UNIVERSIDADE FEDERAL DE SÃO CARLOS

CENTRO DE CIÊNCIAS BIOLÓGICAS E DA SAÚDE

PROGRAMA DE PÓS-GRADUAÇÃO EM FISIOTERAPIA

TESE DE DOUTORADO

O uso da crioterapia em pacientes com osteoartrite de joelho

Lucas Ogura Dantas

São Carlos

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Tese de doutorado apresentada ao Programa de Pós-Graduação em Fisioterapia da Universidade Federal de São Carlos como parte dos requisitos para obtenção do título de Doutor em Fisioterapia.

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Centro de Ciências Biológicas e da Saúde
Programa de Pós-Graduação em Fisioterapia

Folha de Aprovação

Defesa de Tese de Doutorado do candidato Lucas Ogura Dantas, realizada em 03/12/2020.

Comissão Julgadora:

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Os projetos de pesquisa apresentados nesta tese foram desenvolvidos com o apoio financeiro da Fundação de Amparo à Pesquisa do Estado de São Paulo (**FAPESP**; processos 2015/21422-6 e 2018/07462-3), do Conselho Nacional de Desenvolvimento Científico e Tecnológico (**CNPq;** processo #302169/2018) e da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (**CAPES**; processo 1662695 – 001).

Dedico esta tese aos meus pais, Neusa e Moacir e ao meu irmão, André. Sempre foi e vai ser por vocês. Sempre.

Dedico também a todos os meus mentores acadêmicos, pacientes e colegas de Pós-Graduação. Vocês me ensinaram ciência de verdade.

“An idea is like a virus, resilient, highly contagious.

The smallest seed of an idea can grow.

It can grow to define or destroy you.”

Inception - Movie

“Imagination means nothing without doing.”

Charles Chaplin

SUMÁRIO

Resumo em português

A osteoartrite (OA) do joelho é uma doença crônica progressiva que traz uma carga socioeconômica substancial para a sociedade e os sistemas de saúde. A crioterapia é uma intervenção não farmacológica amplamente utilizada por profissionais de saúde pelo seus efeitos na dor e no processo inflamatório. Compilar evidências sobre o uso da crioterapia e sua eficácia pode ajudar a gerar estratégias para a reabilitação da OA do joelho. Assim, os objetivos desta tese foram: 1) Investigar os efeitos da crioterapia na dor e função física em individuos com OA de joelho; 2) Responder à pergunta: A crioterapia de curta duração melhora a dor, a função e a qualidade de vida em pessoas com OA de joelho? Para atingir o *primeiro objetivo*, conduzimos uma revisão sistemática seguindo as recomendações propostas pelos Itens do Relatório Preferencial para Revisões Sistemáticas e Meta-análises e a Colaboração Cochrane para revisões sistemáticas. Dos 338 estudos identificados, apenas cinco foram incluídos na análise final. Nossa revisão mostrou que as modalidades de crioterapia apresentaram um nível de evidência de baixa qualidade para o controle da dor e melhora da função física em indivíduos com OA de joelho. Além disso, o escore PEDro médio foi de 4,20/10, indicando a baixa qualidade metodológica dos estudos disponíveis. Portanto, havia uma importante lacuna na literatura a ser preenchida. Para preencher essa lacuna e atingir o nosso *segundo objetivo*, conduzimos um ensaio clínico randomizado (ECR) de acordo com a declaração de normas consolidadas de relatórios de ensaios para ensaios randomizados (CONSORT) de tratamentos não farmacológicos e a lista de verificação do modelo para descrição de intervenção e replicação (TIDieR) para verificar os efeitos da aplicação de crioterapia de curto prazo sobre dor e função física de indivíduos com OA de joelho. O estudo foi conduzido por um período de 6 dias consecutivos e 60 pacientes foram randomizados em dois grupos: um grupo experimental que recebeu crioterapia (sacos de gelo) e um grupo controle que recebeu uma intervenção simulada (sacos de areia). Nosso estudo mostrou que a crioterapia não foi superior ao grupo controle em termos de alívio da dor ou melhora da função física e qualidade de vida em pessoas com OA de joelho.

Outras pesquisas incluídas: com os resultados de nosso primeiro ECR, desenvolvemos um protocolo para um segundo ECR com o objetivo de verificar os efeitos complementares da crioterapia na dor e na função quando associada a um programa de exercícios terapêuticos personalizado para pacientes com OA de joelho. Além disso, incluímos nesta tese um artigo de "masterclass" sobre OA de joelho para orientar fisioterapeutas em sua prática clínica e tomada de decisão. Todos os manuscritos incluídos nessa tese estão publicados.

Palavras-chave: fisioterapia; dor crônica; doenças articulares; doenças reumáticas

Resumo em inglês

Knee osteoarthritis (OA) is a chronic progressive disease that brings a substantial socioeconomic burden to society and healthcare systems. Cryotherapy is a non-pharmacological intervention that is widely used by health care professionals for its effects on pain and inflammation. Compiling evidence about cryotherapy use and its efficacy may help to generate strategies for targeted knee OA rehabilitation. Thus, the objectives of this thesis were: 1) To investigate the effectiveness of cryotherapy on pain and physical function in knee OA; 2) To answer the question: Does short-term cryotherapy improve pain, function, and quality of life in people with knee OA? To achieve the *first objective*, we conducted a systematic review following the recommendations proposed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and the Cochrane Collaboration for systematic reviews. From the 338 studies identified, only five were included in the final analysis. Our review showed that cryotherapy modalities presented a low-quality level of evidence for pain control and functional outcomes among knee OA individuals. Besides, the mean PEDro score was 4.20/10, indicating the low methodological quality of the available studies. Therefore, there was an important literature gap to fill. To fill this gap and achieve the *second objective*, we conducted a randomized controlled trial (RCT) reported according to the Consolidated Standards of Reporting Trials Statement for Randomized Trials (CONSORT) of Nonpharmacologic Treatments and the Template for Intervention Description and Replication checklist (TIDieR) to verify the effects of short-term cryotherapy application on pain and physical function of individuals with knee OA. The trial was conducted over a period of 6 consecutive days and 60 patients were randomized into two groups: an experimental group that received cryotherapy (ice packs), and a control group that received a sham intervention (sand packs). Our study showed that cryotherapy was not superior to a sham intervention in terms of relieving pain or improving function and quality of life in people with knee OA.

Other research included: with the results of our first RCT, we developed a protocol for a second RCT to verify the complementary effects of cryotherapy (long-term use) on pain and function when associated with a tailored therapeutic exercise protocol for patients with knee OA. Also, we included on this thesis a masterclass about knee OA to guide therapists on their clinical practice and decision making. All manuscripts included on this thesis are published.

Keywords: physiotherapy; chronic pain; joint diseases; rheumatic diseases

Histórico e reflexões sobre minha trajetória acadêmica e científica

Eu acredito que vamos transformar a saúde do Brasil através da tecnologia. Nasci em uma cidade no interior de Mato Grosso do Sul, Nova Andradina, com menos de 30 mil habitantes. Desde pequeno, eu e meu irmão viajamos o Brasil inteiro com nossos pais e fomos doutrinados - até hoje acredito que somos - para pensar e agir como pessoas autênticas, humildes, calculistas, e que vão no limite pelo trabalho. Tenho muito orgulho dos meus pais, são pessoas extraordinárias: foram do zero ao topo na cadeia econômica do país com muita raça, honestidade e humildade. Sempre assisti tudo, em primeira mão. Nunca tiveram diplomas de faculdade para mostrar e, mesmo assim, nunca deixaram faltar *nada* durante nossas vidas. Buscaram sempre dar a melhor educação a nós e ensinaram valores que o **dinheiro não compra**. Eu e meu irmão, o **André**, desde muito pequenos éramos viciados em tecnologia, videogame, música e em criar coisas juntos. Sempre juntos. Ele, um ano mais velho, é um exemplo de pessoa. Engenheiro de computação, já morou em diversos lugares do mundo e hoje reside na Califórnia, sendo um dos melhores desenvolvedores do país. Sempre me ajudou e me apoiou em todos os projetos que fiz, principalmente os que envolviam saúde e tecnologia. Acredito que os maiores "poderes" que nossos pais nos ensinaram na vida foram: organização, cuidar de quem se gosta, dividir sempre, dar valor para tudo o que se tem e se conquista com honestidade e, principalmente, ter um jogo de *consistência* e *execução* a **longo prazo** em quase tudo o que se for fazer. É incrível como essas habilidades se desenvolveram ao longo dos anos e transformaram as nossas realidades. Hoje, fica claro que podemos alcançar qualquer objetivo na vida.

Em 2008, prestava o curso de Engenharia Ambiental junto com Fisioterapia - sim, Engenharia Ambiental - era uma época em que eu estava bem confuso sobre a carreira profissional e o caminho que gostaria de trilhar. Hoje, após cinco longos anos de faculdade - nunca fui um aluno exemplar e tomei reprovações durante a faculdade - e seis longos anos de doutorado, consigo ter clareza do meu propósito como fisioterapeuta e cientista: alterar a estrutura da saúde e da nossa classe no país, através da ciência e tecnologia. Olhando para trás, fica nítido que todas as experiências que aconteceram na minha jornada, todas as decisões e todas as pessoas que conheci, eram de fato para acontecer. Nesta tese, condenso grande parte dos meus aprendizados no período de doutorado e, principalmente, como fizemos tudo o que fizemos. Obviamente, muito ficará de fora. Muitas histórias, pessoas e projetos pessoais que fiz e levo para a vida. Porém, o mais importante da minha jornada científica está aqui.

Acredito em uma cultura de conhecimento compartilhado. Hoje, infelizmente, vejo muitas pessoas extraordinárias na ciência que fazem discursos maravilhosos sobre grandes resultados, publicações e lugares que a ciência os levou, mas nunca ensinam como fizeram tudo o que fizeram para que outros pares consigam desfrutar das mesmas experiências que tiveram. Pouquíssimos ensinam o *como fazer*. Isso, na minha opinião, é a parte mais importante do jogo!

*Vencer **sozinho** é legal? É.*

*Mas vencer **junto** é libertador!*

"Science never solves a problem without creating ten more."

George Bernard Shaw

"*Eu nunca mais vou fazer ciência*." Foi isso que eu disse à minha **mãe**, em 2014, quando estava no meu último ano de graduação e tinha acabado de chegar de uma coleta do meu primeiro projeto envolvendo ciência, o de iniciação científica (IC). A minha jornada começa em 2013, quando esbarrei com o meu *primeiro mentor científico* e atual grande amigo, o professor *João L. Q. Durigan*. Na época, ele estava terminando o doutorado e nos demos muito bem. Ele sempre foi de me desafiar e até hoje faz isso. Com ele, tive a minha primeira experiência científica onde conduzimos do zero um *ensaio controlado randomizado (ECR)* envolvendo correntes elétricas e níveis de desconforto em mulheres. Ao escrever o projeto junto com ele, aprendi a fundamentação básica de como funcionava a ciência. Tudo tinha que ser metrificado e controlado o máximo possível. Aprendi que ECR's são os únicos estudos que podem responder uma pergunta que me fascinava: Será que isso funciona? Além disso, entendi que as respostas desses estudos, quando bem conduzidos, ditam muitas regras nesse mundo, como por exemplo, quais informações de fato as pessoas podem ou não confiar.

**** O João sempre falou que eu levava jeito para a ciência, que tinha o domínio total da língua inglesa e que isso já era um grande diferencial. Hoje, graças aos meus pais, à música e aos videogames durante a infância e adolescência, enxergo o tanto de portas que o idioma abriu para mim. Estude inglês. Muito! Caso não tenha dinheiro para pagar escolas, use softwares ou aplicativos online disponíveis gratuitamente (duolingo, busuu, drops, memrise), mídias sociais para conversar com pessoas de fora, escute muitas músicas ou veja séries! ****

Em 2014, quando me formei fisioterapeuta, havia concluído o meu projeto de IC com sucesso. Escrevemos o manuscrito em inglês e o João havia ficado de enviar para a publicação. Estava clinicando nesse ano e sentia-me meio descontente, pois não sabia ao certo se era aquilo que gostaria de fazer pelos próximos anos. Recebo uma ligação do João, que estava todo empolgado para me falar que nosso manuscrito havia sido publicado em um jornal internacional (*Muscle & Nerv*e). Até hoje não entendo o porquê, mas ele me colocou como primeiro autor do manuscrito. Eu nem sabia o que significava isso, mas parecia importante um aluno de IC ser o primeiro autor de um manuscrito publicado nesse jornal. Após clinicar por um ano, com a ajuda do João, decidi entrar no mestrado, em São Carlos. Ele fez questão de me apresentar para a minha *segunda mentora científica*, a professora *Tania F. Salvini*. Aqui, conheci de perto uma *lenda* da fisioterapia no país e o jogo mudou de nível.

Tive muita *"sorte"* com meus mentores, como costumo relatar em palestras e para colegas da academia. Dou muito valor a cada um deles. Na época que entrei, o Programa de Pós-Graduação da UFSCar oferecia bolsa apenas para os quatro primeiros colocados da prova. Nesse contexto, lembro-me que, conversando com a Tania, ela me disse bem tranquila: *"-Fica tranquilo Lucas! É só você passar entre os primeiros que você tem essa bolsa, isso te ajuda por enquanto, até a gente pedir uma*

maior...você consegue sim!". Senti-me desafiado. Criei uma rotina onde estudava 6 horas por dia, 6 dias por semana por 2 meses. Estudei todo o material disponibilizado pelo Programa de Pós-Graduação e coloquei na minha mente que precisava ler no mínimo um artigo científico por dia de cada área da fisioterapia, para acostumar a mente com o que estava por vir. Isso me ajudou muito. O que me ajudou muito também foi conversar horas com quem já havia feito a prova e passado. Acredito no poder de visualização mental das coisas. O que sua mente enxerga com total clareza, tende a acontecer. Fiz a prova para o mestrado em 2014 e felizmente consegui passar em *primeiro lugar* na classificação do Programa de Pós-Graduação em Fisioterapia da UFSCar. Começamos bem.

**** A Tania tem habilidades que me surpreendem até hoje: uma visão além do alcance sobre assuntos acadêmicos, ou seja, ela consegue ter total clareza dos objetivos e dos desdobramentos de cada passo que a gente faz e, como em um jogo de xadrez, está sempre jogando um ou dois passos à frente dos desafios. Além disso, sabe dar total* ***liberdade*** *para os alunos fazerem ciência, com as devidas responsabilidades e prazos. Isso me ajudou muito e me impressiona até hoje. É do tipo de pessoa que fala a realidade para você, sem* ***enrolação****. Preto no branco. Tem muita influência e sabe formar líderes. Quanto mais conversava com ela, mais motivado e cheio de perguntas saia. Sou eternamente grato por ela ter sido a minha principal mentora na academia. ****

Em 2015, ingressei no meu primeiro ano de mestrado, que mais tarde tornar-se-ia doutorado direto. Na primeira conversa que tive com a Tania, ela percebeu que havia uma alta chance de termos sucesso com uma bolsa da FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo) de *doutorado direto*. Ela me mostrou as pesquisas do laboratório, conversamos sobre possibilidades de estudos e me deu um prazo de 2 semanas para criar um rascunho de projeto que eu gostaria de executar durante a Pós-Graduação. Na primeira semana, li 10 artigos por dia sobre manuscritos publicados pelo laboratório e sobre desenhos de estudo. Me interessei por patologias crônicas que afetavam a população em larga escala, como diabetes, doenças cardiovasculares e doenças reumáticas. Em específico, me interessei por osteoartrite. A Tania havia comentado que tinha em um dos joelhos e lembro que meus avós também tinham a patologia. A possibilidade de poder ajudar pessoas próximas e em larga escala, me motivou. Comecei a direcionar os meus estudos para osteoartrite de joelho. Agora faltava encontrar uma intervenção. Lendo as pesquisas feitas no laboratório, me interessei por crioterapia, pois enxergava muito potencial no agente físico: analgésico, de baixo custo e fácil aplicação tanto pelo profissional de saúde quanto pelos pacientes. Era uma intervenção escalável para a população mundial e principalmente, a do Brasil. Na segunda semana, decidi levantar todos os artigos relevantes sobre a combinação dos temas, ou seja, todas as possíveis formas de crioterapia existentes e como pesquisadores utilizavam esse recurso em pacientes com osteoartrite.

Mantive a consistência de ler 10 artigos por dia, porém, não encontrei muitos resultados relevantes, o que me surpreendeu. Fui conversar com a Tania e apresentar o que havia estudado e encontrado de resultados. Decidimos fechar um ECR para enviar à FAPESP para responder a seguinte

pergunta: será que a crioterapia funciona para quem tem osteoartrite de joelho? Além disso, mostrei os poucos resultados das minhas buscas sobre crioterapia e osteoartrite de joelho para a Professora Roberta F. C. M. Padovez, expert em revisões sistemáticas, e vimos a possibilidade de desenvolver uma revisão sobre os efeitos da crioterapia em pacientes com osteoartrite de joelho. Apostamos aqui que a minha busca, para começar o ECR enviado à FAPESP, estava correta.

**** Uma dica que dou a todas as pessoas que pretendem entrar em algum Programa de Pós-Graduação no país: por mais estressante e desgastante que seja, busquem terminar todas as disciplinas obrigatórias do Programa o quanto antes. É uma tarefa difícil e seu cérebro vai querer desistir. Foco no longo prazo. Faz total diferença para as suas liberdades acadêmicas e para você conseguir prospectar contatos com novas pessoas, realizar novos projetos e alçar vôos maiores! Outra dica é você focar em matérias optativas que realmente irão agregar valor para o seu atual projeto. Nunca faça uma disciplina apenas por fazer ou porque "todo mundo faz". Você não vai reter esse conhecimento pois nunca irá aplicar. Isso é um desperdício de tempo (vida). ****

A ideia dos projetos era simples: Com a revisão, queríamos mostrar que não havia estudos de qualidade sobre o tema. Se conseguíssemos, abriríamos portas para um excelente estudo de eficácia com uma pergunta interessante. Com o ECR, literalmente apostamos nossas fichas nos meus estudos preliminares, ou seja, de que não havia na literatura estudos controlados com uma qualidade metodológica boa para responder à pergunta em questão. Desenharíamos então, um estudo de qualidade para responder se a crioterapia traria benefícios positivos para desfechos como dor e função física quando comparada com uma intervenção simulada em pacientes com osteoartrite de joelho. Nossa hipótese era de que o agente físico traria benefícios para melhora da dor e função nessa população. Nitidamente, se tudo desse certo, um estudo iria se encaixar no outro, era um par forte.

Inscrevemos ambos os estudos em bancos de registros internacionais de forma prospectiva (isso é muito importante) e submetemos o ECR para a FAPESP, solicitando uma bolsa de doutorado direto com um período de estudos no exterior. Lembro que nos anos de 2015 e 2016, estudava cerca de 15 horas por dia. Eram infinitas aulas da pós-graduação, leitura de artigos científicos e começo de coletas do ECR. Aprendi muito sobre manejo do tempo e que havia um universo de estudos à frente apenas sobre osteoartrite de joelho para desbravar. Nessa época, aprendi quais eram os melhores jornais internacionais em osteoartrite e que é *muito* importante você ter foco em sua área de estudo. Aprendi que querer abraçar o mundo e dominar diversas áreas simultaneamente é bobagem. Apesar da sede por conhecimento ser alta, *tentar ser bom em tudo é literalmente não ser bom em nada.*

**** Na minha opinião, a melhor tática para desenhar um estudo de qualidade é utilizar listas de checagens (ex: CONSORT Statement para ensaios clínicos, PRISMA para revisões sistemáticas, etc). O banco de dados da rede Equator (https://www.equator-network.org/) é gratuito e um local fantástico para melhorar a qualidade dos seus estudos, escrita científica e encontrar exatamente quais listas seguir de acordo com o tipo de estudo que você busca conduzir. Além disso, uma outra tática que desenvolvi ao longo dos anos e uso até*

hoje para escrever é filtrar os três melhores estudos de alto impacto sobre o tema ou relacionados ao tema e utilizar como ***modelos****. Conforme os anos passam, esses três estudos estão sempre se atualizando, pois você lê novos estudos e encontra metodologias cada vez melhores, até que um dia você não precisa mais de modelos, pois criou os seus próprios. Quando esse dia chegar,* ***compartilhe*** *seus modelos com todos os colegas e veja se eles se beneficiam. Essa estratégia deixa a sua escrita em um nível muito acima da média e a metodologia do seu estudo, que é o coração do seu projeto, fica bem mais robusta.* ***

Era um sábado de manhã e eu estava indo a uma coleta do ECR no final de 2016. Acordo, abro o meu e-mail e descubro que fui contemplado com a bolsa de doutorado direto da FAPESP. O sentimento de felicidade foi *indescritível*. Entendam que aqui eu já estava no segundo ano de mestrado e se essa bolsa não saísse, eu teria que defender o mestrado com literalmente nada pronto. A tensão era alta. Receber essa bolsa da FAPESP, foi como respirar aliviado depois de ficar por muito tempo embaixo d'água. Como a bolsa contemplava um período de estágio de pesquisa no exterior (BEPE), precisávamos encontrar grupos de qualidade para escolher o melhor local para ir.

No início de 2017, fui em um dos maiores Congressos do mundo sobre osteoartrite, o Congresso da OARSI (Osteoarthritis Research Society International). Aconteceu em Las Vegas e fui apresentar um pôster aceito sobre os resultados preliminares do nosso ECR. Um mês antes do Congresso, fiz uma lista por ordem de interesse, com os 10 pesquisadores que estariam lá e que eu gostaria de conversar. Para isso, estudei um pouco da linha de pesquisa de cada um e preparei uma apresentação rápida para falar em cada situação específica. O fato de você conhecer melhor a pessoa antes de falar com ela e saber as suas melhores pesquisas, com comentários únicos sobre, abrem portas. No Congresso, apenas não consegui falar com um único pesquisador da minha lista. Quando o chamei para conversar em um corredor de pôster, lembro-me claramente das palavras dele: *"- Agora não dá, quem sabe te dou uma oportunidade depois!"* Achei meio rude e arrogante da parte dele falar da forma que falou, mas, aparentemente estava com pressa.

