected by osteoarthritis[4] and the KAM will further increase. Due to lateral laxity and varus alignment of the knee joint, the medial compartment transfers substantially higher loads compared to the lateral compartment.[5] Considering that the medial compartment is not adapted to extreme loads, cartilage may deteriorate when the knee is repeatedly exposed to high joint forces during locomotor activities.[6] Therefore, the evaluation of knee mechanics during walking is of importance to understand the development and progression of knee OA.[7]

In **chapter 2**, higher KAM magnitudes were detected during gait in obese knee OA patients, normalized and non-normalized for weight, compared to lean patients and healthy controls. At higher walking speed this difference was substantially larger. Lean OA patients showed minor changes in KAM compared to BMI matched healthy controls. These findings suggest that obesity in combination with knee OA has a more

prominent role on KAM compared to the presence of knee OA itself. We did not find a relationship between the severity of knee OA and KAM, although a correlation between high KAM and the onset and progression of knee OA has been described in several studies.[8-10] An explanation for this discrepancy might be that study groups were not completely comparable for BMI or severity of knee OA. Body weight is an important factor contributing to joint loading; it has been shown that obese subjects have an increased ground reaction force compared to normal-weight controls.[11]

While KAM has been thoroughly investigated during gait, little is known about KAM during stair negotiation[12], where knee loads tend to be higher compared to (level) walking.[13] In **chapter 3** we showed that there were no significant differences in KAM between knee OA patients with and without obesity, and healthy controls during stair negotiation. A possible explanation could be increased stance time for obese knee OA patients which lower vertical GRF and thus KAM.[14] Furthermore, increased toe-out gait may also lower KAM.[15] However, there were no indications for differential use of such compensatory strategies between our study groups. In addition, a significant correlation between toe-out gait and KAM impulse was found during stair descent, but there were no indications for differential use of toe-out gait between groups.

In **chapter 4** we investigated the differences in knee and hip kinetics during STS movement between healthy controls and lean and obese knee OA patients. We showed reduced knee and hip range of motion (ROM) in the sagittal plane, accompanied by reduced peak hip and knee moments in the obese knee OA group. In addition, GRFz (vertical vector GRF) corrected for bodyweight was lower in the obese knee OA group compared to the control group. Obese subjects also showed a greater GRFx (mediolateral vector GRF) than both other groups, indicating the use of compensatory mechanisms to unload the affected knee. Total time to perform STS and KAM were not different between groups. Furthermore, none of the investigated STS parameters was different between the lean knee OA group and controls.

In this thesis, the results indicate that osteoarthritis has no effect on KAM but obesity in combination with osteoarthritis has a more prominent effect on KAM. Therefore, KAM might be difficult to use for clinical use in terms of diagnostics, decision making and therapy. This raises the question whether accelerometer bases derived motion parameters can be more useful for clinical practice, next to the widely used patient-reported outcome measures (PROMs) which are characterizes by subjectivity and pain dominance, and they suffer a ceiling effect.

Accelerometer based derived motion parameters

Physical activity is an important determinant of general health and is negatively affected by many chronic degenerative diseases.[11,16] To understand the association between physical activity and diseases, and to determine the effectiveness of interventions, it is crucial for clinicians and researchers to assess and monitor physical activity during daily life circumstances.[17]

In **chapter 5** we confirmed that the accelerometer is able to provide good and reproducible measurement of temporal stair climbing parameters in healthy subjects in daily life, non-laboratory situations. In our study we found that average step times up were higher than step times down as expected by the difference in energy expenditure. Individuals with slower step times down were all elderly and we found a strong significant difference in descending the stairs between age groups. In contrast to step times, overall asymmetry and irregularity during stair ascending and descending did not change between young and old individuals.

In **chapter 6** we demonstrated that an ambulant accelerometer- based physical activity monitor allows objective assessment of the four FITT components of physical activity during daily life circumstances. Frequency, Intensity, Time and Type (FITT) of physical activity in patients with advanced knee OA were significantly different to an age-matched healthy control group. Accelerometer-based levels of actual physical activity were moderately correlated to self-reported levels of perceived physical activity. This could suggest that both methods partially overlap in the domain of physical activity but also capture different aspects of physical activity.[18-21] These findings might also explain discrepancies that have been found between self-reported and objectively assessed levels of physical activity required to meet current recommended physical activity guidelines.[18-21]

Studies on gait of healthy subjects have shown great potential of detailed motion analyses, proficient in discerning a number of different action categories[22] and determining the smoothness and rhythm[23], stability[24], harmony[25] and naturalness of locomotion.[26] In **chapter 7** we investigated if such kinematic signatures and activity patterns were distinctive for knee OA. Our findings demonstrated clear similarities between general activity levels, different types and levels of physical activity. Taking temporal characteristics, such as total amount, type and level of activity, into account, this study revealed distinct temporal signatures segregating healthy volunteers from knee OA patients, independent of BMI. Although healthy volunteers did not show higher levels of physical activity in general, they demonstrated daily physical activity in a more bimodal fashion, with clear peaks in the late morning and early afternoon. In contrast, lean and obese knee OA patients did not show this early afternoon peak in

their activity patterns. Furthermore, knee OA patients needed more time to recuperate after physical activity, except for standing, compared to healthy individuals. Again, this effect was independent of BMI. Finally, fractal analysis on bouts of walking activity revealed significantly higher long-range correlations in stride-to-stride time intervals (DFA index) in healthy individuals compared to both knee OA groups, whereas other typical gait parameters were similar.

The study results suggest that parameters of physical activity derived by one ambulant tri-axial accelerometer can be used as an objective measurement system to supplement PROMs and provide more insight into the actual physical activity behavior and limitations of knee OA patients in their daily life. More in detail, it provides evidence of temporal specific kinematic signatures in amount and quality of movement between people with and without osteoarthritis of the knee.

Clinical implementations

Management of knee OA and the development of effective conservative and operative treatment and rehabilitation strategies requires more insight in the peak loads and repetitive loading patterns during ADL and exercise. Subsequently, these interventions need a proper evaluation. This thesis provides a better understanding in knee mechanics during walking, stair climbing and STS movement. Given the increasing burden of OA for health care resources and costs, there is a great necessity for a better health care infrastructure and tools for patient self-management. Findings can be used to further design and tailor the multi-factorial based treatment program which is currently used for general OA patients.

Results of this dissertation provide evidence that it seems essential to reduce medial knee compartment loading in order to prevent progression of disease and to decrease symptoms as a result of knee OA.

This thesis indicates that when there is a positive temporal specific kinematic signature for knee osteoarthritis (ambulatory), a further analysis in laboratory setting may be advised to analyze potential adaptations in biomechanics to lower the amount of load to the knee joint.

