CRITICALLY APPRAISED TOPIC

FOCUSED CLINICAL QUESTION

In a young male adult following a partial meniscectomy, does lower body progressive-resistance (strength) training reduce the likelihood of acquiring knee osteoarthritis?

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CLINICAL SCENARIO

Earlier this year I sustained a torn meniscus in my knee after slipping on ice in a parking lot. When the orthopaedic surgeon found that a meniscal repair was no longer an option, a partial meniscectomy was performed to address the injured tissue. As a physical therapy student, I'm aware of the increased risk for developing knee osteoarthritis (OA) after a meniscectomy, so I began thinking about what I could do to prevent, delay the onset of, or decrease the risk for developing the condition.

In the knee, the meniscus functions to increase contact area and decrease the time of loading (shock absorption), thereby decreasing the contact pressure through the joint. This load-bearing mechanism acts to protect articular cartilage from excessive force. In the absence of meniscal fibrocartilage, the articular cartilage is exposed to degradation from wear and tear, a hallmark of osteoarthritis. For this reason, meniscectomy is a risk factor for OA. Osteoarthritis is a common musculoskeletal disease and a cause of pain and disability in adults. Most interventions focus on reducing pain and increasing function in adults who have already acquired OA. Considering this, and my personal situation of having a partial meniscectomy but not yet having developed OA, the aim of my investigation is to determine if strength training is effective in reducing the likelihood of acquiring knee osteoarthritis.

SUMMARY OF SEARCH

- Ten studies were identified that met the inclusion/exclusion criteria. Three RCTs of higher quality were chosen for review and discussion based on relevance to the clinical question and methodological quality.
- No studies to date have explicitly examined whether progressive resistance (strength) training is effective in reducing the likelihood of acquiring knee osteoarthritis in young adults following a partial meniscectomy. Interventional studies generally address pain and function in middle-aged to older adults who have already acquired osteoarthritis. Of those that address interventions aimed at decreasing the risk of acquiring OA, none specifically address strength training following partial meniscectomy.
- Moderate exercise that incorporates muscle strengthening and neuromuscular control was found to improve knee joint cartilage composition in patients at risk for OA. Furthermore, muscle-strengthening exercise training supplemented with glucosamine was found to positively affect the mechanical properties of muscle and prevent the build-up of factors associated with OA.
- Future research should include RCTs of larger sample sizes to examine the effect of strength training on prevention of knee osteoarthritis in young adult patients with recent history of partial meniscectomy. Since a large number of current trials focus on older adults who have already acquired OA or interventions other than strength training, further investigation should examine young adults who are at risk for developing OA.

CLINICAL BOTTOM LINE

While there is currently no evidence regarding the prevention of knee osteoarthritis through the use of strength training exercise in young adults following partial meniscectomy, the current evidence shows moderate exercise positively influences knee joint cartilage composition, reducing the likelihood of developing OA. When supplemented with glucosamine, muscle-strengthening exercise positively affects muscle collagen and prevents the build-up of factors associated with OA. More research is needed that specifically addresses (1) young adults, (2) young adults with a history of partial meniscectomy, and (3) prevention and/or delayed onset of osteoarthritis, instead of modification of symptoms once OA has already been acquired.

This critically appraised topic has been individually prepared as part of a course requirement and has been peer-reviewed by one other independent course instructor

SEARCH STRATEGY

Terms used to guide the search strategy			
Patient/Client Group	**I**ntervention (or Assessment)	**C**omparison	**O**utcome(s)
young adult* male* meniscectomy meniscus surgery injury athlete*	intervention rehabilitation physical therapy physiotherapy exercise* training program strength progressive resistance	Not applicable	osteoarthritis [MeSH] arthritis knee risk

Final search strategy:

For PubMed

1. Male* AND young adult* AND athlete*
2. Meniscus OR surgery OR meniscectomy
3. Rehabilitation OR physical therapy OR physiotherapy
4. Strength OR progressive resistance OR training OR exercise
5. Osteoarthritis AND knee
6. Osteoarthritis [MeSH]
7. #1 AND #2
8. #3 AND #4
9. #5 AND #6
10. #7 AND #8 AND #9

Databases and Sites Searched	**Number of results**	**Limits applied, revised number of results (if applicable)**
PubMed	358	118 – applied "Article types" filters "Clinical trial" and "Review" and "Publication dates" filter "10 years"
CINAHL	95	82 – "Age" filter "all adults" 23 – Second "Age" filter "adult: 19-44 years"
Cochrane Library	201	87 – "Cochrane Reviews" filter "Review"
PEDro	11	Reduced original search to "menisc*" AND "*arthritis"

