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Review

Osteoarthritis of the knee: Why does exercise work? A qualitative study of the literature

David Beckwée[a], Peter Vaes[a], Maarten Cnudde[a], Eva Swinnen[a], Ivan Bautmans[b,*]

[a] Rehabilitation Sciences Research Department, Vrije Universiteit Brussel, Laarbeeklaan 103, B-1090 Brussels, Belgium
[b] Frailty in Ageing Research Department, Vrije Universiteit Brussel, Laarbeeklaan 103, B-1090 Brussels, Belgium

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ABSTRACT

The effectiveness of exercise to reduce pain and improve functioning in osteoarthritis of the knee (OAk) is well substantiated. Underlying mechanisms are still under debate and better understanding of the pathways involved may contribute to more targeted treatment strategies. The present qualitative analysis of the literature aims to provide an overview of theoretical models that are put forward to explain the beneficial treatment effects of exercise in OAk. An inductive qualitative approach, based on the 'grounded theory' of Glaser and Straus, was used. Twenty-two studies emphasizing on exercise therapy for OAk, collected from three Cochrane reviews and nine guidelines of the Physiotherapy Evidence Database (PEDRO) published between 2000 and 2012, were included. The introduction and discussion parts of these papers were screened for explanations of exercise-induced benefits in OAk patients. Seventy-three key points were identified which were subdivided into 16 core theoretical concepts. Finally, 5 categories were formed: neuromuscular, peri-articular, intra-articular, psychosocial components, and general fitness and health. We referred to scientific evidence that was used in the included studies to describe and categorize the concepts. Future research on exercise in OAk should allow distinguishing the contribution of different potential pathways to the treatment effects.

1. Introduction

Osteoarthritis (OA) is characterized by a degeneration of articular cartilage in synovial joints. Pain and disability occur in 17% of people aged 45 years and over due to osteoarthritis in the knee (OAk) (Lawrence et al., 2008) and in 40% of people aged 65 years and over due to OAk or OA in the hip (Dawson et al., 2004; Mannoni et al., 2003). Because till now OA is an irreversible condition, the treatment is focused on reducing physical disability and handicap, and controlling pain while minimizing the potentially harmful side effects of medications (Zhang et al., 2007). In this context, exercise therapy is considered as an effective conservative treatment for OAk-related pain and disability (Fransen and McConnell, 2008), and recommended as 'first choice conservative treatment' by several clinical guidelines (Peter et al., 2010; Royal Australian College of General Practitioners, 2009 (South Melbourne); Zhang et al., 2008). However, underlying mechanisms for these beneficial exercise-induced effects are still scarcely understood. Understanding the pathways through which exercise influences pain and function in OAk patients may contribute to the design of a comprehensive treatment plan. Potential explanations for the favourable effects of exercise in OAk are frequently proposed in the introduction and discussion sections of scientific papers reporting the effects of exercise interventions. Sometimes these hypotheses are (partly) empowered by scientific data. To our knowledge, comprehensive overviews of these potential working mechanisms of physical exercise are lacking. The present literature study aims to provide an overview of the potential underlying mechanisms that are proposed in the literature to explain the exercise induced improvements in OAk pain and function.

2. Methods

A systematic literature search was performed and extracted data were further analyzed with a qualitative approach, based on the 'grounded theory' of Glaser & Strauss, which is inductive in nature (Strauss and Corbin, 1998). This approach implies 4 steps: (1) data gathering; (2) extracting key points from the collected data; (3) grouping key points into similar concepts; and (4) forming categories from the concepts. First, in order to gather information, we searched (last search on March 1st 2012) for scientific papers emphasizing on exercise therapy for OAk (systematic reviews and/or practice guidelines) using the search

* Corresponding author. Tel.: +32 02 477 42 07; fax: +32 02 477 63 64.
E-mail addresses: David.Beckwee@vub.ac.be (D. Beckwée), pvaes@vub.ac.be (P. Vaes), mcnudde@vub.ac.be (M. Cnudde), eswinnen@vub.ac.be (E. Swinnen), ivan.bautmans@vub.ac.be (I. Bautmans).

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engines of the Cochrane Library (www.cochrane.org; keywords: osteoarthritis, exercise, and knee) and the Physiotherapy Evidence Database (Pedro, www.pedro.org.au; keywords: osteoarthritis, practice guideline, and body part: lower leg or knee). If exercise therapy was recommended in a practice guideline, the studies that were used to empower this recommendation were retrieved for further analysis and data extraction. All studies, reported in the included Cochrane reviews, were analyzed as well. In a first step, introduction and discussion sections of the included studies were systematically screened for potential underlying mechanisms for the effects of exercise on OAk symptoms. Secondly, these mechanisms were listed as key points. Thirdly, these key points were grouped into concepts by 2 researchers (DB and IB). Finally, concepts that may explain the exercise induced improvements in OAk pain and function were ordered in categories and the corresponding scientific foundations to empower the theoretical models were extracted from the papers.

3. Results

Three Cochrane reviews and nine guidelines were identified (see Table 1).

