DEVELOPMENT AND PREVENTION OF KNEE OSTEOARTHRITIS

JOS RUNHAAR

DEVELOPMENT AND PREVENTION OF KNEE OSTEOARTHRITIS;

THE LOAD OF OBESITY

Jos Runhaar

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	Prof.dr. J.M.W. Hazes
	Prof.dr. J. Dekker

Content

CHAPTER 1

General introduction

Osteoarthritis

According to the World Health Organization, more than 150 million (± 2.5%) people suffer from osteoarthritis (OA) worldwide [1]. Above the age of 60 years, these figures even rise to 10% [2]. In almost 30% of these cases, OA leads to moderate to severe disability [1]. Thereby, it is the most common joint disease for the middle-aged and older population [3]. In the Netherlands, OA is estimated to affect more than 650.000 people. Annual health care costs associated with OA are estimated to be 540 million euro, equivalent to 0.8% of the total costs of health care in the Netherlands [4].

Before, OA was thought of as being mainly driven by wear and tear of the articular cartilage within the synovial joint. In recent years, it is shown that not only cartilage, but also the subchondral bone, ligaments, the synovial fluid, and surrounding muscles are involved in the OA process [5-7]. Although the exact aetiology is still unknown, OA is in general characterized by loss of articular cartilage, osteophyte formation, and subchondral bone sclerosis [6-8]. Clinically, OA is characterized by joint pain and limited joint function [3]. OA can affect all synovial joints, but is most common in the knee, the hip and the hand joints [3]. Given the predominance of OA in the knee joint compared to other joints, the main focus in scientific studies have been on the knee joint, as is the current thesis.

Defining knee osteoarthritis

The diagnosis of OA is mainly based on reported symptoms. Recent released recommendations of evidence-based criteria for the diagnosis of knee OA are the presence of persisting knee pain, brief morning stiffness, functional limitations with additional features from physical examination (crepitus, restricted movement, and bony enlargements) [8]. The more positive results a patient presents, the more likely the diagnosis of knee OA [8]. For scientific studies, classification criteria developed by the American College of Rheumatology (ACR) in 1986 are often used to define clinical knee OA [9]. To best define the presence of knee OA, the ACR criteria combine outcomes from radiographs and physical examination. Knee OA is defined as the presence of chronic knee pain (pain on most days of the last month) is reported, one or more osteophytes are visible at the radiograph and one out of these three features is scored positive: age > 50, morning stiffness < 30 minutes, or crepitus [9]. For the classification of the structural changes associated with knee OA, Kellgren and Lawrence (K&L) composed criteria for a 5-point grading scale using radiographic features, back in 1957 [10]. These K&L grades range from 0 (no OA) to 4 (severe OA), with grades ≥ 2 defined as definite knee OA [10]. Throughout

the years, these criteria have been used in numerous studies. Although slightly altered in several studies, the original criteria are still recommended for the proper determination of radiographic knee OA today [11]. Minimal joint space width between the femur and tibia, measured on a radiograph, is a surrogate measure for the thickness of articular cartilage in the knee joint. The radiographic response to treatment in knee OA is often measured as the difference in the rate of the change in joint space width (joint space narrowing, JSN), since it is more sensitive to change than the K&L criteria. Despite the fact that the three measurements all define knee OA (the ACR and K&L criteria) or measure a marked feature of knee OA (loss of articular cartilage in JSN), there is only moderate overlap between those measurements [12-13]. Some individuals with distinct structural changes in the knee joint do not report pain, and some individuals with substantial knee pain show no structural alterations at a radiograph [12, 14]. This discrepancy is mainly present in the less severe forms of knee OA. The discordance between the several criteria of knee OA illustrates that the exact aetiology and pathophysiology of knee OA is still unknown. A combination of the three described OA definitions will be used in the preventive randomized controlled trial presented in this thesis.

In recent years, magnetic resonance imaging (MRI) has gained popularity for the visualisation of structural changes in knee OA. With MRI, contrary to conventional radiographs, it is possible to directly visualize the articular cartilage and detect abnormalities to the cartilage, menisci, and in the bone well before knee OA is established or provokes joint complaints [15-16]. Moreover, MRI provides a three-dimensional view of the knee joint and also visualizes abnormalities in the patellofemoral joint, which is often neglected in conventional radiographic evaluations. Despite the advantages of MRI over conventional radiographs for the visualisation of knee OA, for research purposes and especially clinical purposes, the relevance of many MRI findings is still unclear.

Risk factors for the incidence of knee osteoarthritis

Knee OA is a multi-factorial disease. The strongest most prevalent risk factors for the incidence of knee OA are overweight or obesity, a higher age, and female sex [17-18]. In table 1.1, the most studied risk factors for incident knee OA out of the most recent systematic review from Blagojevic and co-workers are presented [18]. After the age of 50, incidence increases markedly and incidence levels among women exceed those of men [19]. In general, two main interlinked pathways are suggested for the onset of knee OA; inflammation and biomechanical loading. Being overweight or obese increases one's risk for developing knee OA by 2 to 7-fold [18, 20-21]. Biomechanically, a higher body weight increases the load on the knee joint due to higher and altered load patterns. Besides, it can induce and

Table 1.1. Most studied risk factors for incident knee OA (selected from [18]).

Risk factor	Number of papers	Number of patients	Pooled odds ratio (95% CI)
BMI			
Overweight	23	639,526	2.18 (1.86 – 2.55)
Obesity	17	346,788	2.63 (2.28 – 3.05)
Previous knee injury	16	16,746	3.86 (2.61 – 5.70)
Gender	8	10,353	1.84 (1.32 – 2.55)
Heberden's nodes	8	6,109	1.49 (1.05 – 2.10)
Age	15	-*	-*

*Although all included studies reported a higher risk for knee OA at higher age, authors were not able to pool the results due to the different categorization of age-groups and ranges [18].

increase the negative effects of unfavourable alterations in knee joint alignment and meniscal and ligament pathologies [5, 22]. On the other hand, being overweight or obese is also linked to the development of knee OA through the inflammatory pathway. Fat mass is shown to be an endocrine organ producing a variety of unfavourable factors affecting the pathogenesis of knee OA [6]. Besides, increased load on the cartilage also activates the mechanoreceptors that might induce tissue breakdown [22]. Activation of mechanoreceptors may initiate inflammation at the joint and induce tissue breakdown [22]. The mechanism behind the increased incidence among women needs to be unravelled still, but the drop in oestrogen levels after the menopause and associated increased sensitivity to inflammatory stimuli is suggested as factor [23].

Treatment of knee osteoarthritis

In Dutch general practice, the consultation rate for knee OA is around 8.9 per 1000 registered persons per year [24]. Over the last decades a wide variety of pharmacological, non-pharmacological, and surgical treatment options for patients suffering from complaints caused by knee OA have been evaluated. Optimal treatment of complaints associated with knee OA requires a combination of non-pharmacological and pharmacological modalities [25]. Non-pharmacological treatment includes, but is not limited to, regular aerobic and resistance exercise for all knee OA patients; losing weight for those patients who are overweight or obese; the use of walking aids and medical devices to counteract possible malalignment of the knee joint. Pharmacological treatment is usually started with Acetaminophen prescription. Additionally, glucosamine sulphate treatment is advocated by the guidelines [25], despite the fact that there are many conflicting results on the effectiveness of glucosamine sulphate [26]. Studies that did show a positive effect of glucosamine sulphate showed the largest effects in an early phase of the disease [27].

In the absence of an adequate response, glucosamine prescription is advocated to be discontinued and stronger medication, as non-steroidal anti-inflammatory drugs, and possibly intra-articular injections can be considered. Ultimately, joint replacement surgery could be considered, if relief of symptoms stays out [25]. In the Netherlands, most of the recommended treatment options, except for joint replacement, are provided in primary care.

Despite the fact that discussed treatment options provide relief of knee OA symptoms for most patients when appropriately administered, at best disease processes are slowed down. Evidence for true disease-modifying treatment options is scarce.

Prevention of knee osteoarthritis

Given the lack of disease-modifying treatments, opportunities for primary prevention of knee OA should be considered. However, up to now, no studies on the prevention of OA in any joint are available. According to the Society for Prevention Research, some basic principles guidelines should be considered when designing a preventive trial [28]. Among others, the Society for Prevention Research states that preventive measures should be applied in an early stage, to those at high risk, and should avoid causing harm. The preventive intervention itself should target modifiable risk factors, should specify clear goals, allow flexible protocols to comply with the individual needs, be available in the local community, and should target the risk factors from a multidisciplinary approach.

Out of the previously indicated most prevalent and strongest risk factors for incident knee OA, a high body weight is the only modifiable factor. From an observational cohort study with 40 years of follow-up, it has been calculated that if overweight and obese women would lose 5 kg body weight, the risk of developing knee OA would be reduced by more than 50% [29]. Despite the considerable effects of overweight and obesity on the development of knee OA and the intuitive beneficial effects of weight loss, the direct effects of weight loss on the incidence of knee OA have never been studied.

The literature shows an array of therapies for weight loss in overweight and obese individuals [30]. Compliance to the weight loss therapy is a major challenge when conducting a weight loss intervention. A combination of dietary and lifestyle interventions is suggested to be the most optimal [30]. Target of a weight loss intervention for overweight and obese individuals should be losing 5 kg or 5% body weight. Losing such amount of weight can be defined as clinically relevant, since it has been associated with health benefits, such as improvement of cardiovascular risk factors and reduced risk of Diabetes Mellitus type 2 [30-31].

Furthermore, glucosamine sulphate could also be considered as treatment option meeting the criteria of the Society for Prevention Research for a preventive measure. Although the evidence for the effectiveness of glucosamine sulphate is questionable, the effects are thought to be the greatest in an early stage of the disease and, more important, it is classified as having an excellent safety profile compared to placebo [26-27]. Therefore, as recommended by the Society for Prevention Research, it could be applied at an early stage of the disease and should cause no harm to the users [28].

Based on the literature and with the guidelines of the Society for Prevention Research in mind, the first ever preventive trial in OA was designed. The results of this trial are presented in this thesis.

Outline of this thesis

As indicated in the title and subtitle, the main focus of this thesis is on the effects of an excessive body weight on the development of knee OA and its role in the primary prevention of the disease. In **Chapter 2**, the biomechanical alterations in every day movements in obese individuals and their possible role in the development of knee OA are evaluated, after a systematic search of the literature. The interplay between a high body weight, alterations in the subchondral bone shape, and early signs of knee OA is assessed in **Chapter 3**. The central part of this thesis – the first ever preventive randomized controlled trial in OA research worldwide – is presented in **Chapter 4**. In this trial, the effects of a diet & exercise program and of glucosamine sulphate on the development on knee OA are evaluated in 407 middle-aged, overweight and obese women. **Chapter 5** presents a detailed description of the results of the diet & exercise program. The true preventive effect of clinically relevant weight loss on the development of knee OA, irrespectively of the applied interventions, is described in **Chapter 6**. In **Chapter 7**, the safety effects of the glucosamine sulphate intervention on blood glucose levels are evaluated. The effects of knee malalignment and the interplay with body weight on the incidence of knee OA, within the for the trial selected population, is presented in **Chapter 8**. Finally, in **Chapter 9** the main findings of the previous chapters are discussed, together with the implications for further research on the development and prevention of knee OA.

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CHAPTER 2

A systematic review on changed biomechanics of lower extremities in obese individuals: a possible role in development of osteoarthritis

J. Runhaar, BW. Koes, S. Clockaerts, SMA. Bierma-Zeinstra

Obesity Reviews 2011; 12 (12), 1071 - 1082

Abstract

Background: Obesity has been identified as a risk factor for osteoarthritis. For the weight-bearing joints, the combination of increased load and changed joint biomechanics could be regarded as underlying principle for this relation. This systematic review of the literature focused on the differences between obese and normal-weight subjects in biomechanics of the hip, knee and ankle joint during every day movements to summarize differences in joint load due to both higher body weight and differences in movement patterns.

Methods: A systematic search, up to November 2010, was performed in the Pubmed and Embase databases.

Results: This review showed that obese individuals adjust their movement strategy of every day movements. At self-selected speed, obese individuals walked slower, with shorter and wider steps, had longer stance duration and had a greater toe-out angle compared with normal-weight individuals. Obese sit-to-stand movement was characterized by less hip flexion and greater foot displacement.

Conclusions: Obese individuals showed altered biomechanics during every day movements. These altered biomechanics could be related to the initiation of osteoarthritis by a change in the load-bearing regions of the articular cartilage in the weight-bearing joints.

Introduction

Obesity has been identified as a risk factor for the development of osteoarthritis (OA) [1-2]. Apart from a proposed inflammatory component as shown in hand OA [3-4], for the weight-bearing joints an increase in joint load is often indicated as underlying principle for this relation [1,5-6].However, moderate levels of running did not increase the risk of OA in hips and knees and might even have a protective effect [7-8], healthy knee cartilage thickness was increased with an increased load on the knee during walking [8-9], and cadaveric studies showed that cartilage stiffness of hip, knee and ankle were correlated with joint loads during walking [6]. This suggests that healthy cartilage can adapt to higher repetitive loads [9-10] and extra load on the weight-bearing joints caused by being obese alone cannot be linked to the development of OA [11].

A study on weight loss and accompanied joint biomechanics showed a 1:4 ratio of loss of body weight to decrease of load on the knee joint [12]. Although these participants had radiologic signs of knee OA and joint biomechanics might therefore be altered compared with non-OA subjects, these results show that higher body weight accounted only for a small part of total knee joint load [12]. Accompanied unfavourable joint biomechanics accounted for a greater part of the total knee joint load. The combination of increased load on the weight-bearing joints and changed biomechanics in obese individuals (O) may be a risk factor for the development of OA [13–17]. For example during gait, malalignment and hyperextension in the knee joint have been linked to development of OA in obese subjects [14-15,17] and in the ankle joint, altered kinematics may contribute to the degeneration of the tibiotalar cartilage [18-19]. It has been suggested that changes in contact position of the articular cartilage in the weight-bearing joints could be a factor in the degenerative changes [9-10]. Hence, it is suggested that differences in biomechanics in obese subjects during activities of daily living could lead to the onset of OA [14].

In a theoretic overview in 2006, Wearing et al. [20] showed that there were differences in lower limb function between O and normal-weight individuals (NW). However, their overview was not based on a systematic search of the literature and conclusions were also based on studies that included subjects with OA. Because OA influences lower limb biomechanics [21], these findings could be hampered by OA. The purpose of the present study was to give a systematic review of the present literature on the differences in the biomechanics of the hip, knee and ankle joints during every day movements between otherwise healthy obese and normal-weight subjects. In order to summarize alterations in load on the weight-bearing joints due to both higher body weight and differences in movement patterns.

Methods

A systematic search was performed in the Pubmed and Embase databases up to 3 November 2010. Search items included joints of interest, biomechanical items, every day movements and description of the population of interest. The complete search strategy is specified in the Appendix.

Studies had to meet the following inclusion criteria to be eligible for this systematic review:

- Ten or more subjects (no case reports or very small studies).
- Subjects had to be 19 years or older (to rule out the influence of growth on movement patterns).
- Subjects had to be free of degenerative rheumatic or neurological disease.
- Description of joint angles and/or joint moments of weight-bearing joints during stance, walking, rising from a sitting position or climbing stairs.
- Description of differences between obese versus normal-weight subjects.
- Original research (no review, letter to the editor or comments).

No limitations were set on language, year of publication or publication status. After screening all abstracts on these criteria, all references of the eligible studies were additionally screened. One review author (J. R.) extracted all data from the eligible studies. Data were checked by a second author (S. B.). All data were derived from text, tables and figures of the eligible studies. No authors were contacted for additional information. For these observational studies, no validated risk of bias items exists. Therefore no quality assessment of the eligible studies was performed.

Data presentation

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was used for data presentation throughout the systematic review [22]. All biomechanical results are presented per joint. All presented moments are external joint moments.

Studies concerning gait differences between O and NW measured kinematic and kinetic variables during several different phases of gait. All study results were classified by the gait phases defined by Perry [23] and reduced to stance phase, because main focus of this review was on joint loads, which do not occur during swing phase (see Figure 2.1). Vismara et al. measured in both a horizontal treadmill position and a 15% inclined condition [24]. Since the objective was to describe biomechanics during activities of daily live, only data from the normal condition was used in the present study.

For readability reasons, for kinematic and kinetic variables only significant differences between O and NW will be presented in the text. When measured in multiple studies,

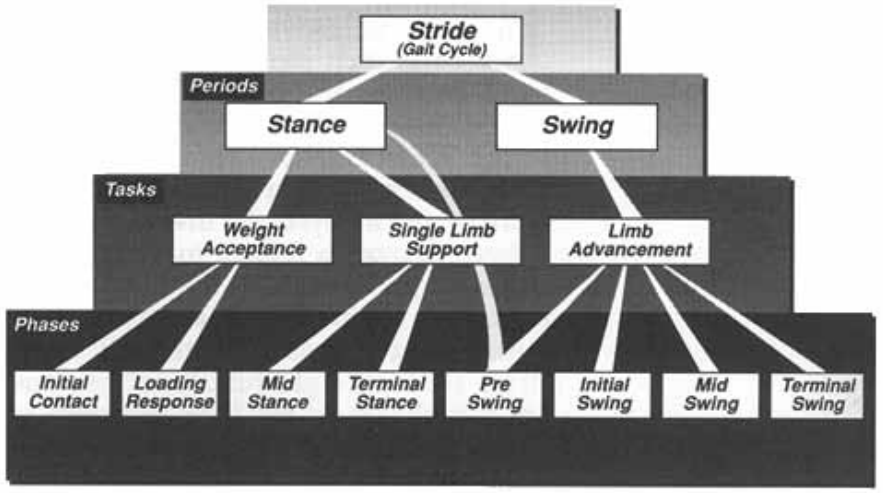

Figure 2.1. Divisions of the gait cycle by Perry [23]

average differences between O and NW will be presented with number of subjects per study taken in to account (all individual scores summed and divided by the total amount of subjects). Because of the high number of variables measured in the eligible studies, an overview of all measured variables and the direction of the differences between both groups are presented in several tables in the Appendix (see Tables A2.1–A2.7). In the text mentioned differences between O and NW were all statistically significant with P-values of <0.05.

Results

The search strategy resulted in 1,516 unique potentially relevant articles. Figure 2.2 shows the flow diagram from all 1,516 potential articles to the 12 observational studies that were eligible for this systematic review. All 12 studies, with some of their study characteristics, are listed in Table 2.1. Not all eligible studies had equal pre-defined criteria for O, but, as shown in Table 2.1, with a range of average body mass index from 33 to 42 kg/m^2 in O, obesity is well established among the eligible studies.

Gait

There were 10 eligible studies on kinematic and kinetic differences between obese and normal-weight subjects during walking. These studies can be divided in two groups. In

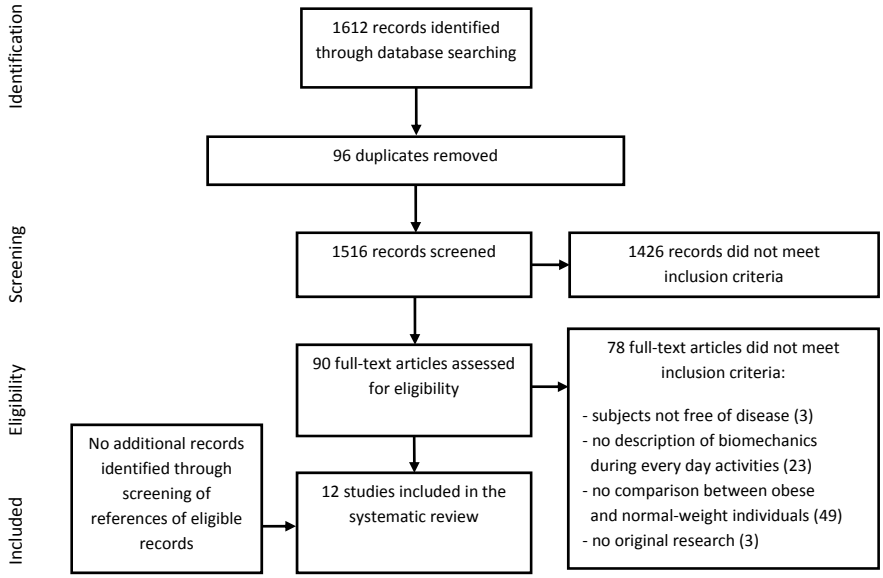

Figure 2.2. Selection of eligible studies

six studies, subjects walked at a self-selected speed [25–30]. Whereas in the other four studies walking velocity was kept constant in both groups [24,31–33]. This resulted in differences in outcomes and will therefore be discussed separately.

Spatial and temporal kinematics

Walking at self-selected speed

Studies reported a lower absolute walking speed of 0.3 ms^{-1} on average [25–28,30] and a lower walking speed relative to body height of 0.1 s^{-1} in O [29]. Absolute stride length [25,28,30], stride length relative to body height [26,29] and absolute step length [25] were respectively 0.2 m, 0.1 mm^{-1} and 0.2 m smaller on average in O. Step width was 0.1 m greater in O [25,28]. Several studies reported no difference between O and NW on cadence [26,29], whereas Spyropoulos et al. [28] reported that O walked at 13 steps per minute less than NW. Russell et al. also measured cadence and reported lower values for O, but these were not tested for significance [30]. Relative to total cycle time, stance time was 3% greater on average in O [26,28-29]. Two per cent greater double support time relative to total cycle time [26] and 2% smaller single limb support time relative to total cycle time [29] were found in O.

Table 2.1. Eligible studies

Author	N (O vs. NW)	Age* (O vs. NW)	BMI* (O vs. NW)	Motion assessed	Joints assessed	Orientation	Measurement method
Vismara et al., 2007 [29]	14 vs. 20	29.4 vs. 30.2	39.2 vs. 21.4	Gait (self-selected speed)	Hip, knee, ankle/foot	all joints in sagittal plane and toe-out angle	Motion analysis system (100 Hz)
Spyropoulos et al., 1991 [28]	12 vs. 9	38.9***	-	Gait (self-selected speed)	Hip, knee, ankle/foot	all joints in 3D and toe-out angle	High-speed video (50 Hz)
Segal et al, 2009 [27]	40 vs. 19	49.2 vs. 48.7	35.8 vs. 22.8	Gait (self-selected speed)	Knee, ankle/foot	knee joint in coronal plane and toe-out angle	Motion analysis system (60 Hz)
Lai et al., 2008 [26]	14 vs. 14	35.4 vs. 27.6	33.1 vs. 21.3	Gait (self-selected speed)	Hip, knee, ankle/foot	all joints in 3D	Motion analysis system (60 Hz)
De Souza et al. 2005** [25]	34	47.2	40.1	Gait (self-selected speed)	-	spatial and temporal measurements and toe-out angle	-
Russell et al. 2010 [30]	10 vs. 10	25.3 vs. 25.1	33.1 vs. 22.7	Gait (self-selected speed)	Knee	coronal plane	Motion analysis system (240 Hz)
Vismara et al. 2006 [24]	10 vs. 10	26.7 vs. 29.4	36.1 vs. 20.9	Gait (standardized speed)	Hip, knee, ankle	all joints in sagittal plane	Motion analysis system
Browning & Kram, 2007 [31]	10 vs. 10	young adults	35.6 vs. 22.1	Gait (standardized speed)	Hip, knee, ankle	all joints in sagittal plane	High-speed video (200 Hz)
DeVita & Hortobagyi, 2003 [32]	21 vs. 18	39.5 vs. 20.8	42.3 vs. 22.7	Gait (standardized speed)	Hip, knee, ankle	all joints in sagittal plane	High-speed video (60 Hz)
Messier et al. 1994b [33]	16 vs. 13	30.0 vs. 35.2	41.4 vs. 20.8	Gait (standardized speed)	Ankle/foot	coronal plane and toe-out angle	High-speed video (100 Hz)
Galli et al. 2000 [34]	30 vs. 10	39.7 vs. 27.0	40 vs. 22	Sit-to-stand	Hip, knee, ankle	all joints in sagittal plane	Motion analysis system (50 Hz)
Sibella et al., 2003 [35]	40 vs. 10	48.5 vs. 26.5	37.9 vs. 23.0	Sit-to-stand	Hip, knee, foot	all joints in sagittal plane and foot position	Motion analysis system (500 Hz)

O – obese individuals; NW – normal-weight individuals; * Mean per group presented; ** only includes an obese group. Scores are compared to reference values; *** no age of NW given.

Walking at standardized speed

Browning and Kram [31] measured O and NW at six different walking velocities, starting at 0.5 ms^{-1} up to 1.75 ms^{-1} with steps of 0.25 ms^{-1}. DeVita and Hortobagyi [32], Messier et al. [33] and Vismara et al. [24] measured all subjects at one standardized speed of 1.5 ms^{-1}, 0.893 ms^{-1} and 0.833 ms^{-1} respectively. Vismara et al. found 3 cm greater step length in O on the standardized walking velocity [24]. However, DeVita and Hortobagyi did not found any difference on absolute step length step length [32], neither did Browning and Kram [31] on absolute stride length at each walking velocity. Besides, a longer stance time of 3% [31-32] and a longer double support time, both relative to total gait cycle time, of 6% [24,31], and a greater step width of 0.1 m on average [24,31] were found in O (with exception of step width at 1.25 ms^{-1} where no difference was found).

Biomechanics

Walking at self-selected speed

The hip joint. Spyropoulos et al. [28] reported 14° greater hip abduction in O on average during single limb support. Contrary, Lai et al. [26] reported no significant difference at mid stance and reported 3° greater hip adduction on average at terminal stance and pre swing. No differences were found on hip joint moments between the two groups.

The knee joint. Lai et al. [26] reported 5° higher maximal knee adduction in O during stance phase. On absolute moment in the knee joint, Segal et al. [27] reported significant higher peak adduction moment during weight acceptance phase in both obese groups (22 Nm higher in central obese and 11 Nm in lower obese) and during single limb support phase in central obese group (14 Nm). Contrary, Russell et al. reported no difference on absolute peak adduction moment between O and NW during the stance phase [30]. Relative to body weight [27] and body weight and height [26], peak knee adduction moment was not significantly different between the groups.

The ankle joint. In the sagittal plane conflicting results were found. Some studies reported no significant differences between O and NW [26,29], while Spyropoulos et al. [28] found significant higher dorsiflexion angles of 19° on average in O at loading response, mid stance, terminal stance, pre swing, maximal stance dorsiflexion and maximal stance plantar flexion. Besides, on average 5° greater eversion at mid stance, terminal stance and pre swing [26] and 7° greater toe-out angle during the stance phase [25,29] were reported in O. Peak relative plantar flexor moment during stance was 0.1 Nm kgm^{-1} lower in O [26]. Relative to body weight and velocity, Vismara et al. [29] reported no significant differences

on peak plantar flexor moment between O and NW during terminal stance. Lai et al. [26] found 0.04 Nm kgm^{-1} higher peak inversion moment in O during stance.

Walking at standardized speed

The hip joint. No significant differences between O and NW in hip angles at mid stance [31] and initial contact [24] were reported in the sagittal plane. Contrary, averaged over the entire stance phase, DeVita and Hortobagyi [32] reported a 5° greater hip extension angle in O. Browning and Kram [31] reported a 47 Nm higher peak hip extension moment in O during stance phase at all speeds, with exception of 0.75 ms^{-1}. DeVita and Hortobagyi [32] averaged absolute hip extension moment over the entire stance phase and found no difference between O and NW. Relative to body weight Browning and Kram [31] found no significant differences between O and NW at any speed.

The knee joint. In the sagittal plane, no significant differences in knee angles between O and NW at mid stance on all velocities [31] or on total range of motion [24] were reported. Contrary, Vismara et al. [24] reported 5° less flexion in O at initial contact at their standardized walking velocity. Besides, 8° lower maximal and 4° average knee flexion were reported in O [32]. On absolute peak knee extension moment, Browning and Kram [31] reported only significant differences between O and NW during stance phase at 1.75 ms^{-1}, where O showed 47 Nm higher values. There were no significant differences between O and NW on peak knee extension moment relative to body weight on each walking velocity [31]. Controversially, DeVita and Hortobagyi [32] reported a 0.5 $Nmkg^{-1}$ lower peak knee extension moment in O during the stance phase at their standardized speed of 1.5 ms^{-1}. Browning and Kram [31] calculated absolute peak knee adduction moment from the medio-lateral resultant of the ground reaction force and found significantly higher values in O at 0.75 ms^{-1}, 1.25 ms^{-1} and 1.50 ms^{-1} (20 Nm on average).

The ankle joint. No significant differences were reported for plantar flexion at initial contact [24] and mid stance [24,31]. Contrary, 5° lower plantar flexion in O was reported at terminal stance [24] and 7° greater plantar flexion in O at pre swing [32]. Besides, DeVita and Hortobagyi [32] reported 6° higher average plantar flexion during stance phase. Messier et al. [33] reported 8° greater ankle inversion in O at initial contact and 6° greater total eversion in O during stance phase. In the transverse plane, Messier et al. [33] reported 4° greater toe-out angle during stance phase in O. Averaged over the stance phase, DeVita and Hortobagyi [32] found a 100 Nm greater ankle plantar flexion moment in O. Browning and Kram [31] reported no significant differences on absolute peak ankle plantar flexion moment. A lower peak plantar flexion moment relative to body weight during stance phase was found in O at every walking speed; however, no data were given [31].

Sit-to-stand

From all eligible studies, there were two studies on biomechanical differences between obese and normal-weight subjects when rising from a chair [34-35]. Galli et al. [34] included subjects with lower back pain in the obese group. This influenced the trial-by-trial outcomes of the obese group. Authors concluded that fatigue did not influence the measurements in the first trial, but did in the last trial. Therefore, only results of the first trial are included in this review. Besides this difference, studies had very similar methods and participant characteristics (see Table 2.1). By taking only the first trial results of the studies of Galli et al. [34], results of the studies were very consistent [34-35].