INCLUSION and EXCLUSION CRITERIA

Inclusion Criteria
Randomized controlled trials, controlled trials, uncontrolled trials, or systematic reviews Published during or after January 2000 Published in English Male participants between the ages of 20-40 were included in experimental group Studied subjects with history of partial meniscectomy Included resistance and/or strength training as intervention Included osteoarthritis as measured outcome
Exclusion Criteria
Studies solely on total meniscectomy Studies involving females, adolescents, or ages over 40 Case studies or case series Abstracts, conference proceedings, letters to the editor, dissertations, narrative review articles

RESULTS OF SEARCH

Summary of articles retrieved that met inclusion and exclusion criteria

Author (Year)	Study quality score	Level of Evidence	Study design
Neogi (2013)	PEDro: 4/11	2b	Prospective, non-controlled study
Mattiello-Sverzut (2013)	PEDro: 9/11	1b	RCT
Segal (2012)	D&B: 18/29	4	Longitudinal study
Segal (2010)	D&B: 18/29	4	Longitudinal study
Roos (2005)	PEDro: 9/11	1b	RCT
Karatosun (2006)	PEDro: 7/11	1b	Prospective RCT
Fransen (2015)	AMSTAR: 9/11	1a	Systematic review
Hall (2015)	PEDro: 9/11	1b	RCT
Glass (2013)	D&B: 19/29	4	Longitudinal study
Herrlin (2013)	PEDro: 8/11	1b	Prospective RCT

BEST EVIDENCE

The following 3 studies were identified as the 'best' evidence and selected for critical appraisal. Reasons for selecting these studies were:

- **Hall (2015)** – this study is a single-blind randomized controlled trial (level of evidence 1b) that scored 9/11 on the PEDro scale. The study included patients with partial meniscectomy, exercise as an intervention, and an outcome measure that's a key predictor of osteoarthritis progression. These elements have direct relevance to the patient in my clinical question.
- **Mattiello-Sverzut (2013)** – this study is a randomized controlled trial (level of evidence 1b) that scored 9/11 on the PEDro scale. Although the study includes the analysis of some medications, it specifically uses resistance training as an intervention and explores the effect on skeletal muscle matrix, an important component when considering osteoarthritis. The measured correlation of resistance training and potential OA management/prevention relate to my clinical question.
- **Roos (2005)** – this study is a randomized controlled trial (level of evidence 1b) that scored 9/11 on the PEDro scale. The study also included patients with partial meniscectomy, exercise as an intervention, and an outcome measure that's a key indicator of osteoarthritis. These elements have direct relevance to the patient in my clinical question.

SUMMARY OF BEST EVIDENCE

(1) Description and appraisal of *Neuromuscular exercise post partial medial meniscectomy: randomized controlled trial* by Hall M, Hinman RS, Wrigley TV, et al. (2015)

Aim/Objective of the Study/Systematic Review:
The purpose of this assessor-blinded randomized controlled trial was to evaluate the effect of a neuromuscular exercise program (ALIGN) on knee adduction moment in subjects with arthroscopic partial medial meniscectomy.
Study Design
• Assessor-blinded randomized controlled trial • Subjects were recruited by screening the records of eight orthopaedic surgeons between May 2012 to July 2013 • Eligibility confirmed by posteroanterior weight-bearing knee radiographs • Randomization schedule prepared by independent researcher using computer-generated random number table

- Subjects were stratified by gender and randomized in blocks of six or eight
- Subjects were randomly assigned to an experimental or control group using a concealed allocation procedure with group allocations sealed and stored in central locked location
- Separate independent researcher retrieved and disclosed allocations to participants; participants were blinded to hypothesis, but not group allocation
- A blinded assessor performed measurements at baseline and follow-up at Week 13
- A priori power calculation was conducted to determine sample size, and the study was designed to detect a 10% change in peak external knee adduction moment (KAM) between groups, with two-tailed alpha level of 0.05 and 80% power
- Blinded to group allocation, an intention-to-treat approach was used for between-group comparative analyses
- ANCOVA was used to measure mean change in continuous outcome measures; residual plots were used for model diagnostic checks; Pearson chi tests were used for medication use and cointerventions; log binomial regression was used to compare likelihood of improvements

Setting

- Subjects in the experimental group received treatment from one of seven different physiotherapists in one of seven different private practices in and around the metropolitan area of Melbourne, Australia.

