Hip Osteoarthritis in General Practice

Course and Therapies

Rianne Rozendaal

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Hip Osteoarthritis in General Practice:

Course and Therapies

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beloop en therapieën

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General introduction

BACKGROUND

Osteoarthritis

Osteoarthritis (OA) is one of the leading causes of disability among elderly people[1]. The disease is characterized by joint pain and functional limitations. Osteoarthritis is a disease of the whole joint. Cartilage degradation is one of the main features, which is also easily recognized on a radiograph. But not only the cartilage is affected, osteoarthritis is also characterized by the occurrence of osteofytes, cysts and subchondrol sclerosis. The muscles, ligaments and synovium surrounding the joint also become affected[2].
Knee osteoarthritis is twice as prevalent as hip osteoarthritis. The prevalence of symptomatic and radiographic knee OA is 12.2%, whereas it is 7.4% for symptomatic and radiographic hip OA in adults over 60 years[3]. This has resulted in a focus on knee osteoarthritis in most studies to date. Most of the studies assessing the effectiveness of therapies are done in patients with knee osteoarthritis. It is easily assumed that results are also applicable to hip osteoarthritis. However, there are major differences between knee and hip osteoarthritis. First of all, the joints are very different in anatomy, therefore the load patterns on the joint are not comparable. Also, the type of pain in hip OA is thought to be different than that of knee OA. Hip pain is thought to progress more rapidly from mild to severe and is described as more intense[4]. Hip osteoarthritis is a large problem in the older population, which is somewhat underrepresented in the literature until now. Therefore, the focus in this thesis will be on hip osteoarthritis.

Treatment

The treatment of osteoarthritis has long been focused on relieving symptoms. Pain medication such as paracetamol and NSAIDs are commonly used drugs for the treatment of pain caused by osteoarthritis. Other treatments such as physical therapy and possibly braces have also been reported to have a positive effect on symptoms. The effect sizes of these common therapies in general are small to moderate[5]. However, besides surgical joint replacement, the most rigorous treatment of OA, there is no treatment available yet that will alter the progression of osteoarthritis with respect to symptoms or to the degenerative process. In the last decade the search for a disease modifying treatment has been intensified. The therapies that seem most promising are risedronate, a biphosphonate, doxycycline, an antibiotic, diacerein, and glucosamine. All of these therapies are claimed to work as disease

modifiers. For all of these interventions further evidence is needed to confirm or refute their efficacy. This thesis, in part, has focused on glucosamine.

Glucosamine

Glucosamine has been the topic of much debate in the last decade. It is a natural building block of cartilage[6]. The exact mechanism of action in the possible effectiveness of glucosamine on osteoarthritis is not known, but it is thought to have anti-inflammatory activities, and to affect cartilage metabolism[6]. Glucosamine is registered in most countries as a dietary supplement. It has been tested in different compounds, being glucosamine hydrochloride and glucosamine sulfate.
At the time of the start of our study glucosamine had already been tested in a number of trials that focused on knee osteoarthritis, with the exception of 3 early trials that also included patients with other affected joints[7-9]. The earlier trials were all very positive, but the more recent ones showed smaller effects on pain, or no effect at all. Most studies had a short follow up and could therefore only study the effect of glucosamine on symptoms, and not the underlying disease process.
The different compounds tested showed different results. Glucosamine sulphate was found to be effective in most of the trials, whereas glucosamine hydrochloride did not yield positive effects in all of the trials in which it was tested[10].
Two trials were published that tested the effect of glucosamine over a 3-year period. These two long term trials[11 12] not only found that glucosamine relieved the symptoms of knee OA, but also reported that it slowed down the radiographic progression of OA. This was first indication that glucosamine could act as a disease modifier, not only as a symptom modifier. Some, however, expressed concern about the non standardised radiography protocol used in these two trials[13-15], and further study was therefore needed to clarify these findings. Because of the lack of data on the effect of glucosamine on patients with hip osteoarthritis, we designed a trial on the effectiveness of glucosamine sulfate in primary care patients with hip osteoarthritis.

Subgroups of patients

Osteoarthritis is a multifactorial disease, different systemic and biomechanical factors play a role in the onset and development of the disease[16]. Generalized disease, in which multiple joints are involved is thought to be a different disease than localised OA, in which only one joint-site is involved[17]. Different risk factors seem to be related to osteoarthritis in different joints[17]. The presentation of the disease can be very variable between patients. Some patients have little complaints while

they have extensive damage to their joints, whereas others have little damage, but disabling complaints.
Because osteoarthritis is such a multifactorial disease, and the course of the disease varies greatly, it is very likely that not all patients will benefit from the same therapies. Current guidelines for the management of OA include a proposition which states that treatment of knee and hip OA should be tailored according to joint risk factors, general risk factors, level of pain intensity and handicap, and location and degree of structural damage[18 19]. However these recommendations are largely based on consensus, as there is not much evidence to support it. Although for glucosamine there were indications that patients with milder radiographic OA responded better to treatment with glucosamine sulphate[20 21].
In this thesis we have tried to find evidence for the existence of subgroups of patients that benefit more from different interventions, being glucosamine sulphate, and exercise therapy.
In the design of the trial we used stratified randomisation, which divided our patients into 4 groups based on severity of the radiographic osteoarthritis, and localisation of osteoarthritis, to allow subgroup analyses.

Course of hip OA

The course of OA is difficult to describe as it varies depending on whether one evaluates symptoms or radiographic change, and depending on the joint of interest[22]. Radiographic osteoarthritis does not seem to progress as rapidly as was assumed before[23]. We know that on group level, pain and functional status seem to deteriorate slowly over time for both knee and hip OA[24 25]. Over the short term we know that osteoarthritis symptoms can vary substantially within patients on a weekly basis[26].
However, we do not know to what extent the individual symptoms vary when patients are followed for a longer period of time. In most intervention studies or cohorts, patients are assessed for symptoms every 6 months or every year, and group averages are reported.
Most studies up to now have tried to assess what determinants are related to a progression in radiographic disease. Recent studies found radiographic severity, as well as different factors obtained by history taking and physical examination to be associated with total hip replacement surgery [27-29].
Data concerning factors associated with progression of symptoms in knee and hip osteoarthritis is scarce. A review from 2006 found limited evidence for factors that were associated with deterioration of functional status in knee OA patients, however for hip OA no evidence was found due to the low quality of the studies [24].

We used the data of our trial to assess what the course of hip OA symptoms was over a period of two years, with intermediate measurements every 3 months. This data was also used to assess what determines whether someone is going to progress with respect to pain and function complaints.

Shape and bone density

In most studies the Kellgren & Lawrence score and joint space width or narrowing are used to assess what patients are likely to progress with respect to symptoms and radiographic measures. However, the associations between these classic measures and pain and function is questionable[30 31], although not as discordant as it was previously thought[32]. In a recent study the shape of the femoral neck as measured on an x-ray was shown to be different between subject that were to develop hip OA and those that were not[33]. This study showed that radiological changes from an x-ray could show development of the disease before the more classical measures of radiological OA (Kellgren & Lawrence) could detect hip OA. On the basis of these results we hypothesised that variations in the shape and bone density of the proximal femur, which were measured on a DXA scan in our study, could predict radiographic and maybe even symptomatic progression.

Medical consumption

Osteoarthritis is currently the number 12 most expensive disease in the Netherlands[34]. What part of these costs is attributable to patients with hip osteoarthritis is not known. We know that the direct medical costs for knee osteoarthritis per patient were around €590 in 2000-2001[35]. However, for hip osteoarthritis, the direct costs are unknown. There is also not much data available concerning what determines whether a patient with hip OA seeks health. What we do know, however, is that the costs for OA are expected to increase over the coming decades due to the ageing of the population in Western societies.
The management strategies of GPs and orthopaedist will comprise a large part of the costs involved, as they are the medical doctors mostly involved with the treatment of OA. We used data of our study to describe the determinants and costs of medical consumption in a group of hip OA patients that had recorded their medical consumption for a period of two years. These data will give an insight into when patients visit their medical doctor and what the management strategies of GPs and orthopaedists are.

AIM OF THE THESIS

The overall objective of the studies in this thesis is to describe the course of symptoms and radiographic progression in patients with hip OA in primary care, and to test effectiveness of glucosamine sulphate and exercise therapy to alter this progression. By looking at determinants of the course of progression and by looking at effectiveness of therapies in subgroups of patients, we have tried to find different characteristics within hip osteoarthritis patients that may be relevant for the development and evaluation of future interventions.

Outline of the thesis

Chapter 2 gives an extensive overview of the methods of the trial that we have performed to study the effect of glucosamine sulphate in primary care patients with hip osteoarthritis. The results of the trial are presented in **chapter 3**. In **chapter 4** the results of the trial are again analysed but now in prespecified and exploratory subgroups of patients.
The aim of **chapter 5** is to examine whether there are subgroups of patients with osteoarthritis that benefit more from exercise therapy. In **chapter 6** the course of hip osteoarthritis symptoms is described over a two-year period, and the factors associated with progression of these symptoms. **Chapter 7** is a first attempt to use variations in the shape and density of the proximal femur to predict the symptomatic and radiographic progression of hip osteoarthritis. **Chapter 8** describes the medical consumption of patients with hip osteoarthritis and the associated determinants and costs. **Chapter 9** reflects on the main findings of the previous chapters, as well as the study limitations and their implications.

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2

The effect of glucosamine sulphate on osteoarthritis: design of a long-term randomised clinical trial

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ABSTRACT

Background

Pharmacological treatment for osteoarthritis (OA) can be divided into two groups: symptom-modifying drugs and disease-modifying drugs. Symptom-modifying drugs are currently the prescription of choice for patients with OA, as disease-modifying drugs are not yet available in usual care. However, there has recently been a lot of debate about glucosamine sulphate (GS), a biological agent that is thought to have both symptom-modifying and disease-modifying properties. This assumption has yet to be proved.
The objective of this article is to present the design of a blind randomised clinical trial that examines the long-term symptom-modifying and disease-modifying effectiveness of GS in patients with hip OA. This trial is ongoing and will finish in March 2006.

Methods/Design

Patients with hip OA meeting the ACR-criteria are randomly allocated to either 1500 mg of oral GS or placebo for the duration of two years. The primary outcome measures, which are joint space narrowing (JSN), and change in the pain and function score of the Western Ontario McMaster Universities Osteoarthritis index (WOMAC), are determined at baseline and after two years of follow-up during the final assessment. Intermediate measures at three-month intervals throughout the trial are used to study secondary outcome measures. Secondary outcome measures are changes in WOMAC stiffness score, quality of life, medical consumption, side effects and differences in biomarker CTX-II.

BACKGROUND

Pharmacological treatment for osteoarthritis (OA) can be divided into two groups: symptom-modifying drugs and disease-modifying drugs[1]. Symptom-modifying drugs are at present the prescription of choice for patients with OA. Drugs in this group are: simple analgesics (such as acetaminophen) and non-steroidal anti-inflammatory drugs (NSAIDs). Both acetaminophen and NSAIDs are effective in relieving symptoms of OA. In more severe stages of the disease NSAIDs are more effective, however, they are also the cause of serious side effects[2].

Disease-modifying drugs (i.e. drugs which alter disease progression) are not yet available in usual care. Although there has recently been a lot of debate about some biological agents that are thought to have both symptom-modifying and disease-modifying properties, results from previous trials have not been convincing. Of these biological agents, glucosamine sulphate seems to be the most promising.

Glucosamine sulphate (GS) has been shown to be an effective symptom-modifying agent, with effect sizes ranging from moderate to high[3 4]. In four trials that compared GS and NSAIDs, GS was found to be as effective as, or slightly more effective than NSAIDs[4]. Together with the fact that no serious adverse events have been reported concerning GS[3 4] this implies that GS may be a good alternative to NSAIDs. However, due to publication bias and due to quality issues in the trials studying GS, it may well be that reported effect sizes are exaggerated. A more recent trial studying the effect of GS did not find a difference between GS and placebo[5]. Also, several other uncertainties exist concerning the symptom-modifying properties of GS. For example, most trials were only of short-term duration (e.g. mean 6.25 weeks[4]) and it is therefore not possible to draw conclusions about the long-term efficacy. Another problem is that the mechanism behind the improvement of symptoms due to GS is not known. If GS directly influences the remaining cartilage, it would seem plausible that the symptomatic effect is greater in people with mild to moderate OA than in people with more severe OA, because there is more cartilage remaining in the first group. However, this possible difference in effect between different stages of OA has not been tested yet in a randomised clinical trial (RCT). These uncertainties make further study into the magnitude of long-term symptom-modifying effects in different stages of the disease justified.

Concerning disease-modifying effects, two recent long-term (three years) trials in patients with knee OA did report some evidence that GS affected the progression of OA[6 7]. Progressive joint space narrowing in the narrowest medial compartment of the tibiofemoral joint was used to define progression of knee OA (as recommended by a task force of the OA research society[8]). Whereas joint space narrowing (JSN), had significantly progressed in the placebo groups, it had not in the groups that

were taking GS. This implies that daily intake of GS acted against progression of OA. However, these results are controversial, because both trials lacked appropriate and standardised protocols for taking radiographs. Although it is not likely that this influenced the results much[9], it is necessary to reproduce them in a study with well-standardised protocols. These two long-term trials both looked at the effect of GS on knee OA, no trial has been or is being performed yet that looks at its effect on hip OA.

Based on the above, we designed a long-term trial to answer our main question: Does glucosamine sulphate favourably modify progression of osteoarthritis? Because there still is uncertainty about the symptom-modifying properties of GS we will also try to answer three secondary questions: Does GS have the same effects in all stages of OA? What is the long-term cost-effectiveness of addition of GS to usual care? And, does GS prevent the onset or progression of OA in the contralateral hip joint? Additional to these clinical questions, the data will be used to look at changes on cell-level caused by GS to learn more about its possible mechanisms of action. All results derived from this trial will be published using our International Standardised Randomised Controlled Trial Number (ISRCTN).

In this article we will present the detailed protocol of the trial. This trial is ongoing; at the moment all patients are included and have passed the first 9 months of the follow-up period.

METHODS/DESIGN

Study Design

This study is a randomised, blinded, placebo-controlled trial. All actors in this trial, who may cause bias, are blinded to treatment allocation: the patient, who is the assessor of the symptomatic outcomes, the researcher, who is the assessor of the objective outcomes, and the caregiver. The analyses will also be performed blind. The study design was approved by the Medical Ethics Committee at the Erasmus MC - university medical centre Rotterdam. All patients gave written informed consent.

Patient selection

General practitioners in the Rotterdam area agreed to search their electronic medical record for patients diagnosed with hip OA and for patients with symptoms associated with hip OA (i.e. persistent hip pain in combination with NSAID use).

These patients are contacted by their general practitioner and informed about the trial. For more information, patients can forward their contact details to the researchers. These patients then receive an extensive information folder containing all the information needed to make an informed decision about participation in the study. This folder has been reviewed and approved by the medical ethics committee.
The information folder also contains an informed consent form, which patients need to fill out if they want to participate in the study. Patients who give written informed consent are contacted by phone for a preliminary check of the inclusion and exclusion criteria. People meeting these criteria are invited to the research centre of Erasmus MC for a baseline-measurement, during which the criteria can be checked more precisely.

In- and exclusion criteria

Patients are eligible for inclusion when they meet one of the ACR criteria for hip OA[10]. Patients that have already undergone hip replacement surgery or those on the waiting list for joint replacement are not included in the study. Neither eligible patients with a Kellgren & Lawrence (K-L) score of 4[11], nor people with renal and/or hepatic disease, diabetes mellitus or a disabling co-morbidity are included. Finally, patients unable to understand Dutch questionnaires are excluded from participation.

Sample size

The sample size was calculated primarily to detect clinically relevant differences in radiological progression of the affected joints between the two groups (treatment and placebo) after two years of follow up. To detect a difference of 0.25 mm in radiological progression (SD 0.5) between the intervention and placebo groups (power 80%, alpha 5%, one-tailed testing) after two years of follow-up, 63 patients with hip osteoarthritis are needed per group. These calculations are based on an average change of 0.33 mm in joint space (SD 0.5) during one year of follow-up of patients with hip osteoarthritis[12].
Fewer patients are needed to detect relevant clinical differences: to detect a difference of 25% in pain (Western Ontario McMaster Universities Osteoarthritis index (WOMAC)) with one-tailed testing, a power of 80%, and alpha 5% (Mean 4.83, SD 2.25[13]) 55 patients per group are needed. To detect the same difference in function (WOMAC) (mean 4.81, SD 2.18[13]) 51 patients are needed per group.

As we expect a 20% loss to follow-up, we need to include 150 patients. However, to create options for studying effect-modification by type and severity of osteoarthritis, we oversized this trial to 220 patients (110 in each group).

Intervention

Patients who participate in the trial are randomised to either GS or a placebo for the duration of two years. To ensure a daily intake of 1500 mg GS, they are required to take two pills each day. The GS and placebo pills are identical in taste and appearance and were delivered in identical plastic bottles. This will ensure true blinding of the patients and of the researchers. Blinding of the patients will be tested after two years; if people can guess what sort of pills they were taking, this might have an influence on the subjective measures. This will therefore be taken into account in the analysis of the data. The Department of Nutritional Sciences at Numico Research BV manufactured the pills used in this trial.

Randomisation

Following informed consent and baseline assessments, patients are allocated to the intervention or control group using a blinded randomisation list. The randomisation list contains four different strata and is randomised per block of six numbers. This list was generated with a computer by an independent researcher. This researcher also handled labelling the pill-bottles with the randomisation numbers. The researchers involved in this project received all bottles after they were labelled, ensuring blinding to treatment allocation. The randomisation list with the key to treatment allocation will be kept in a safe until the end of the trial. To be able to perform the analyses blinded, the allocation to treatment A and treatment B will be provided, but not the key to A and B.
People are assigned to one of the four different strata on the basis of the Kellgren-Lawrence score of the hips, knees and hands. A researcher (RMR) will score all the radiographs according to the Kellgren-Lawrence score. The outline of the four different strata is given in Table 1. Once the correct stratum is established at baseline, the patient is given the subsequent unique four-digit randomisation number from his/her stratum on the randomisation list. This number is used for labelling study materials and data. By stratifying, patients are optimally distributed to GS and placebo in the different strata, which makes comparing people with mild OA to people with moderate-severe OA, and comparing people with local OA to people with generalised OA possible. In this way, we will be able to study whether effect of treatment depends on severity or localisation of OA.

Table 1: Outline of the randomisation strata

	Hip radiograph	*Knee and hand radiographs*	*Type*
Group 1	K-L score < 2	K-L score < 2 for hands and knees	mild + localised
Group 2	K-L score < 2	K-L score ≥ 2 for hands and/or knees	mild + generalised
Group 3	K-L score ≥ 2	K-L score < 2 for hands and knees	moderate/severe + localised
Group 4	K-L score ≥ 2	K-L score ≥ 2 for hands and/or knees	moderate/severe + generalised

Measurements

Data for the primary and secondary outcome measures are being collected at different time-points throughout the trial. An overview of the timing of the measurements and the outline of the primary and secondary outcome measures is given in Table 2.
In brief, the trial starts for every patient with a baseline assessment at the research centre. At the end of this assessment, patients receive a supply of GS or placebo sufficient for seven months. After the baseline assessment, patients will receive a questionnaire every three months, which has to be returned to the researchers, except from those at 6, 12 and 18 months after baseline, which will be collected by the researchers during a home visit. After two years, patients return to the research centre for the final assessment, which marks the end of the trial. The collection of the outcome measures is described in the following sections.

Radiographs

Radiographs are taken during the baseline assessment and during the final assessment two years later.
At baseline, three anteroposterior (AP) radiographs are taken, one of the pelvis, one of both knees, and one of both hands. All radiographs are used to establish what stratum the subject belongs to (Table 1). The radiographs of hands and knees will not be used to determine outcome measures and will therefore not be repeated at follow up. As follows from Table 1, people with knee and/or hand OA are stratified to one of the 'generalised OA' groups (2 or 4).
A highly standardised protocol is used to make the weight-bearing, AP pelvic radiographs at baseline and follow-up, allowing for a correct measurement of our primary outcome variable: joint space narrowing. The patients' feet are positioned alongside a frame, which was designed to ensure 15° internal rotation of the hips. A second frame (no internal rotation) is available for patients with severe mobility restrictions of the hips. The frame used during the baseline radiograph of a patient will also be used two years later for his/her follow up radiograph. Patients

Table 2: Timing of measurements and outline of primary and secondary outcome measures

	0m B.A.	*3m* Q	*6m* Visit	*9m* Q	*12m* Visit	*15m* Q	*18m* Visit	*21m* Q	*24m* F.A.
Primary outcome measures									
Joint space width	x								x
Pain score (WOMAC)	x								x
Function score (WOMAC)	x								x
Secondary outcome measures									
Subchondral bone quality	x								x
Stiffness score (WOMAC)	x	x	x	x	x	x	x	x	x
Quality of life (EuroQol EQ-5D)	x	x	x	x	x	x	x	x	x
Medical consumption	x	x	x	x	x	x	x	x	x
Side effects		x	x	x	x	x	x	x	x
CTX-II	x		x		x		x		x
Possible confounders/ Effect modifiers									
Type of OA (localised – generalised)	x								
Radiological severity	x								x
Joint function	x								x
Age	x								
Gender	x								
Activity level	x	x	x	x	x	x	x	x	x
Co-interventions	x	x	x	x	x	x	x	x	x
Compliance (BMQ)		x	x	x	x	x	x	x	x
Compliance (pill count)			x		x		x		x

Note: 0m: 0 month of follow up, 3m: 3 months of follow up etc. B.A.: baseline assessment. Visit: 6 monthly visit. F.A.: final assessment

are asked to stand upright. If present, flexion in hips or knees is recorded. Protocol for the pelvic X-ray further states that focus-to-film distance should be 130 cm and that the X-ray beam should be centred on the superior aspect of the pubic symphysis. The X-rays are digitised.

The X-rays from baseline and final assessment will be analysed side by side. The minimal joint space width (JSW) will be identified from the baseline X-ray by assessing four different points: medial, axial, superior and lateral[14]). The researcher will also identify a point that appears to be the minimal JSW. From these five points the actual minimal JSW will be determined. This point will be used to measure changes in joint space width over the two-year follow up period.

Dexa-scan

During the baseline and final assessment, a Dual Energy X-ray Absorptiometry (DEXA) scan will be used to make scans of the pelvis. A frame similar to the one used for the radiograph of the hips is also used to make the DEXA-scan, ensuring 15° internal rotation of the hips. The scan will be used to study quantitative changes in subchondral bone density both of the affected joint and of the contralateral joint. Subchondral bone-density alterations might indicate osteoarthritic progression. This long-term trial can be helpful to determine whether pre-clinical OA can be recognised from a DEXA-scan. And, if so, whether GS prevents the onset or progression of OA in the pre-clinical stage.

Physical examination

A physical examination is carried out at baseline and is repeated during the final assessment. At baseline, this test is first of all used to check part of the inclusion criteria. Various tests are also carried out to check for co-existing musculoskeletal disorders. Findings from the physical examination will be used as baseline characteristics, and to register clinical signs and joint function after two years of follow up. Joint function is established by assessing pain due to joint motion, and by measuring limitation of joint motion with a two-arm goniometer.

Questionnaires

Throughout the study, patients will fill out a total of nine questionnaires. The first during the baseline assessment, followed by a questionnaire every three months in the following two years (including the last one during the final assessment).
The baseline questionnaire is used to measure different patient characteristics (age, gender, race, social status, Body Mass Index (BMI)), disease related characteristics (localisation of symptoms, duration of symptoms, family history) and co-morbidities. Of these characteristics, BMI and co-morbidities will be monitored throughout the trial.
Three validated instruments are used in all nine questionnaires: the WOMAC questionnaire will be used to establish severity of clinical status. It contains subscales for pain, stiffness and function. The WOMAC questionnaire is extensively validated and recommended for clinical assessment in osteoarthritis trials by the WHO[15]. The EuroQol (EQ-5D) will be used to measure quality of life, because of the usefulness of this scale in cost-effectiveness analysis[16 17]. The cost-effectiveness analysis will also be based on employment status, sick leave, changes in work-tasks

or other work-related adjustments, and on medical consumption. The SQUASH questionnaire is used to measure load level in work and sports[18].
In the eight follow-up questionnaires, patients will be asked to answer questions about alterations in their symptoms (i.e. whether they improved or deteriorated), which will be measured with a 7-point Likert scale. Also, compliance to treatment is measured with the Brief Medication Questionnaire (BMQ)[19].

Laboratory assessments

At baseline, two samples of blood are collected. The first to measure the erythrocyte sedimentation rate (ESR), which is used for the inclusion criteria (ACR-criteria). The second sample is stored at −20°C to create options for future DNA-research, for which patients gave separate written informed consent.
Throughout the study, we will collect samples of second-morning void urine of all patients. In urine a marker of cartilage degradation can be found, called CTX-II. In the Rotterdam study[20] this marker was found to be predictive of radiological progression of hip and knee OA. It may therefore be used to assess the effect of treatment on the progression of OA. Urine samples will be collected at baseline and once every six months during follow up. At the end of the study a total of five samples will be available from every patient. These urine samples are stored at −80°C. If promising new markers are discovered during the course of the study, these can also be included in the analysis.

Half-yearly visits

Every six months one of the researchers will visit the patients at home. The main reason for this visit is to provide the patient with new pills (sufficient for seven months). To be able to calculate compliance to treatment, the pills remaining of the previous supply will be collected. The amount of remaining pills combined with the score on the compliance questionnaire (BMQ) will give a good indication of the actual amount of pills the patient has been taking. Finally, a sample of second-morning void urine on the day of the visit will be collected.

Analyses

The researchers will be aware of allocation to treatment A or B at the time of the statistical analyses, but will not know which group received GS and which group received the placebo. All analyses will take place after the trial has finished, no intermediate analyses will be performed.

Success of randomisation and normality of outcome measures will be checked before actual analyses are done. Differences in the primary outcome measures JSN and WOMAC (pain and function) between the intervention and placebo group will be analysed on the basis of the 'intention to treat' principle using linear regression models. Additionally a per-protocol analysis will be done. When it turns out that randomisation was (partially) unsuccessful, we will adjust for differences in prognosis. Using baseline characteristics, we can identify factors that influence outcome of the study. Factors that change the outcome with 10% will be regarded as confounders and will therefore be added to the regression-model.
A cost-effectiveness analysis will be performed from a social and a patient perspective, looking at differences in direct and indirect health care cost between the two groups (GS and placebo). If the trial does not show a difference in disease parameters (WOMAC) and quality of life (EuroQol) between the GS and the placebo group, the analysis will be reduced to a cost minimisation analysis. This form of analysis evaluates the efficacy of treatment based solely on direct and indirect costs. If the study does find a positive difference in disease parameter and/or quality of life a cost-effectiveness ratio can be determined with on the one hand the costs and savings and on the other hand the disease-specific parameters and also quality of life.

Current status

A total of 40 GP's were found willing to participate in the study. They sent a total of 600 letters to inform possible eligible patients of the study. We received 417 requests for additional information and thus sent an equal amount of information folders. Of these 417 people 250 returned a written informed consent. Eventually 222 people entered the study. Of the 28 people that did not enter the study, most did not meet the inclusion criteria and a few people changed their mind and withdrew their informed consent before randomisation.
We started including patients at the end of September 2003 and the last patient was included on March 15th of 2004. This means the study will run until March 2006. The first results will be available around September 2006.

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3

Effect of glucosamine sulfate on hip osteoarthritis: a randomized trial

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ABSTRACT

Background: The effectiveness of glucosamine sulfate as a symptom and disease modifier for osteoarthritis is still under debate.
Objective: To assess whether glucosamine sulfate has an effect on the symptoms and structural progression of hip osteoarthritis during 2 years of treatment.
Design: Randomized, controlled trial.
Setting: Primary care in the Netherlands.
Patients: 222 patients with hip osteoarthritis who were recruited by their general practitioner. Patients were eligible if they met the American College of Rheumatology clinical criteria for hip osteoarthritis.
Intervention: 2 years of treatment with 1500 mg of oral glucosamine sulfate or placebo once daily.
Measurements: Primary outcome measures were Western Ontario and McMaster Universities (WOMAC) pain and function subscales over 24 months and joint space narrowing after 24 months. The main secondary outcome measures were WOMAC pain, function, and stiffness after 3, 12, and 24 months.
Results: At baseline, both groups were similar in demographic and clinical variables. Overall, WOMAC pain did not differ (mean difference [glucosamine sulfate minus placebo], -1.54 [95% CI, -5.43 to 2.36]), nor did WOMAC function (mean difference, -2.01 [CI, -5.38 to 1.36]). Joint space narrowing also did not differ after 24 months (mean difference, -0.029 [CI, -0.122 to 0.064]). Only 1 of the sensitivity analyses, based on extreme assumptions regarding missing assessments due to total hip replacement, provided results consistent with a glucosamine effect.
Limitations: Twenty patients had total hip replacement during the trial. Half of the patients had a Kellgren and Lawrence score of 1.
Conclusion: Glucosamine sulfate was no better than placebo in reducing symptoms and progression of hip osteoarthritis.

International Standard Randomised Controlled Trial Number: ISRCTN54513166.

BACKGROUND

The effectiveness of glucosamine sulfate for treating osteoarthritis is controversial. A 2005 systematic review of 20 trials found evidence to be inconclusive[1]. In the 15 trials comparing glucosamine with placebo, the overall effect on pain favored glucosamine, but 8 of the trials found no effect on pain. More recent trials[2-4] have also yielded inconclusive results. In the Netherlands and other countries, glucosamine is sold as an over-the-counter dietary supplement and is used by many patients, often on the advice of their physicians. Given the prevalent use of glucosamine, definitive evidence about its effectiveness is needed.

Some studies suggest that glucosamine may provide greater benefit to patients with less severe radiographic osteoarthritis than to patients with more severe disease[5 6]. Most previous trials have studied only patients with knee osteoarthritis, with the exception of 3 early trials that included patients with other affected joints[7-9].

Trials specifically testing glucosamine in patients with hip osteoarthritis have not been available. Although osteoarthritis of the knee is more common than hip osteoarthritis, hip osteoarthritis is common enough to warrant assessment of glucosamine for this condition.

To date, only 2 trials have published data on the effects of glucosamine sulfate on joint structure[10 11]. Some expressed concern about the radiography protocol used in these trials[12-14], and further study is needed to clarify these findings.

To explore some of the uncertainties regarding the effectiveness of glucosamine sulfate, we conducted a 2-year, blinded, randomized, placebo-controlled trial to evaluate the effect of glucosamine sulfate on the symptomatic and radiographic progression of hip osteoarthritis in patients recruited from primary care settings.

METHODS

Study Design

In this trial, all outcome assessors, patients, data analysts, and researchers were blinded to group assignment. The Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, the Netherlands, approved the study design, and patients provided written informed consent.

We reported the detailed study protocol in 2005[15] and summarize it here.