Biomechanics

Studies found 22° less hip flexion on average [34-35] and 5 cm greater foot displacement in O [35]. Galli et al. [34] found 7° greater dorsal flexion in O. Sibella et al. [35] also measured plantar flexion angles, but did not analyse or present any data.

Both studies describe their kinetic data as moments relative to body weight and height; however, data were presented as $Nmkg^{-1}$ instead of $Nmkgm^{-1}$ or Nkg^{-1}. Because data were in the same range and were presented as $Nmkg^{-1}$, it is assumed to be normalized to body weight alone. The different movement strategies of O and NW led to a 0.3 $Nmkg^{-1}$ lower peak hip flexion moment and a 0.5 $Nmkg^{-1}$ higher peak knee extension moment on average in O [34-35]. Both studies measured peak ankle flexion moment but did not analyse or present any data.

Discussion

The purpose of this study was to give a systematic review of the studies on biomechanical differences of the lower limb between otherwise healthy O and NW during every day movements. Most of the eligible studies focussed on gait, but with considerable diversity in their measurements. The six eligible studies on gait at a self-selected velocity measured 99 different variables. Of these, only 38 were measured in two or more studies and in 12 of the 38 variables conflicting results were found. Summarizing all differences between O and NW that were confirmed in two or more studies, we can conclude that when walking freely, O had a lower absolute walking velocity of 0.3 ms^{-1} on average [25–28,30], a smaller absolute stride length of 0.2 m [25,28,30]. and 0.1 mm^{-1} relative to body height [26,29], a longer stance duration relative to total cycle time of 3% [26,28-29], a greater absolute step width of 0.1 m [25,28] and walked with 7° greater toe-out angle on average [25,29] compared with NW. As the studies on gait at a standardized velocity confirm, part of

the differences between O and NW at a self-selected velocity were caused by the lower walking velocity of O rather than by obesity per se [20]. However, because the purpose of the present study was describing differences in joint biomechanics during every day movements, focus will not be on the studies of gait at a standardized speed. Because O and NW will not walk at equal velocities during every day movement.

In normal gait, it has been shown that lowering walking velocity led to lower peak relative joint flexion and extension moments in hip, knee and ankle [36] and lower peak absolute joint moments in hip and knee in the sagittal and coronal plane [37]. Besides that, greater toe-out angle has been associated with decreased knee adduction moment relative to body weight and height in normal gait, because it shifts the force vector closer to the knee joint [38]. Therefore, some authors suggested that O lower their walking velocity to lower the load on their joints [26,28,31-32]. In the present systematic review, relative joint moments were mostly equal between groups. So alterations in walking velocity and toe-out angle in O were not large enough to lead to lower relative joint moments. However, with exception of relative knee joint moment in the coronal plane, none of the relative joint moments were measured in two or more studies.

Although relative knee adduction moment was not higher in O compared with NW [26-27], this variable has been associated with development of knee OA, especially in obese [14-15]. Relative knee adduction moment during gait and relative medial cartilage thickness are negatively correlated in obese, whereas in NW there is a positive correlation [14]. Equal knee adduction moments relative to body weight (and height) will lead to higher absolute adduction moments in obese because their body weight is much higher. Therefore, the contradicting relation between the relative medial cartilage thickness and the relative adduction moment suggests that the absolute knee adduction moment in NW stays within levels wherein healthy cartilage can adapt to the repetitive loads. While in O, articular cartilage may not be able to respond to the higher level of absolute knee adduction moment during gait [14]. The systemic inflammatory effect of the surplus fat tissue in O may play a role in this alteration of cartilage characteristics. Hence, increased body weight and fat mass and accompanied higher absolute knee adduction moment during walking in O can lead to cartilage degeneration prior to OA signs in O [14]. A lack of power in the study of Russell et al. [30] seemed to have kept results from the present study supporting this theory with uniform results.

The studies on sit-to-stand movement showed similar results; higher loads on the knee joint and lower loads on the hip joint in O [34-35]. Unfortunately, none of the studies measured biomechanical variables in the coronal or transverse plane. Therefore, it is not possible to give a good analysis of the total loads on the weight-bearing joints during the sit-to-stand movement.

All results of the eligible studies in the present systematic review have to be seen in perspective to the limitations of their measurements. There are known instrumental issues concerning human movement analysis [39] and, especially in obese subjects, soft tissue artefacts are a major source of error [40]. Even in NW, soft tissue artefacts are around 4° to 5°. Most differences in joint angles found among the eligible studies, especially ab-/adduction and rotational angles, have a similar magnitude, troubling the interpretation of the results [40].

The systematic review has its limitations as well. First, no quality assessment of eligible studies has been performed because no validated risk of bias items exist. A frequently indicated item at risk of bias is blinding of outcome assessors. However, it seems unlikely that blinding could influence study results in the eligible studies, because all joint angles and moments were calculated digitally. On the other hand, not assessing the quality of the eligible studies could have led to possible ignorance of confounding influences on the study results. For example, age differed greatly between the O and NW in all sit-to-stand studies [34-35] and some studies on gait [26,32-33]. However, it is suggested that there is no evidence that biomechanics are affected by age in these ranges [32]. Second, because of the relative small number of eligible studies per activity of daily live, results were not subdivided by method characteristics that might have influenced the outcomes. Such as walking surface (overground vs. treadmill) or footwear (barefoot vs. shoes). When taken into account, these factors might diminish found differences between O and NW or could lead non-significant differences between both groups into significance when results were divided by these factors.

Although the present study was based on a systematic search of the literature, it did not cover all aspects of obese biomechanics. Factors not taken in to account, that do have influence on obese biomechanics, include lower maximal muscle strength relative to body weight [20], significant reduced joint range of motion [41] and foot pressure patterns [42].

Despite these limitations and despite the heterogeneity of the eligible studies regarding subject characteristics, measurement equipment and study design, still several distinct differences between O and NW were found. The results from this systematic review confirmed that O altered their movement strategies during every day walking, walking at a standardized speed and sit-to-stand movement. During freely walking, O lowered their walking speed and increased their toe-out angle. In theory to lower loads on their joints in the sagittal and coronal plane, but with that they introduce a rotational malalignment. This rotation could lead to cartilage degeneration in the affected joints because of a shift of the contact area towards infrequently loaded regions of the cartilage that, at some point, can no longer adapt to the altered loading [9]. Neutralizing toe-out angle in O to counteract the rotational malalignment does not seem to

be an advantageous intervention, because of an increase in the knee adduction joint moment, that already seemed to be above acceptable ranges [14]. Whether alterations in sit-to-stand movement among O could be associated to cartilage degeneration remains unclear, because only sagittal analyses were available. It cannot be ruled out that there are more biomechanical differences between O and NW during every day movements, but more consistent, high quality research, with more equality among measured variables, is needed. More sophisticated movement analysis systems with higher precision, for instance biplane radiography [43], should be considered in future studies to analyse the difference in movement patterns between O and NW in more detail. By combining movement analyses with magnetic resonance imaging techniques, cartilage properties associated to the development of OA, such as volume, thickness and defects, could be studied in relation to the differences in movement patterns between O and NW, to confirm the role of adjusted biomechanics in the development of OA. Of course, these studies should have a longitudinal design, contrary to the cross-sectional design of all eligible studies in the present study.

Overall, although the current literature is not comprehensive, the eligible studies are very heterogeneous, and remarks can be made on the precision of the measurements, it can be concluded that O alter their movement strategies of every day movements. There are indications that these alterations could be associated to the osteoarthritic process of cartilage degeneration.

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CHAPTER 3

Exploring the mediator and moderator effects of BMI and bone shape on early knee OA

J. Runhaar, D. Schiphof, BM. de Klerk, D. Haverkamp, H. Weinans, A. Hofman, SMA. Bierma-Zeinstra, JH. Waarsing

(under review)

Abstract

Background: In the knee joint, BMI is associated with bone shape. Also, both BMI and bone shape are related to early signs of knee osteoarthritis (OA). In theory, there could be a causal effect of BMI on bone shape, which in turn leads to early OA signs (mediation). On the other hand, aspects of bone shape might only be related to incident OA in the presence of a high BMI (moderation). The objective of this study is to explore these relationships.

Methods: Using 2D Statistical Shape Models, shapes of both the femur and tibia were analysed in 397 non-OA (K&L-grade 0), middle-aged females. The mediating role of femur and tibia shape features on the relation between BMI and early signs of knee OA (as seen on MRI) and the moderating role of BMI on the relation between shape features and these early OA signs were tested.

Results: BMI was indicated as moderator on the relation between one femur and 7 tibial modes and the presence of cartilage defects and bone marrow lesions. Only one tibial mode, representing knee flexion angle, showed a mediator effect on the relation between BMI and the presence of cartilage defects.

Conclusions: Certain tibial shape characteristics play an initial role in the development of knee OA, among subjects with a high BMI. Besides, greater extension of the knee joint, as a result of a high BMI, seems to be a protective mechanism on the presence of cartilage defects.

Introduction

Development of osteoarthritis (OA) is known to be a multifactorial process [1]. In the knee joint, obesity is known to play a major role in the pathogenesis of the disease [2]. The presence and development of bone marrow lesions (BMLs) and cartilage defects in the tibiofemoral joint are associated to high body mass index (BMI) and are seen as early structural changes leading to knee OA [3-5]. Besides the negative systemic effects of surplus fatty tissue, subjects with a high BMI suffer from altered load patterns on the weight-bearing joints, due to a higher body weight and adjusted biomechanics of every day movements which could lead to OA [6].

Altered loads on the knee joint as seen in people with a high BMI, which are higher and are accompanied by changed kinematics, could lead to changes in bone shape. For instance, in both OA and non-OA individuals, relative knee adduction moment and BMI were positively correlated to tibial plateau area [7-9]. Hypothetically, a greater tibia plateau will keep stresses in the joint within limits, because higher loads are distributed over a greater surface [10]. Still, a larger tibia plateau has been associated with increased tibiofemoral cartilage defects [7, 11]. Possibly since the tibia plateau does not increase proportionally with increase in body size [12]. Furthermore, the fact that biomechanical factors, as the relative knee adduction moment, were among the best predictors of distribution of bone mineral density in the proximal tibia [13], supports the notion that altered knee joint loads can influence bone characteristics. High local bone mineral density has been linked to the presence of BMLs, which suggests that these alterations of bone characteristics can indeed play an initial role in the development of knee OA [7-8, 11].

The above demonstrates that in the knee joint, BMI is associated with changes in bone shape and that both factors are related to early signs of knee OA. It is however unclear how these factors influence one another. Certain bone shape features might only be related to cartilage defects and BMLs in subjects with a high BMI. In that case, BMI could be regarded as a moderator of the relation between bone shape and early OA signs [14]. Alternatively, there could be a causal effect of BMI on bone shape, which in turn might lead to BMLs and cartilage defects and eventually OA. If so, bone shape could be regarded as mediator in the association between BMI and early OA signs [14]. By exploring these associations, we hope to provide further information on the factors involved in the development of knee OA, which might be used for identifying subjects at risk and designing new interventions in order to prevent the disease.

Using Statistical Shape Models (SSM) [15], association between femoral bone shape features and incident OA features in the hip joint have been established (e.g. [16-17]). Also in the knee joint, SSM has been used to demonstrate altered knee shape in women with OA [18]. In the present study, we used SSM to analyse the shape of both the distal femur

and proximal tibia in a population of non-OA, middle-aged females. We will explore a) the moderating role of BMI on the association between femur and tibia shape features and the presence of cartilage defects and BMLs in the knee as seen on Magnetic Resonance Imaging (MRI) and b) the mediating role of femur and tibia shape features on the association between BMI and the presence of cartilage defects and BMLs.

Materials and Methods

Population

In this study we used data from the Rotterdam Study. This is a prospective population-based study of subjects of 45 years and over, aiming to investigate determinants of cardiovascular, neuro-degenerative, locomotor and ophthalmologic diseases in the general elderly population. In total 14,926 persons were included [19]. At baseline, all subjects were examined. Examination consisted of an interview, physical examination focussing on possible causes of diseases in the elderly and an X-ray of both knees. These examinations were repeated every 3-4 years. Since incidence of knee osteoarthritis is higher in women, all women (aged 45-60 years) of the RS-III sub cohort underwent additional MRI of both knees at their baseline visit [19]. All women that had MRI and X-rays of the knees available at the time of this study were selected for the present study. The Medical Ethical Committee of the Erasmus Medical Centre approved the present study and all subjects gave written informed consent.

Measurements

All radiographs of the knees were weight-bearing antero-posterior radiographs taken at 70 KV, a focus of 1.8 mm2, and focus-to-film distance of 120 cm, using High Resolution G 35x43 cm film (Fujifilm Medical Systems, Stamford, CT). Radiographs of the extended knees were obtained with the patella in central position. A multi-sequence MRI protocol in a sagittal plane on a 1.5-T MRI scanner (General Electric Healthcare, Milwaukee, Wisconsin) was performed. All participants were scanned with an 8-channel cardiac coil, so two knees could be scanned at once, just by re-localizing. The multi-sequence protocol contained: a fast spin echo (FSE) proton density T2 weighted sequence (TR/TE 4900/11/90, flip angle of 90-180, slice thickness 3.2mm, field of view 15 cm), a FSE T2 weighted fatsat sequence (TR/TE 6800/80, flip angle 90-180, slice thickness 3.2 mm, field of view 15cm), a spoiled gradient echo sequence (TR/TE 20.9/2.3, with fat saturation, flip angle 35, slice thickness 3.2 (1.6)mm, field of view 15 cm) and a Fiesta C-T1/T2 weighted sequence (TR/TE 5.7/1.7, no fat saturation, flip angle 35, slice thickness 1.6 mm, field of view 15 cm).

Data

Body height and weight were used for calculation of BMI and date of birth to calculate age at time of this study. Two trained readers (DS and BMdK) who were blinded for clinical data scored all radiographs using Kellgren and Lawrence (K&L) scale [20]. Reproducibility was checked using kappa statistics after scoring a random sample of all X-rays twice. Knee alignment was assessed on the X-rays by digitally determining the angle between the line connecting the midpoint between the tibial spines with the midpoint of the femur approximately 10 cm. proximal of the knee joint and the line connecting the midpoint between the tibial spines with the midpoint of the tibia 10 cm. distal of the knee joint [21-22].

Using freely available software (Active Shape Models toolkit, Manchester University, Manchester, UK developed by T.F. Cootes), a statistical shape model of the tibia and femur was constructed on the radiographs (see Figure 3.1). After all contour points were applied to the radiographs (46 on the femur, including cartilage area on the medial condyle, and 51 on the tibia), the program overlays all contours using the mathematical centre (left knees were mirrored onto the right). The contours are corrected for size and rotation to obtain an optimal fit. Through Principal Component Analysis, independent modes of shape variation in femur and tibia were produced. Each mode is expressed

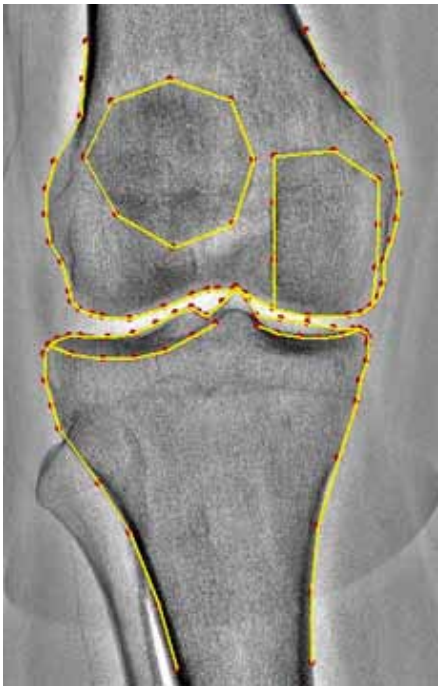

Figure 3.1. Applied shape models using Active Shape Models (frontal view of a right knee).

numerically, where 0 is the mean shape and negative and positive values represent the deviation from this mean, in either direction. We selected the number of modes such that 95% of the shape variation in the study population was described.

All MRIs were assessed by a trained reader (DS) using the Knee Osteoarthritis Scoring System (KOSS) [23]. From this semi-quantative scoring system, diffuse and focal cartilage defect scores (on FSE proton density T2 sequence) and BML score (on FSE fatsat sequence) of medial and lateral femur condyle and medial and lateral part of the tibia plateau were selected to evaluate early signs of OA. For both cartilage defect scores, depth of the defect and the surface extend were scored on a scale from 0 to 3 (absent, minimal, moderate and severe). These scores were combined into one dichotomous score (absent/present), with cartilage defects being scored as absent if both scores were 0. Present was scored if both scores were 1 or higher. BMLs were also scored on a scale from 0 to 3 and recoded into absent/present (0 / ≥1).

Statistics

All analyses were done using a selection of the data. Because the aim of this study was to investigate moderator and mediator effects on early OA signs, only subjects with a K&L score of zero in both knees were selected. Mode values were normalized to zero mean and unit standard deviation.

To test whether certain joint shape features are only related to the presence of early OA signs in the presence of a high BMI (moderation), the independent relations of BMI, mode values and the interaction between the two variables to the presence of all cartilage defects and BMLs (for femoral modes, only femoral cartilage defects and BMLs scored in the femur were tested. For tibial modes, only the early OA signs scored on the tibia were used) were determined using Generalized Estimating Equations (GEE), which takes the correlation between both knees within subjects into account, controlled for continuous measures of age and alignment angle (see Figure 3.2A). A moderator effect is present if the interaction term explains a significant amount of variance in the dependant variable [14]. If a significant moderator effect was found, the relation between the corresponding mode values and the early OA signs was determined using GEE, controlled for BMI, age and alignment angle, in subgroups based on BMI (BMI < 27 kg/m^2 and BMI ≥ 27 kg/m^2). Odds ratios will be tested on significant differences between these subgroups [24].

Further, we tested whether bone shape has a mediating role on the effect of BMI on early OA signs. A mediating role is present if the indirect path from BMI, via bone shape to early OA signs (path *a* x *b*, see Figure 3.2B) is significant, as indicated by the Sobel-test [25]. The Sobel operator was calculated based on results of GEE, with age and alignment angle (for *a*) and age, alignment angle and BMI (for *b*) as covariates. A significant mediation effect can be further classified into three subtypes using the decision tree by Zhao

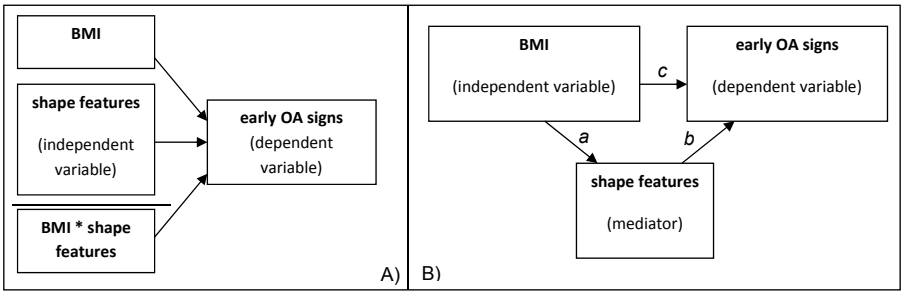

Figure 3.2. Illustration of the moderator (panel A) and mediator (panel B) design.

et al. [26]. Depending on the direct path *c* (Figure 3.2B), a mediation effect is 'indirect-only' (direct path *c* is not significant), 'complementary' (direct path *c* is significant and has the same sign as the mediation effect) or 'competitive' (direct path *c* is significant but its sign is opposite to that of the mediation effect).

Although the number of statistical tests would require a lower significance threshold, due to the exploratory intentions of the present study, a p-value < 0.01 was considered statistically significant in all tests. All statistical tests were performed using SPSS 17.0 (Chicago, IL).

Results

Characteristics of the women from the total sub cohort that underwent additional MRI (N = 891) and the population selected for the present study (N = 397) were not significantly different (age 53.8 ± 3.8 year, BMI 27.0 ± 4.8 kg/m^2 vs. 53.8 ± 3.9 year, 26.4 ± 4.6 kg/m^2 respectively). The interrater reliability for scoring radiological OA on the X-rays was good (κ = 0.62). Presence of the early OA signs, as seen on MRI, is given in Table 3.1.

BMI as moderator on the relation between shape features and early OA signs

Table 3.2 presents all statistically significant mode x BMI interaction terms. In total one femur mode (out of 19 femur modes) and seven tibial modes (out of 28) showed a statistically significant interaction term on the presence of several early OA signs. For these modes, subgroup analysis showed that only three tibial modes (modes 8, 12 and 15) had significant odds ratios in the subjects with BMI ≥ 27 kg/m^2. These odds ratios were significantly different from odds ratios in subjects with a BMI < 27 kg/m^2 (p = 0.001 for all mode values).

Tibial mode 8 represents variation in size of the lateral tibial spine, with concurring variation in both depth of the proximal rim of the medial plateau and width of the lateral

Table 3.1. Count of bone marrow lesion and cartilage defect scores.

	Right		Left	
	absent	**present**	**absent**	**present**
Femur				
Medial condyle BMLs	353	41 (10%)	348	49 (12%)
Lateral condyle BMLs	378	16 (4%)	379	18 (5%)
Medial condyle CDs	368	28 (7%)	369	26 (7%)
Lateral condyle CDs	382	14 (4%)	381	14 (4%)
Tibia				
Medial plateau BMLs	381	13 (3%)	391	6 (2%)
Lateral plateau BMLs	382	12 (3%)	388	9 (2%)
Medial plateau CDs	375	21 (5%)	381	14 (4%)
Lateral plateau CDs	389	7 (2%)	391	4 (1%)

BML: bone marrow lesion; CD: cartilage defect.

Table 3.2. Significant results for GEE of mode x BMI interaction term on presence of early OA signs (left) and accompanied subgroup analysis (right) for GEE of mode values on presence of early OA signs.

			Relation of mode to presence of early OA signs[b]			
			BMI < 27		**BMI ≥ 27**	
	mode x BMI to presence of[a]:	**p-value**	**odds ratio[c]**	**95%-CI**	**odds ratio[c]**	**95%-CI**
Femur						
mode 11	lateral CDs	**0.008**	0.99	0.69 – 1.40	1.12	0.65 – 1.93
Tibia						
mode 8	lateral CDs	**0.002**	1.85	1.09 – 3.15	12.52[d]	**4.40 – 35.66**
mode 12	lateral CDs	**0.005**	1.11	0.73 – 1.69	17.70[d]	**3.63 – 86.31**
mode 13	lateral CDs	**0.001**	1.43	0.94 – 2.18	0.38	0.10 – 1.52
mode 15	medial BMLs	**0.002**	1.31	0.80 – 2.15	0.43[d]	**0.28 – 0.68**
mode 19	medial BMLs	**0.002**	1.26	0.70 – 2.28	0.49	0.22 – 1.10
mode 25	lateral CDs	**0.001**	1.56	0.68 – 3.60	0.04	0.00 – 0.51
mode 26	lateral CDs	**< 0.001**	1.86	0.87 – 3.98	0.45	0.09 – 2.23

CD: cartilage defect; BML: bone marrow lesion; 95%-CI: 95% confidence interval; [a] adjusted for mode score, BMI, age and alignment angle; [b] adjusted for BMI, age and alignment angle; [c] odds ratio based on z-scores of the mode values; [d] odds ratio significantly different between groups ($p = 0.001$). Bold 95%-CI represent statistically significant odds ratio ($p < 0.01$).

proximal tibia. Lateral cartilage defects were associated to a large tibial spine and a deep rim in subjects with a BMI ≥ 27 kg/m^2. Tibial mode 12 seems to represent variation in size of the lateral tibial spine with concurring variation in the inclination medial plateau. In

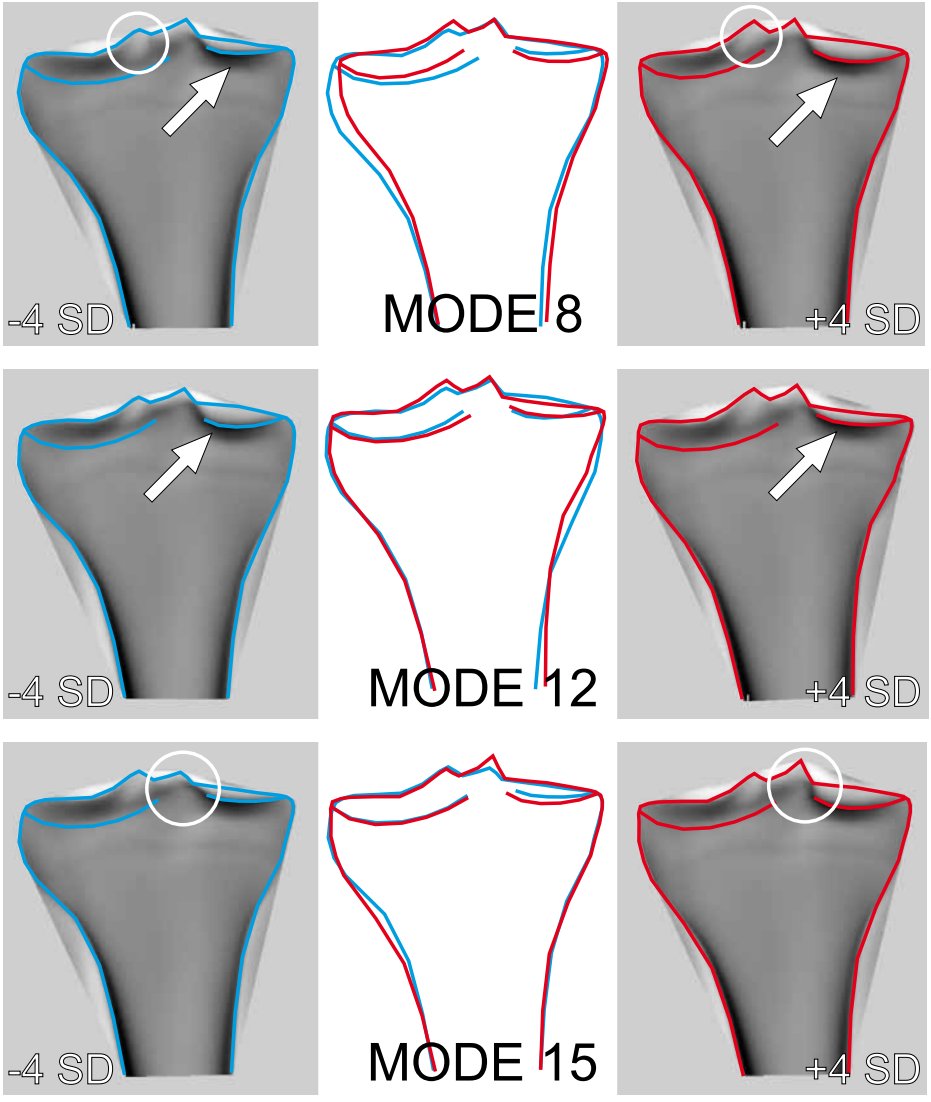

Figure 3.3. Modes with moderator effect on presence of early OA signs (+/- 4 SD; in order to illustrate relatively small differences within modes properly). A) Tibial mode 8, represents variation in size of the lateral tibial spine, with concurring variation in depth of the proximal rim of the medial plateau and width of the lateral proximal tibia. B) Tibial mode 12, representing forward rotation of medial tibia plateau in low mode values. C) Tibial mode 15, representing medial spiking, lowering of the medial anterior ridge of the tibia plateau and a less concave transition from the shaft to the plateau in higher values.

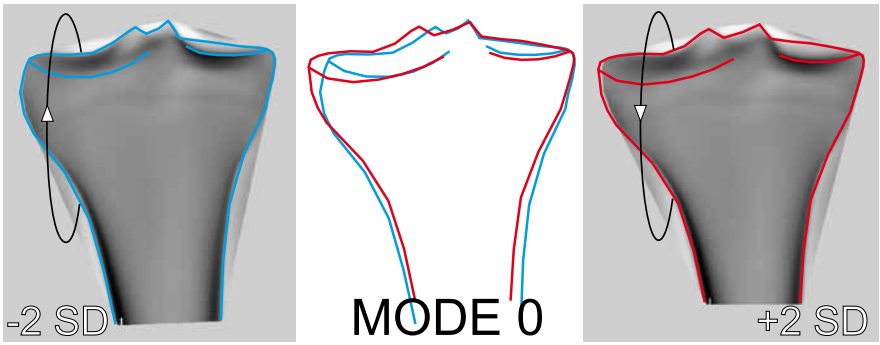

Figure 3.4. Tibial mode 0, representing greater knee flexion in higher mode values

subjects with a BMI ≥ 27 kg/m^2, lateral cartilage defects were associated to a large tibial spine and a flat medial plateau. Tibial mode 15 appears to represent variation in size of the medial tibial spine. BMLs on the medial side were associated to a relatively small medial tibial spine in subjects with a BMI ≥ 27 kg/m^2 (see Figure 3.3).

Mode values as mediator between BMI and presence of early OA signs

For all mode values and all cartilage defect and BML scores, the indirect effect of BMI on the presence of early OA signs through the mode values was determined (relation *a* x *b*, see Methods and Figure 3.2B). Only the relationship between BMI and the presence of lateral cartilage defects through tibial mode 0 was significantly different from zero ($p = 0.001$). The direct relation between BMI and the presence of lateral cartilage defects was not significant ($p = 0.934$). Based on the decision tree of Zhao et al., 'indirect-only' mediation is established for these mode values and it is unlikely there are other omitted mediators [26]. Tibial mode 0 values seemed to represent a difference in knee flexion angle, with higher values representing greater knee flexion (Figure 3.4).