To improve knee biomechanics, reducing KAM seems the most important measure to prevent progression. Gait modifications and orthopedic supplies can aid reducing KAM[27], either by reducing the total GRF (eg. weight loss or use of a walking stick), or by modifying the frontal plane moment arm from the knee joint center to the line of action of the force.[28]

There are some characteristics of gait that reduce medical compartment loading. The first consists in increasing the foot progression angle (FPA), i.e. placing feet externally to the forward progression line (out-toeing).[27] In contrast, other research has indicated that gait with decreased FPA (in-toeing) is more effective for individuals with medial knee OA.[29] Secondly, increased internal hip abduction moment during the stance phase also protects against progression of medial knee OA.[30] Thirdly, lateral trunk lean over the stance lower extremity results in KAM reduction. Furthermore, medial thrust, which is a combination of slight knee flexion and internal hip rotation during the stance phase, reduces medial compartment loading in persons with proper alignment and may also reduce KAM.[31]

Examples of orthopedic equipment and supplies which can influence KAM are lateral wedge insoles. KAM is reduced by shifting the center of pressure laterally and thus reducing the frontal plane lever arm.[32-34] Another medical device that may be used is a valgus knee brace which produces constant valgus moment at the knee, resulting in slight medial compartment separation and pain relief.[35]

Unfortunately, there is lack of thorough cohort studies in the field of physiotherapy that have investigated the effectiveness of decreasing varus knee malalignment.[27] Several physiotherapeutic treatments have demonstrated to improve knee function, strengthen knee joint muscles and reduce pain, however KAM reduction was not observed.[27,36]

Finally, if non-operative treatment fails to decrease symptoms and progression of OA, surgical treatment may be indicated. In varus knee malalignment and moderate medial compartment knee OA, the aim is to restore proper distribution of loads on the tibiofemoral articular surface by correcting the lower extremity axis in the frontal plane such as with a high tibial osteotomy (HTO). This procedure restores lower extremity alignment from varus to normal and the effect of KAM reduction after HTO is obvious. (Figure 1.2).[27]

Besides qualitative improvement of knee loading, one may also improve the quantity of knee loading in order to reduce symptoms and further progression of knee OA. The frequency, intensity, type, and time (FITT) of physical activity may well play a crucial role in the development and progression of knee OA. Therefore, a better understanding of physical activity in daily life, in patients with and without knee OA, is essential to investigate this relationship. This may lead to more effective non-operative treatment strategies and lifestyle interventions.

Accelerometry seems the most promising method for ambulant and objective assessment of physical activity and has demonstrated its superiority to self-report questionnaires and heart rate monitoring.[11] An accelerometer-based activity-

monitoring allows assessment of physical activity in daily life conditions and could provide real-life feedback to facilitate diagnostics, more compliance and behavioral change to recommend or to advise against certain activities in conservative management of knee OA.[17,37] Furthermore, physical activity has become one of the main determinants of outcome assessment following a total knee replacement (TKR), besides functional capacity tests (e.g. Timed Up and Go test) and self-reported levels of functional outcome and satisfaction (i.e. questionnaires) and could provide personalized feedback for more targeted rehabilitation. Although rehabilitation after TKR aims to improve physical activity[38], still an important minority of patients do not improve postoperatively.[39] Due to difficulty in restoring mobility after surgery, patients in rehabilitation after TKR may explore difficulties to be sufficiently physically active to meet guidelines for healthy persons and to return to living independently.[21,40,41] It is therefore important to use valid and reliable tools to objectively assess levels of physical activity, to capture specific activity impairments patients encounter in daily life and to set new realistic guidelines for objectively assessed levels of physical activity. Moreover, longitudinal assessment of physical activity in daily life conditions with an accelerometer, has the potential to provide real-life feedback via graphics and text messages by mobile health care services and could facilitate more compliance and personal rehabilitation after an intervention.

Our study was designed to investigate potential differences in movement patterns between patients with and without knee OA, taking BMI into account. We found a number of kinematic signatures using temporal, sequence and fractal analyses specific to knee OA. These signatures, i.e. temporary decrease in activity in early afternoon, more time needed to recuperate after physical activity while coinciding on total amount, type and level of activity together with reduced naturalness of gait as measured through long-range stride-to-stride time interval fluctuations, could be used in the future as early behavioral markers for knee OA and could aid in characterization of the pre-osteoarthritic joint.[42,43]

General conclusion

Obese knee OA patients have a significant increased KAM compared to healthy controls with gait analysis. However, presence of knee OA itself does not result in increased KAM. Analysis of stair negotiation revealed no significant differences in KAM (between knee OA patients and healthy controls). Although, significant correlations were found between KAM parameters during stair negotiation and gait. In STS movements, biomechanical alterations were the result of an interplay between high body mass and

knee OA, rather than knee OA itself. These results indicate that obesity in combination with osteoarthritis, has a more prominent effect on KAM.
Accelerometry results suggested that parameters of physical activity derived by one ambulant tri- axial accelerometer can be used as an objective measurement system to supplement patient-reported outcome measures and to provide more insight into the actual physical activity behavior and limitations of knee OA patients in their daily life. The strength of this study is that it documents in great detail the effect of osteoarthritis of the knee in either measuring the biomechanical load and physical activity in a controlled group of elderly women.

Suggestions for further research

Physical performance-based analysis can be used in a wide spectrum of clinical and research applications. To investigate the exact and independent influence of BMI, our suggestion would be for future studies, to include a second control non-OA obese group. Well controlled studies into specific high-risk populations will provide more insight into the underlying mechanisms and the role of physical activity behaviour in the etiology of knee OA.