Setting and Participants

General practitioners in the Rotterdam area recruited study patients. Patients were eligible for inclusion if they met the American College of Rheumatology clinical criteria for hip osteoarthritis during a screening examination at the research center[16]. Patients who had undergone or were awaiting hip replacement surgery were not eligible. We excluded patients who had a Kellgren and Lawrence score of 4[17], renal disease, liver disease, diabetes mellitus, or a disabling comorbid condition that would make visits to the research center impossible, as well as patients already receiving glucosamine and those unable to fill out Dutch questionnaires. We encouraged patients who violated study protocol and those who had total hip arthroplasty during the study to complete data collection to limit the loss to follow-up.

Randomization and Intervention

Eligible patients were randomly assigned to receive either 1500 mg of oral glucosamine sulfate (administered once daily as two 750-mg tablets) or placebo for 2 years. The glucosamine used in this study was provided by Numico Research BV (Wageningen, the Netherlands) but was manufactured by Nutricia Manufacturing USA (Greenville, South Carolina). It contained 2000 mg of D-glucosamine sulfate 2-potassium chloride, which results in a net content of 1500 mg of glucosamine sulfate per 2 pills. The placebo pills were identical in appearance, smell, and taste.

We used a computer-generated, blinded randomization list provided by an independent researcher to randomly assign patients to glucosamine sulfate or placebo. This list, which was randomized per block of 6 numbers, stratified patients by radiologic findings (Kellgren and Lawrence score < 2 vs. ≥ 2) and by local versus generalized osteoarthritis; patients received a number in chronological order[15]. Assignment of patients to the right stratum of the random assignment list was done by the main researcher, who was blinded to therapy.

To evaluate blinding, patients had to indicate in the last questionnaire to which treatment they thought they were randomly assigned.

Outcomes and Follow-up

Primary outcome measures were WOMAC 3.1 (5-point Likert format) pain and function over 24 months and joint space narrowing after 24 months [18, 19]. Secondary outcome measures were WOMAC pain, function, and stiffness after 3, 12, and

24 months; overall WOMAC stiffness; a visual analogue scale (VAS) to measure pain in the past week; and pain medication use. The WOMAC subscales are presented as normalized scores (0 to 100, where 0 equals no symptoms). We recorded the use of pain medication; classified patients as never, occasional, or daily users; and then determined whether people increased, decreased, or did not change their use of pain medication from baseline.

In the case of patients with bilateral hip symptoms, we asked patients to indicate their most affected hip for our analyses of joint space narrowing. For patients who were undecided, we used the hip with the highest Kellgren and Lawrence score or the smallest internal rotation during a physical examination. We used QBone Planner 5.4 (Medis, Leiden, the Netherlands) to measure joint space width on calibrated digital radiographs of the hip joints. We read radiographs from both time points (baseline and 24 months) side by side. One researcher measured joint space width manually on predefined lateral, superior, axial, and medial sites [20]. In addition to these 4 points, we visually identified and measured the minimal joint space width on both the baseline and 24-month radiograph. We used the smallest of these 6 measurements as the actual minimum joint space width for analyses. A second observer also measured the joint space width in a random subset of 28 study patients, and we found high interobserver agreement (intraclass correlation coefficient of minimal joint space width, 0.98).

We collected data for the primary and secondary outcome measures at different time points throughout the study. At baseline and after 24 months, patients came to the Erasmus Medical Center for radiography and to complete study questionnaires. Weight-bearing, anteroposterior digital radiography of the pelvis was performed according to a highly standardized protocol to allow reliable measurement of joint space narrowing[15]. At baseline and then every 3 months through month 24, we asked patients to complete the WOMAC instrument, a VAS for pain in the past week (score range, 0 to 100; 0 equals no pain), and a checklist for specific adverse events and to answer questions regarding pain medication and adherence. We mailed the intermediate questionnaires to the patients for completion at home. A researcher visited patients every 6 months to deliver a new supply of study medication and evaluate adherence by using the Brief Medication Questionnaire (BMQ)[21] and a pill count. The BMQ monitors the amount of days per week that patients have taken their study medication. For overall effect, we considered patients to be adherent if they ingested more than 80% of the total study medication.

Statistical Analysis

We used the data from all nine 3-month questionnaires (at baseline and 3, 6, 9, 12, 15, 18, 21, and 24 months). We also report outcomes for measurements at 3, 12, and 24 months and a mean effect of the therapy over 24 months incorporating all scores. We performed the analyses by using SPSS 11.0.1 (SPSS, Chicago, Illinois) and SAS 8.2 (SAS Institute, Cary, North Carolina).

We used linear mixed models to analyze the data, assuming that data were missing at random. We chose an unstructured covariance structure to model the covariance of repeated measures by patients, because this yielded the lowest Akaike information criterion. Fixed effects were time, time by therapy, and the covariates we adjusted for. For patients who had total hip arthroplasty during the trial, we included observed data before surgery in the analysis and assumed data after surgery to be missing. For patients who were lost to follow-up, we included all observed data in the analysis. We adjusted the WOMAC and VAS pain analyses for body mass index, sex, and age—factors that may have influenced symptoms[22,23]. We also adjusted analyses for pain medication use and Kellgren and Lawrence score. The analyses for joint space narrowing were adjusted for Kellgren and Lawrence score[24], age, and sex[25].

We used ordinal regression analysis to assess the effect of glucosamine sulfate on pain medication use by using data from all patients who completed the study and did not have total hip arthroplasty. We performed additional analyses to assess the effect of adherence on the outcome. To explore the validity of the missing-at-random data assumption for patients who underwent total hip arthroplasty during the study, we did sensitivity analyses on the WOMAC pain data. In 5 scenarios, the missing data for patients who underwent total hip arthroplasty were imputed with extreme scores: mean of the 5 best scores for the glucosamine sulfate recipients and that of the 5 worst scores for the placebo recipients (traditional best case); mean of the best scores for placebo recipients and that of the worst scores for glucosamine sulfate recipients (traditional worst case); mean of the worst scores for all total hip patients (worst case); mean of the best scores for all total hip patients (best case); and the score as given by patients with their artificial hip (extreme best case).

On the basis of the Outcome Measures in Rheumatology– Osteoarthritis Research Society International criteria for moderate improvement, we identified a 10-point difference in scores as the minimal clinically important difference on the WOMAC and VAS[26] and a change of 0.25 mm over 2 years as the minimal clinically important difference in joint space narrowing[27]. We needed to include 63 patients per group to detect a 0.25-mm difference in radiologic progression after 2 years between the

glucosamine sulfate and placebo groups (power, 80%; significance level, 5%)[27] and 150 patients to account for an expected 20% loss to follow-up. However, to allow us to explore effect modification by type and severity of osteoarthritis, we recruited 220 patients.

Role of the Funding Source

Erasmus Medical Center–Breedtestrategie funded the study but had no role in the study design; collection, analysis, or interpretation of the data; or writing of the paper. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit the manuscript for publication.

RESULTS

Patients

Of the 417 patients who were recruited by their general practitioner between June 2003 and February 2004, 250 provided informed consent after receiving more extensive information about the trial. Of these, 16 did not meet the inclusion criteria and another 12 withdrew their consent before random assignment. Between September 2003 and March 2004, 222 patients were enrolled and randomly assigned (Figure 1).

The glucosamine sulfate and placebo groups had similar baseline characteristics (Table 1). Of the 222 randomly assigned patients, 207 (93.2%) were available for the final assessment at 24 months. Thirteen patients in the glucosamine sulfate group and 7 in the placebo group had total hip arthroplasty during the study. Patients in the glucosamine sulfate and placebo groups had similar rates of adherence to therapy. We did not receive 23 WOMAC or VAS assessments from patients who completed the trial and did not have total hip arthroplasty. We included all observed data from these patients in the mixed-model analysis. The amount of missing data per assessment is reported in Table 2.

Patients who did not complete the trial and did not have total hip arthroplasty were younger (mean age, 62.7 vs. 63.4 years; P = 0.77), had a higher body mass index (mean body mass index, 28.8 vs. 27.9 kg/m^2; P = 0.49), and were more often female (71.4% vs. 69.2%; P = 0.86) than the patients who completed the trial. The patients who had total hip arthroplasty were older (mean age, 63.7 vs. 63.4 years; P = 0.89), had higher body mass index (mean body mass index, 28.6 vs. 27.9 kg/m2; P = 0.52), and were less often female (60.0% vs. 70.0%; P = 0.34) than the patients who

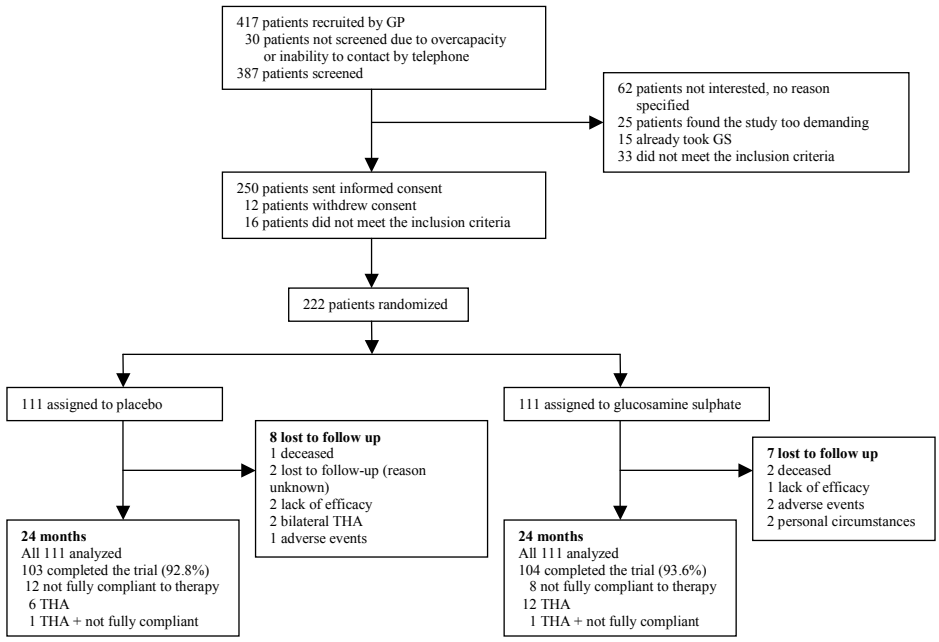

Figure 1: Flow chart of the study

did not have total hip arthroplasty (Table 1). Similar numbers of patients in each group correctly identified their own treatment group (Table 1), which provides some evidence that blinding was successful.

Primary Outcome Measures

In an adjusted analysis, the mean difference (glucosamine sulfate minus placebo) in WOMAC pain scores over 24 months was - 1.54 (95% CI, -5.43 to 2.36), excluding the minimum clinically important difference of 10 points (Table 2). The course of expected mean WOMAC pain is given in Figure 2. The mean difference in WOMAC function scores at 24 months was -2.01 (CI, -5.38 to 1.36), also excluding a clinically important benefit of glucosamine sulfate.

The outcomes for the 4 sites at which we measured joint space narrowing were inconsistent in whether they favored the glucosamine sulfate or placebo group; however, none of the 95% CIs for differences were consistent with the minimal clinically important change of 0.25 mm in joint space narrowing. We did not assess medial joint space narrowing, because overprojection of the acetabulum rendered two thirds of all radiographs not clear enough to measure the medial joint space width.

Table 1: Patient characteristics at baseline by randomized group

Characteristics	*Patients randomized to placebo - no THA[1] (n = 104)*	*Patients randomized to placebo - THA[1] during trial (n = 7)*	*All patients randomized to placebo (n = 111)*	*Patients randomized to GS[2] - no THA (n =98)*	*Patients randomized to GS – THA during trial (n = 13)*	*All patients randomized to GS[1] (n = 111)*
Women, %	73.1	28.6	70.3	67.4	76.9	68.5
Age in years, mean (SD[3])	63.6 (8.5)	65.4 (8.2)	63.7 (8.5)	63.2 (9.7)	62.7 (7.5)	63.1 (9.5)
Body mass index, mean (SD)	28.0 (5.0)	28.9 (2.3)	28 (4.9)	27.8 (4.6)	28.5 (2.3)	27.9 (4.5)
Duration of complaints < 1 yr, %	11.5	0	10.8	12.2	15.4	12.6
1 – 3 yrs, %	35.6	14.3	34.2	36.7	23.1	35.1
> 3 yrs, %	52.9	85.7	55	51.0	61.5	52.3
Generalized OA[4], %	60.6	85.7	62.2	58.2	84.6	61.3
Localised OA[5], %	39.4	14.3	37.8	41.8	15.4	38.7
Unilateral OA[6], %	35.6	85.7	38.7	63.3	76.9	64.9
Bilateral OA[7], %	64.4	14.3	61.3	36.7	23.1	35.1
Kellgren & Lawrence = 1, %	55.8	0	53.2	58.2	15.4	49.5
≥ 2, %	44.2	100	46.8	41.8	84.6	50.5
Minimum JSW[8] in mm, mean (SD)	2.46 (0.87)	0.41 (0.34)	2.33 (0.9)	2.22 (0.97)	1.46 (1.02)	2.13 (1.0)
WOMAC[9,$] pain, mean (SD)	32.1 (23.4)	37.1 (21.8)	32.4 (23.2)	34.1 (23.0)	49.6 (18.5)	35.9 (23.0)
function, mean (SD)	33.5 (21.2)	43.7 (27.9)	34.1 (21.7)	34.6 (24.3)	46.5 (20.2)	36.0 (24.1)
stiffness, mean (SD)	41.0 (23.2)	42.9 (23.8)	41.1 (23.1)	43.0 (27.7)	52.9 (28.3)	44.2 (27.2)
Pain last week in mm, mean (SD)	29.5 (24.0)	44.9 (38.3)	30.5 (25.2)	32.8 (26.1)	45.8 (28.2)	34.3 (26.5)
Pain medication use daily, %	17.3	42.9	18.9	28.6	30.8	28.8
sometimes, %	26.0	57.1	27.9	25.5	23.1	25.2
none, %	56.7	0	53.2	45.9	46.2	46
Assumed sort of medication						
glucosamine, %	13	0	12.6	8.5	30	10.6
placebo, %	46	33.3	45.6	48.9	40	48.1
no idea, %	41	66.7	41.7	42.6	30	41.3

[1]THA: total hip arthroplasty, [2]GS: glucosamine sulphate, [3]SD: standard deviation, [4]Generalized OA: Besides OA in hips also OA in hands and/or knees, [5]Localized OA: Besides OA in hips no OA in hands and knees, [6]Unilateral OA: One-sided hip OA, [7]Bilateral OA: Two-sided hip OA, [8]JSW: joint space width, [8]WOMAC: Western Ontario Macmaster Universities. [$]WOMAC scores are normalized (0-100, 0 = no complaints)

Table 2: Primary and secondary outcomes.

		Change from baseline (SD[1]) Placebo group (N = 111)	*Change from baseline (SD) GS[2] group (N = 111)*	*Unadjusted difference[$] (95% CI)*	*Adjusted difference[$] [#] (95% CI)*
Primary Endpoints					
WOMAC[3,$,#]					
Neg. difference favors GS					
	Pain overall	-0.30 (1.6[‡])	-1.90 (1.6[‡])	-1.60 (-5.60, 2.40)	-1.54 (-5.43, 2.36)
	Function overall	0.38 (1.3[‡])	-1.69 (1.3[‡])	-2.07 (-5.53, 1.39)	-2.01 (-5.38, 1.36)
Joint Space Narrowing (mm)[##]					
Pos. difference favors GS					
	Minimal	-0.057 (0.32)	-0.094 (0.32)	-0.038 (-0.130, 0.055)	-0.029 (-0.122, 0.064)
	Lateral	-0.159 (0.36)	-0.180 (0.34)	-0.020 (-0.124, 0.083)	-0.017 (-0.121, 0.088)
	Superior	-0.129 (0.30)	-0.123 (0.36)	0.006 (-0.090, 0.101)	0.016 (-0.079, 0.111)
	Axial	-0.079 (0.30)	-0.070 (0.48)	0.009 (-0.107, 0.124)	-0.005 (-0.118, 0.108)
Secondary Endpoints					
WOMAC[#]					
Neg. difference favors GS					
Pain	3 months	-1.79 (16.2)	-2.50 (19.2)	-0.71 (-5.47, 4.05)	0.06 (-4.11, 4.22)
	12 months	-0.89 (23.3)	-0.54 (19.9)	0.35 (-5.66, 6.36)	1.42 (-3.82, 6.67)
	24 months	0.88 (26.4)	-1.47 (20.7)	-2.34 (-9.16, 4.48)	-0.77 (-6.53, 4.98)
Function	3 months[a]	-1.08 (12.7)	-3.29 (14.9)	-2.22 (-5.97, 1.54)	-2.04 (-5.48, 1.40)
	12 months	-0.88 (17.6)	-0.98 (14.9)	-0.11 (-4.63, 4.42)	0.11 (-4.14, 4.35)
	24 months[b]	1.92 (19.7)	-0.84 (19.1)	-2.76 (-8.35, 2.84)	-1.63 (-6.73, 3.47)
Stiffness	3 months	-3.39 (17.7)	-4.59 (22.6)	-1.20 (-6.66, 4.26)	-0.12 (-4.94, 4.71)
	12 months	-3.43 (21.6)	-1.38 (22.1)	2.06 (-4.00, 8.12)	3.11 (-2.07, 8.28)
	24 months	-2.19 (24.1)	-3.43 (26.2)	-1.24 (-8.47, 5.98)	0.66 (-5.27, 6.59)
	Overall	-2.27 (1.7[‡])	-3.92 (1.7[‡])	-1.65 (-5.81, 2.53)	-0.98 (-4.99, 3.04)
VAS[4] pain[#]					
Neg. difference favors GS					
	3 months[b]	-3.20 (23.0)	-2.89 (23.2)	0.31 (-5.89, 6.51)	1.47 (-4.16, 7.09)
	12 months	4.51 (24.9)	3.56 (24.8)	-0.95 (-7.83, 5.94)	-1.30 (-7.38, 4.78)
	24 months	5.09 (28.7)	-3.92 (27.5)	-1.17 (-9.24, 6.90)	-1.80 (-8.47, 4.87)
	Overall	2.02 (2.0[‡])	-0.48 (2.0[‡])	-2.49 (-7.38, 2.39)	-2.04 (-6.58, 2.57)

All results from linear mixed models;[1]SD: standard deviation, [2]GS: glucosamine sulphate, [3]WOMAC: Western Ontario Macmaster universities, [4]VAS: visual analogue scale, [a]4 outcomes missing, [b]1 outcome missing, [$]WOMAC scores are normalized (0-100, 0 = no complaints),[‡]Standard Error instead of SD, [#]adjusted for body mass index, gender, age, pain medication use, unilateral/ bilateral disease and Kellgren & Lawrence score, [##]adjusted for gender, age, and Kellgren & Lawrence score

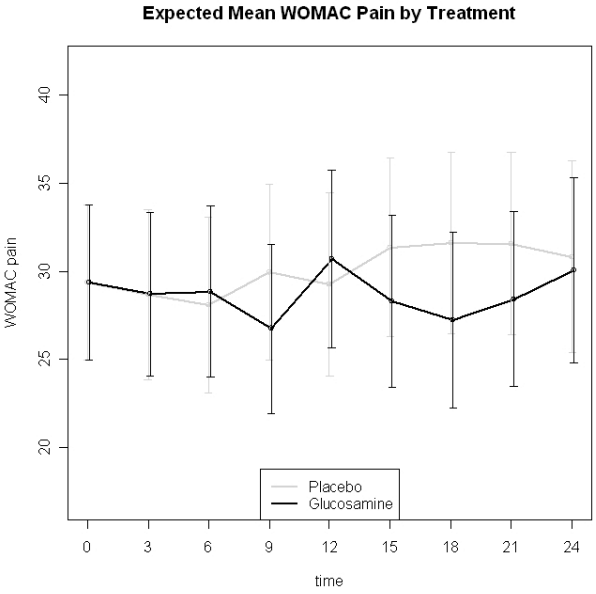

Figure 2. Expected mean WOMAC pain and error bars per treatment arm. p = 0.44

Sensitivity Analysis

Only the traditional best-case scenario provided results consistent with an effect of glucosamine sulfate (Table 3), with a mean difference in WOMAC pain score of -5.65 (CI, -8.82 to -2.47), and the 95% CI excluded the minimal clinically important difference. The other sensitivity analyses were consistent with the outcomes of the main analyses and found no clinically important difference between glucosamine sulfate and placebo.

Table 3: Sensitivity analyses based upon various assumptions regarding missing assessments due to total hip replacement during the trial.

	Adjusted difference (95% CI)
WOMAC pain overall neg. difference favors GS	
Traditional best case	-5.65 (-8.82, -2.47)
Best case	-3.25 (-7.25, 0.76)
Best case using artificial hip	-2.98 (-6.87, 0.90)
Worst case	-0.12 (-4.51, 4.27)
Traditional worst case	2.06 (-2.18, 6.31)

All analyses adjusted for body mass index, gender, age, pain medication use, unilateral/bilateral disease, and Kellgren & Lawrence score.

Table 4: The difference between pain medication use expressed as change from baseline between glucosamine and placebo.

	Less medication use Placebo group (%) (N = 96)	*More medication use Placebo group (%) (N = 96)*	*Unchanged outcome Placebo group (%) (N = 96)*	*Less medication use GS[1] group (%) (N = 92)*	*More medication use GS group (%) (N = 92)*	*Unchanged outcome GS group (%) (N = 92)*	*OR (95% CI)[$]*
3 months	25	1	74	25	5.4	69.6	0.85 (0.45, 1.60)
12 months	25	4.2	70.8	21.7	12	66.3	0.66 (0.36, 1.23)
24 months	19.6	8.2	72.2	26.1	8.7	65.2	1.29 (0.70, 2.37)

Data from completers who did not undergo THA during the trial.
[1]GS: glucosamine sulphate, [$]OR>1: GS group more likely to have less medication use

Secondary Outcome Measures

In adjusted analyses, we found small mean differences in WOMAC pain and function scores at 3, 12, and 24 months between glucosamine sulfate and placebo, and the 95% CIs excluded the minimal clinically important difference of 10 points. The overall difference in WOMAC stiffness score was -0.98 (CI, -4.99 to 3.04), and the 95% CIs for differences of the intermediate measurements were not consistent with a clinically important difference. In an adjusted analysis incorporating all measurements, the mean difference in VAS was -2.04 (CI, -6.58 to 2.57), excluding the minimum clinically important difference of 10 points. The intermediate measures of VAS also did not indicate clinically important differences. In an analysis of the completers who did not undergo total hip arthroplasty, we did not find a difference between glucosamine sulfate and placebo in the use of pain medication (Table 4). Pain medication use decreased after baseline in both groups.

Additional Analyses

We compared the subjective (BMQ) and objective (pill count) measure for adherence and found the level of agreement between these 2 measures to be very high ($\kappa = 0.93$). We therefore chose to report the more complete BMQ data.
For WOMAC pain, the adjusted mean difference, corrected for adherence, was -1.75 (CI, -5.92 to 2.42). The same analysis for WOMAC function yielded a mean difference of -2.88 (CI, -6.48 to 0.71). For minimal joint space narrowing adjusted for adherence, the mean difference was -0.024 (CI, -0.117 to 0.069). All 95% CIs excluded the minimal clinically important difference.

Table 5: Adverse events (reported at least once per patient during use of study medication)

	Placebo group (n=111) n (%)[$]	*GS[1] group (n = 111) n (%)[$]*	*GS − placebo difference % (95% CI)*
No of patients reporting SAE[2]	2 (2)	4 (4)	
No of patients reporting AE[3] resulting in treatment termination	6 (5)	4 (4)	
Total no of patients reporting AE	59 (53)	57 (51)	-2 (-15 to 12)
Abdominal pain	10 (9)	14 (13)	4 (-5, 12)
Stomach complaints	19 (17)	25 (23)	5 (-5, 16)
Intestinal complaints	17 (15)	19 (17)	2 (-8, 12)
Increased blood pressure	19 (15)	11 (10)	-5 (-14, 3)
Decreased blood pressure	3 (3)	4 (4)	1 (-4, 6)
Fatigue	18 (16)	24 (22)	5 (-5, 16)
Headache	26 (23)	16 (14)	-9 (-19, 1)
Vertigo	18 (16)	16 (14)	-2 (-11, 8)
Cardiac problems	9 (8)	6 (5)	-3 (-9, 4)
Depressive mood	6 (5)	10 (9)	4 (-3, 11)
Allergic episode	5 (5)	7 (6)	2 (-4, 8)

[1]GS: glucosamine sulphate, [2]SAE: serious adverse event, [3]AE: adverse event, [$]Numbers are percentage of patients reporting an adverse event during study

Adverse Events

During the study, 52.3% of the patients reported adverse events. Table 5 reports the percentages of patients who reported each adverse event at least once during the study. Four patients, 3 of whom were randomly assigned to glucosamine sulfate, had a stroke. Two patients, 1 in each group, reported cancer. All other occasionally reported adverse events were mild.

Missing Data

Twenty-three patients who completed the trial and did not have total hip arthroplasty had a missing outcome on the WOMAC or VAS data, an average of 2.5 outcomes per quarterly questionnaire. We report the amount of missing data per assessment in Table 2. We handled the missing data by using the mixed-model analysis.

DISCUSSION

We did not find glucosamine sulfate to be more effective than placebo in modifying the symptomatic and radiographic progression of hip osteoarthritis over 24 months of daily therapy.

On the basis of a MEDLINE search for English-language articles to June 2007, we conclude that the trials on glucosamine to date have yielded conflicting evidence[1-4]. The 15 studies with a mean duration of 23.7 weeks, incorporated in the 2005 Cochrane review[1], showed a combined moderate effect on pain in favor of glucosamine. Three studies have since assessed the effect of glucosamine on the symptoms of osteoarthritis over 6 months, again with conflicting results. The GUIDE (Glucosamine Unum In Die Efficacy) study[3] found a small positive effect of glucosamine sulfate on pain, whereas the GAIT (Glucosamine/chondroitin Arthritis Intervention Trial) study[2] and the study by Messier and colleagues[1] did not find an effect of glucosamine.

Part of the differences in outcome can be explained by the compound used. A recent review[28] concluded that glucosamine hydrochloride, as used in GAIT[2] and Messier and colleagues' study[4], was not effective for osteoarthritis symptoms. We used glucosamine sulfate to ensure comparability with previous positive trials. Because some have suggested that the quality or amount of the glucosamine product used in previous studies might have led to a lack of effectiveness[29], we avoided this problem in our study by having patients take study medication once daily as recommended[30] and had the supplier conduct a quality check before delivery of the trial medication to ensure that study pills contained the required amount of active ingredients.

Another potential explanation for the lack of effectiveness that we observed is the difference in disease severity between the patients in this study and those in previous studies that showed effectiveness. Half of the patients included in our study had mild radiographic arthritis with a Kellgren and Lawrence score of 1, but all met the American College of Rheumatology clinical criteria and were receiving treatment for osteoarthritis. Despite the mild radiographic disease, the mean joint space width and pain levels of patients in this study are similar to those of patients in other studies. Our minimal joint space width was 2.23 mm, compared with mean minimal joint space widths of 2.50, 2.50, and 2.03 mm in 3 previous studies that included patients with hip osteoarthritis[31-33]. Furthermore, baseline pain severity in our trial was similar to that of patients in the 2 positive long-term trials[10 11].

A predefined subgroup analysis of the patients with a Kellgren and Lawrence score of 2 and 3 explored whether the severity of radiographic disease might explain the

observed lack of effectiveness. The results of this analysis are consistent with the findings of the main analyses, and we did not find a difference in pain and joint space narrowing that favored glucosamine sulfate.

The mild severity of our group is also reflected in the small amount of joint space narrowing over 2 years. A trial over 3 years might have shown a greater amount of joint space narrowing. However, because we did not find even a borderline difference between the 2 groups, we do not believe that a longer trial is warranted.

An important difference from all previous studies is that we looked exclusively at hip osteoarthritis. Most available systemic osteoarthritis therapies show similar effectiveness in both hip and knee osteoarthritis. However, because the mechanism of action of glucosamine is still not known, we cannot eliminate the possibility that effectiveness of glucosamine is different for the knee than for the hip.

An important limitation of the study deserves mention. Our trial had relatively few patients who dropped out, with only 15 of 222 patients unavailable for follow-up after 2 years. However, we did have a problem with protocol adherence. Many study participants had total hip replacement during the study, and the numbers were not balanced between study groups, making interpretation of outcome measures in these patients difficult. We performed sensitivity analyses to test the validity of the missing-at-random data assumption for patients who had total hip arthroplasty. From these analyses, we can derive that only a traditional best-case scenario yielded a difference in favor of glucosamine sulfate. However, this difference did not reach the level of clinical importance. The traditional best-case scenario is not very realistic. The total hip arthroplasty patients in the placebo group received a very good score, whereas these patients had more severe symptoms (Table 1). The worst-case scenario gave all total hip patients a severe score; this more realistic scenario did not demonstrate a difference between groups.

An unequal number of patients with bilateral disease were assigned to the groups at baseline. Because this may have had an effect on pain level and functional outcomes, we adjusted for this imbalance in the analyses. Patients recorded adverse events during the study. Many patients had comorbid conditions other than osteoarthritis that required medication. They were often unsure whether the adverse events were caused by the study medication, another medication, or simply old age. The reported adverse events were similar in the glucosamine sulfate and placebo groups. However, because this study was designed to assess effectiveness, we do not have enough power to obtain definitive data on whether glucosamine sulfate causes adverse events.

In summary, this trial followed the guidelines for clinical trials in osteoarthritis[34], used blinded outcome assessment, had a high rate of completion, and was performed without pharmaceutical company support. In addition, the patients

are representative of those using over-the-counter glucosamine. Given the lack of clinically important effects on pain, function, and stiffness over 24 months, our results suggest that glucosamine sulfate is not an effective therapy for patients with hip osteoarthritis.

More information on structure modification will become available when the GAIT study[2] publishes its long-term results. A further search of the trial registries revealed 3 ongoing trials (ClinicalTrials.gov registration numbers NCT00513422, NCT00377286, and NCT00294801) on the effect of glucosamine sulfate on knee osteoarthritis symptoms. Additional new insights may come from magnetic resonance imaging measurements of structural changes in both the JOG (Effect of Glucosamine on Joint Structure and Quality of Life) and LEGS (Long-Term Evaluation of Glucosamine Sulphate) studies over 6 and 24 months, respectively. In addition, the JOG study is assessing C-terminal telopeptide crosslinks of type II collagen excretion, a marker of cartilage tissue degradation. These trials will contribute to the discussion on effectiveness of glucosamine sulfate in patients with knee osteoarthritis, but they cannot add to the discussion on its effect on hip disease.