Acredito que quando certas coisas na sua vida têm que acontecer, de um jeito ou de outro, elas acontecem. Como em um filme, no último dia de Congresso, na última apresentação, eu estava saindo da sala de encerramento para ir embora com destino ao aeroporto. Avistei esse pesquisador em uma roda conversando com todas as pessoas da minha lista; ele parecia ser uma pessoa importante. Ele começou a me olhar e, de repente, deixou todo mundo para trás e veio em minha direção. Ele acena e fala: *"- Ei, você aí! Não queria falar comigo? Antes não consegui, perdão, vamos conversar agora?"* Por 3 segundos eu não sabia o que falar. Era isso! Era pra acontecer. Aqui conheci o meu *terceiro mentor científico*, *Timothy E. McAlindon*. O Tim é um cara jovial, apesar da idade, e um dos nomes mais fortes do mundo na área de reumatologia. É autor de artigos publicados nos maiores periódicos do mundo da medicina e das diretrizes das maiores organizações do mundo sobre osteoartrite. Conversando com ele, em março de 2018, convidou-me para uma visita técnica (financiada pela FAPESP) para conhecer o centro médico onde ele e o seu time trabalhavam.

No frio de Boston, fui ao Tufts Medical Center onde, na Divisão de Reumatologia, conheci toda a equipe dele que era formada por médicos e pelos grandes pesquisadores da área de reumatologia. Logo na entrada da divisão estava um mural de vidro com as dezenas de publicações do grupo em jornais de alto impacto no mundo. A lista de contatos e influência do Tim impressionava. O alcance dele era global e tudo estava a um telefonema ou mensagem de distância. Para minha surpresa, não encontrei nenhum fisioterapeuta na Divisão, a maioria eram médicos. Fizemos uma semana de imersão e várias reuniões diárias. Organizamos as ideias sobre as possibilidades de projetos durante a minha visita e ficou marcado que eu voltaria a Boston para executar a BEPE em setembro do mesmo ano. O nosso projeto seria focado no desenvolvimento de tecnologias móveis para auxiliar pacientes da área de reumatologia em ECR's.

**** Uma coisa muito importante aqui é você aprender a utilizar todas as possibilidades que as agencias de fomento te proporcionam. A visita técnica foi uma jogada estratégica que desenvolvi com a Tania. Se eu fosse a Boston e não gostasse, tínhamos outras cartas na manga de potenciais pesquisadores e lugares a ir. Obviamente, escolhi o local e a pesquisa que mais me atraia e que mais me identifiquei para explorar. Isso é muito importante pois é preferível você conhecer mais afundo o laboratório, a equipe e a ideia do projeto que pretende desenvolver durante o período no exterior. Além disso, é imprescindível que você tenha clareza que as oportunidades que uma BEPE te abrem são inúmeras e não somente* ***restritas*** *ao local ou equipe que você vai trabalhar. Em Boston, a cidade era incrível e as possibilidades que criei foram inúmeras.* ***

Quando voltei da visita técnica da BEPE para o Brasil, sabia que era para lá que deveria ir. De volta ao país, fomos convidados a escrever um capítulo de livro sobre o tratamento conservador da osteoartrite de joelho. Abraçamos o desafio e começamos a estruturação do trabalho. Além disso, já tínhamos os resultados finais do nosso estudo de revisão e do nosso primeiro ECR. Como previsto, a revisão mostrou que não existiam estudos de qualidade para responder à pergunta do nosso ECR. Ufa! Porém, o ECR mostrou que, apesar de ambos os grupos terem melhorado as variáveis de dor e função física, a crioterapia não se mostrou superior à intervenção simulada. Isso foi muito interessante, a ponto de nos levantar uma série de outras perguntas sobre o tema: será que o tempo de aplicação foi curto demais? Será que não havíamos controlado algo importante?

Precisávamos de novos estudos para responder algumas dessas perguntas. Desenhamos então um segundo ECR para verificar os efeitos complementares da crioterapia quando associada a um programa de exercícios físicos para pacientes com osteoartrite de joelho. A nossa ideia era verificar se a aplicação, agora em um período maior de tempo, traria benefícios adicionais quando associada ao ao que há de melhor na literatura em tratamento para osteoartrite de joelho nos dias atuais: exercício físico. Começamos o segundo ECR com uma equipe sólida. Todos sabiam que eu iria viajar em setembro para a BEPE, então, decidimos coletar o máximo possível de pacientes antes da minha ida.

Nos primeiros meses, fizemos os principais ajustes de logística de times e estrutura organizacional do projeto. Montamos fluxograma de coletas e delegamos as responsabilidades de cada pesquisador.

Em paralelo com o segundo ECR nós pensamos em desenvolver um estudo menor, para verificar a possibildiade de estudar os efeitos da crioterapia em pacientes com estágio final de osteoartrite. Infelizmente, esses pacientes eram excluídos dos nossos ECR's pelos critérios de eligibilidade. Desenhamos um estudo de casos (erroneamente chamado assim pois na época não nos atentamos ao desenho desse estudo, que na realidade era pra ser um estudo piloto ou de viabilidade) com uma metodologia similar ao primeiro ECR. Nesse estudo, criamos um protocolo padronizado de aplicação de crioterapia onde íamos até as casas dos pacientes realizar às sessões durante um período de 9 semanas, 3x por semana. Infelizmente cometemos um erro crasso de não incluir um grupo controle. Apenas incluímos o grupo de intervenção. Cosneguimos terminar o estudo até antes de eu viajar para a BEPE e percebemos que, apesar de ser possível realizar o projeto em maior escala para esses pacientes, os resultados não eram tão confiáveis pela falta do grupo controle. Foi um ótimo aprendizado.

Antes de setembro chegar, nosso segundo ECR já rodava bem, o time estava sincronizado e tinhamos consistência em coletas. Era hora de embarcar para mais uma jornada. Estava bem animado aqui e ansioso sobre o que estava por vir.

**** Uma coisa que a Tânia me ensinou e nunca vou esquecer: busque **sempre** viajar sem nenhuma pendência. Ou pelo menos, com o mínimo possível. Assim, você consegue aproveitar ao máximo da experiência do outro local, com sua consciência tranquila. Viajei com ambos os manuscritos prontos para as primeiras submissões, o estudo de casos e o capítulo de livro finalizados, e o segundo ECR rodando fluidamente com nosso time no Brasil. Assim, quando cheguei na BEPE, minha mente estava totalmente focada no projeto que iria desenvolver por lá e em todas as atividades extras que surgiram. Claro, eu mantinha contato semanal com os times no Brasil para poder acompanhar a evolução do projeto, mas era algo mínimo. ****

A experiência de pesquisa no exterior

"Most people say that it is the intellect which makes a great scientist.

They are wrong: it is character."

Albert Einstein

Encaro a BEPE (setembro de 2018 - novembro 2019) como uma das experiências mais desafiadoras da jornada acadêmica. Foi um período de aprendizado intenso e o mais turbulento de todos, pois nesse período o jogo era bem diferente, o nível era outro e as pessoas que tive contato trabalhavam de uma forma bem acelerada. Eram médicos, médicos cientistas e uma cultura de resultados desprovida de afetividade e sentimentos, o que favorecia a criação de superegos. No quadro de pesquisas do Tim, ele participava ativamente em mais de 250 projetos e iniciativas globais. Era gente pra todo lado, cada pessoa tinha no mínimo três monitores e dois computadores e as equipes eram formadas por pessoas do mundo inteiro e das melhores universidades do país. No meu primeiro dia de trabalho, ele me deu um canto só meu, dois monitores e dois computadores. Além disso, no final do dia, me chamou na sala dele e me alertou: "- *Cuidado. Algumas pessoas aqui vão tentar fazer você se sentir um lixo. Literalmente. Muitos, não sabem o que falam. O que importa é persistência e perseverança. Pode confiar em mim, que a gente vai fazer o seu projeto dar certo*."

Lembro claramente da minha primeira experiência acadêmica na Divisão de Reumatologia, já na primeira semana, quando apresentei nossa ideia de projeto para o grupo. Eram dezenas de pessoas na sala, sentadas em ordem hierárquica de importância. Tive 30 minutos. Foram perguntas de todos os lados e vários comentários um tanto quanto hostis não apenas sobre o projeto, mas sobre mim, de como um brasileiro poderia estar onde estava e que o Tim havia ficado de certa forma, maluco. Apesar de ficar abalado com alguns comentários durante a apresentação, consegui ir até o final. O Tim se atrasou e quando entrou na sala muitos ficaram calados e sorridentes. Os níveis de interesses da maioria ali me impressionaram. Incrível. Nesse dia voltei para casa muito reflexivo e chateado. Porém, animado, pois aprendi *três* coisas bem importantes: **1.** Se quisesse me dar bem ali o jogo teria que ser diferente e eu teria que me blindar contra críticas e ser muito mais frio e calculista; **2.** A falsidade e malícia de 90% das pessoas era incrível. Eu precisava ter um cuidado extra com o que fazia e principalmente com o que *falava*; **3.** Muitos reclamam dos Programas de Pós-Graduação do Brasil, mas eu tenho muito orgulho do Programa onde estudei, da UFSCar, das pessoas e da cultura que temos. Muito orgulho mesmo dos meus pares de trabalho do Brasil e do nosso laboratório!

No final da primeira semana, o Tim me chamou na sala dele para conversar e pediu desculpas por ter se atrasado para a minha primeira apresentação. Falou que estava feliz, porque eu não tinha ido embora e isso era um ótimo sinal. Ele havia chamado a coordenadora da divisão para me matricular em alguns cursos ofertados pelas universidades sobre escrita científica, pesquisa biomédica, conflitos de interesses, boas práticas clínicas em estudos, segurança e privacidade de dados e claro,

metodologia de ensaios clínicos em larga escala. Além disso, me disse para assistir seminários e participar dos encontros semanais da Divisão para se acostumar com a cultura. Na visão dele, era a fundamentação básica que eu precisava aprender para começar a entender como ele jogava. Utilizei em Boston a mesma estratégia do começo do meu doutorado: acabar todas as aulas o mais rápido possível com qualidade, assistir todos os seminários e fazer as provas necessárias para poder focar no projeto e criar mais possibilidades de colaborações com outras pessoas e grupos.

Foi um ano inteiro ouvindo críticas, algumas totalmente descabidas e outras com algum sentido. Das mais de 60 pessoas que tive significativa interação dentro do centro médico, o Tim, a Yaneth (secretária e coordenadora de projetos do Tim) e a Mikala (uma das únicas amigas que fiz no centro médico e um gênio de pessoa, autora das diretrizes OARSI e de artigos com níveis surreais de metodologia) foram as únicas três pessoas que pude confiar e que ***nunca*** me discriminaram ou me desrespeitaram durante a minha estadia no centro médico. Blindei completamente a minha mente contra as outras pessoas. Aqui fiz uma escolha. Vivi um ano inteiro em estado de alerta. Era engraçado, pois até mesmo fora do centro médico, em alguns relacionamentos pessoais ou situações do dia a dia, a cultura começava a ficar na minha mente. Isso era tóxico. Dá vontade de desistir? Claro! Mas, mentalidade de *longo prazo*. Sabia que precisava me esforçar muito para ter o mínimo de reconhecimento ali. Para isso, me dediquei exclusivamente quase que 100% das minhas horas vagas para estudar e focar nos nossos projetos. Durante a BEPE, tive mínimas interações sociais com outras pessoas. Nos finais de semana, a maior parte deles, passava dentro do centro médico em ligações ou com os times que estavam lá até altas horas trabalhando. Em inúmeras situações, ficava com o Tim até após as dez da noite discutindo ideias e melhorando os projetos. Era incrível como ele conseguia trabalhar por muito tempo e com muita qualidade. Isso me impressionava. Sempre sério, mas de certa forma feliz e manifestando total apoio e motivação para com a minha pessoa.

**** Em momentos como esse, de estresse emocional, é muito importante você se apegar a pessoas e atividades que fazem a sua mente ficar mais leve, mais feliz. Busquei me dedicar a novos hobbies, atividades físicas e a participar de seminários e aulas extras que aconteciam nas universidades e eu tinha acesso. Me ajudou muito. O que me ajudou muito também foi que muitos amigos do Brasil conseguiram ir a Boston me ver, familiares, namorada e meu irmão. Me ajudaram quando precisei lembrar quem eu realmente era e me trouxeram momentos de alegrias inesquecíveis. A Tania sempre me ajudou e motivou em todas as ligações, era sempre um alívio, mesmo que por mais boba a conversa que tínhamos. Graças a essas pessoas, eu consegui passar por tudo isso de uma forma mais tranquila e feliz, e sou eternamente grato a cada uma delas.* ***

Totalmente focado e com total clareza das minhas escolhas, terminei todos os cursos e aulas obrigatórias que deveria fazer. Criei o protótipo de um aplicativo de celular que executava algoritmos específicos para automatizar três testes de função física bem estabelecidos na área da reumatologia: o teste de caminhada de 20 metros, tempo de sentar e levantar da cadeira em 30 segundos e o tempo de

levantar, andar três metros, virar, voltar e sentar em uma cadeira. A ideia do nosso projeto era de entregar acessibilidade e otimizar processos dentro de um ECR: O Tim mencionou que gastava uma fortuna fazendo as pessoas irem ao centro médico para serem voluntárias dos grandes ensaios clínicos. Já usava ferramentas para coletar de forma remota dados de questionários subjetivos, mas não havia nada ainda para coletar a função física dessas pessoas de forma remota e objetiva. Nada escalável. Se conseguíssemos, seria algo inovador, pois, associada à tecnologia disponível no centro médico, poderíamos começar uma *era de ensaios clínicos 100% remotos*. Primeiro, propomos fazer um estudo de confiabilidade e validação de um aplicativo em comparação com os testes físicos tradicionais em grupos de indivíduos saudáveis e com osteoartrite de joelho dentro de um ambiente clínico controlado. Se a ideia desse certo dentro do ambiente clínico, iríamos migrar para os participantes testarem o aplicativo em ambientes domésticos. A ideia era boa e muito trabalho pela frente.

Com a influência do Tim, em menos de 2 meses criamos uma equipe com ampla experiência em pesquisa na área de osteoartrite, disseminação de conteúdo baseado em evidências e desenvolvimento de aplicativos móveis. Ao combinar especialistas na área de reumatologia, fisioterapia e engenharia da computação, criamos uma equipe sólida que estava perfeitamente posicionada para concluir com sucesso o projeto. Na equipe, fui colocado como co-investigador principal, e o Tim me deu total liberdade para liderar o projeto e o nosso time. Para coordenar o time de desenvolvimento da tecnologia, convidei o meu irmão e ele topou na hora.Quanto mais resultados eu mostrava, mais o Tim confiava em mim e me dava subsídios (créditos). Aqui, a experiência de aprendizado foi fantástica. Fizemos um estudo piloto, com algumas pessoas voluntárias da divisão, para calibrar os nossos algoritmos. Quanto mais testávamos o aplicativo, mais melhorávamos os nossos algoritmos. Com os resultados preliminares do piloto, criamos uma base para uma meta de longo prazo, que era a solicitação de bolsas do National Institute of Health (NIH) com fins de validar e amadurecer ainda mais o sistema, para escalar a tecnologia a nível global. Chegamos então em um momento em que nos sentimos preparados para o início do estudo.

Paralelamente ao estudo piloto, nos inscrevemos para um programa de prêmios financiado pelo NIH, o ***Tufts Ctsi Pilot Awards***. Eu sabia que essa premiação não significava nada para o Tim, mas ele compreendia que eu queria muito isso e deixou a gente concorrer com o nosso projeto. Estávamos competindo contra toda a divisão e outras divisões do centro médico por esse prêmio. Eram dezenas de times, de diversas universidades (e portes) e apenas oito iriam ganhar o prêmio. Lembro que foram noites sem dormir e que eu até sonhava com isso. O Tim me forneceu todo o material necessário e me deu duas semanas para estudar como se escrevia um projeto na formatação do NIH e para escrever a proposta. Aqui, aprendi como funcionava o mecanismo de bolsas do NIH, quais tipos de bolsas existiam e como a escrita deveria ser para cada uma delas. Estudei muito por livros e fiz diversos cursos online. Com a proposta escrita, levei para correção. O Tim corrigiu apenas a primeira folha, a de objetivos específicos. Ele falou que no resto confiava em mim e me ensinou uma dica de ouro que nunca vou esquecer: *“ - Foque 75% do seu tempo na escrita dessa única folha e*

condense ao máximo o seu conhecimento aqui com uma linguagem entendível e inesquecível. Eles compram a ideia do seu projeto aqui. O resto é apenas o desdobramento dessa folha." Submetemos sem nenhuma expectativa. Os meses se passaram e demos início ao projeto mesmo assim.

Aperfeiçoamos ainda mais nossos algoritmos nesse tempo e, felizmente, durante o início do estudo com pacientes, recebemos a incrível notícia de que fomos um dos seletos times **premiados**. Aqui, o jogo mudou da *água para o vinho*. Pessoas que **nunca** me olharam na cara agora me cumprimentavam e me chamavam para fazer colaborações em projetos. Pesquisadores líderes de times da divisão começaram a me convidar para *cafés* e discussões de projetos maiores que queriam introduzir tecnologias móveis ou desenvolver protótipos para solicitarem bolsas. O Tim fez questão de dar um evento exclusivo para celebrar nossa conquista e mostrar, para toda a Divisão, que a visão que ele compartilhava para o futuro era sobre a simbiose entre saúde e tecnologia. Nesse dia, lembro-me que ele me deu um aperto de mão e falou: *" - Olha aí! Eles estão diferentes né? Parabéns. Mérito seu".* Nesse dia, voltei muito feliz para casa. Dias depois, a Tania me orientou a enviar a notícia da premiação à FAPESP, para uma reportagem. Fui entrevistado e o nosso estudo acabou sendo divulgado em diversas mídias no Brasil, com alta repercussão em revistas e redes sociais.

Como obtivemos ótimos resultados preliminares com a tecnologia desenvolvida, submetemos um resumo ao Congresso do Colégio Americano de Reumatologia. O Congresso aceitou nosso resumo e apresentamos nossos resultados preliminares em novembro de 2019. Além disso, em 2019, fui ao OARSI e apresentei os dados da nossa revisão sistemática sobre crioterapia e osteoartrite de joelho em formato de pôster. Com o aporte financeiro do NIH para melhorar nosso projeto, investimos mais tempo para ajustar os algoritmos e iniciar o projeto em um novo nível de escala. Após a conclusão dos dados preliminares, atualizamos os algoritmos uma última vez para iniciar os testes de validação da tecnologia. Comecei os testes de validação da tecnologia um pouco antes de sair de Boston e esses testes ficaram congelados por alguns meses devido à pandemia do COVID-19. Atualmente, voltamos com todos os testes no centro médico e pretendemos finalizar esse projeto no começo de 2021. Semanalmente, fazemos chamadas de videoconferência e trabalhamos remotamente para otimizar nossos algoritmos. Hoje, estamos rodando a 72ª versão do aplicativo.

Durante minha estada no Centro Médico, tive a oportunidade de conhecer e colaborar com diversos pesquisadores locais e de outras universidades. Após a premiação, as portas se abriram. Trabalhei com o Dr. Raveendhara R. Bannuru, líder do desenvolvimento de diretrizes da OARSI e fui convidado para escrever um artigo de revisão sistemática onde mostramos a atual evidência sobre a eficácia do ultrassom terapêutico isolado para osteoartrite de joelho. Fui convidado também para um projeto relâmpago com uma médica formada pela Harvard Medical School, Shanthini Kasturi, especialista em pesquisas na área de Lúpus e criamos um projeto onde tínhamos como objetivo identificar o estado da arte das tecnologias móveis de saúde em Lúpus, nos Estados Unidos. Trabalhei com Matthew S. Harkey e Jeffrey B. Driban, especialistas em treinamento atlético, função física e análise de imagem de osteoartrite de joelho, para ser um coautor de um artigo onde buscamos

correlacionar características demográficas de indivíduos com osteoartrite de joelho com sua função física. Além disso, após várias reuniões com o Matthew e o Jeffrey, tivemos a ideia de desenvolver um aplicativo gratuito chamado OAFunction, que hoje está disponível ***globalmente*** nas maiores lojas online de aplicativos. Por meio do aplicativo, possibilitamos que profissionais da área de saúde ou pesquisadores monitorem o nível relativo de desempenho de um paciente com osteoartrite em testes objetivos de função física ao longo de um processo de reabilitação.

É importante ressaltar que, nesse período de BEPE, publiquei dois dos principais artigos científicos incluídos nesta tese. Com a ajuda da Tania, Tim e outros pesquisadores do centro médico, conseguimos solucionar as principais dúvidas dos revisores com êxito. É incrível como é possível solucionar quase todas as dúvidas de um revisor quando você tem por perto pessoas inteligentes e com vasta experiência nisso. Mentores experientes te ajudam a enxergar respostas que você jamais havia pensado. Sabem também quando você pode discutir uma resposta e quando deve aceitar o que foi sugerido. Publicamos primeiro a revisão sistemática em um jornal de excelente visibilidade na área da fisioterapia, a *Clinical Rehabilitation* e, em seguida, publicamos o ECR no maior jornal da área, o *Journal of Physiotherapy*. Foram duas conquistas enormes para o nosso laboratório no Brasil e todos ficaram muito contentes. É, a nossa aposta de 2015 rendeu ótimos frutos!