Discussion

In this study, we found significant moderator effects of BMI on the relation between several femur and tibia shape features and the presence of BMLs and cartilage defects in middle-aged women free of radiographic signs of knee OA. Besides, a significant mediator effect of tibia shape features was found in the relation between BMI and presence of lateral cartilage defects among these women.

Presence of BMLs in this study (in 29% of the subjects) was within ranges found in other studies of healthy, non-OA subjects. In these studies, presence of BMLs ranged

from 13% to 61% of the subjects, probably due to differences in subject characteristics, definitions and the presence of knee OA [4, 27-30]. Presence of cartilage defects in this study was lower than reported in other healthy middle-aged subjects [11]. In the present study, cartilage defects were found in 21% of the subjects. Literature reports ranges from 28% to 71% for healthy, non-symptomatic subjects [11]. However, since radiological OA scores were not always an exclusion criteria in these studies, these populations included subjects with K&L score ≥ 2, whereas in the present study K&L score was limited to 0 in both knees. Therefore, the results give a good insight in factors related purely to the early signs of knee OA and hence, to possible initiation of the disease.

BMI as moderator on the relation between shape features and early OA signs

In the femur and the tibia, several interaction terms (mode value x BMI) showed significant associations to the presence of either BMLs or cartilage defects. Only for three tibial modes, a significant difference in odds ratio was found between subjects with a BMI < 27 kg/m^2 and those with a BMI ≥ 27 kg/m^2 (Table 3.2). The BMI cut-point of 27 kg/m^2 was chosen since beyond this point a clear increase in OA incidence is found [31]. Interestingly, all three tibial modes showing an association with early OA signs in subjects with a BMI ≥ 27 kg/m^2 showed a variation in tibial spine size. This association has not been studied excessively. Studies that did examine the role of height and pointedness of the tibial spines showed an association with presence of several OA features for high, pointed spines [32-33]. As in the present study, these studies showed an association between variation in tibial spine size and cartilage pathologies on the contra lateral side [32-33]. The exact mechanism behind this association is unclear. Some authors suggest the variation in shape of the tibial spines to be osteophytosis and hence part of the disease process [32-34], while other emphasize that the tibial spines are connected to the meniscus and the anterior cruciate ligament, suggesting that tensile forces on these structures might induce shape alterations [33, 35]. Since a high BMI is associated to both high biomechanical loads and systemic inflammation [2], both theories might underlie the associations found in subjects with a BMI ≥ 27 kg/m^2 in the present study, and have to be studied in more detail.

Mode values as mediator between BMI and presence of early OA signs

Only tibial mode 0 had a mediator effect (in this case 'indirect-only') on the relation between BMI and the presence of lateral cartilage defects. A higher BMI was associated to greater extension of the knee joint (see Figure 3.4), which in turn was associated to less cartilage defects on the lateral compartment of the femur. Interestingly, our results thus indicate an indirect protective role of BMI on lateral cartilage defects. Although a systematic review on kinematic differences between normal-weight and obese indi-

viduals [6] did not find differences in knee extension angle, several studies suggested an association between hyperextension of the knee and less OA-related features [36-37]. Data from the present study supports this and hence, greater knee extension might function as a protective mechanism in individuals with a high BMI in order to prevent cartilage damage.

A drawback of our study is that data are limited due to the two dimensional basis of the shape assessment. Thus, it is not always easy to determine whether the found projected shape features are due to true variation in shape of the bones or due to positional variation. Given the cross-sectional design, the defects seen on MRI are only assumed to be precursors of knee OA. The true development of knee OA could not be studied.

In conclusion, certain tibia shape characteristics, mainly of the tibial spines, appear to play an initial role in the development of knee OA, but only in subjects with a high BMI. Further, a greater extension of the knee joint, due to a high BMI, appears to be a protective mechanism and prevent cartilage defects.

Acknowledgments:

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CHAPTER 4

Prevention of knee osteoarthritis in overweight females; the first preventive randomized controlled trial in OA

J. Runhaar, M. van Middelkoop, M. Reijman, S. Willemsen, EH. Oei, D. Vroegindeweij, G. van Osch, BW. Koes, SMA. Bierma-Zeinstra

(under review)

Abstract

Background: The present study shows the results of the first ever preventive randomized controlled trial in osteoarthritis (OA) worldwide.

Methods: In a 2x2 factorial design, the effects of a diet and exercise program and of glucosamine sulphate (double blind and placebo-controlled) on the incidence of knee OA after 2.5 years were evaluated in a high-risk group of 407 middle-aged women with a BMI ≥ 27 kg/m^2 without signs of knee OA at baseline (ISRCTN 42823086). Primary outcome measure was the incidence of knee OA, defined as incidence of either Kellgren & Lawrence grade ≥ 2, joint space narrowing of ≥ 1.0 mm or clinical knee OA according to the combined clinical and radiographic ACR criteria.

Results: Only 10% of all subjects were lost to follow-up after 2.5 years. In total, 17% of all knees showed incident knee OA at follow-up. Intention To Treat analyses showed a significant interaction effect between the two interventions. Accounting for this interaction, no significant main effects of either intervention were found, but both interventions showed trends towards reduced knee OA incidence. These effects were neutralized in subjects receiving both the diet and exercise program and glucosamine.

Conclusions: Hampered by the unexpected interaction between the two interventions, no significant main effects of the diet and exercise program and of glucosamine sulphate were found on incident knee OA in middle-aged women with a BMI ≥ 27 kg/m^2 over 2.5 years. However, positive trends for the two separate interventions were found and should be further explored.

Introduction

Over the last decades, numerous longitudinal studies on risk factors for onset and progression of osteoarthritis (OA) of the knee, hip and hands have been performed [1-2]. These studies have led to the identification of a wide variety of modifiable and non-modifiable risk factors; mainly focusing on knee OA. With this accumulated knowledge, first steps towards primary prevention should be considered [3-4].

The strongest and most prevalent risk factors for incidence of knee OA are overweight or obesity, higher age, female sex, and a history of knee injury [5-6]. After the age of 50, incidence increases markedly and incidence levels among women exceed those of men [7]. A meta-analysis on the effect of overweight and obesity on the onset of knee OA showed odds ratios (ORs) ranging from 2.1 up to 4.3 compared to normal weight [5].

Altogether, women over the age of 50 who are overweight or obese and free of knee OA form a high-risk group for the development of knee OA in subsequent years. Several studies indicate that weight loss in overweight or obese individuals could prevent knee OA [2,8-9]. In an observational cohort, it was calculated that if women with a baseline body mass index (BMI) ≥ 25 kg/m^2 would reduce their BMI with 2 units (~ 5 kg), they would have a substantially reduced risk for developing knee OA (OR = 0.41) [9]. From the Framingham Study it was estimated that the incidence rate of knee OA would decrease by 33% if BMI in obese women (≥ 29 kg/m^2) would be reduced to 25 – 28.9 kg/m^2 (overweight) or if women with overweight would reduce their weight to normal (BMI < 25 kg/m^2) [8]. The direct effects of weight reduction (primary prevention) on subsequent knee OA development have never been studied so far.

Glucosamine has been studied for the treatment of patients with established OA [10], but it has never tested for its preventive effects. Literature shows the largest effects of glucosamine over placebo when used in an early phase of the disease [11] and especially in the knee joint [12]. Since all forms of oral glucosamine have shown to produce no side effects over placebo, even after long-term use [13], investigation of the preventive effect of glucosamine on incident knee OA seems worthwhile.

The objective of the present study was to evaluate the effect of a tailored diet and exercise program and of oral crystalline glucosamine sulphate (double blind and placebo-controlled) in a 2x2 factorial design on incidence of knee OA in overweight females between 50 and 60 years, free of radiological and clinical knee OA at baseline, over a 2.5 year follow-up period.

Methods

The PROOF study (PRrevention of knee Osteoarthritis in Overweight Females, ISRCTN 42823086) was funded by ZonMw, The Netherlands Organisation for Health Research and Development. The study was approved by the Medical Ethics Committee of Erasmus University Medical Centre. The manuscript has been written according to the CONSORT Statement guidelines [14].

Study sample

Fifty general practitioners (GPs) in the region of Rotterdam, The Netherlands, sent study information and a reply-card to all registered women between 50 and 60 years without major co-morbidities. Interested women with a reported BMI ≥ 27 kg/m^2 were contacted by phone to check all inclusion criteria. Besides age and BMI-related inclusion criteria, subjects had to be free of knee OA according to the ACR-criteria [15], not under treatment for knee complaints, free of MRI contraindications, free of rheumatic diseases, not using walking-aids, master the Dutch language and not using oral glucosamine for the last 6 months. All women eligible and willing to participate were invited for baseline measurements (July 2006 – May 2009).

Physical examination

Body weight, body height, waist circumference, skin folds, and blood pressure were recorded. Both knees were examined for pain upon pressure at the joint margins, warmth, crepitations, and laxity of the ligaments, and both hands for Heberden's nodes. All physical examinations were performed at baseline and after 2.5 years follow-up.

Radiography

Semi-flexed posterior-anterior knee radiographs were taken at baseline and follow-up according to the MTP protocol [16]. A trained researcher, blinded for clinical outcomes, scored all radiographs (baseline and follow-up images at once with known sequence) using the Kellgren & Lawrence (K&L) criteria [17]. A random subset of 20% of the radiographs was scored by a second blinded researcher to determine inter-observer variability. Minimal joint space width was measured by visual reading with the use of a digital ruler for each tibiofemoral compartment [18], using the average score of two researchers blinded for clinical outcomes and baseline measurements. Scores with a difference between both readers ≥ 2.0 mm were re-evaluated during a consensus meeting. Medial knee alignment angle was assessed by digitally determining the angle between the line from the centre of the tibial spines through the centre of the femoral shaft at approximately 10 cm from the joint margin and the matching line through the tibia [19].

Questionnaires

At baseline and every 6 months, participants filled in questions on the number of days with knee pain, activity level (SQUASH [20]), co-interventions, quality of life (EuroQol [21]), medical consumption, and nutritional habits. At baseline, 12 months and 30 months, knee complaints, KOOS questionnaire [22], menopausal status, and co-morbidities were additionally assessed. WOMAC pain and function scores were calculated from the KOOS questionnaire.

Randomization

After informed consent procedure and all baseline measurements, subjects were randomized according to a consecutive case number. For the diet and exercise program, subjects were randomized 1:1, using block randomisation with block size 20. A research assistant, not involved in the trial, provided a sealed envelope that was opened by the subject in the presence of the researcher. Allocation to glucosamine or placebo was also done one-on-one using a blocked randomization list with block size 20. However, this intervention was double-blinded (see below).

Home visits

Every 6 months, all participants were visited at home. At this visit, participant´s well-being was discussed, body weight was measured, the questionnaire was checked for missing data, the participant was provided with a new batch of study drugs, compliance to the study drug was scored by the participant, and the remainder of the previous batch was retrieved for an objective compliance calculation.

Diet and exercise program (DEP)

A detailed description of the DEP is given elsewhere [23]. In short, subjects randomized to the intervention group were referred to a dietician and were invited to attend physical exercise classes. Using Motivational Interviewing techniques [24], the dietician set goals regarding nutritional habits and physical activity patterns in agreement with the participant. Thereafter a tailor made strategy was determined. Additionally, subjects were invited to join twenty weekly physical exercise classes (12 to 15 participants) of one hour, supervised by a physical therapist. A variation of low impact sports and exercises were offered in order to regain pleasure in physical activity and find activities for long-term continuation. The control group was not offered an intervention, neither were they actively discouraged to undertake any form of weight reduction on their own.

Crystalline glucosamine sulphate versus placebo (GSvP)

All study drugs were provided in identical packaging by Rottapharm Madaus. Subjects and research staff were blinded for allocation throughout the whole study. Rottapharm Madaus was not involved in study design, data collection, or statistical analyses. Subjects were asked to consume one sachet of 1500 mg of the study drug (powder) a day for the total follow-up period of 2.5 years.

Outcome measures

Predefined primary outcome measure was the difference between the intervention/glucosamine and control/placebo group on the incidence of knee OA, defined as incidence of either K&L ≥ 2, joint space narrowing (JSN) of ≥ 1.0 mm or knee OA according to the combined clinical and radiographic ACR-criteria [15]. Secondary outcome measures were the differences between groups in quality of life, WOMAC pain and WOMAC function scores, actual weight loss, occurrence of OA MRI features, and increase in bone and cartilage degeneration markers. Since MRI scores and biomarkers will only be available in the course of 2013, these outcomes will not be presented here.

Sample size

The study was powered to show an incidence reduction from 20% in the DEP control group/placebo group to 10% in the DEP intervention/glucosamine group. These numbers were based on a twelve year follow-up study with an incidence of K&L ≥ 2 of 39.1% [25]. In the age range of 45 to 49 years, this number was 1.6 fold higher, suggesting an incidence of 13% over 2.5 years. The primary outcome measure combined incidence of K&L grade ≥ 2, ACR criteria and JSN. Since there is only moderate overlap between these measures [26], a 20% incidence in the control group seemed reasonable. No interaction between the interventions was assumed. Based on rates in our previous 2-year OA trial [27], we accounted for 10% lost to follow-up. Therefore, two groups of 200 subjects would be appropriate (one-sided testing, alpha = 0.05, beta = 0.80).

Analyses

Intention To Treat (ITT) analyses on all available data of all knees of all randomized participants served as primary analyses. First, the univariate association between known prognostic variables (age, K&L grade (≥1 vs. 0), varus alignment (<178° versus ≥178°)[28], mild knee symptoms, BMI, a history of knee injury, Heberden´s nodes, and postmenopausal status) and the primary outcome measure was determined using Generalized Estimating Equations (GEE), with the association between two knees within one person taken into account. Variables with a p-value < 0.2 were analysed multivariate. Variables with a p-value <0.05 in the multivariate model were adopted as confounders. Second,

the interaction between both interventions was determined using GEE, adjusted for the confounding variables. Third, the effects of DEP and GSvP were determined using GEE, adjusted for the confounding variables and, if prompted, the interaction between both interventions.

For the Per Protocol (PP) analyses, the latter two ITT analyses were rerun, between those subjects compliant to DEP (≥ 6 dietary consultations and ≥ 7 attended physical exercise classes) and those randomized to the DEP control group and in those compliant to GSvP (≥ 75% of the study taken). All analyses were performed using PASW statistics version 17.0 (SPSS Inc., Chicago, IL).

Available secondary outcomes were analysed using a linear mixed model estimated by restricted maximum likelihood (REML) to test effects of both interventions and their interaction over the follow-up period (SAS 9.2, SAS Institute Inc., Cary, NC). A p-value < 0.05 was defined as statistically significant for all analyses. Randomization code for GSvP was broken after all analyses were completed.

Results

In total, 6691 women were contacted by fifty GPs. Eventually, 407 women were invited for baseline measurements and were randomised. Figure 4.1 shows the complete flow-chart. Mean age at baseline was 55.7 ± 3.2 years and mean BMI was 32.4 ± 4.3 kg/m^2 (see Table 4.1). After 2.5 years, forty-one women (10.1%) were lost to follow-up. Of these, thirty-six women were unwilling to continue their participation; two women withdrew because of side effects; one woman was unattainable; two women died in the course of the study. One woman died shortly after study ending (all deaths not related to study drugs).

Joint space narrowing (JSN; ICC 0.5 – 0.8) was found medially in 5% and laterally in 6% of all knees. Incidence of K&L-grade ≥ 2 was found in 4% of all knees (kappa 0.6). Six per cent of all knees showed incident OA according to the ACR-criteria. Combined into the primary outcome measure, 135 knees (17%) showed incident knee OA after 2.5 years.

BMI, K&L grade (≥1 vs. 0), varus alignment, mild symptoms, and a knee injury in the past were univariately associated with the primary outcome. Multivariate, only K&L grade was associated with the primary outcome.

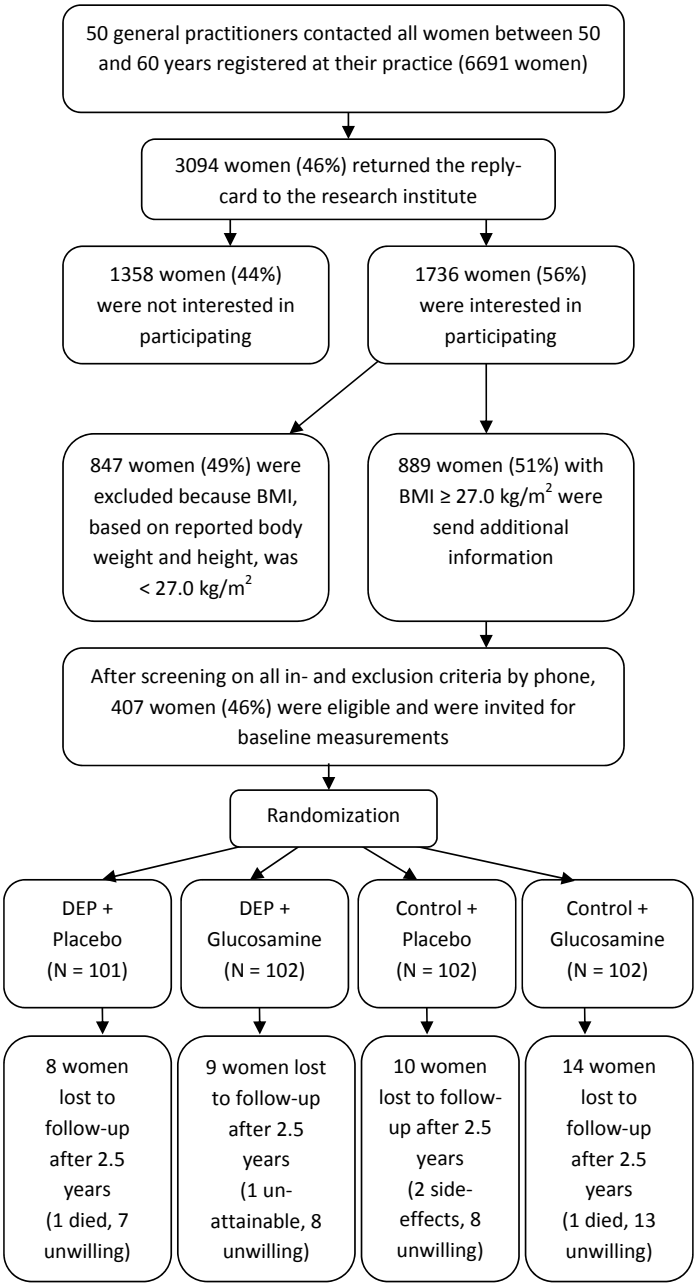

Figure 4.1. Flow-chart of participants in the PROOF study.

Table 4.1. Distribution and mean (± st. dev) of prognostic variables and the primary outcome among the randomized intervention arms.

	Diet & Exercise Program			
	Control group		Intervention group	
	Placebo	Glucosamine	Placebo	Glucosamine
Baseline characteristics				
N - subjects	102	102	101	102
Age (yr.)	55.7 ± 3.3	55.7 ± 3.1	55.7 ± 3.2	55.7 ± 3.1
BMI (kg/m^2)	32.6 ± 4.3	32.4 ± 4.6	32.3 ± 4.5	32.1 ± 3.7
Heberden's nodes				
uni-lateral	15%	16%	12%	12%
bi-lateral	10%	14%	20%	9%
Postmenopausal status	70%	68%	66%	67%
EuroQol (0-1)*	0.90 ± 0.12	0.88 ± 0.13	0.88 ± 0.14	0.90 ± 0.12
WOMAC (0-100)**				
pain	5.1 ± 8.5	7.1 ± 11.7	8.1 ± 13.3	6.6 ± 11.4
function	5.3 ± 8.7	7.1 ± 12.2	7.7 ± 12.2	5.9 ± 10.4
N – knees	204	204	202	204
K&L				
grade 0	53%	47%	53%	50%
grade ≥ 1	46%	53%	46%	50%
Minimal JSW				
medial (mm)	4.4 ± 0.8	4.4 ± 0.8	4.4 ± 0.8	4.4 ± 0.9
lateral (mm)	5.9 ± 1.1	5.8 ± 0.9	5.8 ± 1.1	6.1 ± 1.2
Varus alignment	46%	38%	38%	37%
Mild symptoms	29%	30%	36%	27%
History of knee injury	14%	12%	10%	13%

* Higher scores represent higher quality of life. **Higher scores represent more pain/worse function. JSW: joint space width

Intention To Treat analyses

The ITT analyses on the main effects of the two interventions and their interaction showed a significant statistical interaction ($p = 0.04$). Hence, the effects of one intervention depended on the allocation to either groups of the other intervention and the four groups had to be analysed separately. In none of the four groups, the number of subjects was high enough to reach the numbers required for statistical analyses, as indicated by the sample size calculations, due to the unexpected interaction between the interventions. The power was increased by analysing on knee level instead of subject level, taken the association between two knees within a person into account, the power was increased. Still, the number of knees was around 10% short of the number needed.

Table 4.2. Odds ratios from Intention To Treat analyses for the four randomized groups on incidence of knee OA.

	N (knees)	Incident knee OA	OR (unadjusted)	95% CI	OR (adjusted)*	95% CI
DEP control group / placebo	204	19%	1	(reference)	1	(reference)
DEP control group / glucosamine	204	13%	0.610	0.628 – 1.135	0.591	0.313 – 1.118
DEP intervention group / placebo	202	15%	0.695	0.396 – 1.213	0.685	0.389 – 1.208
DEP intervention group / glucosamine	204	20%	1.010	0.579 – 1.763	0.972	0.553 – 1.710

* adjusted for baseline KL grade (0 vs. ≥ 1). DEP: diet and exercise program, OR: odds ratio, CI: confidence interval.

Table 4.3. Odds ratios from Per Protocol analyses on incidence of knee OA.

	N (knees)	Incident knee OA	OR (unadjusted)	95% CI	OR (adjusted)*	95% CI
DEP control group / placebo	204	19%	1	(reference)	1	(reference)
DEP control group / glucosamine	204	13%	0.610	0.328 – 1.135	0.590	0.310 – 1.122
Compliant to DEP / placebo	58	9%	0.341	0.109 – 1.063	0.349	0.110 – 1.105
Compliant to DEP / glucosamine	56	23%	1.220	0.567 – 2.628	1.277	0.594 – 2.747

* adjusted for baseline KL grade (0 vs. ≥ 1). DEP: diet and exercise program, OR: odds ratio, CI: confidence interval

Given the opposite effects of DEP within the GSvP groups, and vice versa, ITT and PP analyses were performed two-sided, using a p-level < 0.05. Table 4.2 shows the ORs from the ITT analyses for the four groups. The reduced adjusted ORs for DEP (0.69 [0.39 – 1.21]) and GSvP (0.59 [0.31 – 1.12]) did not reach statistical significance.

Diet and exercise program

The effects of DEP on body weight, fat percentage, and BMI have been reported extensively elsewhere [23]. In short, 28% of the 203 women randomized to DEP were compliant to the intervention. Compliant women had a mean weight reduction of 1.4 ± 5.2 kg after 30 months versus 0.0 ± 6.7 kg in the control group. At 6 and 12 months, the number of participants fulfilling the predefined target of 5 kg or 5% weight reduction was significantly higher in the intervention group than in the control group (14% vs. 6% at 6 months, p = 0.01 and 17% vs. 10% at 12 months, p = 0.04). Eventually, 63 women (15%) met this target at 30 months.

PP analyses comparing those women compliant to DEP to those randomized to the DEP control group also showed a significant interaction with GSvP (p = 0.01). Incidence of knee OA was found in 19%, 13%, 9% and 23% of the knees of subjects randomized to the DEP control group with placebo and glucosamine, respectively and subjects compli-

ant to DEP with placebo and glucosamine, respectively. Accompanying ORs are given in Table 4.3.

Oral glucosamine sulphate versus placebo

During the follow-up period, a total of 291 Adverse Events (AEs) were reported by a total of 118 women, equally divided between glucosamine and placebo group (Chi^2 test: $p = 0.23$). All reported Serious AEs (26 by 25 women) were classified as not related to study drug and also equally divided between groups (Chi^2 test: $p = 0.26$). After study ending, 17% of the women in the placebo group and 15% of the women in the glucosamine group were convinced they had received glucosamine. The majority of all women (52% in the placebo group and 46% in the glucosamine group) were convinced they received placebo (Chi^2 test: $p = 0.24$). None of the involved researchers and none of the participants were unblinded during the trial. In total, 250 women were compliant to GSvP (66% in the placebo group, 57% in glucosamine group).

PP analyses showed no interaction between DEP and GSvP ($p = 0.17$). Incidence of knee OA occurred in 20% of the knees of the women compliant to the placebo and in 21% of the knees of women compliant to glucosamine (adjusted OR 0.99 [0.61 – 1.63]).

Secondary outcome measures

Secondary outcome measures are represented in Figures A4.1-A4.4 in the Appendix. There was only a statistically significant difference between the DEP intervention and control group on actual weight loss ($p = 0.04$). Detailed analyses showed a significant difference in weight loss at 6 months ($\beta = 1.79$, $p < 0.01$) and 12 months ($\beta = 1.39$, $p = 0.01$). Also in PP analyses, only the effect of DEP on actual weight loss was statistically significant in favour of the DEP intervention group ($p = 0.01$), with statistically significant differences in weight loss at 6 months ($\beta = 3.08$, $p < 0.01$), 12 months ($\beta = 2.86$, $p < 0.01$), 18 months ($\beta = 1.98$, $p = 0.02$), and 24 months ($\beta = 1.79$, $p = 0.04$).

Discussion

This study presents the first ever preventive randomized trial on knee OA worldwide. Given the medical and economic burden of the disease and all knowledge obtained in the numerous of studies on knee OA carried out in the last decades, evaluation of preventive interventions should be the next step. The diet and exercise program and the glucosamine sulphate intervention showed no significant main effects on the incidence of knee OA over the 2.5 years follow-up period. However, due to the unexpected significant interaction between both interventions, these analyses were slightly under-

powered. The fact that the interaction between the two interventions became stronger in subjects compliant to DEP indicates a true interaction between DEP and GSvP.

This preventive randomised trial focused on subjects with high risk of developing knee OA and used a combined outcome measure to make a trial in such a slowly progressing disease feasible over a relative short time period of 2.5 years. This combination of radiographic and clinical measures of knee OA into the primary outcome measure improves the ability to determine the preventive effects of the studied interventions [3], although one misses the detailed insight in the development of the disease. Explorative evaluation of the separate items confirmed the pattern found in the combined primary outcome measure, even within the scores of JSN of both individual blinded scorers. This suggests that the effects of DEP and GSvP in this trial were similar for the clinical and radiographic features of knee OA.

Although we found no significant main effects of DEP and GSvP on primary and secondary outcomes after 2.5 years, the statistical interaction of DEP with GSvP did show several interesting results. In the ITT analyses, the effect of glucosamine sulphate over placebo was opposite in both groups of DEP and vice versa. Where glucosamine sulphate reduced OA incidence numbers in the group not undergoing DEP (adjusted OR 0.59 [0.31 – 1.12]), OA incidence was increased in the glucosamine sulphate group within the DEP intervention group (adjusted OR 1.44 [0.83 – 2.48]). On the other hand, DEP reduced the incidence numbers within the placebo group (adjusted OR 0.69 [0.39 – 1.21]), but showed an increased OR within the glucosamine sulphate group (adjusted OR 1.63 [0.89 – 3.01]). Only in those subjects compliant to DEP, not GSvP, the effects were magnified (adjusted OR 0.35 [0.11 – 1.10] within placebo group and adjusted OR 2.17 [0.95 – 4.96] within the glucosamine sulphate group). Although tested in subjects with established knee OA, results from Messier et al.[29] might give some indication for the mechanism behind this interaction. Messier and co-workers found that after a 6 months exercise period, subjects randomized to a combination of glucosamine/chondroitin decreased in knee flexion strength, whereas subjects receiving placebo significantly improved their strength. Also balance was better in the placebo group after 6 months [29]. These results suggest that glucosamine might interfere with processes of repair and growth after physical exercise. On the other hand, a 12 week training program combined with glucosamine sulphate did not show a difference in knee extension strength over the placebo group in knee OA patients [30]. The more sensitive and explorative measures of the MRI and biomarkers, which are being assessed within the present study, might provide more detailed information on the underlying mechanism for the interaction between DEP and GSvP.

For implementation reasons, a very pragmatic design was chosen for DEP. Nevertheless, the intervention had a significant effect on the actual weight loss during the first year of

follow-up. Activity levels were higher in the DEP intervention group throughout the total follow-up period. However, due to large variation in activity levels within the groups, the difference did not reach statistical significance. Thus, despite the relatively low compliance figures, similar to other physical exercise and diet interventions in overweight and obese individuals [31], the current DEP succeeded in a low level change in lifestyle of the subjects randomized to the intervention group, also in the ITT population. Contrary to daily practice, the control group in the current trial formed a relatively active control group. Nearly 90% of all subjects stated to have a preference for the DEP intervention group at baseline. For ethical reasons, the DEP control group was not actively refrained from any interventions on weight loss. After 2.5 years, 18% of all women randomized to the DEP control group fulfilled the criterion of losing 5 kg or 5% of baseline body weight. Therefore, the effects of DEP found on incident knee OA may have been underestimated.