All guidelines recommend physical exercise as a conservative treatment for OAk. The selected reviews and guidelines are based on 70 original research papers (see Appendix A) that were published between 1989 and 2010. Twenty-two of these studies (published between 1991 and 2008) mention potential underlying mechanisms for the effects of exercise in OAk and referred to 117 other articles (see Appendix B) for scientific support for the proposed mechanism. From these 22 papers, 73 key points were extracted. Next, these key points were grouped into 16 concepts: "Muscle", "Proprioception, balance and motor learning", "Energy absorbing capacity", "Stability", "Connective tissue", "Bone", "Cartilage", "Inflammation", "Joint fluid", "Comorbidities", "Weight loss", "Aerobic fitness", "Increase of well-being", "Decrease of depression", "Placebo effect", and "Increase of self-efficacy". Finally, the concepts were ordered in 5 categories: (1) Neuromuscular components, (2) Peri-articular components, (3) Intra-articular components, (4) General fitness and health, and (5) Psychosocial components. Of all included papers, the effect of different exercise modes was investigated: strengthening exercises (some with additional modes including ROM, flexibility and balance) ($N = 14$) (Baker et al., 2001; Cochrane et al., 2005; Hinman et al., 2007; Huang et al., 2003b, 2005a; Jan and Lai, 1991; Mikesky et al., 2006; Miyaguchi et al., 2003; O'Reilly et al., 1999; Rogind et al., 1998; Schilke et al., 1996; Thorstensson et al., 2005; Topp et al., 2002; van Baar et al., 1998a), aerobic exercises ($N = 1$) (Fransen et al., 2001), tai chi ($N = 1$) (Hartman et al., 2000), a combination of strengthening, aerobic and ROM exercises ($N = 2$) (Deyle et al., 2000; Keefe et al., 2004), strengthening versus aerobic exercises ($N = 2$) (Penninx et al., 2001, 2002a) (see Tables 2–6). Two included papers were reviews (Lee et al., 2008; Pelland et al., 2004). Information on the mechanisms of exercise induced improvements was given for strengthening exercises ($N = 11$) (Baker et al., 2001; Deyle et al., 2000; Fransen et al., 2001; Huang et al., 2003a, 2005a; Jan and Lai, 1991; Keefe et al., 2004; Miyaguchi et al., 2003; Schilke et al., 1996; Thorstensson et al., 2005; Topp et al., 2002), aerobic exercises ($N = 4$) (Mikesky et al., 2006; Miyaguchi et al., 2003; O'Reilly et al., 1999; Penninx et al., 2002a) or for exercises in general ($N = 8$) (Cochrane et al., 2005; Hartman et al., 2000; Hinman et al., 2007; Lee et al., 2008; Pelland et al., 2004; Penninx et al., 2001; Rogind et al., 1998; van Baar et al., 1998a) (see Tables 2–6).

3.1. Neuromuscular components (see Table 2)

In this category, the proposed underlying mechanisms for the beneficial effect of exercise on pain or function of OAk are mainly focused on the decrease of the mechanical focal peak loading of the cartilage due to the impact of exercise on neuromuscular components: muscles, proprioception and motor learning, energy absorbing capacity and stability.

3.1.1. Muscle

Mikesky et al. suggested that the strength of contraction of the periarticular muscles (i.e. quadriceps and hamstrings for the knee joint) is an important contributing factor for the quality of the cartilage (Mikesky et al., 2006). Therefore, gaining strength through exercise may be beneficial. This statement is based on an assumption of Palmoski et al. (1980). Palmoski et al. studied morphologic changes of articular cartilage of dogs of which one knee was unloaded either by immobilization or amputation (Palmoski et al., 1979, 1980). In one of their studies the unloaded knee was immobilized with a cast for 6 days after which atrophy of the articular cartilage of the knee was observed (Palmoski et al., 1979). In another study, similar atrophy was seen in knees of dogs of which one paw was amputated 6 weeks earlier (Palmoski et al., 1980). Due to this amputation, the dogs were able to ambulate on three legs while the knee joint of the amputated leg could actively move, similarly to the contralateral (i.e. non-amputated) knee but without bearing weight. Based on these observations, Palmoski et al. concluded that joint movement alone may be insufficient to maintain the integrity of the articular cartilage and he suggested that the force of the quadriceps and hamstrings muscles could be involved (Palmoski et al., 1980). He hypothesized that most of the force

Table 1
Included guidelines and Cochrane reviews.

Source	Title
Australian Physiotherapy Association (Royal Australian College of General Practitioners, 2009 (South Melbourne))	Knee joint osteoarthritis position statement
Cochrane collaboration (Bartels et al., 2007)	Aquatic exercise for the treatment of knee and hip osteoarthritis
Cochrane collaboration (Fransen and McConnell, 2009)	Exercise for osteoarthritis of the knee
Cochrane collaboration (Brosseau et al., 2003)	Intensity of exercise for the treatment of osteoarthritis
European League Against Rheumatism (EULAR) (Pendleton et al., 2000)	EULAR recommendations for the management of knee osteoarthritis
Royal Dutch Society for Physical Therapy (KNGF) (Vogels et al., 2001)	Clinical practice guidelines for physical therapy in patients with osteoarthritis of the hip or knee
Osteoarthritis Research Society International (OARSI) (Zhang et al., 2008)	OARSI recommendations for the management of hip and knee osteoarthritis, part II: OARSI evidence-based, expert consensus guidelines
Ottawa Panel (Brosseau et al., 2011)	Ottawa Panel Evidence-Based clinical practice guidelines for the management of osteoarthritis in adults who are obese or overweight
Philadelphia Panel (Albright et al., 2001)	Philadelphia Panel evidence-based clinical practice guidelines on selected rehabilitation interventions for knee pain
(Royal Australian College of General Practitioners, 2009 (South Melbourne))	Guideline for the non-surgical management of hip and knee osteoarthritis
Dutch Medical Association (Swierstra et al., 2009)	Guideline 'Diagnostics and treatment of osteoarthrosis of the hip and knee'
(American Academy of Orthopaedic Surgeons, 2008)	Treatment of osteoarthritis of the knee (non-arthroplasty): full guideline

Table 2
Neuromuscular components explaining beneficial effects of exercise in OAk.