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4

Effect of glucosamine sulphate on joint space narrowing, pain and function in patients with hip osteoarthritis; subgroup analyses of a randomized controlled trial

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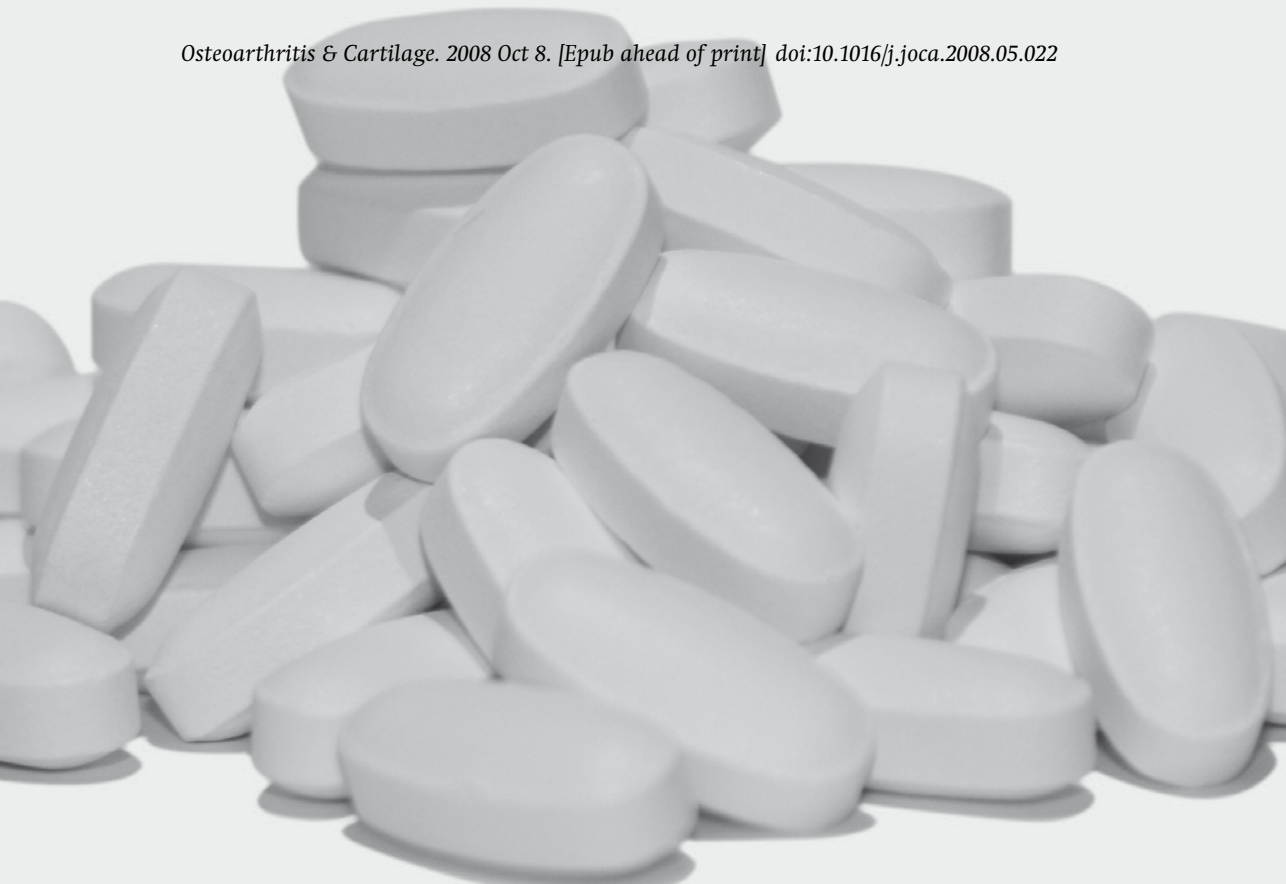

ABSTRACT

Objective

Recently we reported that glucosamine sulphate (GS) did not have an effect on the symptoms and progression of primary care patients with hip osteoarthritis (OA). The aim of this present study was to investigate whether there are subgroups of patients with hip OA for whom GS might be an effective therapy.

Method

We randomized 222 patients with hip OA that met one of the American College of Rheumatology criteria to either 1500 mg of oral GS or placebo once daily for 2 years. Subgroup analyses were predefined for radiographic severity (Kellgren & Lawrence (KL) = 1 vs ≥ 2) and for type of OA (localised vs generalised). Additional exploratory subgroup analyses focused on groups based on pain level, pain medication use, baseline joint space width (JSW), and concomitant knee OA at baseline.
Primary outcome measures were Western Ontario MacMaster Universities (WOMAC) pain and function scores over 24 months, and joint space narrowing (JSN) after 24 months.

Results

In the predefined subgroups based on radiographic severity and type of OA, the outcomes WOMAC pain, function and JSN were similar for the GS and placebo group.

Conclusion

GS was not significantly better than placebo in reducing symptoms and progression of hip OA in subgroups of patients.

BACKGROUND

The effect of glucosamine on the symptoms caused by osteoarthritis (OA) and the progression of the disease is still questionable. The summary effect of glucosamine on pain and progression of the disease calculated from the available randomized controlled trials (RCTs) is in favor of glucosamine[1 2]. The individual results of the trials however differ greatly.

Part of the differences in outcome between different trials may be explained by the compound used. A recent review[2] concluded that glucosamine hydrochloride, as used by GAIT[3] and Messier et al.[4], was not effective on OA symptoms, whereas for glucosamine sulphate (GS) more favorable results are reported. Furthermore, it was suggested that differences in enrolled subjects, outcomes evaluated, and degree of co-intervention could be factors explaining at least some of the differences[5].

Our recently published independent long-term double-blind RCT was the first study to test the effect of GS in patients with hip OA[6]. The results from this trial showed that GS has no effect on the symptoms and radiographic progression of hip OA in primary care patients.

When our trial was designed in 2003, not all trials on glucosamine were uniformly positive[7]. Therefore, we hypothesized that GS might show to be effective only for a subgroup of OA patients. Severity of radiographic OA has previously been suggested to have an influence on the effect of GS[8 9]. Furthermore, it has been suggested that generalized OA may have a different pathophysiology than localized OA. We therefore hypothesized that type of OA could have an influence on the effect of GS[10].

In this study we perform predefined and additional exploratory subgroup analyses on the data of the original trial to assess whether there are subgroups of patients with hip OA for whom GS might be effective in modifying symptomatic and radiographic progression.

METHODS

Design overview

Data of our original study were used for subgroup analyses. This study was a randomized blinded placebo-controlled trial with a duration of 2 years in patients with hip OA6. All outcome assessors, patients and researchers in this trial were blinded to therapy.

In the design of the study, a few of the subgroup analyses to assess the effect of GS in subgroups of patients were pre-specified. The Medical Ethics Committee of the Erasmus MC, University Medical Center, Rotterdam, the Netherlands, approved the study design [MEC226.868/2003/72], and all patients provided written informed consent. A detailed study protocol was published in 2005[11]. A brief summary of the protocol is presented below.

Setting and participants

General practitioners in the Rotterdam area recruited patients. Patients were eligible for inclusion when they met one of the criteria of the American College of Rheumatology for hip OA[12]. This was screened at the research centre. Patients that had undergone, or were on the waiting list for hip replacement surgery were not included in the study. Patients were excluded when they had a Kellgren & Lawrence (KL) score of 4[13], renal and/or hepatic disease, diabetes mellitus or disabling co-morbidity. Patients already taking GS, and those unable to fill out Dutch questionnaires were also excluded.

Patients that violated study protocol or those who underwent total hip arthroplasty were encouraged to stay in the study and fill out questionnaires to limit the loss to follow-up.

For the original study we randomly assigned 222 patients with hip OA to either 1500 mg of GS once daily (in total 2000 mg of D-glucosamine sulphate 2 Potassium Chloride) or a placebo for the duration of 2 years. Both compounds were manufactured by Nutricia Manufacturing USA, Inc. (Greenville, South Carolina, United States of America) and provided by Numico Research BV (Wageningen, the Netherlands).

The randomization was stratified to allow analyses in subgroups of patients. Patients were stratified on the basis of KL score (1 vs ≥ 2) and on type of OA (localized vs generalized OA). Patients were considered to have generalized OA when they had concomitant radiographic hand and/or knee OA, defined as a KL score of 2 or more. Patients with only OA of the hip joint(s) were classified as having localized OA.

Besides the predefined subgroups based on severity of radiographic OA and type of OA, patients were also divided into groups based on baseline level of pain assessed by a visual analogue scale (VAS) (≤ 30 vs > 30) and on joint space width (JSW) at baseline (≤ 2.5 mm vs < 2.5 mm) for exploratory analyses[14]. We also looked at the effect of treatment in a subgroup of patients that did not use pain medication following the baseline measurement. Finally we assessed whether there was an effect of GS in a subgroup that had radiographic concomitant knee OA (KL ≥ 2) at baseline.

Outcome measures

For the subgroup analyses we used the data from the primary outcome measures that were used in the original study. These measures were Western Ontario MacMaster Universities (WOMAC) pain and function scores over 24 months[15 16] and joint space narrowing (JSN) after 24 months. For the exploratory analyses we only report on the outcomes for WOMAC pain and JSN.
At baseline and after 24 months a highly standardized protocol was used to make weight bearing, anteroposterior digital radiographs of the pelvis, to allow reliable measurement of JSN. At baseline radiography of the hands and knees was performed to assess KL score in these joints. The minimal JSW was measured manually on our digital radiographs, using a computer program (QBone Planner 5.4, manufactured by Medis, Leiden, the Netherlands).
The WOMAC (5-point Likert format), VAS for pain in past week (0-100, 0 equals no pain), and pain medication (type of pain medication and frequency of use: never, occasional, and daily use) were assessed with a questionnaire that was filled out at baseline and every 3 months thereafter; the last at the end of the study after 24 months. The WOMAC subscales are presented as normalized scores (0-100, 0 equals no complaints).
In the case of bilateral hip complaints, patients were asked to indicate their most affected hip. This hip was used for the analyses of JSN. For patients with equivalent pain in both hips, the hip with the highest KL score was used, and in case the KL score was equal as well, the hip with smallest internal rotation during a physical exam was used.

Statistical analysis

For the statistical analyses we used the data of all 3-monthly questionnaires (i.e., baseline, and at 3, 6, 9, 12, 15, 18, 21, and 24 months). The outcomes are given as a mean effect over 24 months incorporating all scores.
The analyses were performed with SPSS 11.0.1 (SPSS inc., Chicago, IL) and SAS 8.2 (SAS Institute, Inc., Cary,NC). The data were analyzed using linear mixed model analyses, under the assumption that data are missing at random. We chose an unstructured covariance structure as this yielded the lowest Akaike's information criterion. Fixed effects were: time, time x therapy, and the covariates we adjusted for. Our model did not have random effects.
For patients who had total hip arthroplasty during the trial, observed data before surgery were included in the analysis and data after surgery were assumed missing. For patients who were lost to follow-up, all observed data were included

in the analysis. The analyses for WOMAC and VAS pain were adjusted for factors that may have had an influence on symptoms, being body mass index, gender, and age[17 18]. Analyses were also adjusted for pain medication use and unilateral/bilateral disease as these factors were not fully balanced at baseline, and for KL score. The analyses for JSN were adjusted for KL score[19], age and gender[20].
A total of 24 subgroup analyses were performed of which 20 were reported in the results section, on the basis of this number at least one statistically significant test ($P < 0.05$) can be expected on the basis of chance alone.

RESULTS

In the original study 222 patients were included and randomized to either GS or placebo. The two groups were similar in baseline and demographic characteristics (Table 1), with the exception of an imbalance in daily pain medication use and unilateral/bilateral disease. As stated before these two factors will be adjusted for in the analyses. The mean values of the outcome measures at baseline for the different subgroups are given in Table 2.

Severity of radiographic OA

In an adjusted analysis, the mean difference in WOMAC pain scores over 24 months between GS and placebo in the group with KL = 1 was -1.4 (95% CI [-6.7, 3.8]) in favor of GS (Table 3). In the more severe group with KL ≥ 2 the mean difference was -1.4 (95% CI [-7.4, 4.7]). For WOMAC function the mean difference between GS and placebo in the group with KL = 1 was -1.5 (95% CI [-5.8, 2.9]) whereas this difference was -2.1 (95% CI [-7.5, 3.3]) in the group with KL ≥ 2. For the group with KL = 1 the mean difference in JSN between GS and placebo was -0.09 mm (95% CI [-0.22, 0.04]), in favor of placebo. In the more severe group (KL ≥ 2) this difference was 0.09 mm (95% CI [-0.07, 0.24]) in favor of GS.

Type of OA

In the adjusted analysis the mean difference for WOMAC pain in the group with localized OA was 1.4 (95% CI [-5.6, 8.3]) in favor of placebo whereas the mean difference in the generalized subgroup was -3.5 (95% CI [-8.2, 1.3]) in favor of GS (Table 3). For WOMAC function the adjusted analyses yielded a difference of -0.9 (95% CI [-6.9, 5.1]) for localized OA and -2.9 (95% CI [-7.0, 1.2]) for generalized OA. The mean difference in JSN was -0.02 (95% CI [-0.17, 0.13]) for the localized OA group and -0.05

Table 1: Patient characteristics at baseline by randomized group

Characteristics	*All randomized patients (n = 222)*	*Patients randomized to placebo (n = 111)*	*Patients randomized to GS[1] (n = 111)*
Women, %	69.4	70.3	68.5
Age in years, mean (SD[2])	63.4 (9.0)	63.7 (8.5)	63.1 (9.5)
Body mass index, mean (SD)	28 (4.7)	28 (4.9)	27.9 (4.5)
Duration of complaints < 1 yr, %	11.7	10.8	12.6
1 – 3 yrs, %	34.7	34.2	35.1
> 3 yrs, %	53.6	55	52.3
Localised OA[3], %	38.3	37.8	38.7
Generalised OA, %	61.7	62.2	61.3
Knee OA, %	30.6	30.6	30.6
Unilateral hip OA, %	51.8	38.7	64.9
Bilateral hip OA, %	48.2	61.3	35.1
Kellgren & Lawrence = 1, %	52.7	52.3	53.2
≥ 2, %	47.3	47.7	46.8
Minimum JSW[4] in mm, mean (SD)	2.23 (1.0)	2.33 (0.9)	2.13 (1.0)
JSW < 2.5 mm, %	53.6	48.6	58.6
WOMAC[5] pain, mean (SD)	34.2 (23.1)	32.4 (23.2)	35.9 (23.0)
function, mean (SD)	35.1 (22.9)	34.1 (21.7)	36.0 (24.1)
stiffness, mean (SD)	42.6 (25.2)	41.1 (23.1)	44.2 (27.2)
Pain last week in mm, mean (SD)	32.4 (25.9)	30.5 (25.2)	34.3 (26.5)
VAS pain > 30, %	45.0	39.6	50.5
Pain medication use daily, %	23.9	18.9	28.8
sometimes, %	26.6	27.9	25.2
none, %	49.5	53.2	46.0

[1]GS: glucosamine sulfate, [2]SD: standard deviation, [3]OA: osteoarthritis [4]JSW: joint space width, [5]WOMAC: Western Ontario Macmaster Universities

(95% CI [-0.18, 0.08]) for the generalized OA group, both in favor of the placebo group.

Exploratory analyses

In the group with a pain score at baseline of VAS ≤ 30, the mean difference in WOMAC pain score was -2.4 (95% CI [-7.1, 2.4]) (Table 3). For the group with a pain score at baseline of VAS > 30 the adjusted difference was -3.4 (95% CI [-10.0, 3.2]) in favor of the GS group.

Table 2: Descriptive statistics at baseline for the different subgroups

	WOMAC pain GS group	*WOMAC pain Placebo group*	*WOMAC function GS group*	*WOMAC function Placebo group*	*JSN[1] GS group*	*JSN Placebo group*
KL = 1	32.8 (23.3)	33.7 (24.7)	31.2 (23.6)	34.3 (20.6)	-0.09 (0.36)	0.01 (0.29)
KL ≥ 2	39.5 (22.3)	30.9 (21.7)	41.4 (23.7)	33.9 (22.9)	-0.10 (0.26)	-0.14 (0.35)
Localized OA	34.8 (24.4)	27.3 (20.7)	35.3 (23.6)	29.0 (18.8)	-0.07 (0.30)	-0.07 (0.34)
Generalized OA	36.7 (22.2)	35.5 (24.3)	36.5 (24.6)	37.2 (22.8)	-0.11 (0.35)	-0.05 (0.31)
VAS ≤ 30	20.7 (16.3)	21.0 (14.9)				
VAS > 30	50.9 (18.4)	49.7 (23.0)				
No pain medication	24.0 (20.4)	22.3 (20.0)				
Pain medication	43.7 (21.1)	41.5 (22.4)				
No knee OA	35.2 (23.7)	29.8 (22.8)				
Knee OA	37.5 (21.7)	38.2 (23.4)				
JSW ≥ 2.5 mm					-0.08 (0.34)	0.02 (0.31)
JSW < 2.5 mm					-0.11 (0.32)	-0.15 (0.31)

Values are presented as mean (SD)
[1]JSN: Joint Space Narrowing

For patients not using pain medication during the study the adjusted difference in WOMAC pain was -0.3 (95% CI [-6.4, 5.8]). For patients that used pain medication the adjusted difference was -3.0 (95% CI [-8.4, 2.5]).

For patients that had concomitant knee OA at baseline the adjusted difference for WOMAC pain was -5.7 (95% CI [-12.6, 1.3]), while for patients that did not have concomitant knee OA the difference was -0.1 (95% CI [-4.9, 4.7]). In the subgroup with a JSW of more than 2.5 mm at baseline the adjusted difference in JSN was -0.12 (95% CI [-0.26, 0.01]) in favor of placebo. In the subgroup with a JSW of less than 2.5 mm at baseline the adjusted difference in JSN is 0.04 (95% CI [-0.09, 0.18]) and is more in favor of GS.

Table 3: Effect of GS in subgroups

		Change from baseline after 24 months (SD) Placebo group	*Change from baseline after 24 months (SD) GS group*	*Unadjusted difference after 24 months (95% CI)*	*Adjusted difference over 24 months (95% CI)*
Predefined subgroupanalyses					
WOMAC pain[#]	**KL = 1**	-1.5 (26.0)	-4.7 (19.3)	-3.3 (-11.9, 5.4)	-1.4 (-6.7, 3.8)[$]
	KL ≥ 2	3.8 (26.8)	3.6 (21.8)	-0.2 (-11.3, 10.9)	-1.35 (-7.4, 4.7)[$]
WOMAC function[#]	**KL = 1**	-1.0 (18.1)	-2.6 (19.0)	-1.6 (-8.6, 5.5)	-1.5 (-5.8, 2.9)[$]
	KL ≥ 2	5.6 (21.3)	1.9 (19.3)	-3.7 (-12.8, 5.5)	-2.1 (-7.5, 3.3)[$]
JSN[+]	**KL = 1**	0.01 (0.29)	-0.09 (0.36)	-0.10 (-0.22, 0.03)	-0.09 (-0.22, 0.04)[$$]
	KL ≥ 2	-0.14 (0.35)	-0.10 (0.26)	0.03 (-0.11, 0.17)	0.09 (-0.07, 0.24)[$$]
WOMAC pain[#]	**localized**	1.8 (31.2)	-1.1 (20.4)	-2.9 (-14.5, 8.8)	1.4 (-5.6, 8.3)[$]
	generalized	0.3 (22.8)	-1.8 (21.1)	-2.1 (-10.4, 6.3)	-3.5 (-8.2, 1.3)[$]
WOMAC function[#]	**localized**	1.2 (23.0)	-2.2 (20.2)	-3.4 (-13.0, 6.2)	-0.9 (-6.9, 5.1)[$]
	generalized	2.4 (17.3)	0.3 (18.3)	-2.2 (-9.0, 4.7)	-2.9 (-7.0, 1.2)[$]
JSN[+]	**localized**	-0.07 (0.34)	-0.07 (0.30)	-0.00 (-0.14, 0.14)	-0.02 (-0.17, 0.13)[$$]
	generalized	-0.05 (0.31)	-0.12 (0.35)	-0.07 (-0.19, 0.06)	-0.05 (-0.18, 0.08)[$$]
Exploratory analyses					
WOMAC pain[#]	**VAS ≤ 30**	6.1 (23.7)	1.1 (21.0)	-5.0 (-13.5, 3.5)	-2.4 (-7.1, 2.4)[$]
	VAS > 30	-8.0 (28.5)	-4.5 (20.1)	3.5 (-7.5, 14.5)	-3.4 (-10.0, 3.2)[$]
WOMAC pain	**No pain medication**	4.0 (23.6)	1.1 (19.7)	-2.9 (-12.3, 6.4))	-0.3 (-6.4, 5.8)[$]
	Pain medication	-2.0 (28.5)	-3.6 (21.3)	-1.6 (-11.5, 8.3)	-3.0 (-8.4, 2.5)[$]
WOMAC pain	**No knee OA**	0.1 (26.2)	0.3 (21.5)	0.3 (-7.9, 8.5)	-0.1 (-4.9, 4.7)[$]
	Knee OA	2.9 (27.1)	-5.8 (18.1)	-8.7 (-21.2, 3.8)	-5.7 (-12.6, 1.3)[$]
JSN[+]	**≥ 2.5 mm**	0.02 (0.31)	-0.08 (0.34)	-0.10 (-0.23, 0.03)	-0.12 (-0.26, 0.01)[$$]
	< 2.5 mm	-0.15 (0.31)	-0.11 (0.32)	0.04 (-0.09, 0.17)	0.04 (-0.09, 0.18)[$$]

[#]negative value: GS favours placebo, [+]positive value: GS favours placebo, [$]adjusted for body mass index, gender, age, pain medication use, unilateral/bilateral disease, and Kellgren & Lawrence score, [$$]adjusted for gender, age, and Kellgren & Lawrence score

DISCUSSION

Subgroup analyses in our trial did not show an effect of GS on symptomatic or radiographic progression in subgroups of patients with hip OA. The predefined subgroup analyses based on radiographic severity of OA and type of OA did not yield differences between GS and placebo in outcomes for pain, function and JSN over 24 months. None of the exploratory analyses based on pain medication use, baseline pain level and JSW at baseline showed any differences.

To get a sense of the magnitude of the effects we can express the results for WOMAC pain and function as effect sizes (ES). In order to reach a clinically relevant effect of ES ≥ 0.5, we would need a difference of 11.5 points on WOMAC pain and function outcomes. The ES of all trials on glucosamine is 0.35[2], which can be interpreted as a small effect. The average lower bound of the confidence intervals in our subgroup analyses was around -7, consistent with an effect size of 0.3. This means that, despite the wider confidence intervals found in subgroup analyses, we can practically rule out even a small effect of GS.

The possible positive effect of GS in patients with knee OA[1] raised the question whether the patients within our trial with concomitant knee OA benefited more from GS then the patients without. We hypothesized that it would be possible to find such an effect in our trial, because complaints due to knee OA are likely to have an influence on the WOMAC questions for hip pain, in particular the ones regarding walking, ascending and descending stairs, and standing.

In the exploratory analysis on the patients with concomitant radiographic knee OA at baseline, we found a mean effect on WOMAC pain of -5.68 (95% CI [-12.62, 1.26]) in favor of GS whereas the effect is almost 0 in patients without concomitant knee OA. The ES for the lower bound of the confidence interval is 0.56 in favor of GS, this means we cannot rule out a clinically relevant effect for knee OA.

This difference in effect between hip and knee OA may be due to a difference in inflammatory component, which is thought to be larger in knee OA. This assumption is supported by the finding that some interventions targeting inflammation seem to be more effective for knee than for hip OA[21 22]. Also, in a study by Meulenbelt et al.[23] knee OA was positively associated with the inflammation component, whereas hip OA was not.

That glucosamine acts on the inflammatory processes was already shown by Uitterlinden et al.[24], who found that glucosamine protects against Interleukin-1b (IL-1b) mediated extracellular matrix breakdown in in vitro studies. IL-1b is one of the cytokines that plays an important role in the inflammatory cascade in OA[25].

However, the finding for knee OA may also be based on chance alone, due to the multiple tests that we have performed. Also, there is a chance of residual con-

founding, especially since we did not have other information concerning knee OA than a radiograph of the knees at baseline.

The patients in the original study had milder radiographic OA than patients in previous positive trials[26-28]. While other studies included only patients with KL 2 and 3, about 50% of the patients in this study had a KL score of 1. However, when the effect of GS in a subgroup of patients with KL score of 2 and 3 was tested, we still found no effect. The outcomes in this subgroup were very similar to the outcomes of the overall study population6 for WOMAC pain and function.

In addition we performed a subgroup analysis based on JSW, an objective measure of radiographic severity. With a chosen cut-off value of 2.5 mm based on the literature[29], no effect of GS was seen in the two subgroups.

As far as we know we are the first study to investigate the relationship between type of OA and effect of a therapy. It has been hypothesized that generalized OA may have a different pathophysiology than localized OA[10], which could result in a different reaction to therapy. The results from this current study do not necessarily support this assumption, but they have implications for other studies that study therapeutic effects on a single joint, in which patients are included with OA in other joints as well. The influence of co-existing disease in other joints should be further investigated.

By performing predefined and exploratory subgroup analyses we increased the possibility of chance findings, the results from our analyses should therefore be interpreted with caution. We chose not to adjust for multiple comparisons. The exploratory analyses were performed to answer questions that emerged during the main analyses, not to draw conclusions on. Adjusting for multiple comparisons would have increased the risk for a type II error. Finally, we found no significant differences without adjusting for multiple comparisons, adjusting for it would have led to even smaller ES.

For the sake of clarity we chose to report only the outcomes for WOMAC pain in the exploratory subgroup analyses. The outcomes for WOMAC function were very similar.

We made subgroups based on baseline level of VAS pain with a cut-off value of 30 as this is often used in literature. In this analysis no differences were found between GS and placebo. In the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) study however, a subgroup of patients with a high baseline level of pain (WOMAC pain = 301-400 mm) was found to benefit from the combination of glucosamine hydrochloride and chondroitin sulphate[3]. We did not have enough patients with a level of pain similar to the subgroup in the GAIT study to perform a meaningful analysis on.

The patients in our study were receiving usual care during the study. As a result, half of our patients used pain medication daily or occasionally, as prescribed by their general practitioner or as over-the-counter medication. To rule out a dilution of effect due to pain medication use, we assessed the effect of GS in a subgroup of patients that reported no use of pain medication throughout the study period. In this group with mild OA complaints (WOMAC pain = 23.1 ± 20.1 (Mean ± SD)) there was still no effect of GS on pain and function.
In the design of this study subgroup analyses were predefined and the trial was oversized in order to have sufficient power to perform these analyses. However, the standard deviation of the WOMAC pain and function data in our study is much higher than was anticipated, probably due to the inclusion of primary care patients. Future trials with primary care patients should take this into consideration when calculating the sample size. However, despite the large standard deviations in our trial, we were able to rule out minimal clinical important differences in almost all analyses.

Conclusion

GS was not better than placebo in reducing symptoms and progression of hip OA in subgroups of patients based on severity of radiographic OA, type of OA, severity of pain at baseline, pain medication use and baseline JSW.

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5

The influence of disease characteristics of knee and hip osteoarthritis on effectiveness of exercise therapy: a systematic appraisal

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Submitted

ABSTRACT

Objectives

In this review we try to answer the research question: Does the effectiveness of exercise therapy in management of pain and function in patients with osteoarthritis depend on severity of radiographic osteoarthritis (ROA) or duration of illness?

Methods

We searched PubMed and the Cochrane library to find systematic reviews on effectiveness of exercise therapy. All randomised controlled trials (RCTs) from the selected reviews were collected and screened for the following inclusion criteria: comparison of exercise vs. non-exercise therapy, pain and function measures, documentation of severity of ROA and/or duration of illness, data suitable to calculate effect size.
Due to lack of free access to original data we used a second best method and calculated effect sizes of pain and function scores per study. Linear regression analysis was used to analyse the data.

Results

We included eleven RCTs. Effect sizes for pain ranged from 0.03 – 1, for function from 0.04 – 3. Percentage of patients with moderate and severe ROA ranged from 21.2% – 100%. Mean duration of illness ranged from 2.2 – 12.3 years. Seven of the included studies were of high quality.
There is a tendency that patients with less severe ROA benefit more from exercise therapy in terms of function than severely affected patients. For pain we could not find the same relation, nor could we find a relation between duration of illness and effectiveness of exercise therapy.

Conclusion

There is no clear indication that effectiveness of exercise therapy in patients with osteoarthritis depends on severity or duration of illness.

BACKGROUND

Osteoarthritis (OA) is the most common form of arthritis[1]. It can lead to pain and dysfunction of the joints. The impact on patients can be substantial; 80 % of people with OA have limitation in movement, 25% cannot perform major daily activities of living[2].

Numerous therapies exist to treat the symptoms of OA. To help physicians and patients choose the most appropriate treatment, evidence based clinical guidelines for the management of OA have been issued[3 4].

These guidelines are however lacking a clear proposition on the optimal timing of individual treatment options. Although the guidelines include a proposition which states that treatment of knee and hip OA should be tailored according to joint risk factors, general risk factors, level of pain intensity and handicap, and location and degree of structural damage; these recommendations are based on consensus, as there is not much clear supportive evidence available.

In this article we will focus our attention on exercise therapy, one of the most common recommendations in OA treatment. Most effectiveness studies on exercise therapy either compare two different types of exercise, or compare one exercise therapy with receiving another conservative treatment. These studies are usually not designed to analyze influence of disease severity on the effect of treatment, either due to power being too low for such subgroup analyses or due to using study populations restricted to a certain severity of osteoarthritis. So far, to our knowledge, the only data on this subject is from a randomised clinical trial (RCT) by Fransen et al.[5], who found that the effect of exercise therapy was higher in a group with mild radiographic OA than in a group with a more severe form of radiographic OA.

Nevertheless, the recommendations by Roddy et al[6] on the role of exercise in the management of OA, state that effect of exercise therapy is independent of presence or severity of radiographic findings.

The uncertainty surrounding the influence of radiographic severity of OA and other disease characteristics on effect of exercise therapy led us to design a systematic appraisal with the following question: Are there indications that the effectiveness of exercise therapy in management of pain and function in patients with osteoarthritis depend on severity or duration of disease?

METHODS

A review of RCTs

Many RCTs have been carried out to test the effectiveness of exercise therapy on complaints due to OA. In addition, a number of systematic reviews have been carried out to summarise these results. Our main question is not to assess effectiveness in general, but to see whether disease characteristics influence the effectiveness of the treatment. We decided to use the data from the RCTs included in the systematic reviews.

Selection of systematic reviews

To find the systematic reviews (or meta-analyses) on effectiveness of exercise therapy we searched PubMed and the Cochrane library with the following search terms and MeSH headings: physical education and training, physical fitness, relaxation, physical endurance, physical therapy, exercise, motion therapy, physiotherapy, osteoarthritis, quantitative review, systematic review, and meta analysis. The reviews that dealt with effect of exercise therapy on osteoarthritis of the knee and/or hip were screened for RCTs that could be included in our appraisal. To be complete, we also searched PubMed for RCTs published after the inclusion date used in the most recent systematic review. This search was performed in September 2008 and used the same search terms for exercise therapy as were used for the systematic reviews, with the 'type of article' limited to 'randomized controlled trial'.