Participants

- 62 total subjects (31 in experimental group; 31 in control group)
- Eligibility criteria: must have had medial arthroscopic partial meniscectomy (APM) within past 3-12 months and be 30-50 years of age
- Subjects were recruited by screening medical records of eight Melbourne-based orthopaedic surgeons; one participant volunteered after responding to an advertisement
- Gender: Experimental group – 23 males (74%); Control group – 22 males (73%)
- Mean age (std dev): Experimental group – 42.8 years (5.4); Control group – 43.2 years (5.6)
- Mean time from surgery (std dev): Experimental group – 6.4 months (2.5); Control group – 6.6 months (2.6)
- 2 subjects withdrew (both in control group) due to relocation and time commitment
- At baseline, characteristics were similar between groups

Intervention Investigated

Control

- "Participants in the control group (did) not receive any interventions during the 12-week study period" (p.238)
- Hall M, Hinman RS, Wrigley TV, et al. The effects of neuromuscular exercise on medial knee joint load post-arthroscopic partial medial meniscectomy: "SCOPEX' a randomized control trial protocol. BMC Musculoskeletal Disorders. 2012; 13:233-244

Experimental

- Subjects in the experimental group completed 8 physiotherapy visits over 12 weeks; two sessions during Week 1, then a single session during Weeks 2, 4, 6, 8, 10, and 12
- Initial session duration was 45 minutes, with each subsequent visit lasting 30 minutes
- Subjects visited the physiotherapist of his/her choice; 7 physiotherapists administered treatment in one of 7 different private practice settings in and around the Melbourne, Australia metropolitan area
- Subjects were introduced to the ALIGN neuromuscular exercise program at the initial visit, with each subsequent visit used to progress as appropriate
- ALIGN program consists of 6 exercises: abdominal crunches, bridges, lunges, single-leg hip abduction/semi-circular motion, single-leg taps on ground while standing on stepper, and knee bends (mini squats)
- Participants begin the study performing 2 sets of 12 repetitions, then progress (as directed by therapist) to 2 sets of 15 repetitions, then 3 sets of 12 repetitions, and finally, 3 sets of 15 repetitions
- Participants were also instructed to perform individualized home exercises at least 3 times per week over the 12-week study
- A standardized treatment note was required of therapists

Outcome Measures

- Measurements were obtained at baseline (Week 0) and follow-up (Week 13) by the same blinded assessor
- Outcome measures included three-dimensional movement analysis, self-reported pain and physical function, muscle strength, physical performance tasks, and other measures
- Three-dimensional movement analysis: external knee adduction moment (KAM) and external knee flexion moment (KFM) were measured during walking, single-leg sit-to-stand, and single-leg hop using a motion

analysis camera system and floor force plates; KAM and KFM were expressed as a percentage
- Self-reported pain and physical function: self-reported pain was measured using a 0-10 numeric rating scale; the Knee Injury Osteoarthritis Outcome Score (KOOS) was used to obtain measurements of physical function
- Muscle strength: an isokinetic dynamometer was used to measure isometric and isokinetic quadriceps and hamstring strength; a handheld dynamometer was used to measure hip adductor and abductor muscle strength
- Physical performance tasks: repetitions were counted for maximum number of single-leg raises and knee bends performed in 30 seconds (separately); distance in meters was recorded for maximum distance jumped during a single-leg hop
- Other measures: the Kellgren-Lawrence grading system was used to measure osteoarthritis level of severity; home exercise adherence was measured as the number of sessions recorded by patients compared to the maximum number prescribed (expressed as a percentage); a 0-10 scale was used by therapists to record perceived impression of patient adherence; the Lower Extremity Activity Scale was used as a general measure of patient physical activity level; an inclinometer was used to measure knee alignment in the frontal plane

Main Findings

- No significant difference between groups for changes in peak KAM during normal-paced gait (mean difference 0.22 N*m/(BWxHT), 95%CI, -0.11 to 0.55; p=0.19) or single-leg sit-to-stand (-0.01 N*m/(BWxHT), 95%CI, -0.33 to 0.31; P=0.95)
- No significant difference for within-group change in peak KAM for normal-paced gait (-0.12; 95%CI; -0.33 to 0.09) or single-leg sit-to-stand (-0.08; 95%CI; -0.34 to 0.19)
- Experimental group: significant improvements in number of knee bends (4.3; 95%CI; 2.3 to 6.2), single-leg raises (2.5; 95%CI; 1.3 to 3.7), single-leg hop (0.11; 95%CI; 0.05 to 0.18), KOOS quality of life (9.0; 95%CI; 1.9 to 16.1), walking speed for normal-paced gait (0.03; 95%CI; 0.00 to 0.05), and peak KFM during single-leg hop (1.36; 95%CI; 0.11 to 2.61)
- Control group: significant improvements in number of single-leg squats (3.5; 95%CI; 1.6 to 5.4), single-leg raises (3.3; 95%CI; 2.0 to 4.6), KOOS quality of life (5.4; 95%CI; 0.6 to 10.2), and walking speed for normal-paced gait (0.04; 95%CI; 0.00 to 0.07)
- No significant between-group difference for improvement in pain (relative risk (95%CI) 0.57 (0.09 to 1.17); P=0.32)
- Participant-perceived improvement in physical function more likely in experimental group (relative risk (95%CI), 0.29 (0.09 to 0.91); P=0.04)
- Participant-reported overall improvement more likely in experimental group (relative risk (95%CI), 0.38 (0.16 to 0.92); P=0.03)