References

1. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. Lancet. 2011;377:2115-26.
2. Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, et al. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis. 2003;62(12):1145-55.
3. Kutzner I, Trepczynski A, Heller MO, Bergmann G. Knee Adduction Moment and Medial Contact Force – Facts about Their Correlation during Gait. PLoS One. 2013;8(12):e81036.
4. Cicuttini F, Wluka A, Hankin J, Wang Y. Longitudinal study of the relationship between knee angle and tibiofemoral cartilage volume in subjects with knee osteoarthritis. Rheumatology (Oxford). 2004;43(3):321-4.
5. Schipplein OD, Andriacchi TP. Interaction between active and passive knee stabilizers during level walking. J Orthop Res. 1991;9:113-9.
6. Andriacchi TP, Koo S, Scanlan SF. Gait mechanics influence healthy cartilage morphology and osteoarthritis of the knee. J Bone Joint Surg Am. 2009;91 Suppl 1:95-101.
7. Andriacchi TP, Mundermann A, Smith RL, et al. A framework for the in vivo pathomechanics of osteoarthritis at the knee. Ann Biomed Eng. 2004;32:447-57.
8. Miyazaki T, Wada M, Kawahara H, et al. Dynamic load at baseline can predict radiographic disease progression in medial compartment knee osteoarthritis. Ann Rheum Dis. 2002;61:617-22.
9. Mundermann A, Dyrby CO, Andriacchi TP. Secondary gait changes in patients with medial compartment knee osteoarthritis: increased load at the ankle, knee, and hip during walking. Arthritis Rheum. 2005;52(9):2835-44.
10. Thorp LE, Sumner DR, Block JA, et al. Knee joint loading differs in individuals with mild compared with moderate medial knee osteoarthritis. Arthritis Rheum. 2006;54:3842-9.
11. Browning RC, Kram R. Effects of obesity on the biomechanics of walking at different speeds. Med Sci Sports Exerc. 2007;39(9):1632-41.
12. Iijima H, Shimoura K, Aoyama T, Takahashi M. Biomechanical characteristics of stair ambulation in patients with knee OA: A systematic review with meta-analysis toward a better definition of clinical hallmarks. Gait Posture. 2018;62:191-201.
13. Kutzner I, Heinlein B, Graichen F, Bender A, Rohlmann A, Halder A, et al. Loading of the knee joint during activities of daily living measured in vivo in five subjects. J Biomech. 2010;43(11): 2164-73.
14. Protopapadaki A, Drechsler WI, Cramp MC, Coutts FJ, Scott OM. Hip, knee, ankle kinematics and kinetics during stair ascent and descent in healthy young individuals. Clin Biomech. 2007;22(2):203-10.
15. Guo M, Axe MJ, Manal K. The influence of foot progression angle on the knee adduction moment during walking and stair climbing in pain free individuals with knee osteoarthritis. Gait Posture. 2007;26(3):436-41.
16. Zhang W, Nuki G, Moskowitz RW, et al. OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthritis Cartilage. 2010;18:476-99.
17. Messier SP, Gutekunst DJ, Davis C, DeVita P. Weight loss reduces knee-joint loads in overweight and obese older adults with knee osteoarthritis. Arthritis Rheum. 2005;52:2026-32.
18. Dunlop DD, Song J, Semanik PA, Chang RW, Sharma L, Bathon JM, Eaton CB, Hochberg MC, Jackson RD, Kwoh CK, Mysiw WJ, Nevitt MC, Hootman JM. Objective physical activity measurement in the osteoarthritis initiative: Are guidelines being met? Arthritis Rheum. 2011;63:3372-82.
19. White DK, Tudor-Locke C, Felson DT, Gross KD, Niu J, Nevitt M, Lewis CE, Torner J, Neogi T. Walking to meet physical activity guidelines in knee osteoarthritis: is 10,000 steps enough? Arch Phys Med Rehabil. 2013;94:711-7.
20. Farr JN, Going SB, Lohman TG, Rankin L, Kasle S, Cornett M, Cussler E. Physical activity levels in patients with early knee osteoarthritis measured by accelerometry. Arthritis Rheum. 2008;59:1229-36.

21. Wallis JA, Webster KE, Levinger P, Taylor NF. What proportion of people with hip and knee osteoarthritis meet physical activity guidelines? A systematic review and meta-analysis. Osteoarthritis Cartil. 2013;21:1648-59.
22. Lugade V, Fortune E, Morrow M, Kaufman K. Validity of using tri-axial accelerometers to measure human movement – Part I: Posture and movement detection. Med Eng Phys. 2014;36:169-76.
23. Menz HB, Lord SR, Fitzpatrick RC. Acceleration patterns of the head and pelvis when walking on level and irregular surfaces. Gait Posture. 2003;18:35-46.
24. Doi T, et al. The harmonic ratio of trunk acceleration predicts falling among older people: results of a 1-year prospective study. J Neuroeng Rehabil. 2013;10:1-6.
25. Iosa M, et al. Stability and harmony of gait in patients with subacute stroke. J Med Biol Eng. 2016;36: 635-43.
26. Stergiou N, Harbourne R, Cavanaugh J. Optimal movement variability: a new theoretical perspective for neurologic physical therapy. J Neurol Phys Ther. 2006;30:120-9.
27. Fryzowicz A, Lechoslaw BD, Koczewski P. Prohylaxis of medial compartment gonartrosis in varus knee – current state of knowledge. Arc Med Sci 2018;14:454-9.
28. Richards R, van den Noort JC, Dekker J, Harlaar J. Gait retraining with real-time biofeedback to reduce knee adduction moment: systematic review of effects and methods used. Arch Phys Med Rehabil. 2017;98:137-50.
29. Shull PB, Shultz R, Silder A, et al. Toe-in gait reduces the first peak knee adduction moment in patients with medial compartment knee osteoarthritis. J Biomech. 2013;46:122-8.
30. Chang A, Hayes K Dunlop D, etal. Hip abduction moment and protection against medial tibiofemoral osteoarthritis progression. Arthritis Rheum. 2005;52:3515-9.
31. Gerbrands TA, Pisters MF, Theeven PJR, et al. Lateral trunk lean and medializing the knee as gait strategies for knee osteoarthritis. Gait Posture. 2017;51:247-53.
32. Crenshaw SJ, Pollo FE, Calton EF. Effects of lateral-wedged insoles on kinetics at the knee. Clin Orthop Relat Res. 2000;375:185-92.
33. Haim A, Rozen N, Dekel S, Halperin N, Wolf A. Control of knee coronal plane moment via modulation of center of pressure: a prospective gait analysis study. J Biomech. 2008;41:3010-6.
34. Kakihana W; Akai M, Nakazawa K, Takashima T, Naito K, Torii S. Effects of laterally wedged insoles on knee and subtalar joint moments. Arch Phys Med Rehabil. 2005;86:1465-71.
35. Minzlaff P, Saier T, Brucker PU, Haller B, Imhoff AB, Hinterwimmer S. Valgus bracing in symptomatic varus malalignment for testing the expectable “unloading effect” following valgus high tibial osteotomy. Knee Surg Sports Traumatol Arthrosc. 2015;23:1964-70.
36. Bennel KL, Hunt MA, Wrigley TV, et al. Hip strengthening reduces symptoms but not knee load in people with medial knee osteoarthritis and varus malalignment: a randomised controlled trial. Osteoarthr Cartilage. 2010;18:621-8.
37. Vignon E, Valat JP, Rossignol M, Avouac B, Rozenberg S, Thoumie P, Avouac J, Nordin M, Hilliquin P. Osteoarthritis of the knee and hip and activity: a systematic international review and synthesis (OASIS). Joint Bone Spine. 2006;73:442-55.
38. Peiris CL, Taylor NF, Shields N. Patients receiving inpatient rehabilitation for lower limb orthopaedic conditions do much less physical activity than recommended in guidelines for healthy older adults: an observational study. J Physiother. 2013;59:39-44.
39. Beswick AD, Wylde V, Gooberman-Hill R, Blom A, Dieppe P. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. BMJ Open. 2012;2:e000435.
40. Groen JW, Stevens M, Kersten RF, Reininga IH, van den Akker-Scheek I. After total knee arthroplasty, many people are not active enough to maintain their health and fitness: an observational study. J Physiother. 2012;58:113-6.
41. Brandes M, Ringling M, Winter C, Hillmann A, Rosenbaum D. Changes in physical activity and health-related quality of life during the first year after total knee arthroplasty. Arthritis Care Res. (Hoboken). 2011;63:328-34.
42. Ryd L, et al. Pre-osteoarthritis: Definition and diagnosis of an elusive clinical entity. Cartilage. 2015;6: 156-65.

43. Chu CR, Williams AA, Coyle CH, Bowers ME. Early diagnosis to enable early treatment of pre-osteoarthritis. Arthritis Res Ther. 2012;14:212-22.