**** Um dos meus maiores aprendizados na BEPE foi o de como é possível estruturar times para fazer ciência com **qualidade e velocidade**. Tive uma experiência incrível ao lado da Dra. Shanthini, uma pessoa acelerada e genial. Junto com o Tim, ela me ensinou muito sobre como selecionar as pessoas ideais para compor um time científico, a delegar as responsabilidades de cada pessoa e a focar na publicação. Todos os autores tinham participação ativa no projeto. Escrevemos um manuscrito de revisão sistemática da literatura e de lojas online em três meses que foi publicado no maior periódico da área de Lúpus. Segundo ela, se não fosse publicado ali, não iríamos submeter em nenhum outro jornal. O foco dela era impressionante. Ela parecia ter certeza de que seria publicado no jornal, desde o primeiro dia. Foi o meu único artigo publicado com apenas correções de formatação e repleto de elogios dos editores-chefes. Hoje, esse artigo já foi matéria de diversos veículos de mídia internacionais e nos rendeu outras possibilidades de bolsas pelo NIH. Uma outra experiência fantástica que tive foi com o Dr. Raveendhara R. Bannuru; que me ensinou que não é preciso ter domínio de todos os mínimos detalhes de um projeto para você ter sucesso como pesquisador ou publicar com qualidade. O Ravi me ensinou a confiar na equipe selecionada e me mostrou que preciso entender muito sobre a ideia principal do projeto e que o resto, posso confiar e deixar com quem realmente domina o assunto. Isso mudou a minha visão sobre como fazer ciência. Essa cultura de times fortes criam projetos fortes, eu vou levar pra vida****

O retorno ao Brasil

"Share your knowledge. It's a way to achieve immortality."

Dalai Lama

Quando voltei do meu período de BEPE (novembro de 2019) para o Brasil, estava com uma mentalidade muito diferente. No mesmo mês que cheguei, comecei uma série de relacionamentos com pesquisadores de outros laboratórios dentro e fora da UFSCar para delineação de novos projetos envolvendo tecnologias móveis e saúde. Criamos times na área de reumatologia e saúde da mulher e me conectei com referências nacionais e internacionais de grande porte. Como em Boston havia aprendido na prática a montar times de excelência, procurei aplicar as mesmas táticas aqui. Ninguém faz ciência sozinho, da mesma forma que ninguém faz ciência de qualidade com times medíocres. Encontrei pares que compartilhavam da mesma visão e, juntos, começamos novos projetos.

****Ao meu ver, um time para ser bom necessita de alguns membros com características chave: dois executores da ideia principal, ou seja, pessoas que realmente coloquem a mão na massa e tenham total clareza do propósito do estudo; um suporte, ou seja, uma pessoa que entende o projeto e está disposta a ajudar em tudo o que os executores decidirem delegar; e um mentor, aquela pessoa que norteia o grupo quando as coisas parecem dar errado e que consegue fazer a diferença na hora da escrita e submissão do manuscrito a um periódico de qualidade. Com essa estrutura, é possível atingir resultados de forma rápida e com qualidade. ****

Durante o ano de 2020, executei vários projetos de revisão sistemática e começamos a criação de uma linha de pesquisa na àrea de saúde da mulher e reumatologia para a análise e desenvolvimento de tecnologias móveis no país. Fomos convidados pelo Brazilian Journal of Physical Therapy para escrever e publicar uma "masterclass" sobre osteoartrite de joelho e suas implicações para fisioterapia. Publicamos também o protocolo do nosso segundo ECR em um jornal bem conceituado, o BMJ Open. Demos continuidade ao nosso segundo ECR, porém, devido à pandemia do COVID-19, tivemos que parar o estudo. Atualmente, o estudo encontra-se parado e vamos retomá-lo se tudo der certo em 2021. Tive a oportunidade de ajudar vários alunos do Programa de Pós-Graduação que estavam começando ou no meio do caminho a se encontrarem em seus projetos ou a deixarem eles mais robustos. Tive a gratidão de escrever junto com o Rodrigo Py, o meu irmão de vida que a pós-graduação da UFSCar me deu, um editorial sobre a *Fisioterapia digital em tempos de pandemia*.

Durante o ano de 2020, mantive uma relação muito próxima com o Tim, em reuniões semanais e seminários da Divisão. Ele me convidou para ser líder de um projeto global da OARSI e da Pfizer, onde iríamos aplicar para uma premiação e, se ganhássemos, poderíamos desenvolver um aplicativo focado na disseminação das diretrizes OARSI a nível global. Era algo inédito para a OARSI. A ideia era traduzir as diretrizes OARSI para uma forma de consumo muito mais contemporânea, no caso, um aplicativo móvel. Essa ideia surgiu pois ainda existe uma grande barreira

para a disseminação das diretrizes e implementação do que se é produzido. Obviamente, convidei o meu irmão, o André, e ele estava no nosso time para mais essa jornada. O projeto envolveria os maiores nomes do mundo na área de reumatologia e a força tarefa iria se espalhar por mais de 50 países. Estudamos muito, foram mais de 60 modificações e revisões integrais nos protótipos que criei associadas a mais de 30 apresentações diferentes para acharmos o modelo ideal de execução.

Horas sem dormir e ligações semanais infinitas com diversos pesquisadores do mundo. Aplicamos para a premiação e em menos de 1 mês recebemos o resultado: ***Aprovados***!!! A sensação de ser aprovado nesse projeto global e ter a possibilidade de trabalhar lado a lado com pessoas que eu apenas lia nomes em grandes artigos científicos, foi *indescritível*. Um marco de conquista na minha carreira. Hoje, no final de 2020, já estamos com o produto pronto para lançamento global no mercado e com uma infraestrutura na nuvem capaz de suportar milhões de usuários. Isso é apenas o começo. A nossa ideia é criar um ecossistema completo para o manejo da osteoartrite e disseminar isso de forma global com **ZERO** custos para o consumidor final (pacientes). Além disso, a infraestrutura que criamos para disseminação das diretrizes é uma plataforma altamente escalável, ou seja, é possível comportar novas diretrizes de outras organizações e escalar a tecnologia para diversas áreas.

Acredito em um mundo com menos desigualdades no sistema de saúde. Principalmente no Brasil e em países subdesenvolvidos. Tenho clareza que a tecnologia com o suporte da ciência é a chave para alcançar isso. Durante esses seis longos anos tive oportunidades incríveis. Participei de projetos fantásticos e conheci pessoas extraordinárias. Levo no coração os ensinamentos de cada experiência. O nosso país, cada vez mais carece de qualidade em saúde. A nossa classe, a da fisioterapia, quando comparada com outros países desenvolvidos, carece de respeito. Porém, em um país onde a educação é negligenciada e as condições de ensino tanto para alunos quanto para professores estão cada vez piores, fica difícil formar pessoas que saibam ter um raciocínio clínico e científico mínimo para adotar boas práticas baseadas em evidências. Sei que fui formado em uma bolha dentro do país, a UFSCar. O programa de Pós-Graduação também, uma bolha ainda maior. A realidade em outras cidades e estados é muito discrepante. A possibilidade de quebrar as barreiras geográficas e econômicas do conhecimento concentrado no Brasil e de prestar assistência para milhares de pessoas me fascina. Tenho total convicção de que tecnologias móveis unidas a cientistas vão transformar a vida de profissionais de saúde que não tiveram oportunidades como eu tive. Vou fazer dessa convicção o meu propósito para os **próximos seis anos**. Quem sabe para a vida! Ao lado de pessoas fantásticas e times incríveis, vamos mudar a estrutura da classe no país e entregar saúde com mais qualidade e acessibilidade para a população brasileira. Conto com vocês!

Juntos, seguimos criando.
Somente juntos, crescemos!

Contribuição dos resultados da pesquisa para o avanço científico

Os resultados dos estudos incluídos nessa tese preenchem uma importante lacuna na literatura científica com relação ao uso da crioterapia em pacientes com osteoartrite de joelho. Com os nossos estudos, conseguimos mostrar que o uso da crioterapia não é eficaz para pacientes com osteoartrite de joelho para melhorar a dor e a função física. Esses resultados são de primordial importância para a atualização das informações disseminadas pelas diretrizes internacionais sobre o manejo da doença, uma vez que algumas organizações são a favor do uso da crioterapia para essa população e outras não. Além disso, os resultados e as limitações do nosso ensaio clínico abriram portas para a realização de outras pesquisas na área de osteoartrite e crioterapia, como verificar a eficácia a longo prazo do gelo.

Com o nosso artigo de "masterclass" buscamos guiar fisioterapeutas na tomada de decisão clínica, resumindo o que há de melhor na literatura em tratamento e em variáveis de interesse quando o tema é a osteoartrite de joelho. Reforçamos que existe uma necessidade de os profissionais de saúde abandonarem tratamentos de baixa qualidade e ineficazes e se auto educarem para as melhores práticas clínicas na reabilitação desses pacientes. Atualmente, o exercício físico, a educação do paciente e manejo do peso são os pilares para uma reabilitação de excelência. Além disso, de forma condensada, mostramos que a maior parte das terapias adjuntas, que são amplamente utilizadas para o manejo da doença, carecem de evidências científicas de qualdiade. Isso abre diversas portas para pesquisadores realizarem novos estudos, principalmente novos ensaios controlados randomizados.

Relevância social da tese

Por muitos anos, a crioterapia foi utilizada para reduzir a dor e melhorar a função de pacientes com osteoartrite sintomática de joelho. Porém, nós mostramos que a terapia não é mais eficaz que uma terapia simulada. Além disso, nessa tese, mostramos os tratamentos chave para pacientes com osteoartrite de joelho, variáveis de interesse para pesquisas em osteoartrite, e a falta de evidência científica para diversas terapias. Acreditamos que essas informações irão ajudar clínicos e pesquisadores do mundo inteiro a contribuir mais para com esses pacientes.

Descrição da tese para o público leigo

Nessa tese, buscamos identificar os benefícios do gelo quando aplicado em pacientes que tem osteoartrite ("artrose" ou "desgaste") de joelho. Queríamos ver se o gelo poderia melhorar sintomas como a dor e a função física dos pacientes. Descobrimos que o gelo não funciona para essa população. Além disso, condensamos todo o nosso conhecimento sobre osteoartrite de joelho para ajudar profissionais da área de saúde, em específico fisioterapeutas, a melhor tratarem os seus pacientes.

Link do currículo Lattes e ORCID;

- Endereço para acessar Lattes: http://lattes.cnpq.br/8247198058882947
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AGRADECIMENTOS ESPECIAIS

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ARTIGOS PUBLICADOS E INCLUÍDOS PARA DEFESA DA TESE

ARTIGO I

Título: *The effects of cryotherapy on pain and function in individuals with knee osteoarthritis: a systematic review of randomized controlled trials*
Autores: Lucas Ogura Dantas, Roberta de Fátima Carreira Moreira, Flavia Maintinguer Norde, Paula Regina Mendes Silva Serrão, Francisco Alburquerque-Sendín, Tania Fatima Salvini
Objetivo: Sintetizar evidências sobre a eficácia da crioterapia no controle da dor e melhora da função física em indivíduos com osteoartrite do joelho.
Principais achados: Embora algumas diretrizes clínicas recomendem o uso de crioterapia para gerenciar sintomas de osteoartrite do joelho, nossa revisão mostrou que ainda não há evidências suficientes para apoiar o seu uso para esta população com relação ao manejo da dor e função física.
Publicação: *Clinical Rehabilitation* (Fator de impacto: 2.59). **DOI:** 10.1177/0269215519840406

ARTIGO II

Título: *Short-term cryotherapy did not substantially reduce pain and had unclear effects on physical function and quality of life in people with knee osteoarthritis: a randomised trial*
Autores: Lucas Ogura Dantas, Carolina Carreira Breda, Paula Regina Mendes da Silva Serrao, Francisco Aburquerque-Sendín, Ana Elisa Serafim Jorge, Jonathan Emanuel Cunha, Germanna Medeiros Barbosa, Joao Luiz Quagliotti Durigan, Tania de Fatima Salvini
Objetivo: Determinar os efeitos da crioterapia de curto prazo em relação à dor e função física em pessoas com osteoartrite de joelho.
Hipótese: A crioterapia aliviaria a dor e melhoraria a função e a qualidade de vida quando comparada com uma intervenção simulada.
Principais achados: A crioterapia de curto prazo não foi superior a uma intervenção simulada em termos de alívio da dor ou melhora da função e qualidade de vida em pessoas com osteoartrite de joelho.
Publicação: *Journal of Physiotherapy* (Fator de impacto: 5.44). **DOI:** 10.1016/j.jphys.2019.08.004

ARTIGO III

Título: *Cryotherapy associated with tailored land-based exercises for knee osteoarthritis: a protocol for a double- blind sham-controlled randomised trial*
Autores: Lucas Ogura Dantas, Ana Elisa Serafim Jorge, Paula Regina Mendes da Silva Serrão, Francisco Aburquerque-Sendín, Tania de Fatima Salvini
Objetivo: Desenhar um ensaio randomizado controlado para verificar os efeitos complementares da crioterapia, associado a um protocolo de exercícios personalizados em relação à dor, função e qualidade de vida em indivíduos com osteoartrite de joelho.
Hipótese: A crioterapia, combinada com o protocolo de exercícios, irá alcançar melhores resultados com relação aos desfechos clínicos em pacientes com osteoartrite de joelho quando comparados com os outros grupos.
Publicação: *BMJ Open* (Fator de impacto: 2.49). **DOI:** 10.1136/bmjopen-2019-035610

ARTIGO IV

Título: *Knee osteoarthritis: key treatments and implications for physical therapy*
Autores: Lucas Ogura Dantas, Tania de Fátima Salvini, Timothy E. McAlindon
Objetivo: Fornecer informações atualizadas para fisioterapeutas e mostrar que exercícios, manutenção de peso e a educação do paciente são vitais para o tratamento ideal da osteoartrite de joelho. Também pretendemos descrever as principais medidas de interesse usadas em estudos com osteoartrite de joelho para aumentar a consciência sobre ferramentas úteis para coleta de dados para clínicos e pesquisadores.
Principais achados: É necessário que profissionais de saúde abandonem tratamentos de baixa qualidade, ineficazes e eduquem a si próprios e aos seus pacientes sobre as melhores práticas baseadas em evidências para osteoartrite de joelho.
Publicação: *Brazilian Journal of Physical Therapy* (Fator de impacto: 2.1). **DOI:** 10.1016/j.bjpt.2020.08.004

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The effects of cryotherapy on pain and function in individuals with knee osteoarthritis: a systematic review of randomized controlled trials

Lucas Ogura Dantas[1], Roberta de Fátima Carreira Moreira[1], Flavia Maintinguer Norde[1], Paula Regina Mendes Silva Serrao[1], Francisco Alburquerque-Sendín[2] and Tania Fatima Salvini[1]

Abstract

Objective: To investigate the effectiveness of cryotherapy on pain and physical function in knee osteoarthritis.

Data sources: An electronic search was performed up to February 2019 on PubMed/MEDLINE, EMBASE, CINAHL, Lilacs, Cochrane, Web of Science, Ibecs, and Scielo databases with keywords knee osteoarthritis and cryotherapy.

Methods: Two authors independently performed the study selection. All languages and publication dates were considered. The PEDro scale was used to assess the methodological quality of the studies, and the body of evidence was analyzed and synthesized using the Grading of Recommendations, Assessment, Development, and Evaluation approach. The clinical relevance of the included studies was evaluated using the criteria proposed in the Cochrane Handbook for Systematic Reviews of Interventions.

Results: Of the five studies, 202 subjects were included. All studies included participants with established knee osteoarthritis. The mean PEDro score was 4.20/10, and meta-analysis was not possible due to heterogeneity among the studies. The mean clinical relevance was 3/5. Only two studies were considered for analysis based on the GRADE approach, and low level of evidence was synthesized regarding the effectiveness of cryotherapy for pain management, knee stiffness, knee range of motion, and physical function. Application techniques, frequency, and duration did not affect outcomes.

Conclusions: There were insufficient primary studies to draw any conclusions about the effectiveness of cryotherapy on pain and physical function on individuals with knee osteoarthritis.

Keywords
Physiotherapy, osteoarthritis, cryotherapy, chronic pain

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Previous systematic reviews regarding cryotherapy effectiveness on knee osteoarthritis are outdated and show controversial results about its use for pain management.[1–3] In addition, although some guidelines recommend cryotherapy as an intervention used in clinical practice,[4,5] others found insufficient evidence to support its application for the non-pharmacological treatment of knee osteoarthritis.[6–9] Thus, due to the controversial evidence in the available literature, there was a need to analyze and synthesize evidence to provide updated clinical and scientific evidence regarding the effectiveness of cryotherapy on pain and function of individuals with knee osteoarthritis.

Compiling evidence about cryotherapy use may help to generate strategies for targeted knee osteoarthritis rehabilitation, help pain management, and thereby improve physical function and quality of life of these patients. The main objective of this systematic review was to synthesize evidence regarding the effectiveness of cryotherapy for pain control and physical function improvement in individuals with knee osteoarthritis. A secondary aim was to assess whether cryotherapy could improve the quality of life of these individuals.

Methods

This review followed recommendations proposed by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[10] and Cochrane Collaboration[11] for systematic reviews to answer the following research question: Is cryotherapy effective on pain control and functional improvement in knee osteoarthritis patients? Moreover, the protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO), registration code: CRD42017048993.

Inclusion criteria

Randomized controlled trials and quasi-randomized controlled trials that compared different modalities of cryotherapy for treatment of knee osteoarthritis patients aiming at improving pain, function, and quality of life were included. These studies were eligible for inclusion as long as they compared individuals, males and/or females, with an established diagnosis of unilateral or bilateral knee osteoarthritis. Articles were excluded if the authors studied individuals with other comorbid knee conditions or after knee surgery.

The types of cryotherapy modalities included were ice packs, ice cubes, cold compresses, cold sprays, cold tubs, ice massage, and cold chambers. The experimental group could have been compared to no intervention, placebo or sham treatment, other physical therapy procedures, or even with surgical intervention or injection. The intervention could be the only treatment or an add-on treatment. If a combination of therapies was applied, the main intervention and the co-interventions must have been clearly defined to assign the study to a specific comparison group. The follow-up time was defined as immediate posttreatment (less than one day), short-term follow-up (one day to three months), midterm follow-up (between three months and one year), and long-term follow-up (greater than or equal to one year).

Search strategy

The search strategy is shown in Figure 1 of the Supplementary file. Systematic searches were conducted for relevant studies on PubMed/MEDLINE, EMBASE, CINAHL, Lilacs, Cochrane, Web of Science, Ibecs, and Scielo from the earliest year available to February 2019. No restriction on language or publication year was applied. To maximize the search results, controlled vocabulary was searched in Medical Subject Headings (MeSH) database. The strategy adopted the following (MeSH terms) combinations: knee osteoarthritis and cryotherapy. Electronic search results were exported to State of the Art through Systematic Review (START), a reference manager software. In addition, a manual search was performed through the screening of reference lists from the included primary studies and systematic reviews to identify possible relevant studies not retrieved during the electronic search.

Selection process

Considering these inclusion criteria, all identified studies were initially assessed for eligibility by title to exclude those that were clearly not related to the

review's purpose. Then, abstracts of the selected titles were analyzed to identify those that matched the inclusion criteria regarding study design, participants, interventions, and outcomes of interest. The full texts of the potentially relevant articles were retrieved for final assessment, and their reference lists were checked independently by two reviewers to identify potentially relevant studies not found in the electronic search. Two independent reviewers (L.O.D. and F.M.N.) performed the selection process, and disagreements were solved through consensus by a third reviewer (R.F.C.M.).

Data collection and analysis

Data collection was performed through a standardized form adapted from Cochrane Collaboration[11] to register data regarding participants, comparison groups, settings, interventions, care providers, trial methods, types of outcome measures, follow-up, failure to follow-up, and results. Treatment effect was analyzed through effect size calculation. The effect size of each intervention was calculated considering a 95% confidence interval for continuous outcomes in each comparison group and considering the values before and after intervention when possible. Treatment effects were further classified as small (<0.20), moderate (between 0.21 and 0.79) and large (>0.80), according to Cohen's criteria.[12]

Methodological quality assessment

The methodological quality of the included studies was assessed through the PEDro scale (http://www.pedro.fhs.usyd.edu.au), which is a critical and reliable appraisal tool for experimental studies in physical therapy based on the Delphi list.[13,14] Articles not indexed in PEDro database had their methodological quality assessed by two independent reviewers (L.O.D. and F.M.N.), and rating disagreements were resolved through consensus by a third reviewer (R.F.C.M.).

The criteria proposed in the Cochrane Handbook for Systematic Reviews of Interventions, recommended by Higgins and Green,[11] were used to evaluate the clinical relevance of the included studies.

Evidence synthesis

The body of evidence was analyzed and synthesized using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach that analyzes the following domains: trial design limitations due to risk of bias, inconsistency of results, indirectness of assessment of the quality of a body of evidence, imprecision of results, and publication bias.[15] The strength of evidence was presented on a rating system with four categories: high, moderate, low, or very low evidence, according to the GRADE system.[15] Meta-analysis was not possible to perform due to several sources of heterogeneity among primary studies.

Results

A total of 338 records were initially identified. After selection of titles and abstracts, 22 were retrieved for full-text analysis. Five studies,[16–20] with 202 subjects in total, matched our inclusion criteria and were included for the qualitative synthesis. A flow chart of the selection process is shown in Figure 1.

Characteristics of the five studies are presented in Table 1. The total number of participants ranged from 16 to 68 per study. There were discrepancies in the applied protocols in terms of the number of sessions, the frequency of application, and the cryotherapy modalities used. The mean frequency of sessions was 10, with an average duration of 20 minutes of cryotherapy application per session.