Original Authors' Conclusions

- "Overall, our findings concur with and further substantiate evidence from clinical trials that report no effect of exercise, regardless of type, on KAM in people with knee osteoarthritis" (p.1564)

Critical Appraisal

Validity

- PEDro Scale score: 9/11; eligibility criteria: yes; random allocation: yes; concealed allocation: yes; baseline comparison: yes; blind subjects: no; blind therapists: no; blind assessors: yes; >85% participant outcomes: yes; intention to treat analysis: yes; between group comparison: yes; point estimates and variability: yes
- Participants were not blinded to group allocation and therapists delivering interventions were not blinded; outcomes could be biased
- Authors appear to have maintained rigorous study design and measurement analysis; carefully concealed allocation, blinded assessor, excellent subject participation and retention, an intention-to-treat approach, and transparency of methods all contribute to excellent design
- Instead of a control group that did not receive any intervention, the results of the study may have been strengthened if the test group was compared against a group that received only standard therapy. Any group participating in therapeutic rehabilitation will likely naturally improve compared against a group receiving no intervention
- Outcome measures used appear appropriate for the purposes of this study

Interpretation of Results

- The authors found no evidence that the neuromuscular exercise program alters peak knee adduction moment in participants who are at a high risk of developing osteoarthritis
- Despite peak KAM during normal-paced walking being a primary outcome, this study found no difference between groups; the authors suggest this may be the result of poor transfer of trained skills to gait
- The authors suggest a larger sample size may have "produced a statistically significant difference" (p.1563)

when measuring peak KAM during walking between groups (the measured difference was 7%, but the study was powered to detect 10%); the authors also suggest KAM measurement error may have contributed to this
- Despite peak KAM during single-leg sit-to-stand being a primary outcome, this study found no reduction in peak KAM; the authors point out that "it is unknown whether people after APM have a higher peak KAM during one-leg sit-to-stand than that of controls" (p.1563), variations during testing could be responsible for reductions found in other studies, and "the clinical relevance of reduced peak KAM during one-leg sit-to-stand remains unknown" (p.1564)
- Statistically insignificant results indicate that neuromuscular exercises do not significantly impact the knee adduction moment (KAM) in patients with a recent history of partial medial meniscectomy
- Since KAM is relates to structural cartilage damage and the onset of osteoarthritis, the results can be extrapolated to mean that neuromuscular exercises are not effective in preventing knee osteoarthritis
- However, favourable outcomes were noted in the experimental group (compared to control group) regarding self-reported pain, physical function, and overall improvement; there was also a 7% difference between groups regarding changes in peak KAM during normal and fast-paced walking (this was insignificant since the study was powered to detect a 10% change); these findings suggest that there may be some clinical significance for neuromuscular exercises to positively impact patients at risk for knee osteoarthritis after all

(2) Description and appraisal of *Morphological adaptation of muscle collagen and receptor of advanced glycation end product (RAGE) in osteoarthritis patients with 12 weeks of resistance training: influence of anti-inflammatory or glucosamine treatment* by Mattiello-Sverzut AC, Peterson SG, Kjaer M, Mackey AL (2013)

Aim/Objective of the Study/Systematic Review:

The purpose of this double-blind randomized controlled trial was to evaluate the effect of 12-week resistance training with drug intake (glucosamine, ibuprofen) on AGE (advanced glycation end product) receptors and collagen types in skeletal muscle of patients with knee osteoarthritis.

Study Design

- Double-blind randomized controlled trial
- Subjects allocated to one of three groups (glucosamine, ibuprofen, control). Details of allocation not provided.
- Sample size calculation not disclosed.
- Muscle biopsies collected before and after 12-week training period. Details of assessor blinding not provided.
- Collagen analysis used primary antibodies for Collagen I, III and IV; scored and graded using Kurose, et al scale
- RAGE localization determined using double-staining technique with laminin; classified as intracellular, extracellular, and total (intracellular + extracellular)
- Analysis of capillaries obtained by double-staining with two primary antibodies; analysed as capillary to fiber ratio and number of capillaries around each fiber type
- SAS software used to perform statistical analysis; data analysed using mixed-effects linear models; normal probability plots used to check normality of the residuals of linear models
- Level of significance set at 0.05

Setting

- Although not explicitly stated, the study seems to take place in either an outpatient physical therapy setting, or an exercise gym, since the subjects used several pieces of exercise equipment commonly found in both settings and were accompanied by physical therapists each training session
- The experimental protocol was approved by the local Ethical Committee for Copenhagen and Frederiksberg Communities, and the protein drink provided to subjects came from Arla, a dairy company in Denmark. Both of these facts indicate the study was conducted in Denmark.

