Non-traumatic knee complaints in adolescents and young adults in general practice

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Niet-traumatische knieklachten in adolescenten en jong volwassenen in de huisartspraktijk

Proefschrift

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Table of Contents

1

General introduction

HONEUR

HONEUR stands for ‘Huisartsen Onderzoeks Netwerk Erasmus Universiteit Rotterdam’, which translates to ‘General Practitioners Research Network Erasmus University Rotterdam’. This network was founded in 2001 for the purpose of facilitating patient based research into subjects that are relevant to general practice. The following HAGROs (HuisArtsenGROepen, i.e. collaborating GPs) are represented in HONEUR:

Brielle, since October 2001
Capelle aan den IJssel, since Februari 2002
Etten-Leur, since May 2002
Krimpen aan den IJssel, since August 2002
Hillegersberg (Rotterdam), since October 2002

These practices represent a population of around 84,000 patients in the south-west of the Netherlands. The first study to start in HONEUR was the knee cohort.

Background of the HONEUR knee cohort

A recent nationwide study in Dutch general practice states that non-specific knee complaints form the 17th most frequent reason for consulting the general practitioner (GP), with an incidence of 13.7 per 1000 patients per year[1]. Combined with specific knee complaints the incidence is 24.6 per 1000 per year.

The Dutch College of General Practitioners (NHG) is the scientific organization of GPs. The NHG has developed Practice Guidelines for specific complaints or diagnoses reflecting the 'state of the art' in medical science. The NHG also attempts to identify lacking evidence in the field of general practice.
For knee complaints the NHG has developed 3 guidelines. The guideline 'non-traumatic knee complaints in children and adolescents'[2] deals with genua vara and valga, Osgood-Schlatter's disease, jumper's knee and patellofemoral pain syndrome, the most frequent diagnoses in patients under 25 years of age. The guideline 'non-traumatic knee complaints in adults'[3], deals with bursitis prepatelllaris, iliotibial friction syndrome, Baker's

cyste and knee osteoartritis. The guideline 'traumatic knee complaints'[4] deals with distorsions, contusions, patellar luxation and ligament and meniscus lesions.
For all three guidelines research questions have been formulated addressing the lacking evidence. These questions often concern the unknown effectiveness of treatments, for which new clinical trials are needed. Designing clinical trials requires background information about the natural course of complaints and possible prognostic determinants. However, in 2000 no prospective studies of patients with knee complaints presenting in general practice were available in scientific literature. This is why the HONEUR knee cohort was conceived.

The overall aim of the HONEUR knee cohort is to describe the prognosis and to study the prognostic factors of knee complaints. This will provide the GP information for advising their patients. It may also serve as basis for future trials addressing the effectiveness of interventions.
Analogous to the NHG guidelines the HONEUR knee cohort was divided into traumatic and non-traumatic knee complaints, and non-traumatic knee complaints were further divided into different age groups. Since osteoarthritis is the only diagnosis of a progressive nature, we used the age from which osteoarthritis starts to play a role as the cut-off point. This resulted in three subgroups of the cohort:

1. Non-traumatic knee complaints in adolescents and young adults (aged 12 to 35)
2. Non-traumatic knee complaints in adults (aged 36 and over)
3. Traumatic knee complaints.

This thesis first gives an overview of the entire cohort, before focussing on the subgroup of adolescents and young adults with non-traumatic knee complaints.

Non-traumatic knee complaints in adolescents and young adults

The incidence of non-traumatic knee complaints in adolescents and young adults (aged 12 to 35 years) in general practice is estimated at 19 per 1000 per year and the prevalence at 27 per 1000 per year [1]. The guidelines state that the prognosis of these

patients is good[2]. What that statement means in terms of duration or severity of complaints is not specified. The statement is consensus rather than evidence based. With regard to the management of complaints, conservative treatment is advised, in which knee loading and knee loading capacity are adapted to each other.

In our prospective cohort study[5], we aim to describe the course of non-traumatic knee complaints in adolescents and young adults, aged 12 to 35 years, over the course of one year by actively tracking their symptoms and limitations. Our second objective is to determine any prognostic factors for persistent knee complaints. Identification of prognostic factors is important in order to improve the advise the GP may give to the patient, and if any of the prognostic factors are modifiable this may offer potential ways to develop new interventions in order to avoid chronicity of the complaints.
Our third objective is to give insight into the burden of non-traumatic knee complaints in adolescents and young adults compared to other subgroups. In order to do so, validation of the questionnaires used to assess functional disability is necessary, since no knee specific questionnaire has been validated in this population so far. We chose the WOMAC Index[6] because it is widely used to assess disability in osteoarthritis, an important diagnosis in the older subgroup of non-traumatic complaints. For traumatic knee complaints the Lysholm scale is widely used. This questionnaire has also been applied in patients with chondral lesions[7] and patients with patellofemoral pain syndrome[8].

With respect to the effectiveness of treatments we performed two systematic reviews focussing on treatments for patellofemoral pain syndrome. This is the diagnosis with the highest incidence in this subgroup[9].

Overview of the contents of this thesis

Chapter 2 presents the design and methods of the knee cohort study. It also presents the distribution of patients over the subgroups and additional measurements of the cohort and compares participants with non-participants to determine if the cohort is an adequate representation of patients consulting the GP for knee complaints.

Chapter 3 compares the different subgroups of the cohort with respect to patient characteristics, the severity of knee complaints and initial management by the GP.

In chapter 4 we analyse the validity and responsiveness of WOMAC index and Lysholm scale to clinically relevant changes in functional knee status over time in patients aged 12 through 35 in general practice.

Chapter 5 describes the course of knee complaints in adolescents and young adults with non-traumatic knee complaints consulting the GP. Prognostic factors associated with persistence of knee complaints are identified.

Chapter 6 contains a systematic review of available evidence for the effectiveness of exercise therapy for patients with patellofemoral pain syndrome (PFPS). Exercise therapy is the most widely accepted treatment of PFPS. PFPS is the most common diagnosis in adolescents and adults with non-traumatic knee complaints.

Chapter 7 reviews the evidence for the effectiveness of pharmacotherapy for patients with patellofemoral pain syndrome (PFPS). Though not advised in NHG guidelines, prescriptions for pain medication are often given.

Chapter 8 summarises the findings.

Chapter 9 discusses the findings, limitations and implications for clinical practice of this thesis.

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2

Knee disorders in primary care: design and patient selection of the HONEUR knee cohort

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BMC Musculoskeletal Disorders. 2005 Aug 23;6:45.

Abstract

Background

Knee complaints are a frequent reason for consultation in general practice. These patients constitute a specific population compared to secondary care patients. However, information to base treatment decisions on is generally derived from specialistic settings. Our cohort study is aimed at collecting knowledge about prognosis and prognostic factors of knee complaints presented in a primary care setting. This paper describes the methods used for data collection, and discusses potential selectiveness of patient recruitment.

Methods

This is a descriptive prospective cohort study with one-year follow-up. 40 Dutch GPs recruited consecutive patients with incident knee complaints aged 12 years and above from October 2001 to October 2003. Patients were assessed with questionnaires and standardised physical examinations. Additional measurements of subgroups included MRI for recent knee traumas and device assessed function measurements for non-traumatic patients.

After the inclusion period we retrospectively searched the computerized medical files of participating GPs to obtain a sample to determine possible selective recruitment. We assessed differences in proportions of gender, traumatic onset of injury and age groups between participants and non-participants using Odds Ratios (OR) and 95% confidence intervals.

Results

We recruited 1068 patients. In a sample of 310 patients visiting the GP, we detected some selective recruitment, indicating an underrepresentation of patients aged 12 to 35 years (OR 1.70; 1.15-2.77), especially among men (OR 2.16; 1.12-4.18). The underrepresentation of patients with traumatic onset of injury was not statistically significant.

Conclusions

This cohort is unique in its size, setting, and its range of both age and type of knee complaints. We believe the detected selective recruitment is unlikely to introduce significant bias, as the cohort will be divided into subgroups according to age group or traumatic onset of injury for future analyses. However, the underrepresentation of men in the age group of 12 to 35 years of age warrants caution. Based on the available data, we

believe our cohort is an acceptable representation of patients with new knee complaints consulting the GP, and we expect no problems with extrapolation of the results to the general Dutch population.

Background

Knee complaints rank among the most frequent reasons for consulting primary care physicians. A nationwide study into the incidence and prevalence of diseases and complaints in Dutch General Practices revealed that the incidence of unspecified knee complaints in General Practice is 13.7 per 1000 patients per year, ranking 16th in the list of most frequent reasons for visiting the General Practitioner (GP). Specified knee complaints (knee distortion, acute injury to meniscus or ligaments, chronic internal traumatic knee injuries, knee osteoarthritis, and Osgood Schlatter) account for an incidence 11.3 per 1000 on top of that[1].

Nonetheless, clinical research in this area is usually carried out in hospital settings and only covers serious or persistent injuries, usually meeting stringent inclusion criteria. The applicability of results from this research to patients presenting knee complaints in general practice is therefore limited. Open population studies[2,3] offer a broader view of knee complaints, but often target specific age groups and also include patients that do not seek medical care for their complaints. To our knowledge, publication of studies dealing with patients with knee disorders in general practice is limited to cross-sectional registration studies that report incidence and prevalence of diagnostic codes and their corresponding referral rates to physical therapy or specialist care[1]. This type of study is not informative with respect to disease burden, the (natural) course of complaints, treatments strategies or even diagnosis, because the diagnostic codes are often non-specific. As a result, our understanding of knee complaints in primary care is far from complete. But knowledge about the determinants of the clinical course is essential for making management decisions and to inform patients about their prognosis. Furthermore, decisions about management and referral of knee complaints in primary care are to a large extent based on test results from physical examination. Physical signs and symptoms may also play an important part in predicting the course of knee complaints. Nevertheless, the value of physical examination in general practice has never been evaluated.

To fill in the gaps in the information available to GPs, we performed a prospective, observational cohort study including the whole range of incident knee complaints presented to the GP, by adolescents as well as adults. The primary objectives of our cohort study are as follows:

What type of knee complaints are presented to the GP, and what is their severity and impact on daily activities?
What is the one-year prognosis of knee complaints presented to the GP?
What are the factors predicting prognosis?
How are knee complaints managed by GPs?

The wide range of knee complaints included in our cohort study enables us to focus on specific aspects for specific subgroups and on the validity of measurement tools in a primary care setting. Therefore our secondary objectives for specific subgroups are as follows:
What is the predictive value of physical examination and history taking for detecting lesions that can be seen with Magnetic Resonance Imaging (MRI) in patients with acute traumatic knee injuries in General Practice?

1. What is the additive predictive value of MRI over physical examination and history taking for the prognosis of knee complaints in patients with acute traumatic knee injuries in General Practice?
2. What is the validity and responsiveness of disease specific questionnaire assessed disability measurements compared to device assessed disability measurements?

In this paper we will outline the composition of our cohort and define its subgroups. The objectives of our cohort demand that we give an accurate account of the population of patients that visit the GP with knee complaints. As we depended on active cooperation from the GPs for recruitment of patients, we need to ascertain that our cohort represents this population. Therefore objectives for the present paper are twofold:

1. To describe the methods used for data collection
2. To determine whether the recruitment procedures resulted in a patient selection that accurately represents the patients visiting the GP.

Methods

Design

This is a prospective, observational cohort study, with a follow-up period of one year. Data were collected using questionnaires and physical examinations. The researchers did not interfere with usual care with respect to advice, diagnostics or treatment. The study was approved by the ethics committee of the Erasmus Medical Centre Rotterdam.

Inclusion criteria

Patients aged 12 years or above, consulting their GP for a new episode of knee complaints, were invited to participate in the study. New complaints were defined as complaints that were presented to the GP for the first time. Recurrent complaints for which the GP was not consulted within the last 3 months were also considered new complaints. Knee complaints that required urgent medical attention, such as fractures or infections were excluded. Patients with malignancies, neurological disorders or systemic musculoskeletal diseases that affect the outcome measures used in this study (i.e. Parkinson's disease, Rheumatoid Arthritis, Amyotrophic Lateral Sclerosis, etc.), as well as patients that were incapable of understanding the ramifications of participation, were excluded from participation.

Recruitment

40 GPs from 5 municipalities in the southwest region of the Netherlands, connected to the Erasmus Medical Centre GP Research Network HONEUR and representing a total patient population of around 84,000 patients, participated in this prospective cohort study. We started recruitment in October 2001 in 1 municipality and a new municipality was added approximately every 3 months. All GPs recruited up to October 2003.

Patients were alerted to the existence of the study through posters in the waiting room. Participation of patients was voluntary and did not affect the care given to the patient. Patients received no compensation for participation. During consultation, the GP briefly informed the patient of the existence of the study and handed over written information and a baseline questionnaire. Interested patients forwarded their contact details to the researchers. The researchers contacted the patients to further inform patients of the study and to make an appointment for signing informed consent and performing a

comprehensive standardized physical examination of both knees. Informed consent forms for minors (aged 12 through 17) were co-signed by a parent or guardian.
Participating GPs agreed to note the following items in their computerised medical files: relevant anamnestic findings, treatment details, a preliminary prognosis, and a diagnostic code from the International Classification of Primary Care (ICPC)[4], chosen from a list provided by the researchers.

Table 1: Item list for physical examination

inspection[18,19]	palpation[18,19]	specific diagnostic tests
coloration	temperature	sustained flexion test[20]
valgisation/varisation	swelling: balottable patella sign	patellar grinding test[19]
overextension / limited extension	swelling: fluid shift / fluctuation sign	patellar axial pressure test[21]
tibial tuber swelling	pain tibial tuber	patellar apprehension test[21]
atrophy quadriceps	pain joint line	Steinmann II test[22]
flexion contracture hip	pain patellar edges	McMurray test[23]
internal/external rotation femur	pain patellar ligament	Apley's grind/traction tests[24]
internal/external rotation tibia	pain collateral lateral / medial ligaments	valgus / varus test[25]
foot pronation	pain insertion pes anserinus	anterior drawer test[25]
leg length difference	pain insertion iliotibial band	Lachman test[26]
	swelling fossa poplitea / Baker's cyst	pivot shift test[27]
function assessment	hypertrophy synovial plica	posterior drawer test[25]
flexion / extension active / passive	bursa prepatellaris pain / swelling	tibial posterior sag[28]
resisted flexion / extension	bursa infrapatellaris pain / swelling	

Physical examination

Two physiotherapists employed as research assistants (DC and EB) developed the standardized protocol for physical examination under supervision of two physiotherapists with over ten years of experience in both physiotherapy and research (SMAB and HW). Standardisation of the examinations among research assistants was accomplished by a series of training sessions before starting the inclusion of patients. These training sessions were repeated regularly over the course of the inclusion period. In total five physiotherapists (DC, EB, CV, AV and RvB) with clinical experience varying from one to 14 years performed the physical examinations of the patients.

The physical examination was planned as close to the date of consultation of the GP as possible. Irrespective of the type of symptoms presented, a standard range of tests was performed on both knees. The physical examination covered inspection of postural aspects, signs of inflammation, tests of swelling, locating tender areas, patellofemoral joint compression, crepitus, knee extensor and flexor strength, joint laxity, range of motion and meniscus tests (see table 1).
Discussion about diagnosis and/or appropriate management between patient and physiotherapist was discouraged, to avoid influencing the management initiated by the GP. The physical examination was repeated after one year, to enable comparison of perceived recovery with changes in test results.

Self-report questionnaires

Baseline questionnaires were filled in by the patients before the baseline visit, and checked for completeness by the physiotherapist during the baseline visit after physical examination. Any uncertainties on behalf of the patient were discussed at that point and any necessary corrections made accordingly. The three monthly follow-up questionnaires were mailed to the participants, and returned by mail, except for the last questionnaire, which coincided with the follow-up physical examination. The questionnaires included possible prognostic factors as well as outcome measures. Details of questionnaire items are listed in table 2. For possible prognostic factors we enquired after socio-economic status, comorbidity, history of knee complaints, characteristics of the knee complaints, daily activities and coping behaviour. To determine whether the complaints were recurrent, we asked patients if they had experienced similar knee complaints in the past, with complaints disappearing at least several weeks before returning again now. We also asked if they had consulted the GP for that previous episode. Occupations were accredited with a level of knee loading ranging from 1 (e.g. office jobs) to 3 (e.g. construction workers and mail men) and sports activities with a level from 1 (strolling and swimming) to 5 (contact sports). Physical activities from level 2 upward are considered substantial knee loading sports activities. Contact sports and sports involving rapid changes of direction are considered heavy loading activities (levels 4 and 5).
Medical advice and interventions by the GP were recorded at baseline. During follow-up patients also recorded visits to other medical professionals with a short description of interventions.

Table 2. Questionnaire items

	evaluation at (months)	validation / reliability
demographics		
age, gender	0	-
composition of the household	0	-
type of medical insurance, education level	0	-
comorbidity	0	-
knee complaints		
history, duration, recurrence, consultation previous episode, perceived cause of knee complaint, mechanism of traumatic injury	0	-
pain 11 point numeric rating scale	0 3 6 9 12	numeric rating scales have compared favourably to visual analogue scales for children and adults[5-7]
Lysholm knee scale[8]	0 3 6 9 12	developed for ligament ruptures, sensitive and reliable for meniscus tears, (patellar) chondral disorders[11,12]
Knee Society Score[29] - function score (patient, questionnaire) - knee score (observer, physical exam)	0 12	intra- / interobserver reliability poor[30] - function score moderate agreement - knee score poor agreement
WOMAC osteoarthritis index[9,10]	0 3 6 9 12	validated and reliable for osteoarthritis [10]
pain and difficulty with cycling, running, jumping, squatting, kneeling	0 3 6 9 12	
knee loading		
daily activities: employment, volunteer jobs, household chores, study:	0 3 6 9 12	-
physical exercise / sports participation frequency, intensity, duration, association with knee complaints	0 12	-
impact of knee complaint		
hindrance during daily activities sick leave from daily activities	0 3 6 9 12	
health related quality of life		
SF-36[31-33]	0 3 6 9 12	sensitive to change in common orthopaedic diagnoses[14], invalid for adolescents[15]
COOP/WONCA charts[34,35]	0 3 6 9 12	valid for adults[34]
treatment		
advise given by the GP	0	-
medication for knee complaint	0 3 6 9 12	-
medication for comorbidity	0 3 6 9 12	-
visits to health care professionals	3 6 9 12	-
operations	3 6 9 12	-
coping		
Tampa Kinesiofobia Scale, (TKS)[36] catastrophizing	0	

Outcome measures

Patients filled in their experienced recovery after one year on a 7 point Likert scale, ranging from 'fully recovered' to 'worse than ever'. Pain intensity was determined using a numeric rating scale (NRS) ranging from 0 (no pain) to 10 (unbearable pain). Numeric rating scales have compared favourably to visual analogue scales for children[5,6] as well as adults[7], though the number of points on these scales differed. Function assessments on disability level were determined using the Lysholm knee scoring scale (0-100)[8] and the WOMAC Hip and Knee Osteoarthritis Index (0-100)[9,10]. The Lysholm knee scoring scale was developed for ligament injuries, but was validated for use in various other knee disorders as well[11,12]. The questions from the WOMAC Hip and Knee Osteoarthritis Index were adapted to specifically address only the knee complaints.

The SF-36 was chosen for the assessment of health related quality of life because of its responsiveness[13] and its sensitivity to change in common orthopaedic diagnoses[14], though it has been shown to be invalid in adolescents[15]. We therefore also included the COOP/WONCA charts, which have not been validated in adolescents, but can be easily interpreted through illustrations. From the age of 18, patients filled in both SF-36 and COOP/WONCA charts, younger patients only filled in the COOP/WONCA charts.

Definition of subgroups

As different pathologies are expected to show different prognoses, we defined three subgroups. Patients with non-traumatic knee complaints are divided into a group aged 12 to 35 (I) and a group aged 36 years and over (II), because around 35 years of age the predominance of specific diagnoses shifts from patellofemoral pain syndrome[16] to osteoarthritis[17]. The group of patients with traumatic knee complaints (III) includes all patients whose knee complaints were caused by a sudden impact or wrong movement within one year before consulting the GP. All other patients were considered to have non-traumatic complaints, based on the assumption that the immediate effects of traumatic injuries will have worn off after one year.

Additional MRI

Patients aged between 18 and 65 years of age with an onset of trauma up to 5 weeks before consulting the GP were invited to participate in an additional MRI study. Participants were informed that patient and GP would not be informed of the presence or absence of detected lesions to prevent influencing the treatment strategy employed by

the GP. Exceptions to this rule were lesions where urgent intervention was deemed necessary. For this additional study patients signed an additional informed consent form. MRI was performed between 3 to 6 weeks after the initial trauma, to allow swelling to subside while still observing the relatively acute stages of trauma. Following MRI a trained physiotherapist repeated the standardised physical examination. The assessors performing MRI and physical examination were blind to each other's results. The patients themselves recorded pain intensity and Lysholm score. After one year MRI and physical examination were repeated. If participants consulted medical specialists at a later date, the specialists were able to request MRI reports to prevent unnecessary duplication of diagnostic procedures.

Device assessed disability

Adult patients with non-traumatic knee complaints living in three municipalities close to the research facility were invited to participate in the additional device assessed disability measurement using the Dynaport knee scoring system[17]. This system registers accelerations of torso, hip, upper and lower legs during simulations of daily activities like walking stairs, sitting down, or walking with grocery bags or loaded trolleys. Measurements were repeated after 6 months.

Assessment of selective recruitment

To check whether the cohort adequately represents the patients that consulted the GP with a new episode of knee complaints during the inclusion period, the GPs computerized patient records were searched retrospectively for all occurrences of the relevant ICPC codes after the inclusion period had ended. As data collection from medical files is very labour-intensive, the search in each general practice was limited to a randomly assigned 4-month period within the total recruitment period. Within each municipality we made sure the 4-month periods covered all seasons. From all identified patients ICPC-code, diagnosis, age, sex and possible reasons for exclusion were registered anonymously on structured forms. ICPC-code and textual notes were both taken into account to determine whether onset of symptoms was considered traumatic by the GP. From the collected data we determined whether patients were eligible for inclusion in the cohort study. Eligible patients were then dichotomized according to age (12 to 35 years or above), gender, and traumatic onset of knee complaints. Participation rates within these dichotomized subgroups were compared using Odds Ratios (OR) and

95% confidence intervals, indicating their relative chances for inclusion into the study. Within each dichotomised subgroup we again compared the participation rates for the two other patient characteristics.

As the randomly chosen sample period was in itself a potential cause for bias of our analysis, we also compared the proportions of age, gender, and traumatic onset of knee complaints between participants from the sample periods and participants from the rest of the inclusion period. Furthermore, we compared proportions of ICPC codes in participants and non-participants from the sample periods, and in the participants of the sample periods and participants of the rest of the inclusion period, using Chi-square tests. For the statistical analyses we used SPSS for Windows, release 11.0.1.

Study sample

General cohort

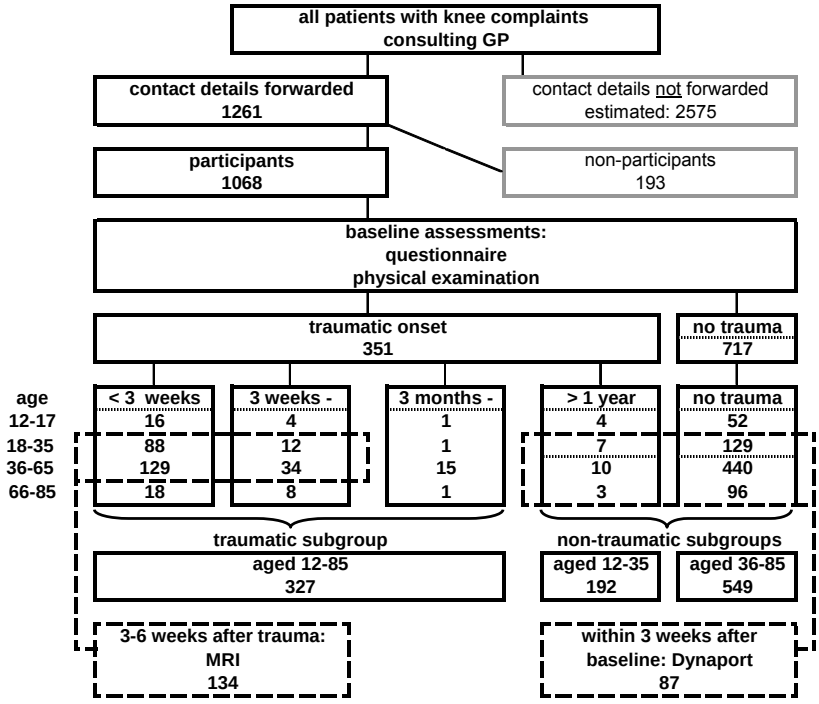
Of the 1261 patients that forwarded their contact details to the researchers, 1068 (85%) signed informed consent. Reasons stated by contacted patients for non-participation are listed in table 3. The majority stated lack of time for participation (37%) or lack of personal gain (24%). The category miscellaneous included family circumstances, other health problems, language problems, and several patients judged themselves too old for participation. Ten patients were excluded: five because they were under 12 years of age, three because their complaints were not new, one because of rheumatoid arthritis and one patient was hospitalized with a bacterial infection of the knee.

Table 3 Reasons for non-participation of patients that forwarded their contact details to the researchers

	N
Lack of time / could get no time off from work / could not make an appointment for examination	72
No personal gain / too much bother	47
No longer any complaints at time of contact and no longer interested	19
Could not be contacted	15
Miscellaneous	30
Non-compliance with inclusion criteria	10

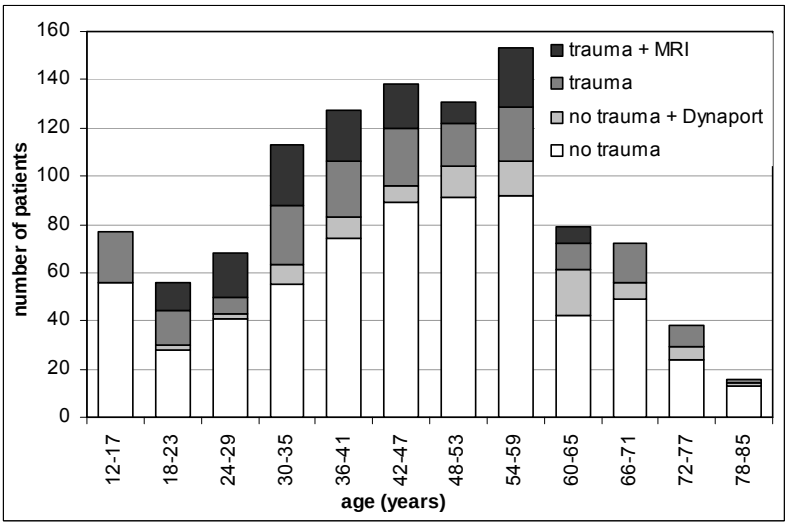
The flow diagram (fig. 1) shows the distribution of participants over different subgroups of the cohort and the additional measurements. 51% of the participants were assigned to the subgroup of non-traumatic knee complaints in patients aged over 35 years of age. 18% were assigned to the group of non-traumatic knee complaints in the age of 12 to 35 years. 31% were assigned to the traumatic knee injury subgroup. Figure 2 shows the age distribution of the entire cohort, identifying subgroups and additional measurements. The percentage of female participants in each subgroup was 50%, 47% and 44% respectively.

Figure 1. Patient recruitment and subgroup assignment



Of 1031 of the 1068 participants both questionnaire and physical examination results are available; 27 (2.5%) underwent a physical examination, but did not return their baseline questionnaire. Ten patients (0.9%) underwent no physical examination due to external circumstances like holidays and intervening commitments, but did return their baseline questionnaire. Data from the computerized medical files of 13 patients were not available.

Figure 2. Age distributions of subgroups



Proportion of traumatic injuries and additional measurements per age category

Additional assessments

Since starting inclusion for the MRI study in April 2002 there were 184 eligible patients, of which 134 patients participated. Reasons for non-participation were (in order of their contributions) unwillingness or inability to find time for these extra measurements, distance to the research facility, and the fact that detected lesions would only be reported to the patient and their GP if urgent intervention was deemed necessary.

Since starting inclusion for the knee function assessments study in August 2002 there were 330 eligible patients, of which 87 patients participated. Reasons for non-participation were unwillingness or inability to attend the extra visits required for these measurements.

Patient selection

The search in the computerized patient records for occurrences of defined ICPC codes during the 4-month sample periods identified 310 eligible patients. 153 (49%) of those forwarded their contact details to the researchers, and 130 (42%) were included in the study and signed informed consent. The actual number of patients from which we received contact details during those same sample periods was 176, of which 150 patients were included in the cohort study (15% declined). When we looked up the

medical files of the 150 participants we found that 20 of them lacked ICPC codes, explaining the 130 participants that were identified during the search. Likewise, a lack of ICPC coding in the medical records explains the discrepancy between the 176 contacted patients and the 153 that were identified in the search. Over the entire inclusion period the medical files of 15% of all participants lacked ICPC-codes.

Comparing the 130 participants and 180 non-participants identified through ICPC codes in the sample periods, we find significant selection with respect to age groups (table 4): we recruited relatively more patients over 35 years of age (OR 1.70; 1.15-2.77). This selective recruitment was more pronounced in the male population (OR 2.16; 1.12-4.18), than the female population (OR 1.22; 0.58-2.55). Overall, participation rates of women were not significantly higher than that of men (OR 1.13; 0.72-1.78). Participation rates of traumatic patients were lower than those of non-traumatic patients, though not significantly (OR 0.60; 0.26-1.43). Figures 3 and 4 show graphical representations of the proportions of included patients for each age group, subdivided for gender and traumatic onset of complaints.

Figure 3. Inclusion rate of eligible patients per age group and gender

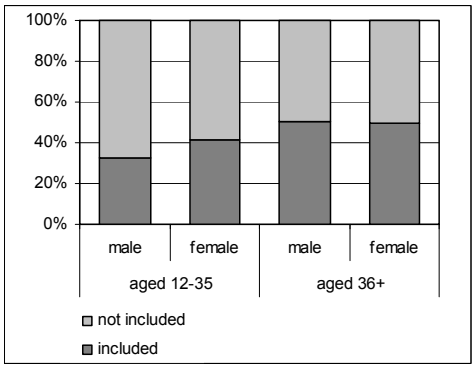
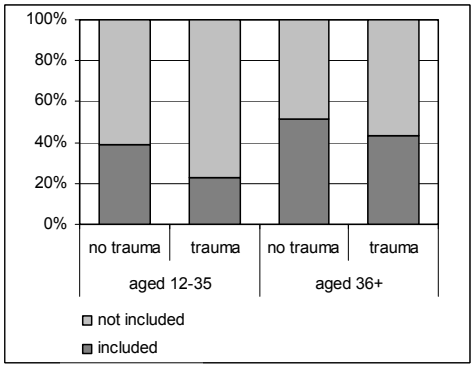


Figure 4. Inclusion rate of eligible patients per age group and traumatic onset



When comparing participants from the sample periods with participants from the entire inclusion period, we found equal proportions of gender and age groups (see table 4). However, the proportions of traumatic injuries differed significantly: 12% of the patients in the sample periods were labelled 'traumatic injury' against 19% in the rest of the inclusion period (OR 0.59; 0.35 - 0.98).

We compared ICPC codes of participants and non-participants from the sample periods with a Chi-square test, pooling the codes L15 and L94.2 to prevent empty cells. We

found a significant difference between the groups (Chi-statistic 11.2, p = 0.025). The differences are caused mainly by codes L78 and L96 for acute traumatic injuries and code L90 for osteoarthritis of the knee, all of which are less frequent in the participants. Comparison of ICPC codes of participants from the sample period with those of the rest of the inclusion period using the Chi-square test reveals no significant difference (Chi-statistic 5.6, p = 0.234).