Concepts	Citations	Aim of study	Mechanism*
Muscle	"Stronger hip abductors can reduce the adduction moment (or compressive force) at the knee" (Hinman et al., 2007)	S	NS
	"Improved muscle strength" (Penninx et al., 2001)	S or A	NS
	"Changes of cartilage atrophy were mediated primarily by a reduction in the strength of contraction of the periarticular muscles"(Mikesky et al., 2006)	S + ROM	A
	"Quadriceps strength might further increase joint load by the muscles compressing the articular surfaces" (Thorstensson et al., 2005)	S	S
	"Greater muscle strength and improved agility permits a greater level of general physical activity, leading to increased functional capacity" (Rogind et al., 1998)	S + F + C	NS
Proprioception, balance and motor learning	"Resistance training has been shown to increase the alpha-motor discharge or tone of the muscles trained" (Topp et al., 2002)	S	S
	"Resistance training attenuates the impact and impulsive loads through the knee joint by increasing the sensitivity and coordination of the proprioceptors within the quadriceps muscle" (Topp et al., 2002)	S	S
	"Decrease of reflex inhibition of M. Quadriceps (through stimulation of proprioceptive receptors) = >increase stability" (Miyaguchi et al., 2003)	S	S + A
	"Motor learning, can improve the mechanical and energetic costs of completing a functional task" (Pelland et al., 2004)	NA	NS
	"Increased balance" (Penninx et al., 2001)	S or A	NS
	"Beneficial effect on muscle spasms" (van Baar et al., 1998a)	S + ROM + C	NS
Energy absorbing capacity	"Stronger muscle may absorb more energy" (Baker et al., 2001)	S	S
	"The knee extensors function to attenuate peak loading rate at heel strike" (Fransen et al., 2001)	A	S
	"Resistance training attenuate the impact and impulsive loads through the knee joint by increasing muscle strength" (Topp et al., 2002)	S	S
	"Attenuation of impact by neuromuscular mechanisms depends on an adequate mass of conditioned muscle" (Cochrane et al., 2005)	S + R + C	NS
	"Muscles can absorb a large amount of energy" (Cochrane et al., 2005)	S + R + C	NS
Stability	"Weak and unbalanced muscles may overload specific compartments—exercise may evenly distribute force in the joint" (Baker et al., 2001)	S	S
	"Muscular strength provides greater support for the knee" (Keefe et al., 2004)	S + A + ROM	S
	"Muscle strength is important for joint stability to maintain normal alignment" (Jan and Lai, 1991)	S	S
	"Muscle strength provides added support to the osteoarthritic joint" (Schilke et al., 1996)	S	S
	"Quadriceps is one of the key muscles controlling the stability of the arthritic knee" (Huang et al., 2005b)	S	S
	"Improve joint stability" (Lee et al., 2008)	NA	S
	"Improve joint stability" (Pelland et al., 2004)	NA	NS

Citations extracted from original reports (*as described by the cited author; S: strength, A: aerobic, ROM: range of motion; F: flexibility; C: coordination; NA: not applicable; NS: non-specified).

across the knee joint is generated by contraction of these muscles and suggested that unloading the knee by amputation causes less muscle force exertion required for stabilizing the knee. Remarkably his conclusion points to axial compression generated by the muscles rather than generated by ground reaction force during stance phases. In fact, the assumption refers rather to the beneficial effects of articular cartilage loading through movement without weight bearing than through movement with weight bearing (e.g.

Table 3
Peri-articular components explaining beneficial effects of exercise in OAk.

Concepts	Citations	Aim of study	Mechanism*
Connective tissue	"Provides a strong stimulus to connective tissue, resulting in pain relief" (Deyle et al., 2000)	S + A + ROM	S
	"Mechanical forces modulate morphology and structure of skeletal tissue, including ligament and tendon" (Cochrane et al., 2005)	S + R + C	NS
	"Increased flexibility" (Penninx et al., 2001)	S or A	NS
Bone	"Improved bone mass" (Penninx et al., 2001)	S or A	NS
	"Positive corollary effect on bone mineralization" (Pelland et al., 2004)	NA	NS
	"Mechanical forces modulate morphology and structure of skeletal tissue, including bone" (Cochrane et al., 2005)	S + R + C	NS

Citations extracted from original reports (*as described by the cited author; S, strength; A, aerobic; ROM, range of motion; C, coordination; NA, not applicable; NS, non-specified).

Table 4
Intra-articular components explaining beneficial effects of exercise in OAk.

Concepts	Citations	Aim of study	Mechanism*
Cartilage	"Positive effect on the loss of protein" (Pelland et al., 2004)	NA	NS
	"Higher cartilage proteoglycan content" (Mikesky et al., 2006)	S + ROM	A
	"Prevention of cartilage degeneration" (Mikesky et al., 2006)	S + ROM	A
	"Maintenance of healthy cartilage" (Mikesky et al., 2006)	S + ROM	A
	"Chondroitin sulfate levels decrease after quadriceps training" (Miyaguchi et al., 2003)	S	S + A
	"Increase of molecular weight of (high molecular weight) hyaluronan after quadriceps training" (Miyaguchi et al., 2003)	S	S + A
	"Increase in pH" (Miyaguchi et al., 2003)	S	S + A
	"Decrease in albumin concentration" (Miyaguchi et al., 2003)	S	S + A
	"Chondrocytes within the articular cartilage recognise mechanical signals" (Cochrane et al., 2005)	S + R + C	NS
	"Mechanical stress has a direct effect on the synthetic and catabolic activities of chondrocytes" (Huang et al., 2003b)	S	S
	"Mechanical forces modulate morphology and structure of cartilage" (Cochrane et al., 2005)	S + R + C	NS
Inflammation	"Increased blood flow and mixing of synovial fluid disperse the inflammatory exudates from the joint cavity" (Cochrane et al., 2005)	S + R + C	NS
	"A positive effect on the loss of protein, and associated increase in fat linked to chronic inflammation in arthritis" (Pelland et al., 2004)	NA	NS
	"Low physiological levels of tensile compressive strains are anti-inflammatory and activate anabolic pathways" (Cochrane et al., 2005)	S + R + C	NS
Joint fluid	"Joint fluid viscosity increase" (Miyaguchi et al., 2003)	S	S + A
	"Deformation of the cartilage provides a hydrostatic lubrication mechanism (which is essential for optimal nutrition of the cartilage)" (Cochrane et al., 2005)	S + R + C	NS
	"Adequate nutrition depends on the pump effect of synovial fluid with alternate compression and decompression of cartilage" (Cochrane et al., 2005)	S + R + C	NS
	"Biochemical changes in joint fluid viscosity" (Cochrane et al., 2005)	S + R + C	NS

Citations extracted from original reports (*as described by the cited author; S, strength; A, aerobic; ROM, range of motion; C, coordination; NA, not applicable; NS, non-specified).

as seen during respectively open and closed kinetic chain exercise). However, the statements of Palmoski et al. do not take the importance of axial loading of the knee joint through weight bearing into account.