Participants

- 65 total subjects (23 in ibuprofen group, 21 in glucosamine group, 21 in control group)
- Eligibility criteria: 50-70 years of age and radiographic evidence of bilateral tibiofemoral knee osteoarthritis
- Gender: ibuprofen group – 14 females (60%), glucosamine group – 13 females (62%), control group – 9 females (42%)
- Mean age: ibuprofen group – 61.5 years; glucosamine group – 62.2 years; control group – 62.2 years
- X-ray (Kellgren-Lawrence score): ibuprofen – 2.3; glucosamine – 2.2; control group – 2.2
- Groups appear comparable at baseline on key demographic variables
- There is no mention of lost subjects, so the assumption is that 65 subjects began and completed the study

Intervention Investigated

Control

- The control group performed the exercise protocol while receiving a placebo tablet

Experimental

- The two test groups performed the exercise protocol while receiving either an ibuprofen or glucosamine tablet
- Tablet intake began 4 weeks prior to exercise training; active ibuprofen began only one week before training
- All subjects completed 45-minute sessions 3 times per week for 12 weeks, with a minimum requirement of 30 total sessions
- Protocol consisted of 10-minute warmup on stationary bicycle, then seated single-leg knee extension and leg-press exercises in adjustable machines
- 15 repetition maximum used for weeks 0-6, 8 rep max used for weeks 7-12; relative workload was 70-80% of 1 rep max through all 12 weeks
- Physical therapists were present for every workout and provided exercise performance instruction; training load was adjusted weekly
- Participants consumed a protein drink after each training session
- All exercise training was suspended for 48 hours prior to biopsy sampling

Outcome Measures

- Collagen analysis used primary antibodies for Collagen I, III and IV; scored and graded by three evaluators using the Kurose, et al scale: (-) absent, (±) weakly positive, (+) lightly positive, (++) moderately positive, (+++) strongly positive
- RAGE localization determined using double-staining technique with laminin; classified as intracellular, extracellular, and total (intracellular + extracellular)
- Analysis of capillaries obtained by double-staining with two primary antibodies; analysed as capillary to fiber ratio and number of capillaries around each fiber type
- Each of these three were primary outcomes, with no secondary outcomes presented

Main Findings

- Comparing pre- and post-training period measurements, 100% (n=5) of the glucosamine group showed a decrease in immunoreactivity of Type I collagen fibers, compared to 43% (n=3) for the ibuprofen group and 33% (n=2) for the control group
- Comparing scores for Type III collagen fibers, 60% (n=3) of subjects in the glucosamine group demonstrated an increase, compared to only 14% (n=1) of the ibuprofen group and 16% (n=1) of the control group
- The majority of each group demonstrated increases in Type IV collagen fibers, with 80% (n=4) of the glucosamine group showing this result, 57% (n=4) of the ibuprofen group, and 83% (n=5) of the control group
- No significant difference was found between pre- and post-training for any of the groups regarding capillary counting
- Effect sizes of drug type on capillaries per fiber were 0.08 (ibuprofen), 0.02 (glucosamine), and 0.05 (control); effect sizes on capillaries per Type I fiber were 0.03 (ibuprofen), 0.13 (glucosamine), and 0.12 (control); effect sizes on capillaries per Type II fiber were 0.06 (ibuprofen), 0.05 (glucosamine), and 0.26 (control)
- Statistical differences in pre- and post-training measurements of RAGE were found only in the control group: intracellular (5.86; 95%CI 1.6-10.1), extracellular (20.3; 95%CI 7.6-33), and intracellular + extracellular (26.1; 95%CI 9.3-43)
- Significant differences were found between post-treatment measurements between the control and glucosamine groups, with between group effect sizes of 4.29 (intracellular), 15.34 (extracellular), and 19.61 (intra+extra)

Original Authors' Conclusions

- "In conclusion, the present study showed that exercise training combined with, or without, different drug intake produces different alterations in collagen and RAGE immunoreactivity. It suggests that AGEs could be influenced by these exogenous factors, modulating tissues such as extracellular matrix and skeletal muscle fibres." (p.2223)

Critical Appraisal

Validity

- PEDro Scale score: 9/11; eligibility criteria: yes, random allocation: yes; concealed allocation: no; baseline comparison: yes; blind subjects: yes; blind therapists: yes; blind assessors: no; >85% participant outcomes: yes; intention to treat analysis: yes; between group comparison: yes; point estimates and variability: yes
- Lack of clarity regarding allocation process, blinding of participants, therapists, and assessors; design seems to be excellent and rigorous study design upheld, but further clarification could confirm this
- Control group was appropriate and necessary to uphold blinding and accurate comparison of data
- Outcome measures used appear appropriate for the purposes of this study, although validated pre-intervention baselines for each measure of each group should be established