All studies included participants with established knee osteoarthritis diagnoses, one with Kellgren-Lawrence scale grade I only[19] and other with Kellgren-Lawrence scale grade II or greater.[18] The remaining studies, despite studying knee osteoarthritis diagnoses, did not present the grade of the disease.[16,17,20] Only one study evaluated participants with only patellofemoral knee osteoarthritis.[20] Only two studies presented data regarding quality of life.[18,19]

In general, the presence of signs and symptoms of knee osteoarthritis was required for subject inclusion, and one study[16] excluded patients that had been symptomatic less than six months. All five

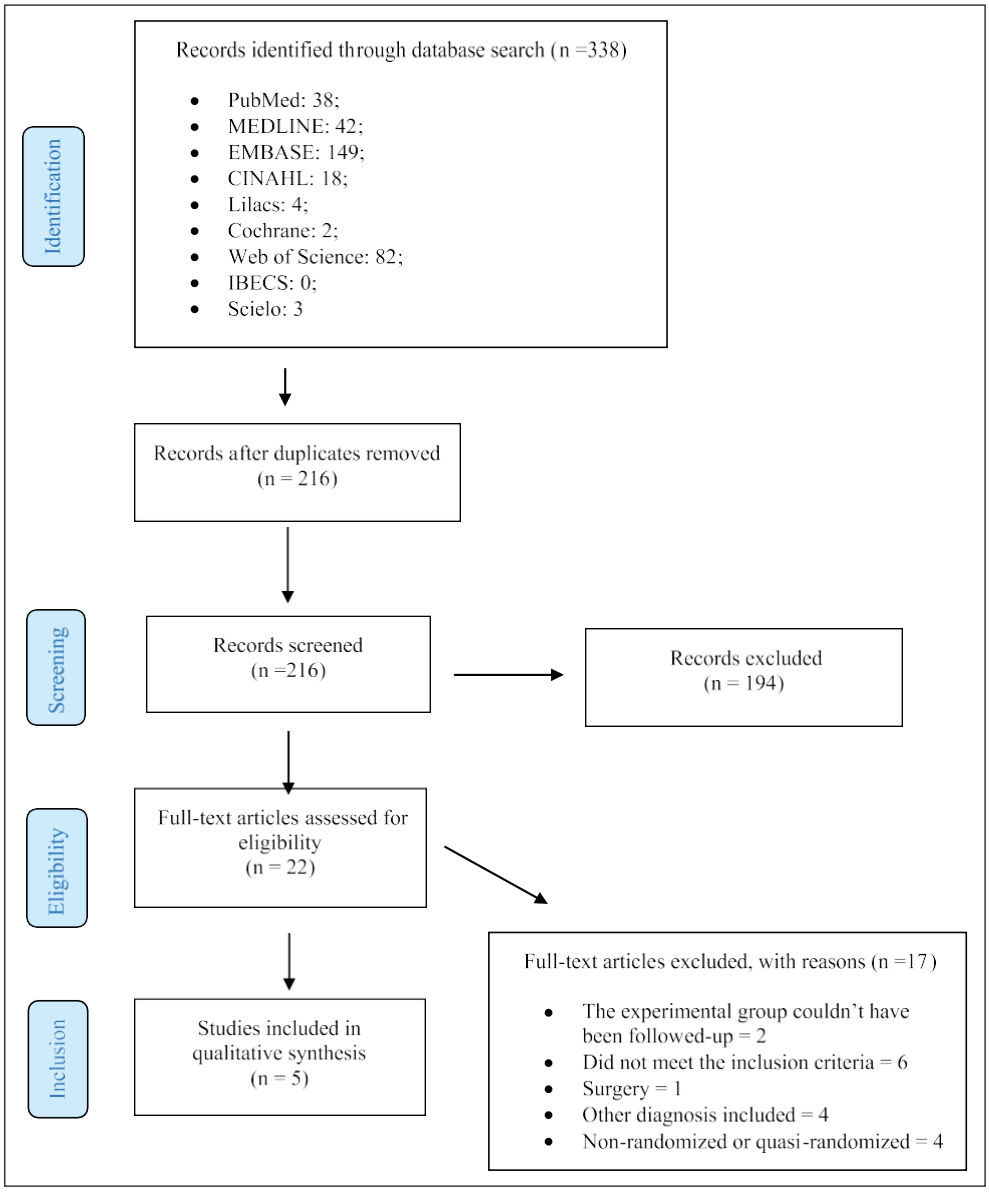

Figure 1. Preferred reporting items for systematic reviews and meta-analyses 2009 flow diagram for literature search results.

studies clearly reported their exclusion criteria. The most frequent exclusion criteria adopted were participants who underwent knee surgery, presented skin or cognitive/mental diseases, or neurological, cardiac, vascular, andsensoryproblems. Participants who had a history of an adverse reaction to cold application were also excluded. Furthermore, one study[18] excluded participants who received either hyaluronic acid or corticosteroid injections to either knee within the past six months.

The methodological quality assessment and clinical relevance of the primary studies included are

Table 1. Characteristics of the included studies.

Study setting and design	Intervention group	Control group	KL grade of knee osteoarthritis	Follow-up and number of sessions	Intervention type	Intervention frequency and duration	Intervention type	Control frequency and duration
Clarke *et al.*[17] Oxford, United Kingdom RCT	*n* = 15: 4M, 11F Mean age (years)*: ± 64.0 y BMI (kg/m^2): 39.79 ± 2.11	*n* = 13: 4M, 9F Mean age: ± 63 y BMI: 39.80 ± 1.99	ND	3 weeks and 3 months 9	Ice packs (Ice cubes)	3 times per week for three weeks ND	Untuned short-wave diathermy	3 times per week for three weeks ND
Yurtkuran and Kocagil[16] Bursa, Turkey RCT	*n* = 25: 0M, 25F Mean age (years): ND BMI (kg/m^2): ND	*n* = 25: 3M, 22F Mean age: ND BMI: ND	ND	ND 10	Ice cubes on a wood stick	5 times per week for 2 weeks 20 minutes	Electrodes with no electrical current	5 times per week for 2 weeks 20 minutes
Silva *et al.*[19] Sao Paulo, Brazil RCT	*n* = 9: ND, ND Mean age (years): ND BMI (kg/m^2): ND	*n* = 7: ND, ND Mean age: ND BMI: ND	Grade 1	ND 10	Ice packs (crushed ice) + Lower limb exercises	2 times per week for 5 weeks 20 minutes (cryotherapy) + ND	Lower limb exercises	2 times per week for 5 weeks ND
Denegar *et al.*[18] Connecticut, United States RCT	*n* = 34: ND, ND Mean age (years): ND BMI (kg/m^2): ND	*n*= 34: ND, ND Mean age: ND BMI: ND	Grades 2, 3, and 4	ND 10	Cold water	2 times per day for 5 days 20 minutes	No treatment	2 times per day for 5 days 20 minutes
Basu *et al.*[20] Pune, India RCT	*n* = 20: 6M, 14F Mean age (years): 57.45 ± 7.87 y BMI (kg/m^2): ND	*n* = 20: 12M, 8F Mean age: 60.40 ± 5.88 y BMI: ND	ND	ND 15	Ice cubes + Analgesic	1 time per day for 15 days 20–25 minutes	Taping + Analgesic	1 time per day for 15 days 20–25 minutes

(Continued)

Table 1. (Continued)

Study	Relevant outcome measures for this systematic review	Within IG ES	Within CG ES	Between groups ES	IG mean score ± SD at 95% CI	CG mean score SD ± at 95%CI
Clarke *et al.*[17]	Pain: 0–17 Point Scale	(+) ES: NPC	(=) ES: NPC	ES: NPC	9.9–4.8[a]; $P < 0.05$	9.5–7.5; $P < 0.05$
	Stiffness: 0–3 Scale	(+) ES: NPC	(=) ES: NPC	ES: NPC	1.80 ± 0.84[b]; $P < 0.05$	ND; $P > 0.05$
	Knee ROM (degrees):	(=) ES: NPC	(=) ES: NPC	ES: NPC	1.91 ± 8.70[b]; $P > 0.05$	ND; $P > 0.05$
	goniometer	(=) ES: NPC	(=) ES: NPC	ES: NPC	0.96 ± 2.14[b]; $P > 0.05$	ND; $P > 0.05$
	Walking Time: m/s					
Yurtkuran and Kocagil[16]	Pain: 5 Levels Scale	(+) ES: 0.59	(=) ES: 0.32	ES: 0.17	0.7 + 0.6–0.4 + 0.4[c]; $P < 0.05$	0.7 + 0.8–0.5 + 0.4[c]; $P > 0.05$
	Stiffness: Verbally	(+) ES: 0.56	(=) ES: 0.14	ES: 0.49	7.2 + 5.4–4.3 + 4.9[c]; $P < 0.05$	7.8 + 4.2–7.2 + 4.1[c]; $P > 0.05$
	Knee ROM (degrees):	(=) ES: 0.11	(=) ES: 1.15	ES: 1.29	127.20 + 7.50–128.0 + 6.90[c]; $P > 0.05$	128.10 + 7.2–119.20 + 8.30[c]; $P > 0.05$
	goniometer	(+) ES: 1.44	(=) ES: 1.49	ES: 0.66	28.4 + 6.70–19.40 + 5.80[c]; $P < 0.001$	34.70 + 3.80–29.10 + 3.70[c]; $P > 0.05$
	Walking Time: m/s					
Silva *et al.*[19]	Pain: Borg Scale	(+) ES: 1.36	(=) ES: 0.24	ES: 1.02	7.43 ± 2.15–4.0 ± 2.83; $P P < 0.05$	5.56 ± 2.46–6.22 ± 3.03; $P > 0.05$
	QoL: Lequesne	(+) ES: 1.65	(+) ES: 1.16	ES: 0.45	15.36 ± 3.42–9.50 ± 3.67; $P < 0.05$	15.12 ± 3.65–10.89 ± 3.74; $P < 0.05$
	Algofunctional Questionnaire	(+) ES: 0.50	(+) ES: 0.78	ES: 0.12	105.14 ± 17.38–113.29 ± 14.82; $P < 0.05$	116.44 ± 12.28–126.33 ± 13.11; $P < 0.05$
	Knee ROM (degrees): goniometer					
Denegar *et al.*[18]	Pain: VAS	(+) ES: NPC	(=) ES: NPC	ES: NPC	0.15 ± 0.25[d]; $P < 0.05$	0.04 ± 0.50[d]; $P > 0.05$
	KOOS Pain	(+) ES: NPC	(=) ES: NPC	ES: NPC	5.6 ± 15.4[b]; $P < 0.05$	1.1 ± 16.6[b]; $P > 0.05$
	KOOS Symptoms	(+) ES: NPC	(=) ES: NPC	ES: NPC	6.1 ± 15.2[b]; $P < 0.05$	0.5 ± 14.0[b]; $P > 0.05$
	KOOS FDL	(+) ES: NPC	(=) ES: NPC	ES: NPC	6.1 ± 16.1[b]; $P < 0.05$	0.11 ± 5.5[b]; $P > 0.05$
	KOOS QoL	(+) ES: NPC	(=) ES: NPC	ES: NPC	8.0 ± 14.9[b]; $P < 0.05$	3.3 ± 12.6[b]; $P > 0.05$
Basu *et al.*[20]	Pain: VAS	(+) ES: 1.36	(+) ES: 2.54	ES: 0.83	6.25 ± 1.62–3.95 ± 1.76; $P < 0.001$	6.0 ± 1.65–2.40 ± 1.14; $P < 0.001$
	WOMAC Pain	(+) ES: 1.35	(+) ES: 2.25	ES: 0.62	12.0 ± 3.57–7.30 ± 3.39; $P < 0.001$	10.40 ± 3.69–3.70 ± 2.03; $P < 0.001$
	WOMAC Stiffness	(+) ES: 1.09	(+) ES: 1.87	ES: 0.43	2.85 ± 1.46–1.30 ± 1.38; $P < 0.001$	2.35 ± 1.49–0.25 ± 0.55; $P < 0.001$
	WOMAC Function	(+) ES: 1.33	(+) ES: 2.11	ES: 0.82	38.80 ± 10.01–26.20 ± 8.92; $P < 0.001$	33.85 ± 12.32–13.40 ± 6.02; $P < 0.001$
	Knee ROM (degrees): goniometer	(+) ES: 1.62	(+) ES: 1.54	ES: 0.07	127.30 ± 3.51–131.80 ± 1.74; $P < 0.001$	128.05 ± 3.75–132.75 ± 2.15; $P < 0.001$

RCT: randomized controlled trial; n: number of individuals; ND: not described; M: male; F: female; y: years; BMI: body mass index; KL: Kellgren and Lawrence; IG: intervention group; CG: control group; VAS: visual analog scale; KOOS: knee injury and osteoarthritis outcome score; FDL: function in daily living; QoL: quality of life; WOMAC: Western Ontario and McMaster Universities osteoarthritis index; ROM: range of motion; NPC: not possible to calculate; ES: effect size; CI: confidence interval; +: positive effect of the treatment; =: treatment with no effect.

[a]Mean group change score.

[b]Mean group improvement ± SD.

[c]Insufficient information to determine what was calculated. The author presented only those values.

[d]Percent change of improvement (group average ± SD, the values range from 0 to 1, where the number one equals to 100% of improvement).

*This study reported ages in this less specific format.

shown in Table 2. Among the five included studies, two[19,20] were not indexed in the PEDro database. The methodological quality of these studies was evaluated by L.O.D. and F.M.N. through consensus. The mean PEDro score was 4.20 (range 4–6), which indicates low methodological quality of the available studies. None of the studies achieved themaximal score of five points on the clinical relevance criteria and presented a mean score of three.

Only two studies[16,17] were considered for analysis based on the GRADE approach. The quality of the evidence for each intervention analyzed according to the GRADE system is presented in Table 3. The evidence synthesis showed a low-quality level

Table 2. Methodological quality evaluated according to the PEDro scale and clinical relevance criteria.

Study	Risk of bias (PEDro Scale)												Clinical relevance					
	1	2	3	4	5	6	7	8	9	10	11	Total score	12	13	14	15	16	Total score
Clarke[17]	–	+	–	+	–	–	+	+	–	+	+	6/10	–	–	+	–	+	2/5
Yurtkuran and Kocgil[16]	+	+	–	–	–	–	+	+	–	+	–	4/10	–	+	+	+	+	3/5
Silva *et al.*[19]	+	+	–	–	–	–	+	–	–	+	+	4/10	–	–	+	+	+	3/5
Denegar *et al.*[18]	+	+	–	–	–	–	–	+	–	+	+	4/10	+	–	+	–	+	4/5
Basu *et al.*[20]	+	+	–	–	–	–	–	+	–	+	+	4/10	–	–	+	+	+	3/5
Frequency	4/5	5/5	0/5	1/5	0/5	0/5	3/5	4/5	0/5	5/5	4/5	–	1/5	1/5	5/5	3/5	5/5	

1: eligibility criteria (This item is not counted toward the PEDro score); 2: random allocation; 3: concealed allocation; 4: baseline comparability; 5: blind subjects; 6: blind therapists; 7: blind assessors; 8: adequate follow-up; 9: intention-to-treat analysis; 10: between-group comparisons; 11: point estimates and variability; 12: are the patients described in detail so that you can decide whether they are comparable to those that you see in your practice?; 13: Are the interventions and treatment settings described well enough so that you can provide the same for your patients?; 14: were all clinically relevant outcomes measured and reported?; 15: is the size of the effect clinically important?; 16: are the likely treatment benefits worth the potential harms?

Table 3. Quality of evidence according to the grade approach for studies comparing cryotherapy with control groups.

Grade analyzed trials	Clarke[17] and Yurtkuran[16]	Inconsistency	Indirectness	Imprecision	Cryotherapy		Control			
Outcome	Limitations				n	ES[a]	n	ES[a]	Magnitude of effect	Grade quality
Cryotherapy X Control groups										
Pain	Serious 1	No serious inconsistency	No serious inconsistency	Serious 2	15	0.59	13	0.32	Moderate	Low
Stiffness	Serious 1	No serious inconsistency	No serious inconsistency	Serious 2	25	0.56	25	0.14	Moderate	Low
Knee ROM	Serious 1	No serious inconsistency	No serious inconsistency	Serious 2		0.11		1.15	Low	Low
Physical performance	Serious 1	Serious 3	No serious inconsistency	Serious 2		1.44		1.49	High	Low

ROM: range of motion; n: number of individuals; ES: effect size.
Serious 1—Low methodological quality for Yurtkuran and Kocagil.[16]
Serious 2—Only two studies evaluated a total of 78 participants.
Serious 3—Only Yurtkuran and Kocagil[16] presented positive results with high effect size for cryotherapy group.
[a]The values of effect size presented are only for Yurtkuran study.

of evidence that cryotherapy applied through ice cubes and ice massage are more effective than control groups using untuned short-wave diathermy and electrodes with no electrical current, respectively, for pain, stiffness, knee range of motion, andphysical performance improvements.

The included studies did not report how the sample size was calculated. Only one study provided the effect size,[20] while two others provided enough data to calculate it.[16,19] The remaining two studies[17,18] did not provide enough information to calculate effect size and the authors, when contacted, did not reply.

Discussion

The results of this systematic review were based on five randomized controlled trials and showed that cryotherapy modalities presented a low-quality level of evidence for pain control and functional outcomes among knee osteoarthritis individuals. The reduced number of studies and the several sources of heterogeneity among them were the main factors which hindered the evidence synthesis. Quality of life improvements[17,19] become questionable because of several methodological shortcomings of the studies.

The effect sizes presented in the results showed high within-group values when cryotherapy was combined with other types of therapy, for instance, lower limb exercises[19] or analgesics.[20] However, when it was used alone,[16] the effect sizes were in general moderate for both the within-group and between-group comparisons. This could have happened due to a small sample sizes, implicating in a possible type II error.

For research, these results are clear and indicate that there is still a lack of quality in evidence regarding the use of cryotherapy in individuals with knee osteoarthritis. None of the included studies reported how the sample size was calculated and neither presented the smallest detectable difference (SDD) and the minimal clinically important difference (MCID) for the analyzed outcomes. Providing statistical significance (*P*-values) does not offer an indication of how important the results of the studies are.[21] In some cases,[16,17,19] statistical significance could not have been attained due to small sample sizes and high inter-subject variability, potentially hiding some clinically relevant results which could contribute to the clinical practice.

Main limitations and scientific recommendations

Strength of evidence was mostly downgraded due to the poor methodological quality of the included studies, the small number of partici- pants, and the lack of basic quantitative informa- tion regarding the main outcome. Although some of the included studies used valid and trustable pain scales,[18–20] knee osteoarthritis question- naires, and physical function tests in the thera- peutic context,[22,23] some[17,18] did not present the mean group scores with their respective standard deviations. Thus, it was not possible to clearly compare the groups and to calculate the effect sizes of the interventions.

Despite using a general search strategy aiming at recovering the maximum number of studies as possible, a restricted number was identified. This could be considered a limitation of the present study. However, this does not mean that the topic is not relevant. On the contrary, it demonstrates the importance of clinical research on this field.

Future clinical trials are necessary to provide scientific evidence for the effects of cryotherapy in knee osteoarthritis, since the criteria of internal validity of the previous studies were compromised. Investigators should consider improving the validity following adequate procedures to report better randomized controlled trials, for instance, the Consolidated Standards of Reporting Trials (CONSORT),[24] Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)[25] statements, or using the Template for Intervention, Description, and Replication (TIDieR)[26] checklist and guide. This would further improve methodological quality and internal validity by implementing concealed allocation, intention-to-treat analysis, improving the inclusion criteria, and including better participant and intervention descriptions, thereby contributing to evidence synthesis and creating protocols that

would allow better replication for clinicians to treat people with knee osteoarthritis.

Clinical messages

- Although some clinical guidelines recommend the use of cryotherapy to manage knee osteoarthritis symptoms, there is insufficient evidence regarding its use for this population.

Author Contributions

All authors contributed to the conception and design of this study. L.O.D. and F.M.N. contributed to the analyses of the data. All authors contributed to the interpretation of the data. Article drafts were written by L.O.D. and critically revised by all authors. The final version of the article was approved by all authors. L.O.D. takes responsibility for the integrity of the work as a whole (oguralod@outlook.com).

Declaration of Conflicting Interests

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Supplemental material

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Research

Short-term cryotherapy did not substantially reduce pain and had unclear effects on physical function and quality of life in people with knee osteoarthritis: a randomised trial

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KEYWORDS

Osteoarthritis
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Randomised trial
Knee
Physical therapy

ABSTRACT

Objective: Does short-term cryotherapy improve pain, function and quality of life in people with knee osteoarthritis (OA)? Design: Randomised controlled trial with concealed allocation, blinded assessment of some outcomes, and intention-to-treat analysis. Participants: People living in the community with knee OA. Interventions: The experimental group received cryotherapy, delivered as packs of crushed ice applied to the knee with mild compression. The control group received the same regimen but with sham packs filled with sand. The interventions were applied once a day for 4 consecutive days. Outcome measures: Participants were assessed at baseline and on the day after the 4-day intervention period. The primary outcome was pain intensity according to a visual analogue scale. Secondary outcomes were baseline to post-intervention changes according to the Western Ontario and McMaster Universities Osteoarthritis, Knee injury and Osteoarthritis Outcome; Timed Up and Go test; and 30-Second Chair to Stand test. Results: Sixty participants were randomised into the experimental group (n = 30) or the control group (n = 30). Twenty-nine participants from each group completed the trial. The mean between-group difference in change in pain severity was 20.8 cm (95% CI 21.6 to 0.1), where negative values favour the experimental group. This result did not reach the nominated smallest worthwhile effect of 1.75 cm. The secondary outcomes had less-precise estimates, with confidence intervals that spanned worthwhile, trivial and mildly harmful effects. Conclusion: Short-term cryotherapy was not superior to a sham intervention in terms of relieving pain or improving function and quality of life in people with knee OA. Although cryotherapy is considered to be a widely used resource in clinical practice, this study does not suggest that it has an important short-term effect, when compared with a sham control, as a non-pharmacological treatment for people with knee osteoarthritis. Registration: NCT02725047. [Dantas LO, Breda CC, da Silva Serrao PRM, Aburquerque-Sendín F, Serafim Jorge AE, Cunha JE, Barbosa GM, Durigan JLQ, Salvini TdF (2019) Short-term cryotherapy did not substantially reduce pain and had unclear effects on physical function and quality of life in people with knee osteoarthritis: a randomised trial. *Journal of Physiotherapy* 65:215–221]

Introduction

Knee osteoarthritis (OA) is a prevalent and costly chronic musculoskeletal condition associated with pain and disability.[1] Clinical guidelines recommend a combination of non-pharmacological treatments[2] – including patient education, exercise and some other physiotherapy interventions – together with pharmacological treatments[3] to improve pain and symptoms.

