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Review

Impact of a daily exercise dose on knee joint cartilage – a systematic review and meta-analysis of randomized controlled trials in healthy animals

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SUMMARY

Objective: To investigate the impact of a daily exercise dose on cartilage composition and thickness, by conducting a systematic review of randomized controlled trials (RCTs) involving healthy animals.
Methods: A narrative synthesis of the effect of a daily exercise dose on knee cartilage aggrecan, collagen and thickness was performed. A subset of studies reporting sufficient data was combined in meta-analysis using a random-effects model. Meta-regression analyses were performed to investigate the impact of covariates.
Results: Twenty-nine RCTs, involving 64 comparisons, were included. In the low dose exercise group, 21/25 comparisons reported decreased or no effect on cartilage aggrecan, collagen and thickness. In the moderate dose exercise group, all 12 comparisons reported either no or increased effect. In the high dose exercise group, 19/27 comparisons reported decreased effect. A meta-analysis of 14 studies investigating cartilage thickness showed no effect in the low dose exercise group (SMD −0.02; 95% CI −0.42 to 0.38; $I^2 = 0.0\%$), large but non-significant cartilage thickening in the moderate dose exercise group (SMD 0.95; 95% CI −0.33 to 2.23; $I^2 = 72.1\%$) and non-significant cartilage thinning in the high dose exercise group (SMD −0.19; 95% CI −0.49 to 0.12; $I^2 = 0.0\%$). Results were independent of analyzed covariates. The overall quality of the studies was poor because of inadequate reporting of data and high risk of bias.
Conclusions: Our results suggest that the relationship between daily exercise dose and cartilage composition, but not necessarily cartilage thickness, may be non-linear. While we found inconclusive evidence for a low daily dose of exercise, a high daily dose of exercise may have negative effects and a moderate daily dose of exercise may have positive effects on cartilage matrix composition in healthy animals.

Introduction

Osteoarthritis (OA) is considered to be caused by a combination of mechanical, cell biology, and, in some cases, pro-inflammatory factors[1] that ultimately lead to the breakdown of the articular cartilage extracellular matrix (ECM)[2]. Cartilage ECM largely consists of aggrecan molecules and collagen fibrils[3]. The aggrecan molecules, with covalently attached glycosaminoglycans sugar chains, are linked non-covalently to hyaluronic acid to form proteoglycan aggregates[4]. The main functions of this structure are to resist compressive forces and contribute to cartilage lubrication[5]. The loss of these molecular components is a hallmark of cartilage degradation and OA[6].

Daily dynamic physiological loading is crucial for the biosynthesis of various EMC molecules[7] and emerging evidence suggests that knee joint loading may be a risk factor for developing OA[8,9], emphasizing the important role of biomechanics in OA. Physical activity, including exercise, is considered a cornerstone in the management of both healthy and osteoarthritic joints across the lifespan[10]. Activities such as walking produce loading frequencies of ≤1 Hz, while high impact activities (e.g., pivoting sports) can

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produce up to 6000 Hz[11]. The amounts and types of external mechanical loading are therefore factors that regulate cartilage development and homeostasis[7,12,13].

Animal studies investigating the effect of exercise dosage on cartilage health show conflicting results. Some studies in dogs and rodents showed that performing either a low[14] or high[15,16] dose of exercise increased the risk of developing knee OA, while another study showed the opposite effect[17]. Yet other studies in dogs found that moderate exercise could promote positive cartilage compositional changes[18,19]. Taken together, these studies could indicate a non-linear dose–response relationship between exercise dose and cartilage aggrecan content, collagen content and thickness. However, this relationship may differ depending on animal type, cartilage outcomes and exercise characteristics. A systematic review and meta-analysis of animal studies may help clarify if a dose–response relationship exists in healthy cartilage, which could guide future studies of normal and diseased cartilage in animals and humans.

Our aim was to investigate the impact of a daily exercise dose on knee cartilage aggrecan content, collagen content and cartilage thickness in randomized controlled trials (RCTs) in healthy animals.