Rogind et al. suggested that improved muscle strength acquired through strengthening exercise permits a greater level of general physical activity, which may lead to an increased functional capacity in OAk patients (Rogind et al., 1998).

Hinman et al. mentioned that "stronger hip abductors" can reduce the compressive force (adduction moment) at the knee (Hinman et al., 2007). They concluded that their findings of exercise induced improvement of hip and knee muscle strength might have been responsible for knee pain reduction and improved physical function in their participants. Hinman et al. refer hereby to the results of Chang et al. who observed that a greater hip abduction moment during gait at baseline had a protective effect against ipsilateral medial OA progression after 18 months follow up (Chang et al., 2005). The rationale is that during the single-limb stance phase of gait, weakness of the hip abductor muscles (of the stance limb) causes excessive pelvic drop towards the contralateral side (MacKinnon and Winter, 1993); thereby shifting the body's center of mass towards the swing limb and consequently increasing forces across the medial tibiofemoral compartment of the stance limb.

However, it should be mentioned that in misaligned and lax (unstable) OA knees, high quadriceps strength is a significant risk factor for radiographic progression of OA (Fransen et al., 2001; Sharma et al., 2003). This finding encouraged others to suggest that strength training may lead to damage of joints at-risk for OA, e.g. knee joint showing varus or valgus misalignement (Mikesky et al., 2006; Thorstensson et al., 2005; van Baar et al., 1998a).

A strengthening program for knee extensor muscles may improve the stability of the knee (Huang et al., 2005a) (see Section 3.1.4).

3.1.2. *Proprioception, balance and motor learning*

Several investigators have reported declines in the sensorimotor function at the knee in OA patients (Barrett et al., 1991; Koralewicz and Engh, 2000; Sharma et al., 1999). The sensorimotor system covers all afferent, efferent and central integration and processing components involved with maintaining functional joint stability (Lephart and Fu, 2000). Topp et al. hypothesized that resistance training increases the sensitivity in the sensorimotor structures

Table 5
General fitness and health components explaining the beneficial effects of exercise in OAk.

Concepts	Citations	Aim of study	Mechanism*
Comorbidity	"Positive corollary effect on blood pressure" (Pelland et al., 2004)	NA	NS
	"Positive corollary effect on cholesterol levels" (Pelland et al., 2004)	NA	NS
	"Preventing or favorably influencing the course of frequently disabling other conditions, such as cardiovascular disease, respiratory diseases, diabetes mellitus, and osteoporosis" (Penninx et al., 2001)	S or A	NS
Weight loss	"Greater weight loss" (Penninx et al., 2001)	S or A	NS
	"Reducing excess weight"(Lee et al., 2008)	NA	NS
	"Maintenance of a healthy weight" (Pelland et al., 2004)	NA	NS
	"Positive effect on symptoms after weight reduction" (O'Reilly et al., 1999)	S	A
Aerobic fitness	"Positive corollary effect on aerobic fitness" (Pelland et al., 2004)	NA	NS
	"Increased aerobic capacity" (Penninx et al., 2001)	S or A	NS

Citations extracted from original reports (*as described by the cited author; S, strength, A, aerobic,; NA, not applicable; NS, non-specified).

Table 6
Psychosocial components explaining beneficial effects of exercise in OAk.

Concept	Citations	Aim of study	Mechanism*
Increase of well-being	"Reduced fear of falling" (Penninx et al., 2001)	S or A	NS
	"Self-perceived reduction in pain and disability may lead to improved mental health (O'Reilly et al., 1999)	S	A
	Positive corollary effect on mood and on overall QOL" (Pelland et al., 2004)	NA	NS
	"Improvement in well-being and QOL will indirectly affect pain" (Pelland et al., 2004)	NA	NS
	"Enhance the sense of general well-being" (Rogind et al., 1998)	K+F+C	NS
	"Give opportunity for recreation" (Rogind et al., 1998)	K+F+C	NS
Decrease of depression	"Decreased depressed mood" (Penninx et al., 2001)	S or A	NS
	"Reduces depression in depressed participants"(Penninx et al., 2002a)	S or A	A
	"Buffers non-depressed participants for events in life that may trigger depressive symptoms" (Penninx et al., 2002a)	S or A	A
	"Explanations for the effect that physical activity has on depression: "Increases in circulating concentrations of brain amines and beta-endorphine" (Penninx et al., 2002a)	S or A	A
	"Explanations for the effect that physical activity has on depression: reduced activity of the hypothalamo–pituitary–adrenocortical axis "(Penninx et al., 2002a)	S or A	A
	"Explanations for the effect that physical activity has on depression: increased feelings of mastery" (Penninx et al., 2002a)	S or A	A
	"Explanations for the effect that physical activity has on depression: reduction in negative thought patterns" (Penninx et al., 2002a)	S or A	A
	"Explanations for the effect that physical activity has on depression: social interaction between study participants" (Penninx et al., 2002a)	S or A	A
Placebo effect	"Placebo effects are common in knee OA "(Hinman et al., 2007)	S	NS
Increase of self-efficacy	"Improved physical fitness may increase perceptions of mastery and self-efficacy" (Hartman et al., 2000)	T	NS
	"Increased feelings of self-efficacy" (Penninx et al., 2002a)	S or A	A

Citations extracted from original reports (*as described by the cited author; S, strength, A, aerobic, F, flexibility; C, coordination; T, tai chi; NA, not applicable; NS, non-specified).