In conclusion, the primary analyses showed no significant main effects of DEP or GSvP on incidence of knee OA over 2.5 years. These analyses, however, were hampered by an unexpected significant interaction between the two interventions. The current trial provides many new insights in the possibilities for prevention of knee OA within a high-risk group of middle-aged, overweight women. The low dropout rate of 10% strengthens results of this first attempt to prevent OA in subject at high risk. The trends towards preventive effects of the two interventions separately and their interaction needs further elaboration. A longer follow-up period and more sensitive outcome measures (e.g. MRI data) will provide a better insight in the development of knee OA and in the exact preventive effects of the applied interventions and their interaction.

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CHAPTER 5

Effectiveness of a tailor made weight loss intervention in primary care

BC. De Vos, J. Runhaar, SMA. Bierma-Zeinstra

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Abstract

Background: Weight loss interventions have been studied extensively, but methodological limitations negatively affecting applicability in everyday clinical practice are a very common problem in these studies. Despite the fact that obesity is treated mostly in a primary care setting, studies that investigate weight loss interventions in a primary care setting are scarce. Our objective was to assess the effectiveness of a tailor made weight loss intervention in achieving a clinically significant weight loss in overweight (BMI ≥ 27 kg/m^2) women aged 50 – 60 years in a primary care setting.

Methods: As part of a randomised controlled trial on the effects of a tailor made weight loss intervention and oral glucosamine sulphate on the incidence of osteoarthritis of the knee in 407 overweight women aged 50 – 60 years, we analysed the effectiveness of the weight loss intervention in achieving clinically relevant weight loss.

Results: At baseline, the mean body weight for all participants was 88.7 ± 13.2 kg, and the mean BMI was 32.4 ± 4.3 kg/m^2. The percentage of participants that lost ≥ 5 kg or 5% of their baseline body weight was 14.8% versus 6.3% (p=0.012) at six months for the intervention group and the control group, respectively. At twelve months, this was 18.7% versus 14.9% (p=0.027). Mean weight gain at six months was -0.9 kg versus 0.9 kg (p<0.001) for the intervention group and the control group, respectively. At twelve months, this was -0.6 kg versus 0.6 kg (p=0.01). At 30 months of follow-up, no significant differences were found between both groups.

Conclusions: This weight loss intervention, which, at short notice, is easily applicable in everyday clinical practice, is effective in achieving clinically significant weight loss in overweight women aged 50 – 60 over a 12 month period. Long-term weight loss maintenance however, occurred only marginally. Magnitude of the effect is comparable to that achieved in many other, more intensive weight loss interventions.

Introduction

Numerous studies have investigated the health benefits of weight loss in obese individuals [1-3]. A systematic review of long-term weight loss interventions reported that, besides surgical interventions, dietary and lifestyle therapy as well as drug therapy have the potential to provide modest weight loss and may improve cardiovascular risk factors [4]. However, drop-out rates were as high as 31-64% and only two of the 44 eligible studies presented intention to treat results [1]. The other 42 studies based their conclusions on per protocol results, which lead to overestimation of the effects and hence, makes the results less applicable in everyday clinical practice [4]. Besides, because of high drop-out rates, the majority of the studies based their outcomes only on 'study-completers', or used methods such as 'last observation carried forward' or 'baseline observation carried forward' methods. This may overestimate the total weight loss because study completers may have lost more weight than participants who quit the intervention earlier [4]. Because of these limitations, these studies have shown that particular interventions, when completed, have the potential to result in clinically relevant weight loss, but have failed to investigate whether an intervention would be applicable in everyday clinical practice [4].

In this past year, there have been some trials published reporting on weight loss interventions in a primary care setting. A weight loss intervention study by Wadden et al. [5] for example, included counselling with pharmacotherapy, while the study by Appel et al. [6] tested an intervention which was delivered by care providers other than primary care providers. The latter solely played a supporting role.

The majority of weight loss trials conducted in the last few decades used a pre-defined scheme of dieting, exercise or psychological treatment to apply to all participants, regardless of their age, sex, baseline body mass index (BMI), etc. [7]. However, a systematic review reported that the most effective way to promote weight loss in large groups of overweight and obese individuals is to offer a 'tailor made' intervention with diet and exercise. This could reduce the high drop-out rates [8].

Motivational Interviewing, a method of consulting patients based on Self Determination Theory, claims to be effective especially in promoting long-term weight loss maintenance [9]. Motivational Interviewing is a technique developed to change people's behaviour by manipulating there intrinsic motivational patterns [10]. A systematic review clearly stated motivational interviewing as being superior in lowering BMI compared to traditional methods of consulting [10].

The purpose of the present study was to analyse whether a tailor made weight loss intervention with diet and exercise, based on motivational interviewing, would be effective in achieving ≥ 5 kg or 5% of baseline body weight in a group of overweight women in a primary care setting. Several studies found this amount of weight loss to

be associated with health benefits, including improvement of cardiovascular risk factors and reduced risk of incident diabetes and hypertension [1-3]. Douketis et al. reported that this amount of weight loss improves lipid levels and glycaemic and blood pressure control, especially in people with cardiovascular risk factors [4]. Our expectation was that by offering a tailor made intervention, instead of dictating the participants on the quantity and quality of their diet and exercises, our drop-out rates would be much lower than in comparable studies.

Methods

PROOF study

The intervention we studied was part of a randomised controlled trial that investigated the preventive effect of a weight reduction program and oral glucosamine sulphate versus placebo on the development of knee osteoarthritis, in a 2x2 factorial design in overweight women, called the PROOF Study (ISRCTN 42823086; Chapter 4) [11]. This trial was approved by the local Medical Ethical Committee of Erasmus University Rotterdam and all participants provided written informed consent. The PROOF Study was open labelled for the tailor made intervention to reduce weight, and double blinded for the intervention with crystalline glucosamine sulphate (1:1 block randomization within both interventions, using block size 20). For the present study, all data was derived from the complete dataset of the PROOF Study. Only the data concerning the tailor made intervention to reduce body weight was used in the present study.

Recruitment

A detailed description of the recruitment and measurements of the PROOF study can be found elsewhere (Chapter 4) [11]. In short, 50 general practitioners recruited participants, by sending an information letter to all women between 50 and 60 years registered at their practice. All interested women with a self-reported BMI ≥ 27 kg/m^2 received additional information by mail. Subsequently these women were checked for inclusion criteria by phone. Inclusion criteria were: female gender, age 50 to 60 years, overweight (BMI ≥ 27 kg/m^2), free of knee osteoarthritis according to the ACR criteria [12], free of contraindications to MRI, free of rheumatic diseases, and not using oral glucosamine during the past six months. Thereafter all eligible women were invited to the research centre for physical examination and X-rays as well as MRI scans of both knees. Exclusion criteria were: already consulted a physician, a physical therapist or an alternative health provider for knee pain possibly indicating osteoarthritis of the knee, presence of radiologic signs indicating knee osteoarthritis (Kellgren-Lawrence index of 2 or more),

not being able to communicate in the Dutch language, presence of severely disabling co-morbidity. Figure 5.1 shows the study selection process.

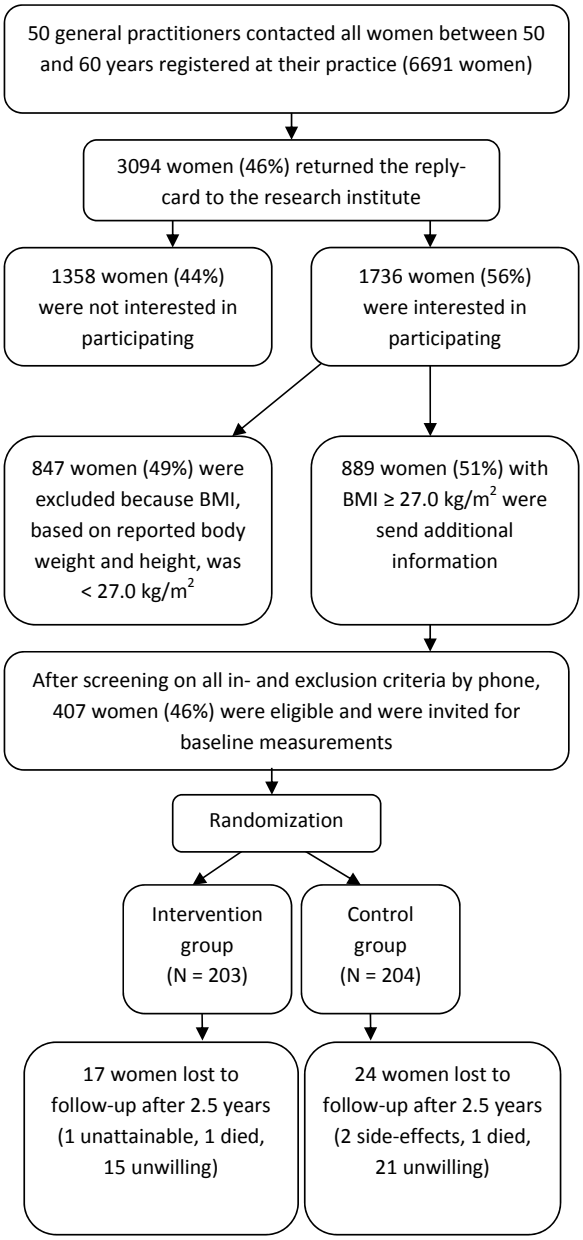

Figure 5.1. Study selection process

Intervention

The relevant intervention consists of an individual tailor made intervention to reduce weight, which has been constructed in cooperation with the Dutch Society of Dieticians. As said, literature suggests the focus of any weight loss intervention should be on changing food patterns and habits in physical activity. The Health Council of the Netherlands also emphasises the importance of these components [13].

To make the intervention easily applicable in everyday clinical practice, all participants were given the opportunity to visit a dietician and a physical therapist nearby their home address. All dieticians were trained in Motivational Interviewing [10]. At baseline, the participant discussed nutritional habits and physical activity patterns with a dietician. Based on the goal setting theory of Strecher [14] and the specific implement technique [15], they agreed on the intentions. Subsequently, the dietician composed the individual tailor made strategy to accomplish these goals. Primarily, a tailor made advice was given for a low fat or a low calorie diet, or both, as well as for physical activity. During the first month the participant had an appointment with the dietician once in every two weeks; during the consecutive period the frequency of appointments was determined in dialogue by the dietician and the participant. These appointments were used to evaluate the plan, and if indicated, to adjust the plan. The total duration of these sessions was limited to a total of four hours per year. No limit was set on the total period during which they were under treatment.

Besides, the participants in the intervention group were given the opportunity to participate in physical activity classes. In these classes (groups of 12-16 persons) they tried a broad range of different low-intensive sport activities under the supervision of a physical therapist, such as Nordic walking, volleyball, bowling, salsa dancing, tai chi, softball, belly dance, modern dance. The aim of these lessons was to regain pleasure in physical activity and to find an activity which they could maintain for themselves for long-term continuation. Twenty group activities, one lesson of one hour weekly, were spread over a period of half a year. Because participants in every group were recruited per general practice and lived in the same neighbourhood, continuation of activities together was stimulated in case they were interested. Both the dietician appointments and the physical activity lessons were free of cost to the participants in the intervention group.

The participants in the control group have not received this active (i.e. initiated by the research group) intervention to reduce body weight, but were free to undertake any actions to lose weight at their own initiative.

Physical examination

At baseline and after two and a half years of follow-up, physical examination was performed at the research centre to measure body weight, body height, blood pressure, abdominal circumference and skin folds. Fat percentage was calculated using the following formula: body fat percentage = (0.730 * BMI) + (0.548 * triceps skin fold) + (0.270 * age) – 5.9. According to Lean et al., this is the most reliable method of assessing body fat percentage based on simple anthropometric measurements in women [16]. Skin folds were measured using The Harpenden Skinfold Caliper HSK-BI. BMI was calculated as body weight in kilograms divided by the height in meters squared. Additionally, serum samples were taken to measure serum HbA1c and total cholesterol.

Questionnaire

At baseline, the participants filled out a questionnaire to record characteristics such as smoking status, educational level, co morbidity, menopausal status, quality of life, social participation, physical activity level and nutritional habits. Every sixth month the participant was visited by the research assistant to fill out a shorter questionnaire to determine compliance to the interventions, physical activity level, nutritional habits, co-interventions, medical consumption and quality of life. In addition, body weight was measured during these visits.

Quality of life was measured using the EQ-5D EuroQol questionnaire, which has been thoroughly validated [17]. Physical activity level was measured using the validated SQUASH questionnaire [18-19]. Intensity scores of Ainsworth were used to calculate the activity score of the participants [20-22]. To calculate the total activity score, each physical activity in Ainsworth's compendium received an intensity score ranging from 1 to 9 [18]. These intensity scores were based on the Metabolic Equivalent Tasks (MET's), which are the ratios of a person's metabolic rate while performing the activity and their metabolic rate while seated and resting [20-21]. Total activity scores were calculated by multiplying total minutes of activity per week and the intensity score. The sum of all activity scores formed the total score [19]. Nutritional habits were assessed with a validated questionnaire [23], which was extended to meet our study requirements.

Assessment of compliance to the intervention

Dieticians kept record of participant's body weight and gave them two scores each visit; one to indicate to what extent they had reached their set goals concerning physical activity, the other to indicate to what extent they had reached their set goals concerning nutritional habits. Physical therapists solely recorded presence of participants during the physical activity classes.

Statistical analyses

Analysis was performed using SPSS PASW statistics version 17.0 (SPSS Inc., Chicago, IL). Baseline characteristics were presented using descriptive statistics as mean ± standard deviation (SD). Body weight data was presented as mean ± standard error of the mean. The primary objective was to assess the number of participants that lost ≥ 5 kg or 5% of their baseline body weight. Secondary objectives were to evaluate differences between the intervention and the control group in fat percentage, BMI, quality of life, physical activity level and nutritional habits. All results presented are intention-to-treat results.

The relationship between assignment to the intervention group and chance of success, which was defined as losing ≥ 5 kg or 5% of baseline body weight, was calculated using Generalized Estimating Equations (GEE), taking into account the correlation of repeated measurements within one participant. This analysis is the most reliable, because it does not require imputation and, moreover, it does not take only the completers into account, but all measurements of the complete dataset. Furthermore, this analysis is widely recommended in literature [24-25]. All covariates, which included physical activity level, nutritional habits and quality of life, were tested for being mediators of the intervention effect using Sobel's test [26-27]. Also, following the recommendations by Kraemer et al. [28], all baseline characteristics were tested for being moderators of the intervention effect, using the GEE analysis.

Group differences at set times were analysed using 2-tailed independent t-tests for scale variables, and 2-tailed chi-squared tests for categorical variables. For categorical variables, significance was calculated with Fisher's exact test. For each outcome multiple linear or logistic regression models were conducted to identify what the intervention effect on each outcome was. Also, logistic regression was used to determine which variables were correlated with the primary outcome (≥ 5 kg or 5% of baseline body weight reduction). In all analyses, a 5% significance level for testing was used.

Since data were derived from a RCT on the preventive effects of a diet and exercise program on the development of knee osteoarthritis, the corresponding power calculation was done on incidence figures, rather than on weight loss. In retrospect, we calculated a power of more than 80% to detect a significant difference between both groups in losing ≥ 5 kg or 5% of their baseline body weight.

Results

Participants

Of the 6691 women who were contacted by their general practitioners, 3094 women (46%) returned the reply-card to the research institute, of which 1736 women (56% of

the repliers) were interested in participating. 847 women (49% of interested women) were excluded because calculated BMI, based on reported body weight and height, was below 27.0 kg/m^2. 889 women (51% of interested women) with BMI of 27.0 kg/m^2 or higher were sent additional study information. After screening on all inclusion criteria by phone, 407 women (46%) were eligible and were invited for baseline measurements and randomised to either the intervention or the control group. Of these participants, 70% were postmenopausal at baseline, 93% were of European or North-American

Table 5.1. Baseline characteristics

		Control group			Intervention group		
		Mean	Standard Deviation	N %	Mean	Standard Deviation	N %
Age, year		55.7	3.2		55.7	3.2	
Body weight, kg		89.2	13.6		88.2	12.9	
Body Mass Index, kg/m^2		32.5	4.5		32.2	4.1	
Fat %*		44	5.5		44	5.1	
Abdominal circumference, cm		106	10		105	9	
Approximate body weight 1 year ago, kg		87	15		86	15	
Approximate body weight around 40th year, kg		76	12		74	14	
Smoking status	Non-smoker			77%			87%
	Smoker			23%			13%
Education level	Low			35%			32%
	Mid-low			45%			51%
	Mid-high			17%			16%
	High			3%			2%
Co morbidity**				34%			35%
Premenopausal				29%			31%
Quality of Life (Dutch EuroQol EQ-5D) Range: 0-1		0.89	0.13		0.89	0.13	
Social participation***		9.00	2.18		9.10	2.06	
Ethnicity	European/North American			93%			94%
	South American			1%			1%
	African			1%			1%
	Asian			1%			2%
	Other			5%			2%
Physical activity (SQUASH score)		7094	3817		6525	3608	
Blood HbA1c, %		5.8	0.7		5.8	0.8	
Blood total cholesterol, mmol/L		6.1	1.2		6.0	1.1	
Snacks consumed per week****		10.0	0.8		9.4	0.8	

* Calculated with formula by Lean et al. [16]. ** Defined as ≥1 condition currently under treatment. *** Defined as hours per week spent on paid/voluntary/household work or studying. **** Defined as food consumed between or after main meals of the day, such as cookies, chips, chocolate, etc.

origin. Mean age was 55.7 (SD=3.2) and mean baseline BMI was 32.36 (SD=4.29). Table 5.1 shows all baseline characteristics. There were no significant differences between the intervention group and the control group.

Participation rates

Since no pre-defined scheme of dieting or exercising was presented, but instead participants decided together with the dietician on their diet, exercise pattern and goals, the participation rates varied widely. Of the 203 participants randomised to the intervention, 181(89.2%) went at least once to the dietician. 50.8% of the participants had 6 appointments or more. The mean period between the first and the last visit was 36.3 weeks (SD=31.4). 50.8% of the participants were less than half a year under treatment by a dietician, and 22.0% was under treatment for more than a year. Mean weight loss from first to last consult recorded by the dieticians was 1.89 kg (SD=3.93). Of these 203 participants, 79% attended at least one physical activity lesson. 57% of the participants attended 7 classes or more. Mean attended lessons were 8 (SD 6).

Weight loss

After randomisation, body weight was recorded at 6 months for 371 participants (91.1%), at 12 months for 368 participants (90.4%) and at 30 months for 361 participants (88.7%). At 6 months, mean change (± standard error (SE)) from baseline in body weight was 0.9 ± 0.3 kg in the control group, and -0.9 ± 0.3 kg in the intervention group ($p<0.001$). At 12 months, the mean body weight change was 0.6 ± 0.4 in the control group, and -0.6 ± 0.4 in the intervention group ($p=0.014$). At 18, 24 and at 30 months, there were no significant differences between both groups. Figure 5.2 shows all weight change data.

Primary objective

Table 5.2 shows the percentages of participants who lost body weight or retained their baseline body weight, and the percentages of participants who lost ≥ 5 kg or 5% of their baseline body weight. At 6 months, significantly more people in the intervention group lost weight or retained their baseline body weight (58.2% vs. 37.4%, $p<0.001$) and there was a higher percentage of people in the intervention group who lost ≥ 5 kg or 5% of their baseline body weight (14.8% vs. 6.3%, $p=0.012$). Also at 12 months, both the percentage of participants who lost weight or retained their baseline body weight (51.9% vs. 39.2%, $p=0.016$), and the percentage of participants who lost ≥ 5 kg or 5% of their baseline body weight (19.7% vs. 11.0%, $p=0.027$) was significantly higher in the intervention group. At 18, 24 and at 30 months, there were no significant differences for both outcomes. The overall intervention effect on the primary outcome of losing

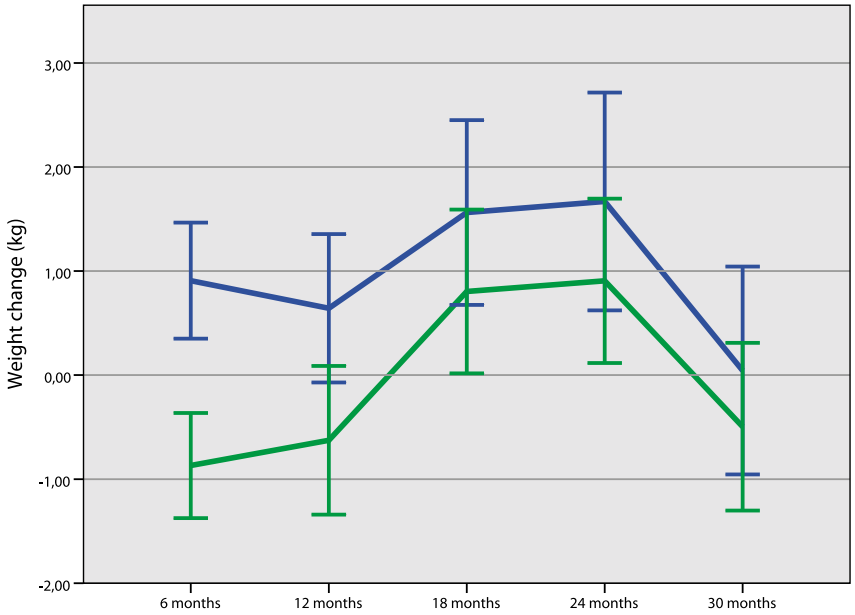

Figure 5.2. Mean body weight change (95% CI) compared to baseline body weight according to randomized groups (blue line: control group, green line: intervention group).

Table 5.2. Results of primary objective and figures on weight loss

Criterion	All	Intervention group	Control group	p-value
		no. of participants (%)		
≤ baseline body weight				
6 months	178/371 (48)	110/189 (58)	68/182 (37)	<0.001
1 year	168/368 (46)	97/187 (52)	71/181 (39)	0.02
2.5 year	169/361 (47)	95/184 (52)	74/177 (42)	0.07
Lost ≥ 5 kg or 5% of baseline body weight				
6 months	40/371 (10.8)	28/189 (14.8)	12/182 (6.3)	0.012
1 year	55/368 (14.9)	35/187 (18.7)	20/181 (11.0)	0.027
2.5 year	63/361 (17.5)	27/184 (14.7)	36/177 (20.3)	0.10

Figures presented as: number of participants who fulfilled the criterion/total participants at that time (percentage of total). Exact significance calculated with Chi-squared tests and Fisher's exact test.

≥ 5 kg or 5% of baseline body weight, taking into account all measurements, was not significant (OR 1.12, 95% CI 0.70-1.80).

Secondary objectives

Secondary objectives were to evaluate differences between the intervention and the control group in fat percentage, BMI, quality of life, physical activity level, the percentage of participants who measure up to the Dutch Physical Activity Guideline [29] and nutritional habits.

In the overall study population, fat percentage declined from 43.5% to 42.6% respectively (p<0.001) from baseline to 2.5 years of follow-up. There was no significant difference between both groups in decline in fat percentage. For BMI, the same pattern is found as in body weight change; at 6 months, BMI change in the intervention group was -0.3 against 0.3 in the control group (p<0.001) and at 12 months, BMI change was -0.2 against 0.3, respectively (p=0.007). With logistic regression analysis, we identified baseline BMI to be a positive predictor of the chance of losing ≥ 5 kg or 5% of baseline body weight (OR 1.08; 95% CI 1.02 – 1.15), although no interaction of this effect and the intervention effect was found. There were no significant differences between both groups in quality of life at any of the time points. At 6 months the change in physical activity compared to baseline, measured with the SQUASH questionnaire, was significantly higher in the intervention group. Change of score was 117.3 (1.8% of baseline score) in the intervention group against -682.7 (9.6% of baseline score) in the control group (p=0.03). The percentage of participants who complied with the Dutch Physical Activity Guideline, was higher at 6 months in the intervention group (58.5% against 46.1% in the control group, p=0.019); not at 12 and 30 months. Regarding nutritional habits, solely the amount of consumed snacks differed between the two groups. Snacks were

Table 5.3. Differences between both groups at set times for primary and secondary outcome measures.

	6 months	12 months	2.5 years
Percentage of participants losing ≥ 5 kg or 5% of baseline body weight	8.5%*	7.7%	-5.6%
Body weight change, kg	-1.8***	-1.3*	-0.5
Change in fat percentage	n.m.	n.m.	0.2
Change in body mass index, kg/m^2	-0.1***	-0.2**	-0.4
Change in quality of life, Dutch EuroQol EQ-5D	n.m.	n.m.	0.2%
Change in physical activity, SQUASH score	800*	600	392
Participants that comply to Dutch Physical Activity Guideline	12%*	-2%	-0.3%
Snacks eaten per week, no.	-1.1*	-0.5	-0.2

Figures represent the difference between the intervention group and the control group for the given measures at the indicated time points (compared to baseline). *P<0.05. **P<0.01. ***P<0.001. n.m.: not measured.

defined as food, other than fruit, consumed between or after the three main meals of the day, such as cookies, chips, chocolate, etc. The amount of snacks consumed at 6 months was significantly lower in the intervention group. Participants in the intervention group consumed on average 7.0 snacks per week, against 8.1 in the control group (p=0.034). The other secondary objective measurements at other measurement times in the follow-up showed no significant differences between both groups. Change in serum HbA1c and total cholesterol also showed no significant difference between both groups. No significant differences were found at 2.5 years of follow-up. Table 5.3 summarizes the results of primary and secondary objectives.

None of the covariates were identified as being mediators of the intervention effect. In addition, the GEE analysis showed that none of the baseline characteristics were identified as being moderators of the intervention effect on weight loss. Also, it was found that after controlling for various covariates, the odds of losing 5 kg or 5% of baseline weight was not affected by any of the covariates, such as age, smoking status, educational level or ethnicity.

Discussion

In this effectiveness study, a tailor made intervention to reduce body weight was proven to be effective on short-term. After 6 months, the percentage of participants who lost ≥ 5 kg or 5% or more of their baseline body weight was twice as large in the intervention group compared to the control group. This amount of weight loss has been associated with improvement in cardiovascular risk factors by numerous studies [1-4]. In addition, mean weight loss, reduction in BMI, increase in physical activity and reduction in snacks consumed per week was significantly greater in the intervention group at 6 months. At 12 months, the difference between both groups in the primary objective slightly declined. Still, the weight loss and reduction in BMI were significantly greater in the intervention group at this point. The intervention proved to have no long term effect; after 2.5 years of follow-up, no significant differences between both groups were found.

In contrast to other weight loss intervention studies, we did not dictate the participants how and to what extent they should exercise and diet. Instead, we offered them the possibility of attending physical activity lessons and dietician appointments, in order to reach, in dialogue, an individual tailor made scheme [4]. This approach was chosen to minimize the drop-out rates, in order to obtain results which are more applicable to everyday clinical practice than results from many other weight loss intervention studies [4]. Our drop-out rates of 9.4% at one year of follow-up and 11.1% at 2.5 years of follow-up were considerably lower than the mean drop-out rates of many comparable

intervention studies [4]. It is a very pragmatic approach, much more accessible and easier to prescribe to large groups than most weight loss interventions with stricter diet and exercise schemes [4]. Moreover, this approach was recommended in literature as being superior to more traditional methods [8]. The inevitable consequence of this method is that the duration of the intervention itself, the dietician appointments and physical activity lessons, is subject to great variation. In our study, we have seen that only 22% of the participants were under treatment by a dietician for more than a year. Furthermore, 51% of the participants quit seeing a dietician within half a year from baseline. Results in primary and secondary objectives reflected this pattern; the largest intervention effect is seen at 6 months of follow-up, at 12 months of follow-up there is still a small intervention effect observable, but after this intervention effects are levelled out. Weight loss only seems to occur during the intervention, despite the fact this intervention was designed to promote long-term weight loss maintenance.

One of the reasons that may have caused underestimation of the intervention effect is the fact that in our control group also a substantial amount of weight loss has occurred. This could have been caused by the recruiting process. Since the participants were recruited for participation in the PROOF Study, the participants who were randomised to the control group had already received information regarding the increased risk of knee arthritis, due to their overweight. This information could have motivated a substantial proportion of the people randomised to the control group to lose weight at their own initiative. Another explanation as to why weight loss maintenance has occurred in such small rates is the limitation imposed on dieting by insurance companies. Just four hours per year was reimbursed. Participants who wished to visit the dietician for more than four hours in one year, had to pay for these visits themselves. Also, in this intervention the participants were offered a maximum of 20 physical activity lessons, assuming this would be enough to stimulate the participants to continue physical activities themselves after seizure of the lessons. A final factor that could have contributed to an underestimation of the intervention effect is the mean baseline body weight and BMI of our participants. We have identified baseline BMI to be a positive predictor of the chance of losing ≥ 5 kg or 5% of baseline body weight. The higher the baseline BMI is, the higher the chance of success is, an effect also found in many other studies [30]. In comparison to other weight loss studies, the baseline BMI and baseline body weight of our participants is relatively low [4].

Very few trials were designed to test the effectiveness of weight loss interventions, rather than the efficacy [4]. The facilities used in the present trial are already available in everyday clinical practice. Besides, few trials were conducted in a primary care setting [31]. Moreover, most studies dictated a very restrictive diet and exercise scheme, whereas our study let the participants decide on their scheme themselves [4]. Nevertheless, the

amount of weight loss occurred in the first year of follow-up in our pragmatic weight reduction intervention was similar to the amount of weight loss achieved in many efficacy studies [4].

This trial has several limitations. Firstly, the participants got the opportunity to attend only 20 exercise lessons for free. Secondly, due to the inclusion criteria of the PROOF study, the results are only applicable to women aged 50 – 60, without knee complaints. Thirdly, the well-established relationship between weight loss and improvement of cardiovascular risk factors was not confirmed in our study. Literature suggests a follow-up time of at least four years to examine any effect on these factors [4]. Therefore effects might be found, when prolonging follow-up. The fact that both the dietician appointments and the physical activity lessons were free of cost to the participants in the intervention group could have caused an overestimation of the intervention effect. However, during the trial, insurance covered the costs for the dietician appointments, also for the participants in the control group, in case they decided to visit a dietician on their own initiative.