Table 4 Patient characteristics of participants and non-participants

		all participants in cohort		participants in sample		non-participants in sample		comparison[#] of particpation rates
		N	n (%)	N	n (%)	N	n (%)	OR (95% CI)
gender	(n_{women})	1045	494 (47%)	150	76 (51%)	180	83 (46%)	1.20 (0.78-1.85)
age	($n_{>35\ years}$)	1045	741 (71%)	150	110 (73%)	180	109 (61%)	1.79 (1.12-2.86)*
in men		551	380 (69%)	74	51 (69%)	97	50 (52%)	2.08 (1.11-3.93)*
in women		494	361 (73%)	76	59 (78%)	83	59 (71%)	1.41 (0.69-2.90)
in traumatic		197	134 (68%)	18	13 (73%)	34	17 (50%)	2.60 (0.80-8.98)
in non-traumatic		848	607 (72%)	132	97 (73%)	146	92 (63%)	1.63 (0.98-2.72)
trauma[$]	($n_{positive}$)	1045	197 (19%)	150	18 (12%)	180	34 (19%)	0.59 (0.32-1.09)
in men		551	109 (20%)	74	10 (12%)	97	20 (21%)	0.60 (0.26-1.38)
in women		494	88 (18%)	76	8 (11%)	83	14 (17%)	0.58 (0.23-1.47)
ICPC codes								
L15	unspecified		519 (50%)		84 (56%)		82 (46%)	
L78	acute knee distortion		107 (10%)		8 (5%)		20 (11%)	
L90	osteoarthritis		77 (7%)		10 (7%)		28 (16%)	
L94.2	Osgood-Schlatter		10 (1%)		1 (1%)		0 (0%)	
L96	acute meniscus / ligament ruptures		87 (8%)		13 (9%)		14 (8%)	
L97	chronic internal trauma		245 (23%)		34 (23%)		36 (20%)	

[$] patient described onset of complaints in questionnaire as immediate, due to impact or twisting, maximally 1 year before consultation
[#] comparing participation rates of age groups and traumatic injuries in sample
* p-value < 0.05
N = total number of patients
n = number of patients in a subset

Discussion

We succeeded in starting a unique cohort study of patients with incident knee complaints in general practice. From October 2001 to October 2003 we included 1068 patients. Apart from its size, this cohort is unique in the range of knee complaints we studied: we included all ages from adolescents to the elderly, and we included both traumatic and non-traumatic complaints. Furthermore, this is the first cohort to include a standardised physical examination as well as questionnaires in patients who seek medical care for their knee complaints in general practice. We therefore think our cohort has a high potential for giving insight into the natural course of a range of knee complaints, and will give valuable information to base future effectiveness studies in primary care on. But in order to extrapolate the results of future publications ensuing from this cohort to clinical practice, we need to determine whether selective recruitment could induce bias.

Selective recruitment

Patients below the age of 36 years were significantly less inclined to participate in our cohort study, and this trend was even stronger in the male population. Other comparisons did not produce statistically significant differences. However, the sample size may have been too small to prove that patients with traumatic injuries were underrepresented, again to a greater extent in the younger age group. Comparison of ICPC codes of the non-participants with those of the participants from the sample periods using a Chi-square test reveals a significant difference with respect to types of knee complaints. The difference is mainly caused by lower frequencies of the codes for the acute traumatic injuries L78 and L96, but lower frequencies of osteoarthritis of the knee (L90) also contribute.

The lack of ICPC codes in 15% of the participants indicates that our method for determining patient selection depends on the coding behaviour of the GPs. So is our sample a good representation of the situation during the entire inclusion period? We cannot identify the non-participants without ICPC codes to verify that, so we compared the proportions of gender, age groups and traumatic injuries of cohort and sample (table 4). We found a significantly smaller proportion of participants with traumatic injuries in the sample (12%) than in the cohort (19%) (OR 0.59; 0.35 - 0.98). As we made sure that the 4-month sample periods were distributed over all seasons in each municipality before randomly assigning them to the resident practices, we have ruled out seasonal

fluctuations as a possible cause. But the working definition of 'traumatic injury' might explain something. In the medical records traumatic injuries can be recognised either by their ICPC code, or by the textual notes made by the GP. Some GPs tend to choose non-specific codes (L15) for any knee complaint, in which case recognition of traumatic injuries depends on the amount of detail in the textual notes. However, for further analyses in our cohort we use the patients perceived cause of the knee complaint together with the duration of the complaint to determine whether the complaint was of recent traumatic onset. With this definition we no longer detected any differences (29% in sample versus 31% in cohort). This indicates that the seemingly low participation rates of traumatic patients may have been an artefact caused by variations in the amount of detail in the medical files, rather than reflecting a non-representative sample. Furthermore, comparison of ICPC codes from the sample period with those of the rest of the inclusion period using the Chi-square test revealed no significant difference. One limitation remains: we have no insight into the possible differences in severity of knee complaints of participants and non-participants.

Comparing our results with those reported for the nationwide registration study[1], we found similar distributions of ICPC codes, suggesting that our population does not substantially deviate from patients with knee complaints in other Dutch general practices.

Conclusion

Based on these results, we expect that the effects of selective recruitment will not cause significant bias, as future analyses will be performed separately for subgroups of patients, and adjustments will be made for gender and other possible risk factors and confounders.

We are confident that the present cohort study will provide new insights into the prognosis and management of knee complaints in primary care, and that the results can be extrapolated to all Dutch general practices.

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3

Management, characteristics and impact of knee complaints in General Practice: the HONEUR knee cohort

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Submitted

Abstract

Background

With an incidence of around 25 per 1000 patients per year knee complaints in Dutch general practice are common. Nevertheless, no prospective studies of knee complaints presented in general practice were available that described the three major subgroups of knee complaints outlined in Dutch GP guidelines.

Aim

To determine the relative severity, impact and management by the GP of patients with traumatic and non-traumatic onset of knee complaints and of different age groups of patients consulting the GP for new episodes of knee complaints.

Design and setting

Cohort study in general practice.

Methods

We recruited 1042 patients consulting the GP with new episodes of knee complaints. Non-traumatic knee complaints were divided in two groups according to age, the third group consisted of traumatic injuries. We compared knee characteristics, severity measures and initial management by the GP, extracted from self-administered questionnaires.

Results

Traumatic patients reported shorter duration of complaints before consultation, less recurrences and less bilateral complaints. Pain, WOMAC, and Lysholm scores were worst for the traumatic group. X-ray requests and prescribed pain medication were most frequent in the older non-traumatic subgroup, referral to orthopedic surgeons in the traumatic group, and

advice to exercise knee extensors and referral to physiotherapists in the younger non-traumatic subgroup.

Conclusion

The severity and impact of knee complaints was greatest in the traumatic group, and smallest in the younger non-traumatic age group, although differences between the non-traumatic groups may not be relevant. The amount of interventions by the GP exceeds expectations based on guidelines for GPs.

Introduction

A recent report of incidence and prevalence of diseases in Dutch general practices shows that musculoskeletal complaints are the most frequent reason for consulting the GP. After back pain, knee complaints show the highest incidence figures, with around 25 in 1000 patients consulting the GP for knee complaints each year [1]. Guidelines for Dutch GPs[2-4] assume prognoses for the most common non-traumatic knee complaints other than osteoarthritis are good, and advise a 'wait and see policy' for most knee complaints. However, little is known about disease burden, prognosis and actual management of knee complaints presented in general practice, and the guidelines are based on consensus rather than evidence. A search of the literature for studies of knee complaints in general practice reveals one retrospective study of patients with retropatellar chondropathy[5], a prospective cohort of a heterogeneous group of knee complaints presented to the GP[6], a trial for the effectiveness of patients with hip or knee osteoarthitis[7], and open population studies using general practice records for identification of elderly patients to be screened for knee complaints[8-10]. The focus on elderly patients was prompted by the fact that the disease burden of osteoarthritis and associated health care use is considerable. We do not know the impact of knee complaints in younger patients with non-traumatic knee complaints or patients with traumatic complaints. Therefore we started a cohort of three major groups of knee patients outlined in the practice guidelines for Dutch GPs[2-4]: traumatic injuries, and non-traumatic knee complaints divided in a younger and an older age group. In this paper we compare these subgroups to determine actual differences in disease burden and initial management by the GP, and we evaluate to what extent the guidelines are followed.

Methods

The design and methods of data collection of this cohort are described in detail elsewhere [11]. We summarise the relevant items for this paper below.

Participants

Forty GPs in the southwest of the Netherlands recruited consecutive patients consulting for incident knee complaints from October 2001 up to October 2003, during an average period of 1.5 years per practice. Incident complaints were complaints for which the GP had not been consulted in the past 3 months and which the GP recorded as a new episode. The Medical Ethics Committee of Erasmus Medical Centre approved the study and informed consent was obtained at baseline. Informed consent forms for minors were co-signed by a parent or guardian.

Subgroup definition

As different pathologies are expected to show different prognoses, we defined three subgroups in our cohort. Patients with non-traumatic knee complaints are divided into a group aged 12 to 35 (I) and a group aged 36 years and over (II), as around this age the predominance of specific diagnoses shifts from patellofemoral pain syndrome[12] to osteoarthritis[1]. The group of patients with traumatic knee complaints (III) includes all patients whose knee complaints were caused by a sudden impact or wrong movement within one year before consulting the GP. All other patients were considered to have non-traumatic complaints, based on the assumption that the immediate effects of traumatic injuries will have worn off after one year.

Questionnaires

Patient characteristics

From the baseline questionnaires we extracted patient characteristics such as age, gender, education level, type of health insurance and co-morbidity. Recorded daily activities included daily duties (i.e. paid employment, studies, household chores and volunteer jobs), and participation in exercise. Any exercise except those requiring minimal knee loading forces (e.g. strolls and swimming) were considered activities with substantial loading. Contact sports and sports involving rapid changes of direction are considered heavy loading activities[13].

Characteristics of knee complaints

These include duration of the knee complaint before consulting the GP, the perceived cause of the complaint (traumatic or not), bilateralism and recurrence (i.e. experiencing similar knee complaints in the past, with previous consultation of the GP at least 3 months ago and complaints disappearing at least several weeks before returning presently). Previous consultation of the GP for recurrent episodes was also recorded.

Impact of knee complaints

We asked patients if they were bothered by their knee complaints during daily duties such as paid employment, volunteer jobs, studies and housekeeping. We also asked if they refrained from these duties because of their knee complaints. Employment was also evaluated separately.

Severity

Pain intensity over the last 48 hours was assessed with a numerical rating scale (NRS), ranging from 0 (no pain) to 10 (unbearable pain)[14,15].We evaluated disability due to compromised knee function using the WOMAC hip and knee Osteoarthritis Index, adapted to assess knee complaints alone[16,17] and the Lysholm knee score[13]. All scores ranged from 0 (worst) to 100 (best), and were obtained from self-administered questionnaires. The validity of these questionnaires for each of the subgroups has been described elsewhere[18]. Patients with bilateral complaints filled in pain and function scores for the most affected knee.

Management by GP

Patients checked the option boxes provided in the baseline questionnaire as to which treatment or advice was given by the GP.

Statistical analysis

Frequencies of demographic and knee-specific characteristics as well as management of the complaint are presented as percentages of the number of patients within each subgroup of our cohort, where informative subdivided by gender. No statistical comparisons were performed for demographics, general knee characteristics and management of the complaints. Differences in impact of knee characteristics on daily duties, between traumatic and non-traumatic patients, and between age groups, are expressed as Odds Ratios (OR) with 95% confidence intervals. OR of > 1 indicate a higher frequency of the item in the traumatic group and the younger age group respectively.

To determine whether pain score, Lysholm score and WOMAC score showed differences for traumatic onset or age group, we used an ANOVA model (SAS 8.2 statistical software package, proc GLM) initially containing the factors trauma (yes/no), age (≤35 / >35) and gender and their interaction terms. Gender was included because women generally report more pain for musculoskeletal disorders, for which we wanted to adjust (ref). An interaction between age and trauma indicated different effects of age on severity in traumatic and non-traumatic patients. We then analysed the effect of age on severity measures adjusted for gender in traumatic and non-traumatic patients separately.

Table 1 Patient characteristics

			non-traumatic aged 12-35	**non-traumatic aged 36-85**	**traumatic* aged 12-83**
questionnaire available (n)			184	540	318
age (mean (sd))			24.1 (7.7)	53.8 (11.4)	41.9 (15.6)
gender (% male)			52	50	57
health insurance (% public)			40	47	52
level of education (%)					
low			14	30	19
intermediate			38	37	42
high			48	33	40
paid employment (%)					
male			75	77	85
female			70	50	67
regular physical exercise (%)					
male	none		20	41	28
	light loading		5	4	3
	moderate loading		20	37	20
	heavy loading		55	18	49
female	none		30	39	33
	light loading		4	9	6
	moderate loading		39	39	38
	heavy loading		27	13	23
musculoskeletal comorbidity (%)					
male			48	33	29
female			61	49	25
BMI (%)					
male	<25	healthy	61	28	41
	25-30	overweight	30	53	40
	> 30	obese	9	18	19
female	<25	healthy	70	38	42
	25-30	overweight	24	40	41
	> 30	obese	7	22	17

* traumatic injuries occurring maximally 1 year before consultation

Results

A detailed flow chart for inclusion is published elsewhere [11]. Baseline questionnaire data of 1042 patients were available, but the number of patients per analysed item may vary because of varying response rates. The traumatic subgroup comprised 31% of our total cohort. The non-traumatic group aged 36 to 85 makes up 50% of the cohort, and the group aged 12 to 35 makes up 19%. Gender proportions are not significantly different among the groups.

Patient characteristics

Patient characteristics per subgroup are stated in table 1. Subgroups show comparable gender ratios. Co-morbidity of the musculoskeletal system is more frequently seen in women in both non-traumatic subgroups. Younger patients with non-traumatic complaints have the highest co-morbidity rate. Heavy loading sports activities are more frequent in the male population, especially in the younger age group of the non-traumatic patients.

Table 2 Characteristics of knee complaints

	non-traumatic aged 12-35	**non-traumatic aged 36-85**	**traumatic* aged 12-83**
questionnaire available (n)	184	540	318
bilateral knee ocomplaints (%)	45	32	15
recurrent knee complaint (%)			
first time consulting GP	23	19	9
consulted GP before	29	24	18
duration before consulting GP (%)			
<1 week	13	18	40
1-3 weeks	25	25	37
3 weeks - 3 months	29	29	18
3 months - 1 year	19	16	6
>1year	15	13	0
did your knee complaint			
make you refrain from: (% 'yes')[$]			
any daily duties[#]	19	16	36
employment alone	16	12	35
bother you during (% 'yes')[$]			
any daily duties	57	64	70
employment alone	51	50	64

* traumatic injuries occurring maximally 1 year before consultation
[$] ratio of the number of participants reporting bother or sick leave to the number of participants that report performing these activities
[#] daily duties include employment, volunteer work, studies and housekeeping

Characteristics of knee complaints

The characteristics of knee complaints are stated in table 2. 77% in the traumatic subgroup and 42% in the non-traumatic subgroup consult the GP within 3 weeks of the onset of knee complaints. Bilateral knee complaints are more common for non-traumatic knee complaints (42% versus 15% in traumatic patients), and even more so in the younger age group (45%). Patients with non-traumatic complaints indicate having had previous episodes of similar knee complaints more often (45%) than patients with traumatic injuries (27%). 25% of the patients with non-traumatic complaints and 18% of the traumatic group visited the GP in previous similar episodes. The duration of knee complaints before consulting the physician is considerably shorter for traumatic patients.

Impact

Patients with traumatic complaints significantly more often refrain from daily duties (OR 2.80; 2.07-3.79) and employment specifically (OR 3.65; 2.50-5.31). The differences between traumatic and non-traumatic patients are less pronounced for bother caused by the knee complaints ($OR_{daily\ duties}$ 1.74; 1.26-2.38 and $OR_{employment}$ 1.41; 1.06-1.87).

Table 3. Mean knee severity measures and gender adjusted mean differences between age groups of patients with non-traumatic knee complaints

	Non-traumatic aged 12-35 years			Non-traumatic aged 36 and over			difference 12-35 years - 36 and over		
	n	mean	95% CI	n	mean	95% CI	mean	95% CI	P-value
pain intensity	185	4.00	(3.70;4.30)	540	4.32	(4.14;4.50)	-0.32	(-0.67;0.03)	0.089
WOMAC	184	79.4	(76.7;82.1)	540	71.5	(69.9;73..1)	7.86	(4.73;11.0)	<0.001
Lysholm	185	73.3	(71.0;75.6)	540	68.6	(67.3;69.9)	4.66	(2.03;7.30)	<0.001

Table 4. Mean knee severity measures and gender adjusted mean differences between traumatic and non-traumatic subgroups

	traumatic group			non-traumatic group			difference traumatic - non-traumatic			
	n	mean	95% CI	n	mean	95% CI	mean	95% CI	P-value	P-value*
pain intensity	318	4.51	(4.27;4.75)	725	4.24	(4.08;4.40)	0.27	(-0.02;0.55)	0.054	0.007
WOMAC	316	66.7	(64.5;69.0)	724	73.5	(72.0;75.0)	-6.75	(-9.44;-4.05)	<0.001	<0.001
Lysholm	318	67.1	(65.3;68.9)	725	69.8	(68.6;71.0)	-2.69	(-4.87;-0.52)	0.008	<0.001

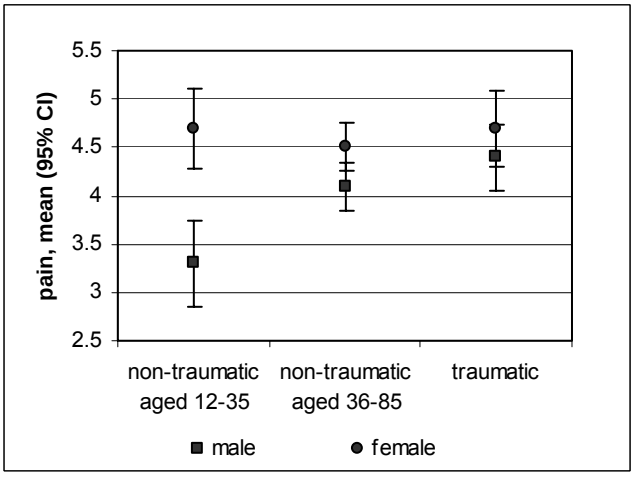
* age adjusted

Severity

Outcome measures assessing the severity of knee complaints are summarised in table 3 and 4. Women scored consistently worse on all severity measures, and therefore we

adjusted comparisons of the subgroups for gender. We found significantly worse Lysholm and WOMAC scores in the older non-traumatic subgroup compared to the younger one. For pain we found no significant difference, but we did find an interaction between age and gender, with male patients in the younger age group showing significantly lower pain scores (figure 1). The comparison of traumatic and non-traumatic complaints was adjusted for age groups because of the observed differences between the age groups in the non-traumatic subgroups. The traumatic subgroup showed consistently worse scores for all severity measures.

Figure 1. Gender differences in pain intensity per subgroup



Management by GP

The management of knee complaints is summarised in table 5. Referrals for diagnostic imaging are by far the most frequent in the older non-traumatic subgroup (21%), followed by the traumatic group (14%) and the younger non-traumatic group (4.4%). The majority (95%) of all imaging requests are for X-rays. Patients with non-traumatic knee complaints aged 36-85 are least often advised to give the knee some rest or to wait and see how the complaints will develop. This advice was more often given in patients with short duration of knee complaints. The proportion of patients advised to exercise knee extensors is greater in the younger non-traumatic subgroup, as is the proportion of referrals to physical therapy. The proportion of referrals to orthopaedic surgeons is greater in the traumatic subgroup.

30% of all patients report medication use for their knee complaints, 80% of which consists of pain medication. 86% of all taken pain medication is prescribed by the GP. Other medication includes muscle relaxants (prescribed), glucosamin and gels intended to improve blood circulation (self medication). Medication use (prescribed or self medication or both) in the younger non-traumatic subgroup was approximately half that of the other subgroups.

The GP advised 20% of all patients with a BMI > 25 to lose weight. The advice to exercise was slightly less frequently given than referrals to physical therapists. Both were most often given to the younger non-traumatic age group.

Table 5. Management of knee complaints

	non-traumatic aged 12-35 % (N=182)	**non-traumatic aged 36-85** % (N=523)	**traumatic aged 12-83** % (N=312)
Management / advice from GP			
X-ray / echo / MRI	4.4	21	14
wait and see	28	18	31
rest	26	15	42
avoid knee loading activities	34	36	47
reevaluation by GP at later date	3.3	4.7	11
lose weight BMI < 25	0.0	1.8	3.3
BMI 25-30	2.0	2.8	4.9
BMI > 30	23	20	10
exercise (no therapist)	26	20	21
referral to physical therapist	32	26	26
referral to orthopedic surgeon	11	11	15
compresses	9.3	8.0	18
intra-articular injection	0	0.6	1.0
prescribed medication	14	29	25
NSAID	11	22	18
paracetamol	0.5	1.7	1.0
other medication / unknown	2.7	5.1	4.8
Patient initiative			
Self medication	2.2	5.6	5.1
NSAID	0.5	3.8	1.9
paracetamol	1.1	1.1	2.2
other medication	0.5	0.8	1.0

Discussion

Knee characteristics, severity and impact

We found significant differences between the three major groups of knee complaints with respect to characteristics and severity of the complaints. The scores of the severity measures as well as the impact on daily activities were greatest in patients with traumatic injuries. Comparison of the age groups of the non-traumatic knee complaints revealed that the older group showed significantly worse pain and functional disability scores. The proportion of patients reporting that their knee complaints bother them during daily duties is also slightly larger in the older subgroup. However, the proportion of patients refraining from these daily duties because of the knee complaints is slightly larger in the younger age group. Therefore we suggest that although the difference between the age groups are significant, the relevance of these differences in terms of impact on daily activities may be limited. Age differences were only detected in the non-traumatic group, which supports the idea that the subgroups of our cohort reflect different groups of knee complaints. This may also play a role in the way patients complete their questionnaires and may be a contributing factor to the significant differences we find.
The function assessments are for a considerable part dependent on pain scores. However, the larger gender difference in the pain scores of the younger non-traumatic group (figure 1) is not reflected in the function scores. This suggests that the interaction between age and pain scores is not clinically relevant. The finding that female patients scored consistently worse on all severity measures is in line with reports in literature[19].

The proportion of bilateral complaints (15%) in the traumatic group seems rather high, although they are considerably greater in the non-traumatic groups. We cannot deduct from our data if both knee complaints are of traumatic origin, or if compensation for one knee causes complaints in the other. Another surprise was the high number of recurrences in the traumatic group (27%). A cross-check did not suggest any relation between participation in high risk sports activities (heavy loading, pivoting, contact sports) and recurrences.

Management of knee complaints

With respect to diagnostic imaging techniques, the practice guidelines developed by the Dutch College of General Practitioners[2-4] only recommend X-rays when suspecting

fractures, osteomyelitis or tumours. It is not recommended for determining the extent of osteoarthritis (OA) because of the poor correlation between radiological signs and symptoms. However, the number of X-rays requested by the GP is rather high, especially in the non-traumatic subgroups. A British study[20] showed that the decision to X-ray older patients with knee symptoms and subsequent referral rates to secondary care are not influenced by clinical features. Dutch practitioners may follow the same strategy, but we do not have data to verify this hypothesis.

Exercising the musculature around the knee, and especially the quadriceps is recommended for nearly all knee complaints[2-4], though for traumatic injuries and Osgood-Schlatter disease only after a period of rest. In patellofemoral pain syndrome and OA exercising can start immediately, though it is recommended to avoid pain-provoking activities. Physical therapy is only recommended for patients with OA that have insufficient effect when exercising by themselves, and patients with traumatic injuries with high demands of their knees. Frequencies of rest, avoiding pain provoking activities and exercise reflect good compliance with these guidelines. However, the highest frequency of referral to physical therapy is observed in the younger non-traumatic patients, in spite of the guidelines. The proportion of younger non-traumatic patients that is referred to orthopaedic surgeons is also rather high. The lower frequency of prescribed pain medication in the younger subgroup of non-traumatic patients is in concordance with the guidelines: pain medication would interfere with the advice to adjust activities to pain levels. The more frequent prescription of pain medication in the older non-traumatic group and the traumatic patients is in accordance with the guidelines, although the guidelines recommend paracetamol as a first choice, and prescriptions are mainly for NSAIDs.

Strengths and limitations

This is the first study to compare the management and impact of different subgroups of knee complaints in general practice. This study provides insight in the extent to which GPs adhere to the guidelines. In a previous publication [11] our cohort was shown to be an acceptable representation of the patients visiting the GP with incident knee complaints, though patients in the age of 12 to 35 were underrepresented, especially male patients of this age group. It is possible that the lower pain scores we found for male patients in the non-traumatic subgroup was influenced by that.

Conclusion

As expected, the severity and impact on daily activities of patients with traumatic knee complaints at first consultation of the GP is greater than that of non-traumatic knee complaints. The severity of knee complaints seems higher in the older non-traumatic group than the younger one, but their impact on daily activities seems comparable.
The proportion of younger non-traumatic patients referred to physical therapy or orthopaedic surgeon is rather high, and not in line with GP guidelines. The proportion of older non-traumatic patients referred for X-rays is high, considering the GP guidelines advise against it.

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4

Lysholm scale and WOMAC Index are valid and responsive in adolescents and young adults with knee complaints in general practice

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Submitted

Abstract

Objective

To determine the construct validity and responsiveness of the Lysholm knee scoring scale and the WOMAC osteoarthritis index in adolescents and young adults with knee complaints in general practice.

Study design and setting

In the framework of a prospective cohort study with one year follow-up we included 314 patients aged 12 through 35 consulting the general practitioner for incident knee complaints. Subgroup analyses of traumatic and non-traumatic knee complaints were performed.

Results

Construct validity was adequate for both the Lysholm scale and the WOMAC index in both subgroups. Effect size and standardized response mean were moderate in the non-traumatic group (Lysholm 0.76 and 0.73, WOMAC 0.65 and 0.74) and large in the traumatic group (Lysholm 1.15 and 1.14, WOMAC 1.14 and 1.16) as well as the total population (Lysholm 0.92 and 0.86, WOMAC 0.83 and 0.84). Guyatt's responsiveness statistic was high for both Lysholm and WOMAC global scores in both total population and subpopulations (ranging from 0.81 to 1.31), with lowest values for the traumatic group.

Conclusion

Though neither of the scales was specifically developed for use in adolescents and young adults in general practice, both scales show adequate content and construct validity and good responsiveness in this population.

Introduction

Within the frame-work of a descriptive prospective cohort of knee complaints in general practice [1] we needed measures of knee function that could be self-administered by the patients. No questionnaires have been specifically developed for the wide variety of knee complaints encountered in general practice. We therefore chose two questionnaires that together largely covered the symptoms and problems we expected to encounter in a primary care population: the Lysholm knee scoring scale[2] and the WOMAC hip and knee osteoarthritis index[3,4]. Both questionnaires are frequently used internationally and were validated to some extent in various study populations.

The Lysholm score was developed to determine the functional status of patients with anterior cruciate ligament injuries of the knee. Validation studies in orthopedic clinics have shown that the questionnaire can also be used for evaluation of patients with patellofemoral pain syndrome, patellar tendinitis, meniscal injuries and various other chondral lesions of both traumatic and degenerative nature[5-8]. In fact, it was found to be more responsive for patellofemoral pain syndrome and meniscal tears than for anterior cruciate ligament lesions[5]. The WOMAC osteoarthritis index was developed for patients with hip or knee osteoarthritis. Validation studies in patients with osteoarthritis or rheumatoid arthritis have been summarised by McConnell[9]. Since the WOMAC index focuses on daily activities, it may also be applicable in patient groups with other knee complaints.

In this paper we aim to determine the content validity, construct validity and responsiveness of the Lysholm knee scoring scale and the WOMAC osteoarthritis index in patients aged 12 through 35 consulting the general practitioner (GP) for knee complaints. Content validity implies that all relevant aspects are represented. All relevant aspects can either be interpreted as covering every aspect, or as representing all items affecting the overall outcome. Omission of items may still result in an acceptable assessment of knee complaints. Convergent construct validity exists when the measure to be validated performs as expected when compared to other measures. Responsiveness is established when an instrument is able to detect minimal clinically important differences, a requirement for measuring change within persons [1]. This also implies that no floor or ceiling effects are present to prevent detection of further deterioration or improvement. We will determine these properties separately for knee complaints of traumatic and non-traumatic onset.

Methods

Participants

The HONEUR knee cohort consists of patients consulting the GP for new episodes of knee complaints. This cohort study was approved by the Erasmus MC ethics committee and all participants signed informed consent. Recruitment procedures are described elsewhere [1]. All patients aged 12 through 35 are included in the present study.

Data collection

At baseline and 12 months follow-up patients filled in the Lysholm knee scoring scale and the WOMAC osteoarthritis index. Lysholm scores can range from 0 (worst score) to 100 (best score). We used the Dutch Likert version of the WOMAC osteoarthritis index[4], with answer categories none, mild, moderate, severe and extreme. We calculated standardized total scores and subscores for pain and function, all potentially ranging from 0 (worst score) to 100 (best score). Pain was measured on a numeric rating scale (NRS) ranging from 0 (no pain) to 10 (unbearable pain) over the last 48 hours. Patellofemoral pain syndrome, Osgood Schlater and jumper's knee are the most common diagnoses in adolescents and young adults with non-traumatic knee complaints[10]. Both Lysholm scale and WOMAC index do not include questions specifically aimed at the symptoms associated with these diagnoses. Therefore we added questions to our questionnaire about pain and difficulty when walking stairs, prolonged sitting with flexed knees, running, jumping, cycling, kneeling and squatting analogous to the Likert format used in the WOMAC questionnaire. We calculated the sum of these items to represent a patellofemoral pain syndrome score. Furthermore, we asked patients at each time point whether their knee complaints bothered them during daily activities (employment, school, study, household chores), and whether they refrained from those duties due to their knee complaints. We also determined the patient's participation in sports activities, the extent to which this taxes the knee and whether patients adjusted their sports activities because of the knee complaints. At one year follow up we asked how patients rated recovery from their knee complaints on a 7 point Likert scale (1 = total recovery, 2 = major improvement, 3 = minor improvement, 4 = no change, 5 = minor deterioration, 6 = major deterioration, 7 = worse than ever). We tried to complete missing items by contacting the participants. If we failed to contact the

patient within one month after receiving the questionnaire, the question remained unanswered.

Content validity

The Lysholm scale[2] evaluates functional disability of the knee using the items limp (5 points), use of a support (5 points), locking (15 points), knee stability (25 points), pain (25 points), swelling (10 points), stair climbing (10 points), and squatting (5 points). A summary score of 100 points represents excellent knee function. The WOMAC index [11] consists of three domains: pain (5 items), stiffness (2 items) and function (17 items). The patient's difficulty with a wide variety of specific activities are queried to assess knee function. Locking and instability as well as sports activities are not accounted for. In our population patients often report symptoms consistent with patellofemoral pain or jumper's knee. These symptoms include pain when walking stairs, sitting with flexed knees for prolonged periods of time, squatting, running, jumping, cycling or kneeling. Though both Lysholm scale and WOMAC index include walking stairs, and the Lysholm scale includes squatting, other symptoms are not covered specifically by either questionnaire. However, these symptoms may be correlated to other symptoms that are represented. This way, the Lysholm scale and WOMAC index may still be able to distinguish between patients with less or more of these symptoms. This distinguishing ability reflects on the construct validity and will therefore be tested in one of the hypotheses. To that end we determined if patients reported moderate to severe pain on at least 4 of the seven symptoms.

Construct validity

To determine the construct validity we tested 7 hypotheses. To demonstrate satisfactory construct validity at least 75% (6) of these hypotheses should be confirmed. The hypotheses 1 and 4 to 7 cover aspects of cross-sectional discriminative ability, hypotheses 2 and 3 represent longitudinal convergence. For Pearson's correlation coefficients the following interpretation is suggested: 0.1-0.3 is small, 0.3-0.5 is moderate and >0.5 is large[12]. Because pain is related to the function of the knee, but is not equal to it, a moderate correlation is expected. The same holds for physical fitness. Recovery is expected to show a closer relation, and therefore it should be highly correlated. The following hypotheses were tested.