of the quadriceps (including the muscle spindles and Golgi sensors in tendons) (Topp et al., 2002). This hypothesis was based on the fact that the alpha motoneuron activity is reciprocally influenced by muscle spindles and Golgi complexes within the muscle. They referred to the review of Hutton & Atwater on adaptations of muscle proprioceptors in response to increased use (Hutton and Atwater, 1992), as well as to the studies of Hakkinen et al., who found increased neural activation (α-motor discharge) accompanying the improvements in knee extensor muscle strength after strength training (Hakkinen et al., 1998; Hakkinen and Komi, 1983). Topp et al. concluded that regular resistance training may "*attenuate the impact and impulsive loads through the knee joint*", not only by increasing the strength of the muscles surrounding the knee (see Section 3.1.3) but also by increasing the intra- and intermuscular coordination of the knee extensor muscles (Topp et al., 2002). This may influence the "*timing of the eccentric contraction*" of the quadriceps during weight-bearing activities, resulting in lower impact and impulsive loadings being transmitted through the joint (see also Section 3.1.3). As demonstrated in rabbits by Radin et al., impulsive loadings may lead to micro-traumata to the articular cartilage and/or the subchondral bone (Radin et al., 1984). Pelland et al. suggested that the positive effects of an exercise program incorporating functional activities may be a "by-product of motor learning" (Pelland et al., 2004). This statement was based on the fact that the mechanical and energetic costs of completing a functional task might be improved due to motor learning (Gentile, 1987).

Another possible pathway through which exercise may influence OAk symptoms is its beneficial effect on muscle spasms, which are known to induce pain and disability (van Baar et al., 1998b). Although van Baar et al. referred to the work of Hurley and Newham (1993), they did not investigate the effect of exercise on muscle spasms but on reflex arthrogenous muscle inhibition (AMI) of the quadriceps. In fact, ten patients with unilateral OAk showed a significant improvement of the quadriceps muscle strength in both legs after the exercise program. This finding was partly endorsed by the AMI-mechanism that has been advocated by Miyaguchi et al. as an important cause of quadriceps weakness in OAk patients in addition to disuse atrophy (Miyaguchi et al., 2003). AMI consists of a neurogenic inhibition of the quadriceps muscle that is initiated and maintained by various proprioceptive receptors which are stimulated by pain, ligament stretching, capsule pinching and effusion (de Andrade et al., 1965; Ekholm et al., 1960; Spencer et al., 1984; Stener, 1969). According to Miyaguchi et al., the presence of quadriceps weakness in the asymptomatic stage confirms this mechanism (Miyaguchi et al., 2003). In addition, Schilke et al. proposed that pain might be the cause of weakened muscles (Schilke et al., 1996), referring to the work of Lubkin et al. but they did not further explain their suggestion (Lubkin, 1986).

Stimulation of proprioceptive receptors may decrease the reflex inhibition of the M. Quadriceps (see also Section 3.1.1) and consequently increase the stability which may be another mechanism of exercise induced improvements in OAk pain and function (see Section 3.1.4) (Miyaguchi et al., 2003).

3.1.3. Energy absorbing capacity

Joint loading is necessary to maintain healthy cartilage; as proven in animal studies (Otterness et al., 1998; Palmoski et al., 1980; Van den Hoogen et al., 1998). According to Cochrane et al. not only the subchondral bone may serve as a shock absorber protecting the overlying cartilage (Cochrane et al., 2005). Other shock absorbing mechanisms may involve proprioception and the use of muscles and tendons during negative work (eccentric quadriceps activity) (Cochrane et al., 2005); supported by the fact that knee extensor muscles attenuate peak loading rate at heel strike (Jefferson et al., 1990). In this context, muscle atrophy would reduce the effectiveness of the muscles as a shock-absorbing mechanism. Baker et al. stated that "stronger muscles may absorb more of the energy" that would otherwise be transferred across the joint (Baker et al., 2001). Their statement was based on the findings of Radin et al., who found that volunteers with knee pain ($n = 18$) hit the ground with a stronger impact than age-matched controls and that the quadriceps remained longer active in the controls than in the knee pain group (Radin et al., 1991). It must be said that no information on quadriceps strength was provided in this study and the

average knee flexion at heel strike was significantly ($p < .05$) different between the two groups ($3.0 \pm 5.1^\circ$ in the control group and $-1.5 \pm 5.1^\circ$, i.e. hyperextension, in the knee pain group).

3.1.4. Stability

In several studies it was suggested that an improved joint stability can be an explanation for the beneficial effect of exercise on OAk symptoms (Jan and Lai, 1991; Keefe et al., 2004; Lee et al., 2008; Pelland et al., 2004; Schilke et al., 1996). Baker et al. suggested that "*weak and unbalanced muscles may overload specific compartments*" (Baker et al., 2001) and thus, "*exercise may evenly distribute force in the joint*". Huang et al. suggested that a strengthening program for knee extensors and flexors may improve the stability of the OA knee (Huang et al., 2005a); and by increasing the stability, further deterioration of the joint might be prevented (Huang et al., 2003a, 2005a). Indeed, the degeneration of an OA joint can be accelerated by normal loads if the joint is unstable or when "*unevenly loaded*" (Moskowitz, 1992).

Huang et al. suggested that instability of a joint may be the result of a muscle contracture (Huang et al., 2005b). Such a contracture might be the result of increased connective tissue density in muscles following immobilization in a shortened position for more than 3 weeks. However, no scientific empowerment was provided to explain this potential mechanism of exercise induced improvements in OAk pain and function.

3.2. Periarticular components (see Table 3)

3.2.1. Connective tissue (excl. bone)

Deyle et al. suggested that exercise may provide a "*stimulus to connective tissue*" which may result in pain relief (Deyle et al., 2000). Neither rationale nor scientific empowerment was provided for this hypothesis. Cochrane et al. stated that mechanical forces may "*modulate morphology and structure of skeletal tissue, including ligament and tendon*" (Cochrane et al., 2005). An "*increased flexibility*" was put forward by Penninx et al. as a pathway to explain the preventive effect of exercise on the occurrence of disability in activities of daily living (ADL) in patients with OAk (Penninx et al., 2001).