Chapter 9

Valorisation

Valorisation

Osteoarthritis (OA) of the knee is one of the leading causes of global disability[1] and the most common reason for pain in older adults with a significant individual and economic burden.[2,3] It is estimated that between 20% and 30% of adults and elderly suffer from this condition.[4] The cumulative costs of OA for society are calculated to be around 0.5% of Gross National Product (GNP).[2] Given this increasing burden of OA for health care resources and costs, there is a great necessity for a better health care infrastructure and tools for patient (self-)management.

Different treatments are not always effective, and effectivity of treatment strategies are not only based on invasive interventions, but also on knowledge and understanding of the patient and patient's context. Social, physical and mental factors, way of life, age, patient's preferences play a crucial role in decision-making, which and when an intervention is most effective. Solutions for patient problems must be found in daily life circumstances, and not only in-hospital. Coaching and advise, appropriate for the real care demand and self-management, play an important role in effective treatment strategies.

Findings of this thesis can be used to evaluate, further design, and to tailor the multi-factorial based treatment program, which is currently used for OA patients.

Non-operative management of knee OA, the development of effective treatment and rehabilitation strategies require more insight in the peak loads and repetitive loading patterns during ADL and exercise. This thesis provides a better understanding in knee mechanics during physical activities that are essential for a good quality of life such as walking, stair climbing and the sit-to-stand movement. It also demonstrates that it is essential to reduce medial knee compartment loading in order to prevent progression of disease and to decrease symptoms as a result of knee OA, especially in obese knee osteoarthritis patients. To reduce medial compartment loading, one can change biomechanics of the knee joint.

In order to improve knee biomechanics, reducing KAM seems an important measure to prevent progression.[5] Gait modifications and orthopedic supplies can aid reducing KAM[6], either by reducing the total GRF e.g. weight loss or use of a walking stick, or by modifying the frontal plane moment arm from the knee joint center to the line of action of the force.[7] There are some characteristics of gait that reduce medical compartment loading, for example out-toeing[6] and in-toeing[8], increased hip abduction moment during stance phase[9] and lateral trunk lean over the stance lower extremity.[10] Examples of orthopedic equipment and supplies which can influence KAM are lateral wedge insoles.[11-13] Another medical device that may be used is a valgus knee brace.[14]

Besides improvement of knee biomechanics, one may also try to change physical activity patterns to reduce the cumulative knee loading in order to reduce symptoms and further progression of knee OA. The frequency, intensity, type, and time (FITT) of physical activity may well play a crucial role in the development and progression of knee OA.[15] Therefore, a better understanding of physical activity in daily life, in patients with and without knee OA, is essential to investigate this relationship. This may also lead to more effective non-operative treatment strategies and lifestyle interventions and may be an efficient tool for patient self-management.

Accelerometry seems the most promising method for ambulant and objective assessment of physical activity. An accelerometer-based activity-monitoring allows assessment of physical activity in daily life conditions. It may also provide real-life feedback to facilitate diagnostics, more compliance and behavioral change for certain activities in conservative management of knee OA.[16,17] Furthermore, physical activity has become one of the main determinants of outcome assessment following an intervention, for example a total knee replacement. Compared to functional capacity tests (e.g. Timed Up and Go test) and self-reported levels of functional outcome and satisfaction (i.e. questionnaires), accelerometry can provide personalized feedback for more targeted rehabilitation. Moreover, physical activity is also an important determinant in prehabilitation whereby recovery time following surgery may be improved.

Although rehabilitation aims to improve physical activity[18], still an important minority of patients do not improve postoperatively.[19] Due to difficulty in restoring mobility after surgery, patients in rehabilitation may explore difficulties to be sufficiently physically active to meet guidelines for healthy persons and to return to living independently.[20-22] It is therefore important to use valid and reliable tools to objectively assess levels of physical activity, to capture specific activity impairments patients encounter in daily life and to set new realistic guidelines for objectively assessed levels of physical activity. Furthermore, longitudinal assessment of physical activity in daily life conditions with an accelerometer, has the potential to provide real-life feedback via graphics and text messages by mobile health care services and could facilitate more compliance and personal prehabilitation and rehabilitation after an intervention.

Our study was designed to investigate potential differences in movement patterns between patients with and without knee OA. We found a number of kinematic signatures using temporal, sequence and fractal analyses specific to knee OA. These signatures could be used in the future as early behavioral markers for knee OA, aid in characterization of the pre-osteoarthritic joint[23,24] and are a potential indication for further analysis.

In conclusion, accelerometry can be used to measure results and evaluate patient-specific advises to decrease the risk for knee OA. This improves healthcare for patients with OA and creates a more personalized treatment.
The results of this thesis can be used in the concept of integrated care, to revise knee biomechanics and simultaneously to modify physical activity.

References

1. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. Lancet. 2011;377:2115-26.
2. Britton R. The economic burden of osteoarthritis. Am J Manag Care. 2009;15:230-5.
3. Felson DT. Clinical practice. Osteoarthritis of the knee. N Engl J Med. 2006;354:841-8.
4. Yoshimura N, Muraki S, Nakamura K, Tanaka S. Epidemiology of the locomotive syndrome: The research on osteoarthritis/osteoporosis against disability study 2005-2015. Mod Rheumatol. 2017;27:1-7.
5. Browning RC, Kram R. Effects of obesity on the biomechanics of walking at different speeds. Med Sci Sports Exerc. 2007;39(9):1632-41.
6. Fryzowicz A, Lechoslaw BD, Koczewski P. Prohylaxis of medial compartment gonartrosis in varus knee – current state of knowledge. Arc Med Sci 2018;14:454-9.
7. Richards R, van den Noort JC, Dekker J, Harlaar J. Gait retraining with real-time biofeedback to reduce knee adduction moment: systematic review of effects and methods used. Arch Phys Med Rehabil 2017; 98:137-50.
8. Shull PB, Shultz R, Silder A, et al. Toe-in gait reduces the first peak knee adduction moment in patients with medial compartment knee osteoarthritis. J Biomech 2013;46:122-8.
9. Chang A, Hayes K Dunlop D, etal. Hip abduction moment and protection against medial tibiofemoral osteoarthritis progression. Arthritis Rheum 2005;52:3515-9.
10. Gerbrands TA, Pisters MF, Theeven PJR, et al. Lateral trunk lean and medializing the knee as gait strategies for knee osteoarthritis. Gait Posture 2017;51:247-53.
11. Crenshaw SJ, Pollo FE, Calton EF. Effects of lateral-wedged insoles on kinetics at the knee. Clin Orthop Relat Res 2000;375:185-92.
12. Haim A, Rozen N, Dekel S, Halperin N, Wolf A. Control of knee coronal plane moment via modulation of center of pressure: a prospective gait analysis study. J Biomech 2008;41:3010-6.
13. Kakihana W; Akai M, Nakazawa K, Takashima T, Naito K, Torii S. Effects of laterally wedged insoles on knee and subtalar joint moments. Arch Phys Med Rehabil 2005;86:1465-71.
14. Minzlaff P, Saier T, Brucker PU, Haller B, Imhoff AB, Hinterwimmer S. Valgus bracing in symptomatic varus malalignment for testing the expectable “unloading effect” following valgus high tibial osteotomy. Knee Surg Sports Traumatol Arthrosc 2015;23:1964-70.
15. J. N. Farr, S. B. Going, T. G. Lohman, L. Rankin, S. Kasle, M. Cornett, et al. Physical activity levels in patients with early knee osteoarthritis measured by accelerometry. Arthritis Rheum. 2008;59:1229-36.
16. Messier SP, Gutekunst DJ, Davis C, DeVita P. Weight loss reduces knee-joint loads in overweight and obese older adults with knee osteoarthritis. Arthritis Rheum 2005;52:2026-32.
17. Vignon E, Valat JP, Rossignol M, Avouac B, Rozenberg S, Thoumie P, Avouac J, Nordin M, Hilliquin P. Osteoarthritis of the knee and hip and activity: a systematic international review and synthesis (OASIS). Joint Bone Spine. 2006;73:442-55.
18. Peiris CL, TaylorNF, Shields N. Patients receiving inpatient rehabilitation for lower limb orthopaedic conditions do much less physical activity than recommended in guidelines for healthy older adults: an observational study. J. Physiother. 2013;59:39-44.
19. Beswick AD, Wylde V, Gooberman-Hill R, Blom A, Dieppe P. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. BMJ Open. 2012;2:e000435.
20. Wallis JA, Webster KE, Levinger P, Taylor NF. What proportion of people with hip and knee osteoarthritis meet physical activity guidelines? A systematic review and meta-analysis. Osteoarthritis Cartilage. 2013;21:1648-59.
21. Groen JW, Stevens M, Kersten RF, Reininga IH, van den Akker-Scheek I. After total knee arthroplasty, many people are not active enough to maintain their health and fitness: an observational study. J Physiother. 2012;58:113-6.
22. Brandes M, Ringling M, Winter C, Hillmann A, Rosenbaum D. Changes in physical activity and health-related quality of life during the first year after total knee arthroplasty. Arthritis Care Res. (Hoboken) 2011;63:328-34.