1. Baseline pain and instrument scores should be moderately correlated (Pearson's r > 0.3)
2. Changes in pain and instrument scores should be moderately correlated (Pearson's r > 0.3)
3. The correlation between recovery scores and change scores on the instruments adjusted for baseline scores should be high (Pearson's r > 0.5)
4. Patients with good baseline COOP/WONCA physical fitness scores should have better instrument scores than patients with poor physical fitness scores (t-test, $p<0.05$)
5. Patients refraining from daily duties because of their knee complaints (employment, domestic work, school) should show lower scores than patients that don't (t-test, $p<0.05$)
6. Patients bothered by their knee complaints during daily duties (employment, domestic work, school) should show lower scores than patients that are not (t-test, $p<0.05$)
7. Patients reporting moderate to severe pain with at least 4 out of 7 activities (walking stairs, prolonged sitting with flexed knees, running, jumping, squatting, kneeling and cycling) should show lower scores (t-test, $p<0.05$).

Because for Lysholm scale and WOMAC index a high score represents good function, but for pain, COOP/WONCA and recovery scores low scores represent better results, we used 100 - the instrument score for the calculation of correlations. Because the magnitude of possible change scores depends on the magnitude of the baseline scores, we used a two way ANOVA to adjust the correlation coefficient for baseline scores in hypothesis 3. For hypothesis 4 the COOP/WONCA physical fitness score was dichotomized, combining light and very light exercise (i.e. being able to walk at a slow or medium pace) and moderate to very heavy exercise (i.e. being able to walk at a fast pace to running at a fast pace for at least two minutes).

Responsiveness

The effect size (ES) is calculated as the ratio of mean change scores over one year to the standard deviation of the baseline scores[13]. The standardized response mean (SRM) is calculated as the ratio of mean change scores over one year to the standard

Table 1. Population characteristics at baseline and follow-up

		non-traumatic		traumatic		combined	
		baseline	1 year	baseline	1 year	baseline	1 year
		n=184	n=137	n=117	n=91	n=301	n=228
age	mean (sd)	24.0 (7.8)	24.1 (7.7)	25.6 (7.0)	25.4 (7.2)	24.6 (7.5)	24.6 (7.6)
male gender	n (%)	95 (52)	69 (50)	72 (62)	54 (59)	167 (57)	123 (54)
ICPC code*	n (%)	baseline	1 year	baseline	1 year	baseline	1 year
L15	unspecified	96 (52)	72 (53)	51 (44)	39 (43)	147 (49)	111 (49)
L78	distortion	6 (3)	3 (2)	26 (22)	20 (22)	32 (11)	23 (20)
L90	osteoarthritis	2 (1)	2 (1)	3 (2)	3 (3)	5 (2)	5 (3)
L94.2	Osgood-Schlatter	8 (4)	7 (5)	1 (1)	1 (1)	9 (3)	8 (3)
L96	acute trauma	9 (5)	6 (4)	18 (15)	15 (16)	27 (9)	21 (8)
L97	chronic internal derangement (retropatellar)	63 (34)	47 (34)	18 (15)	13 (14)	81 (27)	60 (26)
Lysholm	mean (sd)	73.5 (14.4)	83.9 (16.4)	65.6 (18.4)	89.1 (12.5)	70.4 (16.5)	85.9 (15.2)
WOMAC	mean (sd)	79.7 (17.1)	91.4 (13.1)	66.6 (24.8)	95.5 (8.9)	74.6 (21.3)	93.0 (11.8)
pain	mean (sd)	75.4 (18.2)	89.8 (14.3)	67.5 (22.2)	95.3 (9.7)	72.3 (20.2)	92.0 (13.0)
stiffness	mean (sd)	79.0 (23.0)	89.0 (17.7)	63.4 (29.1)	92.1 (16.0)	73.0 (26.6)	90.2 (17.1)
function	mean (sd)	81.0 (18.2)	92.1 (13.3)	66.7 (27.0)	96.0 (8.7)	75.5 (23.1)	93.6 (11.8)

*ICPC = International Classification of Primary Care[16]

deviation of those change scores[12]. Guyatt's responsiveness statistic is calculated as $\Delta_X / \sqrt{2 * MSE_X}$, in which Δ_X denotes the minimal clinically important change, and MSE_x denotes the mean squared error of the instrument scores obtained from a repeated measurements analysis of variance of stable patients[14]. Because this is a descriptive study with one group and only two measurement times, $\sqrt{2 * MSE_X}$ can be substituted with the standard deviation of the change scores of stable patients[15]. The minimal clinically important change is estimated by the average change scores among patients reporting major improvement (recovery score 2) of their knee complaints minus the average change scores among those patients reporting minor or no change (recovery scores 3, 4 and 5). Although Guyatt's responsiveness statistic is expected to be higher than ES and SRM, values of >0.2 are regarded as low, >0.5 as moderate, and >0.8 as high for all three responsiveness statistics[15].

Ceiling and floor effects

Ceiling or floor effects occur when large amounts of patients have a baseline score that leaves no room for improvement or deterioration, i.e. maximum or minimum scores. Floor and ceiling effects of < 30% were considered acceptable[6,16].

Results

Participants

Our cohort study included 314 first-consulters aged 12 through 35 with knee complaints in general practice [1]. Baseline questionnaire data were available for 184 patients with non-traumatic knee complaints and for 117 patients with traumatic knee complaints. These patients were used in the hypotheses for construct validity. Their characteristics are listed in table 1. The mean age of the participants was 24.6 ± 7.5 years. The proportion of male participants was slightly higher in the traumatic group (62% against 52% in the non-traumatic group). International Classification of Primary Care codes from the GP[17] files show a predominance of unspecified knee complaints (52%) and chronic internal derangement (i.e. mainly retropatellar chondropathy, 34%) in the non-traumatic group. Predominant codes in the traumatic group are unspecified complaints (44%) and

Table 2 Construccct and content validity

Hypothesis		Non-traumatic n	Non-traumatic Pearson's r	Traumatic n	Traumatic Pearson's r	Combined n	Combined Pearson's r
1. Baseline pain and instrument scores should be moderately correlated (Pearson's r > 0.3)	Lysholm	184	0.44¥	117	0.5¥	301	0.48¥
	WOMAC	183	0.61¥	116	0.54¥	299	0.58¥
2. Changes in pain and instrument scores should be moderately correlated (Pearson's r > 0.3)	Lysholm	137	0.59¥	91	0.52¥	228	0.59¥
	WOMAC	136	0.58¥	91	0.56¥	227	0.59¥
3. The correlation between recovery scores and change scores on the instruments adjusted for baseline scores should be high	Lysholm	136	0.73¥	88	0.89¥	224	0.82¥
	WOMAC	135	0.65¥	88	0.95¥	223	0.91¥
		n/N	**mean difference**	**n/N**	**mean difference**	**n/N**	**mean difference**
4. Patients with good baseline COOP/WONCA physical fitness scores should have better instrument scores than patients with poor physical fitness scores (t-test, p<0.05)	Lysholm	183	11.7**	117	8.4*	300	11.6**
	WOMAC	182	16.2**	116	10.5*	298	15.9**
5. Patients refraining from daily duties because of their knee complaints (employment, domestic work, school) should show lower scores than patients that don't (t-test, p<0.05)	Lysholm	35/183	4.8	46/116	11.0**	81/299	9.4**
	WOMAC	35/182	12.6**	46/116	23.6**	81/298	20.4**
6. Patients bothered by their knee complaints during daily duties (employment, domestic work, school) should show lower scores than patients that are not (t-test, p<0.05)	Lysholm	106/184	12.1**	82/116	16.6**	188/300	14.4**
	WOMAC	105/183	13.6**	82/116	28.5**	187/299	20.2**
7. Patients reporting moderate to severe pain with at least 4 out of 7 activities (walking stairs, prolonged sitting with flexed knees, running, jumping, squatting, kneeling and cycling) should show lower	Lysholm	87/184	19.0**	77/116	16.8**	164/300	20.7**
	WOMAC	87/183	23.4**	77/116	32.6**	164/299	28.2**

¥ hypothesis confirmed *p-value < 0.05 ** p-value < 0.01

distortion (22%). Patients reporting an instantaneous onset of complaints after impact or a wrong movement within one year before consulting the GP were assigned to the traumatic group, disregarding the ICPC codes.

For responsiveness analyses we needed baseline scores, 1 year follow-up scores as well as perceived recovery scores, which were available for 137 non-traumatic patients and 91 traumatic patients. Characteristics of these patients are also provided in table 1.

Construct and content validity

The results of hypotheses testing are stated in table 2. All hypotheses were confirmed for both subgroups and both instruments, with one exception. Patients refraining from daily duties because of their knee complaints did not show significantly lower Lysholm scores in the non-traumatic group (p=0.11). For both traumatic and non-traumatic subgroups as well as the total population more than 75% of the hypotheses were confirmed, indicating that construct validity was adequate for both Lysholm and WOMAC index.

Responsiveness

Table 3 lists change scores and responsiveness statistics.

Lysholm

The Lysholm scale is moderately responsive for non-traumatic patients when overall change scores are considered (ES = 0.76, SRM = 0.73). Nevertheless, Guyatt's response statistic is high (1.11), indicating that the ability to detect actual change is strong. Overall change scores in the traumatic group are larger, which is reflected in the higher overall responsiveness (ES = 1.15, SRM = 1.14). Though also high, Guyatt's responsiveness statistic is lower (0.94) due to the larger variability of scores in stable traumatic patients. In the total population all responsiveness statistics are high (ES = 0.92, SRM = 0.86, Guyatt = 1.31).

WOMAC

The WOMAC index also shows moderate overall responsiveness for non-traumatic patients (ES = 0.65, SRM = 0.74). Again, the ability to detect actual change is strong (Guyatt = 1.04). In traumatic patients overall responsiveness is high (ES = 1.13, SRM = 1.16), as well as the ability to detect change (Guyatt = 0.81). In the total population all responsiveness statistics are high (ES = 0.83, SRM = 0.84, Guyatt = 1.27).

In the non-traumatic subgroup the ES and SRM are low for stiffness and moderate for pain and function WOMAC subscores. Guyatt's statistic is moderate for stiffness and

high for pain and function. In the traumatic subgroup ES and SRM is high for all subscores, but Guyatt's statistic is low for pain, moderate for stiffness, and high for function. In the total population ES and SRM are moderate for pain and stiffness, and high for function, whereas Guyatt's statistic is high for all subscores.

Table 3. Change scores and responsiveness

	$mean_{change}$ overall (sd)	$mean_{change}$ stable (sd)	$mean_{change}$ major improvement (sd)	$mean_{change}$ major improvement + total recovery (sd)	mcid	Guyatt	ES	SRM
	$n_{non-traumatic}$ 137 $n_{traumatic}$ 91	$n_{non-traumatic}$ 64 $n_{traumatic}$ 13	$n_{non-traumatic}$ 38 $n_{traumatic}$ 40	$n_{non-traumatic}$ 69 $n_{traumatic}$ 75				
Lysholm								
non-traumatic	10.6 (14.5)	3.4 (11.7)	16.4 (11.8)	18.2 (12.9)	13.0	1.11	0.76	0.73
traumatic	22.6 (19.9)	6.9 (21.8)	27.4 (20.7)	25.3 (18.4)	20.5	0.94	1.15	1.14
combined	15.4 (17.8)	4.0 (13.8)	22.0 (17.7)	21.9 (16.3)	18.0	1.31	0.92	0.86
WOMAC								
non-traumatic	10.5 (14.2)	5.4 (12.5)	18.3 (15.9)	15.6 (14.1)	12.9	1.04	0.65	0.74
traumatic	28.5 (4.6)	15.0 (22.8)	33.6 (25.5)	30.9 (24.3)	18.6	0.81	1.13	1.16
combined	17.6 (20.9)	7.1 (15.0)	26.1 (22.6)	23.6 (21.4)	19.1	1.27	0.83	0.84
WOMAC $_{pain}$								
non-traumatic	13.5 (17.2)	7.2 (16.0)	22.6 (17.6)	19.8 (16.2)	15.4	0.96	0.77	0.79
traumatic	27.9 (22.8)	18.1 (25.9)	29.0 (21.9)	29.6 (22.0)	10.9	0.42	1.26	1.22
combined	19.2 (20.8)	9.1 (18.3)	25.9 (20.0)	24.9 (20.0)	16.8	0.92	0.96	0.92
WOMAC $_{stiffness}$								
non-traumatic	9.6 (23.3)	2.9 (21.6)	16.8 (25.9)	16.1 (23.6)	13.8	0.64	0.42	0.41
traumatic	30.3 (30.8)	17.3 (28.2)	34.1 (32.1)	32.5 (30.9)	16.8	0.59	1.02	0.98
combined	17.7 (28.3)	5.4 (23.2)	25.6 (30.3)	24.7 (28.7)	20.3	0.87	0.66	0.62
WOMAC $_{function}$								
non-traumatic	9.7 (14.6)	5.2 (13.1)	17.2 (16.8)	14.3 (14.8)	12.0	0.92	0.57	0.66
traumatic	28.5 (26.7)	13.8 (23.2)	34.8 (28.1)	31.1 (26.6)	21.0	0.91	1.04	1.07
combined	17.1 (22.2)	6.6 (15.5)	26.3 (24.8)	23.0 (23.3)	19.6	1.27	0.75	0.77

ES = Effect size = $mean_{change\ overall}$ / $sd_{baseline}$
SRM = Standardized Response Mean = $mean_{change\ overall}$ / $sd_{change\ overall}$
mcid = mean clinically important difference = $mean_{change\ major\ improvement}$ - $mean_{change\ stable}$
Guyatt = Guyatt's responsiveness statistic = mcid / $sd_{change\ stable}$

Ceiling and floor effects

Only one of the non-traumatic patients (0.5%) and one (0.9%) of the traumatic patients received the maximum Lysholm score. None of the patients received the minimum score for either the Lysholm scale or the WOMAC index total score. We did find minimum

scores in the subscales pain (1 traumatic patient (0.9%)), stiffness (2 traumatic patients (2%) and 2 non-traumatic patients (2%)) and function (2 traumatic patients (2%)). As this falls well below the acceptable limit of 30%, the floor effects were negligible. WOMAC subscales for stiffness and function did exceed the acceptable ceiling effect of 30% with 72 (39%) and 26 (34%) patients in the non-traumatic group. The pain subscale and total score stayed below that limit with 12 (6.5%) and 17 (9%) patients respectively. The number of traumatic patients with ceiling scores was 3 (3%) for the WOMAC total score, 6 (5%) for the pain subscore, 28 (25%) for the stiffness subscore, and 8 (7%) for the function subscore, all well below 30%.

Discussion

Content validity

Content validity of the Lysholm knee scoring scale and WOMAC index was not self-evident for adolescents and young adults in general practice. Nevertheless, both instruments proved able to distinguish between patients exhibiting symptoms that were not represented in their list of items, such as jumping, running, cycling and kneeling. We therefore concluded that although content validity is not optimal, it seemed adequate for use in this population.

Construct validity

Construct validity of the Lysholm scale as well as the WOMAC index was established for both the traumatic and non-traumatic subgroups, as at least 6 out of 7 hypotheses were confirmed for each combination of instrument and population. The small difference in Lysholm scores between patients refraining from daily duties because of their knee complaints and patients who don't in the non-traumatic group, suggests that the specific activities that make patients refrain from duties may not be well represented in the questionnaire. The WOMAC index enquires about many more daily activities and shows greater discriminative ability in this respect.

Responsiveness

ES and SRM are both measures that consider the change scores of all patients in a population. This approach is appropriate when an instrument is used for evaluation of a treatment. However, in descriptive cohort studies the expectation that all patients will improve over time is not tenable. Guyatt's responsiveness statistic uses the recovery

scores to distinguish between patients that consider their knee complaints improved and those who consider them relatively unchanged. Because the mean change and its variability in stable patients (noise) is taken into account, Guyatt's responsiveness statistic is more appropriate to determine the usefulness of an instrument for evaluation of knee complaints in a cohort study.

Our analyses clearly demonstrate the differences between the methods of determining responsiveness. For both the Lysholm scale and the WOMAC index the overall responsiveness (ES or SRM) was higher in the traumatic patients, due to the lower mean baseline scores and the higher mean follow-up scores. Nevertheless, Guyatt's statistic shows that the ability to detect actual changes in the patient's status is better in the non-traumatic group, due to the smaller variability of stable patients in this group. When accepting Guyatt's statistic as the superior responsiveness statistic in non-intervention studies, both Lysholm scale and WOMAC index total score are highly responsive in the total population as well as the traumatic and non-traumatic subgroups. The responsiveness of the WOMAC subscores stiffness and function is only satisfactory in the total population. This is due to the direct relation between Guyatt's statistic and sample size. Before considering the use of the WOMAC subscores in future studies, Guyatt's statistic should be used for power calculations[14].

Ceiling effect

The proportion of patients with maximum scores at baseline ranged from 0.5% (non-traumatic) to 0.9% (traumatic) for the Lysholm scale and from 2.6% (traumatic) to 6.6% (non-traumatic) for the WOMAC index. This is well within the acceptable range of < 30%. The WOMAC subscores for pain and function also showed acceptable ceiling effects ranging from 5.2% (traumatic) to 9.2% (non-traumatic) and from 6.9 (traumatic) to 14.2 (non-traumatic) respectively. The stiffness subscore showed an unacceptable ceiling effect of 39.1 for non-traumatic patients (24.4% for traumatic patients).

Context

Lysholm

Irrgang et al.[18] reported effect sizes ranging from 0.82 to 1.13 in a heterogeneous population including ligament injuries, meniscal tears, arthritis, tendinitis and patellofemoral pain. This is very similar to our 0.76 to 1.15. Kocher et al.[6] similarly reported an ES of 1.16 in patients with various chondral disorders of the knee and an

SRM of 1.10. Marx[7,8] reported an SRM of 0.9 for a heterogeneous population of athletic patients. This corresponds to our overall SRM of 0.86. None of these studies have used Guyatt's responsiveness statistic. No unacceptable ceiling effects were reported by any of these authors. Generally our findings are in line with those of other authors.

WOMAC

McConnell[9] performed a structured literature review of the measurement properties of the WOMAC in a wide variety of intervention studies in patients with hip and knee osteoarthritis. She summarized effect sizes, standardized response means and Guyatt's responsiveness statistics. Overall, the effect sizes of the WOMAC varied from small (0.07) to large (0.94) in drug studies (pain killers or glucosamine). One study reported effect sizes of 0.26 for placebo and 0.74 for glucosamine, with corresponding Guyatt's responsiveness statistics of 1.8 to 4.14 for the total WOMAC score[19]. Mean change scores for glucosamine (9.8) were comparable to the change scores of our non-traumatic group (10.5), but with an ES of 0.65 and Guyatt's statistic of 1.04 responsiveness was considerably smaller in our study. Effect sizes of two exercise studies ranged from 0 to 0.32 for the placebo groups and from 0.28 (6 months) to 1.19 (4weeks) in the exercise groups[20,21]. Interestingly, one 6 month study found small effect sizes for pain (0.15) and function (0.10) subscores in patients with OA symptoms managed by the family doctor[22]. In this context the range of our effect sizes (0.42 - 0.77 in non-traumatic patients and 1.02 - 1.26 in traumatic patients) indicates that the WOMAC may be more suitable for other diagnoses than osteoarthritis when measuring changes over time.

Limitations

Although we did not determine the test-retest reliability in our population, we assume it will be acceptable based on results of studies in other (heterogeneous) populations[5-8].

Conclusion

Both Lysholm and WOMAC have shown sufficient construct validity and responsiveness for use in long-term evaluation studies of adolescents and young adults with knee complaints in general practice.

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5

Prognosis of non-traumatic knee complaints in adolescents and young adults in general practice

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Submitted

What this paper adds

What is already known on this subject

The incidence of adolescents and young adults consulting Dutch general practitioners for non-traumatic knee complaints is 19 per 1000 patients per year. The prognosis is generally assumed to be good, but no studies were available to confirm this belief.

What this study adds

In our cohort only 53% of incident patients report full recovery or major improvement after one year. Prognostic factors for persistence are a prominent tibial tuberosity, painful patellar ligament, bilateral complaints, locking of the knee, a history of knee operation and self-reported knee swelling. The assumption of a good prognosis may need to be revised.

Abstract

Objectives

Non-traumatic knee complaints of adolescents and young adults are common in general practice, and are presumed to have a good prognosis. However, no prospective studies in this setting are available to confirm this. We aim to describe the course of knee complaints and prognostic factors for persistence in this population.

Design, setting and participants

40 Dutch general practitioners included 191 consecutive patients aged 12 through 35 consulting for knee complaints in a prospective cohort study. Participants received usual care from their general practitioner.

Main outcome

After one year patients rated their recovery on a 7 point scale, which was dichotomized into recovery or persistence. Prognostic factors for persistent knee complaints were identified through multivariate logistic regression using characteristics extracted from a baseline questionnaire and standardized physical examination. Three-monthly questionnaires provided pain and functional disability scores to describe the course of knee complaints during one year follow-up.

Results

26% of the patients reported major improvement and 27% total recovery. Prognostic factors for persistent knee complaints were poor overall health, a lower education level, a prominent tibial tuberosity, painful patellar ligament, bilateral complaints, locking of the knee, a history of knee operation and self-reported knee swelling. Improvement of pain and functional disability is greatest in the first three months after consultation.

Conclusions

After one year 47% of adolescents and young adults with incident non-traumatic knee complaints have persistent knee complaints. The assumed good prognosis should be reconsidered. These results emphasize the need for randomized controlled trials to assess the effectiveness of treatment options in order to improve the prognosis.

Introduction

Knee complaints are one of the most frequently encountered reasons for consultation of the general practitioner (GP) [1](Heintjes EM et al., submitted data). Non-traumatic knee complaints include patellar chondropathy, jumper's knee (tendinitis), Osgood-Schlatter disease, bursitis, iliotibial tract friction syndrome, popliteal cysts and osteoarthritis. Osteoarthritis is of progressive nature and becomes increasingly predominant from age 35 onward. Non-traumatic knee complaints of adolescents and young adults are usually regarded as self limiting, and account for 20% of all non-traumatic knee complaints in general practice [1](Heintjes EM et al., submitted data). The incidence is estimated at 19 per 1000 per year and the prevalence at 27 per 1000 per year [1]. To our knowledge, no prospective follow-up studies of adolescents and young adults consulting the GP for knee complaints have been published so far. Evidence from controlled randomised trials for the effectiveness of interventions is also lacking. Dutch GP guidelines[2-4] therefore generally advise GPs to inform patients of a good prognosis, to limit pain provoking activities for some time, and to gradually strengthen the knee musculature, preferably by providing advise on home exercises. Pain medication is not advised, and referral to physical therapists or orthopaedic surgeons should only be considered when complaints persist.

Before setting up trials to determine the effectiveness of interventions basic information is required about the course of knee complaints with the current conservative treatment as well as insight into possible determinants for chronicity. Modifiable determinants may be targeted by interventions. Non-modifiable determinants should be stratified or corrected for in trials focussing on other aspects or may be used as basis for more adequate patient education.

With our prospective cohort study[5], we aim to describe the course of non-traumatic knee complaints in adolescents and young adults over the course of one year and to identify prognostic factors for persistent knee complaints. Furthermore we will compare the patients' perceived recovery at follow-up with the GPs expectations at baseline.

Methods

Data collection

We performed a prospective descriptive cohort study of consecutive patients, aged 12 and over, visiting the GP for incident knee complaints. The ethics committee of Erasmus MC approved the study and all patients signed informed consent. The methods of recruitment and data collection have been described in detail elsewhere[5]. From our cohort (N=1068), we extracted all patients with non-traumatic knee complaints aged 12 through 35 (N=191). Patients underwent a standardised physical examination at baseline and one year follow-up. Patient characteristics, medical history, knee anamnesis and other possible prognostic factors were recorded in the baseline questionnaire (table 2). Three monthly follow-up questionnaires recorded knee symptoms, functional disability and repeated GP consultations during the course of one year. We strived to contact patients dropping out during this period by telephone, to determine the state of their knee complaints at that point.

GPs were also asked to note working diagnoses according to the International Classification of Primary Care (ICPC)[6] and their predicted prognosis in the patient's computerized medical file at first consultation. We dichotomised the GPs predictions into recovered (improvement or recovery within one year) and persistent (no change or worsening over the course of one year) for descriptive statistics.

Course of knee pain and disability

Pain over the last 48 hours was measured on a numeric rating scale ranging from 0 (no pain) to 10 (unbearable pain). The Lysholm scale[7] and WOMAC osteoarthritis index[8,9] both evaluate functional disability of the knee with global scores ranging from 0 (poor) to 100 points (excellent). Both Lysholm scale and WOMAC index were shown to be sufficiently sensitive to change in the present population (Heintjes EM, et al., submitted data). Means and 95% confidence intervals of each outcome measure at three-monthly intervals were displayed graphically to indicate the course of the knee complaints.

One-year prognosis

The primary outcome measure was experienced recovery after 12 months follow-up. We asked the patients how they rated their current knee complaints compared to baseline, measured on a 7-point Likert scale ranging from total recovery (=1) to worse than ever

(=7). The categories 'total recovery' and 'major improvement' represent clinically relevant improvement. All other categories represent persistent knee complaints.

Prognostic factors

Possible prognostic factors were assigned to one of 4 domains: patient characteristics, psychosocial factors, anamnesis, and physical examination (see table 1). To enable easy interpretation of prognostic factors in a clinical setting continuous variables were dichotomised based on the median, with the exception of body mass index (BMI), which was cut of at 30 (obesity).

Prognostic factors for the outcome 'persistent knee complaints' were identified with univariate logistic regression using a threshold of $p<0.15$. Per domain we performed stepwise multivariate regression with the 'backward Wald' method to eliminate redundant factors (entry $p<0.10$, removal $p<0.15$). We subsequently combined the remaining factors of each domain into one model and repeated the elimination process, always adjusting for gender and age.

Table 1. Possible prognostic factors tested with logistic regression

Patient characteristics	**Psychosocial factors**
gender	coping with pain score[20]
age (continuous or ≥ 24)	Tampa kinesiofobia score[21]
BMI ≥ 30	COOP-WONCA charts item 'feelings'[22]
COOP-WONCA charts item 'overall health'[22]	
comorbidity of musculoskeletal system	
other comorbidity	
Anamnesis and symptoms	**Physical examination**
duration of complaint (< 3 weeks or < 3 months)	postural aspects of foot, tibia and femur
bilaterality	quadriceps atrophy
history of non-traumatic knee complaints	raised knee temperature
history of knee trauma or knee operation	swelling: ballottable patella and fluctuation test
bothered by knee during daily activities	pain and crepitations during flexion and extension
knee locking or instability	pain or prominence of tibial tuberosity
intermittent or continuous knee swelling, crepitations or raised temperature	pain at palpation of patellar edges, bursae, joint line and ligaments
pain during prolonged sitting with flexed knees,kneeling, squatting, cycling, running jumping	pain or crepitations during patellar axial pressure test, apprehension test or patellar grind test
WOMAC total score and subscores[8,9]	muscle resistance tests
Lysholm total score[7]	laxity medial, lateral and cruciate ligaments

Results

Study population

The mean age of the patients was 24.1 (±7.7), 53% was male. ICPC codes from the GP's computerized medical files yielded 100 patients (52%) with unspecified knee complaints (L15), 74 patients (39%) with retropatellar chondropathy (L97), and 8 patients (4%) with Osgood-Schlatter disease (L94.2). The GPs diagnosed 9 patients (5%) with knee distortions or acute traumatic knee injuries (L78 or L96). Since these patients indicated that overuse rather than trauma caused the injuries, and no signs of recent trauma were evident during physical examination, they were included in the non-traumatic subpopulation of the cohort.

Table 2. Baseline characteristics

	recovery scores available	
	yes[1] (N=165)	no (N=26)
general		
age, mean (sd)	24.2 (7.7)	23.7 (7.8)
male, n (%)	84 (51%)	16 (62%)
female, n (%)	81 (49%)	10 (38%)
working diagnosis GP (ICPC[2])		
unspecified (L15) , n (%)	86 (52%)	14 (54%)
acute distortion (L78) , n (%)	2 (1%)	2 (8%)
Osgood Schlatter (L94.2) , n (%)	8 (5%)	0 (0%)
acute meniscus/ligament rupture (L96) , n (%)	4 (2%)	1 (4%)
chronic internal trauma (L97) , n (%)	65 (39)	9 (35%)
knee complaints		
duration at consultation < 3 months, n (%)	104 (65%)	18 (78%)
bilateral , n (%)	71 (44%)	12 (52%)
recurrent , n (%)	88 (55%)	10 (43%)
measures of severity		
pain (0-10 numeric rating scale), mean (sd)	4.0 (2.2)	4.3 (2.4)
Lysholm scale (0-100), mean (sd)	73.4 (14.7)	72.7 (15.7)
WOMAC index (0-100), mean (sd)	79.9 (16.9)	75.5 (22.0)

[1] Patients included in prognostic analyses [2] ICPC = International Classification of Primary Care
Due to missing data N may vary slightly per characteristic

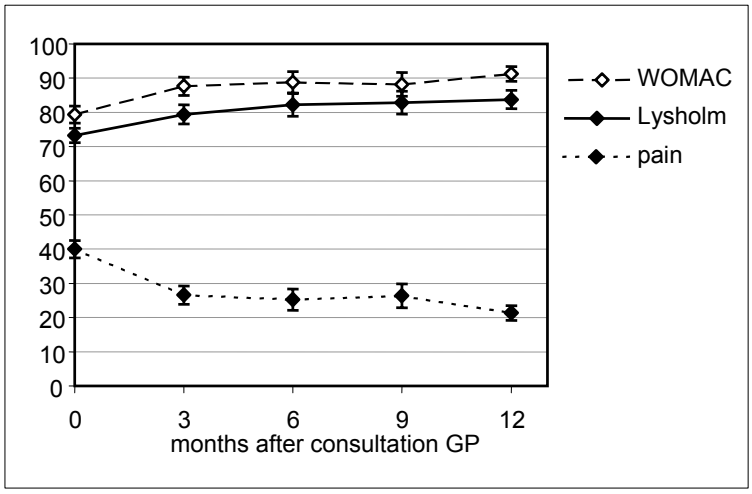
Follow-up

We obtained baseline questionnaires for 184 patients (96%), baseline physical examination for 187 patients (98%) and recovery scores for 165 patients (86%). All three were obtained for 158 patients (83%), thus meeting the requirements for logistic regression analysis to identify prognostic factors. Response rates for the follow-up questionnaires to determine the course of knee complaints, was 61%, 50%, 48% and 74% for 3, 6, 9 and 12 months respectively.

Comparison of baseline characteristics between dropouts and patients with recovery scores (table 2) revealed no statistically significant differences with respect to gender (OR 0.65, (95% CI 0.28 to 1.51)), age (mean difference (MD) -0.4 years, p=0.79), pain scores (MD=-0.3, p=0.48), Lysholm scores (MD=-4.4, p=0.84) or WOMAC scores (MD=-12.1, p=0.27).

Only 28% of all patients visited the GP again during one year follow-up, representing 33% of patients with persistent complaints after one year and 23% of patients that had recovered.

Figure 1. Course of knee complaints (mean scores and 95% CI)



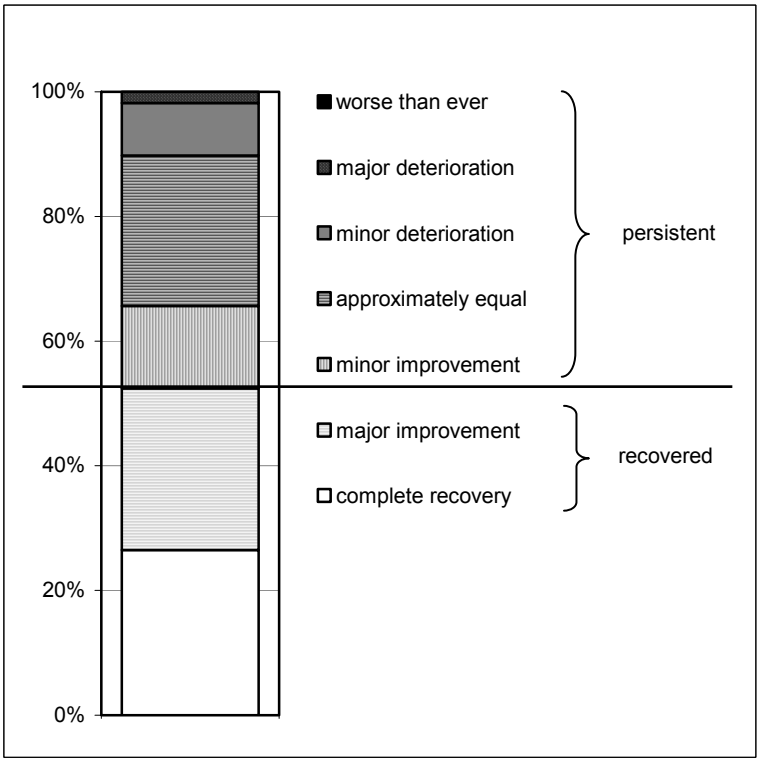
Pain scores were multiplied with a factor 10 for graphical display

Course and prognosis

Mean pain and functional disability scores show the largest improvement in the first three months after consultation of the GP (figure 1). Distribution of the patients' perceived

recovery after one year follow-up is displayed in figure 2. 27% reported total recovery (men 29%, women 24%) and 26% reported major improvement (men 20%, women 32%), totaling 53% 'recovery'. The GP recorded the expected prognosis at baseline for only 78 patients (41%). The GP expected 77% of these patients to recover completely, and an additional 12% to improve within one year.