Cryotherapy is a non-pharmacological intervention that is widely used in various rheumatic joint diseases[4,5] for its effects on pain, inflammation and oedema.[6] It is considered to be relatively safe, inexpensive, and easy to administer for healthcare professionals and patients. Moreover, it can be prescribed in isolation or in conjunction with other therapies,[5] and seems to be well accepted by people with knee OA.[7,8]

Some international knee OA guidelines recommend cryotherapy as a treatment option,[9,10] but others have found insufficient evidence to recommend it.[11–13] Recent and relevant systematic reviews conclude that further trials are needed to evaluate the isolated effects of cryotherapy on pain, function and quality of life in people with knee OA.[14–16] The most recent of these reviews[16] identified five randomised trials, almost all of which scored only 4 out of 10 on the

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PEDro scale. When the authors applied the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to the evidence, they concluded that the review identified only low-level evidence regarding cryotherapy for pain management, knee stiffness, knee range of motion and physical function.[16]

Some consistent methodological limitations among the existing studies were: unconcealed allocation, lack of blinding, poor baseline comparability of the groups, lack of confirmation of OA grade of the participants, and analysis not according to the principle of intention to treat.[16] Future studies should therefore seek to achieve these methodological criteria, where possible. In this way, the generated information is likely to contribute to strategies for targeted knee OA rehabilitation, and improve pain management and overall quality of life of people with knee OA.[5,14,16]

The aim of this study was to determine the effects of short-term cryotherapy in people with knee OA. We hypothesised that cryotherapy would relieve pain and improve function and quality of life when compared with a sham intervention.

Therefore, the study question for this randomised trial was:

Does short-term cryotherapy improve pain, function and quality of life in people with knee osteoarthritis?

Methods

Design

This study was a randomised sham-controlled trial carried out over a period of 6 consecutive days. A baseline assessment was per- formed on the first day, followed by 4 days of intervention and a post-intervention assessment on the final (sixth) day. Each participant was assessed in the same period of the day (morning or afternoon) in a physiotherapy research laboratory by the same assessor. To reduce bias, both the therapist responsible for applying the intervention and the outcomes assessor followed standardised scripts to give explanations regarding the general objective of the study.[17] Moreover, the therapist responsible for the intervention participated in a 10-hour training module before the start of the study, which consisted of scientific information and clinical training regarding cryotherapy effects and application for people with knee OA. Intervention adherence, medication intake and adverse events were tracked with a 4-day assessment diary given to the participants at the baseline assessment. All the participants were told to not practise any kind of physical exercises/activities during the intervention week.

Participants were randomly allocated into two groups of 30: an experimental group that received cryotherapy, and a control group that received a sham intervention. Random allocations were determined by a computer-generated random numbers program and matched for gender (15 men and 15 women in each group). Allocation was concealed by placing the random allocations in opaque sealed envelopes that were locked in a central location. Each participant's random allocation was revealed just before the intervention was commenced.[17]

Verbal and written explanations of the objectives and methodology of the study were provided to the patients, and those who were willing to participate signed a written informed consent form approved by the local ethics committee. The study was reported according to the Consolidated Standards of Reporting Trials(CONSORT) Statement for Randomised Trials of Nonpharmacologic Treatments[18] and the Template for Intervention Description and Replication checklist (TIDieR).[19]

Participants

Participants were recruited through public announcements and waiting lists from local orthopaedic and rheumatology outpatient clinics. People who expressed interest in participating in the study underwent lateral, anteroposterior and axial radiography of both knees to determine whether they had knee OA based on the clinical and radiographic criteria of the American College of Rheumatology.[20] Participants were required to have a symptomatic and radiographic grade (Kellgren-Lawrence scale) of ≤2(at least mild radiographic OA) in at least one knee compartment.[17] To be included in the study prospective participants also needed to: be aged between 40 and 75 years; be engaged in , 45 minutes/week in accumulated physical activity of at least moderate intensity;[21] have a body mass index ≤ 35 kg/m^2; and have pain intensity in the previous week of ≤ 4 cm on a 10-cm visual analogue scale.[17] Exclusion criteria were: physiotherapy in the previous 3 months; intra-articular knee injections in the pre- vious 6 months; medical restrictions such as cardiorespiratory, neurological or any other rheumatology dysfunctions; previous hip, knee or ankle surgery; and any other chronic condition that leads to pain.

Intervention

Experimental group

The experimental intervention consisted of four cryotherapy sessions performed by a trained physiotherapist over 4 consecutive days. Cryotherapy was only applied to the more-affected knee, in an air-conditioned room controlled at 21 °C (6 2). The therapist explained that the intervention consisted of cryotherapy applied to the more-affected knee for 20 minutes. Participants were positioned in dorsal decubitus with both legs extended and relaxed. To protect the skin from possible frostbite, the entire knee surface was covered with a moist surgical gauze (45 3 50 3 0.01 cm). Next, two plastic bags (24 3 34 3 0.08 cm), each containing 1 kg of crushed ice, were placed on the knee, covering the anterior, posterior, medial and lateral surfaces. A comfortable, non-painful compression was applied over the ice packs by wrapping an elastic bandage around them, and the therapy was left in situ for 20 uninterrupted minutes. The main purposes of compression were to maintain the ice packs in position on the knee[22] and to enhance the effects of the cryotherapy.[23] To allow participants to mimic the usual clinical setting treatment, they were provided all the necessary materials (plastic bags, elastic bandage and surgical gauze) to use cryotherapy at home whenever they felt in pain or discomfort. Moreover, they received a booklet with illustrated pictures and all the instructions needed for cryotherapy application.

Control group

For the control intervention, the bags were filled with 1 kg of dry sand instead of ice. The sand bags were applied according to the same regimen in the same locations. The therapist's explanation about the intervention was changed to mention 'application of sand packs' instead of 'cryotherapy application'. The sand packs were applied with the same gauze underneath and the same bandage for compression. Participants in the control group were provided with the sand bags and other materials for application at home whenever they felt in pain or discomfort. The booklet was modified to refer to the application of sand bags.

Outcome measures

All the outcomes were measured by the same blinded assessor before and after intervention. Table 1 describes the main outcome measures included in this study and the recommended estimate of the minimum clinically important difference for each outcome measure. Pain intensity, knee subjective and objective physical function, and quality of life were measured.

Primary outcome

The primary outcome was pain intensity assessed using a visual analogue scale. This self-reported pain score is a valid and reliable measure among people with OA.[24] The visual analogue scale was administered at baseline and on the final assessment day.

Table 1
Detailed description of the study's outcome measures.

Outcome measure	Description of the test	Scoring	Minimum clinically important difference
Visual analogue scale	The scale is placed in front of the patient who is asked to rate their pain intensity in the previous week.[24]	The scale ranges from 0 (no pain) to 10 cm (maximum pain intensity).	A pain reduction of 1.75 cm is recommended in OA research.[33]
Western Ontario & McMaster Universities Osteoarthritis questionnaire	This self-report questionnaire assesses the problems experienced by people with lower limb OA in the previous 72 hrs. It contains 24 questions in three domains: pain, stiffness and physical function.	Each question is scored from 0 to 4. The maximum score is 96. High scores indicate worse status.	An improvement of 12% from baseline is recommended in OA research.[34]
Knee Injury and Osteoarthritis Outcome Score	This self-report questionnaire assesses the problems experienced by people with lower limb OA in the previous week, by measuring quality of life and knee function. It contains 42 questions in five domains: pain; other symptoms; function in daily life; sports-related function and recreation; and knee-related quality of life.	The answers are standardised and scored from 0 to 4. The total score is 168. High scores indicate worse status.	A difference of 8 to 10 in the total score is recommended in OA research.[35]
Timed Up and Go test	This test assesses: balance moving from sitting to standing, stability in walking, and gait course changes without using compensatory strategies. The participant is asked to stand up from a chair, walk 3 m, turn around, return and sit back in the chair.	Total time to complete the test.	A reduction of 0.8 to 1.4 s is recommended in OA research.[36]
30-Second Chair to Stand test	A chair with no arms is placed against a wall to prevent oscillations. Patients sit in the middle of the chair, with their back straight and feet resting on the floor in line with their shoulders. The participant is asked to rise from sitting to standing as many times as possible in 30 s.	Total number of repetitions within 30 s.	An increase of 2 to 3 repetitions is recommended in OA research.[36]

OA = osteoarthritis.

Secondary outcomes

The Western Ontario and McMaster Universities Osteoarthritis (WOMAC) questionnaire was used to assess knee function and associated problems. The Knee Injury and Osteoarthritis Outcome Score (KOOS) was used to assess knee function and quality of life. Two objective physical functional tests were also used: the Timed Up and Go test and 30-Second Chair to Stand test.

To collect preliminary data to support future randomised controlled trials, pressure pain thresholds (algometry) and knee skin temperature (thermography) were measured. The data from these outcomes are presented in Appendix 1 on the eAddenda.

Data analysis

A blinded biostatistician performed all analyses using commercial software[a]. The Kolmogorov-Smirnov test was applied to evaluate data distribution and all variables showed $p > 0.05$. A two-factor analysis of variance was conducted for the primary outcome (visual analogue scale for pain) and secondary outcomes, with time (baseline and post-intervention) as the within-subject factor and group (experi- mental or control) as the between-subject factor. Tukey's test was used for post-hoc analysis when necessary and an intention-to-treat analysis was performed for all randomised participants. Missing data were replaced using the expectation maximisation method. Between- group differences and their 95% CIs were reported and interpreted against the nominated thresholds for minimum clinically important difference. For the algometry and thermography data, where mini- mum clinically important differences were not nominated, Cohen's d coefficient was calculated to aid interpretation. An effect size ≥ 0.8 was considered large, around 0.5 moderate, and ≤ 0.2 small.[25]

Sample size was based on a significance level of 0.05 and power of 0.90 to detect a difference of 1.75 cm on the visual analogue scale, assuming a standard deviation of 2.00 cm.[26] Based on these criteria, 29 participants with knee OA were required in each group. To allow for possible dropouts during the intervention period, 30 participants were recruited per group.

Results

Flow of participants through the study

Figure 1 shows the design of the trial and flow of participants through the trial. Of the 188 volunteers, 83 attended the physical and radiographic screening. Of these, 60 participants matched the eligibility criteria and were randomised, of whom 58 completed the intervention. The baseline demographic characteristics of each group of participants are presented in Table 2. The baseline scores on the outcome measures are presented in the first two columns of Table 3.

Adherence to the study protocol

All registered outcome measures are reported in this manuscript. One participant in each group did not complete the four scheduled intervention sessions. These participants also declined to attend the post-intervention assessments, so their data were imputed as described above.

In the experimental group, the adherence diary showed that 12 (41%) of the participants used the cryotherapy intervention at home. Of these, 10 participants used it between one and three times and two participants used it more than three times.

In the control group, the adherence diary showed that 19 (66%) of the participants used the sham intervention at home. Of these, five participants used it between one and three times and 14 participants used it more than three times.

Effect of intervention

Primary outcome

The data about pain severity measured using the 10-cm visual analogue scale are presented in Table 3. The individual participant data are presented in Tables 4 and 5 on the eAddenda.

The mean between-group difference in change in pain severity was −0.8 cm (95% CI −1.6 to 0.1). That is, although pain severity reduced in both groups, the mean between-group difference favoured the experimental group by indicating 0.8 cm greater reduction in pain severity than in the control group. Neither that mean estimate nor the 95% CI reached the nominated threshold (ie, a reduction in pain severity of 1.75 cm) for the minimum clinically important difference. Therefore, the data in this study are consistent with a range of possible effects on pain severity that are not beneficial enough to make undertaking the intervention worthwhile.

Secondary outcomes

Pre-intervention and post-intervention results of the WOMAC, KOOS, Timed Up and Go test, and 30-Second Chair to Stand test are

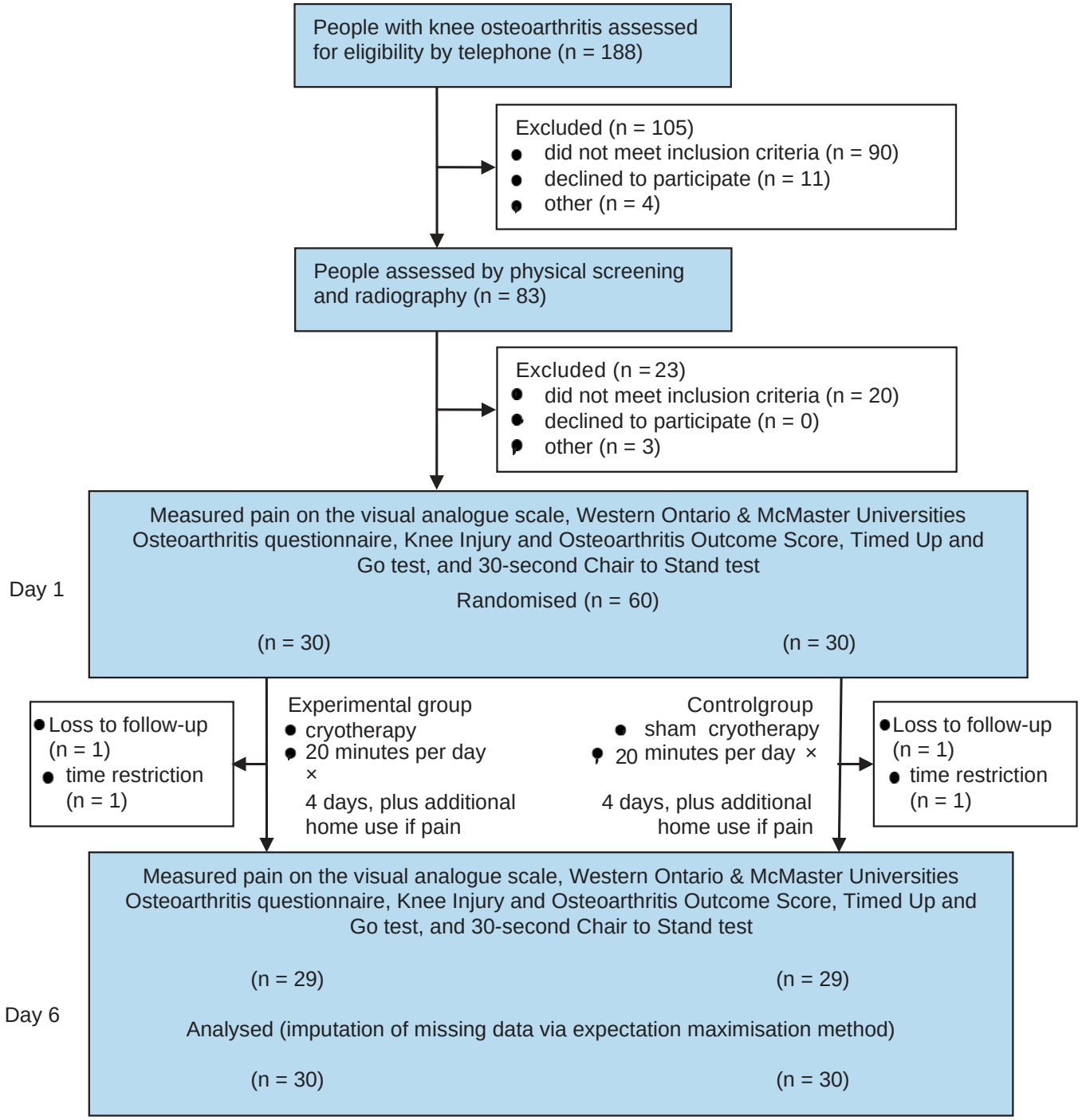

Figure 1. Design and flow of participants through the trial.

shown in Table 3. The individual participant data are presented in Tables 4 and 5 on the eAddenda.

The mean between-group difference in change in WOMAC score was 26 points (95% CI 213 to 2). That is, the mean difference favoured the experimental group by indicating 6 points greater reduction (ie, improvement) in the WOMAC score than in the control group. In order to compare this result with the minimum clinically important difference, the score can be converted into percentage change: 28% (95% CI 221 to 5). The mean estimate of 28% does not reach the nominated threshold (ie, a change of 212% from baseline), whereas the 95% CI spans the smallest worthwhile effect and also spans no effect. Therefore, the WOMAC data in this study do not provide a very precise estimate; the true average effect of cryotherapy may be worthwhile (221 to 212%), too small to be worthwhile (211 to 0%), or mildly harmful (1 to 5%).

Table 2
Baseline characteristics of the participants.

Characteristic	Exp (n = 30)	Con (n = 30)
Age *(yr)*, mean (SD)	60 (7)	60 (7)
Gender, n (%) female	15 (50)	15 (50)
Weight *(kg)*, mean (SD)	85.0 (18.4)	83.5 (19.6)
Height *(cm)*, mean (SD)	166 (9)	164 (9)
Body mass index *(kg/m²)*, mean (SD)	30.7 (5.8)	31.0 (7.6)

Con = control group, exp = experimental group.

The results for the remaining secondary outcome measures are similar to the results for WOMAC (Table 3). For each outcome measure, the 95% CI spans the minimum clinically important difference and no effect, so the study data are consistent with worthwhile, trivial and mildly harmful effects, as detailed below.

Table 3
Mean (SD) of groups and mean (95% CI) within and between-group differences.

Outcome	Groups				Difference within groups		Difference between groups
	Day 1		Day 6		Day 6 minus Day 1		Day 6 minus Day 1
	Exp (n = 30)	Con (n = 30)	Exp (n = 30)	Con (n = 30)	Exp	Con	Exp minus Con
Pain visual analogue scale *(0 to 10)*	6.8 (1.8)	6.8 (1.2)	1.6 (1.7)	2.3 (1.9)	−5.2 (2.5)	−4.4 (2.3)	−0.8 (−1.6 to 0.1)
WOMAC *(0 to 96)*	44 (15)	41 (18)	12 (12)	15 (14)	−32 (19)	−26 (22)	−6 (−13 to 2)
KOOS *(0 to 168)*	89 (23)	84 (25)	27 (18)	30 (23)	−62 (29)	−54 (33)	−8 (−20 to 4)
Timed Up and Go test *(s)*	8.6 (1.7)	9.0 (2.1)	7.5 (1.2)	8.3 (1.5)	−1.1 (2.2)	−0.8 (6.0)	−0.3 (−1.1 to 0.4)
30-s Chair to Stand test *(repetitions)*[a]	10 (2)	10 (3)	13 (3)	12 (4)	3 (3)	2 (3)	1 (−1 to 2)

Shaded row = primary outcome.
Small anomalies in subtraction are due to the effects of rounding.
Negative between-group differences favour the experimental group, except where indicated.
Con = control group, exp = experimental group, KOOS = Knee Injury and Osteoarthritis Outcome Score, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
[a] A positive between-group difference favours the experimental group for this outcome.

The mean between-group difference in change in KOOS was −8 points (95% CI −20 to 4). That is, the mean difference favoured the experimental group by indicating 8 points greater reduction (ie, improvement) in the KOOS than in the control group. However, the confidence interval spanned from −20 points (ie, a worthwhile reduction in KOOS because it is greater than the minimum clinically important difference) to 4 points (ie, a mildly harmful effect).

The mean between-group difference in change in the Timed Up and Go test was −0.3 seconds (95% CI −1.1 to 0.4). That is, the mean difference favoured the experimental group by indicating a 0.3-second greater reduction (ie, improvement) in the Timed Up and Go test than in the control group. However, the confidence interval shows that the effect of cryotherapy on the Timed Up and Go test may be worthwhile (95% CI −1.1 to −0.8), trivial (−0.7 to 0.0), or mildly harmful (0.1 to 0.4).

The mean between-group difference in change in the 30-Second Chair to Stand test was 1 repetition (95% CI −1 to 2). That is, the mean difference favoured the experimental group by indicating greater improvement by 1 repetition than in the control group. However, the confidence interval shows that the effect of cryotherapy on the 30-Second Chair to Stand test may be worthwhile (2 repetitions), trivial (1 repetition), or mildly harmful (−1 repetition).

Medication use

In total, 27 (93%) of the participants in the cryotherapy group did not use any analgesic or anti-inflammatory drugs during the intervention period; two participants (7%) used medication only once for other symptoms but not knee pain. In the control group, 29 (100%) of the participants did not use any analgesic or anti-inflammatory drugs during the intervention period.

Adverse events

All 29 patients in each group who were followed up at the end of the study reported no adverse events during the intervention period.

Discussion

We believe that this is the first study to assess the isolated effects of short-term cryotherapy compared with a sham control in people with knee OA. The results showed that the effects of short-term cryotherapy application were not sufficiently superior to a sham control to make the intervention worthwhile. The study's estimate of the effect on pain severity was small enough that the confidence interval did not exceed the nominated smallest worthwhile effect. Therefore, although this study indicates that the effect of short-term cryotherapy on pain severity is beneficial, the effect is small enough that people with knee OA typically would not consider that the effect on pain severity justifies the use of cryotherapy on a short-term basis. The estimates of the effect of short-term cryotherapy on the secondary outcome measures were less precise. For each secondary outcome, the confidence interval ranged from worthwhile to mildly harmful effects. Therefore, this study does not generate any clear implications about whether or not short-term cryotherapy should be recommended to improve WOMAC, KOOS, Timed Up and Go test or the 30-Second Chair to Stand test in people with knee OA.