23. Ryd L, et al. Pre-osteoarthritis: Definition and diagnosis of an elusive clinical entity. Cartilage. 2015;6:156-65.
24. Chu CR, Williams AA, Coyle CH, Bowers ME. Early diagnosis to enable early treatment of pre-osteoarthritis. Arthritis Res. Ther. 2012;14:212-22.

Chapter 10

Summary

Summary

Osteoarthritis (OA) of the knee is one of the leading causes of global disability and the most common reason for pain in older adults. It is estimated that between 20% and 30% of adults and elderly suffer from this condition. Besides OA, obesity is also becoming an increasing problem in public health. Predictive numbers will even rise. Research has shown that obese subjects have almost four times the risk of developing knee OA when compared with non-obese subjects. Following the current rise in obesity and concomitant increase in life expectancy, prevalence of OA is expected to grow. This poses OA as an increasing future health problem. Besides age and weight, further risk factors for OA include female gender, genetics, poor diet, joint overuse, trauma, muscle weakness, physical inactivity, and poor habitual movement patterns. While the exact pathophysiology of OA remains to be elucidated, it is currently believed that altered joint loading and cartilage metabolism are both key factors in cartilage degradation and subsequent OA development. Being the largest weight-bearing joint, the knee is most affected. To avoid pain and overcome movement limitations, knee OA patients adopt compensatory strategies in activities of daily life, such as gait, stair negotiation and sit-to-stand (STS) tasks.

Several approaches can be used for assessment of physical function and to approve alterations in movement patterns. In this thesis we first focus on biomechanical analysis in knee OA patients to derive spatio-temporal, kinematic and kinetic parameters. We especially focus on the knee adduction moment (KAM) during gait, stair climbing and STS tasks. A high KAM is related to the onset and progression of knee OA. Therefore, the evaluation of knee mechanics, especially KAM, during these activities is of importance to understand the development of knee OA. Furthermore, we focus on physical activity in knee OA patients with and without obesity, to get a good understanding of subtle and small changes in behavior of physical activity. Physical activity is an important determinant of general health and is negatively affected by many chronic degenerative diseases. To understand the association between physical activity and these chronic degenerative diseases, and to determine the effectiveness of interventions, it is crucial for clinicians and researchers to assess and monitor physical activity during daily life circumstances. Accelerometry has demonstrated its potential to provide an estimation of activity quantity, to provide qualitative assessment of physical activity such as spatiotemporal gait analysis and activity intensity measures. Furthermore, accelerometer-based physical activity monitoring permits to differentiate between different activities of daily living (ADL) such as walking or sitting and could select only those activities that are challenging and clinically relevant for specific patient populations.

The primary aim of this thesis is to evaluate the effect of knee OA on spatio-temporal, kinematic and kinetic parameters during gait, stair climbing and STS movement in healthy controls and lean and obese knee OA patients. Secondary, to evaluate physical activity and kinematic signatures distinctive for knee OA.

In **chapter 2**, knee loading during walking was examined in patients with knee OA. Next to this, the effect of BMI and walking speed on knee loading was evaluated. Three homogenous groups were included: obese patients with knee OA, lean patients with knee OA and lean, healthy controls. Higher KAM magnitudes were detected in obese knee OA patients compared to lean patients and healthy controls. Lean OA patients showed minor changes in KAM compared to weight matched healthy controls. These findings suggest that the combination of a high body mass and the presence of knee OA are associated with high KAM, whilst knee OA pathology alone has not a major impact on KAM.

The same study design was used in **chapter 3**. Instead of performing gait, all subjects ascended and descended a three-step staircase at a self-selected, comfortable speed. No significant differences were found between knee OA patients with and without obesity and healthy controls in KAM during stair negotiation. Absence of statistical significance of KAM parameters may be explained by compensatory movement strategies, such as ambulatory velocity.

The differences in knee and hip kinetics during STS movement were investigated in **chapter 4**. All subjects, including obese and lean patients with knee osteoarthritis and lean, healthy controls, were instructed to perform STS transfers at self-selected, comfortable speed. Strikingly, lean subjects with knee OA did not show any signs of movement alterations during STS. Contrarily, we showed that only obese knee OA patients have different STS movement patterns.

Accelerometers facilitates analysis outside traditional gait laboratories. In **chapter 5** we presented an accelerometer-based reference database for stair climbing in healthy subjects. The effect of age was studied with different parameters, such as step time up and down, asymmetry and irregularity. Average step times were slightly higher ascending compared to descending. Step time difference, between ascending and descending, was significant between the young and elderly group. Irregularity and asymmetry did not diverge between the age groups. Stair climbing based findings support the application of accelerometer-based gait analysis for routine clinical use and in daily life.