Figure 2. Experienced recovery after 1 year



Prognostic factors

Factors showing univariate and multivariate associations with persistence (α=0.15) are listed in table 1. Patients with a history of knee operation (n=15) were significantly more at risk of persistence (OR 5.56). Because this characteristic might be considered inappropriate for an analysis of non-traumatic knee complaints, we performed a secondary analysis without these patients. Their elimination resulted in the inclusion of self reported knee swelling (OR 2.45), but otherwise the model remained the same.

Table 3. prognostic factors for persistent knee complaints

	frequency	univariate	multivariate[¥] N = 155[$]	multivariate[¥] without history of knee operation[#] N=140
		OR (95% CI)	OR (95% CI)	OR (95% CI)
patient characteristics				
low education level	50%	2.42 (1.29 to 4.57)[3]	2.56 (1.22 to 5.38)[3]	3.37 (1.48 to 7.64)[3]
BMI ≥ 30	8%	2.76 (0.81 to 9.35)[2]		
poor overall health	11%	3.69 (1.14 to 12.1)[3]	3.62 (0.99 to 13.2)[2]	6.88 (1.60 to 29.6)[3]
psychosocial factors				
-				
knee anamnesis				
duration > 3 months	34%	1.68 (0.87 to 3.22)[1]		
bilateral knee complaints	44%	2.05 (1.09 to 3.86)[3]	2.48 (1.16 to 5.35)[3]	2.85 (1.22 to 6.66)[3]
history of knee trauma	21%	1.92 (0.90 to 4.12)[2]		
history of knee operation	9%	5.10 (1.38 to 18.9)[3]	5.56 (1.33 to 23.3)[3]	
warm sensation of the knee	29%	1.82 (0.91 to 3.64)[2]		
self-reported knee swelling	34%	1.97 (1.01 to 3.84)[3]		2.45 (1.04 to 5.81)[3]
stiffness	47%	1.69 (0.90 to 3.17)[1]		
locking of the knee	16%	2.69 (1.09 to 6.67)[3]	3.13 (1.11 to 8.85)[3]	2.57 (0.87 to 7.73)[2]
pain when squatting	57%	1.67 (0.89 to 3.13)[1]		
difficulty with squatting	53%	1.86 (0.99 to 3.48)[2]		
difficulty with cycling	41%	1.63 (0.86 to 3.09)[1]		
knee bothersome during daily activities	57%	1.67 (0.89 to 3.14)[1]		
physical examination				
balottable patella	27%	2.00 (0.97 to 4.12)[2]		
painful patellar ligament	16%	2.43 (1.01 to 5.85)[3]	2.76 (0.95 to 8.00)[2]	3.08 (1.01 to 9.38)[3]
painful patellar edges	48%	1.89 (1.00 to 3.57)[3]		
prominent tibial tuberosity	6%	2.81 (0.70 to 11.2)[1]	6.67 (1.03 to 43.5)[3]	5.93 (0.93 to 37.7)[2]

only determinants with p-values < 0.15 are listed: [1] <0.15, [2] < 0.10, [3] < 0.05
[¥]adjusted for gender and age
[$] due to missing values of variables, 3 patients were excluded from the logistic analysis
[#] a history of knee operation might not be interpreted as non-traumatic knee complaints, therefore this analysis was repeated without patients with a history of knee operation (n=15).

Other prognostic factors from anamnesis and history taking are bilateral knee complaints (OR 2.48 to 2.85) and locking of the knee (OR 2.57 to 3.13). Patient characteristics associated with persistent complaints are lower education level (OR 2.56 to 3.37) and poor overall health (OR 3.62 to 6.88). No psychosocial factors were associated with persistence. From the physical examination only painful patellar ligament (OR 2.76 to 3.08) and prominence of the tibial tubercle (OR 5.93 to 6.67) were associated.

Discussion

Course and prognosis

Improvement in the mean pain and function scores was most pronounced in the first three months, but continued throughout the entire follow-up period. After one year only 27% of all patients reported total recovery, and 26% reported major improvement. These patients showed improvement throughout the year, whereas the 47% with persistent complaints only showed some improvement in the first three months.

In the sample for which the GP recorded the expected prognosis the GPs predicted 77% total recovery and 12% improvement, which is considerably less than the recovery rate of 47% recorded by the patients in that same sample. With a representative distribution of the ICPC codes, and predictions being done by two thirds of the participating GPs, we have no reason to believe that this sample does not represent the cohort's patients or the GPs' beliefs. In literature several studies with patients that represent at least part of our population have also found disappointing recovery rates. A retrospective study in general practice of older patients with retropatellar chondropathy reported 44% recovery after 6 months[10]. A review of exercise therapy in patients with patellofemoral pain syndrome in orthopedic clinics reveals the participant's duration of complaints often exceeds one year, and many participants retain symptoms[11]. Studies carried out in British orthopedic clinics also challenged the view that non-traumatic knee complaints have a good prognosis. They found that after 4 years 46% of the adolescents had less pain and 6% was pain free[12]. After 10 years 9% of the children was pain free[13]. One might expect a more favourable prognosis in our cohort, as populations in specialistic settings are likely to present more serious complaints, and in older populations osteoarthritis may contribute to the symptoms.

So what explains the discrepancy between the GPs expectations and the patients' reported outcome? We found that only 1 in 3 patients with persistent complaints, and 1 in

4 of the patients that ultimately recover, return for follow-up consultations, mostly within 3 months after the first consultation. The 'wait and see' approach of the GP and the advise that the complaints are self limiting may discourage patients to return to the GP with persistent complaints. The GP possibly assumes that patients who don't return have recovered. This may explain the optimistic views on prognosis of both the GP and the available clinical guidelines[2,3].

Prognostic factors

A lower education level was found to be a risk factor for chronicity. In the literature lower school grades were given as part of an explanation for the relation between lower socio-economic status and a higher frequency of musculoskeletal disorders at age 30[14]. Poor overall health is also associated with lower socio-economic status in the literature. The association between poor health and persistent knee complaints are likely to have common determinants. In fact, we also found an association between education level and poor health, but although comorbidity of the musculoskeletal system is associated with poor health, it is not with persistence of knee complaints. We found no association between persistence and any psychosocial factors.

We did find a strong association with a history of knee operation. Knee operations in the past may be the cause of current non-traumatic knee complaints, but in a multivariate model may also obscure other factors that are associated with the persistence of other non-traumatic knee complaints. We therefore presented models with and without these patients. Exclusion of patients with a history of knee trauma led to the inclusion of self-reported intermittent or continuous swelling as prognostic factor. As swelling usually indicates intra-articular pathology we determined how many patients also exhibited signs of patellofemoral pain syndrome. We found that 59% of the patients reporting swelling also have painful patellar edges, and the risk of persistence with swelling is twice increased in patients with concurrent painful patellar edges. It is noteworthy that overlap between self-reported swelling and balottable patella sign is only 40%, and balottable patella sign is not retained in the model. The GP would therefore be advised to take the patient's report of swelling rather than swelling during physical examination into account for prognostic purposes.

The prognostic factor locking of the knee can be a sign of meniscal damage or patellofemoral complaints[11]. In our cohort it is a sign of patellofemoral complaints, since

only 2 out of 26 patients with locking reported a history of traumatic injury, whereas 19 out of 26 reported painful patellar edges, of whom 14 had persistent complaints.

Our finding that bilateral complaints are a risk factor for persistent knee complaints concurs with the findings of a seven-year follow-up study of patients with unilateral patellofemoral pain syndrome. Patients developing bilateral complaints during follow-up had worse pain and Lysholm scores[15].

Physical examination produced three univariate prognostic factors associated with the extensor mechanism of the knee: painful patellar edges, painful patellar ligament and a prominent tibial tuberosity. The patellar ligament connects the patella and tibial tuberosity. Painful patellar edges are a sign of retropatellar chondropathy, or patellofemoral pain, and painful patellar ligament for jumper's knee. Overloading the extensor mechanism may affect several structures simultaneously[16], making it hard to distinguish between diagnoses[17]. GP guidelines[2] propose similar treatments for these diagnoses: limiting exercise levels to acceptable pain levels in order to adjust physical knee loading to the actual loading capacity. So distinguishing between diagnoses has at present no bearing on treatment. But for prognostic purposes it seems useful to distinguish between isolated and combined symptoms: prognoses for patients with jumper's knee have been reported to be worse with concurrent symptoms of patellofemoral pain syndrome[18]. Upon closer inspection of our own data we found that 76% of the patients with combined painful patellar ligament and painful patellar edges (n=21) had persistent complaints, versus 20% in patients with only a painful patellar ligament (n=5) and 52% in patients with only painful patellar edges (n = 54). This may indicate that although painful patellar edges were eliminated from the multivariate model because of the overlap with a painful patellar ligament, it is useful to look for the combination of both.

A prominent tibial tuberosity is another sign of overloading the extensor mechanism. It may represent the end-stage of Osgood-Schlatter disease[16], and in fact most affected patients had either a long duration of the complaints (over one year) or a history of non-traumatic complaints. A prominent tuberosity might in it's own right influence forces in the extensor mechanism, predisposing for chronicity of the complaints.

Strengths and weaknesses of this study

The major strength of this study is that it is the first prospective cohort to determine the prognosis of non-traumatic knee complaints in adolescents and young adults consulting

the GP. The predicted prognoses of the GPs are far more positive than the patients' reported outcome, indicating that our study provides useful information to GPs.

It is also interesting to compare the results of our study to a recent prognostic study in general practice, which combined non-traumatic and traumatic knee complaints in patients aged 18 and above[19], and did not include physical examination. They found musculoskeletal comorbidity, a longer duration of the complaint, history of knee complaints and distress to be determinants for persistent complaints. The limited similarity with our findings (only univariate association with duration and history of knee trauma) emphasizes the need for studying subgroups of knee complaints in general practice.

Medical treatment and physical loading of the knee were not included in the prognostic model because they were hard to standardise, depend on severity and duration of symptoms (which in themselves are possible prognostic factors), and they vary throughout the follow-up period. However, our study does provide basic information for future trials to investigate the effect of treatment and physical loading.

Implications for clinicians

The presumed good prognosis of non-traumatic knee complaints in adolescents and young adults need revision, which should be reflected in the advice given by GPs during consultation. In light of this less favourable prognosis the call for more effective measures becomes stronger. Effectiveness studies should therefore be carried out.

It is worth mentioning that there are no significant differences between the sexes either with regard to the number of patients with (specific) knee complaints, or the prognosis.

Although patellofemoral pain syndrome did not survive elimination from the multivariate model, its signs often occur concurrent with the remaining prognostic factors. Thus patellofemoral pain syndrome seems to be an important confounder of the prognostic factors remaining in the model, and clinicians should be aware of the worse prognosis when signs of patellofemoral pain syndrome are found concurrent with these prognostic factors.

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6

Exercise therapy for patellofemoral pain syndrome A systematic Cochrane review

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Abstract

Background

Patellofemoral pain syndrome (PFPS) is a common problem among adolescents and young adults, characterised by retropatellar pain (behind the kneecap) or peripatellar pain (around the kneecap) when ascending or descending stairs, squatting or sitting with flexed knees. Etiology, structures causing the pain and treatment methods are all debated in literature, but consensus has not been reached so far. Exercise therapy to strengthen the quadriceps is often prescribed, though its efficacy is still debated.

Objectives

This review aims to summarise the evidence of effectiveness of exercise therapy in reducing anterior knee pain and improving knee function in patients with PFPS.

Search strategy

We searched the Cochrane Musculoskeletal Injuries Group and Cochrane Rehabilitation and Related Therapies Field specialised registers, the Cochrane Controlled Trials Register, PEDro - The Physiotherapy Evidence Database, MEDLINE, EMBASE, CINAHL, up till December 2001 for controlled trials (randomised or not) comparing exercise therapy with control groups, or comparing different types of exercise therapy.

Selection criteria

Only trials focusing on exercise therapy in patients with PFPS were considered. Trials in patients with other diagnoses such as tendinitis, Osgood Schlatter syndrome, bursitis, traumatic injuries, osteoarthritis, plica syndrome, Sinding-Larssen-Johansson syndrome and patellar luxations were excluded.

Data collection & analysis

From 750 publications 12 trials were selected. All included trials studied quadriceps strengthening exercises. Outcome assessments for knee pain and knee function in daily life were used in a best evidence synthesis to summarise evidence for effectiveness.

Main results

One high and two low quality studies used a control group not receiving exercise therapy. Significantly greater pain reduction in the exercise groups was found in one high and one low quality study, though at different time points. Only one low quality study reported significantly greater functional improvement with exercise. Five studies compared exercise therapies that could be designated closed kinetic chain exercise (foot in contact with a surface) versus open kinetic chain exercise (foot not in contact with a

surface). Two of these studies were of high quality, but no significant differences in improvement of function or reduction of pain were apparent between the types of exercise in any of the studies. The remaining four studies, all of which were of low quality, focused on other treatment comparisons.

Reviewers' conclusions

The evidence that exercise therapy is more effective in treating PFPS than no exercise was limited with respect to pain reduction, and conflicting with respect to functional improvement. There is strong evidence that open and closed kinetic chain exercise are equally effective. Further research to substantiate the efficacy of exercise treatment compared to a non-exercising control group is needed, and thorough consideration should be given to methodological aspects of study design and reporting.

Background

Patellofemoral pain syndrome (PFPS) is a common complaint in adolescents and young adults. The symptom most frequently reported is a diffuse peripatellar (around the knee cap) and retropatellar (behind the knee cap) localised pain, typically provoked by ascending or descending stairs, squatting and sitting with flexed knees for prolonged periods of time. Other common symptoms are crepitus and giving-way[1-5].

Several factors have been implicated in the etiology of PFPS. Malalignment of the lower extremity, sometimes due to excessive pronation of the foot, may result in a compensatory internal rotation of the tibia and increased valgus stress[6]. The vastus medialis obliquus (VMO) plays a major role in stabilising patellar glide through the femoral groove. Weakness of the VMO relative to other muscle groups of the quadriceps and aberrant firing patterns of the nerves innervating the VMO and vastus lateralis (VL) have been demonstrated in patients with PFPS[7]. This muscle imbalance may cause maltracking of the patella through the femoral groove, resulting in an abnormal distribution of the patellofemoral joint reaction stress (PFJRS)[8]. Tight anatomical structures (hamstrings, iliotibial band, patellar retinaculum)[9,10] and overactivity[5,10,11] may also increase the PFJRS. Poor congruence angles between the posterior aspect of the patella and the intercondylar sulcus of the femur predispose for subluxation or even dislocation of the patella, causing cartilage damage[12]. Clinical studies have not however been able to demonstrate biomechanical or alignment differences between patients with PFPS and healthy individuals[5,13,14] argues that the combination of malalignment and muscle function deficit may increase the risk of overload and thus PFPS. Increased intrapatellar pressure may cause subchondral degeneration which progresses to the surface and ultimately results in chondral lesions[5,14,16]. As cartilage is not innervated, subchondral bone may cause the pain. However, many authors[2,5,17,18] report a poor correlation between pain and cartilage damage. Peripatellar soft tissues, such as the patellar retinaculum may also play a role.

The uncertainty regarding the etiology of the complaint also extends to the diagnostic criteria and terms. PFPS is sometimes referred to as 'anterior knee pain'[19], a term that may also indicate other medical conditions causing pain in the anterior part of the knee[1,17] and which often refers more to symptoms than a clear diagnosis. Chondromalacia patellae or chondropathy are often used as a synonyms for PFPS. Nevertheless, in literature there is some agreement that chondromalacia or

chondropathy are applied to patients with actual patellar cartilage damage and PFPS is a term to be applied only to patients with retropatellar pain in which no cartilage damage is evident[1,5,11,20-22]. However, retropatellar pain is generally thought of as a self-limiting condition with a good prognosis, especially for patients who are young[23], patients who have unilateral complaints and patients in which crepitation is absent[18]. This means that patients are usually managed in primary care and are rarely referred to specialist care[17]. Therefore reliable diagnostic techniques for determining cartilage damage such as computed tomography (CT), magnetic resonance imaging (MRI) or arthroscopy[1,2] are seldom applied. In fact a diagnosis based solely on symptoms and physical examination of the knee is not uncommon. Diagnostic tests often applied are listed here. Palpation of the lateral and medial aspects of the patella can determine sensitivity of the retropatellar surface. "Clarke's test", "compression test" or "axial pressure test" are synonyms for pressing the patella against the femur and asking the patient to contract the quadriceps. The test is positive when pain or crepitations are present. The patellar grind test is similar but requires pressure to the patella in distal direction. Resisted knee extension can also elicit pain with PFPS. The specificity and sensitivity of these tests is debated in literature, but validation studies are absent. Gaffney found that only half of the patients with PFPS were positive on Clarke's test[24]. In the apprehension test a lateral pressure is applied to the patella. Patients with a history of (sub)luxation will react with sudden contraction of the quadriceps muscles. The relevance of determining cartilage damage with more reliable techniques than physical examination is minimal, as Natri found that neither the radiologic nor the MRI changes seen in affected knees showed a clear association with the seven year outcomes for pain and knee function[18]. All things considered the distinction between chondromalacia and PFPS seems theoretical rather than practical, so patients with chondromalacia as well as PFPS will be included in this review.

Most researchers advocate conservative treatment of PFPS or chondromalacia[1,5,20,21], though there is still insufficient clarity about the effectiveness of the conservative treatment methods[3,4,22]. This review is being undertaken to clarify the effectiveness of quadriceps strengthening exercises, the most promising conservative treatment method for patellofemoral pain syndrome available[3,5,10,18,25,26].

Quadriceps strengthening exercise therapy encompasses a broad range of possible variations and accompanying terms. To offer the reader some support with the interpretation of these terms, an overview of the possibilities is given here. Exercises

involving contact of the foot with a surface are referred to as "closed kinetic chain exercises", as opposed to "open kinetic chain" exercises which are often prescribed because of the limited forces they elicit in the knee joint. Contractions of the quadriceps muscles can either be concentric, eccentric or isotonic. During concentric contractions the muscles shorten (e.g. when raising a straight leg, extending a bent knee or squeezing a pillow between both legs), whereas during eccentric contractions they lengthen in an actively controlled manner (e.g. when slowly lowering a straight leg, descending stairs or squatting down). Isotonic contractions require a constant strain without changes in the length of the muscle (e.g. during wall squats with knees flexed in 90 degrees and the back against the wall). Exercises in which the position of the knee does not change are referred to as static or isometric. Hence, exercises can be described in three dimensions: the presence of reaction forces caused by contact of the foot with a surface (open versus closed kinetic chain), type of muscle activity (concentric, eccentric, isotonic), and knee movement (flexion/extension versus isometric or static). Combinations of above denominations apply to every type of exercise, and the terminology used for exercise programs reflects the emphasis intended by the therapist.

Quadriceps strengthening exercises are usually combined with stretching exercises, to loosen tight structures like hamstrings, the iliotibial band and the patellar retinaculum. Additional tools provided by therapists to facilitate exercise therapy are patellar taping[26] or Coumans bandaging to adjust the patellofemoral congruence angle and thereby relieve pain and facilitate exercising. Therapists may also apply additional technology in treatment programs. Isokinetic exercises (exercises in which the lower leg moves at a predetermined, constant speed) require an isokinetic dynamometer to control the velocity with which the knee goes through a large range of motion. This device can also measure the concentric as well as eccentric force applied by knee extensors (quadriceps) or flexors (hamstrings) at predetermined velocities. The velocity spectrum for these dynamometers ranges from 0 to 360 degrees per second. Electromyographic biofeedback visualises specific muscle contractions and may help the patient target the Vastus Medialis Obliquus (VMO) during exercise. Electrostimulation provides external stimuli for specific muscles resulting in contractions and thus exercise.

Objectives

The objective of this review was to assess the effectiveness of exercise therapy in the treatment of PFPS, by

- comparing exercise therapy with 'placebo' treatment or no treatment/waiting list controls
- comparing different types of exercise therapy
- comparing exercise therapy with other conservative or surgical treatment

using anterior knee pain and knee function as clinically relevant outcome measures. Measurements up to one year follow-up were considered short term outcomes, thereafter long term.

Methods

Types of studies

Concurrent, randomised or quasi-randomised controlled trials (RCTs) and concurrent controlled trials without randomisation (CCTs) on exercise therapy for patellofemoral pain were considered. Quasi-randomised treatment allocation pertains to which were not strictly random, such as date of birth, alternation etc. Retrospective studies were excluded.

Types of participants

Adolescent and adult patients suffering from patellofemoral pain syndrome (designated by the author as such or as "anterior knee pain syndrome", "patellar dysfunction" "chondromalacia patellae" or "chondropathy"). Studies which specifically focused on other named knee pathologies such as Hoffa's syndrome, Osgood Schlatter syndrome, Sinding-Larsen-Johansson syndrome, iliotibial band friction syndrome, tendinitis, neuromas, intra-articular pathology including osteoarthritis, rheumatoid arthritis, traumatic injuries (such as injured ligaments, meniscal tears, patellar fractures and patellar luxation), plica syndromes, and more rarely occurring pathologies were excluded[2,5].

Types of interventions

Only controlled trials including at least one treatment arm consisting of exercise therapy aimed at strengthening knee extensor musculature, either at home or under supervision of a therapist were included in this review.

Types of outcome measures

The primary outcome was knee pain. Secondary outcomes focus on functional disability level (i.e. decreased knee function in activities of daily living) and subjective perception of recovery. Questionnaires focusing on knee function (such as Functional Index Questionnaire, WOMAC Osteoarthritis Index, and Kujala Patellofemoral Function Scale, Lysholm scale etc.) and the ability to perform tests (squatting, hopping on one leg etc.) were considered measures for functional disability. Adverse effects like knee swelling or substantially increasing pain levels as a direct effect of treatment were taken into consideration as well. As changes in knee function on impairment level alone (i.e. range of motion, muscle strength etc.) do not directly represent changes in the symptoms of patellofemoral pain or the resulting disability, they were not considered clinically relevant outcome measures in this review.

Identification of trials

We searched the Cochrane Musculoskeletal Injuries Group and Cochrane Rehabilitation and Related Therapies Field specialised registers, the Cochrane Controlled Trials Register, MEDLINE (1966 to December 2001), EMBASE (1988 to December 2001), CINAHL (1982 to December 2001), PEDro - The Physiotherapy Evidence Database (http://ptwww.cchs.usyd.edu.au/pedro), and reference lists of articles. No language restriction was applied. Using the optimal trial search strategy [46] we looked for trials containing the terms anterior knee pain, words containing 'patell',: chondromalacia or chondropathy, in combination with physical therapy, exercise, training or strengthening.

Two reviewers (MB, SBZ) independently selected the trials, initially based on title and abstract. From the title, keywords and abstract they assessed whether the study met the inclusion criteria regarding diagnosis, design and intervention. Of the selected references, the full article was retrieved for final assessment. Next, they independently performed a final selection of the trials to be included in the review, using a standardised form. Disagreements were solved in a consensus meeting.

Methodological quality assessment

The methodological quality was assessed by two reviewers (BK, JV) independently using the Delphi list (table 1)[27]. Disagreements were solved in a consensus meeting. For each item Cohen's Kappa and the percentage agreement between both reviewers was calculated, after dichotomising the data into optimal and suboptimal scores (i.e. value 1 was converted to 0). Trials presenting an adequate or concealed randomisation

procedure and adequate blinding (Cochrane code A), or a maximum score of five or more Delphi items were labelled "high quality" trials.

Table 1 Methodological quality assessment

Delphi list[27]
D1. Was a method of (quasi) randomisation performed?
D2. Was the assigned treatment adequately concealed prior to allocation?
Cochrane code: Clearly Yes = A; Not sure = B; Clearly No = C.
D3. Were the treatment and control group comparable at entry?
D4. Were the inclusion and exclusion criteria clearly defined?
D5. Were the outcome assessors blinded to treatment status?
D6. Were the treatment providers blind to assignment status after allocation?
D7. Were the participants blind to assignment status after allocation?
D8. Were point estimates and measures of variability presented for the primary outcome measures?
D9. Were the outcomes of patients who withdrew described and included in the analysis (intention to treat)?

Data extraction

Two reviewers (EH, RB) independently extracted the data regarding the interventions, type of outcome measures, follow-up, loss to follow-up, and outcomes, using a standardised form.

Analysis

Analysis of pooled study outcomes was only to be implemented if the studies or subgroups of studies were considered clinically homogeneous and if statistical heterogeneity was not demonstrated. If the trial results were heterogeneous, the factors possibly underlying this phenomenon were considered and summarised. A further analysis using a rating system with levels of evidence based on the overall quality, and the outcome of the studies, was used[28,29]:

- strong evidence - provided by generally consistent findings in multiple high quality RCTs;
- moderate evidence - provided by generally consistent findings in one high quality RCT and one or more lower quality RCTs, or by generally consistent findings in multiple low quality RCTs;
- limited evidence - provided by only one RCT (either high or low quality) or generally consistent findings in CCTs;

- conflicting evidence - inconsistent findings in multiple RCTs and CCTs;
- no evidence - no CCTs or RCTs.

Where possible, the results of each RCT were expressed as Relative Risks (RR) with corresponding 95 per cent confidence intervals for dichotomous data and weighted mean differences and 95 per cent confidence intervals for continuous data. MetaView, the statistical analysis component of RevMan[30], was used to graphically present the comparisons of each study.

Results

Of the 750 titles and abstracts identified by the systematic search of the literature, two reviewers (SB, MB) selected 16 studies that met the inclusion criteria. Four studies[31-34] had to be excluded from the review: Beetsma[31] and Eburne[32] due to lack of detail in description of procedures and outcomes; Kowall[33] because both treatment arms performed the same exercises, and the objective of the study was to evaluate the effectiveness of additional taping. Furthermore, Roush[34] also included patients with Osgood-Schlatter and plica syndromes. Twelve studies were included in the review, representing 697 patients, with an equal number of males and females, and an age ranging from 11 to 65, with an average of 24.

Description of studies

A total of 12 studies were included in this review: three CCTs and nine RCTs. The studies proved to be rather heterogeneous with respect to participant characteristics (including diagnostic criteria), the type, intensity and duration of therapy, follow-up duration, outcome measures and measurement instruments. Methodological quality was also variable. The studies are presented here, classified for similarities in comparisons. Descriptions of the participants, methods, interventions, outcomes and drop-outs can be found in the tables of included studies (table 2-4).

Three studies compared exercise therapy with a control group not receiving exercise therapy: Clark (2002)[19], Timm (1998)[35] and McMullen (1990)[36].

The remaining studies compared different types of exercise with each other. Descriptive terms used by the authors differ, but closer consideration of the descriptions of the exercises performed in the trials, enables five studies to be classified as closed kinetic chain exercise versus open kinetic chain exercise: Witvrouw (2000)[37], Wijnen (1996)[38], Gaffney (1992)[24], Stiene (1996)[39] and Colón (1988)[40].

Four studies compared exercise programs that could not be classified as open versus closed kinetic chain exercise. They fit the inclusion criteria for this review, but cannot be compared to any other study and hence are not used in the best evidence synthesis: Dursun (2001) 41, Thomee (1997) 14, Harisson (1999) 42 43, and Gobelet (2001) 44.

Methodological quality of included studies

Percentage agreement ranged from 67% for item 9 ('Were the outcomes of patients who withdrew described and included in the analysis') to 100% for items 6 and 7 (table 1). Overall agreement was 86%. Cohen's Kappa ranged from 0.23 for Delphi item 4 to 0.66 for item 3, but could not be calculated for items 6 and 7 because agreement between reviewers was 100%. The disagreements were solved in a single consensus meeting. Three studies were of high quality, as they scored positive on at least 5 Delphi items, and were allocated Cochrane code A. Delphi scores ranged from 0 to 6 (listed in tables 2-4).

Analysis

Two reviewers (EH, RB) extracted data from the publications. Quantitative meta-analysis of pooled high quality studies was impossible due to the heterogeneity of the interventions used for comparison, heterogeneity of gathered outcome measures and applied instruments and heterogeneity of assessment times. For qualitative analysis we identified two comparisons that were addressed by more than one trial. First of all, the question whether patients receiving exercise therapy improve more than patients on a waiting list or patients receiving conservative treatment without exercise. Second, the question whether weight bearing exercises, more closely resembling activities of daily living (closed kinetic chain) provide better results than non-weight bearing exercises (open kinetic chain). Descriptions of each treatment were closely examined to determine whether the study under investigation could contribute to a best evidence synthesis for either one of these questions. Evidence provided by these studies is summarised in figures 1 and 2. Four studies describe unique comparisons not addressing these questions.