3.2.2. Bone

Pelland et al. referred to the positive effect of physical exercise on "*bone mineralization*" to explain symptom relief in OAk (Pelland et al., 2004). Also Penninx et al. and Cochrane et al. suggested that exercise may influence OAk symptoms through its effect on bone (Cochrane et al., 2005; Penninx et al., 2002b). However, the pathway through which improved bone density would reduce OAk symptoms remains unclear.

3.3. Intra-articular components (see Table 4)

In the context of intra-articular components that may explain the beneficial effect of exercise in OAk, articular cartilage is considered as a mechanosensitive tissue, and thus able to perceive and respond to biomechanical signals.

3.3.1. Cartilage

Several authors suggested that the beneficial effect of exercise on the symptoms of OAk can be explained by modulation of the morphology and structure of the cartilage (Cochrane et al., 2005), a higher cartilage proteoglycan content and the prevention of cartilage degeneration (Mikesky et al., 2006), a positive effect on the loss of protein (Pelland et al., 2004) and an increase in pH and an increase of the molecular weight of hyaluronan (Miyaguchi et al., 2003). Cochrane et al. referred to the review of Deschner et al. to support the statement that chondrocytes have the ability to recognize the magnitude and the frequency of mechanical signals (Cochrane et al., 2005; Deschner et al., 2003). Huang et al. used the findings of studies with dogs (Akeson et al., 1967) and sheep (Caterson and Lowther, 1978) to document the fact that mechanical stress may have a direct effect on the anabolic and catabolic activities of chondrocytes (Huang et al., 2003b). Mikesky et al. referred to animal studies to state that exercise is required for maintenance of healthy cartilage (Mikesky et al., 2006). In one of these studies, a sedentary lifestyle of the hamster has been shown to lead to a lower proteoglycan content in the cartilage (Otterness et al., 1998). In the same study, daily wheel running exercise resulted in "*higher cartilage proteoglycan*" content and prevented cartilage degeneration. In another animal study, it has been shown that the proteoglycan content and synthesis decreases when the hind limb of a dog is immobilized in an orthopaedic cast (Palmoski et al., 1979) but these changes were fully reversible 2 weeks after removal of the cast that had been worn for 6 weeks. In human, Roos and Dahlberg used contrast-enhanced MRI to show that exercise results in an increase of glycosaminoglycan (GAG) content of the articular cartilage (Roos and Dahlberg, 2005). GAGs may link together to form proteoglycans and are crucial for the important viscoelastic properties of cartilage (Lu et al., 2004).

The level of chondroitin sulfate in joint fluid of OA knees with joint effusion of 17 patients aged 65 ± 7 years decreased after a 12-weeks quadriceps exercise regimen (Miyaguchi et al., 2003). Patients performed straight leg raises on average 65 times a day and, according to the interpretation of the authors, the results of the study may indicate that exercise "*inhibits the degradation*" of the articular cartilage and intra-articular components.

3.3.2. Inflammation

According to Cochrane et al., low physiological levels of tensile compressive strains have anti-inflammatory effects and activate anabolic pathways (Cochrane et al., 2005). They also stated that an increased blood flow and mobilization of synovial fluid discards the inflammatory exudates from the joint cavity. No scientific proof has been given for this hypothesis. Pelland et al. suggested that exercise may have "*a positive effect on the loss of protein, and associated increase in fat linked to chronic inflammation in arthritis*" (Pelland et al., 2004). They referred to a review by Roubenoff (2003) in which the effects of chronic inflammation on metabolism, body composition and function are discussed: chronic inflammation induces muscle atrophy and may occur concurrently to the joint damage (Roubenoff, 2003). The author concluded that exercise can reverse this effect of chronic inflammation. However, it has to be noted that the paper of Roubenoff deals with the role of body composition and exercise in rheumatoid arthritis but not in OA.

3.3.3. Joint fluid

Cochrane et al. stated that cartilage is avascular and that it therefore depends on synovial fluid for its nutrition (Cochrane et al., 2005). An alteration of compression and decompression of the cartilage, as seen in exercise, provides a pump effect on synovial fluid which is essential for optimal nutrition of the cartilage (Cochrane et al., 2005). They supported this working pathway by the fact that a sedentary lifestyle has been shown to induce a lower synovial fluid volume in hamsters (Otterness et al., 1998) (see also Section 3.3.1).

Hyaluronan is a GAG that is present in joint fluid and influences lubrication and cartilage metabolism (Ogston and Stanier, 1953). The concentration of hyaluronan in joint fluid and its molecular weight are decreased in knee OA (Belcher et al., 1997; Dahl et al., 1985) but after a 12-weeks quadriceps exercise regime an increase of the molecular weight of hyaluronan has been found (Miyaguchi et al., 2003). Also, in the same study, a higher viscosity of the joint fluid and a significant pain relief has been found after the intervention. A high-molecular-weight hyaluronan has significantly more

pain relieving effects than a low-molecular-weight hyaluronan and causes more viscosity of the joint fluid (Kobayashi et al., 1994; Wobig et al., 1999). Therefore Miyaguchi et al. postulated that exercise increases the joint fluid viscosity which may be in favour of the joint lubrication, consequently contributing to pain relief (Miyaguchi et al., 2003).

3.4. General fitness and health components (see Table 5)

3.4.1. Comorbidity

Penninx et al. (2001) suggested that the effect of exercise in OAk may partly be explained by its effect on influencing the course of frequently disabling other conditions. They referred to studies in which the favourable effect of exercise has been proven in different conditions, e.g. cardiovascular disease (Rodriguez et al., 1994), respiratory diseases (Kushi et al., 1997), diabetes mellitus (Manson et al., 1991) and osteoporosis (Heinonen et al., 1996). Other suggested pathways were the positive effect of exercise on blood pressure and cholesterol levels (Pelland et al., 2004). However, how these may influence OAk symptoms, was not mentioned.