In **chapter 6** patients with end-stage knee OA and age-matched healthy subjects were measured. We demonstrated that an ambulant accelerometer-based physical activity monitor allows objective assessment of the four FITT components of physical activity during daily life circumstances. Frequency, Intensity, Time and Type (FITT) of physical

activity in patients with advanced knee OA were significantly different to an age-matched healthy control group. Accelerometer-based levels of actual physical activity were moderately correlated to self-reported levels of perceived physical activity.
In **chapter 7** we set out to investigate kinematic signatures and activity patterns distinctive for knee OA. This was done by attaching triaxial accelerometers on the non-affected femur of patients suffering from knee OA as assessed clinically and radiological compared with healthy volunteers. Given the modulatory effect of weight we also included a group of obese knee OA patients. Our findings demonstrated clear similarities between general activity levels, different types and levels of physical activity. Moreover, we did not find any congruence between daily patterns of physical activity over days between different subjects within nor between groups. The temporal activity pattern during the day was however significantly different with a bimodal signature in healthy volunteers only. Finally, fractal analysis on bouts of walking activity revealed significantly higher long-range correlations in stride-to-stride time intervals (DFA index) in healthy participants compared to both knee OA groups, whereas other typical gait parameters were similar.
Chapter 8 discussed the key findings in a broader perspective, including their relation to current literature. Furthermore, this chapter contained clinical implementation and suggestions for further research.

In conclusion, obese knee OA patients have a significant increased KAM compared to healthy controls with gait analysis. However, presence of knee OA itself does not result in increased KAM. Analysis of stair negotiation revealed no significant differences in KAM (between knee OA patients and healthy controls). Although, significant correlations were found between KAM parameters during stair negotiation and gait. In STS movements, biomechanical alterations were the result of an interplay between high body mass and knee OA, rather than knee OA itself. These results indicate that obesity in combination with osteoarthritis, has a more prominent effect on KAM.
Accelerometry results suggested that parameters of physical activity derived by one ambulant tri- axial accelerometer can be used as an objective measurement system to supplement patient-reported outcome measures and to provide more insight into the actual physical activity behavior and limitations of knee OA patients in their daily life. The strength of this study is that it documents in great detail the effect of osteoarthritis of the knee in either measuring the biomechanical load and physical activity.

Nederlandse samenvatting

Nederlandse samenvatting

Artrose van de knie is een van de belangrijkste oorzaken van fysieke beperkingen en de meest voorkomende oorzaak van pijn bij ouderen. Men denkt dat 20 tot 30% van de ouderen deze klachten heeft. Naast artrose, wordt obesitas ook een steeds groter probleem voor de volksgezondheid. Voorspellingen zijn dat de aantallen in de toekomst verder zullen toenemen. Onderzoek heeft aangetoond dat mensen met obesitas bijna vier keer zo veel risico lopen op het ontwikkelen van artrose van de knie, in vergelijking met slanke mensen. Als gevolg van de stijging van mensen met obesitas en gelijktijdig de toename van de levensverwachting, wordt er verwacht dat de prevalentie van artrose verder gaat toenemen en daardoor in de toekomst een groter probleem zal worden voor de volksgezondheid. Naast leeftijd en lichaamsgewicht vormen, vrouwelijk geslacht, erfelijkheid, slecht dieet, overbelasting, trauma, spierzwakte, fysieke inactiviteit en verkeerde beweegpatronen, andere risicofactoren voor het ontwikkelen van artrose. De exacte pathofysiologie van artrose is nog niet opgehelderd. Er wordt gedacht dat een verandering in de belasting van het gewricht en het metabolisme van kraakbeen belangrijke factoren zijn, in de afbraak van kraakbeen en artrose. Patiënten met artrose van de knie ontwikkelen compensatiemechanismen tijdens dagelijks activiteiten zoals bij lopen, traplopen en opstaan uit zithouding (STS “sit-to-stand”), om pijn te vermijden en bewegingsbeperkingen te overwinnen.

Er zijn verschillende manieren om fysieke functie te meten en verandering in bewegingspatronen aan te tonen. In dit proefschrift richten we ons eerst op de analyse van biomechanische componenten in patiënten met artrose van de knie om zo spatio-temporele, kinematische en kinetische parameters te verkrijgen. Hierbij focussen we ons op het knie adductiemoment (KAM) tijdens lopen, traplopen en STS. Een hoge KAM wordt geassocieerd met het ontstaan en progressie van artrose van de knie. Hierdoor is het van belang de mechanica, en met name de KAM, van de knie te bestuderen, om zo meer inzicht te krijgen in de ontwikkeling van artrose van de knie. Verder richten we ons op fysieke activiteit bij patiënten met artrose van de knie met en zonder obesitas. Zo willen we meer inzicht krijgen in kleine veranderingen in bewegingsgedrag bij deze patiënten. Fysieke activiteit speelt een belangrijke rol in de algemene gezondheid en wordt negatief beïnvloed door meerdere chronische aandoeningen. Om het verband tussen fysieke activiteit en deze chronische aandoeningen beter te begrijpen en het effect van interventies te bepalen, is het cruciaal voor clinici en wetenschappers om fysieke activiteit in de dagelijkse praktijk te beoordelen en te monitoren. Accelerometrie is een goede manier om inzicht te krijgen in kwantiteit en kwaliteit van fysieke activiteit. Verder kan accelerometrie onderscheid maken tussen verschillende

activiteiten in het dagelijks leven zoals lopen of zitten en kan zo activiteiten selecteren die relevant zijn voor een specifieke patiëntengroep.
Het belangrijkste doel van dit proefschrift is om het effect van artrose van de knie op spatio-temporele, kinematische en kinetische parameters tijdens lopen, traplopen en STS in gezonde proefpersonen en slanke en obese patiënten met artrose van de knie, te onderzoeken. Vervolgens willen we ook de fysieke activiteit en kinematische kenmerken bij patiënten met artrose van de knie onderzoeken.
In **hoofdstuk 2** werd onderzoek gedaan naar de belasting van de knie tijdens lopen bij patiënten met artrose van de knie. Verder werd er ook gekeken naar het effect van BMI en loopsnelheid op de belasting van de knie. Er werden drie onderzoeksgroepen geïncludeerd: obese patiënten met artrose van de knie, slanke patiënten met artrose van de knie en een gezonde controlegroep. Hieruit bleek dat de combinatie van artrose en overgewicht een verhoging van KAM veroorzaakte. De slanke patiënten met artrose van de knie lieten vrijwel dezelfde KAM zien als de gezonde proefpersonen. De bevindingen suggereren dat de combinatie van overgewicht en de aanwezigheid van artrose van de knie een verhoging van KAM geeft, in tegenstelling tot alleen artrose van de knie.
In **hoofdstuk 3** werd dezelfde studieopzet gebruikt. In plaats van lopen, moesten alle proefpersonen, op comfortabele snelheid, een trap van drie treden op- en aflopen. Er werden geen significante verschillen in KAM gevonden tussen de drie groepen. Afwezigheid van deze verschillen kunnen verklaard worden door mogelijk gebruik van compensatiemechanismen, zoals het aanpassen van snelheid.
In **hoofdstuk 4** werden de verschillen in knie- en heupkinetica tijdens STS onderzocht. Alle proefpersonen, obese en slanke patiënten met artrose van de knie en gezonde proefpersonen, voerden een STS op comfortabele snelheid uit. Slanke patiënten met artrose van de knie lieten geen veranderingen zien tijdens STS. Obese patiënten met artrose van de knie lieten daarentegen wel verschillen zien tijdens STS.
Accelerometers maken het mogelijk metingen te verrichten zonder gebruik te maken van de klassieke bewegingslaboratoria. In **hoofdstuk 5** creëerden we een database op basis van metingen met een accelerometer tijdens traplopen bij gezonde proefpersonen. Het effect van leeftijd op verschillende paramaters, zoals staptijd op en neer, asymmetrie en irregulariteit, werd bestudeerd. De gemiddelde staptijden op, waren groter dan neer. Verschil in staptijd tussen op en neer, was significant verschillend tussen jong en oud. Irregulariteit en asymmetrie waren niet verschillend tussen de leeftijdsgroepen. De resultaten op basis van accelerometrie tijdens traplopen ondersteunen het gebruik van accelerometers in de kliniek en het dagelijks leven.
In **hoofdstuk 6** werden patiënten met gevorderde artrose van de knie en gezonde proefpersonen met vergelijkbare leeftijd, onderzocht. We toonden aan dat met behulp