Table 2 Included studies: exercise versus no exercise

Study	Methods	Participants	Interventions	Outcomes	Notes
Clark 2000	RCT Computer generated randomisation High quality: Delphi score 6 Allocation concealment A	AKP/PFPS Duration complaints: median >12 months (<3 to >12) Patients referred from orthopaedic/ rheumatology consultants/GPs 81 patients, 56% male Age 26.0 ± 7.4 (15-40)	Duration 3 months Exercise: 6 sessions in 3 months and training at home: eccentric/isotonic strengthening exercises: bicycle warm-up, wall squats gradually lengthened up to 3 min., sit to stand, proprioceptive balance, exercise gluteus muscles, progressive step down. Education: background of PFPS, footwear, appropriate sporting activities, pain controlling drugs, stress relaxation techniques, ice compresses and massage, diet and weight advice, prognosis and self help Tape: first three sessions, thereafter optional 1) education, exercise, tape (n=20) 2) education, exercise (n=20) 3) education, tape (n=19) 4) education (n=22)	VAS pain: baseline, 3, 12 months WOMAC: baseline, 3, 12 months Patient satisfaction: 3 months ► expressed as N discharged Patient recovery: 12 months ► expressed as N still troubled ► expr. as N continuing therapy	Drop-outs: 1) 3 months: 4 patients 12 months: 10 patients 2) 3 months: 4 patients 12 months: 8 patients 3) 3 months: 1 patient 12 months: 7 patients 4) 3 months: 1 patient 12 months: 7 patients
Timm 1998	RCT Odd-even treat-ment allocation Low quality: Delphi score 3 Allocation concealment B	Unilateral PFPS Duration complaints: 12.5 ± 5 weeks (5-19) Referred from orthopaedic surgeons 100 patients, 60% male Age: 30 ± 6 (24 - 44)	Duration 4 weeks 1) daily use of Protonics® device: high volume submaximal concentric contractions of quadriceps and hamstrings (n=50) 2) no treatment, no contact to follow-up 4 weeks (n=50)	VAS pain: baseline, 4 weeks KPFS: baseline, 4 weeks	No drop-outs reported
McMullen 1990	CCT Group assignment dictated by geo-graphical location Low quality: Delphi score 3 Allocation concealment C	Unilateral chondromalacia Duration of complaint: 4.07 ± 2.52 (1-8 months) 29 patients, 55% male Age: 28.12 ± 9.96	Duration 4 weeks, refrain from excessive, strenuous daily leg activities during the treatment program 1) waiting list control, weekly telephone contact, promised the most effective therapy of the other two groups after the trial (n=9) 2) static exercise, stretching hamstrings, 12 sessions in 4 weeks (n=11) 3) isokinetic exercise, 12 sessions in 4 weeks (n=9)	CRS overall activity level: 4 weeks	No drop-outs

Table 3 Included studies: open versus closed kinetic chain exercise

Study	Methods	Participants	Interventions	Outcomes	Notes
Witvrouw 2000	RCT Randomisation using sealed envelopes High quality: Delphi score 6 Allocation concealment A	PFPS, 45% bilateral Duration complaints: 15.1 (0.5 - 28) months Physical therapy department of hospital 60 patients Age: 20.3 (14-33)	Duration: 5 weeks, three days per week, no sports participation during training program, advised to maintain muscle strength until 3 months follow-up 1) open kinetic chain exercise: maximal static quadriceps muscle contractions in full extension, straight leg raises in supine position, short arc terminal knee extensions, leg adductions in lateral decubitus position (n=30) 2) closed kinetic chain exercise: seated leg presses, one-third knee bends on one and both legs, stationary bicycling, rowing-machine exercises, step-up and step-down, progressive jumping (n=30)	VAS pain: baseline, 5 weeks, 3 months ► during daily activity ► during triple jump test KPFS: baseline, 5 weeks, 3 months N without symptoms during functional tests:: baseline, 5 weeks, 3 months ► uilateral squat ► step-up / step-down	No drop-outs
Wijnen 1996	RCT Randomisation by independent person in blocks of 4 persons, prestratified for gender and duration of symptoms (< or > 1 year) High quality: Delphi score 6 Allocation concealment A	PFPS Duration complaints: 32 (4 - 96) months Orthopaedic outpatient clinic 18 patients, 28% male Age: 22 (16-37)	Duration 6 weeks: 1) closed kinetic chain exercise: McConnell regimen with individual exercise program. 12 sessions twice weekly and twice daily home training (n=7) 2) open kinetic chain exercise: Coumans bandage with standard home exercise schedule (n=8)	11-point pain scale, mean (min-max): baseline, 6 weeks ► walking stairs ► sitting with knees bent ► squatting KPFS: baseline, 6 weeks Ranawat function score: baseline, 6 weeks 11-point scale patient satisfaction: 6 weeks ► with therapy ► with recovery	Drop-outs 1) 1 did not show up 1 found quadriceps contraction too painful 2) 1 could not tolerate Coumans bandage
Gaffney 1992	RCT Randomisation method not specified Low quality: Delphi score 3 Allocation concealment B	PFPS/chondromalacia, 50% bilateral Duration of complaints: 40.7 months 72 patients, 65% male Age: 34 (11-65)	Duration 6 weeks Weekly visits to check correct performance all groups, stretching retinaculum before taping 1) closed kinetic chain exercise: pain free eccentric and isometric exercise with taping (squats, steps with gradually increasing speed, height of step and weights (hand/rucksack)) (n=36) 2) open kinetic chain exercise: concentric isometric exercise (quadriceps setting, straight leg raises and knee extensions from 90o) (n=36)	VAS pain baseline: 6 weeks Function grade: 6 weeks Clarke's test positive baseline: 6 weeks Individual's opinion of success: 6 weeks	1) 8 withdrawals 2) 4 withdrawals Descriptions: 1: too far to attend 2: another injury 2: work commitments / travel 7: unknown

Table 3 Included studies: open versus closed kinetic chain exercise (continued)

Study	Methods	Participants	Interventions	Outcomes	Notes
Stiene 1996	CCT Treatment assigned by investigator with attempts to balance for functional rating and patellar dislocation Low quality: Delphi score 1 Allocation concealment C	PFPS Sports Medicine Center 33 patients included, characteristics stated of 23 patients: 39 % male 1) 4 luxations, duration symptoms 13.1 ± 12.2 months 2) 3 luxations, duration symptoms 31.9 ± 31.8 months Age 19 ± 2	Duration 8 weeks Week 1: stretching only, from week 2: exercise three days per week encouraged to apply ice and stretching during 8 weeks 1) open kinetic chain exercise: joint isolation isokinetic exercise: velocity spectrum from 180°/s to 360°/s with 30°/s increments (n=11) 2) closed kinetic chain exercise: squats, lateral and retro step-ups with increasing dumbbell resistance, progression to stair-master exercise (n=12)	Retro step repetitions until intolerance of symptomatic leg (including patients with luxations): baseline, 8, 52 weeks Questionnaire (without patients with luxations): baseline, 6 months, 1 year. outcomes excellent, good, fair, poor	1) 6 drop-outs 2) 4 drop-outs due to <70% of training sessions attended
Colón 1988	RCT Quasi random, matching for age, physical findings and disability Low quality: Delphi score 3 Allocation concealment B	PFPS, mild or moderate Recreational athletes 29 patients, 66% male Age (15-24)	Duration 6-8 weeks Stretching*, ice application after exercise 1) closed kinetic chain exercise: Pogo stick bounces (isometric exercise + endurance training), incremental increase from 250 bounces twice daily up to 10 minutes (n=13) 2) open kinetic chain exercise: conservative isometric exercises: straight leg raises with increasing weights (n=16)	N >50% improved on 11-point pain scale: baseline, 6-8 weeks VAS pain: baseline, 1, 2, 3 months	1) 2 withdrawals: 1 female increased pain, 1 male vacation interruption 2) 2 female withdrawals, no description

Table 4 Included studies: other exercise comparisons

Study	Methods	Participants	Interventions	Outcomes	Notes
Dursun 2001	RCT Randomisation method not specified Low quality: Delphi score 4 Allocation concealment B	PFPS, all unilateral Duration complaints: 10 ± 8 months Outpatient clinic of university medical faculty physical medicine and rehabilitation 60 patients, 20% male Age: 37 ± 10 (17-50)	Duration 3 months Conventional exercise program: strengthening quadriceps and hip adductors with open and closed kinetic chain exercises, stretching, proprioception and endurance (bicycle) training : 5 days/week supervised during 4 weeks, thereafter three times weekly Biofeedback training of VMO and VL 4 weeks, 3 times per week. Stretching*, proprioception training, endurance training with bicycle 1) conventional open and closed kinetic chain exercise with electromyographic biofeedback (n=30) 2) conventional open and closed kinetic chain exercise (n=30)	VAS pain: baseline, 1, 2, 3 months FIQ: baseline, 1, 2, 3 months	No drop outs
Thomee 1997	RCT Odd-even number treatment allocation Low quality: Delphi score 3 Allocation concealment B	PFPS, 27% bilateral, 75% pain with sports, Duration complaints: 43 ± 31.2 (6-108) months Referred by orthopaedic surgeons 40 female patients Age: 20.2 ± 3.2 (15-28)	Duration: 3 sessions to familiarise with training, then 12 weeks training: week 1 and 2 daily training, 3 days per week supervised, thereafter 3 days weekly training, physical therapist contact once or twice weekly 1) isometric exercise (n=20) 2) eccentric exercise (n=20)	Number of patients participating in sports with/without pain: baseline, 3, 12 months Number of subjects experiencing pain: baseline, 3, 12 months ► during jogging ► during heavy loading ► at rest after activity	No drop-outs reported

Table 4 Included studies: other exercise comparisons (continued)

Study	Methods	Participants	Interventions	Outcomes	Notes
Harrison 1999	RCT Random number table, application not specified Low quality: Delphi score 3 Allocation concealment B	PFPS, 54% bilateral, 15% of patients limitations in activities referred from GPs and orthopaedic surgeons 112 patients, 40% male, Age: 22.2 ± 8.2 (12-35)	Duration 4 weeks, All groups ice application after exercise, stretching 1) conservative home exercise: straight leg raises with progressive weights, knee extensions, education on background PFPS (n=42) 2) similar program monitored by physiotherapist, education background PFPS, supervision 3 times weekly (n=34) 3) exercises with patellar taping and biofeedback progressive exercises: stride standing, standing with foot supination, step downs, plié squats, wall squats, optional adductor strengthening, supervision 3 times weekly, home exercise (n=36)	VAS 3 days average of worst pain: baseline, 1, 3, 6, 12 months FIQ, categorised in 4 groups: baseline, 1,12 months PFS (0 worst -100 best): baseline, 1, 3, 6, 12 months Perceived change in condition at 1 month: none/worse, some improvement, significant improvement Seconds of step test until pain: baseline, 1, 3, 6, 12 months	In particular patients with good results at 1 month dropped out Number of participants baseline, 1, 3, 6, 12 months: 1) 33 23 22 14 18 2) 31 26 20 15 13 3) 29 25 20 23 18
Gobelet 2001	RCT Randomisation method not specified Low quality: Delphi score 0 Allocation concealment C	Chondropathy, type Wyberg I or II (not III), with or without dysplasia of the patella 40 patients per group were included	Duration 4 weeks All groups ice application 1) at home electro stimulation of quadriceps with memory card for compliance, 4 hours a day (n=28) 2) pain free isokinetic training at 30°/s and 300°/s, 3 times a week 25-30 minutes supervised (n=40) 3) proprioceptive static exercise, stretching*, 3 times a week 30-45 minutes supervised (n=26)	Arpège function scale: baseline, 4 weeks	Drop out reasons: 10 incomplete 4 non compliance with instructions 12 stopped because of ineffectiveness of treatment.

*stretching exercises usually focus on knee flexors and extensors and iliotibial band, sometimes patellar retinaculum

ABBREVIATIONS AND ACRONYMS
AKP: anterior knee pain
PFPS: patellofemoral pain syndrome
GP: General Practitioner
RCT: randomised controlled trial
CCT: concurrent controlled trial
VAS: visual analogue scale
WOMAC: osteoarthritis index, measuring pain, disability and stiffness of the knee or hip
FIQ: functional index questionnaire
KPFS: Kujala patellofemoral function scale
CRS: Cincinnati rating scale

Exercise versus no exercise

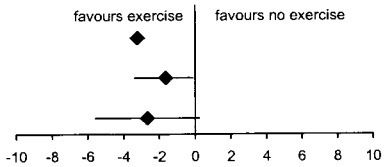
The results and forest plots for the comparisons are displayed in figure 1.

- In the high quality RCT by Clark[19] patient groups receiving exercise therapy were pooled and compared to pooled patient groups not receiving exercise therapy. It was shown that functional ability improves equally in both pooled groups. Pain reduction was not significantly different at 3 months. At the 12 month assessment Clark states that the groups receiving exercise therapy experienced significantly greater pain reduction. Clark reports means and SD of changes only for the 3 month assessment, based on individual changes. Our calculations based on means per time-point do not exactly reproduce these figures nor the statistical difference at 12 months. The number of patients discharged from therapy because they were satisfied with the results were significantly greater for the group that exercised. The number needed to treat was 3 (95%CI: 1.6 to 3.3), so three exercising patients yielded one more satisfied patient than expected in the control group.
- A Protonics® device is a special brace designed to provide progressive resistance exercise during activities of daily living, without restraining motion or protecting knee ligaments. The low quality RCT by Timm[35] showed that resistance during activities of daily living provided by the Protonics® device almost halves the pain-scores compared to the control participants, and drastically improves functional ability after daily use for four weeks. Both effects differ significantly from the control group that did not receive any therapy.
- McMullen[36] found in his low quality CCT that static exercise improved function more than isokinetic exercise, though both types provided only minimal improvement compared to the waiting list controls. Pain levels are not reported, though the author states that they remained unchanged for all groups after four weeks.

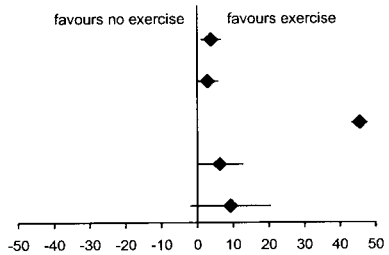
From the best evidence synthesis it follows that there is limited evidence to support the hypothesis that exercise therapy reduces anterior knee pain in patients with PFPS: one high quality RCT and one low quality RCT claim significant pain reduction, and one CCT with a small number of patients contradicts this. There is conflicting evidence of functional improvement: one high quality RCT and one small CCT do not find improvement whereas one low quality RCT does.

Figure 1: Exercise versus no exercise

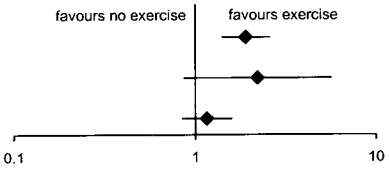
1.1 Pain, continuous data		Time	exercise			no exercise			comparison		
Study ID	**Measurement**	**point**	**N**	**mean**	**SD**	**N**	**mean**	**SD**	**WMD**	**(95% CI)**	
Timm 1998	VAS	1 month	50	3.54	0.97	50	6.74	1.05	-3.20	-3.60	-2.80
Clark 2000	VAS	3 months	32	3.30	3.49	39	4.92	4.05	-1.62	-3.37	-0.13
Clark 2000	VAS	12 months	22	3.66	4.42	27	6.32	5.93	-2.66	-5.56	0.24



1.2 Function, continuous data		Time	exercise			no exercise			comparison		
Study ID	**Measurement**	**point**	**N**	**mean**	**SD**	**N**	**mean**	**SD**	**WMD**	**(95% CI)**	
McMullen 1990	Cincinnatti overall activity level, static exercise versus no exercise	1 month	11	14.8	3.06	9	10.9	3.06	3.90	1.20	6.60
McMullen 1990	Cincinnatti overall activity level, isokinetic exercise versus no	1 month	9	13.9	3.06	9	10.9	3.06	2.94	0.11	5.77
Timm 1998	Kujala Patellofemoral Scale	1 month	50	86.8	6.65	50	41.2	3.95	45.6	43.4	47.7
Clark 2000	100 - WOMAC = inversed WOMAC scale	3 months	32	89.2	11.2	39	82.9	16.1	6.3	-0.1	12.7
Clark 2000	100 - WOMAC = inversed WOMAC scale	12 months	22	84.8	17.4	27	75.5	22.1	9.3	-1.8	20.4



1.3 Recovery, dichotomous data		Time	exercise		no exercise		comparison		
Study ID	**Measurement**	**point**	**n**	**N**	**n**	**N**	**RR**	**(95% CI)**	
Clark 2000	N discharged from therapy because of patient's satisfaction	3 months	39	40	21	41	1.90	1.41	2.58
Clark 2000	N no longer troubled by symptoms	12 months	9	22	5	27	2.21	0.87	5.64
Clark 2000	N discontinuing therapy	12 months	18	22	19	27	1.16	0.85	1.59



Open kinetic chain versus closed kinetic chain

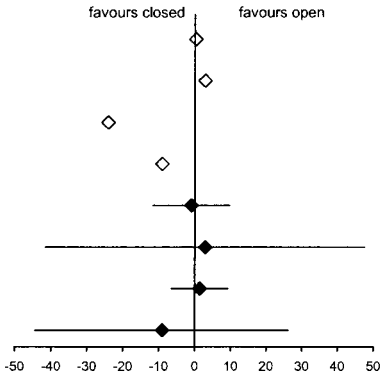
For categorising the studies, the descriptions of the exercises rather than the terminology in the publications was used (table 3). Results of comparisons are displayed in figure 2.

- The high quality RCT by Witvrouw[37] showed that both function and pain improve significantly with both open and closed kinetic chain exercise, though no significant differences between the groups are found.
- The high quality RCT by Wijnen[38] showed no statistical differences for pain and function. However patient satisfaction with the therapy is significantly greater in the group combining closed kinetic chain exercises with McConnell taping than in the home exercise group with Coumans bandages.
- The low quality RCT by Gaffney[24] reported no significant differences in pain and function outcomes between eccentric closed kinetic chain and concentric open kinetic chain exercises.
- The low quality CCT by Stiene[39] shows that though muscle strength improves in both groups, the closed kinetic chain exercise results in significantly better function as determined through retro-step up performance. This result is dubious as baseline values differ significantly between groups. The representation of Functional Index Questionnaire results was inadequate for interpretation. Pain was not reported in this study.
- The low quality RCT by Colón[40] uses a Pogo stick (a stick with foot holds which contains springs to enable bouncing) for closed kinetic chain exercise to compare with straight leg raises. It focuses completely on muscle strength, but does not provide statistical analyses to compare groups. He found that almost all patients in both groups report substantial (>50%) pain relief, but pain levels are not reported and differences between groups are not apparent.

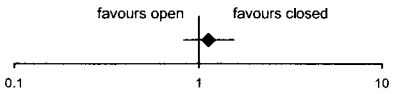
The results of both high and low quality RCTs are consistent for both pain and function, so there is strong evidence to support the hypothesis that closed kinetic chain exercises provide equal results to open kinetic chain exercises for either pain reduction or function improvement.

Figure 2: Closed kinetic chain versus open kinetic chain

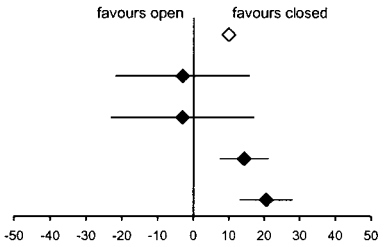
2.1 Pain, continuous data		Time	closed			open			comparison		
Study ID	**Measurement**	**point**	**N**	**mean**	**SD**	**N**	**mean**	**SD**	**WMD**	**(95% CI)**	
Gaffney 1992	VAS (0-100)	6 weeks	28	32.1	-	32	31.7	-	0.40	-	
Wijnen 1996	VAS (0-100) walking stairs	6 weeks	8	44	-	7	41	-	3.0	-	
Wijnen 1996	VAS (0-100) sitting with knees bent	6 weeks	8	19	-	7	43	-	-24.0	-	
Wijnen 1996	VAS (0-100) bending knees	6 weeks	8	51	-	7	60	-	-9.0	-	
Witvrouw 2000	VAS (0-100) during triple jump test	5 weeks	30	12.8	20	30	13.7	22	-0.9	-11.5	9.7
Witvrouw 2000	VAS (0-100) during daily activity	5 weeks	30	40.0	88	30	37.0	88	3.0	-41.5	47.5
Witvrouw 2000	VAS (0-100) during triple jump test	3 months	30	10.5	17	30	9.1	14	1.4	-6.5	9.3
Witvrouw 2000	VAS (0-100) during daily activity	3 months	30	30.0	55	30	39.0	82	-9.0	-44.3	26.3



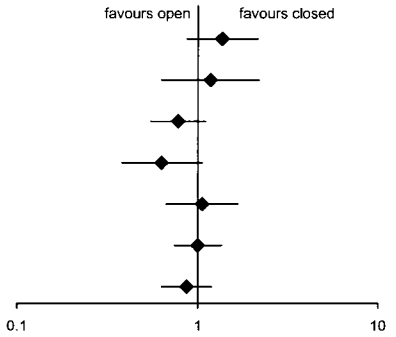
2.2 Pain, dichotomous data		Time	closed		open		comparison		
Study ID	**Measurement**	**point**	**n**	**N**	**n**	**N**	**RR**	**(95% CI)**	
Colón 1988	N >50% improvement	6-8 weeks	13	14	9	11	1.13	0.83	1.55



2.3 Function, continuous data		Time	closed			open			comparison		
Study ID	**Measurement**	**point**	**N**	**mean**	**SD**	**N**	**mean**	**SD**	**WMD**	**(95% CI)**	
Wijnen 1996	Kujala Patellofemoral Scale	6 weeks	7	84.0	0	8	74.1	0	9.9	-	
Witvrouw 2000	Kujala Patellofemoral Scale	6 weeks	30	80.0	37	30	83.0	37	-3.0	-21.7	15.7
Witvrouw 2000	Kujala Patellofemoral Scale	3 months	30	84.0	39	30	87.0	40	-3.0	-23.0	17.0
Stiene 1996	Number of retro-step repetitions until painful	8 weeks	12	18.6	11.9	11	4.3	1.7	14.3	7.5	21.1
Stiene 1996	Number of retro-step repetitions until painful	1 year	12	27.3	12.5	11	6.7	3.5	20.6	13.2	28.0

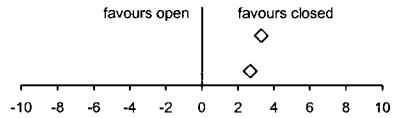


2.4 Function, dichotomous data		Time	closed		open		comparison		
Study ID	**Measurement**	**point**	**n**	**N**	**n**	**N**	**RR**	**(95% CI)**	
Gaffney 1992	Overall assessment of function N improved	6 weeks	18	28	15	32	1.37	0.87	2.17
Witvrouw 2000	N asymptomatic unilateral squat test	5 weeks	13	30	11	30	1.18	0.63	2.20
Witvrouw 2000	N asymptomatic step up test	5 weeks	18	30	23	30	0.78	0.55	1.11
Witvrouw 2000	N aymptomatic step down test	5 weeks	12	30	19	30	0.63	0.38	1.06
Witvrouw 2000	N asymptomatic unilateral squat test	3 months	17	30	16	30	1.06	0.67	1.68
Witvrouw 2000	N asymptomatic step up test	3 months	22	30	22	30	1.00	0.74	1.36
Witvrouw 2000	N asymptomatic step down test	3 months	20	30	23	30	0.87	0.63	1.20

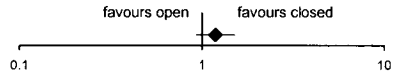


2.5 Function, categorical data		Time	closed				open			
		point	**poor**	**fair**	**good**	**excellent**	**poor**	**fair**	**good**	**excellent**
Study	**Measurement**		**n**	**n**	**n**	**n**	**n**	**n**	**n**	**n**
Stiene 1996	Function Index Questionnaire	6 months	0	4	7	1	1	8	2	0
Stiene 1996	Function Index Questionnaire	12 months	0	2	3	7	1	6	4	0

2.6 Global assessment, 0-10 NRS, continuous data		Time	closed			open			comparison		
Study ID	**Measurement**	**point**	**N**	**mean**	**SD**	**N**	**mean**	**SD**	**WMD**	**(95% CI)**	
Wijnen 1996	Satisfaction with therapy	6 weeks	8	7.6	-	7	4.30	-	3.30	-	
Wijnen 1996	Satisfaction with recovery	6 weeks	8	6.1	-	7	3.40	-	2.70	-	



2.7 Global assessments, dichotomous data		Time	closed		open		comparison		
Study ID	**Measurement**	**point**	**n**	**N**	**n**	**N**	**RR**	**(95% CI)**	
Gaffney 1992	Treatment success	6 weeks	25	28	24	32	1.19	0.94	1.51



Other comparisons

The other comparisons could not be compared to each other, and are therefore not displayed in forest plots. The study characteristics are displayed in table 4.

- The low quality RCT by Harrison[43] showed improvement in all groups for both pain and function, which is stated to be significant for the Patellar Function Scale. However, these outcomes were not significantly different between home exercise and the supervised exercise groups. Interestingly, our analysis of the presented data revealed that significantly more patients from the physical therapy group rated their clinical change as "significant improvement" compared to the home exercise group, though the author states there is no significant difference.
- In the low quality RCT by Thomee[14] a significant reduction of pain in all visual analogue scales is reported, both at three months and again at 12 months, though no differences between isometric and eccentric exercise groups were found. No pain levels are reported, only frequencies of patients with pain in three situations. Lysholm knee function scores are not reported. Muscle strength increased significantly in both groups, though no significant differences were found except in a 25 degree range during eccentric contractions.
- The low quality RCT performed by Dursun[41] did not reveal any differences between the outcomes of the groups exercising with or without EMG-biofeedback.

The low quality RCT by Gobelet[44] found significant increases in clinical evaluation of the knee using the Arpège score list for the groups receiving electrostimulation and isometric exercise. Isokinetic exercise did not improve the status. Isokinetic muscle strength improved in the groups receiving electrostimulation and isokinetic training, but in the group receiving isometric training strength did not improve at all isokinetic velocities at which muscle strength was measured.

Discussion

Exercise versus no exercise

Only one of the three trials comparing exercise with no exercise was of high quality. The best evidence synthesis suggests that there is some indication that exercise is effective, but the data are not straightforward.

McMullen[36] argues the time period of four weeks may be too short, though other authors, such as Timm[35] have found significant improvement in this period. The intensity of the exercises may be the clue, as Timm's participants received daily therapy for several hours during activities of daily living. However, the Protonics® device will not be universally applied and is therefore of clinically limited relevance. The first follow-up assessment by Clark[19] was found after three months, at which time point improvement was made in all groups, though the difference between the exercising and non exercising groups only became apparent after one year. It is possible that the 60% drop-out rate after 12 months in Clark's study contributed to this significant difference by introducing attrition bias.

But what explains the difference in effect seen in different control groups? One might argue that the improvement observed in Clark's study reflects the natural course of the affliction. However, the duration of symptoms prior to the study makes this unlikely. Another explanation may lay in the effect that participating in and fulfilling the requirements of a study alters an individual's behaviour, thereby contributing to the improvement. This is the so called Hawthorne effect. It is also possible that education may affect the behaviour of patients more than mere enrolment in a study when the treatment comes down to being placed on a waiting list. The duration of the trials by Timm[35] and McMullen[36] may also be too short to establish the Hawthorne effect, because it may take longer than four weeks for behavioural changes to result in clinical improvement. However, the assumption that behavioural changes occur, cannot be established from the reported results.

Although the studies performed by Clark[19] (N=81) and Timm[35] (N=100) have the largest number of patients of all included studies, it should be noted that the number of patients in these studies is still modest.

Open kinetic chain versus closed kinetic chain

The concept that closed kinetic chain exercises would be more effective than open kinetic chain exercises because they more closely resemble activities of daily living was not supported by evidence in any of the studies considered in this review. Greater satisfaction with McConnell treatment found by Wijnen[38] could either be attributed to the closed kinetic chain exercises or to the application of McConnell tapes instead of Coumans bandages. This touches a problem that calls for reservations in the interpretation of this best evidence synthesis. It should be noted that though the common factor in these five studies is the contrast of open versus closed kinetic chain exercise, the differences in all other aspects of the interventions are considerable. The terminology the authors use for their exercise programs reflects the factor the author is most interested in and hence the different accents in each exercise program.

Methodolical quality

Quality assessment

Overall the agreement between reviewers on the methodological scoring was reasonable, and consensus was reached without problems. Poor reporting of the studies was partly responsible for the poor agreement between the reviewers for item M-G: "Were care programmes, other than the trial options, identical?". The sometimes meagre descriptions of the treatment programs made evaluation of comparability harder, but interpretation of reported facts also led to problems: is the mention of differences in permission to use patellar taping, analgesics or infra-red treatment part of the trial options, or does it supplement these options? The duration of the treatments was always identical. The different scores for item M-K can be attributed partly to the fact that the term diagnostic tests raised confusion as to whether the tests are used for screening purposes or for outcome assessment. Furthermore, it is open to interpretation whether assessment of symptoms like pain during certain activities can be viewed as diagnostic tests.

Cut-off point for high quality

The nature of exercise therapy makes it impossible to conceal treatment allocation to the patients or for the treatment providers, which results in a maximum feasible score of 7 out of 9 Delphi items. The cut-off point for the number of Delphi items needed for the

qualification "high methodological quality" coincided with the allocation of Cochrane code "A", and the difference between the high quality scores and the low quality scores always amounted to at least 2 Delphi items. Dursun's study is the only study that might be qualified as high quality when a different cut-off point is chosen. However, this study does not answer any of the clinically relevant research questions. Therefore, the cut-off point for classification of high or low quality was deemed justified for use in our planned qualitative analysis and no analysis was performed using an alternative cut-off point.

Methodological shortcomings

Though all studies intend to compare treatments, some authors have failed to provide a statistical analysis between treatment groups. They suffice with stating whether within each group significant changes occur. However, when significant changes occur within each group, the question whether some treatments provide better effects is not answered. Worse, when significant changes occur within one group, but not another, comparison of both groups may not produce statistically significant differences. Especially in studies where blinding of treatment allocators during randomisation was not described (i.e. all low quality studies), and where baseline characteristics and measurements were not equal, the method of reporting within group changes can be very misleading.

Though some authors of low quality trials describe their methods in detail, this detail is sometimes lacking in the reporting of outcome measures. Shortcomings range from failing to report outcomes that are mentioned in the methods section (Thomee[14] (VAS), McMullen[36] (Cincinnatti Rating Scale (CRS))), not mentioning the number of patients (Gaffney[24]: VAS and diagnostic tests), to methods of data reduction that prevent insight in the data. For example originally continuous data are converted to ordinal (Harrison[43] (Functional Index Questionnaire (FIQ))), or even dichotomous data (Thomee[14] (VAS)), which also hampers insight in variability of the data. McMullen[36] and Colón[40] fail to report baseline data. Although McMullen[36] presents ANCOVA outcomes and post-treatment values giving the reader an opportunity to deduce estimators of baseline values, Colón[40] only presents the number of patients with at least 50% pain reduction. Furthermore, drop-outs have rarely been reported properly and intention to treat analyses were even more rare.

Timm[35], McMullen[36] and Dursun[41] include only patients with unilateral afflictions which may give a biased representation of the patient population. Wivrouw[37], Harrison[43], and

Thomee[14] have taken the approach of including both unilateral and bilateral patients, choosing the most afflicted leg as object of investigation. However, Gaffney[24] uses both unilaterally and bilaterally afflicted patients, but has reported data that represent knees instead of patients, without giving the number of patients involved.

Outcome measures

Pain is the symptom that prompts the patient's visit to a doctor, and function may be limited as a result. Muscle imbalance and/or weakness may be the underlying problem or a condition for PFPS to evolve, so muscle strengthening is a means to treat PFPS, but it is not a goal in itself in the management of PFPS. However, isokinetic power and torque measurements as quantifiable measure for muscle strength are used as outcome measures by some authors. Natri[18] showed that restoration of quadriceps strength is important for good recovery of the patient, as determined by the difference between affected and unaffected leg: the smaller the difference in extensor strength, the better the outcome. However, none of the authors in this review chose the difference between legs as outcome parameter, which is understandable, given the fact that some patients have bilateral complaints. Presentation of these results would therefore muddy the overview given here, so we chose to leave them out. Not surprisingly, for all groups receiving exercise therapy, muscle strength increased, and differences found when comparing exercise treatments were usually minimal. Stiene[39] notes that improving muscle strength did not improve the patient's function and Dursun[41] found that improved muscle function appeared to have no effect on the clinical and functional status. Gobelet[44] found that isokinetic training increased muscle strength, though not clinical improvement, whereas isometric training did not increase muscle strength, but improved the clinical outcome. These findings illustrate the difficulty of interpreting the effect of therapy using muscle strength as an outcome measure for knee function. Therefore we chose to determine effectiveness using outcomes more directly related to the wellbeing of the patients involved. Hence, our choice not to include muscle strength as relevant outcome measure in determining the effectiveness of PFPS seems justified.

Compliance and withdrawal

Compliance problems can be viewed as an inescapable element of exercise therapy, so compliance problems in trials can be viewed as truthful representations of medical practice, which is why an intention to treat analysis is imperative. Harrison notes that

many drop-outs showed good results, and suggests an underestimation of the effect of treatment is given. Unfortunately, few authors have reported compliance in a satisfactory manner. Colón[40] reports one participant dropping out because of increased symptoms. Stiene[39] reports non-compliance and unavailability for final testing as reasons for dropping them from analysis. Gobelet[44] has withdrawn patients from analysis because of poor compliance, defined less than 70% attendance of training sessions. If no intention to treat analysis is performed, at least a comparison of baseline values of outcome measures of the drop-outs would be useful, to determine the possible bias of results. As most authors have not reported an intention to treat analysis and most studies struggle with high drop-out rates and small population sizes the effect of compliance as a confounder must be deemed significant, though elusive. High drop-out rates are evident in many studies, and make the feasibility of long term assessments problematic.

Power

If one looks at the limited evidence for the effectiveness of exercise therapy, one can see that benefits from exercise therapy seem relatively small, and variances (if reported) are rather large. When comparing different types of exercise therapy it is only logical that differences between treatment groups are even smaller. It is therefore regrettable that patient numbers in the included studies were, in general, rather small, and in some cases alarmingly so. This makes it almost impossible to detect differences between treatment groups (type II error). When reading this review it should be kept in mind that the low power and the other methodological flaws discussed above make it hard to reach any firm conclusions.

Reviewers' conclusions

Implications for practice

There is limited evidence for the effectiveness of exercise therapy for PFPS. Open kinetic chain exercises and closed kinetic chain exercises are equally effective. Based on the limited evidence for effectiveness, physicians may consider exercise therapy for the treatment of PFPS.

Implications for research

Prior to the study an assessment of the disease burden, the pain levels and the level of function impairment of the expected study population should be made, and patients should be asked how much improvement they expect from exercise therapy for it to be called successful, given the effort it requires. Taking into account the variance of these outcome measures, a power calculation should be made to determine the minimal number of patients required for detection of the desired effect. A factorial design aimed at studying the additional effect of education, taping, or any form of pain relief may be considered to determine the role of various co-interventions commonly applied. The population size required would have to be determined with adequate power analysis.