Interpretation of Results

According to the authors:

- It "appears that glucosamine is a potent agent in preventing the training-associated build up of RAGE in skeletal muscle." (p.2219)
- 72% of all subjects demonstrated an increase in Type IV collage immunoreactivity, despite no significant change in capillaries (which contribute to total Type IV collagen). The increased basement membrane suggests improved "protection against longitudinal and transversal stress". (p.2219)
- The reduction in Type I collagen fibers observed in the glucosamine group is important since Type I fibers are known to create tension and rigidity and increase with ageing and/or disuse.
- The authors point out that the ratio between Type I and III fibers may actually be more important than the single number of each individually, with a higher ratio of Type III to I being preferred. In this study, 100% of the glucosamine groups showed a decrease in Type I fibers, while 60% showed an increase in Type III. This improved ratio "would have a better performance in forced stretching". Furthermore, "it is likely that these changes will affect the mechanical properties of the muscle,… bringing about a more favourable structure for the transmission of high forces." (p.2221)
- Accumulation of AGEs is associated with a number of inflammatory illnesses, including diabetes, atherosclerosis, and osteoarthritis. In this study, when compared to the control group, the glucosamine group showed a reduced number of receptors of AGE (RAGE), leading the authors to suggest that "glucosamine can prevent the accumulation of RAGE observed with resistance training." (p.2222)
- Subjects in the glucosamine and ibuprofen groups demonstrated improved muscle strength and decreased joint pain compared to the control group, suggesting a "beneficial effect of glucosamine or ibuprofen supplementation on the muscle adaptation to resistance training in OA patients." (p.2222)

(3) Description and appraisal of *Positive effects of moderate exercise on glycosaminoglycan content in knee cartilage* by Roos EM and Dahlberg L (2005)

Aim/Objective of the Study/Systematic Review:

The purpose of this double-blind randomized controlled trial was to evaluate the effect of moderate exercise on knee cartilage quality (particularly the presence of glycosaminoglycan) in subjects at high risk or early onset of knee osteoarthritis.

Study Design

- Double-blind (assessor and subject) randomized controlled trial
- Subjects were recruited by surgical code review at a university hospital
- Screening questions used to ensure compliance
- Randomization performed sequentially as letters of acceptance were received
- Subjects were stratified based on self-report of high or low physical activity level in blocks of 4 or 2
- Subjects were randomly assigned to experimental or control group through the use of opaque envelopes organized in blocks to ensure equal number of participants between strata of each group
- A blinded assessor performed MRI measurements at baseline and follow-up
- Clinical outcome measurements were obtained at baseline and follow-up
- A priori power calculation was conducted to determine sample size, and the study was designed to detect a mean difference of (mean ± SD) 40ms ± 40ms in the T1(Gd) with 80% power
- Nonparametric statistics were used; to compare the exercise and control groups, the Mann-Whitney U test was used; Spearman's rho was used when comparing three ranked groups; significance was P values less than or equal to 0.05

Setting

- Although not explicitly stated, the study seems to have taken place at either an outpatient physical therapy setting or hospital-based physical therapy setting, since the subjects received individual clinical examinations and functional assessments by a physical therapist, exercise sessions were led by a physical therapist, and equipment was used that is commonly found in the physical therapy setting
- The study was approved by the ethics committee of Lund University, and the surgical code review was conducted using the records system at Malmo University Hospital. These facts indicate the study was conducted in Sweden.

Participants

- 45 total subjects (22 in experimental group; 23 in control group)
- Eligibility criteria: partial meniscectomy 3-5 years prior, aged 35-50 years, willingness to participate in study, and signed informed consent
- Subjects were recruited by screening surgical codes at a university hospital in Sweden
- 15 subjects withdrew without receiving a follow-up MRI; of those, 7 completed the follow-up questionnaire
- Subjects who were lost to MRI follow-up did not differ significantly from those who received MRI at follow-up regarding baseline characteristics
- At baseline, characteristics were similar between experimental and control groups

Of the 30 subjects for whom an MRI was performed:

- Gender: experimental group – 10 males (62%); control group – 10 males (71%)
- Mean age (std dev): experimental group – 45.8 years (3.1); control group – 45.8 years (3.6)
- Physical activity level: experimental group – 10 high (62%); control group – 10 high (71%)

Intervention Investigated

[Provide details of methods, who provided treatment, when and where, how many hours of treatment provided]

Control

- Participants in the control group did not receive any intervention; however, changes in physical activity level were evaluated in this group