van een accelerometer, metingen van fysieke activiteit in het dagelijks leven zoals de vier FITT-componenten, objectief beoordeeld kunnen worden. Frequentie, Intensiteit, Tijd en Type (FITT) van fysieke activiteit in patiënten met gevorderde artrose van de knie waren significant verschillend ten opzichte van de gezonde controlegroep. De werkelijke fysieke activiteit, gemeten met de accelerometer, toonde een matige correlatie met de zelf-gerapporteerde fysieke activiteit.

In **hoofdstuk 7** onderzochten we bij patiënten met artrose van de knie, kinematische veranderingen en patronen van activiteit. Metingen werden verricht met behulp van accelerometers bij patiënten met artrose van de knie en gezonde vrijwilligers. Gezien het mogelijke effect van lichaamsgewicht, werd er ook een groep met obese patiënten met artrose van de knie, geïncludeerd. Onze resultaten toonden grote overeenkomsten in algemene activiteiten, verschillende types en niveaus van fysieke activiteit. We vonden geen congruentie in het dagelijkse patroon van fysieke activiteit gedurende de dagen tussen de verschillende proefpersonen en tussen de verschillende onderzoeksgroepen. Het tijdsgebonden activiteitenpatroon gedurende de dag was significant verschillend met alleen een bimodaal patroon bij de gezonde vrijwilligers. De fractale analyse van periodes van loopactiviteit liet significant langere tijdsintervallen zien van stap-activiteit (DFA index) bij gezonde vrijwilligers ten opzichte van de twee groepen met patiënten met artrose van de knie. Andere parameters lieten geen verschillen zien.

In **hoofdstuk 8** werden de belangrijkste bevindingen in een breder perspectief besproken, en in context geplaatst met de huidige literatuur. Tevens werden de klinische implementaties en suggesties voor toekomstig onderzoek, besproken.

Concluderend, patiënten met zowel artrose van de knie als obesitas, hebben een significant verhoogde KAM, in vergelijking met gezonde proefpersonen. Echter, aanwezigheid van alleen artrose van de knie, resulteert niet in een verhoogde KAM tijdens lopen.

Tijdens traplopen werden er geen significante verschillen gevonden in KAM tussen de verschillende groepen. Er werden wel significante correlaties gevonden voor KAM-parameters tussen traplopen en lopen. Tijdens STS werden er alleen biomechanische veranderingen gezien bij de combinatie van obesitas en artrose van de knie. Deze resultaten suggereren dat obesitas in combinatie met artrose, een duidelijker effect laten zien op KAM.

We toonden aan dat de accelerometer kan worden gebruikt als een objectief meetsysteem voor het meten van parameters van fysieke activiteit. Deze resultaten kunnen dienen als aanvulling bij de “patient-reported outcome measures” en zo meer inzicht geven in de werkelijke fysieke activiteit en in beperkingen in het dagelijks leven bij patiënten met artrose van de knie.

De meerwaarde van deze studie is dat het een gedetailleerd effect beschrijft van artrose van de knie op de biomechanische belasting en fysieke activiteit.

DankDiagram

Curriculum Vitae

Curriculum Vitae

Loek Verlaan was born in Ubach over Worms on the 24th of June 1978. He attended secondary school at Eijkhagen College in Landgraaf. After his graduation in 1997 he studied Physical Education at Fontys University of Applied Sciences in Tilburg. He completed his teaching degree in 2001 and started working as a teacher in a secondary school at Sophianum in Gulpen. In 2002 he started Medical School at Maastricht University. He attended an internship at the department of orthopaedics at Maastricht University Medical Center. He spent the last year of his study at the orthopaedic department of Atrium Medical Centre in Heerlen, where he participated in a research project. In 2008 he finished his medical studies and started working as a resident at the Emergency department at Sint Jans Gasthuis in Weert.

In 2009 he started his career as an orthopaedic resident in training at Atrium Medical Centre in Heerlen and continued his education at Orbis Medical Centre, Sittard-Geleen; Atrium Medical Centre in Heerlen and Maastricht University Medical Centre. In his last year of training he started his research under supervision of dr. Kenneth Meijer, dr. Pieter Emans and Prof. dr. Lodewijk van Rhijn, Maastricht University Medical Centre. During this period, he also worked in Duayaw Nkwanta (Ghana) at the St John of God Hospital. After his residency he completed an AGA-NVA travelling fellowship in Germany and AO-fellowship at the Uppsala University Hospital in Sweden. In 2016 he started working as an orthopaedic surgeon at Laurentius Ziekenhuis in Roermond, Maastricht University Medical Centre, Catharina Ziekenhuis in Eindhoven and VieCuri Medisch Centrum in Venlo. Since September 2019 he works as a staff member at Maastricht University Medical Centre.

The author is living together with Sofie Moresi. Together they have a son called Jef and a daughter called Fien.

List of publications and presentations

List of publications and presentations

Publications

Verlaan L., Oomen P.W., Schmitz T., Liu W., Peters M., Emans P.J., van Rhijn L.W., Drost M.R., Meijer K. Obese knee AO patients have increased knee adduction moments during gait. (Submitted).

Vangeneugden J. & **Verlaan L**., Oomen P, Liu W.Y., Peters M., Latour N., Emans P.J., Meijer K. Signatures of knee osteoarthritis in the temporal and fractal dynamics of human gait. Clinical Biomechanics 2020;76:105016.

Verlaan L., Boekesteijn R., Oomen P.W., Liu W.Y., Peters M.J.M., Emans P.J., van Rhijn L.W., Meijer K. Knee adduction moments are not increased in obese knee osteoarthritis patients during stair negotiation. Gait and Posture. 2019; 73: 154-160.

Verlaan L., Storken G., Heyligers I.C., Grimm B. Accelerometer based stair climbing in healthy subjects: reference data and demographic differences. Juniper Online Journal of Case Studies. 2019; 9 (5): 1-6.

Verlaan L., Boekesteijn R.J., Oomen P.W., Liu W.Y., Peters M.J.M., Witlox A.M., Emans P.J., van Rhijn L.W., Meijer K. Biomechanical alterations during sit-to-stand transfer are caused by a synergy between knee osteoarthritis and obesity. BioMed Research International. Vol. 2018, Article ID 3519498, 7 pages, 2018.