Future researchers should beware of the misleading notion that muscle function represents the clinical status of PFPS, and use pain and function as the primary outcome measures in any trial studying the effectiveness of exercise therapy for PFPS. Questionnaires to assess the status of knee function often include questions about pain. However, separate pain measures are a valuable addition to the assessment of knee status, as can be seen from Clark's study, where pain reduction is significantly greater in the exercise group, whereas function assessments do not show this significant difference.

The limited evidence for effectiveness of exercise therapy for PFPS shows that the ethical objections of several authors against using a control group not receiving any therapy are based more on the assumption of effectiveness of exercise therapy than on sound scientific evidence. This observation should be considered by investigators who wish to contribute to the discussion on effectiveness of exercise therapy by performing studies of high methodological quality, which should compare exercise therapy to a control group not receiving exercise therapy.

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7

Pharmacotherapy for patellofemoral pain syndrome A systematic Cochrane review

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Abstract

Background

Patellofemoral pain syndrome (PFPS) is common among adolescents and young adults. It is characterised by pain behind or around the patella and crepitations, provoked by walking stairs, squatting, prolonged sitting with knees flexed, running and cycling. The symptoms impede function in daily activities or sports. Pharmacological treatments focus on reducing pain symptoms (non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticosteroids), or restoring the assumed underlying pathology (compounds containing glucosamine to stimulate cartilage metabolism, anabolic steroids to increase bone density of the patella and build up supporting muscles). In studies, drugs are usually applied in addition to exercises aiming at building up supporting musculature.

Objectives

This review aims to summarise the evidence of effectiveness of pharmacotherapy in reducing anterior knee pain and improving knee function in people with PFPS.

Search strategy

We searched the Cochrane Musculoskeletal Injuries Group and Cochrane Rehabilitation and Related Therapies Field trials registers, the Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 4, 2003), PEDro (up to January 2004) , MEDLINE (1966 to January 2004), EMBASE (1988 to January 2004), and CINAHL (1982 to January 2004).

Selection criteria

Controlled trials (randomised or not) comparing pharmacotherapy with placebo, different types of pharmacotherapy, or pharmacotherapy to other therapies for people with PFPS.

Data collection & analysis

The literature search yielded 780 publications. Eight trials were included, of which three were of high quality. Data were analysed qualitatively using best evidence synthesis, because meta-analysis was impeded by differences in route of administration of drugs, care programs and outcome measures.

Main results

Four trials (163 participants) studied the effect of NSAIDs. Aspirin compared to placebo in a high quality trial produced no significant differences in clinical symptoms and signs. Naproxen produced significant short term pain reduction when compared to placebo, but

not when compared to diflunisal. Laser therapy to stimulate blood flow in tender areas led to more satisfied participants than tenoxicam, though not significantly.

Two high quality RCTs (84 participants) studied the effect of glycosaminoglycan polysulphate (GAGPS). Twelve intramuscular injections in six weeks led to significantly more participants with a good overall therapeutic effect after one year, and to significantly better pain reduction during one of two activities. Five weekly intra-articular injections of GAGPS and lidocaine were compared with intra-articular injections of saline and lidocaine or no injections, all with concurrent quadriceps training. Injected participants showed better function after six weeks, though only the difference between GAGPS injected participants and non-injected participants was significant. The differences had disappeared after one year.

One trial (43 participants) found that intramuscular injections of the anabolic steroid nandrolone phenylpropionate significantly improved both pain and function compared to placebo injections.

Reviewers' conclusions

There is only limited evidence for the effectiveness of NSAIDs for short term pain reduction in PFPS. The evidence for the effect of glycosaminoglycan polysulphate is conflicting and merits further investigation. The anabolic steroid nandrolone may be effective, but is too controversial for treatment of PFPS.

Background

Patellofemoral pain syndrome (PFPS) is a common complaint in adolescents and young adults. The symptom most frequently reported is a diffuse peripatellar and retropatellar localised pain, typically provoked by ascending or descending stairs, squatting, and sitting with flexed knees for prolonged periods of time (the so called 'movie sign'). Other common symptoms are crepitus and giving-way[1-5].

In the literature there is some agreement that PFPS is a term to be applied only to people with retropatellar pain in which no cartilage damage is evident[1,4,6-9]. However, retropatellar pain is generally thought of as a self-limiting condition with a good prognosis, especially for people who are young[10], people who have unilateral complaints, and people in which crepitation is absent[11]). This means that people are usually managed in primary care and are rarely referred to specialist care[12]). Therefore reliable diagnostic techniques for determining cartilage damage such as computed tomography (CT), magnetic resonance imaging (MRI) or arthroscopy[1,2] are seldom applied. In fact a diagnosis based solely on symptoms and physical examination of the knee is not uncommon. Furthermore, Natri showed that neither the radiologic nor the MRI changes seen in affected knees showed a clear association with persistent symptoms seven years later[11]. This makes the distinction between chondromalacia and PFPS theoretical rather than practical, so people with either chondromalacia or PFPS will be included in this review.

Increased pressure on the patellofemoral joint seems to lie at the heart of the syndrome[13], either caused by increased activity levels, malalignment of the patella when moving through the femoral groove, muscle imbalance of the quadriceps or tight anatomical structures such as the retinaculum or iliotibial band. However, it remains elusive which structures or tissues cause the pain: several studies during the last two decades have shown a poor correlation between arthroscopic evidence of articular cartilage damage and retropatellar pain[11,14]. Furthermore, cartilage is not innervated, and so subchondral bone as well as peripatellar soft tissues may be involved. Depending on the presumed mechanism at work, different approaches can be taken when applying pharmacotherapy. Therefore a brief outline is given of the presumed mechanisms.

Increased patellofemoral joint reaction stress may cause microscopic damage to the patellar cartilage through friction. In this process proteolytic enzymes are released that cause further fragmentation of the cartilage matrix. Damage to the cartilage is countered

with an increased production of proteoglycans and collagen, the building stones to make repairs[15]. On the other hand, the damaged cartilage is less efficient in absorbing stresses and a vicious circle may be the result, in which the cartilage loses its ability to defer stresses from the subchondral bone. Increased intrapatellar pressure may also impede blood flow through the patella and cause subchondral bone degeneration, which may progress to the surface and ultimately result in chondral lesions[16,17]. Increased physical activity or maltracking of the patella through the femoral groove may lead to peripatellar soft tissue irritation, so that retinacular nerve endings may generate the pain[2,11,14,18]. It is not very likely that pain arises from the synovium because in PFPS there is limited, if any, effusion.

When approaching PFPS as a cartilage problem, pharmacotherapy may focus on chemically disrupting the destructive enzymatic processes or aid constructive processes by providing nutrients for cartilage repair. Glycosaminoglycan polysulphate (GAGPS) inhibits proteolytic enzymes, which degrade proteoglycans and collagen in the cartilage[19]. It has also been shown to increase the rate of synthesis and the degree of polymerisation of hyaluronic acid in the synovial fluid, which would benefit cartilage repair. Aspirin has been shown to inhibit destructive enzymatic processes in cartilage in animal studies[15]. However, when assuming that bone degeneration precedes chondral degeneration, reversal of bone density loss could be considered. The anabolic ester nandrolone phenylpropionate is used to increase bone density and also serves to build up muscles supporting normal patellofemoral glide.

When assuming that irritation of soft tissues causes the pain, suppression of inflammatory (or sub-inflammatory) processes could be targeted, either through the use of NSAIDs or glucocorticosteroids.

Whatever the approach, pharmacotherapy is limited to the chemical processes that result from the increased pressure in the patellofemoral joint. Therefore it usually only plays an auxiliary role in pain reduction (NSAIDs), or reversing or limiting damage (glucosamine containing compounds, anabolic steroids), while at the same time tackling the ultimate cause with physical interventions. These physical interventions are usually conservative: refraining from pain provoking activities and training the knee extensor mechanism to build up muscles supporting normal patellofemoral glide, with or without the use of tape or braces to relieve pressure on the patellofemoral joint[1,6,8,14]. In the literature consensus has been reached that surgical interventions should be avoided,

and should only be considered in very severe cases which have proven to be resistant to conservative treatment [20].

Objectives

This review was undertaken to assess the effectiveness of pharmacotherapy in the conservative treatment for patellofemoral pain syndrome, by:

- comparing pharmacotherapy with placebo treatment or no treatment
- comparing different types of pharmacotherapy
- comparing pharmacotherapy with other conservative treatment or surgical treatment

using anterior knee pain, knee function and subjective assessments of recovery as clinically relevant outcome measures. Measurements up to one year follow-up were considered short term outcomes, thereafter long term.

Criteria for considering studies for this review

Types of studies

Concurrent, randomised or quasi-randomised (i.e. allocation of participants to treatment groups which are not strictly random, such as date of birth, alternation, etc.) controlled trials (RCTs) and concurrent controlled trials without randomisation (CCTs) on pharmacotherapy for patellofemoral pain were considered. Because CCTs are more likely to introduce bias, they were considered only for qualitative analyses, to give a complete overview of published data. Retrospective studies were excluded.

Types of participants

People suffering from patellofemoral pain syndrome (including anterior knee pain syndrome and chondromalacia patellae). Studies which specifically focus on other named knee pathologies such as Hoffa's disease, Osgood Schlatter disease, Sinding-Larsen-Johansson's disease, iliotibial band friction syndrome, tendinitis, neuromas, intra-articular pathology including osteoarthritis, rheumatoid arthritis, traumatic injuries (such as injured ligaments, meniscal tears, patellar fractures and patellar luxation), plica syndromes, and more rarely occurring pathologies were excluded[2,14]. No restrictions on age or setting were applied.

Types of interventions

Only controlled trials including at least one treatment arm consisting of pharmacotherapy for PFPS were included in this review. Oral, topical, intra-articular or intramuscular administration of the following pharmaceutical agents were considered for this review:

- non-steroidal anti-inflammatory drugs (NSAIDs)
- analgesics (including opiates)
- steroids
- biological agents and dietary supplements such as glucosamine, capsaicin, hyaluronic acid, vitamin preparations or fish oil.

Types of outcome measures

The primary outcome was knee pain intensity, measured on a visual analogue scale, numerical rating scale or pain index. Secondary outcomes focus on functional disability level and subjective assessments of recovery. Questionnaires focusing on knee function and the ability to perform tests were considered measures for functional disability (e.g. Lysholm scale for characteristics of knee function, Tegner scale for activity levels, or the ability to perform jumps or squats). Measures of recovery include ordinal rating scales (improved, no change, worse) or percentage ratings (subjective percentage improvement, where each patient estimates his/her own improvement from -100% (deterioration) to 100% (full recovery)).

Adverse effects like increased pain levels were taken into consideration as well. As changes on impairment level alone (i.e. range of motion, muscle strength, etc.) do not directly represent changes in the symptoms of patellofemoral pain or the resulting disability, we will not base conclusions on effectiveness on these outcome measures in this review.

Identification of studies

We searched the Cochrane Musculoskeletal Injuries Group and Cochrane Rehabilitation and Related Therapies Field specialised registers, the Cochrane Controlled Trials Register, MEDLINE (1966 to December 2001), EMBASE (1988 to December 2001), CINAHL (1982 to December 2001), PEDro - The Physiotherapy Evidence Database (http://ptwww.cchs.usyd.edu.au/pedro), and reference lists of articles. No language restriction was applied. Using the optimal trial search strategy trial search strategy[21] we looked for trials containing the terms anterior knee pain, words containing 'patell',: chondromalacia or chondropathy.

Two reviewers (MB, SBZ) independently selected the trials, initially based on title and abstract. From the title, keywords and abstract they assessed whether the study met the inclusion criteria regarding diagnosis, design and intervention. Of the selected references, the full article was retrieved for final assessment. Next, they independently performed a final selection of the trials to be included in the review, using a standardised form. Disagreements were solved in a consensus meeting.

Methods of the review

Selecting trials for inclusion

Two reviewers (SB, MB) independently selected the trials, initially based on title and abstract. For the selected references a final decision about inclusion was made based on the full article, using a standardised form listing the inclusion criteria. Disagreements on inclusion were resolved by discussion.

Methodological quality assessment

The methodological quality was assessed by two reviewers (BK, JV) independently using the Delphi list (table 1)[22]. Disagreements were solved in a consensus meeting. For each item Cohen's Kappa and the percentage agreement between both reviewers was calculated. Trials presenting an adequate or concealed randomisation procedure and adequate blinding (Cochrane code A), or a maximum score of five or more Delphi items were labelled "high quality" trials.

Table 1 Methodological quality assessment

Delphi list[22]
D1. Was a method of (quasi) randomisation performed?
D2. Was the assigned treatment adequately concealed prior to allocation? Cochrane code: Clearly Yes = A; Not sure = B; Clearly No = C.
D3. Were the treatment and control group comparable at entry?
D4. Were the inclusion and exclusion criteria clearly defined?
D5. Were the outcome assessors blinded to treatment status?
D6. Were the treatment providers blind to assignment status after allocation?
D7. Were the participants blind to assignment status after allocation?
D8. Were point estimates and measures of variability presented for the primary outcome measures?
D9. Were the outcomes of patients who withdrew described and included in the analysis (intention to treat)?

Data extraction

Two reviewers (EH, RB) independently extracted the data regarding the interventions, type of outcome measures, follow-up, loss to follow-up, and outcomes. The various outcome measures were presented separately. The results of each RCT are expressed as relative risks (RR) with corresponding 95 per cent confidence intervals (CI) for dichotomous data and standardised mean differences (SMD) and 95 per cent confidence intervals for continuous data. The statistical analysis component of RevMan[23], was used to analyse the data.

Analysis

As the included studies were heterogeneous with respect to pharmacon and/or administration mode, quantitative analysis of pooled results was not possible. A summary is given of all clinically relevant outcome measures. A further analysis was performed, using a rating system with levels of evidence based on the overall quality, and the outcome of the studies[24,25]. The rating criteria are listed here:

- strong evidence - provided by generally consistent findings in multiple high quality RCTs;
- moderate evidence - provided by generally consistent findings in one high quality RCT and one or more lower quality RCTs, or by generally consistent findings in multiple low quality RCTs;
- limited evidence - provided by only one RCT (either high or low quality) or generally consistent findings in CCTs;
- conflicting evidence - inconsistent findings in multiple RCTs and CCTs;
- no evidence - no CCTs or RCTs.

Results

Description of studies

Of the 780 titles and abstracts identified by the systematic search of the literature, two reviewers (SB, MB) selected 13 abstracts to be viewed in full text, which resulted in eight studies that met the inclusion criteria (see table 3 for excluded studies). The included studies (table 2) covered a wide area of pharmaceutical agents, which were roughly attributed to 4 types of pharmaceutical agents, i.e. NSAIDs, glucocorticosteroids, anabolic steroids and glucosaminoglycan.

Table 2 Characteristics of included studies

NSAIDs

Study	Methods	Participants	Interventions	Outcomes	Notes
Bentley 1981	RCT, randomisation by pharmacist High quality: Delphi score 7 Allocation concealment A	Chondromalacia patellae diagnosed by arthroscopy performed in patients that did not improve with 3 months treatment with isometric quadriceps exercises 30 patients, 2 bilateral, worst knee is treated 8 male, 22 female Age 15-35 Many athletic patients	Baseline arthroscopy for grading of cartilage damage, then randomisation 1. aspirin (Aloxiprin) (n=16) 2. placebo (n=13) 10 week period, during which serum levels of aspirin were monitored. Dose not reported. Repeated arthroscopy after 12 weeks	Subjective change in symptoms (improved, unchanged, worse) at 12 weeks Arthroscopic grading of cartilage damage at baseline and 12 weeks Arthroscopic changes (improved no change worse) at 12 weeks	4 of 16 patients did not maintain effective blood levels of between 15 and 25 mg/100 ml, due to side effects or non-cooperation 1 drop out refused repeated arthroscopy, treatment group is not mentioned patients were not allowed aspirin during 3 month exercise period previous to aspirin treatment
Fulkerson 1986	RCT, randomisation through odd - even assignment, not blind Low quality: Delphi score 0 Allocation concealment C	56 patients enrolled, 36 patients with anterior knee pain of mild to moderate severity completed the study 28 women, 8 men, mean age 32.3 years multiple diagnoses per patient: 42% chondromalacia patellae, 39% internal derangement, 30%tendonitis/sprains, 8% inflamed plica, 5% degenerative joint disease, 1% loose body, 1% Sindig-Larsen-Johansson disease	20 patients: NSAID diflunisal initial dose 1000 mg, followed by 500 mg BID (mean duration 19.8 days) 16 patients: NSAID naproxen initial dose 500 mg, followed by 250 mg QID (mean duration 15.2 days)	Severity of pain and swelling at baseline and 1, 2, and 5 days after start of therapy Adverse reactions: common but mild Diflunisal: headache (2), gastric distress (2), tinnitus, nausea, indigestion, urinary retention, rash, cramps, fever Naproxen: drowsiness (2) pounding in head, cramps, inability to concentrate, mild depression, euphoria	The high prevalence of chondromalacia and patellofemoral malalignment and the limited number of trials available for this review have led us to include this study into the review
Marchese 1998	RCT, method not specified Low quality study: Delphi score 0 Allocation concealment D	Anterior knee pain for at least 3 months, no recent trauma, tendinopathy or osteochondrosis of the knee 35 female patients Age 13.8 - 15.8 years 29 patients performed sports activities, none of them at a competitive or amateur level	1. Laser therapy for 15 sessions (n=18) 2. 20 mg Tenoxicam once daily for 15 days (NSAID) (n=17)	Clinical results: patient satisfaction with the results of the treatment Other outcomes (VAS and palpation tests for pain, crepitation, Kujala scale for function) were assessed at baseline, 15 days and 60 days, though the reporting of these outcomes was too poor to be understandable.	The time frame of the laser therapy is not entirely clear.

Table 2 Characteristics of included studies (continued)

NSAIDs (continued)

Study	Methods	Participants	Interventions	Outcomes	Notes
Suter 1998	RCT, randomisation method not defined, double blind. Low quality: Delphi score 4 Allocation concealment B	42 patients, identified through patient database at the University Sports Medicine Center 29 men and 13 women Age: mean 35.6, SD 8.4 Inclusion criteria: unilateral anterior knee pain syndrome of varying duration, no history of knee surgery or knee instability, quadriceps injury, or bone, meniscus or ligament injury, no history of peptic ulceration, no concurrent disease of other organ systems.	20 patients: NSAID naproxen, 550 mg twice daily for 7 days 22 patients: placebo, twice daily for 7 days	Pain reductions of averaged VAS scores before and during testing maximal contraction of knee extensors Muscle inhibition at 30 and 60 degrees of knee flexion Knee extensor moments at 30 and 60 degrees of knee flexion All outcomes were determined for the involved and the noninvolved leg	One man and two women dropped out because of drug intolerance Three men dropped out because of time constraints Analyses were performed with remaining 36 patients (no intention to treat)

Glucocorticosteroids

Antich 1986	RCT, randomisation method not described, but partially dependent on screening outcomes Low quality study: Delphi score 0 Allocation concealment D	Patients with knee extensor mechanism disorders: chondromalacia patella (more than half of patients), infrapatellar tendinitis, peripatellar pain. Patients who only attended the clinic for evaluation and instruction in a home program were excluded. 64 patients randomised, 22 bilateral 6 patients without clear palpable tender area's were assigned to the only treatment not requiring specific localisation: ice bags 51 patients concluded 10 day trial period, 16 bilateral, 5 without palpable tender areas	4 treatment sessions in 7-8 days, all groups received quadriceps training exercises: hip adduction, quadriceps setting, modified straight leg raises and short arc quadriceps exercises with weights 1. Iontophoresis, 1 cc Hexadrol (dexamethazone) and 1 cc 4% xylocaine 20 min (n=21 knees after 10 days) 2. Phonophoresis, 1 cc Hexadrol and 1 cc 4% xylocaine 7 min (n=9 knees after 10 days) 3. Ultrasound/ice bags, 3 times alternating heat (ultrasound 3 min) and cold (ice 2 min) (n=13 knees after 10 days) 4. Ice bags, 10 min after exercises (n=16 tender knees, n=8 non tender knees in 5 patients after 10 days) 29 patients took NSAIDs as concomitant medication	Subjective % improvement estimated by each patient % increase of muscle strength in quadriceps and hamstrings	Number of patients per diagnosis unclear Number of patients and drop-outs per group unclear as only knees at follow-up are mentioned. (6 patients started out with non tender knees, 8 knees of 5 patients are presented, one drop-out in this group) No measures of variability are given for the outcomes.

Table 2 Characteristics of included studies

Anabolic steroids

Study	Methods	Participants	Interventions	Outcomes	Notes
Darracott 1973	RCT, double blind, method of randomisation not specified Low quality: Delphi score 3 Allocation concealment B	43 military patients with severe unilateral painful patella, fulfilling diagnostic criteria of chondromalacia patellae 40 male, 3 female Age 17-34 (mean 22, SD 4) Duration of symptoms 4 - 36 months, onset due to trauma in 12 patients, to surgery in 11, to patellar subluxation, 2 to severe exercise, 1 to kneeling and 16 spontaneous	All patients performed gradually increasing exercises to reverse quadriceps inhibition for 6-8 weeks until return to full circuit and battle training, combined with: 1. Intramuscular administration of nandrolone phenylpropionate 25 mg weekly for 6 weeks (anabolic ester in arachis oil) (n=23) 2. Intramuscular administration of placebo weekly for 6 weeks (arachis oil) (n=20)	Subjective change in clinical symptoms Change in bone density in skyline radiographs (using healthy knee for calibration)	

Glucosaminoglycan polysulphate (GAGPS)

Raatikainen 1990	RCT, randomisation method not defined, double blind High quality: Delphi score 5 Allocation concealment B	31 consecutive patients with patellofemoral pain attending sports clinic at Deaconess Institute 22 men and 7 women Inclusion criteria: resisted patellar movement causes pain, arthroscopy revealed patellar cartilage lesions Exclusion criteria: other pathology at arthroscopy, corticosteroid use or glucosaminoglycan polysulphate within 40 days, NSAIDs within 7 days of commencement of trial, pregnant or nursing mothers, age under 18 years, contraindication for GAGPS.	Baseline arthroscopy 1. 12 intramuscular injections of 50 mg glucosaminoglycan polysulphate (Arteparon) (n=15) 2. 12 intramuscular injections with physiologic saline = placebo (n=14) Standardised quadriceps training after 6 week injection period Paracetamol allowed as an escape analgesic After 1 year a repeated arthroscopy was performed.	All outcomes were assessed at baseline, 6, 10 and 58 weeks on a 4 point scale (0=none, 1=slight, 2=moderate, 3=severe or extensive) Pain on palpation, pain on pressing patella against femur, pain during apprehension test, pain going downstairs, pain when squatting, hindrance to normal life, hindrance to sports activities, overall therapeutic effect, change from initial damage assessed by arthroscopy	1 patient was excluded due to trauma after 6 injections (treatment unknown), 1 patient dropped out after 8 injections (treatment unknown) 1 patient glucosamine group lost to follow-up at final assessment, 2 in placebo group refused re-arthroscopy (1 asymptomatic and 1 with moderate to severe clinical symptoms) Clinical results were dichotom-ised by the authors to indicate "good clinical results"

Table 2 Characteristics of included studies

Glucosaminoglycan polysulphate (GAGPS) -continued

Study	Methods	Participants	Interventions	Outcomes	Notes
Kannus 1992-1999	RCT, randomisation using sealed envelopes, double blind assessments with respect to injections of saline and glucosaminoglycan polysulphate High quality: Delphi score 5 Allocation concealment A	53 patients attending the Tampere Research Station of Sports Medicine with chronic patellofemoral pain syndrome: duration of symptoms mean 16, SD 19 months, all unilateral 17 previous arthroscopy, 8 with pathologic changes in patellar cartilage, no correlation with symptoms 25 men 28 women Age: mean 27, SD 9	Conservative treatment: no symptom-producing activities for 6 weeks, isometric quadriceps tensioning exercises and straight leg raises, ice packs on patella if necessary, 20 mg piroxicam (NSAID) for 20 days 1. conservative treatment only (n=16) 2. conservative treatment and 5 weekly intra-articular injections with saline and lidocaine (10 mg) (n=17) 3. conservative treatment and 5 weekly intra-articular injections with GAGPS (50 mg) and lidocaine (10 mg) (n=16)	Follow-up assessments took place at 6 weeks and 6 months and again after 7 years subjective assessment: - Pain and discomfort during activities on 0-100 mm Visual Analogue Scale (0 = none, 100 = extremely intense pain) - Overall evaluation of condition of the knee on 5 point scale (1 = asymptomatic, 5 = worse than before treatment) - Level of physical activity on 4 point scale (1 = higher than before knee problem and 4 = unable to perform any physical activities) Combined subjective and functional evaluations of the knee: - Lysholm scale (0-100 point scale, 0 = worst score, 100 = best score) - Tegner scale (0-10 point scale, 0 = no physical activity possible, 10 = all kinds of activities possible) Symptoms on tests of function: - Hopping on affected leg (4 point scale, 1 = no problem, 4 = unable) - Duck walking (4 point scale, 1 = no problem, 4 = unable) - 25 repetition full squat (1 = no squat without pain, 2 = 1-5 without pain, 3 = 6-10 without pain, 7 = > 25 squats without pain) Clinical evaluation: - Pain during compression test (0-4 point scale, 0 = none, 4 = intense) - Crepitation during compression test (0-4 point scale, 0 = none, 4 = intense) - Pain during apprehension test (0-4 point scale, 0 = none, 4 = intense) - Physician's opinion of overall therapeutic effect (5 point scale, 1 = complete subjective, functional and clinical recovery and 5 = overall status worse than before treatment) Muscle strength: - Isometric quadriceps muscle strength in 60 degrees of flexion using and isometric dynamometer Radiological signs after 7 years - MRI and radiographs of both knees after 7 years, to look for both early and advanced signs of osteoarthritis in the patellofemoral joint - Bone density of the distal part of the femur, the patella and proximal part of the tibia to determine whether PFPS had caused bone loss or osteopenia in the affected knee compared with the unaffected knee: a 5% deficit was deemed clinically important	2 patients were excluded after enrolment because they had osteoarthritis (group 1 and 3) 1 patient of group 3 never returned 1 patient of group 2 was excluded due to an adverse event: intense aseptic effusion (reactive synovitis) following first injection 45 of the 49 patients of the original study were reassessed after 7 years (Kannus 1999). Because analysis of the data showed no differences among the groups at 6 months the results of all groups were pooled for analysis at 7 years. The results of the 7 year follow-up are therefore only included in the text of this review. MRI and radiograph assessment was blind as to which knee was affected

ABBREVIATIONS: BID: twice a day (from Latin: bis in die), GAGPS: glycosaminoglycan polysulphate, NSAID: non-steroidal anti-inflammatory drug, PFPS: patellofemoral pain syndrome, QID: four times a day (from Latin: quarter in die), VAS: visual analogue scale

Table 3 Characteristics of excluded studies

Study	Reason for exclusion
Berenfeld 1991[35]	Only 26% of all patients suffered from PFPS, the rest suffered from OA. Results were not reported separately for each diagnosis.
Braham 2003[36]	Patients with OA.
Dahlberg 1994[37]	Patients with OA and in two thirds with a history of previous major knee trauma. Of the patients with patellar pain on palpation none had a history of patellar pain syndrome.
Noble 1981[38]	Only 10% patients with PFPS, the rest was diagnosed with injuries that are excluded in this review.
Wang 1997[39]	Non-controlled trial.

The studies by Antich[32] and Fulkerson[31] also included patients with diagnoses mentioned in the exclusion criteria, but because the majority of patients suffered from PFPS these studies were included.
OA: osteoarthritis, PFPS: patellofemoral pain syndrome

Methodological quality of included studies

Kappa scores for agreement between raters BK and JV ranged from 0.50 (items 4 and 7) to 1.00 (item 3), but could not be calculated for items 1, 2 8 and 9 due to empty cells in the contingency tables. Percentage agreement between the reviewers ranged from 50% (item 8) to 100% (item 3) per item. Disagreements were resolved in a single consensus meeting. Of the three studies marked as high quality, only Bentley[15] and Kannus[19,26] received the Cochrane code A for concealment of treatment prior to allocation[27], whereas the study by Raatikainen[28] received Cochrane code B.

Analysis

Quantitative meta-analysis of pooled high quality studies was impossible due to the heterogeneity of the interventions used for comparison, heterogeneity of gathered outcome measures and applied instruments.

The outcome measures pain, function and clinical improvement are represented in the graphs. Outcomes that represent clinical patella tests, swelling, muscle strength, cartilage damage or bone density are only mentioned in the text below, and will not be taken into account for the best evidence synthesis.

NSAIDs

The results of the studies are presented in figure 1. Bentley[15] performed a high quality study comparing the effects of aspirin to that of placebo. Subjective clinical evaluations revealed no significant difference, 4 out of 13 participants in the placebo group showing improvement of symptoms and signs versus 6 out of 16 participants in the aspirin group (see Graphs: comparison 01.01). Due to side effects or non-cooperation four participants in the aspirin group did not maintain effective levels of 15 to 25 mg/100 ml blood during 10 weeks. None of these participants improved, and one deteriorated.

Figure 1 NSAID

1.1 Clinical results, dichotomous data

Study ID	Outcome	Time point	Aspirin n	Aspirin N	Placebo n	Placebo N	Comparison RR	95% CI
Bentley 1981	Number of patients improved	3 months	6	16	4	13	1.22	0.43 3.42

Study ID	Outcome	Time point	Tenoxicam n	Tenoxicam N	Laser therapy n	Laser therapy N	Comparison RR	95% CI
Marchese 1998	Number of patients reasonably to very satisfied	2 months	5	18	11	18	0.45	0.2 1.04

1.2 Pain, dichotomous data

Study ID	Outcome	Time point	Diflunisal n	Diflunisal N	Naproxen n	Naproxen N	Comparison RR	95% CI
Fulkerson 1986	Number of patients reporting significant pain reduction	5 days?	11	20	10	16	0.88	0.51 1.52

1.3 Pain, continuous data

Study ID	Outcome	Time point	Naproxen N	Naproxen mean	Naproxen SD	Placebo N	Placebo mean	Placebo SD	Comparison SMD	95% CI
Suter 1998	Pain reduction non-involved leg (VAS 0-100)	7 days	19	-0.1	4.3	17	-0.17	1.3	-0.78	-1.5 -0.1
Suter 1998	Pain reduction involved leg (VAS 0-100)	7 days	19	-4.9	1.4	17	-2	5.1	0.02	-0.6 0.68

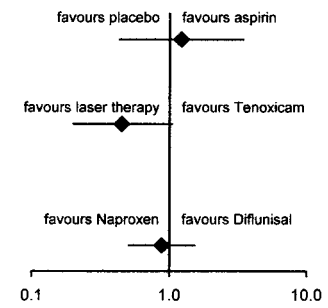


Figure 2 Glucocorticosteroid

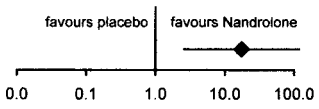
2.1 Clinical results

Study ID	Outcome	Time point	Dexamethasone and xylocaine Ionto-phoresis N_{knees}	Dexamethasone and xylocaine Ionto-phoresis $\%_{improved}$	Phono-phoresis N_{knees}	Phono-phoresis $\%_{improved}$	Controls Ultrasound/Ice N_{knees}	Ultrasound/Ice $\%_{improved}$	Ice N_{knees}	Ice $\%_{improved}$
Antich 1986	Average individual subjective % improvement in knee status	10 days	21	24%	9	32%	13	47%	16	22%

Figure 3 Anabolic steroid

3.1 Clinical results

Study ID	Outcome	Time point	Nandrolone n	Nandrolone N	Placebo n	Placebo N	Comparison RR	95% CI
Darracott 1973	Number of patients improved	6 - 8 weeks	20	23	1	20	17.39	2.56 118



If patients with ineffective levels are left out of the analysis, the difference between the groups is still not significant. No people in the placebo group deteriorated. Comparison of changes in cartilage injuries observed during arthroscopy at baseline and after 13 weeks revealed one improvement and two deteriorations in the placebo group versus no improvements and one deterioration (effective level) in the aspirin group.