Methods

Terminology

In this article, the term 'load' refers to 'the sport and non-sport burden (single or multiple physiological, psychological or mechanical stressors) as a stimulus that is applied to a [human] biological system (including subcellular elements, a single cell, tissues, one or multiple organ systems, or the individual)'[20]. The term 'exercise' is defined as 'physical activity, which is usually regular and done with the intention of improving or maintaining physical fitness or health'[21]. We report investigations of glycosaminoglycan (GAG) and proteoglycan (PG) as measures of aggrecan. The term 'aggrecan' refers to cartilage proteoglycans and their GAG chains, assessed by histology or other biochemical or imaging techniques.

Protocol

Study selection, eligibility criteria, data extraction and statistical analysis were performed according to the Cochrane Collaboration guidelines[22] and a protocol has been published www.radboudumc.nl/Research/Organisationofresearch/Departments/cdl/SYRCLE/Documents/Protocol%20Animal%20studies%20AB.pdf.

Eligibility criteria

Included were RCTs of healthy animals assessing the impact of exercise on cartilage aggrecan content, collagen content and cartilage thickness.

The following studies were excluded: non-RCTs, studies which did not investigate any of the outcomes of interest or knee joints, studies with genetically modified animals, comorbidities, non-English full text, and where treatment arms involved other interventions besides exercise.

Literature search

A systematic literature search was performed within the databases MEDLINE, EMBASE, Web of Science and CINAHL for studies published prior to October 2015 with no restriction on publication year or language.

Search methods and study selection

The studies were identified using the following search strategy in MEDLINE: (exercise OR physical activity) AND (cartilage) AND (knee). It was customized for EMBASE, Web of Science and CINAHL. In MEDLINE (Appendix A) and EMBASE, animal studies were identified using a validated animal filter[23,24], in Web of Science and CINAHL, they were identified using the following filter (animal OR animals OR rodent OR mice OR rat OR guinea-pig OR dog OR horse OR sheep). All terms were searched, if possible, both as keywords and text words in titles and abstracts. At first, two reviewers (AB and CJ) independently screened titles and abstracts and subsequently the full texts of included studies. In addition, reference lists from retrieved publications and systematic reviews published after January 2010 were screened. Disagreements about inclusion were discussed by both reviewers until consensus was reached.

Data collection

A customized data extraction form was developed for each of the outcomes (e.g., proteoglycan content, collagen content and cartilage thickness), estimated from the medial and lateral values of the tibia, femur and patella. Data were extracted by the first and second author (AB and CJ) from tables and graphs of published manuscripts.

The following information was mandatory: number of animals allocated to the experimental and control groups; animal characteristics: species, gender and age; 'Exercise' OR 'Physical Activity' characteristics: type (e.g., running and jumping), equipment (e.g., treadmill and wheel), frequency (sessions/week), duration (weeks) and intensity (km/h) of the intervention.

Definition of exercise dose

In dog studies, we used the British Kennel Club recommendations for exercise: little (<30 min/day), moderate (≤2 h/day), or considerable (>2 h/day), to categorize dogs into low, moderate or high dose of exercise[25].

To classify the dose of exercise programs in rodents as low, moderate or high, we used the American Physiological Society guideline for the design of animal exercise protocols[26]. This guideline defines cut-offs at 6 km/day for moderate and 12 km/day for high dose of exercise.

To determine the dose of exercise in rabbits, we used the authors' own classifications, since no existing exercise dosage classifications were found in the literature. Fifty minutes per day was chosen as the lower cut-off for moderate dose of exercise as reported by Saamanen *et al.*[27], and 2 h of daily exercise for high dose of exercise as reported by Qi and Changlin[28].

The maximum daily distance walked by sheep was reported to be 14 km[29], and we used this as the cut-off for high dose of exercise.

Narrative synthesis of results

When there was a statistically significant ($P < 0.05$) increase or decrease in cartilage aggrecan, cartilage collagen or cartilage thickness in the intervention group compared to the control group we classified the effect of exercise as ('+') or ('−') respectively; and as no effect ('=') when no statistically significant difference was reported between the intervention and control groups.

Analyses of a subset of studies investigating cartilage thickness

Meta-analyses were performed when at least three studies were available for one of the outcomes of interest in the same animal