Selection of RCTs

All RCTs from the selected systematic reviews were collected. To be included in this appraisal, trials needed to have the following aspects:

- Comparison of exercise therapy vs. a non-exercise control group
- Pain and/or function measurements at baseline and follow up
- Documentation of severity of radiographic OA and/or duration of illness of the study population
- Data suitable to calculate an effect size.

Quality assessment of the included studies

As most of the studies that will be included in this appraisal are listed in the PEDro Database (a database archiving randomised controlled trials, systematic reviews

and evidence-based clinical practice guidelines in physiotherapy), we chose to use the quality scoring-system of that database. This scoring system is an adaptation of the Delphi list[7]. A confirmed score was available for all RCTs in the database. The possible scores on the PEDro scale range from 0-10. We decided to regard all studies that scored higher than five (more than 50% of the items positive) as higher quality studies.

Data-extraction and statistical analysis

Due to lack of availability of the original data from the RCTs, quantitative group data on the outcome measures, self-reported pain and function scores, was extracted from all the included studies. Data on mean duration of the illness and on distribution of severity of radiographic osteoarthritis (ROA), the independent variables, was also extracted from the studies. Not all studies measured both outcome measures and/or both independent variables. What data was extracted from each study is presented in Table 1.

Effect sizes (ES) and their confidence intervals were calculated. The ES was calculated using the difference in change scores (post-treatment minus pre-treatment) between the exercise and control group and the pooled baseline standard deviation (SD) of both groups[8].

To calculate the 95% confidence interval of the effect size the correlation between the pre-treatment and post-treatment scores is needed. Because data on such correlations were not available in the articles, we assumed this correlation to be 0.5 in all included individual trials. By doing so, the 95% confidence interval of the effect size could be calculated as the ES +/- $t(1-\alpha/2, n-1)^{*}\sqrt{(1/n)}$.

To be able to compare radiographic severity of the patients per study and thus use this measure as an independent variable, we had to reclassify the categories of different radiographic scoring systems used in the included RCTs. We used the Kellgren & Lawrence (KL) scoring system[9] as our reference; we used the features of this system to convert the scores of the other scoring systems into mild, moderate and severe OA. We calculated the percentage of patients with moderate or severe OA (KL 3 or 4) per study. For our second independent variable, duration of illness, we extracted the mean duration of illness in years per study.

Finally we used linear regression analysis to distinguish whether there was a trend or association between disease characteristics and the ES of the studies. As these analyses are exploratory, we will regard a $p < .20$ as a trend.

To control for factors that might have influenced the effect of treatment, we looked at the amount of therapy sessions. We again used linear regression analysis to assess whether there is a relationship between amount of training sessions and

Table 1: Characteristics of included studies

Author	*N*	*Quality score*	*Joints*	*Intervention*	*Control 'therapy'*	*Intensity + duration of intervention*	*Outcome measures*	*Disease characteristics*
Baker, 2001[21]	46	7/10	Knee	Home based strengthening exercises	Nutrition education	3 x pw for 4 months	Pain Function	Severity
Peloquin, 1999[22]	137	6/10	Knee	Aerobic and strengthening exercises	1-hr education session twice a month	3 x pw for 3 months	Pain Mobility	Severity + Duration
Borjesson, 1996[23]	68	6/10	Knee	Strengthening and ROM exercises	No intervention	3 x pw for 5 weeks	Pain	Severity + Duration
Jan, 1991[24]	61	2/10	Knee	Strengthening exercises with ultrasound or short-wave diathermy	Ultrasound of short-wave diathermy *without* exercise	Min 4 x pw, until symptoms improved significantly/totally relieved	Function	Severity + Duration
Bautch, 1997[25]	30	5/10	Knee	Exercise program including ROM exercises and low intensity aerobic exercises and educational program.	Educational program (1 x pw)	3 x pw for 12 weeks	Pain	Severity
Talbot, 2003[26]	34	5/10	Knee	Home based walking program increasing amount of steps per day + arthritis self-management program	Arthritis self management program (12 hrs over 12 weeks)	Daily for 12 weeks	Pain	Severity
Kuptniratsaikul, 2002[27]	392	5/10	Knee	Strengthening exercises	No intervention	2 x pw for 8 weeks	Pain Function	Severity
Thorstensson, 2005[29]	61	6/10	Knee	Endurance and strengthening exercises	No intervention	2 x pw for 6 weeks	Pain Function	Severity
Bennell, 2005[30]	140	8/10	Knee	Home based strengthening exercises	Sham ultrasound and non-therapeutic gel.	Daily for 12 weeks	Pain Function	Severity Duration
Ravaud, 2004[31]	1495	6/10	Knee + Hip	Home based strengthening exercises	Usual care by rheumatologist	4 x pw for 6 months	Pain Function	Severity Duration
Cochrane, 2005[28]	106	7/10	Knee + Hip	Water based strengthening and aerobic exercises	Education leaflet	2 x pw for 12 weeks	Pain Function	Duration

P = pain, F = function

ES for pain and function. Similarly, we looked whether severity of OA and amount of training sessions were related.

RESULTS

Selection of studies

In our search of PubMed and the Cochrane Library we identified 13 reviews[6 10-20], not all systematic, that concerned exercise therapy and osteoarthritis. From these reviews we were able to extract 37 RCTs. The latest systematic review had included RCTs published until May 2005. We found another 8 studies in PubMed that were published between May 2005 and September 2008.
From the 45 RCTs we found, 34 studies did not meet our inclusion criteria (Fig 1). Seven of them did not have enough contrast between the two therapies tested. Two studies did not have data on pain or function. Nineteen studies were excluded because they did not report a measure of radiographic severity or duration of illness, two because the data was not suitable to calculate a comparable value. Two presented data that were not suitable to calculate an effect size. One study specifically looked at patellofemoral osteoarthritis, we therefore chose not to include this study. One study reported on previously published data that was already excluded.

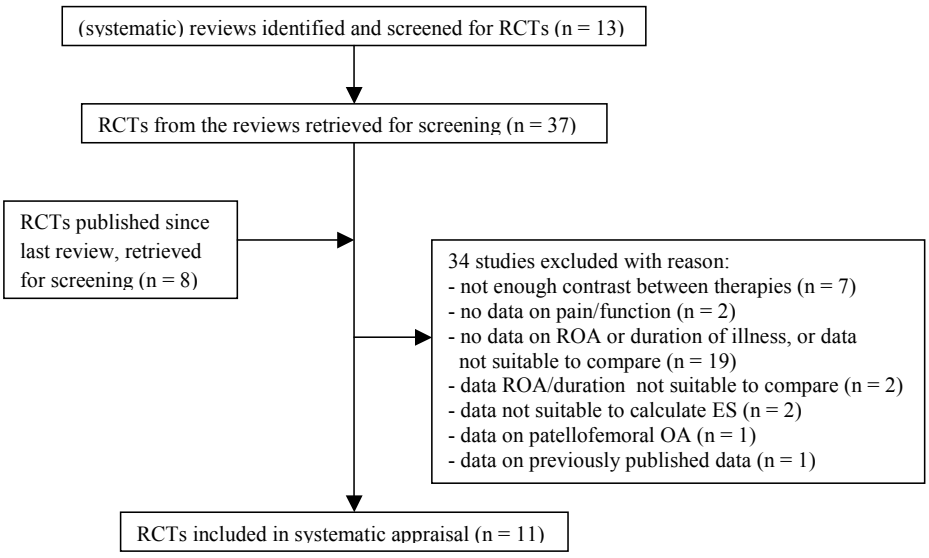

Figure 1: Flow diagram of inclusion of RCTs

Table 2: ES, radiographic severity and duration of illness

Author	*ES (95% CI)*	*Radiographic severity (% moderate + severe)*	*Duration of illness (years)*	*Number of training sessions*
Baker, 2001[21]	P = 0.60 (0.30 – 0.90) F = 0.46 (0.16 – 0.76)	50 %	NR	54
Peloquin, 1999[22]	P = 0.40 (0.23 – 0.57) F = 0.09 (-0.08 – 0.26)	31.3 %	7.15 yrs	39
Borjesson, 1996[23]	P = 0.24 (0 – 0.48)	78 %	7.5 yrs	15
Jan, 1991[24]	F = 3 (2.74 – 3.26)	21.2 %	2.2 yrs	41,2
Bautch, 1997[25]	P = 1 (0.29 – 1.71) F = 0.33 (-0.38 – 1.04)	54 %	NR	36
Talbot, 2003[26]	P = 0.13 (-0.22 – 0. 48)	42.3 %	NR	84
Kuptniratsaikul, 2002[27]	P = 0.33 (0.23 – 0.43) F = 0.04 (-0.06 – 0.14)	44 %	3.78 yrs	16
Thorstensson, 2005[29]	P = 0.11 (-0.15 – 0.37) F = 0.13 (-0.13 – 0.39)	100 %	NR	12
Bennell, 2005[30]	P = 0.04 (-0.13 – 0.21) F = 0.04 (-0.13 – 0.21)	71.6 %	9.15 yrs	84
Ravaud, 2004[31]	P = 0.03 (-0.02 – 0.08) F = 0.07 (0.02 – 0.12)	83 %	5.3 yrs	104
Cochrane, 2005[28]	P = 0.71 (0.52 – 0.90) F = 0.82 (0.63 – 1.01)	NR	12.32 yrs	24

ES = effect size, CI = 95% confidence interval, P = pain, F = function, NR = not reported

Finally, we could use the data of 11 RCTs[21-31]. The characteristics of these studies, including the Pedro score, are shown in Table 1.

Ways of measuring pain and function

Different ways to measure pain and function were used in the individual studies. Three studies[21 28 30] used the Western Ontario MacMaster Universities questionnaire (WOMAC) to measure both pain and function. One study used the WOMAC questionnaire for measuring function[31]. One study used the Arthritis Impact Measurement Scales (AIMS/AIMS2) to measure pain and function[22]. One study used the Knee injury and Osteoarthritis Outcome Score (KOOS) questionnaire to measure pain and function[29]. Three other studies used a Visual Analogue Scale (VAS) or a Numeric Rating Scale (NRS)[23 25 31] to measure pain. One study used the McGill Pain questionnaire (MPW)[26] and one study did not define the way they measured pain[27]. Two studies used the Functional Incapacity Score (FIS)[24 27] to measure function. Based on these measures of pain and function ES were calculated per study (Table 2).

Ways of measuring severity of radiographic OA and duration of illness

Nine studies[21 22 25-31] scored radiographic severity of OA according to the KL criteria[9]. One study[23] used the classification system of Ahlback (1968) and one[24] used the system based on the 'Standard Radiographs of Arthritis'. We calculated the percentage of moderate or severe patients per study (see Table 2). For the studies that used the criteria of KL this means the percentage of patients with grade 3 and 4. Borjesson et al[23] used the Ahlback classification system[32]. We decided to regard an Ahlback grade 2 as being comparable to a KL score 3. We therefore calculated the percentage of patients in Borjesson et al[23] with an Ahlback score of 2 or higher. The system used in Jan and Lai[24] seems very comparable to the KL classification. We therefore calculated the percentage of patients with a score 3.
The mean duration of illness was extracted per study. The results for radiographic severity and duration of illness are presented in Table 2.

Influence of disease characteristics on effectiveness of exercise therapy

When we used linear regression to quantify the relation between severity of radiographic OA and ES for pain found by the included studies, no association was found (β = -.451, p = .223). However, between severity of radiographic OA and ES function the linear regression showed a trend (β = -.564, p = .145) (see Fig 2).
Duration of illness was not associated with the ES for pain (β = .525, p = .284) nor with ES for function (β = -.402, p = .430).

Study characteristics

As amount of training sessions might have an influence on effectiveness of therapy, we assessed the association between this study characteristic and the ES for pain and function. To see whether average amount of training sessions per study is influenced by the severity of the patients we also checked this association.
For pain we found that the studies with the most training sessions generally had the least effect (β = -.408, p = .241). For function no association was present (β = -.13, p = .738).
The number of training sessions does not seem to be influenced by the severity of radiographic OA (β = .013, p = .972).
Seven studies of higher quality[21-23 28-31] and four studies of lower quality[24-27] were included in this review. The conclusions from the lower quality studies generally seem to be in line with the conclusions from the higher quality studies.

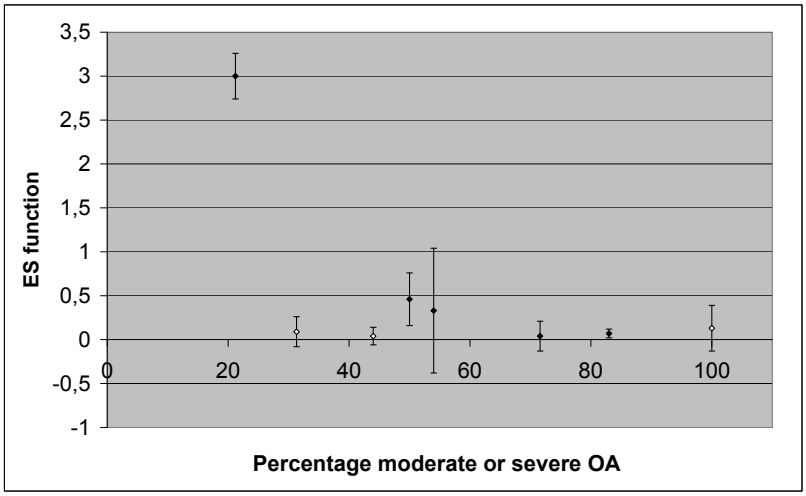

Figure 2: Influence of severity of ROA on effect of exercise therapy on function. White dot: low quality

DISCUSSION

We found a slight indication that exercise therapy was more beneficial in terms of function for patients with a milder form of radiographic OA than for more severely affected patients. For the effect of exercise therapy on pain we did not find such a relation. Based on the data available for this systematic appraisal we could not find a relation between duration of illness and effectiveness of exercise therapy. The amount of training sessions did not influence the effect on pain or function.

We further checked whether amount of training sessions is influenced by the percentage of moderate and severe patients per study. One could imagine that physiotherapists will choose lighter training methods for patients that experience much pain and/or function loss. The data in this review however, do not suggest that the more severely affected patients received less training sessions.

The trend we found for severity of ROA and the effect on function is influenced by the extreme score of the low quality study by Jan and Lai[24]. In an analysis without this study, the trend no longer existed.

The three studies with highest amount of training sessions found small effect sizes for pain and function. These trials used a home-based exercise program. The participants had to exercise daily[26 30] during 12 weeks, or four times per week[31] during six months. Compliance may have been a problem in these studies, which

could explain the lack of effect. Although compliance was recorded, this was self-reported by the patients and therefore subject to bias.

The trials in this review used different types of exercise therapy. Six trials used strengthening exercises, two used aerobic exercises and three used a combination. A review by Roddy et al.[19] already showed that there is no clear difference in effect between these two types of therapy. We therefore did not distinguish between them.

The methods used in this study had its drawbacks. First of all, we could only include a small proportion of the available studies due to the inclusion criteria that we used. We chose to use the Kellgren & Lawrence score as a reference score to calculate the severity of radiographic OA. This scoring system has been criticised for possible inconsistencies in interpretation[33]. However, the majority of the trials used it, which made it the most logical choice for this systematic appraisal. Furthermore, it still is the scoring system for severity of radiological OA most agreed on and it was found to be a reliable indicator of osteoarthritis[34 35].

Also, exercise may not be an appropriate therapy to perform this kind of review on, because the protocol of the therapy is often a black box. Individual preferences of the therapist, and characteristics of individual patients may have an influence on the intensity of training and on the exercises performed. We have chosen severity of ROA and duration of complaints instead of severity of symptoms because these measure are more stable over time. Osteoarthritis symptoms can fluctuate on a weekly basis[36] and would therefore be less reliable as independent variable. Comparing effect sizes has clear disadvantages: when baseline SDs are used as we did to calculate effect sizes, effect sizes will be higher in the studies with a more homogeneous study population. Further, when a larger number of studies are available for such an appraisal, more rigorous multivariable methods can be used to study the independent influence of a certain study characteristic on the effect size[37]. We had no power to execute such analyses. Because of these different drawbacks we have to be very careful when interpreting the results of this study; our findings have to be regarded as hypothesis generating.

Despite all disadvantages of studying non-original data it is possible to find clear indications for different treatment effects for subgroups in osteoarthritis trials. Wang et al[38] performed a meta-regression analysis to study effectiveness of hyaluronic acid injections for osteoarthritis symptoms in different subgroups. One of their findings was that the patients with the most advanced radiographic stage of osteoarthritis were less likely to benefit from injections with hyaluronic acid. The protocol for these injections are clear, and the therapies in the different studies were therefore comparable. For exercise therapy a clear difference in treatment effect for subgroups based on severity or duration of symptoms still is possible, it

is possible that it did not show up because of the diversity of treatment programs found in the studies in our systematic appraisal.
Very few RCTs regarding effect of exercise in OA have published subgroup analyses on severity of disease. The problem with interpreting results from individual RCTs is that they are subject to bias. It is likely that many researchers perform subgroup analyses, but only publish these analyses whenever they find a difference between groups. Such data should therefore be used with caution; they could well be chance findings only. Only subgroup analyses that were included in the study protocol and for which sample size calculations were performed beforehand are really valid.
At this stage, it is not possible to draw firm conclusions based on the data we have gathered. The ideal situation would be to have researchers provide the individual patient data (IPD) of their trials to be used in a meta-analysis; these IPD could then be analyzed according to predefined subgroup analyses. A meta-analysis based on IPD is advocated as a reliable way to perform subgroup analyses[39 40].
However, a more realistic approach will be to have all ongoing trials perform and publish certain subgroup analyses whether or not they are powered for it. Researchers would then be able to pool the data from all these trials. This effort could help physicians and patients choose the most appropriate management strategy for osteoarthritis.
However, what we can deduce from our findings is that there are so far no indications that patients with mild OA will benefit less from exercise therapy than patients with a more severe form of OA. Therefore, based on the present study we clearly support the recommendations by Roddy et al[6] on the role of exercise in the management of OA, stating that effect of exercise therapy is independent of presence or severity of radiographic. We also encourage other guidelines to underline this statement. That the content of exercise therapy may differ depending on severity of disease still needs more attention in OA exercise research.

Conclusion

There is no clear indication that effectiveness of exercise therapy in patients with osteoarthritis depends on severity or duration of disease. Therefore at this stage of knowledge, all patients with OA, independent of severity of disease, are indicated for exercise therapy.

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6

The course and the prognostic factors of symptoms in primary care patients with hip osteoarthritis over two years

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Submitted

ABSTRACT

Objectives

The course and prognostic factors of hip osteoarthritis (OA) are poorly investigated. The aim of this study was to describe the course of pain and to analyse prognostic factors of progression of pain and function in patients with hip OA.

Methods

Primary care patients were included when they met the American College of Rheumatology criteria for hip OA. Patients filled out a questionnaire every 3 months throughout the 2-year duration of the study. Patients' global assessment, a visual analogue scale (VAS), and the Western Ontario MacMaster Universities (WOMAC) for pain and function were used as outcome measures. The average outcome of the first three measurements was compared to the average outcome of the last three measurements.

Results

The complaints of the patients on average stayed relatively stable over time. Individual patients data showed large fluctuations in pain and function scores over time.
After two years a painful hip flexion at baseline and a Kellgren & Lawrence score of ≥ 2 significantly influenced worsening of patients' global assessment.
A higher age and a Kellgren & Lawrence score of ≥ 2 significantly increased VAS pain, whereas a higher VAS at baseline protected against increase.

Conclusions

Primary care patients with hip OA had a stable level of pain on group level, but there is substantial fluctuation in pain level within patients over a 2 year follow up period.
The fluctuating nature of the individual patient data made the analysis of factors that are predictive of progression of hip OA complaints rather complicated.

INTRODUCTION

Osteoarthritis (OA) is one of the main causes of disability among elderly people[1]. Patients with OA often experience persistent but variable pain, and problems in daily activities, such as stair climbing and walking longer distances[2]. Symptomatic hip OA occurs in 3% of the elderly and in a smaller percentage of all adults[3].
The course of OA is difficult to describe as it varies depending on whether one evaluates symptoms or radiographic change, and depending on the joint of interest[1]. Pain and functional status in hip and knee OA seem to deteriorate slowly[1 4]. For knee OA it was shown that pain changed little over time on group level but considerably more in individuals[5 6]. However, most studies on the course of symptoms of OA are based on 2 or 3 measurements, with a considerable length of time in between subsequent moments of measurement. The same difficulties that make it hard to describe the course, make it difficult to predict it.
Different studies have been carried out to unravel the factors relating to symptomatic and radiographic progression of osteoarthritis. The review of Lievense et al[7] found that superolateral migration of the femoral head and atrophic bone response were both associated with a more rapid radiographic progression of hip OA. They also found that body mass index (BMI) was not related to radiographic progression of hip OA.
More recently, studies on the prognosis of hip OA with clinical outcomes have been published [8-10]. They all found radiographic severity to be associated with progression, as well as different factors obtained by history taking and physical examination. These studies focused on the predictors of a total hip replacement (THR), and not specifically on the clinical outcomes pain and function. Also, these studies had few intermediate measurements to assess the outcome. There is still need for further research on the course and prognosis of the symptoms of hip OA[4 7]. Studies on clinical outcomes with a longer follow up period are needed, and for a more accurate prediction of the course of symptoms more frequent measurements over time would be favorable.
The aim of this study is therefore to describe the course of symptoms over two years of patients with hip OA and to identify the predictive factors for progression of these symptoms.

METHODS

Design overview

In our study the data of the study by Rozendaal et al. was used[11]. This study was a randomized placebo controlled trial with a duration of two years to assess the effectiveness of glucosamine sulphate on hip OA. No difference in outcomes was found between the groups using glucosamine sulphate and placebo[11]. Therefore the study can be regarded and analyzed as a prospective cohort study.

Setting and participants

The study protocol of the randomized controlled trial was published in 2005[12]. Following is a brief summary of the protocol.
General practitioners in the Rotterdam area recruited the patients. Patients were included when they met one of the American College of Rheumatology (ACR) criteria for hip OA[13]. Patients were excluded when they received or when they were waiting for a total hip replacement (THR). Also patients with a Kellgren & Lawrence score of 4[14], patients with renal and/or hepatic disease, diabetes mellitus or a disabling comorbidity were excluded. Patients who were unable to understand Dutch questionnaires were also excluded from participation[11].
Nine questionnaires were filled out during the course of the study. The first one was filled out during the baseline assessment. Followed by one questionnaire every three months until the last questionnaire after two years[11].
The baseline characteristics were collected with the first questionnaire and during a physical examination which was done at the baseline assessment. In the original study 222 patients with hip OA were enrolled between September 2003 and March 2004. Patients who received a total hip replacement during the study were encouraged to stay in the study[11]. The total hip replacement was used as an endpoint for these patients.

Outcome measures

We used the Western Ontario MacMaster Universities (WOMAC)[15 16] pain and function, and the Visual Analogue Scale (VAS) to measure pain in the past week as outcome measures. These outcomes measures were collected every three months during the two years follow up period. We also used a question regarding patients' global assessment as compared to baseline as an outcome measure, which was collected every 6 months during the follow up period. The WOMAC pain and

function and the VAS pain are presented as normalized scores (0-100, 0 equals no complaints). The patients' global assessment score was a 5 point Likert scale score (1 = greatly deteriorated, 5 = greatly improved).

Prognostic variables

The continuous variables we used in our analysis were: age, baseline VAS pain, and health status today (0-100, 0 equals worst thinkable state of health, measured with the EuroQol VAS[17]).
The dichotomous variables we used in our analyses are: gender, low education level, body mass index (≥30 kg/m^2), duration of complaints (>3 years), high blood pressure, cardiovascular problems, anxiety / depression, painful internal rotation (one or both hips), limited internal rotation (<15 degrees rotation[13]), painful flexion, limited flexion (≤115 degrees of flexion[13]), type of OA (generalized OA: concomitant hand or knee OA at baseline), bilateral OA, Kellgren and Lawrence score (≥2[14]).

Statistical analysis

The analyses were performed with SAS 8.2 (SAS Institute, Cary, North Carolina) and SPSS 15.0 (SPSS, Chicago, Illinois)
We plotted both the mean values for all patients and the patients' individual data over the nine measurements for VAS pain, WOMAC pain and function and for patients' global assessment.
We performed a Pearson correlation coefficient test to investigate the correlation between our variables. Factors with a correlation of >0.8 were considered to be correlated with each other. In the case of high correlation, we used only the variable with the highest association in the multivariate analysis.
The patients' global assessment data was dichotomized (deterioration of complaints = 1, no change or improvement = 0). Subsequently we analyzed the data using logistic regression analysis. For the VAS pain and WOMAC pain and function data we calculated the mean of the first 3 measurements (baseline, 3 and 6 months follow up) and the mean of the last 3 measurements (18, 21 and 24 months follow up) and used the difference between these two as our outcome. A logit transformation was performed on this data because it was not normally distributed. The data for VAS and WOMAC was analyzed using linear regression analysis.
Model selection was done as follows: first the variables were analyzed with a univariate model. The variables that had a p-value < 0.2 in the univariate analysis were analyzed in a multivariate model. The variables with a p-value < 0.05 in the multivariate model were considered to be statistically significant.

RESULTS

Patient characteristics

A total of 222 patients were enrolled of which 209 (94.1%) completed the trial. Of these 209 completers twenty patients received a THR during the study. 23 WOMAC or VAS assessments were missing from patients who completed the study and did not undergo a THR[11]. The patient baseline characteristics are summarized in Table 1.

Missing values

None of the differences between the patients who did not complete the trial and the patients that did were statistically significant. The patients that underwent hiparthroplasty were not different from the ones that did not.

Table 1: Patient characteristics at baseline

Characteristic	*All patients (n=222)*
Age in years, mean (SD[1])	63.4 (9.0)
Gender, woman, %	69.4
BMI[2] ≥ 30 kg/m^2, %	25.7
Education level, Low, %	52.3
WOMAC[3]	
Pain, mean (SD)	34.2 (23.1)
Function, mean (SD)	35.1 (22.9)
Stiffness, mean (SD)	42.6 (25.2)
VAS[4] pain, mean (SD	32.4 (25.9)
Duration of complaints, >3 years, %	53.6
Cardiovascular problems, %	14.4
High blood pressure, %	26.6
Health status today, mean (SD)	76.7 (16.3)
Anxiety / Depression, %	15.4
Painful internal rotation, %	48.4
Limited internal rotation, %	18.0
Painful flexion, %	61.0
Limited flexion, %	66.7
Generalized OA[5], %	61.7
Bilateral OA, %	48.2
Kellgren & Lawrence score ≥ 2, %	47.3

[1]SD: standard deviation, [2]BMI: body mass index, [3]WOMAC: Western Ontario MacMaster Universities, [4]VAS: Visual Analogue Scale, [5]OA: osteoarthritis.

It was not possible to make plots for patients with missing values. Patients with missing values on the outcome measures were as a consequence removed from the data set. Therefore 177 (79.7%) patients remained in the data set for drawing the plots. The patients with missing values were analysed in the regression analyses.

Course

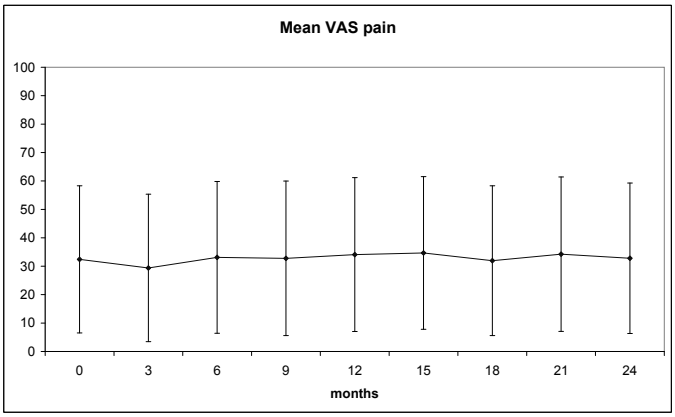
There was hardly any change over time regarding the mean symptom levels. The mean values for VAS pain, WOMAC pain, and patients' global assessment are summarized in Figure 1. The mean patients' global assessment score was on average around 3 throughout the study, indicating that patients perceived no change from baseline.
Figure 2 presents the WOMAC pain values for individual patients over the course of the study. The figures are shown for patients with low, medium and high baseline scores of WOMAC pain. These graphs show a high intra-individual fluctuation over the 2 years that patients were followed. The figures for VAS pain and WOMAC function are not presented but looked very similar.

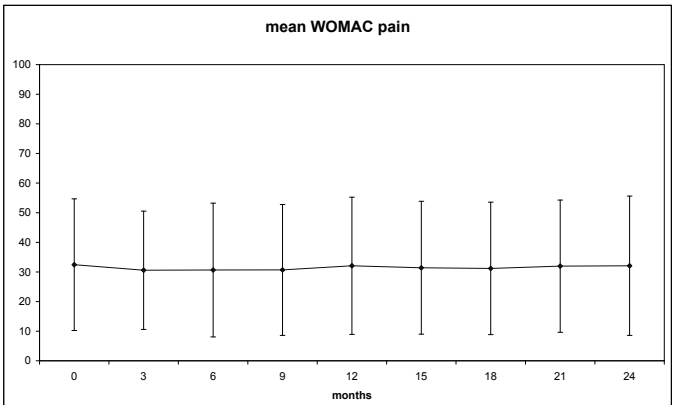
Correlation

The outcome measures WOMAC pain and function and VAS pain were not highly correlated with the baseline variables we examined. The correlation between VAS and WOMAC pain and function was high. Between VAS pain and WOMAC pain the correlation was 0.71 ($p<0.001$). Between VAS pain and WOMAC function the correlation was 0.67 ($p<0.001$). Between WOMAC pain and function the correlation was 0.80 ($p<0.001$). We chose to use only the VAS pain as a covariate in the analysis of all outcome measures.

Univariate analysis

The results of the univariate analyses are presented in Table 2.
When we evaluated the difference between the first 3 measurements and the last 3 measurements, we found that 44.3% of patients had an increased WOMAC pain score, 50.0% had an increased WOMAC function score and 58.8% had an increased VAS pain score. Furthermore, 42.2% of all patients indicated a deterioration of complaints as measured with the patients' global assessment during the 2 year follow up period.
The variables BMI ≥ 30, baseline VAS pain, limited and painful flexion, and Kellgren and Lawrence score ≥ 2 all led to worsening of the patients' global assessment. The





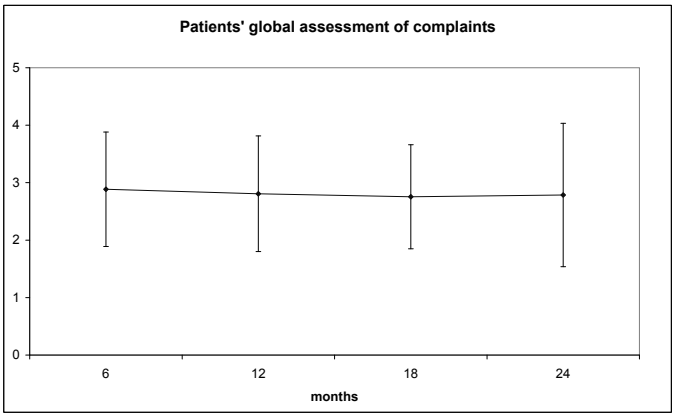


Figure 1: The mean scores (SD) summarized by outcome measure.