As a natural analgesic and anti-inflammatory,[6] cryotherapy is widely used in clinical practice to reduce pain and thereby improve function and quality of life. However, our findings do not support such widespread use. Our results also do not support the tentative observation (based on low-quality evidence) from a previous systematic review that cryotherapy was more effective than control groups using untuned short-wave diathermy and electrodes with no electrical current, respectively, for pain, stiffness, knee range of motion, and physical performance improvements.[16] Our results indicate that any beneficial effect of cryotherapy on pain is meagre, and would not be considered worthwhile, which seems consistent with a study that suggests that people with knee OA prefer heat rather than cryotherapy.[8] However, that result does not seem consistent with a previous study where cryotherapy was found to be as effective as transcutaneous electrical nerve stimulation for quadriceps activation in people with knee OA.[27]

Regarding the secondary outcomes, the between-group differences that were observed were smaller than the smallest worthwhile effects recommended for use in OA research, but the 95% CIs were wide enough to be unclear about whether the effect was or was not of clinical importance. While this suggests that further research into the effect of cryotherapy on the secondary outcomes could be undertaken, worthwhile effects seem unlikely because benefits on the secondary outcomes would presumably occur via reducing pain, and the effect on pain was small.

The differences observed within groups cannot be taken as an indication of the effect of the intervention, since there are a number of factors that can explain what happened. These include regression to the mean,[28] where participants are more likely to improve after a consultation regardless of intervention, due to symptom fluctuation;[29] polite patients effect,[29] where patients do not want to fail the therapist treating them; and the placebo ef- fect,[30-32] where the knowledge of receiving a topical treatment, with the considerable attention given to all the participants, their expectations concerning the upcoming therapy, and bio-psychosocial elements could all have indirectly influenced the responses to the interventions applied.

The recommendations of current clinical guidelines vary regarding cryotherapy for knee OA.[2] The American College of

Rheumatology and the National Institute for Health and Care Excellence conditionally recommend cryotherapy as a complementary treatment option for people with knee OA.[9,10] However, the Osteoarthritis Research Society International, the European League Against Rheumatism, and the Ottawa Panel did not achieve expert panel consensus and failed to report cryotherapy in their final recommendations.[11–13] Our results agree with these latter guidelines. However, the most appropriate interpretation of the total body of evidence will come when our study is incorporated into a high-quality systematic review on this topic.

It is important to underscore that well-established reporting guidelines were followed to improve the evidence synthesis regarding this topic.[18,19] The methodology of this study was designed to minimise potential for bias by including concealed treatment allocation, and blinding of the outcome assessor and biostatistician. Participants presented radiographically confirmed knee OA and a sufficient level of pain to ensure ample scope for improvement. Moreover, the amount of missing outcome data was relatively small for a randomised controlled trial. Despite these strengths, the study also exhibited some limitations. The therapist who delivered cryotherapy or the placebo intervention, and the patients were not blinded. Although this may have resulted in bias, given the study design, a method of blinding patients and therapists to thermal agents has yet to be established. In addition, there was not a no-treatment group and there was not a follow-up period to evaluate the residual effect of each intervention.

In conclusion, in people with symptomatic knee OA, the short-term use of cryotherapy was not substantially superior to a sham control in terms of relieving pain, and it had uncertain effects on function and quality of life. Although cryotherapy is widely used in clinical practice, and recommended by some treatment guidelines, the estimates of its effects in this study suggest that it might not have a worthwhile effect as a treatment for knee OA.

What was already known on this topic: People with symptomatic knee osteoarthritis experience pain and disability. Cryotherapy is sometimes used to treat knee osteoarthritis. Clinical guidelines for osteoarthritis differ in their recommendations about cryotherapy. Recent systematic reviews conclude that further evidence about cryotherapy for knee osteoarthritis is needed.
What this study adds: In people with symptomatic knee osteoarthritis, any beneficial effect of short-term application of cryotherapy on pain was small enough that most people would not consider it to be worthwhile. The effects of short-term cryotherapy on function and quality of life in people with symptomatic knee osteoarthritis were unclear.

Footnotes: [a] SPSS 24.0 software, SPSS Inc, Chicago, USA.

eAddenda: Tables 4 and 5 and Appendix 1 can be found online at https://doi.org/10.1016/j.jphys.2019.08.004.

Ethics approval: This study was approved by the Institutional Ethics Committee of Federal University of Sao Carlos, São Paulo, Brazil. Registration approval number: (CAEE: 65966617.9.0000.5504). All participants gave written informed consent before data collection began. The trial was conducted according to the Helsinki Statement.

Competing interests: All authors have completed a uniform disclosure form and declare that they have no conflicts of interest.

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Cryotherapy associated with tailored land-based exercises for knee osteoarthritis: a protocol for a double-blind sham-controlled randomised trial

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Abstract

Introduction There is an unmet need to develop tailored therapeutic exercise protocols applying different treatment parameters and modalities for individuals with knee osteoarthritis (KOA). Cryotherapy is widely used in rehabilitation as an adjunct treatment due to its effects on pain and the inflammatory process. However, disagreement between KOA guidelines remains with respect to its recommendation status. The aim of this study is to verify the complementary effects of cryotherapy when associated with a tailored therapeutic exercise protocol for patients with KOA.

Methods and analysis This study is a sham-controlled randomised trial with concealed allocation and intention-to-treat analysis. Assessments will be performed at baseline and immediately following the intervention period. To check for residual effects of the applied interventions, 3-month and 6-month follow-up assessments will be performed. Participants will be community members living with KOA divided into three groups: (1) the experimental group that will receive a tailored therapeutic exercise protocol followed by a cryotherapy session of 20 min; (2) the sham control group that will receive the same regimen as the first group, but with sham packs filled with dry sand and (3) the active treatment control group that will receive only the therapeutic exercise protocol. The primary outcome will be pain intensity according to a Visual Analogue Scale. Secondary outcomes will be the Western Ontario & McMaster Universities Osteoarthritis Index; the Short-Form Health Survey 36; the 30-s Chair Stand Test; the Stair Climb test; and the 40-m fast-paced walk test.

Ethics and dissemination The trial was approved by the Institutional Ethics Committee of Federal University of São Carlos, São Paulo, Brazil. Registration approval number: CAAE: 65966617.9.0000.5504. The results will be published in peer-reviewed journals.

trial registration number NCT03360500

strengths and limitations of this study

- The trial will be conducted according to well-established reporting guidelines.
- Participants will present radiographically confirmed knee osteoarthritis and a sufficient level of pain to ensure ample scope for improvement.
- The trial will use both subjective and objective outcome measures of physical function.
- The therapist who delivers cryotherapy or the sham intervention and the patients will not be blinded.
- The loss to follow-up after randomisation in the sham group might be higher than those in the other groups.

Introduction

Knee osteoarthritis (KOA) is a serious disease with a high societal and economic burden,[1] affecting approximately 250 million people worldwide.[2] Current clinical practice guidelines recommend a combination of pharmacological[3] and non-pharmacological[4] treatment strategies to manage KOA symptoms and improve patients' quality of life. However, pharmacological treatment options that have been proven to relieve symp- toms remain limited, and some of the most commonly recommended pharmacological treatments are poorly tolerated, with long-term use resulting in serious systemic adverse events.[5–7]

Physical therapy, specifically the use of strengthening therapeutic exercise (STE) protocols, have been shown to relieve pain, reduce stiffness, increase physical function and improve quality of life in patients with KOA.[1 8] High-quality evidence has demonstrated that the benefits of STE protocols on pain and quality of life in individuals with KOA are sustained for at least 2–6 months after the end of a treatment.[8] There is; however, a call for further research to develop novel insights within STE protocols regarding differences in treatment durations, frequencies, modalities and intensities.[9] The majority of current protocols have reported low adherence and are substantially under-used by patients with

KOA, mainly due to socioeconomic barriers, personal beliefs, fear of movement and aggravation of pain in the early phases of treatment.[10 11] Therefore, there is an unmet need for cost-effective, evidence-based STE protocols that are tailored to the needs of patients with KOA, and that can aid clinicians in targeting rehabilitation goals.

Physical modalities such as thermal agents, laser therapy, therapeutic ultrasound and electrical stimulation are often used as adjunct treatments with therapeutic exercises in individuals with KOA.[4 12] Cryotherapy, a non-pharmacological intervention, has been widely used in some rheumatic joint diseases[13,14] based on its effects on pain, inflammation and oedema.[15 16] In an animal model with induced KOA, clinical-like cryotherapy was beneficial to reduce the synovial inflammation due to lower leukocyte migration to the knee joint cavity and inflammatory cytokine concentration.[17] Cryotherapy is considered safe, and is inexpensive and easy to administer for healthcare professionals and patients. Moreover, it can be prescribed in isolation or as an adjunct treatment and seems to be well accepted by individuals with KOA.[14 18 19] Although cryotherapy is recommended as a treatment option by some international KOA guidelines,[20 21] others have found insufficient evidence to support it.[22–24] Relevant systematic reviews have likewise concluded that further evidence, produced with greater methodological rigour, is needed to evaluate the effects of cryotherapy on pain, function and quality of life in individuals with KOA.[16 25]

In thisstudy,we aimtodesign arandomised trialtoverify the complementary effects of cryotherapy in conjunction with a tailored STE protocol on pain, function and quality of life in individuals with KOA. We hypothesise that cryotherapy combined with the STE protocol will achieve better treatment effects on patients with KOA when compared with the other two groups. The proposed trial will contribute to new evidence to the physical therapy field in KOA by focusing on interventions that target rehabilitation and enhance pain management, thereby improving the physical function and quality of life of these patients. Our research group developed the STE protocol described in this study. The protocol was also used in another randomised trial, testing the complementary effects of Photobiomodulation in individuals with KOA (trial registration number at www.ensaiosclinicos.gov.br: U1111-1215-6510). This manuscript has been submitted simultaneously with the manuscript entitled 'Photobiomodulation therapy associated with supervised therapeutic exercises for people with knee osteoarthritis: a randomised controlled trial protocol .

Methods

To report this study protocol, we followed the Standard Protocol Items: Recommendations for Interventional Trials,[26] the Osteoarthritis Research Society International clinical trials recommendations: design, conduct and reporting of clinical trials for KOA,[27] and the template for intervention description and replication checklist.[28] The randomised trial will be reported according to the Consolidated Standards of Reporting Trials statement for randomised trials of non-pharmacological treatments.[29]

Study design and setting

This study is a single-centre, sham-controlled randomised clinical trial. A baseline assessment (A1) will be performed on the week day before the 8-week intervention period, and a postintervention assessment (A2) will be performed immediately following the last session. To check for residual effects of the interventions, 3-month (A3) and 6-month (A4) follow-up assessments will be performed. Each patient will be assessed in a physiotherapy research laboratory, during the same period of the day and by the same assessor. To reduce bias, the therapists responsible for applying the intervention and the outcome assessors will follow standardised scripts that describe the general objective of the study.[27]

Intervention adherence, medication intake and possible adverse events will be tracked with an 8-week assessment diary that will be given to participants at the baseline assessment and with a 12-week assessment diary for the 3 month follow-up assessment. All the participants will be advised not to practice any other type of regular physical exercise during the course of the study that could interfere with the STE protocol. A verbal and written explanation of the objectives and methodology of the study will be provided to all the participants, and those willing to participate will sign a written informed consent form, approved by the local ethics committee. A detailed timeline of the trial is presented in table 1.

Patient and public involvement

The patients and the public were not involved in the planning and design of this study.

Participants

Participants will be recruited through public announcements on social media, advertisements via local news outlets, university community newsletters and banners or leaflets posted at strategic locations in the city. People who are interested in participating in the study will first be screened to check the eligibility criteria. Eligible participants will then undergo a lateral, anteroposterior and axial radiography of both knees to determine KOA structural severity, which will take place at the University Hospital. Participants will be classified with KOA based on the clinical and radiographic criteria of the American College of Rheumatology,[30] and will be required to have symptoms and a radiographic grade (Kellgren and Lawrence scale) of ≥2 (mild radiographic OA) in at least one knee compartment.[27]

To be included in the study, participants will also need to: be between 40 and 75 years old; be engaged in a total of less than 45 min/week of physical activity of at least moderate intensity;[31] have a body mass index <35 kg/m^2 and to have reported pain intensity in the prior week of

Table 1 Timeline of the measurements to be taken at each point on the trials

Timeline	Enrolment	STE protocol training	Baseline assessment (A1)	Intervention	Postintervention assessment (A2)	Follow-up assessment (A3)	Follow-up assessment (A4)
	−2 weeks (–14 to −7 days)	−1 week (–7 to 0 day)	Day 0		8 weeks (±3 days)	20 weeks (±3 days)	32 weeks (±3 days)
Enrolment							
Eligibility screen	X						
Informed consent	X						
Interventions							
Allocation			X				
STE				X			
STE+cryotherapy				X			
STE+sham cryotherapy				X			
X-ray examination of both knees	X						
Assessments							
VAS			X		X	X	X
WOMAC			X		X	X	X
SF-36			X		X	X	X
Timed-up and Go Test			X		X	X	X
30 s chair to stand test			X		X	X	X
Stair climb test			X		X	X	X
40 m (4×10 m) fast paced walk test			X		X	X	X

A, assessment; KOOS, Knee Injury and Osteoarthritis Outcome Score; SF-36, Short Form-36 questionnaire.STE, Strength therapeutic exercises; VAS, Visual Analogue Scale, WOMAC: Western Ontario & McMaster Universities Osteoarthritis questionnaire.

≥4 cm on a 10 cm Visual Analogue Scale (VAS).[27] Exclusion criteria will comprise physical therapy in the prior 3 months; intra-articular knee injections in the prior 6 months; medical restrictions such as cardiorespiratory, neurological or any other rheumatology conditions; previous hip, knee or ankle surgery and any other chronic condition that leads to chronic painor dysfunction. Additionally, participants presenting with contraindication(s) to cryotherapy application (ie, those that feel a high level of discomfort or pain during the application) will be excluded.

All the participants will be asked to provide a medical certificate stating that they are healthy enough to perform physical activities before the start of theintervention.

Interventions

The cryotherapy intervention protocol is based on a previously accepted methodology developed in our research laboratory.[32] Two physical therapists will administer the interventions in the physiotherapy clinic of the university. The study will take place over the course of 8 weeks, with three 90-min sessions per week occurring on non-consecutive days, for a total of 24 sessions. All randomised participants will perform the STE protocol and then, according to random allocation, each patient will subsequently receive either cryotherapy or sham interventions in individual rooms.

Prior to the beginning of the study, the therapists responsible for the interventions will participate in a 10 hours training module, which will consist of scientific information and clinical training regarding KOA, the STE protocol and the use of cryotherapy. After the first training module is completed, the therapists will do an 8-week training module, which will consist of practicing the full-length protocol and intervention application(s) three times per week. Both therapists will be responsible for delivering cryotherapy and sham interventions.

STE protocol

We designed the 8-week land-based supervised exercise protocol according to the evidence-based recommendations for physical exercise interventions in KOA.[33 34] The STE protocol characteristics are described in figure 1, and a detailed description of all the exercises is presented in the online supplementary file 1 of this protocol. The protocol is divided into two phases. Each phase consists of 4 weeks of progressive exercises, performed three times per week on non-consecutive days (24 hours rest between sessions), with exercise intensity individually tailored for each participant. The

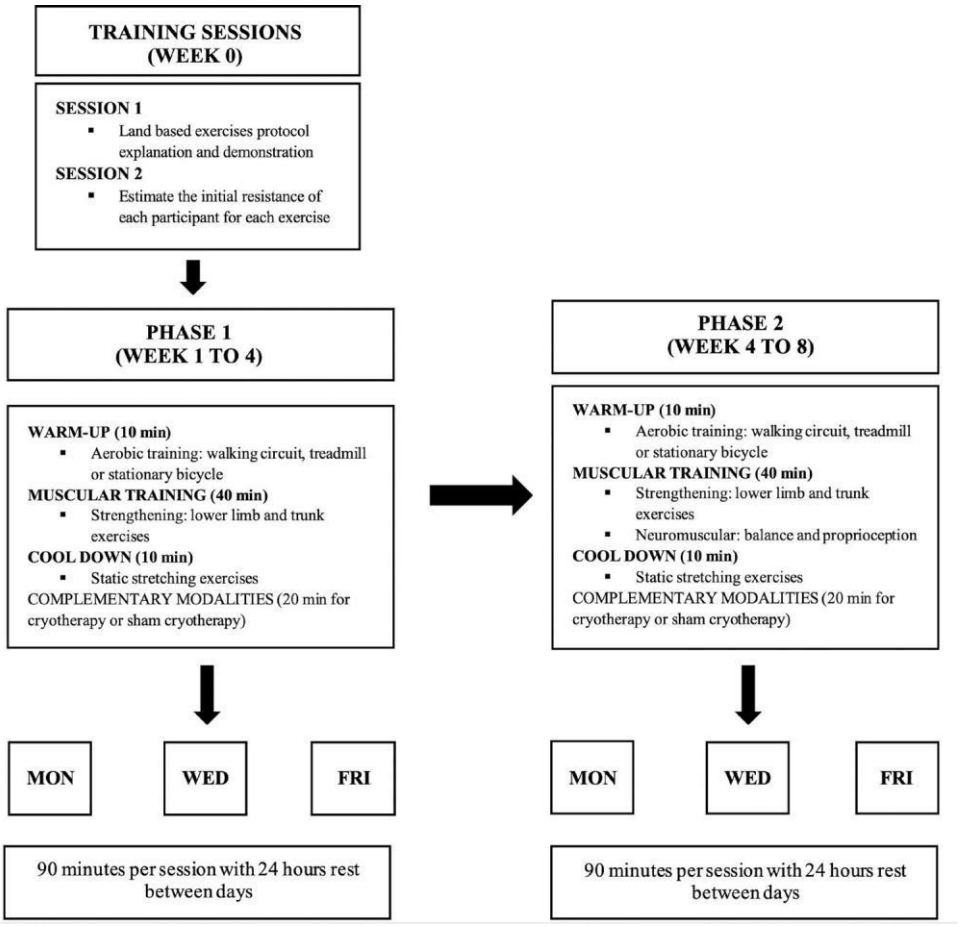

Figure 1 Land based exercise protocol characteristics

first session is used to demonstrate and explain the STE protocol, and to perform an exercise familiari- sation using no loads by the participants. The second session is designed to estimate the initial resistance of each participant for each exercise. All participants start doing the exercises using bodyweight and the volitional interruption method is used in order to achieve the benefits of resistance training and to reduce the risk of musculoskeletal injuries.[35] The loads are gradually increased until the participant can adequately perform 12 repetitions with no voluntary interruption due to muscle fatigue.

The STE protocol sessions consist of three main activities. The first activity is a 10-min warm-up in which the patients can choose, according to their preferences, to walk in a comfortable intensity in an outdoor circuit, treadmill or ride in a stationary bicycle. The second activity consists of 40-min of strengthening exercises, such as lower limb and trunk exercises and neuromuscular training involving balance exercises. The third activity is a 10-min cool-down cycle, consisting of static stretching exercises to reduce the risk of musculoskeletal injuries and to maximise the benefit of the STE protocol.[36] To ensure patient safety, cardiac and respiratory frequencies and blood pressure are monitored if the participant presents an intense rate of perceived exertion according to the Borg scale while performing an exercise.[37 38]

Cryotherapy protocol

To apply cryotherapy, the therapist will explain to the patient that the intervention will consist of crushed ice applied to the more-affected knee for 20 min. Participants will be positioned in dorsal decubitus with both legs extended and relaxed. The entire knee surface will be covered with a moist surgical gauze (45×50×0.01 cm) to protect the skin from possible frostbite. Next, two plastic bags (24×34×0.08 cm), each containing 1 kg of crushed ice, will be placed on the knee, covering the anterior, posterior, medial and lateral surfaces. A comfortable, non-painful compression will be applied over the ice packs by wrapping an elastic bandage around them, and the therapy will be left in situ, uninterrupted, for 20 min. The primary purpose of compression is to maintain the ice packs in position on the knee[39] and to enhance cryotherapy effects.[40]

For the sham cryotherapy intervention, the bags will be filled with 1 kg of dry sand instead of ice. The sandbags will be applied according to the same regimen in the same locations. The therapist's explanation about the intervention will be changed to mention the 'application of sand packs' instead of 'cryotherapy application.' The

Table 2 Description of the outcome measures

Outcome measure	Description of the test	Scoring	Minimum clinically important difference (MCID)
Visual Analogue Scale	The scale is positioned in front of the patient who is asked to evaluate pain intensity in the prior week.[41]	The scale ranges from 0 (no pain) to 10 cm (maximum pain intensity).	A pain reduction of 1.75 cm is recommended in OA research.[49]
Western Ontario & McMaster Universities Osteoarthritis questionnaire	This self-report questionnaire evaluates the difficulties experienced by individuals with lower limb OA in the prior 72 hours. It contains 24 questions in three domains: pain, stiffness and physical function.	Each question is scored from 0 to 4, and the maximum score possible is 96. The higher the scores, the worse the status of a patient.	An improvement of 12% from baseline is recommended in OA research.[52]
Short-Form-Health Survey 36 (SF-36)	The short form questionnaire is intended to measure the patient's quality of life with 36 items referring to the past 4 weeks. It presents a multiple-choice scale that evaluates eight domains of life: physical functioning, role limitations due to physical problems, general health perceptions, vitality, social functioning, role limitations due to emotional problems, general mental health and health transition.	The sum of the total value varies from 0 to 100, with higher indexes indicating a better quality of life. Each of the eight summed scores was linearly transformed into a scale from 0 (negative health) to 100 (positive health) to provide a score for each subscale. Each subscale was used independently.	A difference of 10 points is recommended as an MCID in OA research.[53]
Stair climb test	The participant is positioned in front of the stairs.At the therapist's signal, he/she has to climb the indicated steps (we used the 12-step SCT) and descend promptly, being able to use the handrail as a security instrument. We used 20 cm steps height, a handrail stair in an lighted environment, free of traffic, or external distractions. Moreover, a pretest was conducted to identify the need for safety measures.	The final score is calculated based on the time the participant took to perform the test and compared it to the literature normative values of the test.	A reduction of 5.5 s in the test is the recommended MCID in OA research[44]
40 m (4×10 m) Fast paced walk test	Administered at a distance of 10 m (marked by tapes), a cone is placed 2 m before the start and 2 m after the end of each marking. The participant is instructed to walk as quickly but as safely as possible the first 10 m (from the start mark), to turn around in the cone and walk back the 10 m again, successively until completing the distance of 40 m.	Speed (m/s)	An increase of 0.2–0.3 m per second in the test is the recommended MCID in OA research[44]
30 s Chair to stand test	A chair with no arms is placed against a wall to prevent oscillations. Patients sit in the middle of the chair, with their back straight and feet resting on the floor in line with their shoulders. The participant is asked to rise from sitting to standing as many times as possible in 30 s.	Total number of repetitions within 30 s	An increase of 2 to 3 repetitions is recommended in OA research.[54]

OA, osteoarthritis.

sandbags will be applied with the same gauze underneath and the same bandage for compression.