Geerts R.W.P.M., **Verlaan L**., Arts J.J., Tilman P.B.J., Jansen E.J.P. Abdominal pain caused by bilateral acetabular fractures secondary to an epileptic seizure. Case report and review of the literature. Orthopedic Research Online Journal. 2017; 1 (2): 510-514.

Verlaan L., Bolink S.A.A.N., van Laarhoven S.N., Lipperts M., Heyligers I.C., Grimm B., Senden R. Accelerometer-based physical activity monitoring in patients with knee osteoarthritis. The Open Biomedical Engineering Journal. 2015; 23 (9): 157-163.

Verlaan L., Grimm B., Heyligers I., Senden R. Inertia based motion analysis to support the diagnosis of meniscal tears in patients indicated for knee arthroscopy. Orthopaedic Proceedings. 2010; 92-B, Supp_IV.

Grimm B., Heyligers I., Senden R., **Verlaan L**. Validation of a sit-stand-sit test as an orthopaedic outcome measure using inertia based motion analysis. Orthopaedic Proceedings. 2010; 92-B, Supp_IV.

Verlaan L., Senden R., Storken G., Heyligers I.C., Grimm B. Outcome assessment in orthopaedics using a stair climbing test and accelerometer based motion analysis: a feasibility study. Orthopaedic Proceedings. 2009; 91-B, Supp_III.

Verlaan L., Thijs K., Heyligers I.C. Traumatische posterieure luxatie van de knie. Nederlands Tijdschrift voor Orthopaedie. 2008; 15 (2): 91-94.

Verlaan L., van der Wal B.C.H., de Maat G.H.R., Walenkamp G.H., Nollen-López L., van Ooy A. Primary hyperparathyroidism and pathologic fractures: a review. Acta Orthopaedica Belgica. 2007; 73 (3): 300-305.

Verlaan L., van der Wal B.C.H., de Maat G.H.R., Walenkamp G.H., Nollen-López L., van Ooy A. Ostitis fibrosa cystica: een ongewone oorzaak van een fractuur van het distale femur. Nederlands Tijdschrift voor Orthopaedie. 2006; 13 (2): 129.

Benders J., van Breda E., **Verlaan L**. Als de schokdemper zijn functie verliest. Limburgs Dagblad. November 2012.

Benders J., van Breda E., **Verlaan L**. Oud sloopwerk medisch hersteld. Limburgs Dagblad. November 2012.

Presentations

Knee adduction moments are not increased in obese knee osteoarthritis patients during stair negotiation. **L. Verlaan**, R. Boekesteijn, P.W. Oomen, W.Y. Liu, M.J.M. Peters, P.J. Emans, L.W. van Rhijn, K. Meijer. European Orthopaedic Research Society (EORS), Maastricht. (03-10-2019)

Signatures of knee osteoarthritis in the temporal and fractal dynamics of human gait. **L. Verlaan**, J. Vangeneugden, P. Oomen, W.Y. Liu, M. Peters, N. Latour, P.J. Emans, K. Meijer. International Conference on Ambulatory Monitoring of Physical Activity and Movement (ICAMPAM), Maastricht. (27-06-2019)

Biomechanical alterations during sit-to-stand transfer are caused by a synergy between knee osteoarthritis and obesity. **L. Verlaan**, R. Boekesteijn, P. Oomen, M. Peters, P. Emans, L. van Rhijn, K. Meijer. European Federation of National Associations of Orthopaedics and Traumatology (EFORT), Lissabon. (05-06-2019)

Temporal specific kinematic signatures in knee osteoarthritis independent of body weight. **L. Verlaan**, J. Vangeneugden, W. Bijnens, V. Groen, A. Witlox, P. Emans, K. Meijer. European Orthopaedic Research Society, (EORS) München. (13-09-2017)

Actual physical activity monitoring using single accelerometer in patients with end-stage knee osteoarthritis, TKA patients and healthy subjects. **L. Verlaan**, I. Heyligers, B. Grimm, R. Senden. European Orthopaedic Research Society (EORS), Nantes. (03-07-2014)

Actual physical activity monitoring using single accelerometer in patients with end-stage knee osteoarthritis, TKA patients and healthy subjects. **L. Verlaan**, I.C. Heyligers, B. Grimm, R. Senden. Wetenschappelijk Symposium Atrium MC & Orbis MC, Heerlen. (27-06-2014)

Inertia based motion analysis to support the diagnosis for meniscal tears in patients indicated for knee arthroscopy. **L. Verlaan**, B. Grimm, R. Senden, I.C. Heyligers. European Federation of National Associations of Orthopaedics and Traumatology (EFORT), Vienna. (03-06-2009)

Validation of a Sit-Stand-Sit test as an orthopaedic outcome measure using Inertia based Motion Analysis. B. Grimm, I.C. Heyligers, R. Senden, G. Storken, **L. Verlaan**. European Federation of National Associations of Orthopaedics and Traumatology (EFORT), Vienna. (03-06-2009)

Validity of an acceleration based stair test for clinical use. R. Senden, B. Grimm, **L. Verlaan**, K. Meijer, H.H.C.M. Savelberg, I.C. Heyligers. Bio-Medical Engineering Conference, Egmond aan Zee. (22-01-2009)

Inertia based motion analysis of stair climbing: Demographic differences and validatity in knee arthroscopy. R. Senden, B. Grimm, **L. Verlaan**, K. Meijer, I.C. Heyligers. Bath Biomechanics Symposium. (10-09-2008)

A stair climbing test to score clinical outcome in orthopaedics. **L. Verlaan**, B. Grimm, R. Senden, G. Storken, I.C. Heyligers. Nordic Orthopaedic Federation Congress (NOF), Amsterdam. (12-06-2008)

Early outcome of the Avanta SRTM trapeziometacarpal prosthesis. D. van Deurzen, **L. Verlaan**, M. van Steijn. Nordic Orthopaedic Federation Congress (NOF), Amsterdam. (12-06-2008)

Orthopaedic outcome assessment with accelerometer assessed stair climbing. **L. Verlaan**, R. Senden, I.C. Heyligers, B. Grimm. International Conference on Ambulatory Monitoring of Physical Activity and Movement (ICAMPAM), Rotterdam. (22-05-2008)
Outcome assessment in orthopaedics using a stair climbing test and accelerometer based motion analysis: a feasibility study. **L. Verlaan**, R. Senden, G. Storken, I.C. Heyligers, B. Grimm. European Orthopaedic Research Society (EORS), Madrid. (26-04-2008)

Osteitis fibrosa cystica: an unusual cause of a fracture. **L. Verlaan**, B.C.H. van der Wal, G.H.R. de Maat, G.H. Walenkamp, L. Nollen-López, A. van Ooy. Nationale refereerdag van de Nederlandse Orthopaedische Vereniging (NOV), Utrecht. (19-05-2006)

Maastricht University

Maastricht UMC+

NEDERLANDSE
ORTHOPAEDISCHE
VERENIGING | NOV

smeets loopcomfort

expertisecentrum: voeten | schoenen | bewegen

Penders Voetzorg

ORTHOPÆDIE 2000

NATUURLIJK. BEWEGEN.

Anna Fonds

Nederlands
Orthopedisch
Research en
Educatie
Fonds