Table 2: results of the univariate analyses by outcome measure.

Factor	*Patients' global assessment OR (95% CI[1])*	*p-value*	*VAS pain estimate (95% CI[1])*	*p-value*	*WOMAC pain estimate (95% CI)*	*p-value*	*WOMAC function estimate (95% CI)*	*p-value*
Age	1.00 (0.97, 1.04)	0.845	**0.03 (0.01, 0.05)**	**0.008**	**0.02 (0.00, 0.04)**	**0.018**	0.01 (-0.00, 0.03)	0.238
Gender	0.82 (0.43, 1.57)	0.554	**0.44 (0.02, 0.86)**	**0.039**	0.18 (-0.22, 0.59)	0.370	**0.22 (-0.09, 0.54)**	**0.165**
Education level	1.41 (0.78, 2.52)	0.253	-0.12 (-0.51, 0.27)	0.551	-0.22 (-0.59, 0.15)	0.245	0.01 (-0.28, 0.30)	0.943
BMI[2]	**1.62 (0.82, 3.18)**	**0.164**	0.04 (-0.41, 0.50)	0.851	0.07 (-0.37, 0.50	0.769	0.05 (-0.29, 0.40)	0.760
Duration of complaints	1.32 (0.74, 2.37)	0.347	0.24 (-0.15, 0.62)	0.230	**0.26 (-0.11, 0.64)**	**0.162**	0.03 (-0.27, 0.32)	0.863
Baseline VAS[3] pain	**1.01 (1.00, 1.02**	**0.110**	**-0.02 (-0.03, -0.01)**	**0.001**	**-0.01 (-0.02, -0.00)**	**0.012**	**-0.01 (-0.01.-0.00)**	**0.038**
Cardiovascular problems	1.44 (0.63, 3.30)	0.390	**0.47 (-0.09, 1.03)**	**0.098**	0.12 (-0.41, 0.66)	0.650	0.13 (-0.29, 0.55)	0.547
High blood pressure	**0.58 (0.29, 1.15)**	**0.116**	-0.11 (-0.55, 0.33)	0.611	-0.10 (-0.52, 0.32)	0.638	-0.14 (-0.47, 0.19)	0.406
Anxiety / Depression	1.44 (0.67, 3.10)	0.345	-0.03 (-0.55, 0.49)	0.910	0.27 (-0.23, 0.77)	0.290	0.12 (-0.27, 0.52)	0.539
Health status today	0.99 (0.97, 1.01)	0.312	0.01 (-0.00, 0.02)	0.244	-0.00 (-0.01, 0.01)	0.977	0.00 (-0.01, 0.01)	0.826
Limited internal rotation	1.03 (0.46, 2.32)	0.943	0.33 (-0.19, 0.86)	0.206	0.11 (-0.40, 0.61)	0.678	0.22 (-0.18, 0.61)	0.280
Painful internal rotation	1.09 (0.61, 1.95)	0.772	**-0.32 (-0.70, 0.07)**	**0.107**	**-0.55 (-0.91, 0.18)**	**0.003**	**-0.31 (-0.60, -0.02)**	**0.037**
Limited flexion	**1.61 (0.87, 2.99)**	**0.132**	0.01 (-0.39, 0.42)	0.951	0.07 (-0.31, 0.46)	0.711	-0.08 (-0.39, 0.22)	0.597
Painful flexion	**2.45 (1.32, 4.57)**	**0.005**	-0.24 (-0.64, 0.16)	0.230	**-0.42 (-0.80, 0.04)**	**0.030**	-0.19 (-0.49, 0.11)	0.216
Generalised OA[5]	1.41 (0.78, 2.54)	0.257	0.20 (-0.19, 0.60)	0.306	0.12 (-0.26, 0.50)	0.535	0.15 (-0.14, 0.45)	0.312
Bilateral OA	0.84 (0.47, 1.50)	0.558	0.19 (-0.20, 0.58)	0.330	**0.30 (-0.07, 0.67)**	**0.110**	0.03 (-0.27, 0.32)	0.865
Kellgren & Lawrence score	**4.03 (2.17, 7.47)**	**0.000**	**-0.29 (-0.67, 0.10)**	**0.146**	**0.33 (-0.04, 0.70)**	**0.082**	**0.27 (-0.02, 0.56)**	**0.070**

The data for VAS and WOMAC are logit transformed.

[1]CI: confidence interval, [2]BMI: body mass index, [3]VAS: Visual analogue Scale, [4]WOMAC: Western Ontario MacMaster Universities, [5]OA: osteoarthritis.

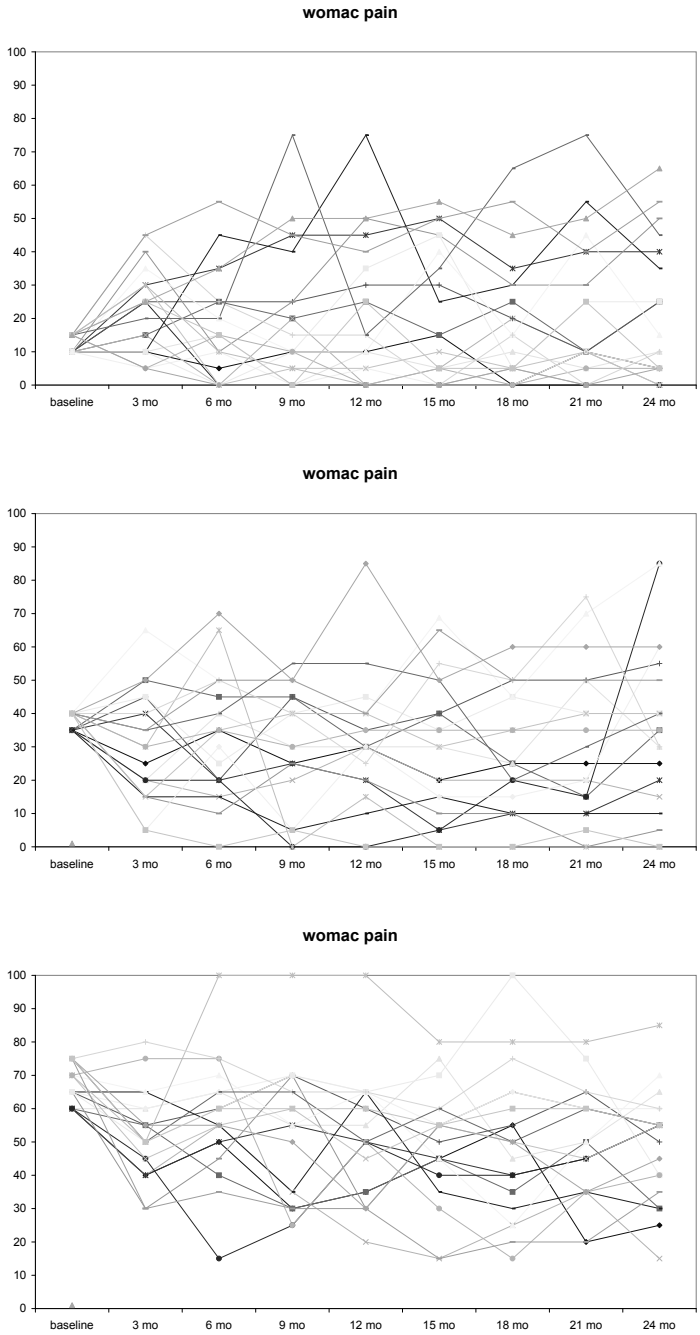


Figure 2: Patients with a low, medium and high baseline level of WOMAC pain.

Table 3: results of the multivariate analysis by outcome measure

Factor	*Patients' global assessment OR (95% CI[1])*	*p-value*	*VAS pain β (95% CI [1])*	*p-value*	*WOMAC pain β (95% CI)*	*p-value*	*WOMAC function β (95% CI)*	*p-value*
Age			**0.02 (0.00, 0.04)**	**0.043**	0.02 (-0.01, 0.04)	0.140		
Gender			0.17 (-0.23, 0.56)	0.412			0.14 (-0.18, 0.46)	0.471
BMI[2]	1.93 (0.88, 4.27)	0.107						
Duration of complaints					0.20 (-0.17, 0.57)	0.291		
Baseline VAS[2] pain	1.01 (0.99, 1.02)	0.392	**-0.02 (-0.03, -0.01)**	**0.000**	-0.01 (-0.01, 0.00)	0.100	-0.00 (-0.01, 0.00)	0.168
Cardiovascular problems			0.52 (-0.00, 1.03)	0.052				
High blood pressure	0.60 (0.28, 1.31)	0.182						
Painful internal rotation			-0.05 (-0.42, 0.32)	0.802	-0.33 (-0.72, 0.06)	0.095	-0.26 (-0.55, 0.04)	0.088
Limited flexion	0.97 (0.46, 2.03)	0.895						
Painful flexion	**2.13 (1.04, 4.37)**	**0.038**			-0.21 (-0.62, 0.19)	0.301		
Bilateral OA[4]					0.20 (-0.16, 0.57)	0.278		
Kellgren & Lawrence score	**3.61 (1.87, 6.95)**	**0.000**	**0.45 (0.09, 0.81)**	**0.015**	0.28 (-0.09, 0.65)	0.140	0.25 (-0.04, 0.54)	0.095

[1]CI: confidence interval, [2]VAS: Visual analogue Scale, [3]WOMAC: Western Ontario MacMaster Universities, [4]OA: osteoarthritis

variable high blood pressure protected against worsening of the patients' global assessment.
For the outcome measure VAS pain the variables baseline VAS pain, painful internal rotation, and Kellgren and Lawrence score ≥2 had a protective effect on deterioration of complaints, whereas the variables age, gender (male), and cardiovascular problems had an influence on progression of VAS pain.
For the outcome measure WOMAC pain the variables age, duration of complaints (>3 years), bilateral OA, and the Kellgren and Lawrence score ≥2 had an influence on an increase in WOMAC pain score. The variables baseline VAS pain, painful internal rotation, and painful flexion all had a protective effect against increased pain.
For the outcome measure WOMAC function the variables baseline VAS pain and painful internal rotation protected against a decrease of function. The variables gender (male), and the Kellgren and Lawrence score ≥2 increased the WOMAC function score, which means a decrease in function.

Multivariate analysis

The results of the multivariate analyses are presented in Table 3.
After 24 months the OR for patients with a painful hip flexion at baseline was 2.10 (95% CI, 1.02 to 4.35) for worsening of the patients' global assessment. Worsening of complaints was also significantly influenced by a Kellgren & Lawrence of ≥ 2 (OR 3.64 [95% CI, 1.89 to 7.03]).
The VAS pain scores were significantly increased with a higher age (β 0.02 [95% CI, 0.00 to 0.04]) and when patients had a Kellgren & Lawrence score of ≥2 (β 0.42 [95% CI, 0.04, 0.80]). A higher baseline VAS score protected against an increase of VAS pain scores (-0.02 [95% CI, -0.03, -0.01]).
For both the outcome measure WOMAC pain and WOMAC function, the multivariate analysis did not yield any variables that had a significant effect on the difference in outcome over time.

DISCUSSION

We found large 3-monthly individual fluctuations in pain and function over two years in patients with hip osteoarthritis in general practice. On group level the mean pain and function scores stayed relatively stable over the course of the study. The average outcome for the patients' global assessment was 'no change'. This measure was also stable over time on group level.

We found that patients with a painful hip flexion at baseline were twice as likely to report progression of complaints while patients with a Kellgren & Lawrence score of 2 or more had a three times higher chance to indicate progression over the study period.

A higher age and a Kellgren & Lawrence score of 2 or more at baseline was shown to be related to deterioration in VAS pain score. The effect on the VAS score after 2 years is approximately 3.4 points per year and 7.2 points for a Kellgren & Lawrence score of more than 2 for a person with a baseline VAS score of 20. For a person with a baseline VAS score of 50 the effect would be 5.0 and 9.9 points respectively. A higher VAS score at baseline actually protected against an increase in pain after two years. This is propably due to the regression to the mean phenomenon.

We found no factors that were related to progression of WOMAC pain and function over 2 years.

The mean pain level of all included patients over the nine measurements was relatively stable, but the large standard deviations indicate a large variation in individual scores, even in successive measurements. This finding is supported by other studies[5 6]. These studies were performed on secondary care patients whereas ours included primary care patients.

The positive association we found between higher age and progression of hip OA has been described before, but in a review the evidence concerning this factor was found to be conflicting[7]. The association of Kellgren & Lawrence score with progression of OA had been reported before[10 18]. The factor painful hip flexion, a measure which is part of a regular physical exam for hip complaints, may be a proxy for a disease process.

Our study yielded only 3 factors that were associated with deterioration of complaints of hip OA. To our surprise, we did not find factors in the multivariate analyses for WOMAC pain and function. The patients in our study probably progressed too little over time on WOMAC pain and function to identify factors. That hip OA on group level progresses relatively slowly was already seen in the review of van Dijk et al[4], who found limited evidence that functional status and pain in patients with hip OA did not change in the first 3 years of follow up. If we had had a longer

duration of follow up, we might have found more progression and therefore more factors associated with it.

We encountered problems during the analysis of the data due to the large fluctuations in individual data. Our first approach was to analyze the data of all 9 measurements using linear mixed model analyses. However, this analysis technique proved unsuitable to filter out those patients that were really deteriorating, due to the fluctuations. We felt that we were finding factors associated with the underlying 'mean pain level' of individual patients, not with deterioration of complaints over time.

When we then tried to identify groups of progressors using cluster analyses, the outcomes were still not very clear. We found a group of patients that improved slightly, others deteriorated slightly and a group that stayed stable over time. But due to the fluctuations in the data, these groups that were formed seemed somewhat arbitrary.

We therefore chose to eliminate some of the fluctuations by using the difference between the mean of the first 3 measurements and the mean of the last 3. Although we may have lost possible important information, we think that this is the most straightforward way to address our research question.

We chose to use only the VAS pain as a predictive factor in the analyses instead of using both VAS and WOMAC scores. We chose the VAS as this is a readily available measure of pain, whereas the WOMAC questionnaire is not an instrument that physicians can easily use.

Our study has several limitations. First of all we used the data from a clinical trial [11]. It is possible that the knowledge of participating in a clinical trial influences the answers on the questionnaires regarding pain and function. Our results may be an over- or underestimation of the true outcome.

Data of the patients that received a THR during the trial were regarded missing after the surgery. These 20 patients, that were most likely progressors, were excluded from the graphs and they had missing data in the analyses. It is possible that due to these missing cases we missed factors that are associated with progression. A sensitivity analysis in which all THR patients were given a 'deteriorated' score on the patients' global assessment yielded one extra factor, having bilateral complaints, which protected against deterioration of complaints.

As far as we know, we are the first study that has tried to predict progression of OA symptoms using frequent measurements over time. What we found is that over a period of 3 months pain and function scores can change drastically within the same patient. This has implications for studies using 2 or 3 measurements only. Due to the fluctuating nature of the complaints, both the baseline and the follow up measurement can be arbitrary outcomes. These measurements could have

been completely different when the study had started and finished 3 months later. While this effect will be handled by randomization in trials, in cohort studies it could have more effect. Patients can be wrongfully classified as progressors or non-progressors. Results from these studies may be under- or overestimations of the true effect or may even be based on chance findings.
We checked the effect of fewer measurements over time on the outcome WOMAC pain. When we used the difference between the baseline and the last measurement as our outcome, we found a significant influence of the factors age, VAS pain at baseline, and painful internal rotation, while we found no significant effects in the original analyses. Although the technique with only two measurements would have led to more results, we feel that, by including more measurements, our results are more sturdy.
It has been suggested recently to measure pain repeatedly on the same time of day, or to ask patients about their low, medium and high levels of pain to find a mean pain level for every patient[19]. This would give a more reliable measure of pain in OA patients.
In our study, pain was measured every 3 months, which gave us new insights into the course of hip OA, however it also led to problems because the individual data was so fluctuating in nature. Finding an answer to our research question was not as straightforward as we had imagined. Still, we feel that measuring the outcome on a regular basis throughout the study will give more accurate and more truthful outcomes than single measurements on a yearly basis.

Conclusion

Primary care patients with hip OA had a stable level of pain on group level, but there is substantial fluctuation in pain level within patients over a 2 year follow up period.
The fluctuating nature of the individual patient data made the analysis of factors that are predictive of progression of hip OA complaints rather complicated.
A painful hip flexion at baseline and a Kellgren & Lawrence score of 2 or more leads to a deterioration of complaints. Higher age and a Kellgren & Lawrence score of 2 or more at baseline was associated with increase of pain over time.

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A statistical model of shape and density of the proximal femur in relation to radiological and clinical OA of the hip

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ABSTRACT

Objective

Common radiological measures of an affected OA joint relate poorly to symptoms as experienced by patients. We created a statistical model of shape and density to see if DXA images of the hip contain symptom related information that is not captured by common radiological measures.

Methods

DXA images of the hip region were made in a prospective study of patients that met the American College of Rheumatology criteria for hip OA. From the DXA scans, made at baseline and 2 year follow-up, we constructed a statistical model of the appearance (shape combined with density) of the proximal femur. The model yields a number of independent descriptors of the appearance (modes) which we related to various measures of status and progression of radiological and clinical OA. These outcome measures were defined using Joint Space Width (JSW), Kellgren and Lawrence (K-L) scores, VAS and WOMAC pain scores and a self-reported global assessment score.

Results

Various modes showed significant relations with radiological and clinical OA. Interestingly, the modes that related well with radiological OA did not relate to clinical OA and vice-versa. Moreover, the modes showed to be predictors of both status and progression of clinical OA, independent from JSW and K-L.

Conclusion

Statistical modeling of the appearance proved to be an effective way to describe the total proximal femur in DXA images. We showed that descriptors of subtle aspects of shape and density of the hip contain information about clinical status which common radiological measures do not. Sophisticated image analysis methods like the one used in this study might prove to be indispensable tools for monitoring disease status and progression in clinical trials.

INTRODUCTION

One of the issues that research on osteoarthritis (OA) is faced with is the poor predictability of development and progression of the disease. Related to this issue is that some difficulties exist in defining what exactly should be considered as progression. Exemplary is the distinction made between radiological and clinical OA. Radiological OA refers to changes in the joint that can be seen on MRI and x-ray images. Generally the status of the joint with respect to OA is assessed through (semi)quantitative measures of which the Kellgren and Lawrence score (K-L) and Joint Space Width (JSW) determined from x-rays are the most widely used. Clinical OA refers mostly to those aspects of the disease that are experienced by the patient, like pain and functioning. These aspects are quantified through self-reported measures obtained via questionnaires filled in by the patient. Progression is then defined as a certain amount of change in one or more measures of OA.

Measures reflecting radiological OA only poorly relate to measures reflecting the clinical aspects of OA, especially when radiological changes are mild to moderate[1 2]. This is rather puzzling since it seems only logical that the degeneration of joint tissues as can be seen on radiological images should somehow be related to how the patient experiences his or her disease process. Explanations of this phenomenon range from the influence of psycho-social factors to methodological issues that might confuse study results. Another possibility is that common radiological measures and scoring systems might not be sensitive enough for relevant changes to reveal the association between clinical and radiological features.

Previously we have shown that the shape of the femoral neck as apparent on x-ray images was different between subjects that were to develop radiological OA of the hip and subjects that were not[3]. Thus radiological changes can be detected on x-rays before classical measures of radiological OA show the development of the disease, indicating a lack of sensitivity in the latter measures. In the before mentioned study we analysed the shape of the femoral head and neck by constructing a Statistical Shape Model of the contour of the femoral head as it appears on x-ray images. This method allows the quantification of shape in a general way without using predefined geometrical measures[4]. In the present study we have extended the methodology and created statistical models of both shape and density of the proximal femur measured from Dual Energy X-ray (DXA) images. We specifically investigated if the applied method yields better relations with status and progression of clinical OA of the hip than classical radiological measures.

METHODS

Study cohort

The data in this study is part of a randomized controlled trial, consisting of patients with in general mild OA symptoms[5]. After having consulted for hip pain at general practices in the Rotterdam area, patients were included when they met one of the American College of Rheumatology (ACR) criteria for hip OA[6]. Patients were excluded when they received or when they were waiting for a total hip replacement (THR) or when they had a K-L score of 4 in either hip. In the original study 222 patients were included that were followed for two years. We excluded DXA scans of the left or right side in which large parts of the proximal femur were not imaged well.

Radiological and clinical measures of OA

Digitized X-ray images of the hips were taken at baseline and 2 year follow-up using a standardized protocol[7]. From these images K-L scores and minimal Joint Space Width (JSW) were derived. All patients filled in questionnaires from which clinical measures of OA were derived. We used the Western Ontario MacMaster Universities (WOMAC) [8] and the Visual Analogue Scale (VAS) to measure pain during the past week. These measures were collected every three months during the two years follow up period. We also used a question regarding patients' global assessment as compared to baseline (Self Reported Change: SRC), which was collected every 6 months during the follow up period. The WOMAC pain and the VAS pain are presented as normalized scores (0-100, 0 equals no complaints). The patients' global assessment score was a 5 point Likert scale score (1 = greatly deteriorated, 5 = greatly improved).

DXA imaging

At baseline and at the final assessment, 2 years later, DXA images were taken of the pelvic area (Lunar DPX, Lunar GE, USA). During imaging, the subjects were lying down with their feet positioned alongside a frame to ensure 15° internal rotation of the hips. The images were split into two images of which each contained either the hip of the left or right side. To be able to create one statistical appearance model for both sides, the images of the left hips were mirrored along the vertical axis such that they appeared to be images of the right hips.

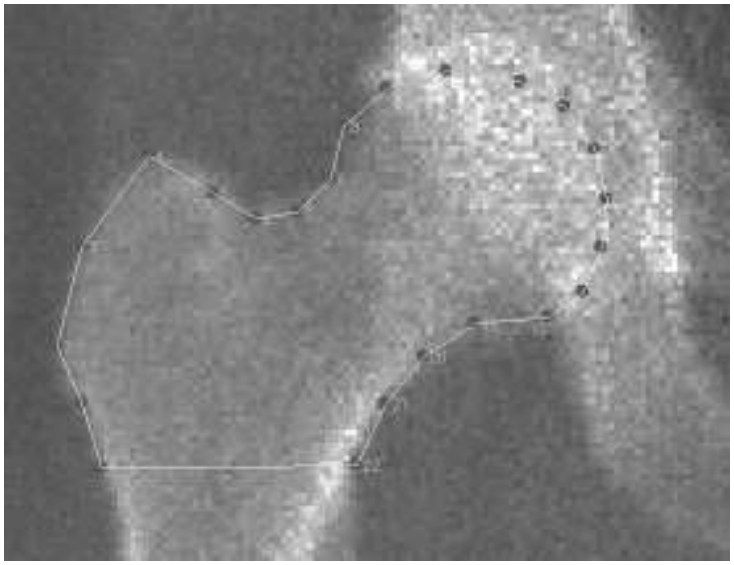

Figure 1: The appearance model is constructed by placing a contour around the proximal femur consisting of 23 landmark points.

Statistical Appearance Models

Statistical Appearance Models were created from the proximal femur in the DXA images of the hips using the freely available ASM toolkit (Manchester University, Manchester, UK)[4 9]. The models were created by placing a contour consisting of 23 points around the proximal femur, starting at the proximal end of the lesser trochanter, covering the femoral head, the neck, the greater trochanter and ending at the cortex on the opposite side of the lesser trochanter (Figure 1). The points (indicating the shape) and the density of the bone sampled from within the contours (together referred to as the appearance) were combined into the model yielding 30 independent parameters, referred to as modes of variation, that together explained 99% of the variation in shape and density in the study population. Together, these modes describe the total appearance of the femur in each image, while each mode separately is a quantitative measure of a specific characteristic of the appearance.

The variation in appearance as described by each mode can be visualized using images and animations. Of the modes that showed relevance for OA, the images and animations were presented blinded and in randomized order to four researchers, who briefly described the observed variation in shape and density of each mode with one or two sentences.

Statistical Analysis

Univariate analysis

Various univariate linear regression models were constructed to test the relation of each appearance mode with status and progression of radiological and clinical OA. When applicable, correlations between sides and/or between baseline and follow-up were taken into account using Mixed Models for the continuous outcomes or Generalized Estimating Equations for the dichotomized outcomes. We used two outcome measures of radiological OA: One was defined as Kellgren & Lawrence (K-L) scores > 1 and the other as minimum Joint Space Width (JSW) < 1.5mm. To represent clinical OA we used VAS pain score and WOMAC pain. Progression was defined as a decrease in joint space width from baseline to follow-up (JSN) of more than 20% in the case of radiological OA and change in VAS and WOMAC scores from baseline to follow-up, as well as a self reported change in global assessment compared to baseline (SRC) in the case of clinical OA.
The pain scores from the questionnaires exhibited large variability from time point to time point within each patient. We assumed that this variance, whether due to natural variability in pain or due to other 'random' effects, would confound an underlying disease status and therefore decided to use an average of three consecutive time points. For status we averaged the first three time points (baseline) and the last three time points (follow-up), for progression we took the difference between the average of the first three time points and the last three time points. To assure normality, the pain scores were logit transformed before averaging.
When the interaction between the appearance measure and the side/time point was significant, we analyzed the model for each side/time point separately.
To account for the many univariate tests we performed, an effect was considered significant when the p-value was lower than 0.005, though all effects with a p-value smaller than 0.05 are reported.

Multivariate analysis

To compare the strength of the appearance modes to describe clinical OA with the strength of classical radiological measures (K-L, JSW) we constructed multivariate models using the various measures of the status and progression of clinical OA as outcome measures, and the appearance modes that related with each clinical measure combined with K-L and JSW as independent variables.
For each clinical outcome measure we constructed three models. The first contained only the radiological measures (K-L and JSW) as predictors. In the second

model the relevant appearance modes were added. In the third model the radiological measures were removed. The contribution of the different predictors was investigated by changes in R2 of the different models.
All statistical analyses were performed using SAS 9.1 (SAS Institute inc., Gary, NC, USA) and SPSS 16.0 (SPSS inc., Chicago, IL, USA).

RESULTS

Included patients

A total of 222 patients were enrolled of which 209 (94.1%) completed the trial. We included DXA scans of 218 patients in this study, though of only 161 patients we could include a complete set of DXA scans (affected and non-affected side both at baseline and follow-up). Of 19 patients we did not include the baseline scans of one or both sides and of 44 patients we did not include the follow-up scans of one or both sides. From the 218 patients included in this analysis, 16 received a total hip replacement before follow-up. The baseline characteristics of the 218 patients included in this study are summarized in Table 1.

Univariate analysis

Many modes (18 out of 30) showed a relation with one or more of the defined OA measures, though most relations were only mild and were not considered significant (Table 2 for status of OA; Table 3 for progression of OA). Apart from 4 non-significant exceptions (mode 11, 14, 25 and 27), none of the modes that related to radiological OA showed a relation with clinical OA and vice-versa.
Below, a number of modes that gave significant relations with the outcome measures or that were otherwise remarkable are highlighted (see also Figure 2).

- **Mode 3**: Differentiates between a broad short neck and a long narrow neck that corresponds with a bigger neck angle. The short broad neck, represented by negative mode values, appears to go together with a higher density of the posterior head and associates mildly with pain (both VAS and WOMAC) at follow-up and is a predictor for progression of VAS pain ($p<0.009$).
- **Mode 6**: Differentiates between deep placement of the femoral head inside the acetabulum and shallow placement. At deep placement, the line along the superior neck forms a pronounced curve, while at shallow placement this line is more gradual. Deep placement, represented by negative mode values, associates

Table 1: Patient characteristics at baseline

Characteristic	*All patients (n=218)*
Age in years, mean (SD[1])	63.5 (9.0)
Gender, woman, %	69.3
BMI[2], mean (SD) kg/m^2	27.9 (4.5)
Duration of complaints, %	
< 1 yr	11.9
1 – 3 yrs	34.4
> 3 yrs	53.7
Kellgren & Lawrence, %	
= 1	52.3
≥ 2	47.7
Osteoarthritis, %	
Localised	38.5
Generalised	61.5
Bilateral	47.7
Unilateral	52.3
JSW, mean (SD)	2.23 (0.99)
WOMAC[3], mean (SD)	
Pain	34.1 (23.3)
Function, mean (SD)	34.9 (22.9)
Stiffness, mean (SD)	42.5 (25.3)
VAS[4] pain, mean (SD	32.4 (26.0)

[1]SD: standard deviation, [2]BMI: body mass index, [3]WOMAC: Western Ontario Macmaster Universities, [4]VAS: Visual Analogue Scale

both with VAS pain (not significant, $p<0.05$) and with WOMAC pain (significant at $p<0.001$). However, this relation could only be found at baseline.

• **Mode 8**: Differentiates between a compact, stocky shape of the femur and a shape that appears more 'stretched'. The compact shape shows a larger trochanter and a more flattened head, while in the stretched appearance the head is more protruding. The stretched appearance, represented by negative mode values, associates with a low joint space width at follow-up, at the non-affected side ($p<0.005$).

• **Mode 11**: Differentiates between a more gradual curvature of the superior neck combined with a head that is placed high relative to the neck axis, and a more pronounced curvature of the superior neck combined with a head that is placed low relative to the neck axis. In the situation of the more gradual neck curvature, the load carrying trabeculae that run from the lower neck into the head appear more distinct. At the non-affected side, a pronounced curvature and lower place-

Table 2: Univariate analysis for OA status: sign of estimate of each mode with corresponding p-value

	Radiological OA		*Clinical OA*	
Modes	JSW<=1.5	KL>1	VAS pain	WOMAC pain
M03	..	..	- 0.01[2]	- 0.036[2]
M04	..	- 0.04[*]	..	..
M06	..	..	- 0.02[1]	- **0.0007**[1]
M07	..	..	+ 0.036	..
M08	- **0.003**[+2]	..	..	..
M10	..	..	- 0.019	..
M11	..	+ **0.0015**[+]	..	..
M14	- 0.03[*]	..	- 0.049	- 0.019
M15	..	..	..	- 0.024
M18	- **0.0013**[+]	..	..	..
M22	+ 0.03			
M23	+ **0.0001**[*]	+ 0.045[*]	..	..
M25	..	..	+ 0.049[2]	..
M27	..	..	+ 0.019[1]	..
M29	+ 0.028			
M30	+ 0.016[*]	+ 0.03		

The p-values denote an effect independent of side and time point, unless otherwise indicated: [*] Most affected side only; [+] Least-affected side only; [1] Baseline only; [2] Follow-up only

ment of the head, represented by positive mode values, is associated with a high K-L score ($p<0.002$).