Outcome measures

The same blinded assessor will measure all outcomes before and after the intervention, and at the 3-month and 6-month follow-up periods. Before the study begins, the two outcome assessors will be trained to conduct interviews and perform data collection following a standard protocol. Table 2 describes the outcome measures that will be included in the trial and the recommended estimate of the minimum clinically important difference (MCID) for each outcome measure. We will measure pain intensity, subjective and objective physical function and quality of life.

Primary outcome

The primary outcome will be pain intensity at rest, assessed with a VAS. This self-reported pain score is a valid and reliable measure for KOA.[41] The VAS will be administered at rest and after each physical function test, occurring at baseline, on the final assessment day and at the 3-month and 6-month follow-up periods.

Secondary outcomes

To subjectively assess physical function and associated problems, the Western Ontario & McMaster Universities Osteoarthritis Index (WOMAC) will be used. The WOMAC is a frequently used questionnaire in KOA and is translated, reproducible and valid to Brazilian Portuguese.[42] The Short-Form Health Survey 36 (SF-36) will

be used to asses quality of life. The questionnaire is translated, reproducible and valid to use in Brazilian Portuguese.[43] Three objective physical function tests will also be used: the 30 s chair stand test, the stair climb test and the 40-m fast-paced walk test. The questionnaires and physical function tests described are well-established core assessment measures of pain and physical function in patients with KOA, and present good scores for reliability, validity and ability to detect change.[44–48]

Randomisation

Eligible patients who consent to participate will be randomly allocated into three groups of 40: (1) active control group that will receive the STE protocol only, (2) STE+cryotherapy group and (3) STE+sham cryotherapy group. The allocation of patients will be performed using permuted block randomisation stratified by gender (20 men and 20 women in each group); randomisation sequences will be determined by a computer-generated random numbers programme (www.randomization.com). Allocation will be concealed by placing randomisation assignments in opaque sealed envelopes that will be locked in a central location. A biostatistician will be responsible for generating the random numbers and each participant's random allocation will be revealed to the therapist administering the intervention just before study onset.[27]

Sample size

We aim to detect a MCID of 1.75 cm units on the VAS for pain intensity at rest.[49] Also, we aim to detect an MCID of 30 points on the WOMAC global score.[50] Calculations were based on an analysis of covariance adjusting for baseline outcome scores, assuming between-patient SD of 2.0 cm for pain and 45 points for WOMAC global score. Based on these criteria, to achieve a significance level of 0.05 and a power of 0.80%, 37 participants with KOA will be required in each group. We will recruit 40 participants per group to allow possible dropouts during the intervention period.

Data analysis

The analyses will be performed by a blinded biostatistician using commercial software. The Kolmogorov–Smirnov test will be applied to evaluate the normality of data distribution. If the distribution is not normal, non-parametric tests will be used. For normal distributions, a 2-factor analysis of variance (ANOVA) will be conducted for the primary outcome (VAS for pain) and secondary outcomes, with time (baseline, postintervention and follow-up) as the within-subject factor and group (STE, STE+cryotherapy and STE+sham cryotherapy) as the between-subject factor. In addition, Tukey's test will be used for post-hoc analysis when necessary, and an intention-to-treat analysis will be performed for all randomised participants. All the missing data will be replaced using the expectation-maximisation method. Between-group differences and their 95% CIs will be reported and interpreted against the nominated thresholds for MCID. For the outcomes where the MCID is not nominated, Cohen's *d* coefficient will be calculated to aid interpretation. An effect size greater than 0.8 will be considered large, around 0.5 moderate, and less than or equal to 0.2, small.[51]

Ethics and dissemination

The Institutional Ethics Committee of the Federal University of São Carlos, São Paulo, Brazil, approved the study under the registration approval number: CAAE: 65966617.9.0000.5504. The trial will be conducted according to the Helsinki Statement. All participants will provide written informed consent following a verbal and written explanation of the study protocol. Participants will be free to withdraw from the trial at any time without prejudice to future treatment. Results will be presented at scientific meetings and published in peer-reviewed journals. All publications and presentations related to the study will be authorised and reviewed by the study investigators.

Trial status

The trial is currently recruiting and is expected to be completed (including follow-up testing) by December 2020.

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Contributors LOD, AESJ, PRS, FAS and TFS designed the study protocol. LOD wrote the first draft of the manuscript, and together with AESJ, PRS, FAS and TFS revised and produced the final version. All authors have read and approved the final version of the manuscript. LOD takes responsibility for the integrity of the work as a whole.

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Competing interests None declared

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MASTERCLASS

Knee osteoarthritis: key treatments and implications for physical therapy

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Abstract
Background: Knee osteoarthritis (OA) is a chronic progressive disease that imparts a substantial socioeconomic burden to society and healthcare systems. The prevalence of knee OA has dramatically risen in recent decades due to consistent increases in life expectancy and obesity worldwide. Patient education, physical exercise, and weight loss (for overweight or obese individuals) constitute the first-line knee OA treatment approach. However, less than 40% of patients with knee OA receive this kind of intervention. There is an unmet need for healthcare professionals treating individuals with knee OA to understand the current recommended treatment strategies to provide effective rehabilitation.
Objective: To guide physical therapists in their clinical decision making by summarizing the safest and most efficacious treatment options currently available, and by delineating the most traditional outcome measures used in clinical research for knee OA.
Conclusion: There is a need for healthcare providers to abandon low-quality and ineffective treatments and educate themselves and their patients about the current best evidence-based practices for knee OA.

Introduction

Life expectancy has increased globally over time; however, the growing burden of chronic diseases results in a large portion of society living longer, but in poorer health.[1] This scenario is indeed a reality for people suffering from one of the leading causes of chronic pain and disability

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worldwide, knee osteoarthritis (OA).[1] The disease is ranked as the 10th largest contributor to global years lived with disabilities,[2] and its prevalence has more than doubled in the last 10 years.[1,3] In addition, medication intake, hospital stays, and joint surgeries associated with managing knee OA impose billions of dollars per year in costs to healthcare systems.[2,3]

The pathology of knee OA affects the whole joint, causing synovial inflammation, cartilage damage, bone remodeling, and osteophyte formation.[4] Typical symptoms include pain, muscle weakness, joint instability, brief morning stiffness, crepitus, and functional limitations.[4] Frequently, symptoms are related to physical inactivity, which has been linked to morbidity and mortality in the contemporary era and is a significant contributor to the incidence of chronic diseases worldwide.[5,6] Methodologically rigorous international guidelines strongly recommend non-pharmacological strategies as the first line of treatment for knee OA.[7---13] Exercise, patient education, and weight loss ---when needed ---are the recommended first-line strategies to manage symptoms of these patients.[7---13]

There is high-quality evidence demonstrating the effectiveness of education and exercise to improve function in individuals with knee OA.[8,13] Data from 9825 patients with hip or knee OA showed that a 6-week combination intervention comprising three sessions of patient education delivered over the course of two weeks and 12 sessions of neuromuscular exercise delivered twice per week had beneficial effects on OA symptoms, physical function, medication intake, and sick leave time.[14] Furthermore, some beneficial effects introduced by the interventions, including increased physical activity and quality of life, were maintained after one year. These results suggest that a combination of education and exercise could result in long-term reductions in the burden of knee OA and its costs to patients and the healthcare system.

Although non-pharmacological strategies are of paramount importance, less than 40% of patients with knee OA receive this kind of treatment approach, indicating that the uptake of evidence-based guidelines in clinical practice and rehabilitation is still suboptimal.[14,15] Instead, pharmacological strategies remain dominant, despite the fact that chronic use of many of these treatments has been associated with severe adverse side effects.[16,17] The neglect of evidence-based strategies in clinical practice applies to both clinicians and patients. Factors such as the strong beliefs regarding old and low-value treatments, the lack of knowledge regarding current evidence, and a significant increase in the number of current published guidelines are considered barriers to the successful adoption of evidence-based clinical practice.[18---20]

A basic understanding of treatment strategies for knee OA is necessary to target and improve rehabilitation. In this article, we aim to provide updated information for physical therapists and show that exercise, weight maintenance, and patient education are vital for the optimal treatment of knee OA. We also aim to describe key outcome measures used in knee OA studies and to increase awareness about useful tools for data collection for clinicians and researchers.

Key treatments

Non-pharmacological strategies

Current clinical practice guidelines recommend education and self-management, exercise, and weight loss (for overweight or obese patients) as the first-line treatments for knee OA.[7---13] We consider these strategies to be the core of knee OA rehabilitation, because they have been proven to effectively decrease pain and improve overall joint function and patient quality of life. In patients for whom knee OA has a significant impact on ambulation or joint stability, or for whom pain is severe, some guidelines strongly recommend the use of tibiofemoral knee braces, canes or walkers, orthopedic footwear, and other assistive technologies.[12,13]

Patient education

Patient education plays an essential role in decision making, disease self-management, and medication adherence of individuals with knee OA.[21] The negative impact of the disease on the patients' self-esteem can be high, and oftentimes, pain becomes a central aspect of their lives. Misleading beliefs that OA is an incurable, progressive disease that is associated with specific causal factors can lead patients to cut down on physical activities and adapt to a restricted lifestyle with less spontaneity, which in many cases results in a great feeling of loss and isolation associated with a reduction in social relationships.[22---24] There is an urgent need to mitigate this negative impact, using proper patient-education strategies to better manage the disease and improve the concordance between patients' expectations and treatment outcomes. Overall, patient knowledge about the disease is still inadequate. Although guidelines organizations attempt to disseminate health information targeting the general public, most patient education materials for people with knee OA are of fair quality and written at inappropriate readability levels, frequently equal to, or more complicated than the recommended level (7th to 8th grade).[25,26]

As healthcare providers, it is essential to develop a clear understanding of the disease to direct patients toward high-quality health information. However, before educating patients with knee OA, it is crucial to understand how they experience the disease. A systematic review of qualitative studies highlighted the importance of considering patient attitudes and experiences to plan and implement the best treatment options for knee OA.[27] From the seven critical themes that emerged, three call for attention: (1) ''*The perceived causes of knee osteoarthritis are multifactorial and lead to structural damage to the knee and deterioration over time*,'' where patients perceived knee OA as a consequence of internal factors such as aging, working occupation, family history, or external factors such as a trauma or weather conditions; (2) ''*Interactions with health professionals can be positive or negative*,'' where patients related that positive interactions resulted in feeling listened to and hopeful for the future, whereas negative interactions were characterized by receiving less attention and less information about the condition and treatment options; and (3) ''*Knee osteoarthritis leads to life adjustments*,'' where

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some patients mentioned climbing fewer stairs, not carrying heavy things, looking for places to sit, and avoiding public transportation, while others reached a point where there was a profound feeling of loss because the disease led to giving up all enjoyable activities of daily living.

In a consensus statement reached by experts and patients with OA in 13 countries, 21 key messages were identified that should be communicated to patients.[28] The top 3 messages were related to (1) how regular physical activity and individualized exercise programs can reduce pain, prevent worsening, and improve daily function in OA; (2) the benefits of losing weight for overweight or obese patients, and the benefits of maintaining a healthy weight using diet changes and exercise; and (3) the fact that OA symptoms can often be significantly reduced without the need of undergoing a surgery. Other key messages pertained to disease knowledge (e.g., ''*The symptoms of osteoarthritis can vary greatly from person to person*'' and ''*Osteoarthritis is not an inevitable part of getting older*''); medication intake (e.g., ''*You should avoid the use of nonsteroidal anti-inflammatory drugs for your osteoarthritis over the long term*''); and about diagnostic methods (e.g., ''*Joint damage on an X-ray does not indicate how much your osteoarthritis will affect you*''). These messages are fundamental to facilitate the translation of evidence into patient knowledge and to optimize the patient---clinician interaction, therefore providing insights into how to conduct education and improve decision-making for patients with knee OA.

Exercise

It is well-established that physical activity and exercise therapy reduce symptoms and improve physical function in individuals with knee OA.[7---13] Literature shows that 150 min/week of moderate intensity aerobic exercise or 2 days/week of moderate-to-vigorous physical activity muscle-strengthening exercises are beneficial for individuals with preexisting knee OA. Translating these two activities into step counts, that would be approximately 7500 steps per day for aerobic exercises and 5750 steps per day for moderate-to-vigorous physical activity. In addition, there is more pain reduction when quadriceps-specific exercises were used compared to general lower-limb exercises and when supervised exercises were performed at least three times per week. However, the current recommendations suggesting one form of exercise over another are mainly based on expert opinion.

Irrespective of pain and function, a wide range of exercise options are available for knee OA.[29] To improve rehabilitation, physical therapists and other health care professionals should focus on patient-centered rehabilitation, considering patient's preferences and access to exercise equipment. The National Institute for Health and Care Excellence (NICE)[7] recommends strengthening exercises and aerobic fitness; the Osteoarthritis Research Society International (OARSI)[8] recommends structured land-based exercise programs of two types: (1) strengthening and/or cardio and/or balance training/neuromuscular exercise or (2) mind-body exercise including Tai Chi or Yoga; the American College of Rheumatology (ACR)[13] recommends aerobic, aquatic, and/or resistance exercises; the Ottawa Panel[9---11] recommends mind-body exercise (Hatha yoga, Tai Chi Qigong, sun style Tai Chi), strengthening exercise in isolation or combined with other types of exercise (coordination, balance, functional), and aerobic exercise in isolation or combined with strengthening exercise; and the European League Against Rheumatism (EULAR)[12] recommends pacing of activity and exercise in general for the management of knee OA.

There is high-quality evidence demonstrating the effectiveness and the clinically meaningful benefits of non-perioperative therapeutic exercise regimens to improve pain, physical function, and quality of life in individuals with knee OA.[29,30] Moreover, these improvements are sustained for at least two to six months after the end of treatment. It is highly unlikely that new research on this area will change these conclusions.[30,31] Therefore, there is no need to develop new trials to verify exercise effectiveness for knee OA. However, there is still a need to develop novel insights regarding treatment parameters used in rehabilitation programs, such as duration, frequency, modality (type), and intensity.[32] The type and dosage of exercise, when prescribing a home-based exercise protocol, should be individualized, based on the clinical evaluation and the patient's preferences.[33,34]

Education plays a vital role when prescribing an exercise protocol. Most current exercise protocols are noticeably under-utilized by individuals with knee OA, mainly due to patient beliefs, socioeconomic barriers, fear of movement, lack of confidence, lack of time to insert the exercise routine in daily life, and early treatment pain aggravation.[33---35] A survey with 123 physical therapists demonstrated that only 39% educated patients about the benefits of exercise for knee OA, 33% involved their patients in the development of the exercise program design, 28% managed to schedule follow-up appointments to review exercises and adherence, and 4% encouraged patients to keep going with exercises.[36] Prior to the beginning of an exercise protocol, patients need to clearly understand that pain/discomfort during the physical activity does not mean increased structural joint damage.[33] To optimize the effectiveness of exercise interventions, it is also essential to create strategies to increase adherence to exercise and overcome barriers, bearing in mind the environmental context and available resources of the patient.

Physical therapists can help patients with knee OA by fostering a positive therapeutic relationship. Some components of a positive therapeutic relationship may include increased relatability, supervision of exercise performance to promote success and confidence in self-management abilities of patients, use of group exercises, and follow-up telephone calls.[37] The top 5 behavior change techniques rated to be the most effective at increasing exercise adherence in patients with knee OA include: (1) review of progress in terms of pain and function at follow-up sessions, (2) development of a therapeutic plan which clearly states how often the patient will exercise and specifically what they will do, (3) development of specific and achievable goals related to the patient's knee pain and function, (4) review, supervision, and correction of exercise techniques at subsequent treatment sessions, and (5) follow-up sessions more than 3 months after the initial session, to check on the exercises and progress the home-based protocol, if needed.[36] Other

strategies such as the use of booster sessions (i.e. returning to a therapist after an initial period of treatment to perform a new session focused on review and progression of the exercise therapy) and the use of graded behavioral exercises (i.e. an exercise routine that is gradually increased into daily living) also promoted adherence in individuals with knee OA.[35]

Weight loss

Over one-third of the world's population is classified as overweight or obese and research shows that if the current trends continue, more than 55% of the world population will be classified as overweight or obese by 2030.[38,39] Because of its systemic effects on the body due to inflammatory and metabolic changes, obesity and overweight are considered primary risk factors related to chronic diseases, including knee OA.[40,41] Therefore, obesity presents a significant burden to society and the public health system.[39]

Weight change directly affects the risk of developing knee OA.[42] A reduction in weight of approximately 5.1 kg decreases the risk of developing knee OA by more than 50% in women with a baseline body mass index (BMI) higher than 25.0 kg/m^2.[42] A meta-analysis showed that in adults with mild to moderate knee OA and a mean BMI ranging from 33.6 to 36.4 kg/m^2, a weight reduction of 5%---10% can significantly improve pain, self-reported disability, and quality of life. Results of the included studies demonstrated that diet strategies such as meal replacements or the use of nutrition powders, together with nutritional education and behavioral therapy, can help individuals with knee OA to achieve weight loss targets.[43]

For individuals with knee OA, diet-only treatments have not been shown to relieve pain; however, a combination of diet and exercise has a moderate effect on this outcome.[44] Physical function, on the other hand, improved moderately with both diet-only treatments and diet combined with exercise. Patients who are classified as overweight should aim for at least a 7.7% body weight loss to achieve a minimal clinically important improvement in physical function.[45] In addition, to lose weight, an intensive diet alone (loss of at least 10% of baseline weight) is better than exercise alone (aerobic and strengthening training). However, the combination of exercise and diet presents the best results for weight loss.[46]

Clearly, there is a dose---response relationship between weight loss and symptom improvement in individuals with knee OA.[45,47---49] However, the maintenance of weight loss in long-term rehabilitation remains a substantial challenge. Successful strategies of weight maintenance are associated with achieving an initial goal of weight loss, creating consecutive weight goals, having a regular meal pattern that includes breakfast and healthier eating, having a physically active lifestyle, and controlling over-eating through self-monitoring behaviors. These strategies can be incorporated, when needed, in knee OA rehabilitation regimens to improve goals and increase patients' overall satisfaction with treatment. Other factors strongly associated with weight maintenance include the presence of social support, better coping strategies, higher self-efficacy, and overall increased in psychological resiliency and stability.[50]

In individuals with other chronic diseases, the contact between patient and therapist seems to be a key factor for weight loss.[51] Furthermore, continuing contacts after the end of the rehabilitation regimen appears to be effective, regardless of whether the contact is face-to-face, through telephone, or via email. Risk factors for regaining weight include a range of eating behaviors that involve a lack of restraint over food intake. These factors can include binge eating disorder (i.e. recurrent episodes of eating large quantities of food), eating as a reaction to emotions and stress, and a general tendency toward passive reactions to problems.

Adjunct therapies

Several adjunct therapies are used as complements to core knee OA treatments with the goal of maximizing outcomes for patients. Thermal modalities, laser therapy, therapeutic ultrasound, electrical stimulation, manual therapy techniques, taping, acupuncture, among others, are some interventions that are commonly used. For this article, we will review some of the adjunct therapies most commonly used by physical therapists in treating knee OA, providing details about the quality of evidence and nature of the recommendation.

Thermal modalities

There is still a lack of evidence to support the use of thermal modalities such as cold and heat in individuals with knee OA.[52,53] The overall quality of evidence for thermal modalities is classified as very low by the OARSI guidelines and as low by the ACR guidelines.[8,13] Research shows that patients with knee OA have individual preferences regarding heat, cold, or contrast therapy to improve pain and physical function status.[54] Women tend to prefer heat treatments and generally respond with more improvements in subjective quality of life and physical function to thermal modalities. Conversely, men favor cold or contrast therapies but were less likely to report benefits.[54,55] In humans, the use of cryotherapy was not superior to placebo to improve pain, physical function, and quality of life in individuals with knee OA.[56] Interestingly, clinical-like cryotherapy was recently shown to improve not only gait and function, but also to modulate the inflammatory process by reducing the number of leukocytes and cytokines in the synovial fluid in animal model with knee OA compared to placebo.[57]

Laser, therapeutic ultrasound, and electrical stimulation

The OARSI guidelines strongly recommended against the use of laser therapy for knee OA, citing an implausible biological mechanism and no efficacy, with a very low overall quality of evidence.[8] The potential mechanisms of pain relief by laser therapy are due to the stimulus of tissue metabolism and modulation of the inflammatory process. However, literature shows contrasting evidence regarding the use of laser therapies, more specifically low-level laser therapy (LLLT), in treating individuals with knee OA. A meta-analysis eval-

uating the effectiveness of LLLT on symptoms and function in patients with knee OA, showed no therapeutic benefit of LLLT compared with placebo for patients.[58] A more recent meta-analysis showed that LLLT seems to reduce pain and disability in individuals with knee OA when compared to placebo in randomized controlled trials.[59]

Studies regarding therapeutic ultrasound, although reporting beneficial effects of the therapy for knee OA, show methodological limitations that hinder the evidence synthesis, such as the inclusion of mixed interventions.[60---64] Thus, there is low quality of evidence to support the use of therapeutic ultrasound for individuals with knee OA.[8] However, the ACR guidelines conditionally recommends its use (i.e. the therapy is considered preference-sensitive to patients), meaning that therapists need to give a complete and clear explanation of benefits, harms, and burdens of the treatment when presenting it as an option to a patient.[13]

Evidence for electrical stimulation shows that there is a lack of adequate studies to support its use in patients with knee OA.[65] OARSI guidelines corroborates this information by presenting a very low quality of evidence for transcutaneous electrical stimulation.[8] In addition, the ACR strongly recommended against the use of transcutaneous electrical stimulation in all patients with OA.[13]

Manual therapy techniques, taping, and acupuncture

There is a low level of evidence to recommend the use of manual therapy techniques for knee OA.[8,13] Available techniques encompass the use of manual lymphatic drainage, massage, mobilization/manipulation, manual traction, and passive range of motion. There is low level of evidence showing that manual therapy techniques provide little additional benefit when compared to exercise alone for managing knee OA symptoms, and the ACR guidelines conditionally recommended against its use.[13]

There is very low level of evidence to support the use of taping for the management of knee OA.[8] With a no efficacy statement, the OARSI guidelines strongly recommends against the use of the therapy.[8] However, regarding Kinesio taping, the ACR guidelines conditionally recommends its use.[13]

For traditional acupuncture with manual stimulation, there is a low level of evidence to support the use of the therapy for patients with knee OA. [8,13] The ACR guidelines conditionally recommended acupuncture.[13] However, the OARSI guidelines stated an implausible biological mechanism and no efficacy for laser acupuncture and an unfavorable efficacy with safety issues for electroacupuncture, strongly recommending against and indicating a very low overall quality of evidence to support the use of either therapy.[8]

There is still an unmet need for quality randomized clinical trials regarding the majority of the adjunct therapies described above. Additionally, for the majority of the adjunct therapies, it remains to be seen whether complementary effects may be observed when they are combined with a gold standard treatment for knee OA (e.g. the complementary effects of cryotherapy when associated with an exercise protocol).[66] Therefore, with the current evidence, we recommend against the use of these therapies by physical therapists in clinical practice. However, if the therapy is still considered, we recommend it to be preference-sensitive to patients, and therapists must give a complete and clear explanation to patients regarding the evidence to support the use of the therapy in knee OA.