Marchese[29] performed a low quality study comparing the NSAID tenoxicam with laser therapy alternated with ice application. In the text of the article the author claims a significant difference in pain reduction in favour of the laser therapy group (mean follow-up value visual analogue scale 2.93 versus 4.52 for the tenoxicam group), though lack of baseline information and variability measures makes verification impossible. Other outcome measures were not reported adequately. Only the patient's satisfaction with the treatments is reported satisfactorily, and amounts to 61% (11 out of 18 participants) in the group receiving laser therapy versus 29% (5 out of 18) in the group receiving tenoxicam. The relative risk 0.45 (95%CI 0.20 to 1.04) does not reveal a significant difference (see Graphs: comparison 02.01).

Suter[30] performed a low quality study comparing the NSAID naproxen with placebo. Pain scores were obtained by averaging Visual Analogue Scale scores before and during maximal knee extensor contraction for each leg. Reported mean differences between baseline and 7 days follow-up for both the involved and the non-involved leg were used for statistical comparison of placebo and naproxen. Pain reduction was significantly greater for naproxen than for placebo in the involved leg (SMD -0.78, 95% CI -1.46 to -0.10), but not in the non-involved leg (SMD 0.02, 95% CI -0.63 to 0.68) (see Graphs: comparison 03.01).

Fulkerson[31] performed a low quality study in which no baseline or follow-up values for pain have been reported, and no definition is supplied for the term "significant pain relief". No significant differences in "significant pain relief" were detected when comparing naproxen (10 out of 16 participants) with diflunisal (11 out of 20 participants) after a period of five days (RR 0.88; 95%CI 0.51 to 1.52) (see Graphs: comparison 04.01).Differences in swelling reduction were almost significant when comparing naproxen (4 out of 9 participants) with diflunisal (2 out of 12 participants) after a period of five days (RR 0.27; 95%CI 0.07 to 1.00).

Glucocorticoid steroids

Antich[32] performed a low quality study with 4 treatment arms, two of which involve dexamethazone / lidocaine (Hexadrol / Xylocaine). Iontophoresis and phonophoresis are both techniques to drive the topical drug into the soft tissue surrounding the patella, to reduce irritation or inflammation in these tissues. Antich reports mean values for 'subjective improvement' which each patient was asked to rate as a percentage relative to the baseline situation. No measures of variability were supplied and no statistical analyses were performed. The highest mean value for 'subjective improvement' was 47% for the group treated with alternating ultrasound and ice application, followed by phonophoresis of dexamethazone/lidocaine (Hexadrol/Xylocaine) with 32%, iontophoresis of dexamethazone/lidocaine (Hexadrol/Xylocaine) with 24% and application of ice bags with 22%. The respective strength increases of quadriceps and hamstrings were 28% and 34%, 13% and 0%, 15% and 15%, and 5% and 15%. Percentages are stated for knees without mention of the number of participants. Furthermore, no variability measures or statistical analyses are given. Therefore, conclusions about relative effectiveness are impossible.

Anabolic steroids

Darracott[20] performed a low quality study and presented individual results determined after 6-8 weeks. A significant difference in the number of participants that improved clinically was observed: 1 out of 20 participants in the placebo group improved clinically compared to 20 out of 23 in the nandrolone group (RR 17.39; 95%CI 2.56 to 118.26) (see Graphs: comparison 06.01). Patellar bone density measurements also revealed a significantly better result for the nandrolone group: bone density increased in 1 out of 20 participants in the placebo group, compared to 16 out of 20 in the nandrolone group (RR 13.91; 95%CI 2.02 to 95.79).

Glycosaminoglycan polysulphate (GAGPS)

Kannus[19,26] performed a high quality study and found that after a treatment period of six weeks two thirds of the participants receiving either GAGPS or placebo injections into the knee showed excellent recovery from PFPS symptoms, as determined by subjective, functional and clinical assessments. When comparing participants receiving intra-articular GAGPS injections with the group receiving no injections[19,26] the number of people without symptoms during a full squat differed significantly after 6 weeks (RR 2.20;

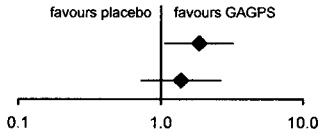
95%CI 1.03 to 4.68), but this difference was no longer observed after six months (see Graphs: comparison 08.03). When comparing means and standard deviations using the analysis tool in RevMan[23], there was a significant difference between scores on the Lysholm functional scale between the groups receiving GAGPS injections and the group receiving no injections after 6 weeks (SMD 0.93; 95%CI 0.19 to 1.66) (see Graphs: comparison 08.05). However, the author did not find a significant difference using repeated measurements analysis that takes individual changes into account. The Tegner activity scores differed significantly between GAGPS injected participants and non-injected participants after six weeks (SMD 1.12; 95%CI 0.37 to 1.88) and after six months (SMD 0.74; 95%CI 0.02 to 1.46) (see Graphs: comparison 08.06).Based on the physician's assessment, the number of people who were fully recovered at six weeks was greater in the injection groups than the group without injections, though the difference was never significant. At six months, three quarters of the participants reported excellent recovery, though there was no significant difference between the groups. Patella tests were performed and differed significantly between the injection and no injection groups after six weeks. Muscle strength relative to the healthy limb improved in all groups and no significant differences were observed. Overall, no beneficial effect of glycosaminoglycan polysulphate was observed.

Raatikainen[28] performed a high quality study and found that pain while going down stairs was significantly less in people receiving intramuscular injections of GAGPS compared to people receiving placebo injections (RR 1.85; 95%CI 1.07 to 3.19; NNT: 3). However, pain when squatting did not reveal a significant difference (RR 1.38; 95%CI 0.73 to 2.62) and neither did hindrance to normal life (RR 1.15; 95%CI 0.95 to 1.41) or hindrance to sports activities (RR 1.79; 95%CI 0.91 to 3.52). Nevertheless, the number of people with moderate to good therapeutic effect assessed by the physician after one year was significantly higher in the group receiving GAGPS injections (10 out of 13 in the GAGPS group and 3 out of 15 in the placebo group: RR 3.85; 95%CI 1.34 to 11.05; NNT: 2). Re-arthroscopy was used to determine the improvement in cartilage lesions and revealed improvement in 3 out of 13 participants in the placebo group and in 8 out of 13 participants in the GAGPS group. This difference was not significant (RR 2.79; 95%CI 0.90 to 7.86). Overall, some very limited beneficial effects of glycosaminoglycans were observed (see Graphs: comparisons 09.01 to 09.05).

Figure 4 Glucosaminoglycan polysulfate (GAGPS)

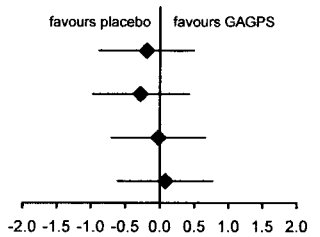
4.1 Pain, dichotomous

Study ID	Outcome	Time point	GAGPS n	GAGPS N	Placebo/none n	Placebo/none N	Comparison RR	95% CI
Raatikainen 1990	Pain going downstairs: number of patients improved	1 year	12	13	7	14	1.85	1.07 3.19
Raatikainen 1990	Pain when squatting: number of patients improved	1 year	9	13	7	14	1.38	0.73 2.62



4.2 Pain, continuous

Study ID	Outcome	Time point	GAGPS N	GAGPS mean	GAGPS SD	Placebo/none N	Placebo/none mean	Placebo/none SD	Comparison SMD	95% CI
Kannus 1992	Pain (VAS 0-100 mm): GAGPS vs placebo	6 weeks	16	30.5	24	17	35.5	26.8	-0.19	-0.9 0.49
Kannus 1992	Pain (VAS 0-100 mm): GAGPS vs no injection	6 weeks	16	30.5	24	16	36.5	18	-0.28	-1 0.42
Kannus 1992	Pain (VAS 0-100 mm): GAGPS vs placebo	6 months	16	23.5	30	17	24	22.7	-0.02	-0.7 0.66
Kannus 1992	Pain (VAS 0-100 mm): GAGPS vs no injection	6 months	16	23.5	30	16	21.5	18	0.08	-0.6 0.77



4.3 Function, continuous

Study ID	Outcome	Time point	GAGPS N	GAGPS mean	GAGPS SD	Placebo/none N	Placebo/none mean	Placebo/none SD	Comparison SMD	95% CI
Kannus 1992	Lysholm Scale: GAGPS vs placebo	6 weeks	16	87.5	10	17	86	10.3	0.14	-0.5 0.83
Kannus 1992	Lysholm Scale: GAGPS vs no injection	6 weeks	16	87.5	10	16	78	10	0.93	0.19 1.66
Kannus 1992	Lysholm Scale: GAGPS vs placebo	6 months	16	90.5	12	17	88	12.4	0.2	-0.5 0.88
Kannus 1992	Lysholm Scale: GAGPS vs no injection	6 months	16	90.5	12	16	85	16	0.38	-0.3 1.08
Kannus 1992	Tegner Scale: GAGPS vs placebo	6 weeks	16	7.5	1.2	17	6.9	1.6	0.41	-0.3 1.1
Kannus 1992	Tegner Scale: GAGPS vs no injection	6 weeks	16	7.5	1.2	16	5.6	2	1.12	0.37 1.88
Kannus 1992	Tegner Scale: GAGPS vs placebo	6 months	16	7.8	1.4	17	8	1.6	-0.13	-0.8 0.55
Kannus 1992	Tegner Scale: GAGPS vs no injection	6 months	16	7.8	1.4	16	6.3	2.4	0.74	0.02 1.46

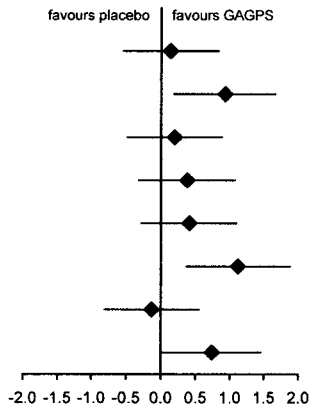


Figure 4 Glucosaminoglycan polysulfate (GAGPS) - continued

4.4 Function, dichotomous			GAGPS		Placebo/none		Comparison		
Study ID	**Outcome**	**Time point**	**n**	**N**	**n**	**N**	**RR**	**95% CI**	
Raatikainen 1990	Hindrance to normal life: number of patients improved	1 year	13	13	13	15	1.15	0.95	1.41
Raatikainen 1990	Hindrance to sports activities: number of patients improved	1 year	10	13	6	14	1.79	0.91	3.52
Kannus 1992	N return to physical activity: GAGPS vs placebo	6 weeks	12	16	9	17	1.42	0.83	2.41
Kannus 1992	N return to physical activity: GAGPS vs no injection	6 weeks	12	16	9	16	1.33	0.8	2.23
Kannus 1992	N return to physical activity: GAGPS vs placebo	6 months	14	16	11	17	1.35	0.91	2.01
Kannus 1992	N return to physical activity: GAGPS vs no injection	6 months	14	16	10	16	1.4	0.92	2.14
Kannus 1992	N symptom free during full squat: GAGPS vs placebo	6 weeks	11	14	9	12	1.05	0.68	1.6
Kannus 1992	N symptom free during full squat: GAGPS vs no injection	6 weeks	11	14	5	14	2.2	1.03	4.68
Kannus 1992	N symptom free during full squat: GAGPS vs placebo	6 months	11	14	9	12	1.05	0.68	1.6
Kannus 1992	N symptom free during full squat: GAGPS vs no injection	6 months	11	14	6	14	1.83	0.94	3.56
Kannus 1992	N symptom free during one leg jump: GAGPS vs placebo	6 weeks	7	13	6	10	0.9	0.44	1.83
Kannus 1992	N symptom free during one leg jump: GAGPS vs no placebo	6 weeks	7	13	3	11	1.97	0.66	5.86
Kannus 1992	N symptom free during one leg jump: GAGPS vs placebo	6 months	8	13	8	10	0.77	0.45	1.31
Kannus 1992	N symptom free during one leg jump: GAGPS vs no placebo	6 months	8	13	5	11	1.35	0.62	2.94

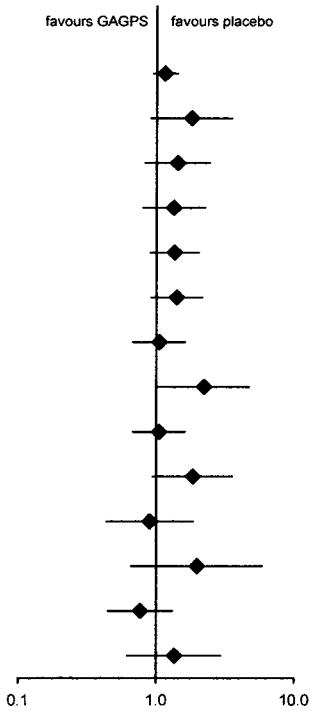
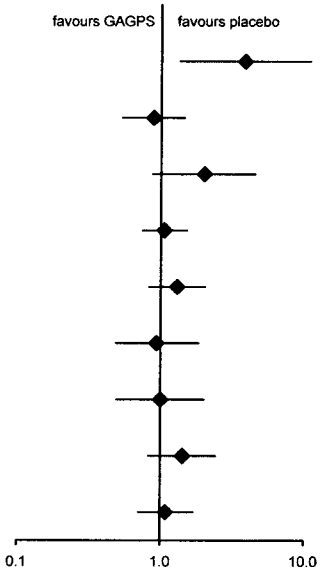


Figure 4 Glucosaminoglycan polysulfate (GAGPS) - continued

4.5 Clinical results, dichotomous

Study ID	Outcome	Time point	GAGPS n	GAGPS N	Placebo/none n	Placebo/none N	Comparison RR	95% CI	
Raatikainen 1990	Number of patients with moderate to good therapeutic effect	1 year	10	13	3	15	3.85	1.34	11.1
Kannus 1992	Complete recovery determined by physician: GAGPS vs placebo	6 weeks	10	16	12	17	0.89	0.54	1.44
Kannus 1992	Complete recovery determined by physician: GAGPS vs no injection	6 weeks	10	16	5	16	2	0.88	4.54
Kannus 1992	Complete recovery determined by physician: GAGPS vs placebo	6 months	13	16	13	17	1.06	0.75	1.51
Kannus 1992	Complete recovery determined by physician: GAGPS vs no injection	6 months	13	16	10	16	1.3	0.83	2.03
Kannus 1992	Subjective overall assessment 'excellent': GAGPS vs placebo	6 weeks	8	16	9	17	0.94	0.49	1.83
Kannus 1992	Subjective overall assessment 'excellent': GAGPS vs no injection	6 weeks	8	16	8	16	1	0.5	2
Kannus 1992	Subjective overall assessment 'excellent': GAGPS vs placebo	6 months	12	16	9	17	1.42	0.83	2.41
Kannus 1992	Subjective overall assessment 'excellent': GAGPS vs no injection	6 months	12	16	11	16	1.09	0.71	1.69



Best evidence syntesis

There is limited evidence from one high quality study that aspirin is not more effective than placebo for improving clinical symptoms and signs in people with anterior knee pain.

There is limited evidence from one low quality study that tenoxicam is less effective than laser therapy for reducing pain in people with PFPS and that patient satisfaction is not different between these treatments.

There is limited evidence from one low quality study that naproxen is more effective than placebo for reducing pain in people with PFPS in the short term.

There is limited evidence from one low quality study that diflunisal and naproxen do not differ in reducing pain in people with anterior knee pain in the short term.

There is limited evidence from one low quality study that nandrolone phenylpropionate is more effective than placebo for improving clinical symptoms and signs in people with PFPS.

There is conflicting evidence from two high quality studies for the effectiveness of glycosaminoglycan polysulphate compared with placebo in people with PFPS. One high quality study found marginally better results from its administration for some outcomes, but the other study found no statistically significant difference between groups.

There is no evidence to support the claim from one low quality study that alternating ultrasound and ice massage improves subjective symptoms more than topical Hexadrol and Xylocaine in people with PFPS, chondromalacia or patellar tendinitis.

Discussion

The literature search resulted in a very small number of trials studying pharmacotherapy for PFPS or chondromalacia. This in itself is remarkable if one considers the widespread use of NSAIDs for pain reduction in patients with PFPS or chondromalacia.

NSAIDs

The study of Bentley[15] (data from 29 participants were analysed) shows that aspirin is not more effective for treating symptoms of chondromalacia than placebo. The anticipated reduction of cartilage lesions was also not observed. Therefore, the hypothesised pathways by which aspirin was expected to influence cartilage metabolism could not be demonstrated. Marchese[29] (data from 35 participants were analysed) found

that tenoxicam is significantly less effective than laser therapy for treating pain in people with chondromalacia, but pain levels were reported poorly and this claim cannot be verified. Suter[30] found that the short term pain reduction in people with anterior knee pain syndrome was significantly higher for naproxen than for placebo (data from 36 participants were analysed). However, although pain ratings ranged from 0 to 57 at baseline, mean values were only 11 ± 13 for the involved leg. The average pain reduction remained below 5 mm for the involved leg, and questions as to the clinical relevance of this reduction are not addressed by Suter[30]. The short term 'significant' pain reduction in people with anterior knee pain reported by Fulkerson[31] (data from 36 participants were analysed) was not measured on a visual analogue scale and can therefore not be compared to the results of Suter[30]. Furthermore, the term 'significant' pain reduction is not defined, preventing insight into the clinical relevance of this outcome. So, although the use of NSAIDs as analgesics in people with PFPS is already widespread, our systematic review of the literature has produced only limited evidence that NSAIDs are effective for pain reduction and clinical relevance of this evidence remains unclear.

Glucocorticoid steroids

Antich[32] used topical Hexadrol (dexamethasone), a class 1 corticosteroid with anti-inflammatory and vasoconstrictive action, in combination with topical Xylocaine (lidocaine), which has an analgetic effect. Iontophoresis and phonophoresis are both techniques to drive the topical drug into the soft tissue surrounding the patella, to reduce irritation or inflammation in these tissues, thought by some to cause the pain in PFPS. Though the trial does not provide statistical evidence, the drug does not seem to give good results (data from 67 knees of 51 participants were reported). Whether this lack of result reflects that the mechanism causing pain resides in other tissues will have to remain a point of speculation.

Anabolic steroids

Darracott[20] used nandrolone phenylpropionate, a steroid which has been shown to have significant anabolic effect at dose levels below the threshold for androgenic response. The use of an anabolic ester yields rather impressive results (data from 43 participants were analysed) when clinical improvement is considered. Whether this clinical improvement may be due to the reversal of patellar osteoporosis, or to the muscular hypertrophy it induces, cannot be derived from these results. Although successful, application of nandrolone is not likely to be widely accepted as anabolic esters are

included in international doping lists and have significant side effects, such as premature closure of epiphyses, virilisation, liver insufficiency and heart failure. Its use in the treatment of PFPS should therefore be considered with great care.

Glycosaminoglycan polysulphate (GAGPS)

Both the studies by Kannus[19,26] (data from 49 participants were analysed) and Raatikainen[28] (data from 27 participants were analysed) are of high methodological quality. Though the pharmaceutical agent is the same, the route and frequency of administration is not. Moreover, the design of both studies differs greatly from the timing of start of exercises to the methods used for outcome assessment. Raatikainen[28] performs repeated arthroscopies to evaluate the appearance of the patellar cartilage. Kannus[19,26] however, views the administration of GAGPS as additional to the conservative treatment that has gained a strong foothold in clinical practice: a combination of reducing activities that cause symptoms, strengthening the quadriceps muscles, and prescribing NSAIDs or other analgesics to facilitate exercising. It should be noted that although no differences were found between the three treatment strategies in the study by Kannus[19,26], three quarters of all participants were deemed clinically recovered after six months. This was reduced to two thirds at seven years follow-up. Raatikainen[28] found that three quarters of the participants in the GAGPS group showed a moderate to good therapeutic effect, versus only 20% of the controls; a significant difference. Because of the different approaches it is impossible to say whether these conflicting results reflect a difference in the effectiveness of the drug, in the route of administration, the frequency of administration, the presence of cartilage damage, or the additional treatment components. For example, it could be argued that the training program used by Kannus[19,26] gives such good results that GAGPS does not substantially add to the positive effect of training.

Choice of outcomes and assessment techniques

The severity of symptoms and of patellar cartilage damage at inclusion varies from study to study. The weight given to the extent of the patellar cartilage lesions has been reconsidered in the previous decade. This is due to changing insights into the nature of retropatellar pain. Pain and crepitations have repeatedly been shown to be poorly correlated with visible cartilage damage[16,17,33]. The gradual acceptance of these insights is reflected in the dates of the studies that employed the technique of arthroscopy for determining cartilage damage[15,28]. Recent developments in MRI techniques provide non-invasive techniques to determine cartilage damage that are risk free for the patient.

Furthermore MRI techniques enable quantification of cartilage volumes and surface area measurements[19,26,34] Kannus[26] used such MRI measurements to determine the cartilage thickness and abnormalities in his 7 year follow-up, and found no abnormalities in 81% of the participants. This is more than the two thirds that were still fully recovered. This is another indication that cartilage damage is not the most relevant outcome measure for PFPS.

Although pain is the symptom that will prompt a patient to seek medical advice, several studies[15,20,32] did not report pain as a separate outcome. instead they reported the outcome measure "clinical symptoms and signs" or "percentage change in condition" (ranging from -100% to +100%). This may well include pain, but definitions of these outcome measures have not been reported. Similarly, Fulkerson[31] does not provide a definition of the main outcome measure: "significant pain reduction". This makes interpretation of the results rather difficult.

Methodology

Because no meta-analysis was performed and because the ranking of high and low quality of the trials did not influence the best-evidence synthesis, analysis of the cut-off point for discrimination between the high and low methodological quality was redundant. We encountered severe problems with the interpretation of the trials because of the low quality of certain studies. Bias could ensue from any of the items listed in the criteria used for determination of methodological quality. Apart from those issues, there are some other aspects that severely impede the interpretation of the results.

Antich[32] did not report the number of participants per treatment arm, the inevitable correlation between results of knees of bilaterally afflicted patients was not taken into account and their distribution over treatments was not reported, and no statistical analyses were performed. The study therefore serves only as an example for possible applications of pharmacotherapy, as it is not suitable for presentation of evidence. Most results from Marchese[29] cannot be used in this review because the baseline and follow-up measures for each treatment were not reported. Therefore, only 'patient satisfaction' remains for evaluation.

In general, the number of participants in each trial is very limited, which seriously reduces the power of the included studies. The relevance of statistical evaluations then becomes questionable, as differences between treatments will be hard to detect and individuals with deviating outcomes can have an enormous effect. Therefore, the

reported estimates and confidence intervals should be interpreted with great caution. On the other hand statistical significance does not always reflect clinical relevance. This is demonstrated by the small reduction of pain levels found by Suter[30], which is nonetheless statistically significant, resulting in the qualification 'limited evidence' for pain reduction.

Patient characteristics

The studies of Fulkerson[31] and Antich[32] included participants with diagnoses other than PFPS or chondromalacia in their study populations. Although clinicians may (in part) prescribe the same therapies for all diagnoses, patients with different diagnoses may show very different responses to these therapies and should therefore have been reported separately. In spite of this severe shortcoming, we decided to include these trials into this review, to give the reader a full scope of the scant literature available on the subject of pharmacotherapy for PFPS. The excluded patients[32] who attended the clinic for instruction in a home program may have had less severe symptoms and may have reacted differently to the treatments.

Both Bentley[15] and Raatikainen[28] only included patients in which cartilage damage had been detected at arthroscopy. Marchese[29] included patients with at least one radiological sign of femoropatellar dysplasia, and Darracott[20] only included patients with severely debilitating symptoms. Of the 53 patients included by Kannus[19] 17 had a previous arthroscopy but this detected cartilage damage in only eight cases.

As most pharmaceutical agents are evaluated in only one study, no observations could be made whether the presence of cartilage damage influences the results. The only exception is GAGPS: Raatikainen[28] included only participants in which cartilage damage was observed, and Kannus[19,26] included participants with and without cartilage damage. The fact that the effectiveness of GAGPS seems greater in the study in which the participants had more cartilage damage, suggests that either cartilage damage is not a predictive factor for recovery, or GAGPS works better when cartilage damage is evident.

The strength of this review is that it gives an overview of the available evidence for pharmacotherapy for PFPS. The poor methodological quality of some of the included studies does not subtract from that, because it emphasises the poverty of the available evidence. That the methodologically poor studies are mentioned in this review may serve to emphasise the need for qualitatively sound research. The fact that we also found some high quality trials indicates that it certainly is possible to conduct valid RCTs in this

field. Future trials should pay more attention to the methodological aspects of design and reporting as well as the number of subjects included in the study.

Reviewers' conclusions

Implications for practice

Despite widespread application of NSAIDs for PFPS there is only limited evidence for their effectiveness in reducing pain and the evidence is limited to the short term only (up to one week). If the use of NSAIDs is considered in spite of that, the drug with the least possible side effects and lowest costs should be first choice for use in people with PFPS, as there is no evidence that one kind of NSAID is superior to another.

The evidence for the effect of GAGPS is contradictory and merits further investigation. There is limited evidence that the anabolic steroid nandrolone may be effective, but the drug is too controversial for use in the treatment of PFPS.

Implications for research

The limited evidence for the effectiveness of NSAIDs and the lack of insight into the clinical relevance of this evidence could constitute an area for medical cost reduction. Therefore, further research on the effectiveness of NSAIDs should be obtained through trials in which NSAIDs are compared to placebo for at least several weeks, with a follow-up period to assess long term effects. The NSAIDs may be given either in addition to other interventions or not. The comparison of NSAIDs to other treatments of which the effectiveness is unknown is undesirable.

The effectiveness of GAGPS would merit further research, to investigate the contradictory results of Kannus[19,26] and Raatikainen[28].

To gather more evidence for the influence of cartilage damage on recovery, future researchers may consider the use of imaging techniques to determine the extent of cartilage damage to use it for stratification of treatment groups and possible subgroup analysis.

Any further research should pay attention to methodological aspects of design and reporting. Power calculations should be provided to ensure that the number of participants is sufficient to obtain both clinically and statistically significant outcomes.

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8

General discussion

Non-traumatic knee complaints in adolescents and young adults in general practice

Non-traumatic knee complaints form a heterogeneous group of complaints. The most common diagnosis is osteoarthritis. Because of its persistence and disease burden it is the diagnosis most under investigation, but this is a complaint that usually starts at a later age. Non-traumatic knee complaints are also common in the younger age groups in general practice, but these have received very little attention in clinical research. As a result, little was known about the persistence and disease burden in this group. This thesis has aimed to fill this gap in our knowledge. In the previous chapters, the findings and limitations of our analyses were discussed. In this chapter we will place the findings in a broader context and discuss the relevance of our findings for clinical practice.

What our study adds

During the course of our study two other prognostic studies focusing on knee complaints in general practice populations were carried out, one in the United Kingdom and one in the Netherlands. The Knee Clinical Assessment Study (CAS(K)) included 819 patients aged 50 years and over that indicated having knee complaints in a health survey sent by 3 British general practices[1,2]. Because of the recruitment method this is actually an open population study, focussing primarily on osteoarthritis. The BewegingsApparaat Study (BAS) followed only adults consulting Dutch GPs for new episodes of musculoskeletal complaints over the course of one year[3]. Prognostic factors were determined in 251 patients with knee complaints of traumatic or non-traumatic onset, and with an average age of 49.3 (±16.2)[4]. Our study is the first to describe knee complaints from the age of 12, including a sufficient number of patients to allow for analysis of a subgroup of 191 adolescents and young adults with non-traumatic knee complaints. Another advantage over the BAS study is that we performed a standardized physical examination and collected more detailed information about knee complaints in the questionnaires. This specific information gives us the opportunity to investigate potential prognostic factors from data that closely resemble the data the GP will use to form a working diagnose and to base treatment decisions on. Therefore, our cohort provides unique and relevant information, especially with respect to non-traumatic knee complaints in adolescents and young adults.

Prognosis and prognostic factors

The primary aim of this thesis was to determine the prognosis of non-traumatic knee complaints in adolescents and young adults. Though non-traumatic knee complaints in adolescents and young adults are common in general practice, their prognosis has never been studied in a prospective cohort study. Dutch guidelines for general practitioners suggest the prognosis is good, a belief that is based on consensus rather than facts[5]. Studies in secondary care[6,7] suggest many patients are still bothered by their knee complaints after many years, and argue that the beliefs about a good prognosis should be reconsidered. Our study was the first to study the prognosis of this patient group in general practice. In chapter 5 we reported that in general practice the recovery rate is also low. With 53% recovered or improved after one year, the recovery in primary care patients is better than that reported in the secondary care populations. However, we feel that this recovery rate is not in concordance with the suggested good prognosis in primary care.

The finding that the recovery rate expected by the GP was 89%, whereas the actual recovery rate was 44% in the patients for which the GP had stated the expected prognosis (chapter 5), illustrates the importance of active follow-up of patients in order to get a good impression of the prognosis. GPs probably use their personal experience to predict the outcome. The fact that only one in three patients with persistent complaints returns to the GP, and that most of these repeated consultations take place within 3 months of the first consultation, means that GPs are unaware of the persistence of the knee complaints in most of their patients.

The persistent complaints one year after the first consultation observed in 47% of the patients were associated with poor overall health (OR 6.9; 1.6 - 29.6) and lower education level (OR 3.4; 1.5 - 7.66). An association between socio-economic status, education level and overall health is a common finding[8]. Other prognostic factors are all associated with specific characteristics of the knee complaints. An important prognostic factor was a history of knee operation (OR 5.6; 1.3 - 23.3), present in 15 of the 191 patients. Patients with a previous knee operation were included in the non-traumatic group, because the present new complaints are not the result of a recent trauma. However, one might argue that patients with previous operations are not typical for non-traumatic knee complaints, and may obscure factors that are important for the rest of the patients. Though the importance of previous knee operations should not be effaced, we focus on the factors that were identified in the analysis excluding these patients. In order

of the strength of their association these are prominence of the tibial tuberosity (OR 5.9; 0.9 - 37.7), painful patellar ligament (OR 3.1; 1.0 - 9.4), bilateral complaints (OR 2.9; 1.2 - 6.7), self-reported locking of the knee (OR 2.6; 0.9-7.7), and self-reported knee swelling (OR 2.5; 1.0 - 5.8). Although painful patellar edges were eliminated from the multivariate prognostic model, it is a confounder of the factors painful patellar ligament and prominent tibial tuberosity. Combined occurrence of these signs results in worse prognoses than isolated signs. This finding has been reported before[9,10].

So how do our results compare to the BAS study? In the BAS study 44% of the patients was no longer bothered by their knee complaints after one year[4]. Prognostic factors in the BAS study were a history of knee complaints, a longer duration of the current episode of knee complaints, and other coexisting musculoskeletal complaints. In our multivariate model a history of knee complaints and a longer duration of the current episode of knee complaints were found to be redundant. With respect to the coexisting musculoskeletal complaints we found no association, not even in the univariate analysis. The difference in age between the study populations may account for this difference in results between our studies. We did find a univariate association with a history of traumatic knee injury, and a longer duration of the current episode of knee complaints, but both factors were found to be redundant in the multivariate model. Furthermore, we found no psychosocial factors to be associated with persistence, a finding that concurs with the findings of the BAS study.

The other major difference between the BAS study and the HONEUR knee cohort apart from the population differences is that we included a physical examination, enabling us to evaluate the prognostic value of an important tool of the general practitioner. We found that out of a large number of signs, only two elements of the physical examination remained in the multivariate model. These elements were found in only a small number of patients. Maybe the true additional value of the physical examination lies in combining several signs or combining signs and symptoms to form prognostic entities, which could be evaluated in future explorative studies. Furthermore, prediction models could be developed, which preferably should be validated in future studies.