• **Mode 14**: Differentiates between a neck with low bone density combined with a steep placement of the head into the acetabulum and a high bone density in the neck with more level placement into the acetabulum. Though the relation with clinical OA was only mild ($p<0.05$), the mode related both with measures of pain and function. Low bone density in the neck and a steep acetabular placement, represented by negative mode values, were associated with worse symptoms.

• **Mode 18**: Although the outline of the femur hardly changes in this mode, the general appearance is that of 3D changes in bone form, similar to the changes described by mode 8. This mode also differentiates between a more compact appearance and a more stretched appearance. The compact appearance goes together with a high bone density especially in the lower neck and trochanteric area. At the non-affected side, the stretched appearance with low bone density in neck and trochanteric area, represented by negative mode values, shows a significant relation with a low JSW ($p<0.002$).

Table 3: Univariate analysis for progression of OA: sign of estimate of each mode with corresponding p-value.

	Radiological OA	*Clinical OA*		
modes	JSN>20%	Self-reported change	VAS	Womac pain
M3	–	–	- 0.0083	–
M4	- 0.012[+]	–	–	–
M11	–	–	- 0.019	–
M21	–	–	- 0.033	–
M22	- 0.01[+]	–	–	–
M23	+ **0.0002***	–	–	–
M24	–	+ **0.0015**	–	–
M25	+ **0.0018**	–	–	–
M27	–	–	+ 0.044	–
M29	–	–	+ 0.023	–
M30	+ 0.026	–	–	–

The p-values denote an effect independent of side, unless otherwise indicated: * Most affected side only; [+] Least-affected side only

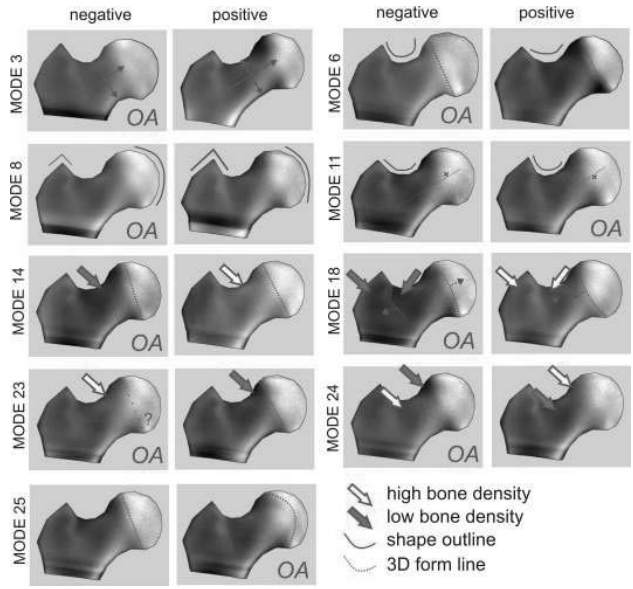

Figure 2: Visual display of the various appearance modes that showed an interesting relation with OA. Of each mode a visual representation of a negative and positive mode value are given (-2 and +2 times the population standard deviation). Changing features within each mode are indicated by lines and arrows.

Table 4: Multivariate analysis of status and progression of clinical OA (p-values)

	Status		*Progression*	
	VAS	WOMAC	SRC	VAS
KL	0.63	0.13	**0.027**	0.33
JSW	0.97	0.60	0.84	0.28
M3	–	–	–	**0.035**
M6	**0.02**	**0.008**	–	–
M7	0.35	–	–	–
M10	**0.005**	–	–	–
M11	–	–	–	**0.018**
M14	0.29	0.18	–	–
M15	–	0.47	–	–
M21	–	–	–	**0.025**
M24	–	–	**0.006**	–
M27	**0.002**	–	–	**0.035**
M29	–	–	–	0.32

Table 5: Percentage of variance explained by the several multivariate models of clinical OA.

	Status				*Progression*			
	VAS		WOMAC		SRC		VAS	
Model	R2	p-val	R2	p-val	R2[+]	p-val[#]	R2	p-val
1	0.007	0.51	0.02	0.23	0.093	0.053	0.24	0.62[*]
2	0.13	**0.002**	0.06	**0.035**	0.225	**<0.001**	0.32	**0.001**
3	0.12	0.13	0.05	0.23	0.142	0.06	0.32	0.53

Model 1: enter classical radiological predictors (KL, JSW)
Model 2: enter relevant modes from appearance model.
Model 3: remove classical radiological predictors.

p-value indicates significance of the change in R2 value compared to the previous model.
[+] Nagelkerke R2
[#] For these logistic models, the p-values correspond to the Log-likelihood ratios of the current and previous model.
[*] Model 0 in this case is a model with only VAS at baseline as predictor

• **Mode 23**: Differentiates between a high and low bone density in the superior head and neck. When bone density is low, the outline of the inferior neck is more curved and the coverage of the acetabulum over the head is delineated more clearly. The latter situation with the low bone density, represented by positive mode values, associates strongly with a low JSW ($p=0.0001$) and is a predictor of JSN ($p=0.0002$).
• **Mode 24**: Differentiates between a situation where the bone mineral density in the head is low relative to the density in neck and trochanteric area and a situation where the bone mineral density in the head is high relative to the neck and trochanteric area. This mode was the only mode that was a strong predictor for change in global assessment as reported by the patient (SRC). A lower bone density in the head, represented by positive mode values, associates with worsening of symptoms ($p<0.002$).
• **Mode 25**: Differentiates between deep placement of the head into the acetabulum in which the coverage line appears straight and a narrower placement in which the coverage line appears curved. This coincided with a shift in position of the line that runs from the major trochanter towards the minor trochanter. The narrow placement, represented by positive mode values, is predictive for JSN ($p<0.002$).

Multivariate analysis

The various models were only able to explain a small part of the variance in the clinical OA outcome measures (ranging from 6 to 13%, Table 5). However, all the explanatory power was solely due to the appearance modes. The classical radiological measures for OA (K-L and JSW) showed up far from significant in the various models (Table 4) and did not contribute to the explanation of any of the outcome variables.
The only exception was the model for prediction of self reported change in global assessment (SRC). In this model K-L had a small but significant contribution, equally or even a bit stronger than the sole appearance mode (mode 24).

DISCUSSION

In this study we constructed so called Statistical Appearance Models. These models yield a number of measures or modes that together describe and quantify the complete appearance of the proximal femur in DXA images. Appearance in this case refers to the combination of the shape or outline and the density distribution within the shape of the proximal femur. Since a DXA image is the 2D projection of a 3D object, the density that can be measured in DXA images is not only the reflection of bone mass, but also of the form of the bone in three dimensions. The modes of the appearance model capture how both form and density vary together and give thus a better description of the 'true' femur than 2D shape alone. It is, however, difficult to describe what aspects of the appearance are represented by a specific mode. Each mode does not just capture 'one thing' but is a combination of sometimes very subtle changes in total 3D form and density. At the same time this is the power of the method, since it captures variations in femur geometry and mass that are not easily defined by pre-thought-of measures.

Several of the modes were related to radiological and clinical aspects of OA. Interestingly, the modes that related well with radiological OA, related poorly to clinical OA and vice-versa. Moreover, in the multivariate models in which the explanatory strength of the classical radiological OA (K-L and JSW) measures were compared to the strength of the appearance modes it showed that the appearance modes were clearly superior in explaining status and progression of clinical OA. JSW did not contribute at all to the models for the status of clinical OA, while K-L only contributed to one measure of clinical progression. These results might indicate that classical measures of radiological OA lack sensitivity for arthritic changes and somehow miss aspects of the affected hip joint that relate with clinical symptoms. Another explanation relates to the fact that the classical radiological measures look at pathological alterations in the joints, while the appearance modes reflect absolute aspects of the joint whether these reflect pathological alterations or variations in the joint as exists within populations. Possibly, the modes that relate with clinical OA reflect certain joint geometries that are more prone to pain when OA is present.

The appearance aspects that relate to OA can roughly be subdivided into three categories, relating to femoral morphology, placement of the femur into the acetabulum and variations in bone mineral density.

The literature on bone mineral density and OA of the hip is seemingly conflicting and rather confusing. One issue concerns the suggestion of an inverse relation between osteoporosis and OA, reviewed by Stewart et al[10]. Some recent suggestion is that the finding that people with OA have higher bone mass might partly be ex-

plained by a difference in bone size and shape rather than bone density itself[11 12]. Another issue concerns the effect the disease has on bone mass of the affected site. Typical is subchondral sclerosis, one of the radiological hallmarks of OA[13]. Some studies report a local increase in BMD of the hip in patients with progressing OA[14 15], while one study reports a thickening of the load bearing trabeculae but a general loss of trabecular number in the femoral head, which the authors refer to as 'local osteoporosis' [16]. The BMD changes in our study would reflect local differences and mainly relate to relative differences within the proximal femur and do not easily fit in the previous findings. Most modes that relate with OA, whether clinical or radiological that include BMD changes (mode 14, 18, 23 and 24), point to lower BMD especially in the head and neck region for subjects with OA. Perhaps this reflects bone loss due to unloading of the affected limb.

The way the proximal femur is positioned inside the acetabulum has been shown to influence development of OA. Acetabular dysplasia has been shown to be a strong predictor of development of OA[17 18], though this association was not found in a population of Sami[19]. Acetabular retroversion, another form of dysplasia, characterized by deficient anterior coverage of the femoral head has been associated with OA as well[20 21]. Retroversion is recognized on AP x-rays by the so called cross-over sign, which arises when the retreated anterior coverage line of the acetabulum crosses the posterior line. Modes 6, 14 and 25 contained aspects that resembled variations in placement of the head inside the acetabulum. Mode 14 links a steep placement of the head into the acetabulum with pain and loss of function. Steep placement could result in mild dysplasia. Mode 25 is interesting since it associates strongly with progression of joint space loss. A narrow placement of the head with a curved coverage line, which strikingly resembles acetabular retroversion, associates with joint space narrowing. Mode 6 is a bit odd, since it links deep placement, not narrow placement, of the head inside the acetabulum with pain at baseline. Perhaps this mode reflects protrusio acetabuli, a progressive condition in which the femoral head sinks deeply into the acetabulum, which is associated with the development of OA[22]. Alternatively, this mode might not so much describe causing or resulting geometrical aspects of OA, but rather point to the fact that people with such a placement of the head into the acetabulum experience more pain and loss of function in the presence of OA.

Hip OA often seems to occur in the absence of a systemic arthritic process and it has been suggested that the majority of hip OA is caused by abnormalities in hip morphology[23 24]. When the shape of the femoral head deviates from being spherical, such that the femoral head and neck resemble a 'pistol grip', the proximal femur will impinge with the acetabulum which is thought to eventually result in cartilage damage and OA[25 26]. Apart from being a causal factor for OA, the shape

of the proximal femur is itself also altered by the osteoarthritic disease process. Typical is the formation of osteophytes, which in a progressed form might even change the shape of the superior neck and head such that it will resemble a pistol grip deformity[27]. The results of this study show that many modes that relate with OA show some variation in femoral morphology. However, for many modes these variations are rather subtle with respect to the other changes in appearance reflected by those modes. For a number of modes the variations in shape are more distinct (modes 3, 6, 8 and 11). Modes 3 and 6 both relate to pain and describe variations related to the femoral neck. A broad neck (mode 3) and a more pronounced curvature of the superior neck (mode 6) are associated with more pain. Mode 8 links a stretched elongated appearance which is strongly reflected in the neck/head transition with a low joint space width. This mode might correspond to mild pistol grip deformities and to OA related shape variations published previously[3]. Mode 11 again describes a pronounced curvature of the superior neck and some offset of the femoral head relative to the neck, which is related to higher K-L scores and could reflect the presence of osteophytes. Though it is hard to link the morphological variation described by these modes to what is known about shape and OA, it is interesting to note that most of these modes reflect aspects of the superior neck.

The wide variation in shape and density reflected by the modes that relate with OA might very well point to different types of OA and/or to different causative factors for OA existent within the cohort used for this study. It would therefore be interesting to relate these modes not only to K-L score and JSW, but to more specific radiological features like cysts, bone edema, femoral or acetabulur osteophytes etc. Another option would be to relate the modes to different classifications of hip OA[28], for instance atrophic vs. hypertrophic and destructive OA, or to the direction of migration of the femoral head. Appearance analysis might then be used to see if a bone shape or density related factor exists behind the findings that OA progresses more rapidly at the presence of an atrophic bone response or of a superolateral migration of the head[29].

One of the limitations of this study, as with any other cohort study on OA, is the problem of defining OA and especially progression of OA. The cohort used in this study consisted of subjects with generally mild OA status at baseline that were followed for 2 years, a period that is rather short for progression of OA[30]. Sixteen of the included subjects received a total hip replacement during the study period, while of the remaining subjects only 4 subjects showed a joint space narrowing of more than 1 mm. Defining clinical OA is another issue in itself. In the current cohort pain questionnaires were taken every three months and this revealed a large variation in pain from time point to time point[31]. The consequence is that

many subjects that would be considered progressive when taking the first and penultimate time point would not be considered progressive when the second and ultimate time point would be taken, showing that a large part of any group of clinical progressors depends on pure chance. We attempted to reduce the variation by averaging the first three and last three consecutive measurements. However, taking one, two or four consecutive time points influenced which modes would be considered significant. For instance, mode 3 would have been considered to be significantly related to VAS pain when taking only 1 or 2 consecutive time points ($p<0.005$). On the other hand, mode 6 was significantly related with WOMAC pain irrespective of whether 1, 2, 3 or 4 time points were averaged.

The analysis of the appearance of the proximal femur on DXA images proves to be interesting with respect to OA. The statistical appearance models provide a general and rather complete way to capture the total variation in both form and bone density of the proximal femur, more than shape alone. We have shown that such an analysis yields radiological information that is related to clinical symptoms, which is not described by classical measures of radiological OA like the K-L score or minimum joint space width. Moreover, several modes showed to be predictive of both radiological and clinical progression. Though further efforts are needed to apply these methods to larger cohorts, statistical models of the appearance of hips on DXA images or X-rays has the potential to become an indispensable tool in clinical trials to monitor disease progression and possibly even in separating progressors from non-progressors at baseline.

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8

Determinants and costs of medical consumption of patients with hip osteoarthritis

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Submitted

ABSTRACT

Objective

The aim of this study was to assess the medical consumption of primary care patients with hip osteoarthritis, and the associated determinants and costs.

Methods

222 Primary care patients meeting the American College of Rheumatology criteria for hip OA were selected for inclusion. Patients filled out a questionnaire every 3 months throughout the 2-year duration of the study to record medical consumption and possible determinants. The direct costs of medical consumption were calculated using self reported data on consultation of health care professionals, and pharmacological and non pharmacological treatments.

Results

More than half of the patients consulted a general practitioner (GP) for their complaints. A third of the patients was referred to an orthopaedist and another third reported treatment by a physical therapist. The direct costs associated with hip osteoarthritis was on average €638.78 per patient per year.
Moderate to severe pain was associated with GP visit for osteoarthritis complaints (OR 1.87 [95% CI, 1.28 to 3.03]), as was having difficulty putting on socks (OR 1.72 [95% CI, 1.19 to 2.49]), and having concomitant knee complaints (OR 1.63 [95% CI, 1.03 to 2.58]). A good health status lowered the chance to visit a GP (OR 0.53 [95% CI, 0.36 to 0.76]).

Conclusion

Many patients with hip osteoarthritis consult a GP and/or another health care professional for their complaints over a period of two years. Having more severe symptoms and other joint complaints increases the chance that a patient will seek care from a GP.

BACKGROUND

Osteoarthritis (OA) is one of the main causes of disability among elderly people[1]. Symptomatic OA affects almost 9.6% of men and 18% of women over 60 years, while these numbers are even higher for radiographic OA[2]. With ageing of the population the number of persons with osteoarthritis will increase over time. The costs of health care for osteoarthritis patients are expected to rise accordingly.
The direct medical costs per patient per year in Europe have recently been estimated to be around €550 for knee osteoarthritis[3]. Currently OA is the number 12 most expensive disease in the Netherlands[4]. No data is available on the direct costs of medical consumption of patients with hip osteoarthritis.
Health care utilization of patients with osteoarthritis or arthritic pain and the factors associated with it have been described before[5-9]. All of these studies found different determinants for GP visits and/or referral to a specialist. Only one common factor was found in two of the studies: severity of pain was associated with visit to a GP[6 9].
The previous studies were conducted for knee osteoarthritis, only two studies combined knee and hip osteoarthritis patients[8 9]. No study has been done to assess determinants of health care utilization of hip OA patients separately, while it has been suggested that health care utilisation is different for hip and knee OA patients[10]. Linsell et al. found that patients with knee complaints were more likely to consult a GP, while patients with hip complaints were more likely to be taking painkillers and to be referred for an x-ray.
Besides the determinants of GP visit and referral to a specialist, it also of interest to know what determines whether a patient gets referred to a physical therapist. Physical therapy in the form of exercise therapy is a recommended treatment for the management of both knee and hip OA[11 12], but only 21% of the patients that had visited a GP for their knee complaints, were referred to a physical therapist[7].
We used the data of the GOAL study to describe the direct costs and determinants of medical consumption of primary care patients with hip osteoarthritis.

METHODS

Study design

The data of our previously published, randomized clinical trial was used[13]. This study, with a duration of two years, was carried out to assess the effectiveness of glucosamine sulphate on patients with hip OA. No difference in outcome was

found between the groups using glucosamine and placebo[13]. Therefore the study can be regarded and analyzed as a prospective cohort study.

Setting and participants

The study protocol of the randomized controlled trial was published in 2005[14]. Following is a brief summary of the protocol.
General practitioners in the Rotterdam area recruited prevalent hip OA patients. Patients were included when they met one of the American College of Rheumatology (ACR) criteria for hip OA[15]. Patients were excluded when they had undergone or were awaiting total hiparthroplasty. Also patients with a Kellgren & Lawrence score of 4[16], patients with renal and/or hepatic disease, diabetes mellitus or a disabling co morbidity were excluded. Patients who were unable to understand Dutch questionnaires were also excluded from participation.
Nine questionnaires were filled out by the patients during the two years they were participating in the study. The first and the last one were completed during an assessment at the research center. Every 3 months we mailed an intermediate questionnaire to the patients for completion at home.
The baseline characteristics were collected using the first questionnaire, and a physical examination which was done at the baseline assessment. A radiograph was made at baseline to establish the severity of radiographic hip OA. In the original study 222 patients with hip OA were enrolled between September 2003 and March 2004.

Medical consumption and costs

Patients were asked every three months whether they had visited the general practitioner, an orthopaedist and/or rheumatologist. For the sake of legibility we will only mention orthopaedist in the rest of the article, since only a couple of patients reported seeing a rheumatologist. Patients were also asked whether they had visited a physical, occupational and/or other therapist in the preceding 3 months.
Also, patients were asked whether they had visited alternative therapists, and whether they had used prescription or over the counter (OTC) pain medication for their complaints.
The study was conducted between 2003 and 2006, we chose to use the price-level of 2004 to calculate the different costs of health care use. Costs were measured over a period of 27 months, direct costs were taken into account.

In the Dutch health care system the costs for common procedures are summarized nowadays in diagnosis-treatment combinations. The price for such a combination entails diagnosis, orthopaedist visits, actual surgery, hospital stay etc. We used the mean of these costs as charged by 4 different hospitals and recalculated it into costs for 2004 and used this (€10993.58) as the price for a total hip replacement (Table 2). For the costs of a GP visit (€24.8), therapist (€21.5) and medical specialist (€56.0) we used the standard prices in 2004[17 18].

Determinants of medical consumption and costs

During the baseline measurement we collected characteristics such as age, gender, educational level, Body Mass Index (BMI), and disease related information. Every three months we collected information on co morbidities, and anxiety and general health status using the EuroQol questionnaire[19].
In our study we used the Western Ontario MacMaster Universities (WOMAC)[20] questionnaire to measure pain, function and stiffness complaints due to hip osteoarthritis, and a Visual Analogue Scale (VAS) to measure pain in the past week. The WOMAC and the VAS pain are presented as normalized scores (0-100, 0 equals no complaints).
Using one of the WOMAC function questions we created a dichotomous variable 'difficulty putting on socks', with the score 1 representing severe or extreme difficulty.

Statistics

The analyses were performed with SAS 8.2 (SAS Institute, Cary, North Carolina) and SPSS 15.0 (SPSS, Chicago, Illinois).
For the descriptive part of the study we calculated the prevalence, sum of all visits and median of all reported health care use. To calculate the direct costs of medical consumption of patients with hip osteoarthritis, we used the costs for visits to a doctor, therapies, pain medication and total hip arthroplasties. For medication we made a distinction between prescription drugs and OTC pain medication.
For the analyses of determinants of medical consumption and costs we checked whether the continuous data was normally distributed. Although age and BMI seemed normally distributed we chose age ≥ 65, and a BMI ≥ 30 as cutoff points because this makes the interpretation of the results much easier. The WOMAC scores and the factor health status today were not normally distributed, we therefore chose to use a cutoff of ≥ 30 points for WOMAC subscales and >80 for health status today, based on the medians of the scores.

For the analyses of the determinants of medical consumption and costs we first assessed all variables with a univariate model. The variables that had a p-value < 0.2 in the univariate analysis were analyzed using a multivariate model (enter-method). The variables with a p-value < 0.05 in the multivariate model were considered to be statistically significant.

For the analyses of GP and physical therapist visits, we used the GEE repeated measurements procedure with a time lag of 3 months between determinants and medical consumption. The outcomes will be presented as population average odds ratio (OR) over the study period.

Due to waiting lists, the period between referral by a GP and actual visit can be quite long. We therefore used logistic regression analyses to assess the relation between determinants and first reported visit to an orthopaedist. Patients who reported a visit to an orthopaedist in the first and second questionnaire were excluded, because we did not have enough data on determinants for these patients. Also, two patients who already regularly visited the orthopaedist before the study were excluded.

For the variables that were measured every 3 months, we summed up the number of periods with exposure (e.g. moderate/severe pain) that were reported, up to the period in which the first visit to the orthopaedist was reported. This number was divided by the total number of periods before the first visit to the orthopaedist, to account for different lengths of measurements. For the variable 'periods with GP visit' the period in which the visit to the orthopaedist was reported was also included.

The measures 'periods with GP visit' and 'periods with physical therapy' were dichotomized based on the median (0.11 for GP, 0 for physical therapy) of the measure.

For the analyses of determinants of referral to physical therapy, we excluded patients that reported physical therapy in more than 3 questionnaires in a row, these patients were regarded to be regular users, and can therefore not be used in an analyses to assess what makes patients seek therapy.

Finally, we assessed the determinants of total costs in an analyses of all patients. Because the costs were not normally distributed, we chose to dichotomize the data into low and high costs, with a cutoff of € 216.30, based on the median. For the variables that were measured every 3 months, we again summed up the number of periods with exposure, but now for the whole study period.

Table 1: Patient characteristics at baseline

Characteristic	*All patients (n=222)*	*Health care*		*Type of health care*		
		Yes (n=155)	**No (n=67)**	**GP (n=125)**	**Orthopaedist (n=69)**	**Physical therapist (n=68)**
Age in years, mean (SD[1])	63.4 (9.0)	63.7 (9.0)	62.6 (8.8)*	64.6 (8.8)	63.9 (8.8)	63.5 (8.6)
Gender, woman, %	69.6	71.0	65.7	72.8	68.1	72.1
BMI[2], mean (SD) kg/m^2	28.0 (4.7)	28.2 (4.6)	27.5 (4.8)	28.3 (4.5)	28.0 (4.4)	28.0 (4.9)
Duration of complaints, %						
< 1 yr	11.8	9	12.9	14.4	10.1	10.3
1 – 3 yrs	34.7	35.8	34.2	31.2	39.1	29.4
> 3 yrs	53.6	55.2	52.9	54.4	50.7	60.3
Kellgren & Lawrence, %						
= 1	52.7	50.3	58.2	50.4	42.0	48.5
≥ 2	47.3	49.7	41.8	49.6	58.0	51.5
Osteoarthritis, %						
Localised	38.3	36.1	43.3	33.8	31.9	35.3
Generalised	61.7	63.9	56.7	67.2	68.1	64.7
Bilateral	48.2	54.8	44.8	45.6	44.9	38.2
Unilateral	51.8	45.2	55.2	54.4	55.1	61.8
JSW, mean (SD)	2.23 (1.0)	2.11 (1.0)	2.50 (0.9)	2.14 (1.0)	1.90 (1.1)	2.10 (1.0)
WOMAC[3], mean (SD)						
Pain	34.2 (23.1)	38.5 (23.4)	24.1 (19.1)*	38.7 (24.2)	39.0 (24.1)	41.8 (26.1)
Function	35.1 (22.9)	39.3 (22.7)	25.1 (20.1)**	40.6 (23.0)	40.9 (22.3)	40.0 (23.9)
Stiffness	42.6 (25.2)	47.7 (24.9)	31.0 (21.9)**	49.4 (25.3)	49.3 (23.9)	48.3 (26.6)
VAS[4] pain, mean (SD	32.4 (25.9)	35.6 (26.8)	25.1 (22.2)*	37.6 (27.8)	33.2 (26.5)	39.0 (27.9)

[1]SD: standard deviation, [2]BMI: body mass index, [3]WOMAC: Western Ontario Macmaster Universities, [4]VAS: Visual Analogue Scale

VAS pain and WOMAC pain, function and stiffness were highly correlated (ranging from 0.56 – 0.93)

* $p<0.05$

** $p<0.001$

RESULTS

Patient characteristics

A total of 222 patients were enrolled of which 209 (94.1%) completed the trial. Of these 209 completers twenty patients received a total hip replacement during the study. The baseline characteristics of all included patients are summarized in Table 1.

Descriptive study

We made a division in patients using health care and the ones that did not, and we separately present the characteristics for patients that visited a GP, orthopedist or physical therapist (Table 1). The mean age in the group that reported health care use during the study was a little higher than in the group that does not. Not surprisingly, the group of patients that sought medical advice had more severe disease, with respect to symptoms.

Table 2: Medical consumption in the total population during 2 years

	Prevalence (%) (n = 222)	*Sum of all visits (n = 222)*	*Median per patient (range)*	*Total costs*
Total medical consumption	69.8	*3226*	1.0 (0 – 210)	€ 319068.60
General practitioner (€ 24.80)	56.3	430	1.0 (0 – 24)	€ 10664
Orthopaedic surgeon (€ 56)	31.8	253	0.0 (0 – 15)	€ 8288
Other specialist (€ 56)	13.5	91	0.0 (0 – 10)	€ 5096
Physical therapist (€ 21.50)	30.6	2145	0.0 (0 – 199)	€ 46117.50
Occupational therapist (€ 21.50)	0	0	0	€ 0
Chiropractor (€ 21.50)	4.5	72	0.0 (0 – 18)	€ 1548
Other therapist (€ 21.50)	1.8	161	0.0 (0 – 63)	€ 3461.5
Alternative therapies	4.1	127	0.0 (0 – 47)	€ 2730.50
Acupuncture (€ 21.50)	0.5	6	0.0 (0 – 6)	€ 129
Magnetizer (€ 21.50)	0.5	47	0.0 (0 – 47)	€ 1010.50
Homeopath (€ 21.50)	0.9	2	0.0 (0 – 1)	€ 43
Other alternative therapist (€ 21.50)	3.2	72	0.0 (0 – 25)	€ 1548
Total hip arthroplasty	9.0	-	-	€219871.60
Prescription pain medication	47.7	-	-	€19043.04
OTC[1] pain medication	41.4	-	-	€2248.35

[1]OTC = over the counter

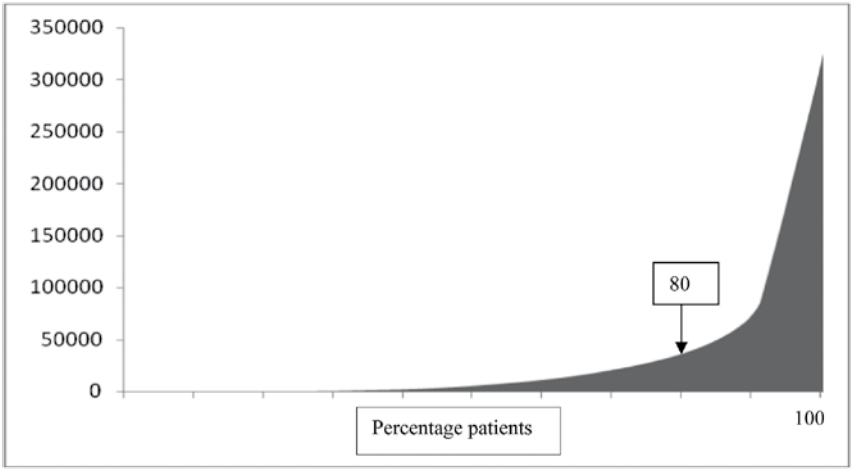

Figure 1. Plot of the cumulative direct medical costs.

Almost 70% of the patients included in the study reported at least one medical contact during the course of the study. More than half of the patients in this study visited their general practitioner (Table 2). A third of the patients consulted an orthopaedist, while more than 10 percent of all patients also visited another specialist for their osteoarthritis complaints. A third of all patients received treatment by a physical therapist, with a median of 22 visits. The maximum number of visits was 199, which is the result of weekly exercise therapy.
We previously reported that the use of pain medication was relatively stable over the course of the study, after a slight decrease following the start of the study[13].

Direct costs of medical consumption

The total direct costs of medical consumption in our trial was almost € 320,000. Figure 1 depicts the cumulative costs of all patients. In this group of primary care patients with hip osteoarthritis 20% of the patients accounted for almost 90% of the costs.
The costs for medical consumption are given in Table 2. The mean cost per patient with hip osteoarthritis per year were €638.78 (median €216.30).
Of all costs 20.2% was attributable to primary care, 6.7% was spent on medication and 73.1% was spent on secondary care. Of the costs for primary care 16.5% was attributable to GP visits, 71.5% to physical therapy and 4.2 % on alternative therapies. More than a third of the total costs was spent on total hip arthroplasties.

General practitioner visit

The results for the analyses of GP visits are given in Table 3. The baseline factors age ≥ 65, a BMI ≥ 30, and low educational level were univariately positively related with GP visits; being female was related with a lower chance of consulting. Of the factors that were measured every 3 months, the following were univariately related to an increased chance to visit the GP in the following 3 months: being anxious/depressed, having a WOMAC pain score ≥ 30, reporting difficulty putting on socks, having concomitant knee complaints, having concomitant back complaints, and daily use of OTC pain medication. The factor good health status led to a decreased chance to visit the GP in the following 3 months.