3.4.2. Weight loss

In four of the included studies, weight reduction was put forward as a possible pathway to explain the effect of exercise on symptoms of OAk (Lee et al., 2008; O'Reilly et al., 1999; Pelland et al., 2004; Penninx et al., 2001). O'Reillly et al. referred to the study of McGoey et al. (1990) to document this hypothesis: 105 overweight patients with musculoskeletal pain that interfered with the ADL were included. Twenty-five percent of them were diagnosed with tibiofemoral arthritis (not specified whether OA or other) and 70% with patellofemoral chondromalacia or degenerative arthritis. They all underwent a vertical banded gastroplasty (narrowing of the stomach). At follow-up (avg. 22.5 months) the average weight loss was 44 kg and 89% of the patients had complete relief of pain in one or more joints. The authors explained these results by stating that weight loss slows the progression of degenerative arthritis, thereby referring to the work of Maquet et al. (1975) who found that the force across the knee during ADL may rise to six times body weight.

3.4.3. Aerobic fitness

The beneficial effect of exercise on OAk functional disabilities may be a consequence of an increased aerobic capacity (Pelland et al., 2004; Penninx et al., 2001). However, the rationale for this hypothesis has not been given. All selected studies empowering this statement, point out the positive effect of exercise (strength and/or aerobic) on measurements of function. Most of these measurements include submaximal aerobic capacity tests (e.g. 50 foot walking time, exhaustive submaximal walking time, and gait velocity). However, no direct relationship between pain and aerobic fitness has been found in the included studies. On the other hand, improved aerobic fitness may indirectly influence pain perception as it has also been mentioned by others as an important component in the effects of exercise-induced ameliorations of depression (see Section 3.5).

3.5. Psychosocial components (see Table 6)

3.5.1. Increase of well-being

Multiple authors suggest that exercise may influence OAk symptoms through an enhancement of general well-being (O'Reilly et al., 1999; Pelland et al., 2004; Rogind et al., 1998).

In the meta-analysis of Pelland et al. it has been shown that the participation in exercise regimens has a positive effect on quality of life (Pelland et al., 2004). They referred to the study of Börjesson et al. to empower the fact that such an improvement could indirectly influence pain (Borjesson et al., 1996). O'Reilly et al. stated that self-perceived reduction in pain and disability may lead to an improved mental health (O'Reilly et al., 1999), which has been demonstrated following aerobic exercise in OA patients (Minor et al., 1989). A reduced fear of falling and the opportunity for recreation are effects of exercise that may contribute to an increase of well-being (Penninx et al., 2001; Rogind et al., 1998).

3.5.2. Increase of self-efficacy

According to Hartman et al., exercising may increase self-efficacy (SE) (Hartman et al., 2000). Penninx et al. suggested that "increased feelings of SE" may decrease depression states (see Section 3.5.3) (Penninx et al., 2002a). SE can be defined as the patient's belief in his own capabilities to successfully execute the behavior required to attain certain goals (Bandura, 1977). There is a high probability that people with low self-efficacy avoid physical activity in daily routine (Bandura, 1977). SE beliefs are task specific, e.g. SE for stair climbing (Rejeski et al., 1998) or SE for adherence to an exercise program (McAuley et al., 1991). On the other hand, enhanced SE may generalize to other activities that are different from those that were trained during treatment (Bandura, 1977).

In a study of McAuley et al. in which they reviewed 38 studies concerning exercise in adults (>45 years), physical activity is positively related to psychological well-being, including self-efficacy (Mcauley and Rudolph, 1995). However, in this review no distinction has been made between healthy people and patients. Rejeski et al. (1998) showed an increased SE for stair climbing in patients with OAk after aerobic or resistance exercise training. When exercise is performed in a group setting, it is also possible that SE is improved by the social interaction between study participants (Bandura, 1977; Penninx et al., 2002a).

3.5.3. Decrease of depression

Penninx et al. referred to the study of Singh et al. to empower the positive effect of exercise on depression: they found a significant reduction of depression symptoms after a resistance exercise program in people aged 65 years or older (Penninx et al., 2001; Singh et al., 1997). Several explanations for the positive effect of exercise on depression were proposed: Blumenthal et al. found a small but statistically significant correlation between changes in aerobic capacity and changes in depression scores, suggesting that aerobic capacity may partly account for the decrease of depression symptoms (Blumenthal et al., 1999). Van der Pompe et al. showed an exercise-induced reduction of plasma cortisol in healthy post-menopausal women (van der Pompe et al., 1999). Depressive disorders are accompanied by hypothalamo–pituitary–adrenocortical axis (HPA) abnormalities, including elevated levels of cortisol (Gold et al., 1987). Therefore the finding of van der Pompe et al. suggests that exercise reduces HPA activity and consequently influences depression state. Another suggested pathway is an exercise-induced increased concentration of brain amines and beta-endorphine (Ransford, 1982).

3.5.4. Placebo effects

Hinman et al. mentioned the importance of the placebo effect when considering potential explanations for the effect of exercise in OA on pain (Hinman et al., 2007). They referred to reported improvements with sham interventions ranging up to 40% in placebo-controlled trials on pharmacological pain reduction (Hassan et al., 2002; Hughes and Carr, 2002), arthroscopic surgery (Moseley et al., 2002), and manual therapy and exercise (Deyle et al., 2000). However, referring to the work of Hrobjartsson et al., Hinman et al. suggests that placebos have the greatest effect on continuous subjective outcomes and in the treatment of pain, with

no significant effect on objective measures (e.g. functional tests and muscle strength) (Hrobjartsson and Gotzsche, 2001).