Pharmacological strategies

For knee OA, local therapies are preferable as core pharmacological treatments. Appropriate monitoring of the patient during a pharmacological treatment, especially for the development of adverse effects, is also recommended.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Due to minimal and mild adverse events, topical NSAIDs are strongly recommended as first-line treatment in both the OARSI[8] and ACR[13] guidelines. OARSI also recommends the use of topical NSAIDs for patients with gastrointestinal or cardiovascular comorbidities and patients with frailty.[8] In addition to topical NSAIDs, the ACR guidelines strongly recommends the use of oral NSAIDs and intraarticular glucocorticoid injections.[13]

Opioids

Opioids, another popular group of drugs that are frequently considered as potent pain-relievers, should be heavily discouraged.[16,67,68] There is high-quality evidence demonstrating that opioids have only small effects on pain and physical function in individuals with knee OA.[69] Furthermore, when compared to placebo, patients that used opioids had three to four times higher risks of serious adverse effects and/or drop-out due to adverse events.

Nutraceuticals

Nutraceuticals, i.e. foods or food supplements thought to have health benefits, are extremely popular in the treatment of OA. Glucosamine and chondroitin sulfate, nutraceuticals that are commonly used by patients with knee OA, lack scientific evidence to support their use. Both were strongly recommended against for the treatment of knee OA by the ACR[13] guidelines and classified as the lowest level of recommendation by the OARSI guidelines.[8] In addition, there are low efficacy and effect sizes of insufficient clinical relevance, when comparing these supplements to placebo.[70---72]

Surgery

Surgery is typically a last resort for the management of knee OA. Unfortunately, a vast majority of physicians deviate from evidence-based practice regarding surgical management of knee OA. From the variety of options available, arthroscopic knee surgery, specifically arthroscopic joint lavage, is the most common procedure performed.[4,73] However, several high-quality studies have demonstrated the low efficacy of arthroscopic surgery in terms of pain relief and physical function improvement in individuals with

Table 1 Patient-reported measures and their psychometric properties for knee OA.

Outcome	Observations	Scoring	Psychometrics
Visual Analogue Scale (VAS)	The purpose of VAS is to measure pain. The scale is placed in front of the patient who is asked to rate their pain intensity according to a pre-determined period of time. VAS can be used before, during, or after physical function tests.	From 0 to 10 cm (0 ---the complete absence of pain, and 10 ---maximum intensity).	A pain reduction of 1.75 cm on the scale is the recommended MCID in OA research.[103]
Numeric Rating Scale (NRS)	The purpose of NRS is to represent a unidimensional measure of pain. Usually, it is a segmented numeric version of VAS, and it can be administered verbally (also by telephone) or graphically for self-competition. The scale is placed in front of the patient who is asked to rate their pain intensity according to a pre-determined period of time. NRS can be used before, during, or after physical function tests.	A 0 10-point numeric scale with 0 representing ''no pain'' and 10 representing ''pain as bad as you can imagine''/''worst pain imaginable.''	A pain reduction of 2 points on the scale is the recommended MCID in patients with chronic musculoskeletal pain.[104]
Western Ontario & McMaster Universities Osteoarthritis Questionnaire (WOMAC)	WOMAC is a self-report questionnaire designed to assess the problems experienced by individuals with lower limb OA in the past 72 h. It contains 24 specific questions divided into three domains: pain, stiffness, and physical function.	The score of each question ranges from 0 to 4. The total questionnaire score is 96, with high scores representing worse results.	An improvement greater than or equal to 12% from baseline is the recommended MCID in OA research.[105]
Knee Injury and Osteoarthritis Outcome Score (KOOS)	This self-report questionnaire assesses the problems experienced by people with lower limb OA in the prior week by measuring the quality of life and knee function. It contains 42 questions in 5 domains: pain, other symptoms, function in daily life, sports-related function and recreation, and knee-related quality of life.	The answers are standardized and scored from 0 to 4. The total score of the questionnaire is 168. High scores indicate worse results than low scores	A difference of 8---10in the total score from baseline is the recommended MCID in OA research.[106]

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Table 1 (*Continued*)

Outcome	Observations	Scoring	Psychometrics
Algofunctional indices for the knee or index of severity for knee disease (Lequesne Index)	This index is used specifically for the evaluation of pain, maximum walking distance, and the daily activities of patients with OA.	The 10-question questionnaire is scored on a 0 24-point scale. Lower scores indicate there is less functional impairment, and higher scores reflect the worst outcomes. The sum of the scores is classified as: little effect (1 4 points), moderate effect (5 7 points), severe effect (8 10 points), very severe effect (11 13 points) and extremely severe effect (greater than or equal to 14 points).	The MCID for the Lesquene Index is still not established in knee OA research.
Short Form-36 questionnaire (SF-36)	The short form questionnaire is intended to measure the patient's quality of life with 36 items referring to the past four weeks. It presents a multiple-choice scale that evaluates eight domains of life: Physical Functioning, Role Limitations due to Physical Problems, General Health Perceptions, Vitality, Social Functioning, Role Limitations due to Emotional Problems, General Mental Health and Health Transition.	The sum of the total value varies from 0 to 100, with higher indexes indicating a better quality of life. Each of the eight summed scores can be linearly transformed into a scale from 0 (negative health) to 100 (positive health) to provide a score for each subscale. Each subscale can be used independently.	A difference of 10 points is recommended as an MCID in OA research.[107]
Short Form-12 questionnaire (SF-12)	The short form questionnaire is intended to measure the patient's general physical and mental well-being, which is based upon the SF-36 score. It has two components, the physical component summary (PCS) and the mental component summary (MCS) scores.	Scores are reported on a scale of 1 100 with a higher score representing a better health status. The score is calculated independently for each component according to the responses recorded on Likert scales of six questions (each). Scores are converted into the validated score using a defined algorithm.	An improvement of 4.5 points for the physical component and 4.8 points for pain relief and function are established as MCID in OA research for patients after knee arthroplasty.[108]

Table 1 (*Continued*)

Outcome	Observations	Scoring	Psychometrics
Health Assessment Questionnaire (HAQ)	A self-administered questionnaire consisting of 20 detailed questions of people's daily activities divided into eight categories: dressing and activities related to taking care of appearance, getting up, eating, walking, hygiene, reaching, gripping, and daily life activities.	Each patient assesses the difficulty they face carrying out each activity on a scale from 0 to 3, where zero means no difficulty performing and three means unable to perform the activity. Increasing scores indicate worse functioning with 0 indicating no functional impairment and 3 indicating complete impairment.	The MCID for the HAQ questionnaire is still not established in knee OA research.

MCID, minimal clinically important difference; OA, osteoarthritis.

knee OA.[73---75] The surgery also increases the chances of subsequent knee replacement surgery,[76,77] and there are multiple harms associated with the procedure, including venous thrombosis, infection, pulmonary embolism, and in some cases, death.[73,75] Clinical practice guidelines, including those published by the Journal of the American Academy of Orthopaedic Surgeons, strongly recommend against the use of arthroscopy in nearly all patients with degenerative knee disease.[75,78]

Joint replacement is another popular surgery in individuals with end-stage knee OA. It is a cost-effective treatment and should be considered when all non-surgical treatment options ---used within a time-frame of 6-months ---were unsuccessful.[4,79] However, although joint replacement is a successful treatment for relieving many symptoms of individuals with knee OA, persistent pain after surgery is reported by some patients.[80] One in five patients who undergo total knee replacement is not satisfied with the outcome.[81] Predictors for poor outcomes after surgery include anxiety/depression, high patient expectations for surgery, low 1-year WOMAC, pain at rest before surgery, and complications after surgery that necessitate readmission.[81,82] Individuals with severe radiographic knee OA who have poor quality of life due to the disease are most likely to report considerable improvements in pain and function after knee replacement.[83] There is low- to moderate-quality of evidence showing that a period of 8 weeks or more of exercise can improve functional outcomes and physical activity in individuals undergoing total knee replacement.[84]

Key outcome measures

For researchers aiming to improve data collection in knee OA studies and for clinicians treating patients in clinical practice, there are well-established core outcome measures that can be used to evaluate the domains of pain and physical function of patients.[8,13,85---87] In Tables 1 and 2, we provide a comprehensive description of some of the critical subjective and objective outcome measures used in knee OA studies, respectively. In addition to the content provided in the tables, the following outcome measures were also classified as ''important'' (according to GRADE criteria) in evaluating the evidence that contributed to the OARSI guidelines: structural progression of the disease measured by joint space narrowing, cartilage thickness, and cartilage volume; withdrawals due to adverse events, the total number of adverse events, serious adverse events, and other treatment-specific harms. Valid scales to measure self-efficacy and depression were also classified as important outcomes.[8,88]

For physical function measures, it is crucial to understand that there is a clear distinction between patient-reported measures and performance-based measures. The first evaluates what patients perceive they can do, and the latter reflects what they can do. Previous reports show that for individuals with knee OA, self-reported measures are not correlated with objective measures of physical function.[89---94] On the other hand, self-reported measures were related to pain, knee strength, and depression. Objective measures of physical function were correlated to functional self-efficacy (i.e. how confident an individual is to perform a physical task).[95] Both are different constructs and are complementary, rather than competing, when assessing individuals with knee OA. Therefore, neither clinical researchers nor clinicians should substitute self-report outcome measures with performance-based measures, or vice versa. Instead, healthcare professionals treating knee OA should focus on collecting both types of outcome measures to obtain the most comprehensive assessment possible.

Future perspectives

Although research in OA has been documented for more than 100 years, there are still no successful therapies to stop or reduce the progression of joint degeneration. However, with technological advancements, new approaches and therapies are emerging to aid these patients.

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Table 2 Objective performance-based measures and their psychometric properties for knee OA.

Outcome	Observations	Scoring	Psychometrics
30-s Chair to Stand Test	A chair with no arms is placed against a wall to prevent oscillations. Patients sit in the middle of the chair, with their back straight, feet apart resting on the floor in line with their shoulders. The test requires to rise from a sitting to a standing position as many times as possible in 30 s.	The total number of repetitions.	An increase of 2---3 repetitions is recommended as the MCID in OA research.[85]
40 m (4 × 10 m) Fast Paced Walk Test	Administered at a distance of 10 m (marked by tapes), a cone is placed 2 m before the start and 2 m after the end of each marking. The participant is instructed to walk as quickly but as safely as possible the first 10 m (from the start mark), to turn around the cone and walk back the 10 m again, successively until completing the distance of 40 m.	Speed (m/s).	An increase of 0.2---0.3 m/s in the test is the recommended MCID in OA research.[85]
Stair Climb Test (SCT)	The participant is positioned in front of the stairs, and, at the therapist's signal, he/she has to climb the indicated steps (we use the 12-step SCT) and descend promptly, being able to use the handrail as a security instrument. We use 20 cm steps height, a handrail stair in an illuminated environment, free of traffic, or external distractions. Moreover, a pre-test was conducted to identify the need for safety measures.	The final score is calculated based on the time the participant takes to perform the test and is compared to the normative literature values available for the test.	A reduction of 5.5 s in the test is the recommended MCID in OA research.[85]
Timed-up and Go Test	This test assesses: balance moving from sitting to standing, stability in walking, and gait course changes without using compensatory strategies. The participant is asked to stand up from a chair, walk 3 m, turn around, return, and sit back in the chair.	The total time to complete the test.	For the MCID, a reduction of 0.8---1.4 s is recommended in OA research.[85]
6-Minute Walk Test	This test assesses the aerobic capacity and long-distance walking activity. In addition, it is used to assess endurance and dynamic balance when changing directions during the walking activity.	The maximum distance walked in 6 min	A small MCID of 20 m and a substantial MCID of 50 m have been estimated for the test in a sample of community-dwelling older adults with mobility dysfunction.[87]

MCID, minimal clinically important difference; OA, osteoarthritis.

Biomaterials such as scaffolds, hydrogels, microspheres, and nanofibers associated with cutting-edge advances in cell-based approaches that focus primarily on cartilage regeneration, hold promise in the regeneration of the OA joint.[96] However, high-quality evidence is still scarce regarding this topic. Computer technologies also hold promise with respect to data mining (i.e. a process designed to search databases for consistent patterns and/or systematic relationships between variables) and machine learning approaches (i.e. a statistical method of data analysis using algorithms where a computer learns from a variety of examples). These technologies can be used in tandem to create patient-specific prediction models that analyze large amounts of patient data to design and develop effective and specific personalized therapeutic interventions for knee OA. The use of such modeling techniques may also result in substantial savings in medical resources and societal costs by reducing the burden of the disease.[97] Moreover, these technologies can help advance the fields of imaging, electronic medical record keeping, genetic/genomic analysis, and serum sample analysis, therefore facilitating the stratification of relevant OA phenotypes.[98,99]

Mobile health is another promising category that offers an unprecedented opportunity to obtain real-world patient data using a smartphone's capabilities and embedded sensors, such as accelerometers, gyroscopes, magnetometers, and barometers, among others.[100] These sensors, when configured correctly, can be used to precisely monitor aspects related to health, such as physical activity and function.[101] Through the development of specific algorithms, data from these sensors can be processed and used to measure and record movement patterns that are commonly assessed in physical function tests. Researchers can collect and store large quantities of objective clinical data, at multiple time points, to help reduce patient's recall bias and to provide more reliable and precise data about patients' fluctuation in symptoms.[101,102]

Conclusion

Osteoarthritis is one of the most frequent diseases worldwide. The burden to society and health care systems is gradually increasing. It is our duty as healthcare professionals to leverage our access to high-quality evidence to increase the number of individuals receiving the appropriate core non-pharmacological treatments for knee OA. By doing so, we can increase the uptake of evidence-based guidelines in clinical practice of physical therapy. Patient education, exercise, and weight maintenance are vital for the successful treatment of these patients.

Conflicts of interest

The authors declare no conflicts of interest.

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ARTIGOS PUBLICADOS E NÃO INCLUÍDOS PARA DEFESA DA TESE

Título: *Mobile health technologies for the management of systemic lupus erythematosus: a systematic review*

Autores: L.O. Dantas, S. Weber, M.C. Osani, R.R. Bannuru, T.E. McAlindon and S. Kasturi.

Objetivo: Realizar uma revisão sistemática dos aplicativos de saúde móvel disponíveis para lúpus eritematoso sistêmico (LES) em lojas online e realizar uma revisão sistemática da literatura sobre tecnologias de saúde móvel para LES.

Principais achados: Embora haja um interesse crescente no desenvolvimento de tecnologias de saúde móvel para apoiar pacientes com LES, as ferramentas atualmente disponíveis são de baixa qualidade e funcionalidade limitada. Além disso, a literatura sobre essa área é esparsa.

Publicação: *Lupus* (Fator de impacto: 2.25). **DOI**:10.1177/0961203319897139

Título: *Digital physical therapy in the COVID-19 pandemic*

Autores: Lucas Ogura Dantas, Rodrigo Py Gonçalves Barreto, Cristine Homsi Jorge Ferreira

Objetivo: Editorial para discutir o papel da fisioterapia digital em épocas de COVID-19.

Publicação: *Brazilian Journal of Physical Therapy* (Fator de impacto: 2.1).
DOI: 10.1016/j.bjpt.2020.04.006

Título: Tratamento Conservador na Reabilitação da Osteoartrite do Joelho.

Autores: SERRÃO, P.R.M.S.; JORGE, A.E.S.; **DANTAS, L.O**.; SALVINI, T.F. In: BARBOSA, R.N.; SILVA; M.F. (org.).

Publicação: Capítulo de livro. Programa de Atualização em Fisioterapia Traumato-Ortopédica (PROFISIO). Porto Alegre: Artmed Panamericana, 2019. p. 79-130. ISBN 978-85-514-0940-4

Título: *Patient-specific reference values for objective physical function tests: data from the Osteoarthritis Initiative*

Autores: Matthew S. Harkey, Lori Lyn Price, Kieran F. Reid, Grace H. Lo, Shao-Hsien Liu, Kate L. Lapane, **Lucas Ogura Dantas**, Timothy E. McAlindon, Jeffrey B. Driban

Objetivo: Nosso objetivo foi estabelecer valores de referência específicos estratificados por sexo, de testes objetivos de função física entre indivíduos com ou em risco de osteoartrite do joelho (OAJ) em subconjuntos de idade, gravidade radiográfica da OAJ e índice de massa corporal (IMC).

Principais achados: Estabelecer o nível relativo de função física objetiva de um indivíduo, comparando seu desempenho com indivíduos similares com relação ao sexo, idade, grau radiográfico da doença ou IMC pode ajudar a melhorar a interpretação dos dados de função física. Criamos uma tabela de valores de referência interativa que fornece aos médicos e pesquisadores uma forma simples de acessar esses dados.

Publicação: *Clinical Rheumatology* (Fator de impacto: 2.39). **DOI**: 10.1007/s10067-020-04972-1.

Título: *Photobiomodulation therapy associated with supervised therapeutic exercises for people with knee osteoarthritis: a randomised controlled trial protocol*

Autores: Ana Elisa Serafim Jorge, **Lucas Ogura Dantas**, Paula Regina Mendes da Silva Serrão, Francisco Aburquerque-Sendín, Tania de Fatima Salvini

Objetivo: Desenhar um ensaio randomizado controlado para verificar os efeitos complementares da terapia por laser, associada a um protocolo de exercícios personalizados em relação à dor, função e qualidade de vida em indivíduos com osteoartrite de joelho.

Hipótese: A terapia por laser, combinada com o protocolo de exercícios, irá alcançar melhores resultados com relação aos desfechos clínicos em pacientes com osteoartrite de joelho quando comparados com os outros grupos.

Publicação: *BMJ Open* (Fator de impacto: 2.49). **DOI:** 10.1136/bmjopen-2019-035711

Título: Neuromuscular electrical stimulation in critically ill traumatic brain injury patients attenuates muscle atrophy, neurophysiological disorders, and weakness: a randomized controlled trial Paulo

Autores: Paulo Eugênio Silva, Rita de Cássia Marqueti, Karina Livino-de-Carvalho, Amaro Eduardo Tavares de Araujo, Joana Castro, Vinicius Maldaner da Silva, Luciana Vieira, Vinicius Carolino Souza, **Lucas Ogura Dantas**, Gerson Cipriano Jr, Otávio Tolêdo Nóbrega, Nicolas Babault and Joao Luiz Quagliotti Durigan

Objetivo: Avaliar o tempo necessário e os efeitos de um protocolo de estimulação elétrica neuromuscular na arquitetura do músculo, distúrbio eletrofisiológico neuromuscular e força muscular. Além disso, avaliar os efeitos na inflamação sistêmica do plasma, respostas catabólicas e outros desfechos clínicos.

Principais achados: O tempo necessário para o protocolo de estimulação elétrica neuromuscular prevenir distúrbios da arquitetura muscular e tratar a fraqueza foi de pelo menos 7 dias e de 14 dias para tratar NED. Os resultados secundários exibiram resultados menos precisos, com intervalos de confiança que abrangeram efeitos úteis ou triviais.

Publicação: Journal of Intensive Care (Fator de impacto: 3.10). **DOI**: 10.1186/s40560-019-0417-X

Título: *Mobile health technologies for the management of rheumatic diseases: a systematic review of online stores in Brazil*

Autores: Lucas Ogura Dantas, Cristiano Carvalho, Beatriz Cardinal Prando, Timothy E. McAlindon, Paula Regina Mendes da Silva Serrão

Objetivo: Realizar uma revisão sistemática dos aplicativos de saúde móvel disponíveis para as principais doenças reumatológicas em lojas online no Brasil.

Principais achados: Há um interesse crescente no desenvolvimento de tecnologias móveis para apoiar os doentes com doenças reumáticas. Embora a maioria dos aplicativos incluídos tenham vindo de organizações sem fins lucrativos, ainda são de qualidade pobre e de função limitada. Este estudo é um apelo ao desenvolvimento de novas aplicações de saúde centradas nos usuários para que possam capacitar os pacientes com doenças reumáticas no Brasil, especialmente na área da osteoartrite, artrite reumatoide e lúpus, uma vez que não foram encontradas aplicativos para essas patologias.

Publicação: *Clinical Rheumatology* (Fator de impacto: 2.39). **DOI**: 10.1007/s10067-020-05561-y