Table 3: Univariate and multivariate analyses of general practitioner visit

Characteristic	*GP visit OR* (95% CI)*	*p-value*	*GP visit OR (95% CI)*	*p-value*
Age ≥ 65	**1.42 (0.92, 2.19)**	**0.111**	1.48 (0.96, 2.29)	0.077
Female	**0.69 (0.43, 1.10)**	**0.121**	0.98 (0.61, 1.60)	0.950
Body Mass Index ≥ 30	**1.38 (0.87, 2.18)**	**0.174**	0.95 (0.61, 1.48)	0.820
Low education level	**1.92 (1.25, 2.94)**	**0.003**	1.44 (0.93, 2.22)	0.101
Duration of complaints ≥ 3 yrs	1.18 (0.76, 1.83)	0.451		
Anxiety / Depression	**1.51 (0.96, 2.39)**	**0.077**	1.25 (0.80, 1.95)	0.326
Good health status today	**0.33 (0.23, 0.47)**	**0.000**	**0.53 (0.36, 0.76)**	**0.001**
WOMAC* pain ≥ 30	**3.40 (2.31, 4.99)**	**0.000**	**1.97 (1.28, 3.03)**	**0.002**
Difficulty putting on socks	**2.44 (1.69, 3.52)**	**0.000**	**1.72 (1.19, 2.49)**	**0.004**
Comorbidities				
Knee complaints	**2.19 (1.47, 3.25)**	**0.000**	**1.63 (1.03, 2.58)**	**0.035**
Back complaints	**1.76 (1.28, 2.42)**	**0.001**	1.04 (0.70, 1.54)	0.826
Cardiovascular problems	1.21 (0.70, 2.08)	0.500		
High blood pressure	0.98 (0.93, 1.03)	0.372		
OTC* pain medication occasionally	0.76 (0.38, 1.53)	0.448		
OTC pain medication daily	**2.32 (1.19, 4.50)**	**0.013**	1.52 (0.86, 2.68)	0.148
Kellgren & Lawrence score	1.25 (0.81, 1.92)	0.317		

*OR = odds ratio, WOMAC = Western Ontario MacMaster Universities questionnaire, OTC = over the counter

The multivariate analysis showed that patients who reported a good health status in a questionnaire were less likely to visit the GP in the following 3 months (OR 0.53 [95% CI, 0.36 to 0.76]). The patients with a moderate or severe score on the WOMAC pain were almost twice as likely to visit their GP (OR 1.97 [95% CI, 1.28, 3.03]). Also, patients that reported difficulty putting on socks had a higher chance to visit their GP (OR 1.72 [95% CI, 1.19 to 2.49]), as did patients with concomitant knee complaints (OR 1.63 [95% CI, 1.03 to 2.58]).

Orthopaedist visit

The results for the analyses of the factors related to a first orthopaedist visit are presented in Table 4.
We found that patients with a high amount of periods with a reported GP visit, and patients that reported physical therapy treatment had an increased chance to be referred to an orthopaedist. Also, the number of periods with WOMAC pain ≥ 30, and the number of periods with difficulty putting on socks was related to referral.
In the multivariate analysis the factor high amount of periods with GP visit was found to highly increase the chance of a referral to an orthopaedist (OR 11.00 [95% CI, 4.23 to 28.63).

Table 4: Univariate and multivariate analyses of first visit to the orthopaedist.

Characteristic	*Visit to orthopaedist OR (95% CI)*	*p-value*	*Visit to orthopaedist OR (95% CI)*	*p-value*
Age ≥ 65	1.56 (0.75, 3.24)	0.231		
Gender (woman)	0.98 (0.44, 2.15)	0.954		
BMI ≥30	1.20 (0.53, 2.71)	0.669		
Low educational level	0.91 (0.44, 1.89)	0.805		
Duration of complaints ≥ 3 yrs	0.92 (0.44, 1.90)	0.818		
Periods with anxiety / depression[#]	7.70 (0.15, 391.24)	0.309		
Periods with good health status[#]	1.24 (0.48, 3.17)	0.658		
High amount of periods with GP visit[#]	**13.97 (5.64, 34.61)**	**0.000**	**10.35 (3.95, 27.15)**	**0.000**
Periods with WOMAC pain ≥ 30[#]	**3.08 (1.16, 8.19)**	**0.025**	1.16 (0.33, 4.08)	0.822
Periods with difficulty putting on socks[#]	**3.74 (1.30, 10.61)**	**0.014**	1.97 (0.47, 8.30)	0.354
Periods with treatment by physical therapist	**4.52 (1.94, 10.54)**	**0.000**	2.00 (0.75, 5.35)	0.166

[#]adjusted for time of exposure before first visit

Physical therapy treatment

The results for the analyses of the factors related to physical therapy treatment are presented in Table 5.
Patients that had a WOMAC stiffness score of ≥ 30, and patients that had concomitant back complaints, were more likely to receive physical therapy in the following 3 months. Patients that reported anxiety had a lower chance to receive physical therapy treatment in the following 3 months.
In a multivariate analysis we only found that patients with moderate to severe stiffness complaints (WOMAC pain ≥ 30) had a significantly higher chance to receive physical therapy treatment (OR 1.76 [95% CI, 1.03 to 3.00]).

Costs of medical consumption

The results for the analyses of the determinants of costs of medical consumption are presented in Table 6.

Table 5: Univariate and multivariate analyses of physical therapist visit

Characteristic	*PT visit OR* (95% CI)*	*p-value*	*PT visit OR (95% CI)*	*p-value*
Age ≥ 65	1.25 (0.67, 2.34)	0.474		
Female	1.11 (0.56, 2.23)	0.762		
Body Mass Index ≥ 30	1.40 (0.81, 2.41)	0.232		
Low education level	1.12 (0.59, 2.13)	0.720		
Duration of complaints ≥ 3 yrs	1.46 (0.77, 2.76)	0.248		
Anxiety / Depression	**0.65 (0.37, 1.13)**	**0.123**	0.57 (0.29, 1.16)	0.121
Good health status today	0.80 (0.51, 1.25)	0.334		
WOMAC Stiffness ≥ 30	**1.44 (0.96, 2.15)**	**0.077**	**1.76 (1.03, 3.00)**	**0.038**
Difficulty putting on socks	1.35 (0.82, 2.24)	0.237		
Comorbidities				
Knee complaints	1.02 (0.68, 1.53)	0.929		
Back complaints	**1.35 (0.95, 1.90)**	**0.091**	1.22 (0.71, 2.10)	0.464
Cardiovascular problems	0.80 (0.48, 1.32)	0.377		
High blood pressure	1.00 (0.99, 1.01)	0.540		
OTC* pain medication occasionally	0.92 (0.44, 1.92)	0.826		
OTC pain medication daily	1.24 (0.40, 3.85)	0.714		
Kellgren & Lawrence score	**1.94 (1.03, 3.63)**	**0.039**	1.46 (0.82, 2.60)	0.195

*OR = odds ratio, WOMAC = Western Ontario MacMaster Universities questionnaire, OTC = over the counter

Table 6: Univariate and multivariate analyses of costs of medical consumption.

Characteristic	*Costs higher than median (€ 216.30) OR* (95% CI)*	*p-value*	*Costs higher than median (€ 216.30) OR (95% CI)*	*p-value*
Age ≥ 65	1.29 (0.76, 2.19)	0.346		
Gender (woman)	1.41 (0.79, 2.50)	0.245		
BMI ≥30	**2.11 (1.14, 3.93)**	**0.018**	1.59 (0.83, 3.07)	0.165
Low educational level	1.24 (0.73, 2.11)	0.420		
Duration of complaints ≥ 3 yrs	1.20 (0.71, 2.03)	0.501		
Total nr of periods with anxiety / depression	1.04 (0.93, 1.16)	0.524		
Total nr of periods with good health status	**0.88 (0.81, 0.95)**	**0.002**	0.96 (0.86, 1.07)	0.436
Total nr of periods with WOMAC* pain ≥ 30	**1.16 (1.07, 1.26)**	**0.000**	1.11 (1.00, 1.24)	0.085
Total nr of periods with difficulty putting on socks	**1.12 (1.01, 1.25**	**0.035**	1.03 (0.92, 1.17)	0.588

*OR = odds ratio, WOMAC = Western Ontario MacMaster Universities questionnaire, OTC = over the counter

In univariate analyses we found that the factors BMI ≥ 30, higher amount of periods with moderate to severe pain, and reporting difficulty putting on socks was associated with costs higher than the median. A higher amount of periods with a good health status resulted in a lower chance on costs above the median.
In the multivariate analysis, none of the variables was significantly associated with a total expenditure over 2 years of more than the € 216.30, although there was a non-significant trend that higher amount of periods with moderate to severe pain led to higher costs (OR 1.11 [95% CI, 1.00 to 1.24]).

DISCUSSION

In our study of the medical consumption of hip osteoarthritis patients in primary care, 70% of the patients reported some form of medical consumption during the two years of study. The most frequented were the GP, orthopaedist and physical therapist. The use of alternative therapies was minimal.
Twenty percent of the patients in this study were accountable for 90% of the total costs. The major part of the costs were spent on total hip arthroplasties, which 20 patients (9%) underwent during the study. The mean annual cost of medical consumption was €638.78 per patient with hip OA.
We further found that moderate to severe pain, difficulty putting on socks and concomitant knee complaints all led to a higher chance to visit a GP in the following 3 months, whereas a self reported good health status lowered it. The only factor that we found to be related to referral to an orthopaedist was a higher level of GP visits. Moderate to severe stiffness was related to referral to a physical therapist. None of the tested variables were multivariately associated with costs above the median (€ 216.30).
The annual costs for hip osteoarthritis were only a little higher than those reported for knee osteoarthritis[3] and osteoarthritis in general[21] in Europe. The fact that we used the data of patients that were participating in a clinical trial could have influenced the data in more than direction. The fact that patients filled out a questionnaire every 3 months reminding them of their complaints may have triggered patients to seek care. For a single questionnaire this does not seem to apply[22], but with nine questionnaires it may be different. We know from meetings with the patients that for a couple of them the trial served as a trigger to ask for referral to an orthopaedist, which led to a total hip arthroplasty. For other patients being in a study with daily study medication could have made them less inclined to visit a doctor and to take other medication. The results from the study by Linsell et al[10], who found that 50.3% of hip OA patients consulted their GP in the last year, are very similar to our findings. We assume that our health care utilization results are generalisable to a normal population of hip OA patients in primary care.
Overall there is little similarity of determinants found in previous studies that have tried to identify determinants of GP consultation and referral to an orthopaedist[5-9]. The differences in results were most likely caused by differences in the populations under study. All studies included patients that had knee complaints[5-8] or complaints of knee or hip[9], however the percentage of patients with diagnosed OA in the studies varied considerably.
Two of these studies also found severity of pain to be associated with GP consultation[6 9], while three others did not, even though the factor was tested[5 7 8]. In

the study by Rosemann et al[9], prescription drugs were found to be related to GP consultation. We chose to use only OTC medication in our analyses, because we did not have enough information to know what was cause and what was effect regarding the use of prescription drugs and GP or orthopaedist visits.

The factor difficulty putting on socks, which describes a limitation in physical function was not tested before; the factor decreased physical function has been related to referral to a specialist[7 9], while it was related to a GP visit in our study.

Rosemann[9] also found the number of GP visits to be related to referral to an orthopaedist.

As far as we know, we are the first study to investigate factors that are associated with referral to a physical therapist.

We only found one determinant of referral in the analyses of visits to an orthopaedist and to a physical therapist. This may be related to the Dutch health care system. GPs function as gatekeepers to secondary care, at the time of the study patients could not consult an orthopaedist or a physical therapist without a referral from their GP. Nowadays, patients do not need a GP referral for the physical therapist. We found 'high amount of periods with GP visits' to be related to a first visit to an orthopaedist. This is probably a proxy for a multitude of factors. Patients that repeatedly consult their GP for their OA complaints are likely to have more serious symptoms, and are likely to be non-responders to medication or physical therapy. But it can also be a proxy for all the factors that a GP considers before he refers a patient, such as age, co morbidities, limitations, and whether a patient is willing to undergo a hiparthroplasty. Most of these factors were not measured in our study. Due to the strength of the association between multiple GP visits and referral we may have missed other valuable determinants.

We found WOMAC stiffness to be related to consultation of a physical therapist. Again, we may not have included the true factors that make a GP consider physical therapy for his patient with hip OA. An additional analysis which included factors from a physical examination did not yield different results, suggesting that still other factors are associated that we did not measure.

Univariately the factors periods with more severe pain and disability were related to both orthopaedist visit and total direct costs, which would make sense as the costs for orthopaedic surgery were accountable for most of the total costs.

Based on the correlations, we chose to use only one WOMAC subscale per analysis. WOMAC pain and stiffness had the highest outcomes in the univariate analyses of GP- and physical therapy visits, and were therefore chosen over WOMAC function. However, we used one defining factor from the WOMAC function questionnaire as a substitute for the total score. We chose the question about problems putting on socks (correlation with WOMAC pain ranged from 0.5 to 0.7), as this is a typical

complaint of patients with more severe hip OA. This variable proved to be an important factor in the analysis of visits to the GP. We did an additional analysis with WOMAC function instead of this one question, but we found that this relation was weaker. It is notable that such a simple, easy to use question is more informative in this analysis than the total WOMAC function score.
It was interesting to compare international and national guidelines for management of osteoarthritis[23 24] to what actually happens in practice. One of the suggestions in both guidelines state that physical therapy can be an effective treatment for patients with osteoarthritis, however only 30% of the patients in this study reported seeing a physical therapist. Another recommendation from the guidelines is that acetaminophen should be the first drugs of choice. NSAIDs can be given to patients when acetaminophen is not effective enough, but it is also specified[23] that long term use should be avoided. When assessing our data, we found that only 17% of our patients had been prescribed acetaminophen by their GP. Whereas almost 25% of the patients reported prolonged (more than 6 months) use of NSAIDs. Although we have no information on the situation preceding the study, it seems that the recommended therapies are not fully explored, which may leave room for improvement in symptoms of patients and maybe even a cost reduction for the group as a whole.

Conclusion

Many patients with hip osteoarthritis consult a GP and/or another health care professional for their complaints over a period of two years. The direct costs associated with hip osteoarthritis was on average €638.78 per patient per year.
Patients were more likely to consult a GP when they had more severe pain, had difficulty putting on socks, and had concomitant knee complaints. When they reported to be in good health they were less likely to consult.
Patients with multiple GP visits were more likely to be referred to an orthopaedist, while more severe stiffness complaints was related to consultation of a physical therapist.

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9

General discussion

INTRODUCTION

Osteoarthritis (OA) is one of the main causes of disability in elderly people[1]. Because of the ageing of society, it is thought that the impact of OA will probably rise in the coming decades. The main symptoms of OA are pain, stiffness of the joints, and limitations in daily activities.
Most of the research related to therapies for OA has been conducted among patients with knee OA, probably because this disease has a higher prevalence than hip OA. In adults aged over 60 years, the prevalence of symptomatic and radiographic knee OA is 12.2% compared with 7.4% for symptomatic and radiographic hip OA [2]. However, because in absolute numbers the group of hip OA patients is still substantial, this thesis focuses on primary care patients with hip OA.
The overall aim of this thesis was to describe the characteristics of patients with hip OA in primary care, and to assess the effectiveness of common therapies for OA.
This chapter summarises the findings from this thesis and discusses the results in a broader context. Implications of the findings for daily practice and future research are also addressed.

TREATMENT IN SUBGROUPS?

Glucosamine

Many trials in patients with OA are performed in a secondary care setting. Patients in these trials mostly have OA as confirmed on a radiograph by an orthopaedist or rheumatologist. The therapies that have proven beneficial in secondary care patients are also prescribed to patients in primary care. However, patients in primary care can differ from patients in secondary care, for example with respect to the severity of complaints and the severity of radiographic OA.
The effect of glucosamine sulphate has been tested in secondary care patients with established radiographic OA, usually based on a Kellgren & Lawrence (K&L) score of 2 and 3[3]. In our trial we chose to test glucosamine sulphate in the population that is most likely to use the compound, i.e. the primary care population. Therefore, we searched the patient records of participating general practitioners (GPs) for prevalent cases of patients with diagnosed hip OA, and patients with complaints that were likely due to OA. Patients that fulfilled one of the ACR criteria for hip OA were eligible for inclusion in the present trial. By selecting primary care patients, the level of OA in the trial was relatively mild compared to the secondary care

populations that were tested earlier. However, the relatively mild level of severity of our patients only applies to the level of radiographic OA. When we compared the pain level of patients who participated in two earlier long-term trials (published in 2001 and 2002[4 5]), the level of pain was very similar to that of the patients in the present study.

As we had anticipated, one criticism evoked by the present trial was that our population was 'too mild' with respect to radiographic severity of OA; this was given as a possible explanation for the lack of effect of glucosamine sulphate[6]. However, we did test the effect of glucosamine sulphate in the subgroup of patients with more severe radiographic OA (K&L score 2 and 3); this was one of our predefined subgroup analyses for which we had enough statistical power. Nevertheless, also in this subgroup, glucosamine sulphate was not more effective when compared with the placebo group.

Moreover, previous results have suggested the opposite: that in fact the more mild cases of OA could benefit more from glucosamine in terms of joint space narrowing[7]. This is also advocated by Felson and Kim, who claim that patients with mild OA who have less damage to their cartilage are more likely to benefit from a disease-modifying agent than patients that already have extensively damaged cartilage[8]. According to this latter hypothesis, we would expect to find a greater effect of glucosamine in the mild OA group (i.e. those with a K&L score of 1). However, the analysis presented in Chapter 4 does not show such an effect in this subgroup of patients. On the other hand, Reijman et al. have shown that progression of OA is slower in patients with less severe radiographic damage[9]; this might indicate that we needed a much longer follow-up time to be able to identify such an effect. We also performed exploratory subgroup analyses in patients with a higher pain level at baseline, but again found no effect of glucosamine sulphate in this group.

Although OA is a multifactorial disease with an unpredictable course, it is assumed that the complaints of most patients will deteriorate over time. The severity and site of OA is thought to be related to different systemic and biomechanical factors[10], while psychosocial and socioeconomic characteristics, as well as co-morbidities, may also contribute to the pain sensation of individual patients.

Differences in disease characteristics of patients may, in part, explain the different disease processes that are observed. The low effect sizes generally found in treatments for OA might be due to the fact that we are testing one treatment in different disease modalities. This may imply that, in the coming years, more tailor-made interventions are required for individual patients with OA.

Identifying treatment effects in subgroups

We made an attempt to identify patients that might be more susceptible to one type of therapy than another. This possibility was assessed in Chapter 4 for the effect of glucosamine sulphate in subgroups of hip OA patients, and in Chapter 5 for the effect of exercise therapy in subgroups of knee and hip OA patients.

Local vs. generalised OA

We tested the assumption that a different aetiology may result in a different effect of glucosamine, by performing predefined subgroup analyses for patients with local hip OA, and patients with hip OA as part of generalised OA. The former may more often be related to intrinsic joint vulnerabilities (such as a trauma or malformation of the joint), whereas the latter could be the result of a systemic disease. Furthermore, Belo et al. showed that there is convincing evidence that knee OA as part of generalised OA shows faster progression than those without generalised OA[11]. However, we did not find any beneficial effects of glucosamine in either of our subgroups. This could be due to different reasons. First, the distinction we made between local and generalised OA may be inadequate; at baseline we only had X-rays of hands and knees on which to base our distinction and this may not be sufficient. It is also possible that there is in fact no difference in effect of glucosamine between these two subgroups. Finally, if the therapy we offered was ineffective, it could never have led to a demonstrable difference between these subgroups. Unfortunately, it is not possible to derive enough information from our trial data to rule out or confirm any of these possibilities.

Hip vs. knee OA

Besides the difference in pathogenesis, the different mechanisms involved in the disease process can also differ per joint. In Chapter 4 it was hypothesised that knee OA is characterized more by inflammatory processes than hip OA. If this is so, the treatment for knee OA should focus more on preventing the inflammation than would be the case with hip OA.
One of the explanations for the possible effectiveness of glucosamine sulphate is that it is thought to act on the inflammatory pathway in OA, by protecting against IL-1 mediated extracellular matrix breakdown[12]. This effect on the inflammatory pathway might also explain its effect on pain, whereas a reduction in cartilage degradation alone cannot explain this effect. This is further supported by the finding that synovial thickening and effusion (some of the results of the OA in-

flammatory process) were associated with more knee pain: i.e. moderate and large effusions, and synovial thickening, were more frequent among patients with knee pain than in patients without pain[13].
Because all the positive results with glucosamine sulphate were found in patients with knee OA, we tested the effect of glucosamine in an exploratory subgroup of patients with concomitant radiographic knee OA. A non-significant difference in both pain and function score was found in the group of patients with concomitant knee OA, whereas the effect was close to zero in the group without knee OA. We suggest that a relief of symptoms in the knees could also have an impact on the scores of a questionnaire we used to measure hip complaints. Particularly in weight-bearing activities, it will be difficult for patients to distinguish between complaints originating from the hip or from the knee. If this assumption is correct, our finding could be an indication that glucosamine is indeed more effective for knee OA than it is for hip OA. However, it could also be just a chance finding, due to the more than 20 analyses that we performed. A well-designed trial testing glucosamine sulphate in patients with knee OA or hip OA is needed in order to compare the effects between the joints.

Exercise therapy for mild and severe OA

The findings from Chapter 5 indicate that patients with both mild and more severe radiographic knee and hip OA could benefit from exercise therapy. With effect sizes of 0.3 and 0.5 for strengthening and aerobic exercises, respectively[14] it is a form of therapy that should be considered by GPs and patients. A recent meta-analysis has confirmed that exercise therapy is indeed effective for hip OA patients[15]; this was suggested earlier, but was largely based on effectiveness in knee OA trials and expert opinion.
In conclusion, in the present thesis no clear evidence was found for the existence of subgroups within patients with OA that benefit more from a particular type of therapy compared with others. We did not find an effect of glucosamine on pain in local and generalised hip OA, and exercise therapy seemed effective for patients with both mild and more severe radiographic OA. The results for the difference in effect of glucosamine in patients with knee and hip OA are inconclusive and are based on indirect data. There seems to be a small benefit from glucosamine in patients with hip OA and concomitant knee OA, while no benefit was seen in hip OA patients without knee OA. However, from this exploratory subgroup analysis we cannot conclude that glucosamine is more effective for knee OA patients.

Optimising treatment in clinical practice

The major part of the costs of hip OA is attributable to total hip replacements (Chapter 8). If a disease-modifying treatment could be found, this might have a great impact on the costs involved with OA. However, it is unlikely that such an agent will be found in the near future[8].
The focus in current practice is to control the symptoms of patients with OA. Although most of the available therapies have only small to moderate effects on pain and functional limitations, when timed properly they can relieve at least part of the symptoms in most patients, possibly for an extensive period of time given that the disease generally does not deteriorate very rapidly[14].
In Chapter 8 we saw that only 30% of all patients received physical therapy during the course of the study. From the data, we cannot deduce whether this is caused by a lack of referral by the GP or is due to a negative attitude of patients towards physical therapy. Moreover, the information we have only concerns the 3 months prior to the study, and the 2-year study period itself. Some of the patients had probably received exercise therapy in the past, especially because many patients had had their complaints for more than 3 years before they entered the trial (Chapter 3).
Our study indicates that GPs do not make full use of the available therapies. This implies that there is room for improvement, which hopefully might lead to a delay in referral to an orthopaedist and thereby a possible delay in surgery. However, we only followed patients for 2 years, which is a relatively short period for a chronic condition such as OA. A study with a longer follow-up is needed to better assess the application of the different available therapies by GPs and orthopaedists.

The long-term use of NSAIDs is still relatively common in the Netherlands for complaints due to hip OA (Chapter 8), despite the lack of evidence to support long-term use of this kind of medication[16]. This might be related to the fact that most patients hold paracetamol in low esteem, due to its long-established availability as an over-the-counter pain medication and its use for many types of different complaints. Patients will be more inclined to ask for a follow-up prescription of pain medication such as NSAIDs when they have experienced a reduction in pain. However, this may not in fact be necessary because, as known from practice and shown in Chapter 6, an episode of pain will naturally regress to the mean. The pain level of most patients will remain at a lower level for a period of time without the use of pain medication.
Two guidelines from the Netherlands[17 18] and the NICE guideline from the UK[19] state that paracetamol is the drug of first choice for (knee) OA. They state that

NSAIDs should only be considered when paracetamol is not effective enough in reducing symptoms. The Dutch GP guideline mentions a time interval of 2 weeks with a possibility to continue with NSAIDs for another 1 or 2 weeks if necessary[18]. The NICE guideline states that NSAIDs should be prescribed for the shortest possible time[19].
More attention paid to the sort of medication and the duration of its use by caregivers might reduce the amount of chronic pain medication used and the risk of adverse events that are associated with prolonged use.

Glucosamine effective as placebo?

The international discussion on the symptomatic effectiveness of glucosamine has recently become focused on possible differences in effect between the compounds tested (i.e. glucosamine sulphate as supposedly effective versus glucosamine hydrochloride as supposedly ineffective), and on a possible impact of the active involvement of the manufacturer of glucosamine sulphate in the most important high-quality trials on glucosamine sulphate[20]. Because the high-quality positive glucosamine sulphate trials used the product made by RottaPharm and were sponsored by this firm, it seems impossible to unravel this issue[4 5 21]. Our trial testing glucosamine sulphate was the first independent trial of high quality (with respect to blinding, daily dose, and a confirmed percentage of glucosamine sulphate in the compound) - and showed no effect in hip OA patients.
The latest long-term trial that tested glucosamine hydrochloride in knee OA patients found no difference between glucosamine and placebo with regard to joint space narrowing[22], which is comparable to our results for hip OA. Two other trials[4 5] did find a small effect on joint space narrowing, but this was not mirrored in long-term symptomatic effectiveness at that time. Together, these findings indicate that if glucosamine is beneficial for patients with OA, the effects are very small both on pain and joint space narrowing. The question then remains: is it worthwhile to encourage patients to spend over 100 euros per year on medication which probably will not give a perceivable effect?
Although patients may not derive much direct benefit from glucosamine sulphate, a finding from our trial suggests that there might be an indirect benefit of using this compound. Patients in our trial showed a decline in the use of NSAIDs after the start of the study, independent of whether they received glucosamine or placebo. Some patients took NSAIDs less frequently, others stopped taking them altogether. This decline remained stable during the total course of the study. Although the reason for the decline may not be directly attributable to the beneficial effects of glucosamine, it nevertheless is a positive finding.

A recent meta-analysis showed that placebo in itself is a relatively potent treatment for the subjective outcomes in OA, especially when the active treatment is thought to be very effective[23]. Should we then advise patients to take glucosamine even though the effectiveness seems doubtful, because we know that it will relieve the symptoms of many patients due to a placebo effect? It is probably best to just inform patients and physicians about the available evidence concerning glucosamine for knee and hip OA. Combined with information about the price and safety of the compound, patients and physicians can then make an informed decision as to whether or not to use glucosamine for their complaints.
The conflicting results from all previous trials are also reflected in the difference in recommendations regarding glucosamine in national and international guidelines. Some guidelines[18 19] state that they do not recommend the use of glucosamine for patients with OA. Other guidelines[17 24] state that patients can use glucosamine for a trial period of 3 or 6 months, to see whether glucosamine is effective in relieving their complaints. However, this could lead to prolonged use by many patients without any real effectiveness of glucosamine. In Chapter 6 we showed what was already known in practice, i.e. that complaints increase and decrease naturally over a period of time. Patients tend to seek treatment for their complaints at a peak level; from this point on the symptoms often naturally decline. However, when a patient starts taking glucosamine sulphate at a peak point regarding symptoms, it may seem as though glucosamine is causing the (natural) decline in symptoms. Therefore, patients will be inclined to keep taking the compound when the symptoms are less severe. Patients should be thoroughly informed by their physician. They should be told about the natural course of complaints, so that they can better judge the true effectiveness of the compound.

Limitations

Due to the long-term design, we allowed patients in our trial to continue receiving usual care; consequently, we tested glucosamine as a supplement to usual care. Almost 25% of the patients reported the use of pain medication throughout the study period. The fact that a quarter of all patients were using a therapy that has an effect size of around 0.2 for paracetamol or 0.3 for NSAIDs[14] (at least for short duration), may have influenced our results. However, because the percentage that used pain medication was similar in both the placebo and the glucosamine sulphate group, this will not have led to differences between groups that were not attributable to the study medication. However, it did lead to 'noise'; a small effect of glucosamine sulphate could have been diluted by the effect of the pain medica-

tion. However, it would not have been feasible to deny patients with chronic pain a beneficial therapy for the two- year study period

In Chapter 5, the appraisal we performed to assess the influence of disease severity on the effect of exercise treatment, has some methodological drawbacks. Unfortunately we had to exclude a large part of the available trials because they did not report the data we needed to answer our question. The inclusion of more studies would of course have provided a more reliable indication of the effect of disease severity on the effect of exercise therapy.

We based this study on the data that were available in the published trials, because we assumed it would be impossible to acquire the original data from the authors of these trials. However, a recent meta-analysis estimating the effect of exercise therapy specifically in patients with hip OA (from published trials that included patients with hip OA as well as knee OA) has shown that gathering more precise data from the trials by contacting the authors is possible[15]. In retrospect this would have been a better approach for our appraisal of disease severity on exercise treatment.

Another drawback of using the data from trials on exercise therapy is the difference that exists in therapies used between the trials. Also, within trials it is likely that patients will have received somewhat different therapies with regard to the intensity and sort of exercises. Despite these known and unknown differences, in the analyses we have regarded all trials to be equal; therefore, the results of the appraisal should be seen as generating hypotheses.

The same applies to the results presented in Chapter 4, the subgroup analyses of the glucosamine trial. Although we pre-specified half of our subgroup analyses, we also added exploratory and theory-driven subgroup analyses. These additional analyses increase the risk of chance findings; moreover, for most of these exploratory analyses the power was too low because the standard deviations for the WOMAC scores in our trial were larger than expected. However, despite the large standard deviations, in almost all analyses we could still rule out minimal clinically important differences.

The results of the trial were also used to assess medical consumption in patients with hip OA. Because patients were part of a trial, their use of usual care may not be completely comparable to that in an open population of patients with hip OA. Patients were treated on a daily basis for their OA complaints, which could have influenced their care-seeking behaviour. Also, the follow-up period was relatively short to measure medical consumption for a chronic disease such as OA. We have no information regarding the period before the trial, despite that half of the patients had had their complaints for more than 3 years. In the years preceding the trial they may have already been referred to different therapies for

their complaints, which we now considered to be under-represented in our study on the basis of recommendations by OA guidelines.

COURSE OF OA SYMPTOMS

The course of OA complaints at the individual level has hardly been described before. From the literature we know that on the group level symptoms stay relatively stable over a prolonged period of time[25], and we know that they can fluctuate in individual patients when measured very frequently over a shorter time period[26]. From Chapter 6 we now know that complaints continue to fluctuate over a longer period of time, when measured every 3 months.

In our study, although 35% of the patients assessed their complaints as having deteriorated compared with 2 years earlier, this was not shown in their pain and function outcomes. In other words, the correlation between the global assessment of the patients and the actual pain and function score was low. This finding indicates that patients base their global assessment of the state of their complaints on more factors than pain and function alone. It could also imply that the WOMAC subscales and the VAS pain measure are not totally suitable to compare the level of pain and function within an individual over a 2-year period.