Experimental

- Subjects in the experimental group completed 1-hour exercise classes 3 days per week for 4 months.
- Exercise classes were led by a physical therapist and focused on neuromuscular control, muscle strength, and aerobic capacity
- Prior to starting the study, each subject received an individual clinical examination and functional assessment by a physical therapist in order to tailor the program to each participant
- Warm-up consisted of ergometer cycling, skipping rope, and jogging on a trampoline

Outcome Measures

- The primary outcome measure was delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) and was obtained at baseline and follow-up by a blinded assessor
- In dGEMRIC, contrast is injected intravenously that distributes inversely to glycosaminoglycans (GAGs) in cartilage. Essentially, a higher concentration of GAGs equates to a lower concentration of contrast and is revealed by an increased T1(Gd) on an MRI.
- The study was powered to detect a mean difference of 40ms ± 40ms in the T1(Gd)
- Secondary outcomes were also assessed at baseline and follow-up and included the Knee Injury and Osteoarthritis Outcomes Score (KOOS), three muscular performance tests, a measure of isokinetic knee extension strength, and aerobic capacity
- The KOOS is a validated measure for meniscectomy follow-up; scores range from 0 (worst) to 100 (best); this data was used to examine the correlation of clinical outcomes change with T1(Gd) change; subscales included pain, symptoms, ADL, sports/recreation level, and quality of life
- Muscular performance tests included single leg hop distance (cm), number of square hops, and number of single leg raise
- Isokinetic knee extension strength (peak torque measured in Nm) was measured at 60deg/sec using a Biodex testing system and was adjusted for bodyweight
- Aerobic capacity (VO2max) was adjusted for bodyweight and measured using a bicycle ergometer test as described by Astrand

Main Findings

- Significant improvement in T1(Gd) in the exercise group (15ms ± 54) compared to the control group (-15ms ± 32) (P=0.036)
- Strong correlation between self-reported change in physical activity level and change in the T1(Gd) in

exercise group (n=16, r_s=0.70, 95%CI 0.31-0.89) and in the total group of all subjects (n=30, r_s=0.74, 95%CI 0.52-0.87)
- Aerobic capacity mean improvements in the total group (n=30) had a positive correlation with self-reported change in physical activity levels (r_s=0.42, 95%CI 0.07-0.68)
- Isokinetic peak torque within the total group also had a positive correlation with self-reported change in physical activity levels (r_s=0.39, 95%CI 0.04-0.66)
- Improved cartilage GAG content (as determined by change in T1(Gd)) correlated with improvement in all 5 KOOS subscales (r_s=0.38-0.52, 95%CI 0.02-0.70)

Original Authors' Conclusions

- "We conclude that moderate, supervised exercise improves knee-cartilage GAG content in patients at risk of OA. Improvements in pain and function are observed in parallel with the structural improvement. Exercise may have important implications for disease prevention in patients at risk of developing knee OA." (p.3513)

Critical Appraisal

Validity

- PEDro Scale score: 9/11; eligibility criteria: yes; random allocation: yes; concealed allocation: yes; baseline comparison: yes; blind subjects: yes; blind therapists: no; blind assessors: yes; >85% participant outcomes: no; intention to treat analysis: yes; between group comparison: yes; point estimates and variability: yes
- Participants were blinded to group allocation, and at least the assessor of the MRI was blinded. Unknown whether therapists delivering intervention were blinded
- Authors appear to have maintained rigorous study design and measurement analysis; carefully concealed allocation, blinded assessor; however, only 30 of the original 45 subjects (66%) were available for MRI follow-up and 37 of 45 (82%) completed the follow-up questionnaire
- Unfortunately, details of the exercise session were not available in this article. Instead, the authors state, "A description of the complete exercise program can be obtained from one of us (EMR)." (p.3509)
- Instead of a control group that did not receive any intervention, the results of the study may have been strengthened if the test group was compared against a group that received another type of intervention (such as progressive resistance training versus aerobic conditioning). Any group participating in therapeutic rehabilitation will likely naturally improve compared against a group receiving no intervention
- Outcome measures used appear appropriate for the purposes of this study

Interpretation of Results

- The authors found that increased exercise results in compositional changes in joint cartilage; they suggest that human cartilage may respond to physiologic loading in a similar manner that muscle and bone do
- The correlation between T1(Gd) measures and physical activity level implies that participating in high levels of exercise increases T1(Gd), meaning a higher GAG distribution. The authors suggest that this means cartilage responds to exercise by increasing its GAG content, which improves viscoelasticity and protects the collagen network from compressive forces; this also support the idea that exercise may protect against cartilage degeneration
- The authors suggest that the individual progression rate of OA may be related to either the quality of the joint cartilage (molecular content of GAGs) or individual differences in matrix integrity (in response to different levels of physical stimuli); this builds on the fact that other studies have found a high correlation between biomechanical properties of cartilage and GAG distribution
- "In a cartilage matrix with low GAG content, as in cartilage disease, insufficient viscoelasticity may cause progressive denaturation of collagen molecules, collagen loss, and subsequent development of OA." (p.3513)