Disease burden

The non-traumatic knee complaints in children and adolescents are portrayed in the NHG guidelines as self-limiting disorders. Apart from the suggested good prognosis, one also might expect the disease burden to be limited. However, this is another aspect that had not been studied before. In chapter 3 we compared the different groups of knee patients presenting in general practice. The Lysholm scale and WOMAC index give a measure for the problems knee complaints cause in daily life. When comparing these measures across the three subgroups, the younger subgroup of non-traumatic patients showed the best scores, followed by the older non-traumatic patients, and the traumatic subgroup showed the poorest scores. Differences between the younger and older non-traumatic patients were -7.9 for the WOMAC index and -4.7 for the Lysholm scale. The difference between the younger non-traumatic patients and the traumatic group were -12.7 for the WOMAC index and -6.2 for the Lysholm scale. To get an idea of the relevance of such differences, we may look at the mean clinically important difference (mcid) as determined in chapter 3 for patients aged 21 through 35. Lysholm scale and WOMAC index showed similar mcid-s, which were both around 13 in the non-traumatic group and around 19 in the traumatic group. The differences between the baseline scores of the three subgroups reported in chapter 4 are generally much smaller than these mcid-s. Therefore one might conclude that the observed differences between the subgroups of our cohort are relatively small, especially between the two non-traumatic age groups. In our opinion it is a noteworthy result that the subjective disease burden in the younger group is almost equal to that of the older group with probably a large proportion of osteoarthritis patients. However, one should keep in mind that mean clinically important differences were not determined for the older non-traumatic group. Because older patients may have lower expectations of their knee function, it is not safe to rely on the mcid determined in younger patients for interpretation of the subgroup differences.

Another way of looking at disease burden is asking patients whether they are bothered by their knee complaints during daily duties such as work or school, and if they refrained from these duties because of their knee complaints. Remarkably, comparison of the age groups of the non-traumatic patients revealed that a higher percentage of the younger group reported refraining from daily duties. This finding confirms the belief that the younger non-traumatic patients experience the disease burden of their knee complaints at least as serious as the older non-traumatic group.

Management

Patellofemoral pain syndrome (PFPS) is the most frequently occurring type of knee complaints in adolescents and young adults with non-traumatic knee complaints[11]. PFPS is the term suggested for knee complaints that have in the past been referred to as retropatellar chondropathy or chondromalacia patellae. The term PFPS was introduced when it became clear that chondral lesions were not always evident in patients with the typical symptoms. These symptoms are pain around the patella with knee-loading activities such as walking stairs, squatting, sitting with flexed knees for prolonged periods of time, jumping, and running.

The NHG guideline for children and adolescents with non-traumatic knee complaints propose the following treatment strategy for non-traumatic complaints: advise patients to limit pain provoking activities for a month, and bring the knee loading activities in line with the knee loading ability of the knee. If complaints have subsided somewhat after a month, gradually increase activities again. Specifically for PFPS the GP should advise the patient that physical activity per se will not harm the knee, and should suggest exercising the quadriceps muscles by repeatedly extending the knee in a sitting position. With this advise referral to a physical therapist will not be necessary. Pain medication is not advised, because pain can have a signalling function. If complaints persist over a period of months despite following this advise, referral to an orthopaedic surgeon should be considered[5].

In our cohort of adolescents and young adults with non-traumatic knee complaints we found that of the specific knee complaints, the ICPC-code[12] for retropatellar chondropathy was the most frequently applied, representing 35% of the adolescents and young adults with non-traumatic knee complaints. In chapter 4 we found that 34% of our cohort of adolescents and young adults with non-traumatic knee complaints were advised to limit knee loading activities, 26% of the patients was advised to exercise, 32% was referred to a physical therapist, 11% was referred to an orthopaedic surgeon and 11% was prescribed pain medication. Bearing in mind that these were first consulters in this new episode of knee complaints, the referral rate and the amount of pain medication prescriptions is rather high, and are not in line with the guideline.

The guideline also states that evidence for the effectiveness of exercise is not sufficient. In the systematic review (chapter 6) we now found that there is limited evidence for the effectiveness of exercise therapy for PFPS. Furthermore, open kinetic chain exercises and closed kinetic chain exercises are equally effective, as are training at home and

training under supervision of a physical therapist[13]. In chapter 7 we found limited evidence for the short term relief of the pain by NSAIDs in patients with PFPS. There is as yet no compelling evidence that other medications are of use in the treatment of patellofemoral pain syndrome.
Analysis of the effect of management by the GP has not been studied in our cohort study. An important reason for this is that treatment initiation depends heavily on the severity and persistence of complaints. Also the details of treatment given are hard to obtain in an observational study. It is therefore hard to distinguish between the influence of complaint characteristics and treatment characteristics on the eventual outcome. Effectiveness studies should preferably be carried out in randomised controlled trials.

Generalisibility of the results of the cohort study

In chapter 2, we evaluated how representative the total HONEUR cohort was of all patients visiting the GP. We found that patients below the age of 36 more often refrained from participation in our study, especially male patients. Patients with traumatic knee complaints also refrained from participation more often, though this was not statistically significant. We concluded that because of the planned analysis of subgroups, dividing the cohort in traumatic knee complaints and two age groups of non-traumatic knee complaints, the possibility that bias was induced by patient selection was slim. The adjustment for gender and age in the prognostic analyses, and the fact that no association with gender or age was found, reduces the possibility of bias even further. However, we do not know the severity of the complaints in the patients that did not participate in our study. We had telephone contact with a small part of the non-participants, and some of those patients indicated that they thought their knee complaints were not serious enough for participation in our cohort. This might indicate that the recovery rates in our cohort underestimate the true recovery rates in the practices participating in our study.

With respect to the representativeness of the general practices participating in our study, we can say that participating practices were not situated in typical rural areas or typical quarters of big cities. As indicator of the socio-economic status of patients we can look at the proportion of patients registered in their practices with certain types of medical insurance. In 2001 the proportion of patients with a type of insurance associated with lower income (ziekenfonds) in the Netherlands was 64%. In the general practices

participating in our cohort study this is 48%, and in our cohort itself it is 53%. This means that in our population the proportion of patients with a lower socioeconomic status is somewhat smaller than in the general population. In terms of the generally worse outcomes in patients with lower socio-economic status, this might in its turn indicate that the recovery rate in our cohort is slightly overestimated when extrapolated to the overall Dutch population.

Validity of outcome measures

For evaluation of the status of knee function in the HONEUR knee cohort we needed questionnaires that could be filled in by the patients themselves, that were applicable to a large group of diagnoses, and that were internationally accepted. Our choice of the Lysholm scale and the WOMAC index was based on the available validation studies in a wide variety of diagnoses for the Lysholm scale and the straightforward and easily interpretable questions in the WOMAC questionnaire. Nevertheless, neither questionnaire had been validated in general practice settings. We chose to perform a validation study in the younger age group alone, because this group was not yet represented in the available validation studies.
We found that both the construct validity and the responsiveness of the Lysholm scale and WOMAC index were adequate for use in adolescents and young adults consulting for knee complaints in general practice (chapter 4).

We also attempted to determine the inter-observer reproducibility of the tests used in the physical examination. Unfortunately, our resources were insufficient to evaluate the number of patients needed to obtain enough positive test results for a reliable analysis. Therefore the results of this effort remain unpublished. However, the reproducibility of the physical examination may be less relevant for the outcomes of our prognostic study for the following reason. The physical therapists performing the physical examination in our cohort attended training sessions in order to standardise the tests and measured many patients with knee complaints every week. GPs see fewer patients with knee complaints each week and do not attend such training sessions. Therefore the reproducibility in clinical practice is likely to be lower than that in our cohort. Furthermore, it is plausible that tests from the physical examination will only be identified as prognostic factors if they are sufficiently reliable, because if reproducibility is poor, the chance of the results correlating with long-term outcomes is small. In fact, the prognostic factors that

we identified (inspection of the tibial tuberosity and palpation of the patellar ligament (and patellar edges for confounding effects)) all represent easily accessible structures and do not require complex techniques, indicating that these tests may indeed have high reliability, also in clinical practice.

In conclusion, we can say that although selection bias can not be excluded, we have no reason to believe it has played a major role in our cohort study. The tools used to evaluate the course of the functional disability associated with the knee complaints were valid for use in our population. Furthermore, the means to collect possible prognostic factors from the physical examination were sufficiently valid to be applicable in clinical practice.

Implications for the GP

In the literature[14] as well as the NHG guidelines[5] certain common beliefs about non-traumatic knee complaints in adolescents and young adults in general practice are stated. These beliefs include the good prognosis as well as the idea that patellofemoral complaints occur mostly and are more persistent in younger female patients. Our cohort study has not provided any support for these beliefs. We also did not find any proof that the disease burden from non-traumatic knee complaints is greater in the older patients compared to adolescents and young adults. This information should be added to the NHG guidelines in future updates.

Our systematic reviews (chapters 6 and 7) showed that there is little evidence of the effect of conservative treatment strategies. Our cohort study does not add any information about the effectiveness of management options. However, it does provide basic information needed to perform intervention studies. One such trial is already underway: the department of general practice of Erasmus MC is performing a randomised controlled trial analysing the additive effect of exercise therapy supervised by a physiotherapist versus usual GP management giving advise about home exercise and adaptation of activities alone[15]. This trial will provide important results that may affect the outcome of the update of the systematic review in chapter 6. This should subsequently be implemented in future updates of the NHG guidelines.

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9

Summary

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Knee complaints are a frequent reason for consultation in general practice and constitute a specific set of patients compared to secondary care patient populations. However, information to base treatment decisions on is generally derived from specialistic settings. Our cohort study is aimed at collecting knowledge about disease burden and prognosis of knee complaints presenting in general practice

Chapter 2 describes the design and methods of the HONEUR knee cohort and addresses the possibility of selective patient recruitment. From October 2001 to October 2003 40 GPs recruited consecutive patients consulting for incident knee complaints. Patients were followed-up for one year with three monthly questionnaires. At baseline and after one year follow-up the patients underwent a physical examination. Primary outcome measure was the patient's reported recovery after one year. Pain and functional disability were assessed every 3 months to determine the course of the knee complaints during the year follow-up.
The cohort is divided into traumatic and non-traumatic knee complaints. The non-traumatic knee complaints are then divided in patients aged 12 through 35 and 36 years and over. This subdivision is based on the predominance of patellofemoral complaints in the younger age group, and the shift to osteoarthritis as the major complaint starting at age 35.
A retrospective search of the computerized medical files of participating GPs determined that 42% of the eligible patients during the inclusion period actually participated in the cohort. Selective recruitment resulted in an under-representation of patients between 12 en 35 years of age (OR 1.70; 1.15-2.77), especially in men (OR 2.16; 1.12-4.18). The under-representation of patients with traumatic onset of injury was not statistically significant. We believe that the detected selective recruitment is unlikely to introduce significant bias because the subgroups will be analysed separately. However, the under-representation of men in the age group of 12 to 35 years of age warrants caution.

In chapter 3 we compared the different subgroups of the cohort with respect to severity, impact on daily activities and initial management by the GP. Adolescents and young adults with non-traumatic knee complaints reported the highest percentage of recurrent knee complaints (52%) or bilateral complaints (45%), but this percentage was also relatively high in the traumatic group (15% and 27% respectively). Traumatic patients reported shorter duration of complaints before consultation, but the duration of

complaints was similar for both non-traumatic age groups. Pain, WOMAC, and Lysholm scores were worst for the traumatic group and best for the younger patients with non-traumatic knee complaints. Though significant, these differences were rather small. The percentage of patients refraining from daily duties such as studies or work was highest in the traumatic group, and slightly higher in the younger non-traumatic group compared to the older non-traumatic group. For the younger non-traumatic group the number of referrals to physical therapists and orthopaedic surgeons exceeds expectations based on guidelines for GPs. Otherwise the guidelines are adhered to fairly well in this subgroup. For the older non-traumatic group the number of referrals for X-rays was relatively high, which is not in line with the guidelines.

Chapter 4 describes the content validity, construct validity and responsiveness of the Lysholm knee scoring scale and the WOMAC osteoarthritis index in patients aged 12 through 35 consulting the GP for either non-traumatic or traumatic knee complaints. Content validity was examined by testing if the instruments could distinguish between patients with and patients without symptoms that were not specifically represented in the instruments. If the distinction could be made, the relevance of the missing items in the instruments was deemed small and content validity was deemed adequate. Construct validity was established if at least 6 out of 7 plausible hypotheses were confirmed. Responsiveness was assessed using three measures: effect size, standardized response mean and Guyatt's responsiveness index. Additionally, we determined the extent of any ceiling effects.

Both Lysholm scale and WOMAC index were able to distinguish between patient groups differing in symptoms not represented in those instruments, hence content validity was deemed adequate for both traumatic and non-traumatic knee complaints. Construct validity was confirmed for both Lysholm scale and WOMAC index in both subgroups. Effect size and standardized response mean were moderate in the non-traumatic group (Lysholm 0.76 and 0.73, WOMAC 0.65 and 0.74) and large in the traumatic group (Lysholm 1.14 and 1.13, WOMAC 1.13 and 1.15) as well as the total population (Lysholm 0.92 and 0.87, WOMAC 0.83 and 0.84). Guyatt's responsiveness statistic was high for both Lysholm and WOMAC global scores in both total population and subpopulations (ranging from 0.81 to 1.31), with lowest values for the traumatic group.

Though neither of the scales was developed for use in adolescents and young adults in general practice, both scales show adequate content and construct validity and good

responsiveness in this population.

Chapter 5 describes the course, prognosis and prognostic factors for persistence of non-traumatic knee complaints in adolescents and young adults. After one year patients rated their recovery on a 7-point scale, which was dichotomised into recovery or persistence. Prognostic factors for persistent knee complaints were identified through multivariate logistic regression using characteristics extracted from a baseline questionnaire and standardized physical examination. Three monthly questionnaires provided pain and functional disability scores to describe the course of knee complaints during one-year follow-up.
26% of the patients reported major improvement and 27% total recovery. Prognostic factors for persistent knee complaints (47%) were poor overall health, a lower education level, a prominent tibial tuberosity, painful patellar ligament, bilateral complaints, locking of the knee, a history of knee operation and self-reported knee swelling. 30% of all variability was explained by the model. Improvement of pain and functional disability is greatest in the first three months after consultation.
After one year 47% had persistent knee complaints. Revision of the assumed good prognosis stated in Dutch GP guidelines should be considered. These results emphasize the need for randomised controlled trials to assess the effectiveness of treatment options in order to improve prognosis.
Because a history of knee operation may be considered inappropriate for determination of prognostic factors of non-traumatic knee complaints, we performed a secondary analysis excluding the 15 patients that had a history of knee operation. This resulted in the addition of self-reported swelling of the knee (intermittent or continuous) to the prognostic model.

In Chapter 6 we performed a systematic Cochrane review to summarise the evidence for effectiveness of exercise therapy in reducing anterior knee pain and improving knee function in patients with patellofemoral pain syndrome (PFPS). PFPS is a common problem among adolescents and young adults, characterised by retropatellar pain (behind the kneecap) or peripatellar pain (around the kneecap) when ascending or descending stairs, squatting or sitting with flexed knees. Aetiology, structures causing the pain and treatment options are all debated in literature, but no consensus was reached so far. Exercise therapy to strengthen the quadriceps is often prescribed,

though its efficacy is still debated. Our database search up till December 2001 yielded 12 trials that focused on quadriceps strengthening exercises in patients with PFPS. Outcome assessments for knee pain, knee function on a disability level, and patient satisfaction or recovery were used in a best evidence synthesis to summarise evidence for effectiveness. Methodological quality was determined with the Delphi list, and determined the weight of a study in the synthesis.
We found only 3 studies with a non-exercising control group, 5 studies comparing open kinetic chain exercises (foot not in contact with a surface) with closed kinetic chain exercises (foot in contact with a surface), and 4 studies dealing with other comparisons of exercises. The studies comparing exercise to no exercise and the studies comparing open and closed kinetic chain exercise were summarized in two best evidence syntheses. The evidence that exercise therapy is more effective in treating PFPS than no exercise was limited with respect to pain reduction, and conflicting with respect to functional improvement. There is strong evidence that open and closed kinetic chain exercises are equally effective. There is limited evidence that exercising at home, and exercising under supervision of a physical therapist is equally effective. Further research to substantiate the effectiveness of exercise treatment compared to a non-exercising control group is needed, and thorough consideration should be given to methodological aspects of study design and reporting.

In Chapter 7 we performed a systematic Cochrane review to summarise the evidence of effectiveness of pharmacotherapy in reducing anterior knee pain and improving knee function in patients with PFPS.
Pharmacological treatments focus on reducing pain symptoms (non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticosteroids), or restoring the assumed underlying pathology (compounds containing glucosaminoglycan polysulphate to stimulate cartilage metabolism, anabolic steroids to increase bone density of the patella and build up supporting muscles).
A systematic search of the literature databases up till January 2004 yielded 8 controlled trials (randomised or not) comparing pharmacotherapy with placebo, different types of pharmacotherapy, or pharmacotherapy to other therapies for patients with PFPS. Three trials were of high quality (i.e. at least 5 positive items on the Delphi list). Data were analysed qualitatively using best evidence syntheses, because meta-analysis was impeded by differences in route of administration of drugs, care programs and outcome

measures. The drugs were generally applied in addition to exercises aimed at building up supporting musculature.

Four trials (163 participants) studied the effect of NSAIDs. Aspirin compared to placebo in a high quality trial produced no significant differences in clinical symptoms and signs. Naproxen produced significantly greater short-term pain reduction when compared to placebo, but not when compared to diflunisal. Laser therapy to stimulate blood flow in tender areas led to more satisfied participants than tenoxicam, though not significantly.

Two high quality RCTs (84 participants) studied the effect of glycosaminoglycan polysulphate (GAGPS). Twelve intramuscular injections in six weeks led to significantly more participants with a good overall therapeutic effect after one year, and to significantly better pain reduction during one of two activities. Five weekly intra-articular injections of GAGPS and lidocaine were compared with intra-articular injections of saline and lidocaine or no injections, all with concurrent quadriceps training. Injected participants showed better function after six weeks, though only the difference between GAGPS injected participants and non-injected participants was significant. The differences had disappeared after one year.

One trial (43 participants) found that intramuscular injections of the anabolic steroid nandrolone phenylpropionate significantly improved both pain and function compared to placebo injections.

We concluded that there is only limited evidence for the effectiveness of NSAIDs for short-term pain reduction in PFPS. The evidence for the effect of glycosaminoglycan polysulphate is conflicting and merits further investigation. The anabolic steroid nandrolone may be effective, but is too controversial for treatment of PFPS.

10

Nederlandse samenvatting

Knieklachten zijn een veel voorkomende reden om de huisarts te consulteren en vormen een specifieke groep patiënten vergeleken met patiënten uit de tweedelijnszorg. Toch is de kennis waarop behandelingen worden gebaseerd over het algemeen afkomstig van specialisten uit het ziekenhuis. Onze cohortstudie richt zich op het verzamelen van kennis over de ziektelast en prognose van knieklachten gepresenteerd in de huisartspraktijk.

Hoofdstuk 2 beschrijft de studieopzet en methoden van het HONEUR kniecohort en behandelt de mogelijkheid van selectieve patiëntenwerving. Van oktober 2001 tot oktober 2003 hebben 40 huisartsen opeenvolgende patiënten die met knieklachten naar het spreekuur kwamen geworven. De patiënten werden een jaar gevolgd met driemaandelijkse vragenlijsten. Bij inclusie en na een jaar werden de patiënten aan een lichamelijk onderzoek van de knie onderworpen. De primaire uitkomstmaat was zelfgerapporteerd herstel na een jaar. Pijn en functionele beperkingen werden elke 3 maanden beoordeeld om het beloop van de klachten te volgen.
Het cohort is onderverdeeld in traumatische en niet-traumatische knieklachten. De niet-traumatische knieklachten zijn onderverdeeld in patiënten van 12 tot en met 35 jaar en 36 jaar ouder. Deze onderverdeling is erop gebaseerd dat in de jongere groep patellofemorale klachten de belangrijkste groep vormen, en dat vanaf 35 jaar artrose langzaam de overhand krijgt.
De elektronische patiëntendossiers werden retrospectief doorzocht en heet bleek dat gedurende de inclusieperiode van alle patiënten die in aanmerking kwamen voor het cohort ook 42% daadwerkelijk meedeed. Selectieve inclusie resulteerde in een ondervertegenwoordiging van 12 tot 35-jarigen (Odds ratio 1.70, 1.15-2.77), met name onder mannen (OR 2.16, 1.12-4.18). De ondervertegenwoordiging van patiënten met traumatische knieklachten was niet statistisch significant. Omdat de subgroepen apart geanalyseerd zullen worden, denken we dat de patiëntenselectie die uitkomsten niet zal beïnvloeden, maar de ondervertegenwoordiging van jonge mannen vraagt om terughoudendheid.

In hoofdstuk 3 vergeleken we de verschillende subgroepen van het cohort met betrekking tot de ernst van de klachten, de impact op dagelijkse activiteiten en behandeling door de huisarts. Adolescenten en jong volwassenen met niet-traumatische knieklachten rapporteerden het hoogste percentage van terugkerende klachten (52%) en bilaterale

klachten (45%), maar dit percentage was ook relatief hoog in de traumatische groep (15% respectievelijk 27%). Traumatische patiënten rapporteerden kortere duur van de klachten voorafgaand aan consultatie, maar de duur van de klachten was vergelijkbaar voor beide niet-traumatische leeftijdsgroepen. Pijn, WOMAC en Lysholm scores waren het slechtst in de traumatische groep en het best in de jongste leeftijdsgroep met niet-traumatische klachten. Hoewel significant, waren deze verschillen tamelijk klein. Het percentage patiënten dat dagelijkse verplichtingen zoals werk of studie verzuimt vanwege de knieklachten was het hoogst in de traumatische groep, en iets hoger in de jongere niet-traumatische groep dan in de oudere. Voor de jongere niet-traumatische groep was het aantal verwijzingen naar fysiotherapeuten en orthopeden hoger dan verwacht mag worden op basis van de NHG standaarden. Voor het overige werden de standaarden redelijk gevolgd. Voor de oudere niet-traumatische subgroep was het aantal verwijzingen voor röntgenfoto's relatief hoog, tegen de NHG standaard in.

Hoofdstuk 4 beschrijft de content en construct validiteit en de responsiviteit van de Lysholm knee scoring scale en de WOMAC osteoarthritis index in patiënten van 12 tot en met 35 jaar die de huisarts consulteren voor traumatische of niet-traumatische knieklachten. Als de vragenlijsten onderscheid konden maken tussen patiënten met en zonder symptomen die niet specifiek in de vragenlijsten waren opgenomen werd de relevantie van deze missende componenten klein geacht, en de content validiteit adequaat. Construct validiteit was bewezen als minstens 6 van 7 plausibele hypothesen bevestigd werden. Responsiviteit werd beoordeeld aan de hand van drie maten: effect size, standardized response mean en Guyatt's reponsiveness index. Verder werd de proportie plafondscores bepaald.
Zowel de Lysholm scale en de WOMAC index konden onderscheid maken tussen patiëntengroepen die verschilden in symptomen die niet in de vragenlijsten waren opgenomen, dus werd de content validiteit adequaat geacht voor patiënten met zowel traumatische als niet-traumatische knieklachten. Construct validiteit werd bevestigd voor zowel Lysholm scale als WOMAC index in beide subgroepen. Effect size en standardized response mean waren redelijk in de niet-traumatische groep (Lysholm 0.76 en 0.73, WOMAC 0.65 en 0.74) en groot in zowel de traumatisce groep (Lysholm 1.14 en 1.13, WOMAC 1.13 en 1.15) als de hele populatie (Lysholm 0.92 en 0.87, WOMAC 0.83 en 0.84). Guyatt's responsiveness statistic was groot voor zowel de Lysholm en de SOMAC global scores in zowel de hele populatie als de subgroepen (variërend van 0.81

tot 1.31) met de laagste waarden voor de traumatische groep.
Hoewel geen van beide vragenlijsten voor gebruik in adolescenten en jong volwassenen in de huisartspraktijk was ontwikkeld, vertoonden beide adequate content en construct validiteit en goede responsiviteit in deze populatie.

Hoofdstuk 5 beschrijft het beloop, de prognose en prognostische factoren voor persistentie van niet-traumatische knieklachten in adolescenten en jong volwassenen. Na een jaar scoorden patiënten hun herstel op een 7-punts schaal, welke werd gedichotomiseerd in herstel en persistentie. Prognostische factoren voor persistente knieklachten werden geïdentificeerd met behulp van multivariate logistische regressie aan de hand van bevindingen uit de eerste vragenlijst en het eerste lichamelijk onderzoek. Driemaandelijkse vragenlijsten verschaften pijn en functie scores om het beloop van de knieklachten gedurende een jaar te volgen.
26% van de patiënten rapporteerden sterke verbetering en 27% totaal herstel. Prognostische factoren voor persistentie (47%) waren matige algemene gezondheid, een lager opleidingsniveau, een prominente tuberositas tibiae, een pijnlijk patella-ligament, bilaterale klachten, slotklachten, een knie-operatie in de geschiedenis en zelfgerapporteerde zwelling. Het model verklaarde 30% van de totale variantie. Verbetering van pijn en functie was het grootst in de eerste 3 maanden na consultatie.
Na een jaar had 47% nog persistente knieklachten. Revisie van de veronderstelde goede prognose zoals vermeld in de NHG standaard zou overwogen moeten worden. Deze resultaten benadrukken dat gerandomiseerde gecontroleerde onderzoeken naar de effectiviteit van behandelalternatieven nodig zijn om de prognose te verbeteren.
Omdat een geschiedenis van knie-operatie niet van toepassing kan worden geacht voor bepaling van prognostische factoren voor niet-traumatische knieklachten, werd een secundaire analyses uitgevoerd, waarbij de 15 patiënten met een knie-operatie in de geschiedenis werden geëxcludeerd. Dit resulteerde in het toevoegen van zelf-gerapporteerde zwelling van de knie (terugkerend of continue) in het prognostische model.

Hoofdstuk 6 beschrijft een systematische Cochrane review die de bewijzen samenvat voor de effectiviteit van oefentherapie voor het verminderen van voorste kniepijn en het verbeteren van kniefunctie in patiënten met patellofemoraal pijn syndroom (PFPS). PFPS is een veelvoorkomend probleem onder adolescenten en jong volwassenen, en

wordt gekarakteriseerd door retropatellaire of peripatellaire pijn (achter of rond de knieschijf) tijdens traplopen, hurken of zitten met gebogen knieën. In de literatuur is nog geen consensus over de etiologie, welke structuren de pijn veroorzaken, en over de behandelingsmogelijkheden. Oefentherapie om de quadriceps te versterken wordt vaak voorgeschreven, maar de effectiviteit ervan wordt betwist.
Het doorzoeken van databases tot December 2001 resulteerde in 12 onderzoeken over quadriceps versterkende oefentherapie in patiënten met PFPS. De uitkomsten pijn, functionele beperkingen, patiënttevredenheid en herstel werden gebruikt in een 'best evidence synthesis' om de bewijzen voor effectiviteit samen te vatten. Methodologische kwaliteit werd bepaald aan de hand van de Delphi lijst, en bepaalde het gewicht van de studie in de synthese.
We vonden slechts 3 studies met een controle groep zonder oefentherapie, 5 studies die een vergelijking maakten tussen open en gesloten kinetische keten oefeningen (voet niet respectievelijk wel in aanraking met een oppervlak), en 4 studies die anderssoortige vergelijkingen van oefentherapie beschreven. De eerste twee groepen studies werden ieder in een 'best evidence synthesis' samengevat. Het bewijs dat oefentherapie effectiever was dan geen oefentherapie is beperkt voor pijnreductie, en tegenstrijdig voor functionele verbetering. Er is sterk bewijs dat open en gesloten kinetische keten oefeningen even effectief zijn. Er is beperkt bewijs dat thuis oefenen even effectief is als oefenen onder begeleiding van een fysiotherapeut. Er is meer onderzoek nodig om duidelijkheid te krijgen over de effectiviteit van oefentherapie ten opzichte van geen oefeningen en er moet goed nagedacht worden over methodologische aspecten van het ontwerp en rapportage van de studie.

Hoofdstuk 7 beschrijft een systematische Cochrane review die de bewijzen samenvat voor de effectiviteit van farmacotherapie voor het verminderen van voorste kniepijn en het verbeteren van kniefunctie in patiënten met patellofemoraal pijn syndroom (PFPS). Farmacologische behandelingen focussen op het reduceren van pijn (non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticosteroïden), of het herstellen van de veronderstelde pathologie die aan de aandoening ten grondslag ligt (glucosaminoglycaan polysulfaatpreparaten om het kraakbeenmetabolisme te stimuleren, anabole steroïden om botdichtheid van de knieschijf te verhogen en de spieren te versterken).
Het doorzoeken van databases tot januari 2004 resulteerde in 8 gecontroleerde onderzoeken (wel of niet gerandomiseerrd) die een vergelijking maakten tussen

farmocotherapie en placebo, verschillende soorten farmacotherapie, of farmacotherapie en andere therapieën in patiënten met PFPS. Drie onderzoeken waren van hoge kwaliteit. De data werden kwalitatief geanalyseerd aan de hand van ‘best evidence syntheses’ omdat meta-analyse niet mogelijk was door verschillen in toediening, behandelschema’s en uitkomstmaten. Meestal werden de geneesmiddelen toegepast in combinatie met oefeningen om de spieren rondom de knie te versterken.

Vier onderzoeken (163 deelnemers) bestudeerden het effect van NSAIDs. Aspirine vergeleken met placebo in een studie van hoge kwaliteit liet geen significant verschil zien in klinische symptomen. Naproxen gaf significant betere pijn reductie op de korte termijn dan placebo, maar niet beter dan diflunisal. Laser therapie om de bloeddoorstroming in gevoelige gebieden te verbeteren gaf meer tevreden patiënten dan tenoxicam, maar niet significant.

Twee gerandomiseerde onderzoeken van hoge kwaliteit (84 deelnemers) bestudeerden het effect van glycoaminoglycaan polysulfaat (GAGPS). Twaalf intramusculaire injecties binnen 6 weken resulteerden in significant meer deelnemers met een goed algemeen therapeutisch effect na een jaar, en in significant betere pijn reductie gedurende een van twee onderzochte activiteiten.

Vijf wekelijkse intra-articulaire injecties met GAGPS en lidocaïne werden vergeleken met intra-articulaire injecties met zoutoplossing en lidocaïne en met geen injecties, allemaal met gelijktijdige quadriceps training. Alle geïnjecteerde patiënten lieten na 6 weken een betere functie zien, maar alleen het verschil tussen GAGPS en niet-geïnjecteerde patiënten was significant. Na een jaar waren er geen verschillen meer.

Een onderzoek (43 deelnemers) vond dat intramusculaire injecties met het anabole steroid nandrolon phenylpropionaat de pijn en de functie significant verbeterden ten opzichte van placebo injecties.

We concludeerden dat er beperkt bewijs is voor de effectiviteit van NSAIDs met betrekking tot pijnreductie op de korte termijn. Er is tegenstrijdig bewijs voor het effect van GAGPS, en meer onderzoek daarnaar zou zinvol zijn. Het anabole steroïd nandrolon zou effectief kunnen zijn, maar is te controversieel voor de behandeling van PFPS.

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Over de auteur

Edith Heintjes werd geboren op 3 juni 1970 te Nijmegen. In 1988 slaagde zij voor haar VWO examen aan het Strabrecht College te Geldrop. In september 1989 begon zij aan haar studie biologie aan de Rijksuniversiteit te Leiden. Tijdens haar studie participeerde zij onder andere in de studierichtingscommissie met als doel de belangen van de studenten te behartigen, en wijzigingen in het curriculum te evalueren. In september 1995 studeerde zij af in de richting medische biologie. Van 1995 tot 1997 was zij onder meer als trial assistent werkzaam in enkele huisartspraktijken voor data-extractie uit medische dossiers. Van mei 1997 tot en met maart 2001 was zij werkzaam bij verschillende contract research organisations voor fase 1 en 2 farmacokinetische studies als biometrics assistent, manager biometrics and data management, en senior biometrician.

Van april 2001 tot augustus 2005 was zij aangesteld bij de afdeling huisartsgeneeskunde van het Erasmus Medisch Centrum te Rotterdam als cohort manager / onderzoeker van het HONEUR kniecohort. Edith zal als eerste van vier onderzoekers promoveren op de data van dit cohort. Verder was zij betrokken bij het HONEUR buikpijncohort en het schrijven van het voorstel voor de PEX studie naar de effectiviteit van oefentherapie voor patellofemoraal pijnsyndroom.

Sinds oktober 2005 werkt zij als onderzoeker bij het PHARMO institute for drug outcomes research in Utrecht.