Perhaps another measure is needed when aiming to measure the course of complaints over time. The most appealing and valid measure seems to be the patient's global assessment, because a range of determinants can be included in this measure that comprises a person's complaints. For example, Tubach et al.[27] found this to be a relevant indicator of change; they found that a difference of 20 points on a VAS (0-100) corresponded to a patient's global assessment score of 4, indicating good response to therapy with occasional episodes of pain or stiffness.

The new questionnaire constructed by OMERACT/OARSI[28] may also improve the way to measure pain nowadays. This pain measure assesses two different sorts of pain, i.e. constant and intermittent pain. Based on our fluctuating intra-individual pain data (Chapter 6) we hypothesised that most patients were experiencing a (mean) constant pain level and, in addition, had temporary increases in pain level. The study by OMERACT/OARSI confirmed this hypothesis[29]. It is hoped that new trials will incorporate this new pain measure as an outcome measure, and will assess complaints on a more regular basis. This will give new insights into the course of pain in patients with OA, and could also provide more information on the effect of a treatment.

Should we still look for progressors with respect to pain, when the overall group shows hardly any deterioration of complaints over 2 years? Do our data and

previous data[25] indicate that, overall, the disease is simply not deteriorating very much? Although this is probably true for the overall group of patients with OA, it is not true for individual patients. In our study, 17% of the patients indicated that their complaints had strongly deteriorated over 2 years; however, only 16 patients reported a somewhat or strongly deteriorated score on all 4 measurements. The fluctuations seen in the pain and function data were also present in the patients' global assessment of complaints. This group of patients that deteriorates more steadily is only a small proportion of the group of OA patients as a whole. Nevertheless, for these patients it is particularly important that we establish why this deterioration occurs, and how we can stop or slow down the progression.

The progression of radiographic OA also goes relatively slowly on the group level. In our study (Chapter 3), and in the GAIT[30] and other studies[31 32] the rate of joint space narrowing at group level was much lower than expected. Consequently, trials that test disease modification in patients with OA should include a longer follow-up period than the 2 years that are generally currently applied. The slow progression on the group level, together with the apparently stable complaints on the group level, indicates the need for better identification of groups within OA patients that are at risk of rapid deterioration. Our trial and numerous other studies have clearly shown that there are symptomatic and radiographic progressors. However, we currently lack valid tools to predict which patients will be the real progressors.

Therefore, a major part of the OA population may receive much benefit from disease-modifying compounds, because their disease is not very progressive. These patients may derive more benefit from pain medication prescribed only for periods of disease 'flare', education about lifestyle changes, and exercises to manage their symptoms.

Perhaps the lack of effectiveness of the disease-modifying agents that we tested so far can be attributed to the population sample itself. All the trials were conducted in patients who already have radiographic signs of OA; this means that at least part of the cartilage is already affected to the point where breakdown of cartilage becomes apparent on a radiograph. Felson & Kim[8] suggested that disease-modifying therapies cannot show effectiveness in these patients because their joint damage is already too severe and the biomechanics of the joint have changed too much. One of their suggestions is to test the efficacy of a possible disease-modifying drug in patients with a much earlier stage of disease. As normal radiography cannot identify these patients, perhaps MRI scans could be used to define stages of very early OA, or biomarkers could be used to find more subtle changes in cartilage breakdown that cannot be measured with either MRI or radiography. However, until now, neither MRI nor biomarkers have been able to supply the answer as to how best to measure changes in the disease process.

Even if the approach suggested by Felson & Kim[8] to test possible disease-modifying treatments in patients with very early disease was successful, and effective agents were found, the implementation of such a preventive drug would be difficult. Implementation should then be aimed at patients at high risk of getting the disease at an early age and who also run the risk of deteriorating fast, such as patients that undergo meniscectomy after injury. Whether it is feasible to search for a therapy that, based on safety and costs, could be implemented in a more general population of patients possibly at risk of getting symptomatic OA remains questionable.
Although the association between radiographic severity and pain remains disputed, it was interesting that the K&L score was the strongest prognostic factor of progression of complaints as assessed by the patients themselves (patients' global assessment), and complaints as measured with a VAS (Chapter 6). In an open population study K&L score was also found to be the strongest predictor for progression of hip OA in terms of radiographic severity, especially when co-existing with hip pain[9].
Perhaps even more interesting was the finding (Chapter 7) that features concerning shape and bone density as measured with a DXA scan seemed much more informative in assessing the progression of symptoms of OA than the well-known radiographic features, i.e. the K&L score and joint space width. Although these are only preliminary results, the results are promising. These new features might be used in the future to better predict which patients will be symptomatic and radiographic progressors.

Limitations

Unfortunately, the patients that underwent total hip replacement could not be included in the assessment of the course of hip OA, or in the analysis to find prognostic factors for the deterioration of complaints. The patients with incomplete data were not used in the descriptive part of the study, and 16 of the 20 patients that underwent a total hip arthroplasty had their surgery before the 7th questionnaire, which meant that they were not included in the analyses. The data of the patients that underwent total hip replacement, however, do not suggest that they were the most severe patients with respect to pain and function, although the average pain level was somewhat higher in this group than in the total group. Although a few patients showed very fast deterioration of complaints, for the most part (based on observations), the pain and function data of patients that underwent total hip replacement seemed to be more stable over time than that of the patients who did not undergo surgery.
The decision of an orthopaedic surgeon to consider total hip replacement surgery will depend on many different factors. A recent observational study[33] showed that

particularly clinical severity and structural degradation were related to a surgeon's decision to plan surgery for a patient in the coming 6 months. In the multivariate analysis, the factors quality-of-life related to physical well-being, amount of joint space narrowing, and cardiovascular co-morbidity, were found to be independently related to the surgeon's decision. This indicates that not only pain or functional limitations are the most important factors, but the total impact of symptoms on a patient's life guides a physician's decision regarding total hip replacement.

IMPLICATIONS FOR PRACTICE

Based on the results of our trial assessing the effectiveness of glucosamine sulphate, there seems to be no evidence to support the use of this compound in patients with hip OA, regardless of radiographic severity. For exercise therapy, there was no indication that the severity of radiographic OA determines the effectiveness of the therapy. We therefore assume that exercise therapy is beneficial for both mild and more severe cases of both knee and hip OA.

Although the information will not change the management strategy of the GP in most cases, and is not necessary for the diagnosis[18], an X-ray can be informative when assessing the risk of progression of complaints. The group of hip OA patients as a whole does not seem to progress very fast with respect to complaints over a period of 2 years. However, individual patients show much variation in complaints over short periods of time, which supports the use of medication as recommended by national and international guidelines for a short duration to alleviate the more severe symptoms[18 19].

It seems that, currently, the therapies of first choice may not be used to their full potential in the management of hip OA. Especially the use of paracetamol does not seem to be advocated by most GPs. Although the effect of paracetamol and NSAIDs are comparable, the data suggest that NSAIDs are more often prescribed by GPs than paracetamol, even for prolonged periods of time (> 6 months). Giving first priority to paracetamol, as recommended in the guidelines, not only has the potential to lower total costs but may also lower the risk of adverse events.

Moreover, the referral of patients to a physical therapist was lower than expected based on its effectiveness as a therapy for OA complaints, and as recommended in multiple guidelines[24]. Since a meta-analysis recently demonstrated the effectiveness of exercise therapy for hip OA[15], and combined with our finding that there is no difference in effect between the different stages of radiographic OA (Chapter 5), we believe more physicians could prescribe physical therapy as a safe treatment with moderate effect sizes.

IMPLICATIONS FOR FUTURE RESEARCH

Our trial was the first to assess the effect of glucosamine sulphate on hip OA. Although we tested glucosamine sulphate (albeit not the RottaPharm compound that was previously found to be effective for knee OA), we have to conclude that for hip OA it was not effective. However, more evidence is needed. The small, non-significant effect in patients with concomitant knee OA may warrant a new trial that tests the effect of glucosamine sulphate in both knee and hip OA.

Also, the finding from the first two long-term trials[4,5] showing that the total amount of total joint replacements after 5 years of follow-up was lower in patients that had received at least 12 months of glucosamine during the trials than in the placebo group[34], warrants further study. It is surprising that these differences were found, bearing in mind that there was hardly any effect on symptoms after 3 years. Severity of clinical symptoms is normally one of the major determinants in the decision of an orthopaedic surgeon to consider total joint replacement surgery[33].

In general, future research should critically consider the methods currently used to find disease-modifying agents. Perhaps we need to focus more on patients with very mild disease status rather than on patients with already extensive damage to the cartilage and concomitant alterations of surrounding tissue. This implicates that studies need a much longer follow-up period (e.g. 5-10 years).

More data are needed on the natural course of OA. More studies should measure pain and function for a longer period of time with more intermediate measures. The new pain measure that examines both the constant pain level and the intermittent pain level should be incorporated in future studies[28]. This will probably lead to a better understanding of the course of pain, and will hopefully address the problem of the fluctuation in pain that arises from the various studies.

The knowledge on fluctuations in pain and function scores implies the need for more careful handling of patients with OA in both cohorts and in trials. In cohorts, fluctuations in pain scores could lead to a wrongful labelling of patients as progressors; although the effect will not lead to wrongful findings in randomized trials it will lead to 'noise'. The underlying fluctuations in the commonly used pain scores (such as WOMAC and VAS) may be an explanation as to why the effect sizes of OA treatments are generally quite low. The use of repeated measurements could reduce this noise. The new OMERACT/OARSI pain measure may be a more appropriate way to assess the beneficial effects of therapies than a pain score that can fluctuate considerably on a daily, weekly or even on a 3-monthly basis.

It would be helpful if more trials on therapies for OA would publish the subgroup analyses that have been performed, even if they are not adequately powered or even if these subgroup analyses were post-hoc. It is very time-consuming and costly

to design trials to test the effect of therapies in a selected group of patients when there is no clear indication that this group may respond differently than another group. If all trials would report findings from commonly assessed subgroups (e.g. based on the severity of radiographic OA), or would allow access to their data for secondary analyses, these data could then be used in meta-analyses to identify important subgroups within the total group of OA patients.

The possibilities of using shape and bone density features of the femur as measured on DXA should be further explored. On the basis of our study it seems that these features may have the potential to explain more of the status and progression of symptoms than the currently available radiographic features. This could lead to a better understanding of the disease process, and to better identification of the true progressors within the total group of OA patients.

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Summary

Osteoarthritis (OA) is one of the leading causes of disability among elderly people. Although knee OA is twice as prevalent, hip OA is still a large problem in the older population. Most of the studies assessing the effectiveness of therapies however, are done in patients with knee OA. It is easily assumed that results are also applicable to hip OA. Hip OA is, as a consequence, somewhat underrepresented in the literature until now. Therefore, the focus in this thesis will be on hip OA.

Pharmacological treatment for OA can be divided into two groups: symptom-modifying and disease-modifying drugs. Symptom-modifying drugs are the prescription of choice for patients with OA, as disease-modifying drugs are not yet available in usual care. However, there has been a lot of debate about glucosamine sulphate, a biological agent that is thought to have both symptom-modifying and disease-modifying properties. The available data comes from trials in knee OA patients. The data are conflicting and there is not enough data concerning the long term effectiveness of glucosamine sulphate. **Chapter 2** describes the detailed study protocol of the trial that we performed to test the effectiveness of glucosamine sulphate in primary care patients with hip OA.
Primary care patients with hip OA meeting the ACR-criteria were randomly allocated to either 1500 mg of oral glucosamine sulphate or placebo for the duration of two years. The primary outcome measures, which are joint space narrowing (JSN), and change in the pain and function score of the Western Ontario McMaster Universities Osteoarthritis index (WOMAC), are determined at baseline and after two years of follow-up during the final assessment. Intermediate measures at three-month intervals throughout the trial are used to also study the main secondary outcome measures WOMAC pain, function, and stiffness after 3, 12, and 24 months.

Chapter 3 describes the results of the randomised controlled trial (RCT) that we performed to assess whether glucosamine sulphate has an effect on the symptoms and structural progression of hip OA during 2 years of treatment. We included 222 patients with hip OA, who were randomised to either 1500 mg of glucosamine sulphate once daily or a placebo for the duration of 2 years. At baseline, both groups were similar in demographic and clinical variables. After two years 207 patients (93.2%) were available for follow up. Twenty patients had had total hip replacement surgery during the trial.
Overall, there was no difference between glucosamine sulphate and placebo in WOMAC pain over two years -1.54 (95% CI [-5.43 to 2.36]), nor in WOMAC function -2.01 (CI [-5.38 to 1.36]). Joint space narrowing also did not differ after 24 months (-0.029 (CI [-0.122 to 0.064]). There was no difference between glucosamine sulphate

and placebo in any of the secondary outcome measures. The conclusion of chapter 3 was that glucosamine sulphate was no better than placebo in reducing symptoms and progression of hip OA.

The objective of **Chapter 4** was to investigate whether there are subgroups of patients with hip OA for whom GS might be an effective therapy. In the RCT that was described in chapters 2 and 3 subgroup analyses were pre-specified for radiographic severity (Kellgren & Lawrence = 1 vs. ≥ 2) and for type of OA (localised vs. generalised). Additional exploratory subgroup analyses focused on groups based on pain level, pain medication use, baseline joint space width, and concomitant knee OA at baseline.
There were no differences between glucosamine sulphate and placebo in WOMAC pain and function and joint space narrowing over 24 months in the predefined subgroups based on radiographic severity and type of OA. For patients that had concomitant knee OA at baseline the adjusted difference for WOMAC pain was -5.7 (95% CI [-12.6, 1.3]) in favour of glucosamine sulphate, while for patients that did not have concomitant knee OA the difference was -0.1 (95% CI [-4.9, 4.7]). Although the difference between glucosamine sulphate and placebo was not significant in this exploratory subgroup analyses, it is interesting because all positive effects of glucosamine were found in patients with knee OA. Whether this finding is based on chance or whether it could be an indication of a stronger effect of glucosamine sulphate in knee OA patients, can only be answered if it is tested again in a trial designed to evaluate a possible difference in effects between joints.
Overall the conclusion was that glucosamine sulphate was not better than placebo in reducing symptoms and progression of hip OA in subgroups of patients.

Whether or not there are subgroups of OA patients that benefit more from a therapy was also studied in **Chapter 5**. We performed a critical appraisal to study whether the effectiveness of exercise therapy in management of pain and function in patients with OA depend on severity of radiographic osteoarthritis (ROA) or duration of illness. We searched PubMed and the Cochrane library to find systematic reviews on effectiveness of exercise therapy. All RCTs from the selected reviews were collected and screened for the following inclusion criteria: comparison of exercise vs. non-exercise therapy, pain and function measures, documentation of severity of ROA and/or duration of illness, data suitable to calculate effect size.
We included eleven RCTs, seven of which were of high quality. Effect sizes for pain ranged from 0.03 – 1, and from 0.04 – 3 for function. The percentage of patients with moderate and severe ROA ranged from 21.2% – 100%. Mean duration of illness ranged from 2.2 – 12.3 years.

Based on the data there seemed to be no difference in effect of exercise therapy in subgroups based on severity of radiographic OA. Also for subgroups based on duration of illness there seemed to be no difference in effectiveness of exercise therapy.

Not much data is available on the course of complaints of hip OA and the factors associated with progression of these complaints. We know that OA complaints progress very slowly on group level, but what happens on individual level, when measured regularly, is hardly known. In **Chapter 6** we used the data of the RCT to describe the course of complaints of hip OA as measured every three months and tried to find factors associated with these complaints.
We found that the complaints of primary care patients with hip OA were stable on group level over a period of 2 years. Individual patient data, however, showed large fluctuations in pain and function scores over time. After two years a painful hip flexion at baseline and a Kellgren & Lawrence score of ≥ 2 significantly influenced worsening of patients' global assessment. A higher age and a Kellgren & Lawrence score of ≥ 2 significantly increased VAS pain, whereas a higher VAS at baseline protected against increase.

Common radiographic measures of an affected OA joint relate poorly to symptoms as experienced by patients. In **Chapter 7** we describe a new approach to assess status of OA and factors that are associated with progression of both radiographic and symptomatic OA. DXA images of the hip region were made at baseline and after 2 years of follow up in the RCT described in previous chapters. From the DXA scans we constructed a statistical model of the appearance (shape combined with density) of the proximal femur. The model yielded a number of independent descriptors of the appearance, which we related to various measures of status and progression of radiographic and clinical OA. Various modes showed significant relations with radiographic and clinical OA. Interestingly, the modes that related well with radiographic OA did not relate to clinical OA and vice-versa. Moreover, the modes showed to be predictors of both status and progression of clinical OA, independent of JSW and K-L. Statistical modelling of the appearance proved to be an effective way to describe the total proximal femur in DXA images. We showed that descriptors of subtle aspects of shape and density of the hip contain information about clinical status, which common radiographic measures do not.

The aim of **Chapter 8** was to assess the medical consumption of primary care patients with hip OA, and the associated determinants and costs. Patients filled out a questionnaire every 3 months throughout the 2-year duration of the study to re-

cord medical consumption and possible determinants. The direct costs of medical consumption were calculated using self reported data on consultation of health care professionals, and pharmacological and non-pharmacological treatments.
We found that more than half of the patients consulted a general practitioner (GP) for their complaints. A third of the patients was referred to an orthopaedist and a third reported treatment by a physical therapist. The direct costs associated with hip OA was on average €638.78 per patient per year, which was similar to costs found for knee OA in Europe. Of all costs 20.2% was attributable to primary care, 6.7% was spent on medication and 73.1% was spent on secondary care. In this group of primary care patients with hip OA 20% of the patients accounted for almost 90% of the costs.
Moderate to severe pain was associated with GP visit for OA complaints, as was having difficulty putting on socks, and having concomitant knee complaints. A good health status lowered the chance to visit a GP. Patients that had frequently visited their GP were more likely to be referred to an orthopaedist.

Chapter 9 reflects on the main findings of this thesis. The limitations of the studies and the implications of the results for practice and future research are also discussed.

Samenvatting

Artrose is een van de voornaamste oorzaken van beperkingen bij oudere mensen. Ook al komt knieartrose tweemaal zo vaak voor, heupartrose is wel degelijk een groot probleem in de vergrijzende samenleving. De meeste studies die zijn gedaan om het effect van een therapie te testen, zijn uitgevoerd bij patiënten met knieartrose. Er wordt vervolgens aangenomen dat de resultaten ook toepasbaar zijn op heupartrose. Als gevolg daarvan is heupartrose wat onderbelicht in de literatuur op dit moment. Daarom ligt de focus van dit proefschrift op heupartrose.

De medicamenteuze behandeling van artrose kan in twee groepen verdeeld worden: symptoombestrijdende en ziektebestrijdende middelen. Symptoombestrijdende middelen zijn de eerste keus voor patiënten met artrose, omdat ziektebestrijdende middelen nog niet beschikbaar zijn in de reguliere zorg. Echter, er is de laatste jaren veel discussie geweest over glucosaminesulfaat, een voedingssupplement waarvan gedacht wordt dat het zowel symptoombestrijdende als ziektebestrijdende aspecten heeft. De beschikbare data tot nu toe komt uit onderzoeken bij patiënten met knieartrose. De data zijn tegenstrijdig en er is nog niet genoeg bewijs over de lange termijns effectiviteit van glucosaminesulfaat. **Hoofdstuk 2** beschrijft gedetailleerd het studieprotocol van het onderzoek dat we gedaan hebben om het effect van glucosaminesulfaat te testen bij eerstelijns patiënten met heupartrose. Eerstelijns patiënten met heupartrose die voldoen aan een van de American College of Rheumatology (ACR) criteria werden at random verdeeld in een groep die gedurende 2 jaar ofwel eenmaal daags 1500 mg orale glucosaminesulfaat of een placebo kreeg. De primaire uitkomstmaten gewrichtsspleet versmalling en het verschil in de pijn en functiescore van de Western Ontario McMaster Universities Osteoarthritis index (WOMAC) vragenlijst, werden op baseline en na 2 jaar studie bepaald. Elke 3 maanden werden tussentijdse metingen verricht om de belangrijkste secundaire uitkomstmaten te meten, waaronder WOMAC pijn, functie en stijfheid na 3, 12 en 24 maanden.

Hoofdstuk 3 beschrijft de resultaten van het gerandomiseerde, gecontroleerde onderzoek dat we hebben gedaan om te bepalen of glucosaminesulfaat een effect heeft op de symptomatische en radiologische progressie van heupartrose gedurende 2 jaar behandeling. We includeerden 222 patiënten met heupartrose, die werden gerandomiseerd tot ofwel 1500 mg orale glucosaminesulfaat eenmaal daags of een placebo voor de duur van 2 jaar. Op baseline waren beide groepen vergelijkbaar wat betreft demografische en klinische variabelen. Na 2 jaar waren nog 207 patiënten (93.2%) beschikbaar voor de eindmeting. Twintig patiënten hadden een totale heupvervangende operatie ondergaan gedurende het onderzoek.

Overal was er geen verschil tussen glucosamine en placebo wat betreft WOMAC pijn na 2 jaar (-1.54 (95% BI [-5.43, 2.36])), noch in functiescore (-2.01 (BI [-5.38, 1.36])). Gewrichtsspleet versmalling was ook niet verschillend na 24 maanden (-0.029 (BI [-0.122, 0.064]). Ook in de secundaire uitkomstmaten waren geen verschillen tussen glucosamine en placebo. De conclusie van hoofdstuk 3 was dat glucosaminesulfaat niet beter was dan placebo in het verminderen van de symptomen en de radiologische progressie van heupartrose.

Het doel van **Hoofdstuk 4** was te onderzoeken of er subgroepen patiënten met heupartrose zijn voor wie glucosaminesulfaat wel een effectieve therapie is. In het protocol van het onderzoek, dat is beschreven in hoofdstuk 2 en 3, werden subgroepen vooraf gedefinieerd, namelijk op basis van radiologische ernst (Kellgren & Lawrence = 1 of ≥ 2) en op basis van type artrose (gelokaliseerd of gegeneraliseerd). Daarnaast werden nog additionele exploratieve subgroep analyses gedaan gebaseerd op pijnniveau, gewrichtsspleet en aanwezig zijn van knieartrose op baseline en pijnmedicatie gebruik gedurende het onderzoek.
Er werden geen verschillen gevonden tussen glucosaminesulfaat en placebo in WOMAC pijn en functie en gewrichtsspleet versmalling na 24 maanden in de vooraf gedefinieerde subgroepen op basis van radiologische ernst en type artrose. Patiënten met knieartrose op baseline hadden een verschil in WOMAC pijn van -5.7 (95% BI [-12.6, 1.3]) in het voordeel van glucosaminesulfaat, terwijl patiënten zonder knieartrose een verschil van -0.1 (95% BI [-4.9, 4.7]) hadden. Ook al is dit verschil niet significant, deze exploratieve subgroepanalyse is wel interessant omdat alle positieve effecten van glucosaminesulfaat tot nu toe werden gevonden in patiënten met knieartrose. Of onze bevindingen toeval zijn of dat ze een indicatie kunnen zijn van een groter effect van glucosamine in knieartrose patiënten, kan alleen worden bepaald als dit opnieuw wordt bekeken in een studie die is ontworpen om een mogelijk verschil in effect tussen gewrichten te onderzoeken.
De conclusie van hoofdstuk 4 was dat glucosaminesulfaat niet beter was dan placebo in het verminderen van symptomen en radiologische progressie van subgroepen patiënten met heupartrose.

Of er subgroepen patiënten met artrose zijn die meer profiteren van een therapie werd ook onderzocht in **Hoofdstuk 5**. We hebben een kritische beoordeling van de literatuur gedaan om te beoordelen of de effectiviteit van oefentherapie voor de behandeling van pijn en functiebeperkingen van patiënten met artrose afhangt van de ernst van radiologische artrose of van duur van de ziekte. We hebben in PubMed en de Cochrane library gezocht naar systematische reviews over effectiviteit van oefentherapie. Alle trials uit de geselecteerde reviews werden gescreend

voor de volgende inclusiecriteria: vergelijking tussen oefen- en niet-oefentherapie, documentatie van pijn en functie metingen, documentatie van ernst van radiologische artrose en/of duur van ziekte, data geschikt om 'effect size' uit te rekenen. We konden 11 trials includeren, waarvan er 7 van hoge kwaliteit waren. Effect sizes voor pijn varieerden van 0.03 – 1, en voor functie van 0.04 – 3. Het percentage patiënten met matige en ernstige radiologische artrose varieerde van 21.2% – 100%. Gemiddelde duur van de ziekte varieerde van 2.2 – 12.3 jaar.
Op basis van de data leek er geen verschil te zijn in het effect van oefentherapie in subgroepen gebaseerd op ernst van radiologische artrose en gebaseerd op duur van de ziekte.

Er zijn niet veel gegevens beschikbaar over het beloop van klachten van heupartrose en factoren die geassocieerd worden met verergering van deze klachten. We weten dat artrose klachten op groepsniveau erg langzaam verslechteren, maar wat op individueel niveau gebeurd, als er regelmatig wordt gemeten, is nauwelijks bekend.
In **Hoofdstuk 6** hebben we de data van onze trial gebruikt om het beloop van heupklachten te beschrijven zoals elke 3 maanden gemeten en we hebben geprobeerd om factoren te vinden die geassocieerd zijn met verergering van deze klachten.
We vonden dat de klachten van eerstelijns patiënten met heupartrose stabiel waren op groepsniveau over een periode van 2 jaar. Individuele patiënten data liet echter grote fluctuaties in pijn en functie scores zien over tijd. Na twee jaar bleken dat een pijnlijke heupflexie op baseline en een Kellgren & Lawrence score van ≥ 2 significant geassocieerd waren met verergering van de globale beoordeling van klachten van patiënten. Een hogere leeftijd en een Kellgren & Lawrence score van ≥ 2 waren significant geassocieerd met een verhoogde Visueel Analoge Schaal (VAS) pijnscore, terwijl een hoge VAS op baseline beschermde tegen verergering.

Veel gebruikte radiologische metingen van een artrotisch gewricht relateren slecht met symptomen van patiënten. In **Hoofdstuk 7** beschrijven we een nieuwe aanpak om status van artrose en factoren die geassocieerd worden met progressie van zowel radiologische als symptomatische artrose te beschrijven.
In het onderzoek beschreven in de vorige hoofdstukken werden op baseline en na 2 jaar Dual Energy X-ray Absorbiometry (DXA) scans van de heupregio gemaakt.
Met de DXA scans konden we een statistisch model maken van het uiterlijk (uitgedrukt in vorm gecombineerd met dichtheid) van het proximale femur. Dit model gaf een aantal onafhankelijke beschrijvingen van het uiterlijk, die we hebben gerelateerd aan verschillende maten van status en progressie van radiologische en klinische artrose. Verschillende modes waren significant gerelateerd met ra-

diologisch en klinische artrose. Het was interessant dat de modes die gerelateerd waren met radiologische artrose niet gerelateerd waren met klinische artrose en vice-versa.
Bovendien bleken deze modes voorspellers van zowel status als progressie van klinische artrose, onafhankelijk van gewrichtsspleet versmalling of Kellgren & Lawrence score. Het statistisch modeleren van het uiterlijk bleek een effectieve manier om het totale proximale femur te beschrijven in DXA scans. We hebben laten zien dat subtiele aspecten van vorm en dichtheid van de heup informatie bevatten over klinische status, iets waar normale radiologische metingen slecht aan relateren.

Het doel van **Hoofdstuk 8** was om de medische consumptie van eerstelijns patiënten met heupartrose en de daarmee geassocieerde determinanten en kosten te beschrijven. Patiënten vulden elke 3 maanden gedurende de 2 jaar durende studie een vragenlijst in om hun medische consumptie en mogelijke determinanten vast te leggen.
De directe kosten van medische consumptie werden bepaald aan de hand van zelfgeregistreerde data over consultatie van zorgverleners en medicamenteuze en niet-medicamenteuze behandelingen.
We vonden dat meer dan de helft van de patiënten een huisarts bezocht voor zijn klachten. Een derde van de patiënten werd doorverwezen naar een orthopeed en weer een derde rapporteerde behandeling door een fysiotherapeut. De directe kosten geassocieerd met heupartrose was gemiddeld €638.78 per patiënt per jaar, wat vergelijkbaar was met kosten gevonden voor knieartrose in Europa. Van alle kosten was 20.2% toe te schrijven aan eerstelijns zorg, 6.7% van de kosten werd besteed aan medicatie en 73.1% werd besteed aan tweedelijns zorg. In deze groep van eerstelijns patiënten met heupartrose was 20% van de patiënten verantwoordelijk voor bijna 90% van de totale kosten
Matige tot ernstige pijn, moeite hebben met sokken aantrekken en knieartrose waren geassocieerd met huisartsbezoek voor artrose klachten. Een goede gezondheid verlaagde de kans om een huisarts te bezoeken. Patiënten die hun huisarts vaak hadden bezocht werden vaker doorverwezen naar een orthopeed.

Hoofdstuk 9 beschouwt de belangrijkste bevindingen van dit proefschrift. De tekortkomingen van de studies en de implicaties van de resultaten voor de praktijk en toekomstig onderzoek wordt ook besproken.

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Curriculum vitae

Rianne Rozendaal is op 23 juni 1978 geboren in Rotterdam. Na het behalen van haar VWO diploma aan het Marnix Gymnasium te Rotterdam begon zij in 1997 aan de studie Bewegingswetenschappen aan de Vrije Universiteit in Amsterdam. Tijdens haar afstudeerproject onderzocht zij het effect van een oefenprogramma op de stabiliteit van kinderen met Cerebrale Parese. In januari 2002 studeerde zij af in de richting Gezondheidszorg. Na haar studie werkte zij gedurende een jaar als onderzoeksassistent bij de faculteit Bewegingswetenschappen van de Vrije Universiteit. Daarna begon zij in februari 2003 als aio bij de afdeling Huisartsgeneeskunde van het Erasmus MC te Rotterdam. Zij deed een gerandomiseerd, gecontroleerd onderzoek bij patiënten met heupartrose naar het effect van glucosaminesulfaat (de GOAL studie), waaruit de artikelen in dit proefschrift voortkwamen. Sinds juli 2008 werkt zij bij de afdeling Huisartsgeneeskunde van het Erasmus MC aan de CHECK data, een cohort dat vroege heup- en knieklachten bestudeert.

PhD Portfolio

Courses

NIHES clinical epidemiology, 2003-2005	*70 ECTS*
Good Clinical Practice, 2003	*24 hours*
Biomedical English Writing and Communication, 2004	*40 hours*

Conferences/Presentations

MUSC symposium, 2004	*16 hours*
Workshop Keele, 2005	*16 hours*
Department of Orthopaedics, 2006	*16 hours*
NOV conference, 2007	*16 hours*
CHECK meeting, 2007	*16 hours*
NHG conference, 2008	*16 hours*
BHS meeting, 2008	*16 hours*
Poster NHG, 2005	*16 hours*
Poster NHG, 2006	*16 hours*
Poster NHG, 2008	*16 hours*

International Conferences

Oral presentation at EULAR conference, 2007	*20 hours*
Poster EULAR, 2006	*16 hours*
Poster OARSI, 2007	*16 hours*
Poster OARSI, 2008	*16 hours*

Teaching activities

Supervising medical student, 2008	*80 hours*