Since the objective of this study was not to show superiority of our intervention to traditional predefined interventions, but to assess the effectiveness of the intervention in itself, we did not compare our tailor made weight loss intervention to a traditional pre-defined intervention. Therefore, from this study, it cannot be determined whether this intervention is more effective in achieving clinically significant weight loss than a traditional intervention.

Several strengths of this trial are the low drop-out rates, the design which makes this intervention easily applicable in everyday clinical practice, the intention-to-treat data, which make a much more valid estimate of the intervention effect in everyday clinical practice than per protocol analyses and, finally, our design including motivational interviewing as a basis for promoting adherence, as has been recommended [8,30].

In conclusion, despite the fact that the diet and exercise schemes in our study are less restrictive than in most weight loss interventions, our tailor made intervention to reduce body weight is effective to induce clinically significant weight loss in one year in an amount which is comparable to that achieved in most other weight loss trials [4]. This effect is not overestimated, since our drop-out rates were relatively low, and we conducted an intention-to-treat analysis. Since the facilities for this intervention are already accessible and it is easy to prescribe to large groups, this intervention could be a realistic option to implement in primary care. In future research, long-term weight loss maintenance, which has occurred marginally in our study, might be achieved by prolonging the intervention or follow-up time, offering more physical activity lessons and dieting consults, and by designing a more representative control group. Also, the use of electronically delivered interventions, such as internet and telephone counselling could help to increase participation rates [32]. Additional studies are needed to provide

general practitioners with an effective tool to achieve especially long-term weight loss maintenance in overweight women.

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CHAPTER 6

The effect of substantial weight loss on incident knee OA in overweight and obese women

J. Runhaar, M. van Middelkoop, M. Reijman, D. Vroegindeweij, EH. Oei, SMA. Bierma-Zeinstra

Abstract

Background: The present study evaluates the effect of a clinically relevant weight loss on the incidence of knee osteoarthritis (OA) in middle-aged, overweight and obese women, without clinical and radiological knee OA at baseline.

Methods: A total of 353 women (87%) with follow-up data available were selected from the PROOF study (ISRCTN 42823086). All radiographs were scored for K&L grades and minimal joint space width was digitally measured in the medial and lateral tibiofemoral compartment. Incidence of knee OA was compared between women that reached the weight loss target of 5 kg or 5% of body weight after 30 months and those that did not reach this target. The predefined primary outcome measure was the incidence of knee OA, defined as onset of K&L ≥ 2 or the onset of clinical knee OA (according to the ACR criteria), or joint space narrowing (JSN) ≥ 1.0 mm in the medial or lateral compartment. Using Generalized Estimating Equations, incidence of knee OA according to the primary outcome, and for all items separately, was compared between both groups (adjusted for randomized groups of the initial trial, K&L grade and BMI at baseline, and a history of knee injury).

Results: The weight loss group had a significant lower incidence of knee OA according to the primary outcome measure (15% vs. 20%; OR 0.5, 95% CI 0.3 – 0.9) and for incidence of K&L ≥ 2 (3% vs. 6%; OR 0.3, 95% CI: 0.1 – 0.9). Moreover, the weight loss also positively affected several health measures. There was no significant effect of weight loss on incidence of clinical OA according to the ACR criteria (5% vs. 7%; OR 0.4, 95% CI 0.1 – 1.3) or on either medial (5% vs. 6%; OR 0.7, 95% CI 0.3 – 1.7) or lateral JSN (6% vs. 7%; OR 0.7, 95% CI 0.3 – 1.7).

Conclusions: A reduction ≥ 5 kg or 5% of body weight over a 30 month period reduces the risk for the onset of radiographic knee OA in middle-aged, overweight and obese women. Due to the slow progress of the disease, a longer follow-up period will be necessary before the number of prevented cases of knee OA by substantial weight loss becomes clinically relevant.

Introduction

The worldwide prevalence of obesity nearly doubled between 1980 and 2008 [1]. According to the most recent estimations by the World Health Organization, 35% of all adults are overweight (BMI ≥ 25 kg/m^2) and more than 12% is obese (BMI ≥ 30 kg/m^2) [1]. A high BMI is a strong risk factor for the onset of knee osteoarthritis (OA) [2-3] and has been associated with the incidence of both clinical [4-5] and structural features [6-10] of knee OA. Given the high medical costs, morbidity and disability associated with knee OA, there is an increasing need for preventive measures.

In trials among subjects with and without established knee OA, weight loss was shown to have advantageous structure modifying, systemic and clinical effects [11-14]. In a systematic review on the effects of weight loss on knee OA patients, a weight loss of at least 5% body weight was indicated for symptomatic relief [15]. Losing ≥ 5 kg or 5% body weight has also been indicated as minimal weight loss for a positive and clinically relevant effect on the cardiovascular risk profile, including significant reduction of blood pressure and improved glucose tolerance [16]. In subjects without knee OA but with overweight or obesity, and hence at high risk for developing knee OA, the preventive effect of such a clinically relevant weight reduction has never been studied. In the Framingham Study it has been estimated that substantial weight loss (± 5 kg) could reduce the onset of knee OA in overweight and obese subjects [17-18].

Recently, the first ever preventive trial in OA research worldwide, the PROOF study (PRevention of knee Osteoarthritis in Overweight Females; Chapter 4) [19], was undertaken. In this randomized clinical trial among middle-aged women with a BMI ≥ 27 kg/m^2 without knee OA at baseline, the effects of a diet and exercise program on incidence of knee OA over 2.5 years was studied. The diet and exercise program did show favourable effects on body weight figures in the intervention group during the first year of the intervention and indications of a preventive effect among subjects compliant to the intervention were found (Chapter 4) [19]. The objective of the diet and exercise intervention was a structural weight reduction of 5 kg or 5% of baseline body weight.

The primary objective of the present study is to evaluate the effects of a clinically relevant reduction in body weight (≥ 5 kg or 5%), irrespective of the original interventions, on the incidence of clinical and radiological knee OA after 2.5 years in middle-aged overweight and obese women.

Methods

For this study we used data from the PROOF study (ISRCTN 42823086). A full description of the study protocol can be found elsewhere (Chapter 4) [19]. In short, this 2.5 year follow-up study aimed to evaluate the preventive effect of a diet and exercise program and oral glucosamine sulphate (double-blind, placebo controlled) on the onset of knee OA in a 2x2 factorial design. Study protocol was approved by the Medical Ethical Committee of Erasmus MC.

Fifty general practitioners in the area of Rotterdam, the Netherlands, contacted all women aged between 50 and 60 years registered at their practice. All women that returned the reply-card, reported a BMI ≥ 27 kg/m^2, and were interested in participation, were sent additional information. One week later, inclusion criteria were screened by phone. Inclusion criteria were: age between 50 and 60 years, BMI ≥ 27 kg/m^2, no knee OA according to the ACR criteria (clinical + radiographic) [20], no contra-indications for MRI, no rheumatic diseases, not using a walking aid, not under treatment for knee complaints, mastering the Dutch language, and not using oral glucosamine during the past 6 months. All women eligible and willing to participate were invited to visit the research institute for informed consent procedure and baseline measurements.

At baseline, body weight and height, waist circumference, and blood pressure were measured. Skin folds of the triceps were measured and used to calculate fat percentage using the formula by Lean et al [21], that was defined as the most reliable method based on simple anthropometric measurements in women (fat percentage = [0.73xBMI] + [0.548*triceps skin fold] + [0.27xage] - 5.9). A blood sample was taken to assess total blood cholesterol and HbA1c concentration and Heberden's nodes on both hands were assessed. A standardized semi-flexed PA radiograph of both knees was taken according to the MTP protocol [22]. All subjects filled in a questionnaire that included questions on knee complaints, number of days with knee pain, past knee injuries, and postmenopausal status. All measurements were repeated after 2.5 years of follow-up.

All tibiofemoral compartments of all knees were scored for knee OA by a researcher blinded for clinical outcomes (baseline and follow-up images at once with known sequence), using Kellgren & Lawrence (K&L) criteria [23]. Minimal joint space width was measured digitally on each radiograph in each tibiofemoral compartment by two blinded researchers independently, according to the method of Lequence [24]. Scores with a difference between both readers ≥ 2.0 mm were re-evaluated by both readers at a consensus meeting. Joint space narrowing (JSN) was calculated for each tibiofemoral compartment by substracting the mean score of both assessors at baseline from the mean score at follow-up.

For the analyses, all subjects with the primary outcome measure and follow-up data on body weight available were selected. Baseline characteristics were tested for significant difference between WL and N-WL group using independent t-test (linear measures) and Chi^2 test (dichotomous measures). Using Generalized Estimating Equations (GEE), which takes into account the association between knees within subjects, incidence of knee OA in subjects that reached the weight loss (WL) target of 5 kg or 5% body weight reduction at 2.5 years was compared to subjects that did not fulfil the target (N-WL). The predefined primary outcome measure was the incidence of knee OA, defined as incidence of either K&L ≥ 2 or ACR criteria or JSN ≥1.0 mm in the medial or lateral tibiofemoral compartment. Additionally, differences between WL and N-WL were also tested for the separate items of the primary outcome measure. All GEE analyses were adjusted for the randomized groups of the initial PROOF study, K&L grade at baseline (0 vs. ≥ 1) ; since it was shown to be related to the incidence of knee OA (Chapter 4) [19], and those factors that were significantly different between WL and N-WL groups at baseline. Results from these analyses were presented in odds ratios (ORs) with 95% confidence intervals (CI). Baseline differences between WL and N-WL groups were tested using Student's t-tests for continuous variables and Pearson Chi-square test for categorical variables. To evaluate the magnitude of the changes in clinical outcomes after a weight reduction of 5 kg or 5% body weight, changes over the 2.5 year follow-up period on total cholesterol, HbA1c level, fat percentage, waist circumference and blood pressure between WL and N-WL were assessed using Student's t-tests. All statistical analyses were performed using performed using SPSS 20.0 (Chicago, IL) with a p-value < 0.05 regarded as statistically significant.

Results

After 2.5 years, the primary outcome measure and follow-up data on body weight was available for 353 women (87 %). From these women, 61 subjects (17%) fulfilled the weight loss target of 5 kg or 5% body weight. Baseline characteristics of both groups are presented in Table 6.1. At baseline, the mean BMI ($p = 0.01$) and the number of knees with an injury in the past ($p = 0.01$) were significantly higher in the WL group. Hence, the analyses were additionally adjusted for these variables. The weight change in the WL group over the 2.5 years of follow-up was -9.9 ± 5.7 kg on average, ranging from -4.2 kg to -24.7 kg. In the N-WL group, subjects gained 1.8 ± 4.0 kg on average, ranging from -4.8 to +21.2 kg. Mean change in BMI was -3.6 kg/m^2 in the WL group and +0.7 kg/m^2 in the N-WL group.

Table 6.1. Baseline characteristics (mean ± st.dev.).

	Non weight loss group	Weight loss group	p-values
N – subjects	292	61	
Age (yr.)	55.8 ± 3.2	55.5 ± 3.2	0.42
BMI (kg/m^2)	32.0 ± 4.1	33.4 ± 4.3	<0.01
Postmenopausal status (yes)	69%	73%	0.33
Heberden's nodes (in ≥ 1 finger)	28%	25%	0.58
Assigned to diet and exercise group*	53%	43%	0.04
Assigned to glucosamine group*	52%	44%	0.14
N – knees	584	122	
K&L grade 0	52%	43%	0.11
K&L grade ≥ 1	48%	57%	
History of knee injury (yes)	12%	21%	0.01
Mild OA symptoms (yes)	31%	33%	0.75
Varus alignment (yes)	39%	43%	0.36

*Randomized groups in the original PROOF study.

Table 6.2. Incidence of knee OA for weight loss and non-weight loss groups.

Outcome	Group	Incidence	Odds Ratio**	95 % CI
Knee OA*	WL group	18/122 (15%)	0.50	0.27 – 0.91
(primary outcome measure)	N-WL group	117/584 (20%)	1	
K&L ≥ 2	WL group	3/118 (3%)	0.28	0.09 – 0.89
	N-WL group	33/545 (6 %)	1	
ACR criteria	WL group	6/122 (5%)	0.39	0.09 – 1.30
	N-WL group	41/584 (7 %)	1	
Medial JSN	WL group	6/122 (5%)	0.65	0.26 – 1.67
	N-WL group	34/583 (6%)	1	
Lateral JSN	WL group	7/122 (6%)	0.73	0.32 – 1.68
	N-WL group	40/583 (7%)	1	

WL group: weight loss group (≥ 5 kg or 5% weight loss). N-WL group: non weight loss group (<5 kg or 5% weight loss). K&L: Kellgren & Lawrence criteria. JSN: joint space narrowing (≥1.0 mm). *Defined as incidence of K&L ≥ 2 or the ACR criteria or JSN ≥1.0 mm. **Analyses adjusted for randomized groups of PROOF study, K&L grade and BMI at baseline, and past injury. N-WL group served as reference group.

Table 6.3. Baseline and 2.5 year follow-up values for several health measures (mean ± st.dev).

Health measure	Group	Baseline	Follow-up	Mean difference	p-value
HbA1c (mmol/mol)	WL group	40.4 ± 9.2	39.4 ± 8.3	-1.4 ± 3.6	0.03
	N-WL group	39.5 ± 8.6	39.8 ± 7.3	0.4 ± 6.1	
Total cholesterol (mmol/L)	WL group	6.0 ± 1.2	5.9 ± 1.4	-0.0 ± 1.5	0.73
	N-WL group	6.1 ± 1.1	5.9 ± 1.1	-0.1 ± 0.9	
Fat percentage	WL group	44.6 ± 5.2	39.9 ± 4.7	-4.7 ± 3.5	<0.01
	N-WL group	43.2 ± 4.9	43.1 ± 4.6	-0.1 ± 3.4	
Waist circumference (cm)	WL group	108 ± 10	101 ± 11	-7.3 ± 6.7	<0.01
	N-WL group	105 ± 9	107 ± 10	1.5 ± 5.5	
Blood pressure (systolic)	WL group	146 ± 24	141 ± 20	-5.3 ± 23	0.04
	N-WL group	146 ± 21	146 ± 21	0.2 ± 18	
Blood pressure (diastolic)	WL group	95 ± 11	87 ± 11	-7.9 ± 11	<0.01
	N-WL group	93 ± 12	91 ± 12	-2.8 ± 10	

WL: weight loss. N-WL: non weight loss. P-values are significance level of differences in mean delta's between both groups.

Incidence figures of knee OA according to the primary outcome and the separate items and corresponding ORs for the WL group relative to the N-WL group are presented in Table 6.2. Incidence according to the primary outcome measure was 20% in N-WL and 15% in the WL group (OR 0.50; 95% CI 0.27 – 0.91). Also the difference in incidence of K& L ≥ 2 between N-WL (6%) and the WL-group (3%) showed to be statistically significant (OR 0.28; 95% CI 0.09 – 0.89).

Subjects in the WL group had a significant reduction of HbA1c level, fat percentage, waist circumference and systolic and diastolic blood pressure over the 2.5 year follow-up compared to subjects in the N-WL group (see Table 6.3).

Discussion

For the first time, the true preventive effect of weight reduction on incident knee OA in a high risk group of middle-aged women with a BMI ≥ 27 kg/m^2 has been studied. The present study shows that a clinically relevant weight reduction of 5 kg or 5% body weight or more leads to significantly less incident cases of knee OA in overweight and obese women.

The PROOF study used a combined outcome measure of radiographic and clinical knee OA features in order to make a preventive randomized trial feasible over a relative short follow-up time (Chapter 4) [19]. In the N-WL group, 6% of all knees had incident radiographic knee OA (K&L ≥ 2) over the follow-up period. This annual incidence of 2.4% is

at the high end of the range found in population based cohorts using the same criterion, such as the Framingham Study (2% in women) [25], the Rotterdam Study (1.4% in men and women with a BMI > 27.5 kg/m^2), the Chingford Women's Study (2.3% in women aged 45-64) [26], and the Road Study (3.6% in women aged 50-59) [27]. Only the latter reported higher incidence numbers than in our study, but these were calculated on a subject level rather than knee level. On a subject level, an annual incidence of 4% was found in the N-WL group. Incidence of clinical knee OA (clinical + radiographic) found in the present study (2.8% in N-WL group) was higher than numbers reported in other studies (1% in women of the Framingham Study [25] and 0.3% in middle-aged women [28]). This might be explained by the fact that our study was conducted in overweight and obese subjects, who are at higher risk for the onset of knee OA than normal weight individuals [2-3].

There is an obvious overlap between incidence of JSN and incidence of K&L ≥ 2, given the fact that JSN is part of the definition of K&L ≥ 2. Nevertheless, we did not find a similar association between weight loss and incident JSN like we found for the incidence of K&L ≥ 2. In additional, K&L ≥ 2 requires definite osteophytes in the tibiofemoral joint. Previously, surplus fat mass has been linked to osteophyte formation, possibly through circulating leptin levels [29]. Since circulating leptin level decrease after weight loss [29], it could be supposed that a clinically relevant weight loss would lead to less osteophyte formation. This hypothesis is supported by our results. None of the knees of the women that reached clinically relevant weight loss showed incidence of a definite osteophyte, versus 3 % of all knees of the women that did not reach this amount of weight loss ($p < 0.05$). Less osteophyte formation could explain why we did find an effect of weight loss on incidence of K&L ≥ 2, which was not found for JSN.

At baseline, the WL group had a significantly higher BMI and reported a higher number of knees with a history of knee injury. The first was to be expected since a high BMI is a predictor for greater weight loss [30-31]. Probably, the higher prevalence of knees with a history of injury in the WL group was also linked through BMI; baseline BMI was significantly higher in subjects with a previously injured knee than in subjects without and a history of injury showed to have a non-significant effect on all outcome measures when adjusted for BMI at baseline (data not shown). Perhaps the former injury led to a less active lifestyle and hence, a higher body weight.

Besides effects on the onset of knee OA, the substantial weight loss also positively affected several health measures, such as blood glucose level, fat percentage, waist circumference and blood pressure. Positive alterations in these features have been linked to lower risk of diabetes mellitus type 2, cardiovascular morbidity and mortality [32]. However, the magnitude of the changes found was not high enough to reduce the 10-year risk of fatal cardiovascular disease [32]. Maintenance of the body weight in the WL

group over a prolonged period will possibly lead to greater reductions in these health measures.

In conclusion, a reduction ≥ 5 kg or 5% of body weight over a 30 month period reduces the risk for the onset of (radiographic) knee OA in middle-aged, overweight and obese women. Also, several health measures were positively altered after this substantial weight loss. Due to the slow progress of the disease, a longer follow-up period will be necessary before the number of prevented cases of knee OA by substantial weight loss becomes clinically relevant.

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CHAPTER 7

The effect of prolonged glucosamine usage on HbA1c-levels in overweight and obese women

J. Runhaar, D. Damen, M. van Middelkoop, SMA. Bierma-Zeinstra

Abstract

Background: In a recent systematic review, negative effects of prolonged glucosamine usage on glucose metabolism were more likely among subjects with impaired insulin resistance or glucose tolerance. Despite this, glucosamine is recommended for the management of osteoarthritis (OA) in international guidelines and is freely available over the counter. The objective of the present study was to evaluate the effect of a 2.5 years, placebo controlled intervention with oral crystalline glucosamine sulphate on HbA1c levels in middle-aged women with a BMI ≥ 27 and therefore at increased risk for impaired glucose tolerance.

Methods: Data from the PROOF study were used. In total, 407 women between 50 and 60 years, with a BMI ≥ 27 kg/m^2, without clinical and radiographic knee OA at baseline were randomized over oral crystalline glucosamine sulphate or placebo. At baseline, 1 year, and 2.5 years, HbA1c level was determined in all subjects. Using restricted maximum likelihood methods, the effect of glucosamine on HbA1c level throughout the follow-up period was determined in all subjects. Thereafter, analyses were rerun for subjects with and without elevated HbA1c level (≥ 42 mmol/mol) at baseline. Finally, the risk of attaining an elevated level of HbA1c after 2.5 years was determined.

Results: Only 10.1% of the subjects were lost to follow-up after 2.5 years. The glucosamine intervention had a non-significant effect on mean HbA1c level over 2.5 years, when analysed among all subjects ($p = 0.94$), and in subjects with a normal ($p = 0.60$) or elevated ($p = 0.82$) HbA1c level at baseline. However, compared to placebo, subjects randomized to glucosamine sulphate had an odds ratio of 2.81 (1.12 – 7.04) for attaining an elevated HbA1c level at follow-up.

Conclusions: A 2.5 year oral glucosamine sulphate intervention did not affect mean HbA1c levels in overweight and obese females, but did lead to significant more women being at 'high risk for developing diabetes'.

Introduction

Despite limited and conflicting evidence, oral glucosamine is a widely used treatment for osteoarthritis (OA). Very likely, two factors that stimulate the use of glucosamine are the recommendations for glucosamine use for the management of OA in international guidelines [1-2] and the safety over placebo as reported in several clinical trials [3-4]. However, there is some evidence that prolonged use of glucosamine might negatively affect the glucose metabolism, especially among subjects with impaired glucose tolerance [5-6]. Since one of the greatest risk factors for OA, a high body mass index (BMI), is also linked to impaired glucose tolerance [7], studies on the effects of glucosamine use on glucose metabolism in subjects with impaired glucose tolerance have been undertaken. In a recent systematic review, Dostrovsky and co-workers [5] showed that indeed studies that included subjects with impaired insulin resistance or glucose tolerance were more likely to detect an effect of glucosamine on glucose metabolism than those excluding these subjects. However, they conclude that the included studies were small, of short duration and had a large heterogeneity. Unfortunately, most recent large clinical trials could not be included in the systematic review since most did not report on measures of glucose metabolism [5].

In the recently completed PROOF study on the preventive effects of a diet and exercise program and of oral glucosamine sulphate on knee OA (Chapter 4) [8], 407 middle-aged women with a BMI ≥ 27 kg/m^2 were randomized over a daily dosage of 1500 mg of either crystalline glucosamine sulphate or placebo, for a 2.5 year follow-up period. For inclusion, subjects were not screened on glucose tolerance, but glucose metabolism was measured using haemoglobin A1c (HbA1c) levels; making the evaluation of prolonged glucosamine usage on glucose metabolism in subject with and without impaired glucose tolerance possible.

Elevated HbA1c levels reflect long-term hyperglycaemia over the preceding two to three months [9-10]. For non-diabetes individuals with increased BMI, normal HbA1c level is set as < 42 mmol/mol [10]. In clinical trials, HbA1c is the most common measure of glycaemic control [11] and quite recently, elevated HbA1c levels (≥ 42 mmol/mol) were set as diagnostic criterion for diabetes [12].

The first objective of the present study was to evaluate the effect of a 2.5 year placebo controlled intervention with glucosamine sulphate on HbA1c levels in middle-aged women with a BMI ≥ 27 kg/m^2 and therefore at increased risk for impaired glucose tolerance. Secondly, the intervention effect on HbA1c level within subjects with and those without elevated HbA1c level at baseline was determined. Finally, the risk of attaining an elevated level of HbA1c after 2.5 years for subjects randomized to glucosamine sulphate was determined.

Methods

The PROOF study (ISRCTN 42823086) was designed to evaluate the effects of a diet & exercise program and of oral glucosamine sulphate in 2x2 factorial design on the incidence of knee OA in middle-aged overweight females, free of radiographic and clinical knee OA at baseline. A full description of the trial design can be found elsewhere (Chapter 4) [8]. In short, 50 general practitioners in the area of Rotterdam, the Netherlands, contacted all women between 50 and 60 years of age registered at their practice. Out of 6.691 women contacted, a total of 407 were interested, fulfilled the inclusion criteria and were randomized. Study protocol was approved by the Medical Ethical Committee of the Erasmus MC.

At the baseline visit, all subjects signed the informed consent. Body weight, body height and waist circumference were measured, a blood sample was drawn for analysis of HbA1c level (mmol/mol), and physical activity was scored by the subjects by filling in the SQUASH questionnaire [13]. After the baseline measurements, all subjects were randomized over either placebo or crystalline glucosamine sulphate (1:1 at subject level, using blocked randomization with block size 20). Subjects received study drugs for the first 7 months and were instructed to solve and consume one sachet (1500 mg) every day. After 6 months, all subjects were home visited to renew the study drug. At the home visit after 12 months, a new blood sample was drawn for HbA1c determination. After 2.5 years, all baseline measurements were repeated at the research lab. All study drugs were provided by Rottapharm Madaus, in identical packaging. Subjects and research staff were blinded for allocation throughout the whole study. Rottapharm Madaus was not involved in study preparations, data collection, or statistical analyses.

The effect of the glucosamine sulphate, compared to placebo, on HbA1c level over the follow-up period was determined using linear mixed models for repeated measurements. Thereafter, the analyses were rerun in subjects with (≥ 42 mmol/mol) and in subjects without elevated HbA1c level at baseline (< 42 mmol/mol). All analyses were adjusted for possible confounders (age, BMI, SQUASH at baseline and change over 30 months, change in waist circumference, and season of baseline measurement [14]) and the randomized groups of the diet & exercise program. The risk of attaining an elevated level of HbA1c after 2.5 years (≥ 42 mmol/mol) was tested in all subjects using logistic regression, additionally adjusted for having an elevated level of HbA1c at baseline. All analyses were performed using SPSS PASW 20 (SPSS Inc., Chicago, IL) and with a p-value < 0.05 set as statistically significant.

Results

From the initial 407 randomized women, only forty-one women (10.1%) were lost to follow-up during the study. Most drop-outs were unwilling to continue participation. Only two withdrew because of side effects (Chapter 4) [8]. Over the total follow-up period, a total of 250 women (61%) reached the pre-specified target of ≥ 75% of study drugs consumption. Mean study drug consumption throughout the entire study was 72%.

The study population consisted of ninety-five per cent Caucasian women. Other baseline characteristics of all participants are given in Table 7.1. HbA1c levels were available for 94% of all subjects at baseline, 82% after 1 year and 85% after 2.5 years. Mean HbA1c level for subjects in the placebo group was 39.6 ± 6.9 mmol/mol after 1 year and 39.7 ± 7.6 mmol/mol after 2.5 years. In the glucosamine group, mean HbA1c level was 39.9 ± 7.4 mmol/mol after 1 year and 39.8 ± 7.2 mmol/mol after 2.5 years. Table 7.2 shows the mean HbA1c levels throughout the follow-up period, for subjects with and without an elevated HbA1c level at baseline. In total, 18% of the subjects had a baseline HbA1c level ≥ 42 mmol/mol.

Table 7.1. Baseline characteristics (mean ± st.dev or percentage)

	All (N = 407)	Placebo (N = 203)	Glucosamine (N = 204)
BMI (kg/m^2)	32.4 ± 4.3	32.5 ± 4.4	32.3 ± 4.1
Age (yr.)	55.7 ± 3.2	55.7 ± 3.2	55.7 ± 3.1
Current smoker (%)	18%	15%	21%
Systolic blood pressure (mm Hg)	146 ± 22	146 ± 20	147 ± 23
Diastolic blood pressure (mm Hg)	94 ± 12	93 ± 11	94 ± 12
Total cholesterol (mmol/L)	6.0 ± 1.1	5.9 ± 1.1	6.1 ± 1.1
HbA1c (mmol/mol)	39.7 ± 8.6	39.8 ± 8.2	39.6 ± 9.1
Elevated HbA1c* (%)	18%	21%	16%

* HbA1c level ≥ 42 mmol/mol.

Table 7.2. HbA1c levels during follow-up for subjects with normal and elevated HbA1c level at baseline.

		Normal baseline HbA1c (< 42 mmol/mol)		Elevated baseline HbA1c (≥ 42 mmol/mol)	
		Placebo	Glucosamine	Placebo	Glucosamine
Baseline	N (%*)	150 (74%)	156 (76%)	43 (21%)	32 (16%)
	HbA1c (mmol/mol)	36.7 ± 2.9	37.1 ± 2.8	50.6 ± 11.1	51.6 ± 16.8
1 year	N (%*)	124 (66%)	129 (63%)	34 (17%)	39 (19%)
	HbA1c (mmol/mol)	37.2 ± 2.8	37.8 ± 3.0	48.1 ± 9.9	48.9 ± 12.9
2.5 years	N (%*)	131 (71%)	136 (66%)	30 (15%)	37 (18%)
	HbA1c (mmol/mol)	37.3 ± 2.8	37.8 ± 3.7	48.6 ± 12.5	50.2 ± 11.8

*Percentage of subjects that were randomized to placebo/glucosamine sulphate.

The glucosamine intervention had a non-significant effect on mean HbA1c level over 2.5 years when analysed among all subjects (p = 0.94), and in subjects with a normal (p = 0.60) or elevated (p = 0.82) HbA1c level at baseline. Logistic regression analysis in all subjects showed a significant odds ratio of 2.81 (1.12 – 7.04) for glucosamine over placebo on an elevated HbA1c level after 2.5 years, in the adjusted analyses. The interaction between the glucosamine intervention and an elevated level of HbA1c at baseline on attaining an elevated HbA1c level at follow-up was not statistically significant (p = 0.43), thus the effect was equal for subjects with and without elevated HbA1c level at baseline.