EVIDENCE SYNTHESIS AND IMPLICATIONS

Implications for clinical practice:

The evidence reviewed indicates that strength-training exercise has beneficial effects on factors associated with osteoarthritis. In the double-blind randomized controlled trial by Roos & Dahlberg (2005), moderate exercise that incorporates muscle strengthening and neuromuscular control was found to improve knee joint cartilage composition in patients at risk for OA.[5] The double-blind randomized controlled trial by Mattiello-Sverzut, et al (2013) found that muscle-strengthening exercise training supplemented with glucosamine was found to positively affect the mechanical properties of muscle and prevent the build-up of factors associated with OA.[2] Finally, the single-blind randomized controlled trial by Hall, et al (2015) found that, although neuromuscular exercise did not significantly impact knee adduction moment, it did produce favourable outcomes in pain, physical function, and knee adduction moment during normal and fast-paced walking, suggesting

neuromuscular exercise may have clinical significance for patients at risk of osteoarthritis.[8]

Increased exercise was found to have a positive effect on knee joint cartilage composition in patients with partial meniscectomies, and implies that human cartilage may respond to physiologic loading in a similar manner as muscle and bone.[5] Increased exercise may result in an increased GAG content, suggesting that cartilage responds to exercise by increasing its GAG content.[5] This is important since glycosaminoglycans improve viscoelasticity and protect collagen networks from compressive forces.[5] This implies that exercise may be an important intervention in preventing or delaying onset of osteoarthritis in patients at risk of developing knee OA, as in the case of the patient in the clinical scenario.[5]

Resistance training alone was shown to increase the osteoarthritis-associated RAGE in skeletal muscle.[2] While further research is required to explore the meaning and cause of this, supplementing resistance training with glucosamine decreased RAGE factors significantly.[2] Since RAGE factors are associated with inflammatory illnesses (i.e. osteoarthritis) and stiffness and reduced muscular function, the results are important for reducing these characteristics of OA.[2] Glucosamine-supplemented strength training also acts to favourably change the ratio of collagen fiber types, decreasing tension and rigidity, promoting tissue compliance, and improving mechanical properties and allowing muscle tissue to perform better when faced against high forces (strength training alone produced mixed results).[2] These findings indicate that when resistance training is used in conjunction with glucosamine, favourable changes occur in factors associated with osteoarthritis.[2]

Peak knee adduction moment is related to structural cartilage change and onset of osteoarthritis.[8] Neuromuscular exercises were not found to have a statistically significant impact on peak knee adduction moment when compared to a control group.[8] However, neuromuscular exercises did produce favourable outcomes in pain, physical function, knee adduction moment during ambulation, and overall improvement.[8] This implies that neuromuscular exercise may possess clinical significance for patients at risk for knee osteoarthritis.[8]

In summary, evidence indicates that strength-training exercise may play a role in reducing the likelihood of acquiring osteoarthritis in a young adult following partial meniscectomy. The extent of that role should be researched further, but current research indicates that strength training contributes to several beneficial outcomes, including improving knee joint cartilage composition (i.e. GAGs), decreasing OA-associated factors (i.e. RAGE), promoting favourable changes to the mechanical properties of muscle (i.e. collagen fiber ratios), and improving the knee adduction moment during ambulation – all of which work against the development of knee osteoarthritis.

Future research:

Currently, limited evidence exists to guide clinical practice that directly addresses the clinical question. The bulk of current research examines interventions that address the symptoms and manifestations of osteoarthritis in older populations. Young adults who have undergone a meniscectomy are at increased risk for developing OA, yet little research targets this population. Furthermore, few studies address interventions aimed at preventing the development of OA. The search for evidence in this assignment revealed no studies that looked specifically at resistance training as a primary intervention for preventing knee OA in young adults following partial meniscectomy.

Future studies might be better served by considering the transfer of trained skills (during neuromuscular exercise) to gait, obtaining a sample size large enough to capture a possible statistically significant change in peak KAM during normal and fast-paced walking, careful attention to foot progression angle, knee flexion, and hip rotation when assessing KAM, and including a quantifiable measurement of osteoarthritis/cartilage structural change.[8]

Future studies should explore the implications of increased RAGE markers following resistance training. Also, studies that explore medication-supplemented resistance training should evaluate the effectiveness of such intervention on delaying onset or preventing osteoarthritis, particularly in younger subjects with an elevated risk for knee OA, such as those who have undergone partial meniscectomies.[2]

Future studies might consider evaluating whether the change in cartilage composition as a result of exercise remains long-term, and further consideration of the long-term effectiveness of exercise intervention in preventing or delaying onset of OA.[5]

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