4. Discussion

This review was focused on the identification of theories that are proposed in the scientific literature to explain the beneficial effects of exercise on OAk-related symptoms. We were able to identify 5 main categories of potential components: neuromuscular components, peri-articular components, intra-articular components, general fitness and health components, and psychosocial components. We used a qualitative approach, based on the 'grounded theory' of Glaser and Strauss, which is a method for systematically analysing qualitative data. We have chosen this approach because it has been used previously to systematically categorize qualitative data into a theory, such as determining patients' perspectives of components of patient-centered physiotherapy (Kidd et al., 2011). Although it was not our intention to form a new theory, we used this method because of the systematic and sequential process that it encompasses. For the scope of this work, proposed theories explaining the beneficial effects of exercise on OAk were extracted from the introduction and discussion parts of studies. We included studies that were used in reviews and guidelines, indexed in two databases (Cochrane reviews and Pedro). It cannot be excluded that other theories might have been missed. The reasons for using the Cochrane and Pedro databases were their high-level methodological standards when including original research reports. However, as a result, all included studies were published before 2008 and new investigations were not yet referred to in the included review articles or guidelines. Here, we discuss our findings in the light of some recent intervention studies in this research area.

Periarticular muscles may help to stabilize the knee during gait (Huang et al., 2005b). As OAk patients show a decrease in quadriceps strength, it is believed that further deterioration may be prevented by means of improving knee extensor strength through strengthening exercises. However, recently it has been suggested that treatment techniques that focus on changing the flow of afferent neurophysiological information instead of strengthening the muscles, may prove more effective to enhance the performance of the muscles (Rice et al., 2011a). This suggestion has been made in relation to the finding of a dysfunction in the gamma-loop pathway in OAk patients, which can lead to deficits in quadriceps activation (Rice et al., 2011b). They suggested that this would be a result of a decrease in afferent information due to damaged sensory endings. Therefore, changing the flow of afferent information may reduce activation deficits in the quadriceps muscle and thus contribute to enhanced muscle force.

It has been shown that exercise improves proprioceptive accuracy in patients with OAk (Knoop et al., 2011) and a potential explanation we found in our literature review is that this might be due to motor learning or increased sensitivity of sensorimotor structures. Recently, another explanation has been proposed: when weight-bearing exercises are performed, the intra-articular pressure increases, thereby stimulating Ruffini nerve endings (which can be found in the knee capsule, the cruciate, meniscofemoral ligaments) and thus providing more afferent input (Jan et al., 2009). The mechanosensitivity of the intra-articular tissues has been addressed in our review, suggesting that exercise has an effect on cartilage metabolism. In a recent study, exercise seemed to increase intra-articular IL-10 (considered as a chondroprotective anti-inflammatory cytokine) in patients with OAk (Helmark et al., 2010). The cartilage protective properties of IL-10 are related to the activation of synoviocytes and chondrocytes, and suppression of the release of pro-inflammatory mediators by macrophages (Hart et al., 1995; Schulze-Tanzil et al., 2009). Another interesting biochemical effect of exercise in OAk is the elevation of serum levels of cartilage oligomatrix protein (COMP) (Andersson et al., 2006). COMP is a matrix protein that is known to influence cartilage metabolism. It is essential for the normal development of cartilage and is believed to play a role in cell apoptosis. However, the role of COMP was not mentioned in the retrieved explanatory models for exercise-induced improvement of OAk symptoms.

Based on the results of this literature review it seems that the effect of exercise on OAk symptoms through weight reduction is mainly explained by a mechanical pathway, i.e. less excessive load on the knee. However, recently, adipose tissue has gained increased attention because of its endocrine function, secreting several hormones (e.g. leptin and adiponectin) which may interact with inflammatory processes (Scotece et al., 2011). As circulating levels of these proinflammatory adipokines are increased in obese people (Ouchi et al., 2011), and since obesity is related to the incidence of OA in both weight-bearing and in non-weight bearing joints (Yusuf et al., 2010), the effect of exercise on inflammatory processes (e.g. through the modulation of adipokines) in OA should be taken into account in future exercise studies.

Some authors suggested that exercise-induced benefits in OAk may be influenced by the supplementary attention that patients receive. However, several studies that controlled for these attention-related effects still demonstrate significant benefits through exercise therapy (Ettinger et al., 1997; Peterson et al., 1993). Our review showed that exercise may increase self-efficacy (SE). This finding is interesting because OA patients with a high SE do not only show higher pain thresholds and pain tolerance in an experimental setting (thermally induced pain) (Keefe et al., 1997) but also greater physical functioning and less self-reported pain (Focht et al., 2005; Pells et al., 2008) compared to those with a lower SE. The positive effect of exercise on depression that was identified as a possible explanatory model in our review, can be important for clinical practice because it has recently been proven that depressive symptoms are predictive of worsening in pain and function outcomes in OAk (Riddle et al., 2011). In this context, high intensity resistance training has been found to be superior to low intensity resistance training when targeting depression in elderly (although not OAk) persons (Singh et al., 2005).

Based on our literature review we propose some recommendations when designing exercise therapy in OAk patients: (1) exercise therapy for OAk should consist of a mixed program including aerobic, strength and proprioceptive exercises; (2) to improve function, aerobic fitness should be increased and task specific exercises can be considered (e.g. stair climbing and descending); (3) before starting exercise therapy, we recommend to assess the depression state of the patient. In case of signs of depression, a high intensity exercise program might be more appropriate; (4) patients with knee misalignment (varus/valgus) might not benefit from strengthening exercise of the M. Quadriceps; and (5) placebo effects should be taken into consideration when interpreting exercise-induced improvement of pain without functional benefit.

We conclude that several explanatory models have been described in the literature for exercise-induced improvement of OAk-related symptoms, which can be categorized in 5 main components. Probably, the clinical benefits of exercise therapy observed in OAk patients are due to a combination of these underlying mechanisms. Future exercise studies taking all possible pathways into consideration should help in providing more targeted exercise recommendations for OAk patients.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.arr.2012.09.005.

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