Discussion

The present study presents HbA1c levels in overweight and obese women during a 2.5 year placebo controlled intervention using oral glucosamine sulphate. There was no effect of glucosamine over placebo on mean HbA1c level throughout the follow-up period. Also within subject with an elevated HbA1c level at baseline, no effect of the intervention was found on mean HbA1c level. We did find a significantly increased risk of glucosamine use on attaining an HbA1c level ≥ 42 mmol/mol after 2.5 years.

Subjects with an HbA1c level ≥ 42 mmol/mol have a high risk of developing diabetes [10]. Besides, a high HbA1c level has a strong predictive value for diabetes complications [9]. This makes concerns about a possible effect of long-term glucosamine usage on HbA1c levels a reasonable subject of debate. Dostrovsky and co-workers were able to evaluate the effects of multiple dosages of glucosamine on glucose metabolism in a total of 172 subjects out of seven trials [5]. Due to large heterogeneity, no quantitative analysis could be done. Out of the systematic review, three of the eligible studies evaluated the glucose metabolism by using HbA1c levels [11, 15-16]. Mean HbA1c levels found in the present study were within the range found in these studies. None of the trials found an effect of glucosamine usage on mean HbA1c levels [11, 15-16]. Even not in subjects with diagnosed Diabetes Mellitus Type 2 [11].

All studies that evaluated the effect of glucosamine usage on HbA1c levels [11, 15-16], including ours, had a reasonable variation within their measurements, troubling the comparison of average HbA1c levels. We therefore, contrary to the previous studies, analysed the effect of the glucosamine intervention on attaining an elevated HbA1c level after 2.5 years. In subjects randomized to glucosamine sulphate, an OR of 2.81 was found for becoming at risk for developing diabetes compared to placebo. Although the progression to diabetes is rather a continuum rather than a threshold [10], these results do suggest that taking glucosamine sulphate for 2.5 years does negatively influence the glucose metabolism in middle-aged, overweight females. However, since the present

study was not designed to evaluate the effects of long-term glucosamine use on glucose metabolism and since attaining an elevated level of HbA1c at follow-up does not mean that diabetes will develop per se [10], these results need to be confirmed in other studies. Such studies should, beside HbA1c levels, take other diabetes risk factors into account as well, in order to make a proper risk profile [9-10] and be able to make final remarks about the effect of long-term glucosamine use on glucose metabolism.

In conclusion, the present study showed that in middle-aged women with a BMI ≥ 27 kg/m^2, a 2.5 year glucosamine sulphate intervention did not affect mean HbA1c levels compared to placebo. However, a significant OR of 2.81 was found for attaining an HbA1c level that is internationally marked as 'high risk for developing diabetes' for glucosamine sulphate over placebo. This is an important finding since at this moment the safety profile of glucosamine is considered to contain no notable side effects and is even available over the counter.

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CHAPTER 8

Malalignment; a possible target for the prevention of incident knee OA in overweight and obese women

J. Runhaar, M. van Middelkoop, M. Reijman, D. Vroegindeweij, EH Oei, SMA. Bierma-Zeinstra

(under review)

Abstract

Background: Knee malalignment is shown to be a modifiable factor. It is unsure whether it is a risk factor for incident knee osteoarthritis. Present study investigates the associations between malalignment and incidence of knee OA over a 2.5 year period, within 351 middle-aged overweight women (BMI ≥ 27 km/m^2), free of clinical and radiological knee OA at baseline.

Methods: Using Generalized Estimating Equations, associations between valgus and varus alignment (compared to neutrally aligned knees) and the incidence of radiographic knee OA (K&L ≥ 2), clinical knee OA (ACR criteria), and medial and lateral joint space narrowing (≥ 1.0 mm) was studied. Secondary, the interaction between varus and valgus alignment and BMI on the separate incidence measures was tested.

Results: Varus aligned knees had a significantly increased risk for the development of radiographic knee OA (odds ratio 2.8, 95% CI: 1.3 – 5.9). A significant interaction between varus alignment and BMI was found for medial joint space narrowing. Among obese subjects (BMI ≥ 30 km/m^2), an increased odds ratio for varus aligned knees on medial joint space narrowing was found (2.6, 95% CI: 1.1 – 6.3).

Conclusions: Current data suggest that varus alignment might be a target for the prevention of knee OA in middle-aged overweight and obese women.

Introduction

To reduce medical costs, morbidity, and disability caused by knee osteoarthritis (OA) through primary prevention, identification of modifiable risk factors is necessary. Excessive body weight has been proposed as a modifiable risk factor for the incidence of knee OA [1]. The preventive effect of a diet and exercise program on incidence of knee OA in middle-aged women was recently assessed in a large RCT (Chapter 4) [2]. Whether malalignment could be regarded as modifiable risk factors for knee OA is subject of debate [3-4]. Malalignment leads to changes in load distribution in the knee joint. Varus alignment leads to higher loads on the medial part of the tibiofemoral joint, while valgus alignment shifts knee load towards the lateral compartment. With the use of wedged insoles [5-8], increased sole stiffness [6], or braces [8-9], the shift in knee joint load can partly be opposed, also in joints free of OA. So malalignment can be regarded as a modifiable factor.

It is unsure whether malalignment is a risk factor for development of knee OA or a risk factor for progression of knee OA. Studies among healthy subjects showed contradicting results on the relationship between malalignment and incident knee OA [4, 10-12]. Besides, malalignment did not lead to greater cartilage volume reduction [13], and was not associated with chondral defect scores [13] or joint space narrowing [14]. However, all these studies were among healthy people with mainly normal body weight. Brouwer et al. [15] showed that in overweight and especially obese individuals, malalignment significantly increased the risk on development of knee OA (odds ratio 2.0 for varus alignment in subjects with BMI ≥ 25 and <30 km/m^2 and 3.3 and 5.1 for valgus and varus alignment in subjects with BMI ≥ 30 km/m^2). In subjects with a normal body weight, no association between malalignment and incident knee OA was found. It is therefore suggested that malalignment can be a risk factor for initiation of knee OA in combination with a high BMI.

Brouwer et al. [15] based their results on a large cohort study. However, in order to confirm that malalignment can be a target for the prevention of knee OA, the effect of malalignment should be confirmed in a target population of subjects at high risk of developing knee OA. The PROOF study (PRevention of knee Osteoarthritis in Overweight Females; Chapter 4 [2]) offers such a high risk group. Hence, the first objective of the current study was to evaluate the effect of varus and valgus alignment on the onset of knee OA over a 2.5 year follow-up period in a high risk group of middle-aged overweight and obese females. The second objective was to evaluate a possible interaction between malalignment and BMI (overweight vs. obese) on the incidence of knee OA within the given population.

Methods

For this study we used data from the PROOF study (ISRCTN 42823086). A description of the study protocol can be found elsewhere (Chapter 4) [2, 16]. In short, this 2.5 year follow-up study aimed to evaluate the preventive effect of a diet and exercise program and oral glucosamine sulphate (double-blind, placebo controlled) on the initiation of knee OA in a 2x2 factorial design. Study protocol was approved by the Medical Ethical Committee of the Erasmus MC.

Participants

The PROOF study was conducted among a group of subjects without clinical and radiological knee OA, with a high risk of developing knee OA; women with a BMI ≥ 27.0 km/m^2 and between 50 and 60 years of age. In the region of Rotterdam, The Netherlands, 50 general practitioners sent an information letter about the study, with a reply-card, to all women between 50 and 60, without major comorbidities, registered at their practice. A total of 6.691 women were contacted. Additional information about the study was sent to all women who returned the reply-card, indicated they were interested in participating and had a BMI ≥ 27 kg/m^2 (as calculated by the body weight and body length as filled in on the reply-card). After several days, all women were contacted by phone to check on all inclusion criteria. Besides criteria on age and BMI, subjects had to be free of knee OA according to the ACR criteria [17], free of contraindications to MRI, free of rheumatic diseases, not using a walking aid, not under treatment for knee complaints, master the Dutch language, and not using oral glucosamine during the past 6 months. All women eligible and willing to participate were invited to visit the research institute to sign the informed consent and undergo physical examination and radiographs of both knees.

Measurements

At baseline, body weight and height were measured and a standardized semi-flexed PA radiograph of both knees was taken according to the MTP protocol [18]. The width of a horizontal beam, centred at the tibiofemoral joint space, was adjusted to fit both knees on a single image. All subjects filled in a questionnaire that included questions on knee complaints, number of days with knee pain. All measurements were repeated after 2.5 years of follow-up.

Data

Measured body height and weight were used for calculation of BMI and date of birth to calculate age. A researcher blinded for clinical outcomes scored all radiographs (baseline and follow-up images at once) using the Kellgren & Lawrence (K&L) criteria [19]. Minimal

joint space width was measured digitally in each tibiofemoral compartment, of both knees, by two blinded researchers individually, according to the method of Lequence [20]. Minimal joint space width of each compartment was defined as the mean score of both assessors. Scores with a difference between both readers ≥ 2.0 mm were re-evaluated by both readers at a consensus meeting. Medial anatomical knee alignment angle was assessed by digitally determining the angle between the line from the centre of the tibial spines through the centre of the femoral shaft at approximately 10 cm from the joint margin and the line from centre of the tibial spines through the centre of the tibial shaft at approximately 10 cm from the joint margin, since it highly correlates to the mechanical axis of the knee and is well assessable on the knee radiographs [21]. Anatomical knee alignment angles were corrected for offset with mechanical knee alignment angle (4^0) and categorized. Anatomical knee alignment angles between 182 and 184 were defined as normal, >184 as valgus alignment and <182 as varus alignment [15]. Reproducibility of K&L grading and anatomical knee alignment assessment was checked after scoring a random sample of 20% of all radiographs twice by a second blinded reader.

Statistical analyses

The primary outcome measure of the PROOF study was the incidence of knee OA, defined as incidence of radiographic knee OA (K&L ≥ 2), clinical knee OA (clinical and radiographic ACR criteria [17]), or medial or lateral joint space narrowing ≥ 1.0 mm (Chapter 4) [2]. Using Generalized Estimating Equations (GEE), which takes into account the correlation between two knees within subjects, the relation between varus/valgus alignment and the onset of knee OA according to the primary outcome measure and for all three items separately was determined. Neutrally aligned knees constituted as reference group in all analyses. To study possible different effects within subgroups of BMI, the interaction between malalignment and BMI was also studied, by adding BMI at baseline and the interaction term between malalignment and BMI at baseline to the GEE in a separate analysis. The associations between malalignment and incident knee OA were determined for overweight (BMI < 30 kg/m^2) and obese (BMI ≥ 30 kg/m2) women separately, for the outcome measures that showed a significant interaction with BMI. All analyses were adjusted for K&L grade at baseline (as in the original trial; Chapter 4 [2]) and the randomized groups of both interventions of the PROOF study. A p value < 0.05 was considered as statistically significant. All statistical tests were performed using SPSS 20.0 (Chicago, IL) and were presented as odds ratio (OR) with corresponding 95% confidence intervals (CIs).

Results

Both knees from all 351 subjects with baseline knee alignment data and incidence measures at follow-up available were selected (86% of all subjects of the PROOF study). BMI at baseline was significantly lower (32.3 ± 4.1 vs. 33.1 ± 5.0 kg/m^2; p = 0.05) and medial joint space width significantly higher (4.8 ± 0.8 vs. 4.6 ± 0.7 mm; p = 0.01) in the selected subjects compared to those with incomplete data.

Valgus alignment was found in 13% and varus alignment in 40% of all knees. Baseline characteristics are given in Table 8.1. At baseline, the percentage of K&L grade ≥ 1 and the mean lateral minimal joint space width were significantly higher in the varus aligned knees. The mean medial minimal joint space width was significantly lower in the varus aligned knees. Tests for reproducibility showed moderate agreement for K&L grade (kappa 0.6), and good agreement for alignment (kappa 0.7) and minimal joint space width (kappa 0.7).

For the primary outcome measure, no significant effects of varus (23% incidence) or valgus alignment (21% incidence) were found, compared to neutral aligned knees (16% incidence). A significant interaction with BMI was found (p < 0.01) for the primary outcome measure. Within obese, a significantly increased OR was found for varus aligned knees (incidence 26% vs. 15% in neutral aligned knees; OR 1.8, 95% CI 1.1 – 3.1). Radiographic knee OA (K&L ≥ 2) was found in 9% of all varus knees and 6% of all valgus knees at follow-up. In neutrally aligned knees, only 3% incidence of radiographic knee OA was found. Only varus aligned knees had a significant OR (2.8, 95% CI 1.3 – 5.9) for the incidence of radiographic knee OA at follow-up. No significant interaction between incidence of radiographic knee OA and BMI was found. Varus aligned knees had a higher incidence of clinical knee OA (8%) compared to valgus (3%) and neutral aligned knees (6%), but these differences did not reach statistical significance. No interaction between

Table 8.1. Baseline characteristics.

	All (N = 702)	Neutrally aligned knees (N = 334)	Varus aligned knees (N = 279)	Valgus aligned knees (N = 89)
Age (yr.)	55.7 ± 3.2	56.0 ± 3.1	55.5 ± 3.3	55.5 ± 3.2
BMI (kg/m^2)	32.3 ± 4.1	32.2 ± 3.8	32.3 ± 4.5	32.3 ± 4.3
K&L grade ≥ 1	50 %	46%	56%	44%
Mild symptoms (yes)	31%	31%	32%	30%
History of knee injury (yes)	14%	12%	15%	18%
Minimal medial JSW (mm)	4.8 ± 0.8	4.9 ± 0.7	4.6 ± 0.9	5.0 ± 0.8
Minimal lateral JSW (mm)	6.2 ± 1.1	6.1 ± 1.0	6.4 ± 1.1	5.8 ± 1.0

All values are calculated on knee level. Neutral: medial anatomical knee angles 182° - 184°. Varus: medial anatomical knee angles <182°. Valgus: medial anatomical knee angles >184°. JSW: joint space width.

Table 8.2. Associations between varus and valgus aligned knees and incident knee OA over 2.5 years (N = 702 knees).

	Knee OA*		Radiographic knee OA		Clinical knee OA		Medial JSN		Lateral JSN	
	Incidence	OR (95% CI)	Incidence	OR (95% CI)	Incidence	OR (95% CI)	Incidence	OR (95% CI)	Incidence	OR (95% CI)
Valgus	21%	1.5 (0.9 – 2.7)	6%	2.4 (0.9 – 6.5)	3%	0.5 (0.1 – 2.1)	9%	2.5 (0.9 – 6.6)	6%	0.9 (0.3 – 2.4)
Varus	23%	1.4 (0.9 – 2.1)	9%	2.8 (1.3 – 5.9)	8%	1.2 (0.6 – 2.3)	7%	1.8 (0.9 – 3.7)	8%	1.3 (0.7 – 2.5)
Neutral	16%	1 (reference)	3%	1 (reference)	6%	1 (reference)	4%	1 (reference)	6%	1 (reference)

*defined as incidence of radiographic knee OA (K&L ≥ 2), clinical knee OA (ACR criteria), or medial or lateral joint space narrowing (≥ 1.0 mm) at follow-up. All analyses were adjusted for K&L grade at baseline (0 vs. ≥ 1) and randomized groups for both interventions of the PROOF study. JSN: joint space narrowing; OR: odds ratio; CI: confidence interval.

malalignment and BMI was found for the onset of clinical knee OA. Malalignment had no significant effect on the incidence of medial or lateral joint space narrowing. Only for varus alignment and medial joint space narrowing, a significant interaction with BMI was found ($p < 0.01$). Varus aligned knees were significantly associated with medial joint space narrowing (incidence 9% vs. 4% in neutral aligned knees; OR 2.6, 95% CI 1.1 – 6.3). See Table 8.2 for full details.

Discussion

Since knee malalignment is a modifiable factor and related to knee loading, its role in the onset of knee OA is important in the search for modifiable risk factors for the disease. Our study shows that among middle-aged women, free of knee clinical and radiographic knee OA at baseline, varus alignment is associated with a significant increase in the incidence of radiographic knee OA, compared to neutrally aligned knees. In obese subjects, varus alignment also showed a significant increase in medial joint space narrowing. Contrary to previous studies, our population was recruited for a preventive trial in a clinical setting. This makes results highly representative for a possible target population selected for a preventive intervention; for instance by counter acting the malalignment.

In the present study, knee alignment was measured on short-limb radiographs. This is a validated measurement of static knee alignment [21], especially in large studies with a wide variety of alignment angles [22]. Definitions of malalignment on the other hand are less undisputed. For comparison, we used definitions of varus and valgus alignment by Brouwer et al. [15]. Probably due to a higher baseline BMI in our study, knee alignment was shifted towards varus alignment (see Figure 8.1). Data from Niu et al. confirm that a shift towards varus alignment is seen in obese non-OA subjects [23]. The applied offset correction of 4° in the present study is within ranges of suggested correction from anatomical to mechanical axis of 3 to 6 degrees [21-22, 24-26]. Nevertheless, alignment measured on radiographs is a static representation of knee alignment and does not fully represent dynamic loads on the tibiofemoral joint [23, 27].

Malalignment can partly be opposed by non-surgical interventions. Although mainly studied in subjects with knee OA [28-29], bracing also has shown to be effective in reducing peak knee adduction moment and angular impulse during walking in healthy subjects with varus aligned knees [9]. Also, full-length wedged insoles have been proven to alter knee joint load in healthy subjects [7]. Whether these interventions have a preventive effect on the development of knee OA has never been studied. Before designing such a trial, efficacy and effectiveness of both interventions should be determined in the target population, since conflicting results have been found in different populations [28-29].

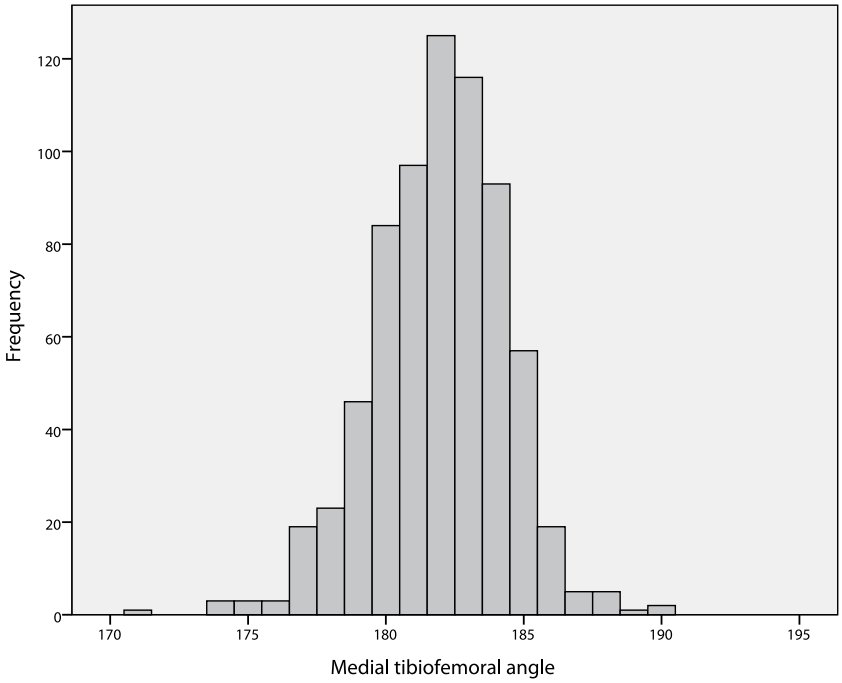

Figure 8.1. Histogram of medial anatomical knee angles.

In a direct comparison of the biomechanical effects of valgus knee brace and lateral wedged insoles in a study among subjects with knee OA, Jones et al. [8] showed that both interventions reduced medial knee joint load. However, the effects of the wedged insoles were significantly greater than the knee brace. Moreover, and very important when administering a preventive intervention, all participants preferred the wedged insole intervention over the knee brace at the end of the trial. Since adherence to the intervention will be an important issue when prescribing an active measure to healthy subjects in order to prevent future disease, subjects' preferences will be very important.

The association between varus alignment and obesity on the one hand and the incidence of knee OA on the other hand, as found in the present study, might be mediated by meniscal extrusion. Since both varus alignment and obesity are associated with a higher prevalence of meniscal extrusion [30-31]. In subjects with K&L grade < 2 at baseline, Madan-Sharma and co-workers [32] showed that subjects with meniscal extrusion had higher rates of joint space narrowing over the subsequent two years. Other studies also showed associations between meniscal extrusion and knee OA features [30-31]. Whether interventions like braces or wedged insoles can counteract the initiated processes by the existing meniscal extrusion and, over time delay or prevent knee OA has never been studied.

The combined knee OA outcome measure was adopted from the original PROOF study. In order to make a preventive randomized trial feasible over a relative short follow-up time, the incidence of radiographic knee OA, clinical knee OA and joint space narrowing were combined into one measure. Hence, the present results are based on secondary analyses. A longer follow-up duration and more sensitive measures (e.g. MRI) would provide more detailed information about the association between malalignment and incidence of knee OA.

In conclusion, our study showed a significant association between varus alignment and incidence of radiographic knee OA after 2.5 years in middle-aged women. Among obese women, varus aligned knees also had a significant increased risk for joint space narrowing. Contrary to previous studies on the association between malalignment and incidence of knee OA that focused mainly on large cohorts, this study shows that, within a relatively easy obtainable population, varus alignment is a risk factor for incident knee OA. Since varus alignment is a modifiable factor, results from the present study suggest that varus alignment might be a target for the prevention of knee OA in middle-aged obese women.

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CHAPTER 9

General discussion

Excessive body weight is one of the strongest and most prevalent risk factors for the development of knee osteoarthritis (OA). The worldwide prevalence of obesity has nearly doubled between 1980 and 2008 and is still rising. The World Health Organization estimates 35% of all adults to be overweight and more than 12% to be obese [1]. Given the burden for patients and the high medical costs associated with knee OA, this shows the importance of full understanding of the role of overweight and obesity in the development of the disease.

Main findings

This thesis focuses on the development and prevention of knee OA and the role of overweight and obesity on these two domains. In **Chapter 2**, we saw that with only 12 eligible studies, relative little research has been done on the biomechanical differences between normal-weight and obese individuals during every day movements; despite the fact that the mechanical effects of excessive body weight have long been regarded as the main factor in the development of knee OA in overweight and obese individuals. This systematic review shows that obese individuals alter their movement strategies during every day movements and provides indications on how these alterations might be involved in the onset of knee OA.

The explorative analyses in **Chapter 3** show that, in women free of radiological signs of knee OA, alterations in the shape of the femur and tibia are present across the whole range of the body mass index (BMI). However, in subjects with a BMI $\geq$ 27 kg/m^2, certain shape variations in the tibia are related to early signs of knee OA, as seen on magnetic resonance imaging (MRI). On the other hand, also a causal path from a high BMI to knee joint shape alterations, leading to early signs of knee OA, was suggested from the shape models. These data add to the knowledge of the association between a high body weight and the development of knee OA, but still no conclusive evidence for the mechanism behind this association is provided.

The core data of this thesis are derived from the first ever preventive trial in OA research; the PROOF study. Two interventions, a diet & exercise program and oral glucosamine sulphate, were tested for their preventive effects on knee OA in a high risk group of overweight and obese, middle-aged women. Both interventions showed non-significant trends towards a preventive effect, but these analyses are hampered by the unexpected interaction between the two interventions (**Chapter 4**). The diet & exercise intervention is analysed in more detail in **Chapter 5**. Despite the low compliance, the intervention resulted in clinically relevant weight loss in the intervention group within the first year. When the clinically relevant weight loss was present after 2.5 years, regardless of the

allocation to the diet & exercise program or the control group, significant preventive effects were found on the incidence of knee OA (**Chapter 6**). A longer follow-up period is needed to see whether the number of prevented cases of knee OA after such weight loss can become clinically relevant.

Despite the fact that oral glucosamine sulphate is generally regarded as a safe supplement, **Chapter 7** shows that this opinion might have to be reconsidered for overweight and obese individuals. Subjects randomized to the active treatment had increased risk of becoming at 'high risk for developing diabetes' compared to the placebo group.

Chapter 8 shows that in the high-risk group selected for the PROOF study, varus alignment of the knee joint also puts subjects at increased risk for developing knee OA over a relatively short time and that this effect is even stronger in those with a BMI ≥ 30 kg/m^2 compared to those with a BMI between 27 and 30 kg/m^2, for several outcome measures.

Development of knee osteoarthritis

For decades, the negative effects of a high BMI on the incidence of knee OA are known. Increased loading of the knee joint due to the excessive body weight has long been regarded as the main factor behind this association. The possible inflammatory aspects involved in the onset of knee OA are only recognised in recent years.

Biomechanics

The results of the systematic review presented in **Chapter 2** give some indications of the biomechanical aspects of obesity in relation to the development of knee OA. However, there is a methodological drawback in the included studies. All eligible studies used surface markers which suffer from relative large measurement errors due to movement of the skin relative to the bone, especially with large subcutaneous fat mass, as in obese. Compared to bone embedded markers, the average rotational error of surface markers ranged between 2.4° and 4.4° and the translational error between 3.3 and 13.0 mm during the stance phase in walking normal-weight individuals [2]. For evaluation of the flexion/extension patterns, these measurement errors might be within acceptable limits, but for exo-/endorotation and ab-/adduction patterns, such errors form a substantial proportion of the total range of movement in these directions. Given the small magnitude of the translational movements within the knee joint, more sophisticated measurement techniques are required to study the effects of obesity on knee joint biomechanics and reveal (or rule out) how biomechanical alterations are linked to the aetiology of knee OA. Fortunately, high-speed biplane radiography and comparable techniques are optimized for clinical research. With measurements errors of only 0.6° and 0.5 mm on average [3],

these techniques should provide valid data on knee biomechanics in obese individuals in future studies.

An important structure in the weight-bearing capacity and stability of the knee joint are the menisci. In contrast to conventional radiographs, menisci can nowadays be visualized and assessed on pathologies with the use of MRI. In recent years, it was shown that meniscal extrusion is an independent risk factor for the development of knee OA [4]. It is very well possible that meniscal extrusion is the factor behind the association between malalignment and increased knee OA development, as was indicated in **Chapter 8**. Since both malalignment and obesity are associated to meniscal extrusion [4-5], meniscal extrusion might be the mediating biomechanical factor in the relationship between obesity, malalignment and incident knee OA. Preliminary data from the MRI acquisition of the PROOF study give some support for this hypothesis; almost half of all knees showed extrusion (≥ 2.0 mm) of the body of the medial or lateral meniscus at baseline. This will probably be a factor in the subsequent development of knee OA, but the exact aetiology within the development of knee OA is unknown. Further studies should be undertaken to work out the exact role of meniscal extrusion in the OA process and to formally test the mediating effect of meniscal extrusion in the association between obesity and the development of knee OA and for the association of malalignment and knee OA.

Throughout this thesis, as in the fast majority of the current literature, BMI is regarded as a valid surrogate measure of body fat. Even though it does not discriminate between muscle mass and fat mass, which are inversely related to knee OA. For instance, lower M. Quadriceps strength, which is equivalent to lower muscle mass, was associated to incident knee OA, lower cartilage volume, and a decrease of cartilage volume over time, while the same holds for a higher body fat measures [6-7]. For example, interestingly, thigh total fat and thigh subcutaneous fat measures were significantly associated with compressive knee forces, anterior-posterior shear forces and patellofemoral compressive forces during walking in OA patients, adjusted for BMI [8]. Unfortunately, this has never been studied in a high-risk non-OA population, but it shows that local fat masses are associated to increased loading of the knee joint independent of BMI. So, more precise measures of body fat distribution and muscle mass seem favourable over BMI when studying the association between body weight and knee OA development.

Inflammation

Besides the biomechanical aspects of overweight and obesity, recent focus has been directed to the systemic effects of surplus fat mass on OA development. Since obesity was also shown to increase the risk for OA in non-weight-bearing joints, biomechanical factors alone are thought to be insufficient to fully explain the relation between obesity and

knee OA development [9]. In a recent review article, Issa and co-workers neatly describe the inflammatory aspects of adipose tissue and its possible role in the development of knee OA [10]. Adipose tissue excretes a decent amount of pro-inflammatory cytokines, often called adipokines. Many of these adipokines have been shown to mediate synovial tissue inflammation and induce cartilage degradation. Besides, cartilage subject to mechanical load also activates signalling pathways that promote tissue homeostasis by balancing the production of anabolic growth factors and catabolic cytokines and pro-inflammatory mediators. With increased loading due to overweight and obesity, pro-inflammatory mediators are highly expressed and will unfavourably disbalance the homeostasis, which eventually leads to tissue breakdown. On the other hand, inflammatory processes are also presumed to cause pain sensitization. This increases the degree and duration of pain after a stimulus [11]. So besides the structural aspect of knee OA, surplus fat mass may also affect the sensation of pain disadvantageously through inflammatory processes, causing en aggravating complaints related to knee OA.

These inflammatory processes associated with overweight and obesity are only recognized over the last years, but are now generally accepted despite the fact that they are not fully understood and not all details of the process are available yet.

Most likely, the alterations in shape of the femur and tibia shown in **Chapter 3** are partly caused by inflammatory processes. Several upregulated factors in overweight and obese individuals are also known to stimulate bone remodelling by osteophyte formation [12-13]. So possibly, due to the low grade chronic inflammation associated with surplus fat mass in overweight and obese individuals, alterations of the shape of the femur and tibia take place. As shown in **Chapter 3**, several of the alterations to the tibia might play a role in the development on knee OA, since they are associated to early OA signs as seen on MRI. Also the biomechanical alterations found in obese individuals shown in **Chapter 2** might have an underlying inflammatory aspect. Inflammation and effusion of the knee joint often co-exist [14]. Recently, effusion of the knee joint was shown to alter gait biomechanics [15]. Again, this was only measured in knee OA patients. Hereby the biomechanical effects are possibly greater that in non-OA subjects, since inflammatory processes are more active in OA knees, but it would be very interesting to study the presence and effects of knee joint effusion in overweight and obese individuals and the accompanied effects on joint biomechanics.

Altogether, a better understanding in the inflammatory processes expressed in overweight and obese individuals and their involvement in the development in knee OA will be necessary to fully understand the increased risk for knee OA development in overweight and obese individuals.

Prevention of knee osteoarthritis

After decades of studies on the aetiology, risk factors and progression of knee OA, the time was right to take the next step in OA research and, for the first time, focus on the prevention of the disease.

The PROOF study

Besides the presented and discussed results in **Chapters 4 – 8**, the PROOF study holds some value information on the preventive possibilities within a high-risk group of overweight and obese, middle-aged women. For instance, despite the fact that all women were free of clinical knee OA (according to the ACR criteria) and thus could not experience any direct beneficial effects of the offered interventions, most were willing to stay in the trial over relative long period of 2.5 years, as shown by the lost to follow-up figure of only 10%. Besides, also without a possible direct advantageous effect, compliance to the glucosamine and placebo was relatively high. A systematic review on medication adherence in a wide variety of complaints across 569 studies revealed an overall average of 75%, ranging from 5 to 100% [16]. With an average compliance to the supplements of 72% in the PROOF study, compliance can be considered as very good given the lack of complaints at baseline and the relative long follow-up period. Unfortunately, compliance to the diet & exercise program lagged behind. We will discuss this issue elsewhere in this chapter. Despite the latter, the overall conclusion of the PROOF study is that a high-risk group of overweight and obese, middle-aged women is highly suitable for the long-term evaluation of preventive measures in knee OA.

At baseline, the inclusion of the knees in the PROOF study was not limited to K&L grade 0, even though it was suggested that knees with 'doubtful OA' at radiographs (equivalent to K&L grade 1) will probably have early OA and true prevention can thus not be established [17]. However, limiting included knees to those with K&L grade 0 in this high-risk group of subjects would probably have led to inclusion of many knees unsusceptible to the OA process [18]. Data from the PROOF study did show that indeed knees with K&L grade 1 at baseline probably already have an early form of OA. One in five knees with K&L grade 1 at baseline showed incident knee OA according to the primary outcome measure, while only one in ten knees with K&L grade 0 did so. For incidence of K&L grade 2 after 2.5 years of follow-up, baseline K&L grade 1 even had a four-time higher incidence compared to the knees with K&L grade 0 (8% vs. 2%). Despite the higher incidence rates of the knees with radiologic signs of knee OA, it seemed that, also within these knees, the preventive measure had their effect; within the knees showing incident knee OA, the proportions of baseline K&L grades 0 and 1 did vary between randomized groups. This suggests that both stages of the disease can be prevented.

However, present incidence rates will require a longer follow-up to test this statement statistically.

Compared to other OA studies, the cut-off for incidence of joint space narrowing (JSN) of ≥ 1.0 mm was fairly conservative. When designing the PROOF study, it was assumed that a lower cut-off would not be clinically relevant given the healthy status at baseline of the included knees. We now can reflect on this assumption. Indeed, the overlap between the number of knees with incident JSN and the number of knees with incident OA according to the other two items of the primary outcome measure drops with 31% to 50% when the cut-off is set at ≥ 0.5 mm, as common in other studies where it is used to define progression among subjects with already evident knee OA. As known, the overlap between JSN, K&L ≥ 2 and the ACR criteria is only modest [19], but this substantial drop in overlap seems to segregate the items of the primary outcome measure into measures of a completely different stage and aspects of the disease. One could highly question the clinical relevance of such measures.

Diet & exercise program

Designing a weight loss intervention for overweight and obese individuals is a complex matter. When designing the PROOF study, a simple and pragmatic intervention was put together that met the criteria for a successful weight loss program; a tailor made design and the use of Motivational Interviewing. As described in **Chapter 5**, these two features were indicated as superior to other designs for long-term weight loss. Given the strong preference of the subjects at baseline for the intervention group over the control group (nearly 90% stated to have a preference for the active group) and the overall compliance figure of only 28%, one could argue that the diet & exercise program was not very successful. However, perhaps the offered interventions (diet counselling and physical activity classes) were not diverse enough. With 51% compliance to the dietician and 57% to the physical exercise classes, both interventions separately were reasonably well conducted by the participants. The combination of these two interventions did not seem to be a great success for the fast majority of the subjects in the intervention group, given the compliance figure. Based on the results of the PROOF study, it is possible to think of other intervention strategies that might be effective and could be combined with either the diet & exercise program and/or the diet counselling; for instance education. At baseline, subjects were asked to rate their general health status on a visual analogue scale from 0 to 100, where 100 was the best possible and 0 the worst possible health status. Despite a mean BMI over 32 kg/m^2, 66% of the subjects being obese, and almost one out of four having severe obesity (BMI ≥ 35 kg/m^2), 89% of all subjects rated their general health status to be 70 or higher and even 69% as 80 or higher. It seems that this population of middle-aged women should be educated on the negative effects of

overweight and obesity on general health, in order to make them aware of the urge of weight loss. Without this knowledge, it is not so surprising that compliance figure remain below the level one would expect given the body weight figures within this population. Besides, incorporating family members into the interventions would probably increase compliance figures. Social support is a known key factor for lifestyle changes and, most of the time, households share unhealthy lifestyles [20].

Glucosamine sulphate

Despite numerous studies, the mechanism of action and the effectiveness of glucosamine in OA is still subject of debate. Results presented in **Chapter 4** will not settle the discussion. The interaction with the diet & exercise program and the effects of glucosamine on the HbA1c level (**Chapter 7**) will possible even provoke new discussions. As stated, there are some hypotheses on the mechanism of action of the found interaction (**Chapter 4**). However, most of the studies that provide such hypotheses did not study the biochemical mechanisms associated with this interaction, but only provide indirect indications [21-22]. Given the strong interaction found in the PROOF study, the biochemical mechanisms involved in physical exercise and glucosamine synthesis should receive further attention.

In previous studies it was suggested that glucosamine sulphate would be most effective in an early stage of the disease [23]. Overall, glucosamine sulphate is thought not to rebuild damaged cartilage, but would slow down cartilage degradation processes [24]. The items of the primary outcome measure involving articular cartilage (K&L $\geq$ 2 and JSN $\geq$ 1.0 mm) required relative large reductions in articular cartilage before they are marked as incident and are therefore relatively insensitive. Despite this, a substantial, but not statistically significant, reduction in odds ratio for incident knee OA was found in the glucosamine sulphate group. Possibly, the more sensitive data of the MRI acquisition will provide further insight in the preventive effects of glucosamine sulphate over placebo. Moreover, since the MRI acquisition covers multiple tissue pathologies in the knee joint that are known to be involved in the OA process, such as cartilage defects, Hoffa synovitis, synovial effusion, and bone marrow lesions, the effects of glucosamine sulphate on cartilage maintenance and as anti-inflammatory factor can be evaluated.

Clinical implications

The PROOF study is the first ever trial on the prevention of OA worldwide. Future preventive studies should learn from results presented throughout this thesis, such as issues on the inclusion of subjects, subject's compliance to the interventions, choice of outcome

measures, and incidence figures. For the design of the PROOF study, some assumptions were made. One such assumption, that there would be no interaction between the diet & exercise program and the glucosamine intervention, proved to be wrong and had major consequences for the direct clinical implications of the trial. Due to the unexpected interaction, the power of the trial was insufficient. Therefore, no firm statements on the effectiveness of the studied interventions can be given. However, given the indications for a possible preventive effect within the subjects compliant to the diet & exercise program (**Chapter 4**) and the effects of substantial weight loss on incidence figures and certain health measures (**Chapter 6**), the current thesis will provide general practitioners with more evidence to inform and convince overweight or obese middle-aged women of the need for weight loss. Until further details on the effectiveness of glucosamine sulphate are studied, there is no need to preventively prescribe glucosamine sulphate to overweight or obese middle-aged women. Especially considering the number of (mild) side effects associated with the studied supplements (glucosamine and placebo, **Chapter 4**) and the possible negative effects of glucosamine sulphate on the blood glucose levels after 2.5 years (**Chapter 7**).

Future studies

Some future studies are already mentioned throughout this chapter and are thus not reconsidered here (e.g. highly accurate movement analyses within obese, the role of meniscal extrusion, body composition rather than BMI as measure of joint load, the inflammatory aspects of surplus fat mass on radiological and clinical OA development). However, there are some remarks left on future studies that deserve attention.

With the extensive knowledge on the development of OA and given the positive results of the PROOF study on the feasibility of a preventive trial in a high-risk population, at least for the knee and hip joint, future preventive trials should be considered. To gather a more detailed insight in the development of knee OA and on the preventive effects of the studied interventions within the PROOF study, MRI data (baseline and follow-up) and inflammatory and metabolic markers from urine and serum samples will be studied at short notice.

With better (higher magnetic field) and new MRI techniques (e.g. dGEMRIC, T1rho, and T2 mapping) becoming available for scientific research, visualization of knee joint pathologies improves, well before OA has developed in a patient. Eventually, these techniques can help identifying pathologies which are important in the development of knee OA. After identification, the exact mechanisms causing the pathologies and its timing in the subsequent knee OA development should be studied. Hereafter, new preventive

measures can be developed and hopefully more individuals can be retained from the pain, disability, and costs associated with knee OA. In order to optimize the treatment (both preventive and symptomatic) of knee OA, MRI has another important role in future studies. In the traditional radiographic definitions of knee OA, the patellofemoral joint is completely neglected. Only in the ACR-criteria, crepitus of the patella is considered. No wonder that scores of knee pain and function in subjects with and without radiological knee OA do not correlate too well with radiological features of knee OA. Obviously, individuals rating their knee complaint will include the patellofemoral joint, while the radiological assessment only focusses on the tibiofemoral joint. With the use of MRI, that can visualize the whole knee joint, the role of patellofemoral pathologies in the development of both clinical and radiological knee OA should be unravelled. Treatment of a patient with or at high risk for knee OA should involve both the tibiofemoral and patellofemoral joint. We therefore also have to examine the preventive effects of the interventions evaluated in the PROOF study on the patellofemoral joint and explore the role of the presence and development of abnormalities in the patellofemoral joint on the development of knee complaints.

As indicated earlier, the content of the weight loss intervention should be optimized further to increase compliance and weight loss figures. Beside the already proposed additions of education and the involvement of family members, some other interesting elements have been reported after designing the diet & exercise intervention of the PROOF study. Wluka and co-workers [25] recently listed a couple; telephone consultation resulted in 3 to 5 kg weight loss over 6 months. Additionally, mobile text messages, mail, and internet-based programs showed positive results and gain more popularity.

In subjects without knee OA, increased joint load due to regular moderate physical activity is known to have positive effects on joint health, as long as injuries are prevented. However, the mechanism behind the positive effects is unknown and hence, the content of the physical exercise classes as incorporated in the PROOF study was optimized based on assumptions rather than on knowledge. It is known that muscle contractions provoke a strong anti-inflammatory response [26], but it is unknown whether this temporary effect plays a role in the OA process. Without knowledge on the mechanism of action, it is hardly possible to optimize physical exercise interventions for future studies on the prevention of knee OA.

Other populations could also be considered for future preventive studies on knee OA. Although not so highly prevalent on a population level, knee injuries form a very strong risk factor for subsequent knee OA development. After knee joint injury, increased load on the joint, either by a high BMI or provoked by high impact sports, is known to induce fast development of knee OA [27]. As soon as the exact aetiology of post-traumatic knee OA development is unravelled (studies are underway, e.g. after ACL rupture [28]), preventive

measures could be designed and tested. Of course, it would be even better to prevent the actual knee injury to occur. Since effective training protocols exist for the prevention of knee injuries within athletes (especially for girls/women) of high-risk contact sports (e.g. [29-30]), more attention should be paid to the implementation of these protocols. Finally, as indicated in **Chapter 8**, malalignment might be regarded as a modifiable risk factor for knee OA, especially in obese subjects. Future studies should be undertaken to confirm effects of insoles or braces on knee malalignment within obese subjects free of knee OA, in order to make a new preventive trial in OA possible.

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Appendices

Appendix to Chapter 2

Specification of used search strategy.

(foot OR knee OR hip OR ankle OR "lower extremity" OR "lower limb*") AND (biomec* OR mechanic* OR kinemat* OR kinetic* OR dynamic* OR force* OR moment* OR torque* OR power* OR load* OR *strength OR angle*) AND (gait OR *walking OR sit-to-stand OR *stairs OR standing OR stance OR locomotion OR rising OR movement OR activity OR exercise OR physical OR posture) AND (overweight OR obes* OR "body mass index" OR BMI). Limits: Human, all adult, title/abstract

Limiting the search strategy to title/abstract did not lead to eligible study being overlooked. This was checked in an earlier stage of the review process with an earlier version of the search strategy.

Table A2.1. Spatial and temporal variables in obese compared to normal-weight subjects in studies on gait at a self-selected velocity.

	walking speed	walking speed relative to BH	stride length	stride length relative to BH	step length	step width	cadence	cycle time	stance time	stance time relative to gait cycle time	double support time relative to gait cycle time	single limb support time relative to gait cycle time
Lai et al.	-			-			**0**			+	+	
Segal et al.	**- / -** [a]											
De Souza et al.	-		-		-	+						
Spyropoulos et al.	-		-			+	-	**0**	**0**	+		
Vismara et al.		-		-			**0**			+		-
Russell et al.	**- / -** [b]		**- / 0** [b]				**0 / 0** [b]					

+: significantly higher in obese. **-**: significantly lower in obese. **0**: no differences. [a] in central obese / lower obese. [b] on overground / treadmill. BH: body height.

Table A2.2. Spatial and temporal variables in obese compared to normal-weight subjects in studies on gait at a standardized velocity.

	speed	stride length	step length	step frequency	stance time relative to gait cycle time	double support time relative to gait cycle time	step width
Browning and Kram	0.50 m/s	**0**		**0**	+	+	+
	0.75 m/s	**0**		**0**	+	+	+
	1.00 m/s	**0**		**0**	+	+	+
	1.25 m/s	**0**		**0**	+	+	**0**
	1.50 m/s	**0**		**0**	+	+	+
	1.75 m/s	**0**		**0**	+	+	+
DeVita and Hortobagyi	1.5 m/s		**0**	**0**	+		
Messier	0.893 m/s						
Vismara et al.	0.833 m/s		+			+	+

+: significantly higher in obese. **-**: significantly lower in obese. **0**: no differences.

Table A2.3. Angular differences between obese and normal-weight subjects in studies on gait at a self-selected velocity.

HIP joint

				flexion		abduction		exorotation	
Vismara et al.	stance phase	weight	initial contact						
		acceptance	loading response						
		single limb	mid stance	**0** [a]					
		support	terminal stance						
			pre swing						
Spyropoulos et al.	stance phase	weight	initial contact	**0**		**0**		**0**	
		acceptance	loading response	**0**		**0**		**0**	
		single limb	mid stance	**0**	**0 / 0** [b]	**+**			
		support	terminal stance	**0**		**+**			
			pre swing	**0**		**+**			
Lai et al.	stance phase	weight	initial contact						
		acceptance	loading response	**0**		**0**		**0**	
		single limb	mid stance	**0**	**0 / 0** [b]	**0**	**0 / 0** [b]	**0**	**0 / 0** [b]
		support	terminal stance	**0**		**-**		**0**	
			pre swing	**0**		**-**		**0**	

+: significantly higher in obese. **-**: significantly lower in obese. **0**: no differences. [a] total range of motion. [b] minimal / maximal angles.

Table A2.3. Angular differences between obese and normal-weight subjects in studies on gait at a self-selected velocity. *(Continued)*

KNEE joint				flexion		abduction		exorotation	
Vismara et al.	stance phase	weight	initial contact						
		acceptance	loading response						
		single limb	mid stance	**0** [a]					
		support	terminal stance						
			pre swing						
Spyropoulos et al.	stance phase	weight	initial contact	**0**					
		acceptance	loading response	**0**					
		single limb	mid stance	**0**	**0** [b]				
		support	terminal stance	**0**					
			pre swing	**0**					
Lai et al.	stance phase	weight	initial contact						
		acceptance	loading response	**0**		**0**		**0**	
		single limb	mid stance	**0**	**0 / 0** [c]	**0**	**- / 0** [c]	**0**	**0 / 0** [c]
		support	terminal stance	**0**		**0**		**0**	
			pre swing	**0**		**0**			

+: significant higher in obese. **-**: significant lower in obese. **0**: no differences. [a] total range of motion. [b] maximal angle. [c] minimal / maximal angle.

Table A2.3. Angular differences between obese and normal-weight subjects in studies on gait at a self-selected velocity. *(Continued)*

ANKLE joint				plantar flexion		eversion		toe-out angle
Vismara et al.	stance phase	weight	initial contact					
		acceptance	loading response					
		single limb	mid stance	**0 / 0** [a]				**+**
		support	terminal stance					
			pre swing					
Spyropoulos et al.	stance phase	weight	initial contact	**0**				
		acceptance	loading response	**-**				
		single limb	mid stance	**-**	**+ / +** [c]			
		support	terminal stance	**-**				
			pre swing	**-**				
Lai et al.	stance phase	weight	initial contact					
		acceptance	loading response	**0**		**0**		
		single limb	mid stance	**0**	**0 / 0** [d]	**+**	**0 / +** [d]	
		support	terminal stance	**0**		**+**		
			pre swing	**0**		**+**		
De Souza et al.	stance phase	weight	initial contact					
		acceptance	loading response					
		single limb	mid stance					**+**
		support	terminal stance					
			pre swing					

+: significantly higher in obese. **-**: significantly lower in obese. **0**: no differences. [a] total range of motion / maximal angle. [b] total range of motion. [c] maximal plantar / dorsi flexion angles. [d] minimal / maximal angles.

Table A2.4. Angular differences between obese and normal-weight subjects on gait at a standardized velocity.

HIP joint				flexion
Browning and Kram	stance phase	weight acceptance	initial contact	
			loading response	
		single limb support	mid stance	**0** [a]
			terminal stance	
			pre swing	
DeVita and Hortobagyi	stance phase	weight acceptance	initial contact	
			loading response	
		single limb support	mid stance	-
			terminal stance	
			pre swing	
Vismara et al.	stance phase	weight acceptance	initial contact	**0**
			loading response	
		single limb support	mid stance	
			terminal stance	
			pre swing	

KNEE joint				flexion	
Browning and Kram	stance phase	weight acceptance	initial contact		
			loading response		
		single limb support	mid stance	**0** [a]	
			terminal stance		
			pre swing		
DeVita and Hortobagyi	stance phase	weight acceptance	initial contact		
			loading response		
		single limb support	mid stance	**- / -** [c]	
			terminal stance		
			pre swing		
Vismara et al.	stance phase	weight acceptance	initial contact	-	
			loading response		
		single limb support	mid stance		**0** [d]
			terminal stance		
			pre swing		

+: significantly higher in obese. **-**: significantly lower in obese. **0**: no differences. [a] on all velocities. [b] maximal angles.
[c] maximal / average angles. [d] total range of motion.

Table A2.4. Angular differences between obese and normal-weight subjects on gait at a standardized velocity. *(Continued)*

ANKLE joint

				plantar flexion	eversion	toe-out angle
Browning and Kram	stance phase	weight acceptance	initial contact			
			loading response			
		single limb support	mid stance	**0** [a]		
			terminal stance			
			pre swing			
DeVita and Hortobagyi	stance phase	weight acceptance	initial contact			
			loading response			
		single limb support	mid stance	+		
			terminal stance			
			pre swing		+	
Messier	stance phase	weight acceptance	initial contact			-
			loading response			
		single limb support	mid stance		+	+
			terminal stance			
			pre swing			
Vismara et al.	stance phase	weight acceptance	initial contact	**0**		
			loading response			
		single limb support	mid stance	**0** [d]		
			terminal stance	**-** [d]		
			pre swing			

+: significantly higher in obese. **-**: significantly lower in obese. **0**: no differences. [a] on all velocities. [b] maximal angles. [c] maximal / average angles. [d] total range of motion.

Table A2.5. Kinetic differences between obese and normal-weight subjects on gait at a self-selected velocity.

HIP joint		flexion	adduction		exorotation		
		relative (Nm/kgm)	absolute (Nm)	relative (Nm/kgm)	absolute (Nm)	relative (Nm/kgm)	
Lai et al.	stance phase	**0**		**0**		**0**	

KNEE joint			flexion	adduction			exorotation
			relative (Nm/kgm)	absolute (Nm)	relative (Nm/kg)	relative (Nm/kgm)	relative (Nm/kgm)
Lai et al.	stance phase	weight acceptance / single limb support	**0**			**0**	**0**
Segal et al.	stance phase	weight acceptance		**+ / +** *	**0 / 0** *		
		single limb support		**+ / 0** *	**0 / 0** *		
Russell et al.	stance phase	weight acceptance / single limb support		**0**			

+: significantly higher in obese. **-**: significantly lower in obese. **0**: no differences.

Table A2.5. Kinetic differences between obese and normal-weight subjects on gait at a self-selected velocity. *(continued)*

ANKLE joint		plantar flexion		inversion		exorotation
		relative (Nm/kgm)	relative (Ns/kg)	absolute (Nm)	relative (Nm/kgm)	relative (Nm/kgm)
Lai et al.	stance phase	-			+	**0**
Vismara et al	stance phase		**0**			

+: significantly higher in obese. **-**: significantly lower in obese. **0**: no differences. * central obese / lower obese.

Table A2.6. Kinetic differences between obese and normal-weight subjects on gait at standardized velocity.

HIP joint			extension	
			absolute (Nm)	relative (Nm/kg)
Browning and Kram	stance phase	0.50 m/s	+	**0**
		0.75 m/s	**0**	**0**
		1.00 m/s	+	**0**
		1.25 m/s	+	**0**
		1.50 m/s	+	**0**
		1.75 m/s	+	**0**
DeVita and Hortobagyi	stance phase	1.5 m/s	**0**	

KNEE joint			extension		adduction
			absolute (Nm)	relative (Nm/kg)	absolute (Nm)
Browning and Kram	stance phase	0.50 m/s	**0**	**0**	**0**
		0.75 m/s	**0**	**0**	+
		1.00 m/s	**0**	**0**	**0**
		1.25 m/s	**0**	**0**	+
		1.50 m/s	**0**	**0**	+
		1.75 m/s	+	**0**	**0**
Browning and Kram	stance phase	0.50 m/s	**0**	**0**	**0**
		0.75 m/s	**0**	**0**	+
		1.00 m/s	**0**	**0**	**0**
		1.25 m/s	**0**	**0**	+
		1.50 m/s	**0**	**0**	+
		1.75 m/s	+	**0**	**0**
DeVita and Hortobagyi	stance phase	1.5 m/s	**0**	-	

+: significantly higher in obese. **-**: significantly lower in obese. **0**: no differences.

Table A2.6. Kinetic differences between obese and normal-weight subjects on gait at standardized velocity. *(Continued)*

ANKLE joint			plantar flexion	
			absolute (Nm)	relative (Nm/kg)
Browning and Kram	stance phase	0.50 m/s	**0**	-
		0.75 m/s	**0**	-
		1.00 m/s	**0**	-
		1.25 m/s	**0**	-
		1.50 m/s	**0**	-
		1.75 m/s	**0**	-
DeVita and Hortobagyi	stance phase	1.5 m/s	+	

+: significantly higher in obese. **-**: significantly lower in obese. **0**: no differences.

Table A2.7. Differences between obese and normal-weight subjects on sit-to-stand movement.

	foot displacement	hip joint flexion anlges	ankle joint plantar flexion angles	hip joint flexion torque (Nm/kg)	knee joint extension torque (Nm/kg)	ankle joint flexion torque (Nm/kg)
Galli et al.		-	-	-	+	**?**
Sibella et al.	+	-		-	+	**?**

+: significantly higher in obese. **-**: significantly lower in obese. **0**: no differences. ?: unknown.

Appendix to Chapter 4

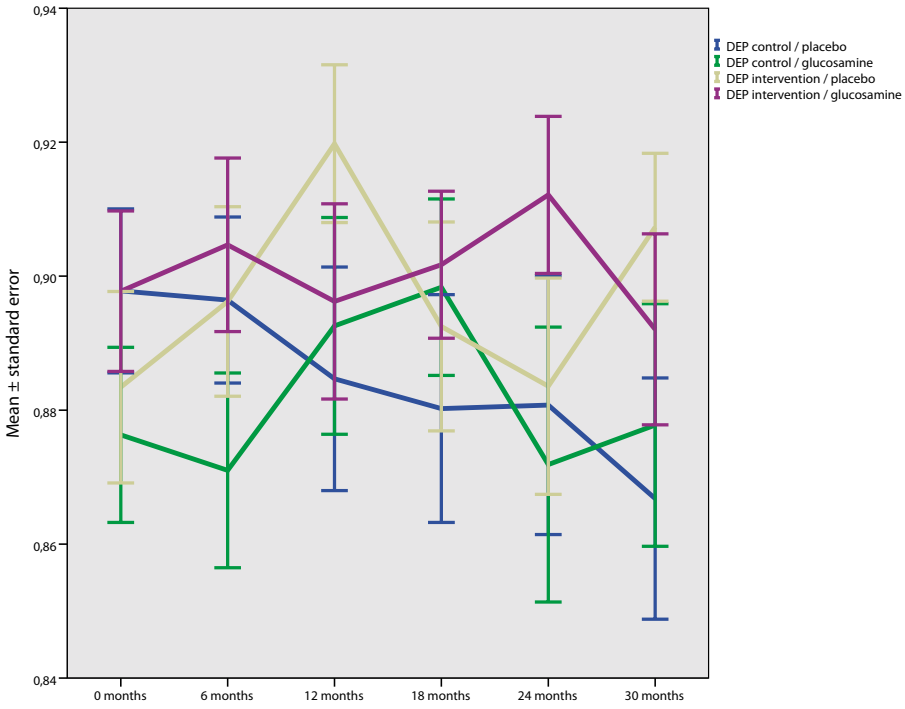

Figure A4.1. Mean quality of life (EuroQol) scores within randomized intervention groups.

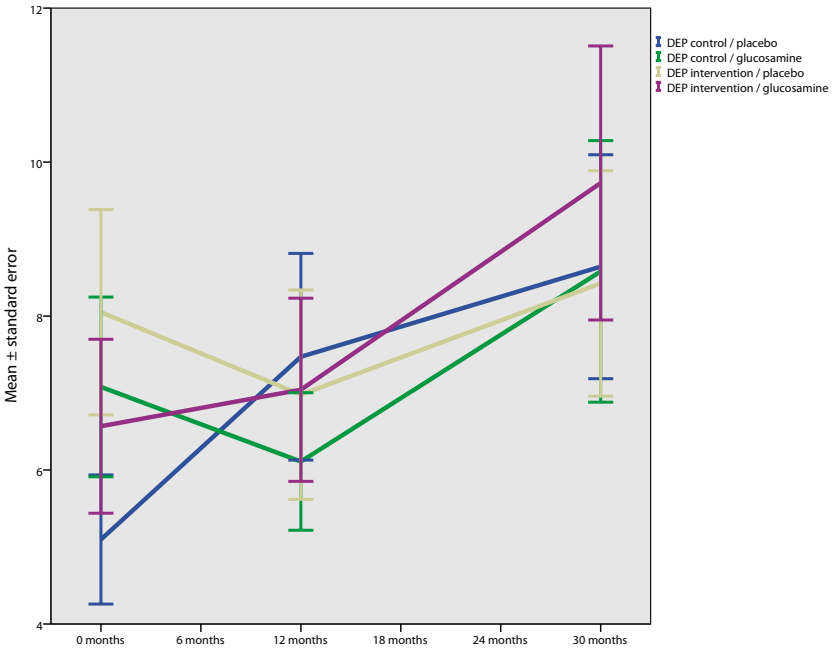

Figure A4.2. Mean WOMAC pain scores (range 0 – 100; higher scores mean more pain) within randomized intervention groups.

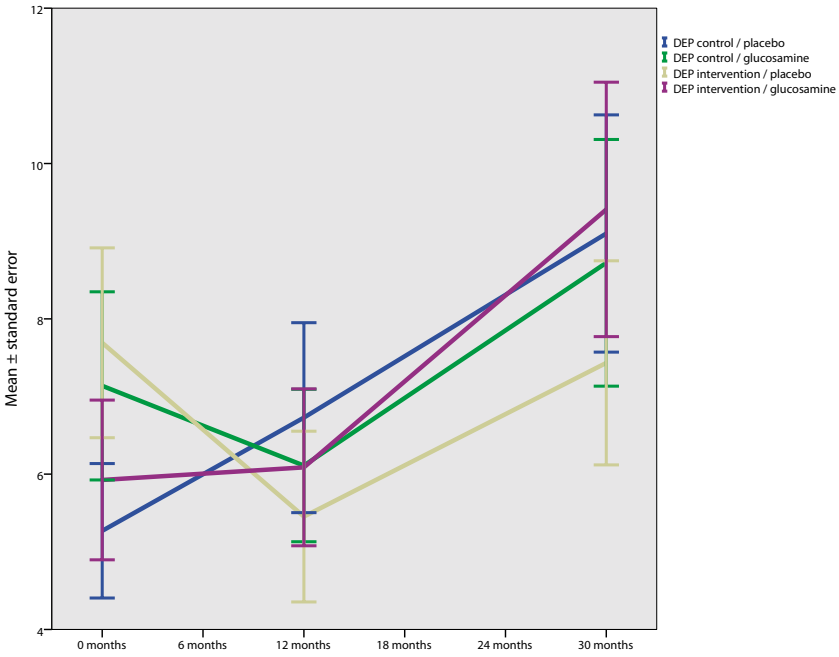

Figure A4.3. Mean WOMAC function scores (range 0 – 100; higher scores mean less function) within randomized intervention groups.

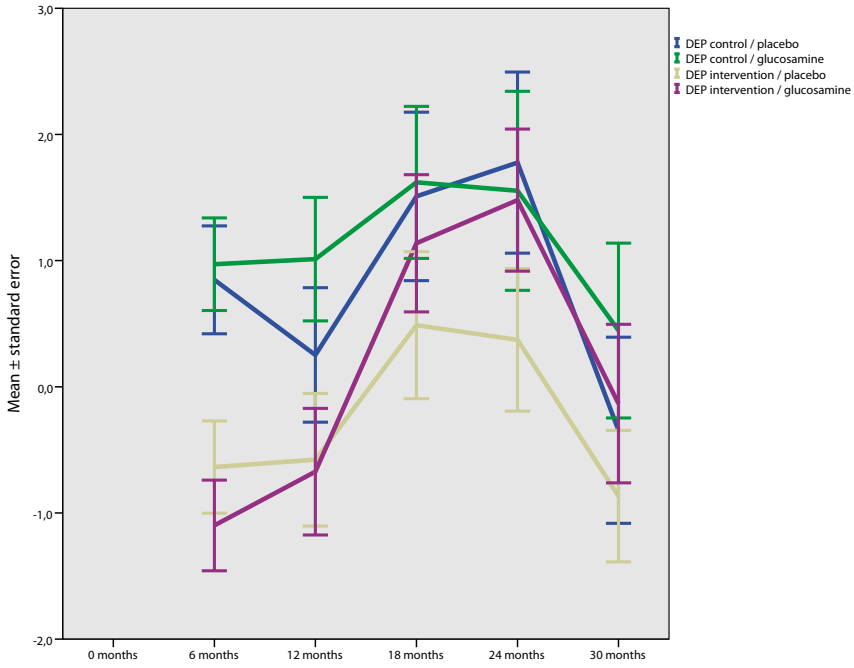

Figure A4.4. Actual weight loss (compared to baseline) within randomized intervention groups.

Summary

Osteoarthritis (OA) is the most common joint disease for the middle-aged and older population worldwide. Clinically, it is characterized by joint pain and limited function. Although the exact aetiology is still unknown, it is generally characterised by loss of articular cartilage, osteophyte formation, and subchondral bone sclerosis. Given the predominance of OA in the knee joint, main focus of scientific studies (including the present thesis) is on the knee joint.

For scientific studies, knee OA can be defined using the ACR criteria for clinical knee OA or the Kellgren & Lawrence criteria for the structural changes. Besides, the change in minimal joint space width (joint space narrowing) is also used as surrogate measure for the change in cartilage thickness. Despite the fact that all three measurements define (marked features of) knee OA, there is only moderate overlap between these measurements.

The strongest and most prevalent risk factors for the incidence of knee OA are overweight or obesity, a higher age, and female sex. In general, two main pathways are suggested for the onset of knee OA; biomechanical overload of the joint tissues and inflammation driven tissue breakdown. Since true disease-modifying treatment options are lacking, at best pharmacological and non- pharmacological treatment of symptomatic patients provide relief of their joint complaints and possibly slowdown disease processes. With accumulated knowledge of risk factors for the development of knee OA, the first step toward disease prevention could be considered. In **Chapter 4**, the results of the first ever preventive trial in OA research are presented.

A high body weight is the only undisputed known modifiable risk factor for the development of knee OA. In theory, based on an observational cohort with 40 years of follow-up, a weight reduction of 5 kg by overweight or obese women would reduce the incidence of knee OA by more than 50%. Since fat mass is known to be an endocrine organ producing a variety of unfavourable pro-inflammatory factors, weight loss might reduce the production of these factors by the loss of fat mass. On the other hand, as demonstrated in **Chapter 2**, the load on the knee joint is also altered in obese compared to normal-weight individuals. The systematic search of the literature on studies evaluating the biomechanical differences between obese and normal-weight individuals during every-day movements showed that obese individuals indeed alter their movement strategies. It could be suggested that the accompanied shift of the contact area towards infrequently loaded regions of the articular cartilage in the knee joint can cause knee OA. In theory, weight loss can also prevent knee OA since it is known that the alterations in movement patterns recover after weight loss.

A high body weight or body mass index (BMI) is known to be related to certain shape features of the femur and tibia. Both these features and a high BMI are related to early signs of knee OA. **Chapter 3** explores two possible pathways through which a high BMI

and bone shape features might be related to early signs of knee OA. The results show that not only a high BMI leads to shape alterations that are associated to early signs of knee OA, it was also shown that several shape features are only related to early signs of knee OA in the presence of a high BMI. Interestingly, the shape of the tibial spines seemed to play a role in all shape variations related to early signs of knee OA in the presence of a high BMI.

The main body of this thesis is formed by the PROOF study; the first ever preventive study in OA worldwide. For this study a high-risk group of 407 women with a BMI ≥ 27 kg/m^2, aged 50 to 60 years without clinical signs of knee OA was studied. In this study, the preventive effects of a diet and exercise program and of oral glucosamine sulphate on the development of knee OA were tested over 30 months of follow-up. Given the fact that the PROOF study was the first ever preventive study in OA, it holds value information about the feasibility of preventive trials in OA. Both the diet and exercise program and the glucosamine sulphate intervention showed trends towards a preventive effect (odds ratio 0.69, 95% CI 0.39 – 1.21 and 0.59; 95% CI 0.31 – 1.12, respectively). Unfortunately, the analyses were slightly underpowered due to the unexpected interaction between both interventions (**Chapter 4**). In **Chapter 5**, the diet and exercise program is evaluated in more detail. Despite the fact that the applied program was very pragmatic and much less restrictive than other reported weight loss interventions, the results of the program over the first year are very comparable. Subject randomized to the intervention group showed greater weight loss at 6 and 12 months compared to those randomized to the control group and also the number of subject fulfilling the target of ≥ 5 kg or 5% weight loss was significantly higher among subjects in the intervention group. Unfortunately, these effects did not last over the entire follow-up period of 30 months.

After 30 months, 17% of all subjects (61 women) reached the weight loss target of ≥ 5 kg or 5% weight loss compared to baseline. The effect of such substantial weight loss on the incidence of knee OA was evaluated in **Chapter 6**. Besides the positive effects of substantial weight loss on several health measures (fat percentage, blood glucose, waist circumference, and blood pressure), we found that subjects who fulfilled the weight loss target had significantly less development of knee OA after 30 months (15%) compared to those who did not fulfil this target (20%; odds ratio 0.50, 95% CI 0.27 – 0.91).

In order to provide the subjects randomized to the control group of the diet and exercise program with a possible preventive intervention as well, the PROOF study adopted a 2x2 factorial design using a glucosamine sulphate intervention. Glucosamine sulphate was thought to be an excellent intervention since there are indications that it is most effective in an early stage of the disease and should cause no harm to the subjects, as advocated by Society of Prevention Research. Over the 30 month follow-up period, the number of Adverse and Serious Adverse Events reported for both the placebo and the

glucosamine sulphate did not differ significantly and none of the events were reported to be related to the study drugs. Nevertheless, secondary analyses from the PROOF study showed that subjects randomized to glucosamine sulphate had a significantly increased risk (odds ratio 2.81, 95% CI 1.12 – 7.04) of attaining an elevated blood glucose level (HbA1c ≥ 42 mmol/mol) at follow-up (**Chapter 7**). This level of blood glucose is internationally marked as a 'high risk for developing diabetes'.

Finally, **Chapter 9** summarizes the main findings of this thesis and discusses the clinical implications and directions for future studies. Besides suggestions for optimizing the diet and exercise program as administered in the PROOF study, directions for new preventive measures are given. Based on the results of the present thesis, the most obvious new preventive measure to test in future studies would be to target varus alignment in overweight or obese subjects. As indicated in **Chapter 8**, knees with a varus alignment (40%) had a significantly increased risk for developing knee OA compared to neutrally aligned knees, especially among obese subjects. Since varus alignment can be opposed by non-surgical interventions, it might be a good target for future preventive studies.

Samenvatting

Artrose is wereldwijd de meest voorkomende gewrichtsaandoening bij mensen van middelbare leeftijd en bij ouderen. Klachten die bij artrose horen zijn gewrichtspijn en beperkte functie van het aangedane gewricht. De exacte oorzaak van artrose is niet bekend, maar het wordt in het algemeen gekenmerkt door een verlies aan kraakbeen in het gewricht, de vorming van vergroeiingen aan het bot (osteofyten) aan de randen van het gewricht en verkalking van het bot direct onder het kraakbeen. Artrose komt het meest voor in het knie gewricht. Vandaar dat de meerderheid van het wetenschappelijk onderzoek (inclusief dit proefschrift) zich focust op dit gewricht.

In wetenschappelijke studies wordt knie artrose gedefiniëerd met behulp van de ACR criteria voor symptomatisch knie artrose of met behulp van de Kellgren & Lawrence criteria, die de afwijkingen in het gewricht zoals die te zien zijn op een röntgenfoto kwantificeert. Daarnaast wordt gewrichtsspleet vernauwing gebruikt als maat voor de afname van gewrichtskraakbeen over tijd. Ondanks dat al deze definities (kenmerken van) knie artrose vaststellen, is de overlap tussen deze definities maar gering. Dit schets de beperkte kennis die er momenteel is over deze aandoening.

De sterkste en meest voorkomende risicofactoren voor het ontstaan van knie artrose zijn het hebben van overgewicht of obesitas, een hoge leeftijd en het vrouwelijk geslacht. Men verondersteld twee specifieke ontstaansmechanismen voor knie artrose; overbelasting en ontsteking van het gewricht. Vandaag de dag is er nog geen medicatie beschikbaar die schade aan het artrotische gewricht kan herstellen. Best mogelijke behandeling, zowel medicamenteuze als niet-medicamenteuze, voor mensen met artrose klachten biedt vermindering van pijn, verbeterde functie en, mogelijkerwijs, vertraging van het artrose proces. Met de kennis die over de afgelopen jaren is vergaard over de risicofactoren voor het ontstaan van knie artrose kunnen nu de eerste stappen worden gezet naar de preventie van deze aandoening. In **Hoofdstuk 4** worden de resultaten van de wereldwijd eerste wetenschappelijke studie naar de preventie van knie artrose gepresenteerd.

Een hoog lichaamsgewicht is de enige bekende risicofactor voor knie artrose die te beinvloeden is. Uit langlopende obeservationele studies in berekend dat als vrouwen met overgewicht of obesitas 5 kg zouden afvallen, het ontstaan van knie artrose, in theorie, met meer dan 50% zou afnemen. Aangezien vetcellen ontstekingsfactoren produceren zou deze afname in lichaamsgewicht leiden tot een verminderde productie door de afname in vetmassa en daarmee kunnen zorgen voor de verminderde incidentie van knie artrose. Daarnaast laten de resultaten van **Hoofdstuk 2** ook zien dat mensen met obesitas niet alleen een hogere, maar vooral ook een veranderde belasting van hun knieën hebben. Uit een vergelijking van alle eerder uitgevoerde studies naar het de biomechanise verschillen tussen mensen met en zonder obesitas tijdens allerdaagse activiteiten bleek dat mensen met obesitas deze taken duidelijk anders uitvoeren dan

mensen zonder obesitas. Deze veranderde uitvoering zou, in theorie, kunnen leiden tot de verschuiving van het contactpunt van het boven- en onderbeen in de knie naar delen van het kraakbeen die daar niet tegen bestand zijn en zo tot knie artrose kunnen leiden. Aangezien het bekend is dat de veranderde uitvoering van de allerdaagse activiteiten zich hersteld indien men sterk afvalt, zou gewichtsverlies dus ook via deze weg kunnen leiden tot een verminderde incidentie van knie artrose.

Een hoog lichaamsgewicht of BMI (Body Mass Index = gewicht / (lengte)^2) hangt samen met de vormafwijkingen van het boven- en onderbeen in het knie gewricht. Zowel deze vormafwijkingen als een hoog BMI zijn ook gerelateerd aan vroege tekenen van knie artrose. In **Hoofdstuk 3** worden twee mogelijkheden onderzocht waardoor vormafwijkingen en een hoog BMI zouden kunnen leiden tot vroege tekenen van knie artrose. De resultaten in dit hoofdstuk laten zien dat een hoog BMI niet alleen kan leiden tot vormafwijkingen die samenhangen met vroege tekenen van knie artrose, maar dat er ook vormafwijkingen zijn die alleen tot vroege tekenen van knie artrose leiden in mensen met een verhoogde BMI. Uit de analyses in **Hoofdstuk 3** blijkt dat met name de vorm van de eminentia (waar de kruisbanden en menisci op aanhechten) op het onderbeen een rol spelen bij het ontstaan van knie artrose bij mensen met een hoog BMI. Tot nu toe is de rol van de eminentia in het artrose proces nog niet veelvuldig onderzocht.

Het hart van dit proefschrift wordt gevormd door de PROOF studie (PRevention of knee Oasteoarthritis in Overweight Females); wereldwijd de eerste studie naar de preventie van artrose. Aan de PROOF studie deden 407 vrouwen met een hoog risico op, maar nog zonder tekenen of klachten van knie artrose mee. Alle deelneemsters waren bij aanvang van de studie tussen de 50 en 60 jaar oud en hadden allemaal een BMI ≥ 27 kg/m^2. Gedurende de studie (30 maanden) hebben we de preventieve effecten van een dieet- en beweeginterventie en van glucosamine sulfaat op het ontstaan van knie artrose getest. Aangezien dit de eerste keer is dat zo'n grootschalige preventieve studie is uitgevoerd, bevat het veel belangrijke informatie over de uitvoerbaarheid van studies naar de preventie van artrose; niet alleen voor knie artrose, maar ook voor artrose in andere gewrichten. Beide interventies lijken een preventief effect te hebben op het ontstaan van knie artrose na 30 maanden (odds ratio 0.69; 95% CI 0.39 – 1.21 en odds ratio 0.59; 95% CI 0.31 – 1.12 voor de dieet- en beweeginterventie en de glucosamine interventie respectievelijk). Echter was het effect van de dieet- en beweeginterventie bij de deelneemsters die placebo kregen tegenovergesteld aan van het effect bij de deelneemsters die de glucosamine kregen, en vice versa. Door deze onverwachtte interactie tussen de interventies zijn de analyses naar de interventie effecten licht '*underpowered*' (**Hoofdstuk 4**). In **Hoofdstuk 5** wordt de dieet- en beweeginterventie gedetailleerd besproken. Voor deze interventie is er voor een eenvoudig en pragmatisch programma gekozen dat veel minder strikt is dan eerder onderzochtte afvalprogramma´s. Desalniet-

temin zijn de effecten over het eerste jaar zeer vergelijkbaar met deze programma´s. Deelneemsters in de interventie groep hebben na 6 en 12 maanden significant meer gewicht verloren dan de deelneemsters in de controle groep. Bovendien was het aantal deelneemsters dat het beoogde doel van minimaal 5 kg of 5% afvallen (t.o.v. het gewicht bij aanvang van de studie) behaald had ook signifcant hoger op deze tijdstippen. Helaas hielden de interventie effecten niet aan tot aan het eind van de studie. In het totaal behaalde 17% van alle deelneemsters het doel van minimaal 5 kg of 5% afvallen na 30 maanden. Het effect van deze mate van gewichtsverlies op het ontstaan van knie artrose wordt besproken in **Hoofdstuk 6**. Hierin wordt aangetoond dat dit gewichtsverlies niet alleen leidt tot aan afname van het vetpercentage, bloedsuiker niveau, middelomtrek en bloeddruk optreedt, maar ook dat er significant minder knie artrose ontstaat (15% vs 20% in de deelneemsters die niet minimaal 5 kg of 5% afvallen. Odds ratio 0.50; 95% CI 0.27 – 0.91).

Om ook de deelneemsters in de controle groep van de dieet- en beweeginterventie een mogelijke preventieve interventie aan te bieden is er in de PROOF studie gekozen voor een 2x2 factorieel design. Hierbij werd de helft van alle deelneemsters in zowel de interventie groep als de controle groep van de dieet- en beweeginterventie gerandomiseerd naar placebo en de andere helft naar glucosaminse sulfaat. Glucosamine sulfaat versus placebo werd gezien als uitstekende interventie aangezien er aanwijzingen zijn dat het met name in de begin fase van het ontstaan van knie artrose effectief zou zijn en, minstens zo belangrijk, het middel bekend staat als voedingssupplement zonder bijwerkingen. Gedurende de 30 maanden dat de deelneemsters van de PROOF studie het voedingssupplement hebben gebruikt is het aantal meldingen van (ernstige) bijwerkingen als gevolg van de glucosamine sulfaat niet significant anders dan die van de placebo. Bovendien werd geen van alle bijwerkingen toegeschreven aan het gebruik van de glucosamine sulfaat. Echter bleek in secundaire analyses dat de deelneemsterd die gerandmiseerd waren naar de glucosamine sulfaat wel een significant verhoogd risico hadden (odds ratio 2.81; 95% CI 1.12 – 7.04) op het krijgen van een verhoogd bloedsuiker level (HbA1c ≥ 42 mmol/mol) na 30 maanden (**Hoofdstuk 7**). Internationaal worden mensen met dit bloedsuiker level aangeduid als personen met een 'hoog risico op het ontwikkelen van diabetes'.

Tot slot worden alle resultaten van dit proefschrift bediscussieerd in **Hoofdstuk 9**; klinische implicaties van de gevonden resultaten en mogelijkheden voor toekomstige studies worden besproken. Naast suggesties om de onderzochtte dieet- en beweeginterventie te optimaliseren worden ook andere mogelijke preventieve maatregelen besproken. De meest voor de hand liggende nieuwe preventieve interventie die onderzocht zou moeten worden, op basis van de resultaten in **Hoofdstuk 8**, is een interventie die zich richt op de belasting van de knie bij mensen met O-benen (varus stand) en

overgewicht of obesitas. In **Hoofdstuk 8** wordt aangetoond dat knieën met een varus stand (40% van de knieën binnen de PROOF studie) een significant hoger risico lopen op het ontwikkelen van knie artrose dan knieën zonder een standsafwijking; met name bij de mensen met obesitas. Aangezien een varus stand (deels) kan worden opgeheven met niet-chirurgische ingrepen zoals een zooltje of een brace, lijkt het een goede mogelijkheid om dit in een nieuwe preventieve studie te onderzoeken.

Dankwoord

Het is 1996; mijn moeder neemt mij mee naar de openbare verdediging van het proefschrift van onze buurman, Simon van der Kerke, in de Spuikerk te Amsterdam. Ik heb op dat moment geen flauw benul waar deze ceremonie voor dient, maar toch ga ik mee. Immers, "misschien maak je dit wel nooit meer mee", aldus mijn moeder en zij heeft altijd gelijk…… Inmiddels staat de teller op 24 bijgewoonde promoties en heb ik zelfs mijn eigen proefschrift afgerond, maar toch had ze gelijk; jong geleerd is oud gedaan.
Uiteraard moet ik een aantal mensen bedanken die mijn proefschrift mede mogelijk hebben gemaakt.

Sita, zonder jouw baanbrekende en gedurfde idee was de PROOF studie er nooit geweest en was dit boekje er dus ook nooit gekomen. Hartelijk dank voor de geboden begeleiding tijdens de uitvoer en analyse van de PROOF studie, alle suggesties voor nieuwe artikelen, presentaties en subsidieaanvragen, de geboden kansen voor een vervolg van mijn carrière in het onderzoek, maar uiteraard ook voor je geweldige manier van het leiden van je onderzoeksgroep. De goede sfeer, zowel op de afdeling en als tussen de onderzoekers, komt grotendeels op jouw conto; volledig terecht dat je bent uitgeroepen tot 'Promotor of the Year´ 2013!

Als er lastige beslissingen genomen moesten worden omtrent de PROOF studie of als onze 'vrienden uit Italië' dwarslagen was jij, Bart, er altijd om tot een juiste oplossing te komen. Bart, met name in de laatste fase ben je meer betrokken geweest bij mijn promotie traject. Het was een fijn idee om te weten dat je altijd bereikbaar bent voor een objectief en betrouwbaar advies. Zeer bedankt voor je bijdrage aan de PROOF studie en dit proefschrift.

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Ik ben zeer veel dank verschuldigd aan Diana, onderzoeksassistent van de PROOF studie. Diana, als iemand het hart van de PROOF studie is, ben jij het wel. Bescheiden als je bent zal je het zelf nooit zeggen, maar jij bent de reden dat de uitval van deelneemsters zo beperkt is gebleven en dankzij jouw precieze en gedreven manier van werken beschikken we nu over een unieke en kwalitatief hoogstaande data set. Dank voor al je inzet. Liana en Marienke hartelijk dank voor jullie voorbereidende werk voor de PROOF studie; het was een gespreid bedje. Metthilde, Toke en Evelien, heel fijn dat jullie konden in-

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Dank ook aan de goede collega's bij de afdelingen orthopedie, radiologie en interne geneeskunde voor hun bijdrage aan de wetenschappelijke en sociale activiteiten tijdens mijn promotieonderzoek.

Hoe leuk ik het ook vind in Rotterdam, toch ben ik blij met de afleiding die vrienden en familie geven. Vrienden van L2K en daar buiten en heren, dames en partners van de Wasvu, jullie weten niet half hoeveel voldoening en energie ik haal uit deze vriendschappen. Dank voor alle gezellige, hilarische, sportieve, grootse, kleine, maar bovenal waardevolle momenten. Arnold en Gertjan, ik ben zeer blij dat ik, niet alleen tijdens mijn promotie, maar ook bij de afsluiting daarvan, kan steunen op twee van zulke goede vrienden.

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Ten slotte, mijn meiden. Judith, allereerst excuses voor de eindeloze verhalen over analyses, artikelen, presentaties en nieuwe subsidie-ideeën. Met andere woorden, dank voor een luisterend oor. In ons drukke leventje ben ik zeer gelukkig met de rust en liefde die jij mij geeft. Britt, sorry dat papa niet beter kan uitleggen wat hij elke keer in Rotterdam gaat doen. Ik ben zeer trots op je en ja, papa is ook een beetje verliefd op jou!

Curriculum Vitae

Jos Runhaar is geboren op 31 december 1980 te Amsterdam. In 1999 behaalde hij zijn VWO diploma aan het Montessori Lyceum Amsterdam. In september 2000 begon hij aan de opleiding Bewegingswetenschappen aan de Vrije Universiteit te Amsterdam. Met een uitvoerige 3D-analyse onderzocht hij in zijn afstudeerproject de rol van onderarmkracht op de verschillen in golfswing tussen ervaren en onervaren golfers. Hij studeerde in mei 2005 af bij de richting Bewegingssysteem. Na zijn afstuderen werd Jos aangesteld als onderzoeksmedewerker bij het EMGO Instituut van het VUmc. Hier werkte hij anderhalf jaar mee aan de verzameling van gegevens voor de iPlay-studie. Aan deze studie naar de preventie van sportblessures bij basisschool kinderen deden meer dan 2200 kinderen uit heel Nederland mee. Na afronding van de iPlay-studie is Jos in maart 2008 begonnen aan zijn eigen promotieonderzoek. Op de afdeling Huisartsgeneeskunde van het Erasmus MC voerde hij de in dit proefschrift beschreven PROOF studie uit. Sinds januari 2013 werkt Jos als wetenschappelijk onderzoeker op de afdeling Huisartsgeneeskunde van het Erasmus MC aan een project naar subgroep analyses binnen studies die de effectiviteit van glucosamine bij artrose onderzocht hebben en werkt hij binnen een groot Europees consortium (D-BOARD) mee aan een studie naar de ontwikkeling van biomarkers voor de vroege herkenning van artrose.

PhD Portfolio

PhD Portfolio

	Year	Workload
Courses		
Methodologie van patiëntgebondenonderzoek en voorbereiding van subsidieaanvragen	2011	8 hours
BROK (Basis Regelgeving en Organisatie voor Klinische onderzoekers) cursus	2011	1 ECTS
Repeated measures in clinical studies (NIHES)	2011	1.4 ECTS
Presentations		
International		
OARSI World Congress Rome, poster	2008	1 ECTS
OARSI World Congress Montreal, poster	2009	1 ECTS
OARSI World Congress Brussels, poster	2010	1 ECTS
Primus Rotterdam, poster	2010	1 ECTS
OARSI World Congress San Diego, poster	2011	1 ECTS
OARSI Imaging Workshop Salzburg, oral	2011	1 ECTS
OARSI World Congress Barcelona, oral	2012	1 ECTS
ACR Annual Meeting Washington, oral	2012	1 ECTS
OARSI World Congress Philadelphia, oral and poster	2013	1 ECTS
National		
KNGF Fysio Congres Amsterdam, oral	2009	
NHG Wetenschapsdag, oral	2013	
Teaching activities		
Supervising medical student	2011	80 hours
Supervising medical student	2012	80 hours

List of publications

List of publications

This thesis

Runhaar J, Koes BW, Clockaerts S, Bierma-Zeinstra SMA. *A systematic review on changed biomechanics of lower extremities in obese individuals: a possible role in development of osteoarthritis.* Obesity Reviews, 2011; 12(12):1071-82.

Runhaar J, Schiphof D, de Klerk BM, Haverkamp D, Weinans H, Hofman A, Bierma-Zeinstra SMA, Waarsing JH. *Exploring the mediator and moderator effects of BMI and bone shape on early OA.* Under review.

Runhaar J, van Middelkoop M, Reijman M, Willemsen S, Oei EHG, Vroegindeweij D, van Osch G, Koes BW, Bierma-Zeinstra SMA. *Prevention of knee osteoarthritis in overweight females; the first preventive randomized controlled trial in OA.* Under review.

De Vos BC, Runhaar J, Bierma-Zeinstra SMA. *Effectiveness of a tailor-made weight loss intervention in primary care.* European Journal of Nutrition, 2013; in press.

Runhaar J, van Middelkoop M, Reijman M, Vroegindeweij D, Oei EHG, Bierma-Zeinstra SMA. *Malalignment; a possible target for prevention of incident knee osteoarthritis in overweight and obese subjects*. Under review.

Others publications

De Vos BC, Runhaar J, Verkleij SPJ, van Middelkoop M, Bierma-Zeinstra SMA. *Identifying latent classes of different weight loss trajectories in participants of a weight loss intervention*. Under review.

Vermaas K, Runhaar J. *Health-Promoting Effects of Eccentric Exercise.* Medicine & Science in Sports & Exercise, 2011; 43(9),1808.

Clockaerts S, Bastiaansen-Jenniskens YM, Runhaar J, van Osch GJVM, van Offel JF, Verhaar JAN, de Clerck LS, Bierma-Zeinstra SMA. *The infrapatellar fat pad should be considered as an active osteoarthritic joint tissue: a narrative review.* Osteoarthritis and Cartilage, 2010; 18(7):876-82.

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Runhaar J, Collard DCM, Singh AS, Kemper HCG, van Mechelen W, Chinapaw M. *Motor fitness in Dutch youth: differences over a 26-year period (1980-2006)*. Journal of Science and Medicine in Sport, 2010; 13, 323–328.

Stellingen

1. Vrouwen van middelbare leeftijd met een BMI ≥ 27 kg/m^2, zonder knieklachten zijn zeer bereid om aan een studie ter preventie van knieartrose deel te nemen. (dit proefschrift)
2. Een op het individu gerichte dieet- en beweeginterventie leidt tot een significante afname in lichaamsgewicht na 1 jaar bij vrouwen van middelbare leeftijd met een BMI ≥ 27 kg/m^2. (dit proefschrift)
3. Vrouwen van middelbare leeftijd met een BMI ≥ 27 kg/m^2 schatten hun gezondheidstoestand (te) hoog in. (dit proefschrift)
4. Vormafwijkingen van de intercondylaire eminentia op het tibia plateau hangen samen met vroege tekenen van knie artrose in vrouwen met overgewicht. (dit proefschrift)
5. Het hebben van O-benen vormt een risico factor voor het ontstaan van knieartrose in vrouwen van middelbare leeftijd met een BMI ≥ 27 kg/m^2. (dit proefschrift)
6. Kijken naar sportreclames leidt bij mensen met een hoog BMI tot een gezonder eetpattroon. (van Kleef et al. 2011)
7. Korte en lichte fysieke inspanningssessies tijdens het werk hebben een positief effect op het zelfvertrouwen, ervaren stress en lichamelijke klachten van werknemers. (Barr-Anderson et al. 2011)
8. Fluoroscopie is een nauwkeurigere methode voor het bestuderen van de biomechanische risicofactoren voor het ontstaan van knieartrose dan de traditionele bewegingsanalyses met huidmarkers. (Anderst et al. 2009)
9. Jonge, actieve volwassenen moeten na een kruisband ruptuur kiezen voor een uitgebreide fysieke revalidatie alvorens alsnog een kruisband reconstructie te overwegen. (Frobell et al. 2013)
10. De effecten van een meniscusscheur op het onderliggende kraakbeen is in de mediale meniscus veel lokaler dan in de laterale meniscus. (Chang et al. 2011)
11. *The time you enjoy wasting is not wasted time* (Bertrand Russell)

DEVELOPMENT AND PREVENTION OF KNEE OSTEOARTHRITIS

Knee osteoarthritis (OA) affects a large portion of the middle aged and older population and has a great burden on healthcare costs worldwide. This thesis focusses on the development of knee OA in subjects with overweight or obesity. The results of the first ever preventive trial in OA research are presented. The primary and secondary effects of a diet and exercise program and of glucosamine sulphate on the development of knee OA are discussed and implications for future (preventive) studies on knee OA are given.