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Nutritional supplements in the clinical management of tendinopathy: A scoping review

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ABSTRACT

Introduction: Tendinopathy has a high prevalence and incidence in the general population and among athletes, with a lack of consensus among medical practitioners on optimal management strategies. This scoping review aimed to map existing evidence on nutritional supplement interventions in the clinical management of tendinopathies.

Methods: This scoping review was reported in accordance with the PRISMA-ScR. Databases searched included MEDLINE, CINAHL, AMED, EMBase, SPORTDiscus, and the Cochrane library (Controlled trials, Systematic reviews). All primary study designs investigating nutritional supplement interventions in the clinical management of tendinopathies were considered for inclusion.

Results: 1527 articles were identified with 16 included in the review. Studies investigated a range of nutritional supplements in the clinical management of various tendinopathies, including several commercially available proprietary blends of several ingredients. TendoActive (Mucopolysaccharides, type-1 collagen & vitamin C) was used in two studies, TENDISULFUR (MSM, hydrolysed collagen, L-arginine, L-lysine, Vitamin C, Bromelain, Chondroitin, Glucosamine, Boswellia, & Myrrh) was used in three studies, Tenosan (Arginine-L-alpha ketoglutarate, hydrolysed collagen type-1, MSM, vitamin C, and bromelain, vinitrox) was used in two studies. Collagen peptides were used in 2 studies, with omega 3 fatty acids, combined fatty acids and antioxidants, turmeric rhizome combined with Boswellia, HMB, Vitamin C in isolation and combined with gelatin, and creatine investigated in one study each.

Conclusion: Despite a paucity of studies to date, findings from this review suggest that several nutritional compounds may be beneficial in the clinical management of tendinopathies, by exerting anti-inflammatory effects and improving tendon healing. Nutritional supplements may have potential as an adjunctive method to standard treatment methods such as exercise, where their pain relieving, anti-inflammatory, and structural tendon effects may augment the positive functional outcomes gained from progressive exercise rehabilitation.

Keywords: Nutrition; Tendinopathy; Dietary supplements; Nutraceutical; Physiotherapy; Tendon

INTRODUCTION

Tendinopathy represents a spectrum of tendon pathology, associated with chronic tendon pain and impaired physical function, and as a disease entity is responsible for 30-45% of all musculoskeletal pathologies requiring medical treatment (Perucca et al. 2016, Millar et al. 2021). The worldwide increase in sports participation and physical activity has been associated with the increased incidence and prevalence of tendinopathies globally in recent years, due to physical loading demands placed on tendons (Knapik et al. 2020, Hopkins et al. 2016, Ahmad et al. 2020). Tendinopathy is considered to have a multifactorial etiology and pathogenesis, with a plethora of intrinsic and extrinsic factors linked to its pathophysiology and risk for onset (Seitz et al. 2011, Sprague et al. 2018, Squier et al. 2021, Bidell et al. 2016, Magnusson et al. 2019, Kjaer et al. 2006, 2009, Millar et al. 2012). Despite a lack of consensus on the optimal management of tendinopathies, several common treatment methods are often clinically implemented such as extracorporeal shockwave therapy (ESWT), low level laser therapy (LLLT), platelet-rich plasma injections, corticosteroid injections and various exercise-based approaches (Burton 2021, Tripodi et al. 2021, Turgay et al. 2020, Girgis et al. 2020, Irby et al. 2020, Challoumas et al. 2021, Mamais et al. 2018, Lyu et al. 2022, Karanasios et al. 2021). Eccentric, isometric, and heavy slow resistance training interventions have shown clinical benefits for both upper and lower limb tendinopathies and are often recommended as the most effective treatment approach (Burton 2021, Burton, 2022, Ortega-Castillo et al. 2016, Lim et al. 2018, Clifford et al. 2020, Murphy et al. 2019). In recent years, increased attention has been given to the potential therapeutic efficacy of dietary interventions and nutritional supplements in the clinical management of musculoskeletal conditions such as tendinopathy in both the general population and athletes (Zdzieblik et al. 2017, Clark et al. 2008, Maughan et al. 2018). Several micronutrients, vitamins, natural compounds, and nutraceutical supplements have been postulated to have beneficial pain-relieving effects in tendinopathy, primarily through targeting inflammatory mechanisms and having anti-inflammatory, pro-collagen, and tendon healing effects (Fusini et al. 2016). Inflammation and inflammatory mediators and cytokines have been recognized as a key component in the pathogenies of tendinopathy, which contribute to tendon degeneration and structural changes (Millar et al. 2010, Dean et al. 2017, Canosa-

Carro et al. 2022, Magnusson et al. 2010, Bedi et al. 2012, Millar et al. 2016, Millar et al. 2009, Millar et al. 2017). Combining nutritional supplements with currently recommended treatments with documented beneficial effects such as resistance training, has been suggested to potentiate clinical improvements (Balius et al. 2016, Praet et al. 2019).

Despite the role of nutrition and dietary factors in tendon health and risk for tendon disease receiving increased research attention, however the relationship between nutrition and clinical tendon health is still relatively unexplored. Increasing evidence suggests there is a link between metabolic diet-related conditions and tendon health and function, such as hypercholesterolemia, obesity, and diabetes mellitus, which are associated with increased risk for tendon rupture (Soslowsky et al. 2016, Ahmed 2016, Tilley et al. 2015, Lui et al. 2017). The pathogenesis of diabetes is associated with increased presence of inflammatory mediators, growth factors, angiogenesis, and collagen synthesis, which may explain its association with increased risk for tendinopathy (Ranger et al. 2016, Batista et al. 2008, Hsu and Sheu 2016). High fat diets can impair metabolic and tendon homeostasis, leading to reductions in genes required for collagen synthesis (COL1A1, COL3A1) and over-expression of matrix metalloproteinases (MMPS) such as MMP2 leading to cellular apoptosis and alterations in tendons structure (Chechi et al. 2006, Grewal et al. 2014). Altered glucose metabolism and utilization can cause increased glycolytic activity, reactive oxygen species production and chondrogenesis, which have been identified as potential factors in the initiation and progression of tendinopathy (Longo et al. 2008, 2009 Greve et al. 2012). The potential link between glucose metabolism and tendon pathology is apparent as tendinopathy is associated with systemic metabolic disorders, with high glucose linked to changes in proteoglycans, MMPs, collagen synthesis, and tenocyte proliferation (Masood et al. 2014, Burner et al. 2012, Tsai et al. 2013, Canalis et al. 1977). Additional metabolic abnormalities associated with altered tendon homeostasis include hypercholesterolemia, hyperuricemia, excessive lactate production, and impaired TGF-B1 signalling, which may alter inflammation and tendon repair processes (Soslowsky et al. 2016, Andia and Abate 2016, Abate et al. 2016, Glueck et al. 1968, Zhang et al. 2018, Sikes et al. 2018, Khan et al. 1999, Jarvinen et al. 1997, Kuzel et al. 2013, Luan et al. 2015, Kannus et al.

1997). This evidence suggests that systematic metabolic disorders, nutritional factors, and dietary intake have a role in tendinopathy pathogenesis and that tendon homeostasis is sensitive to metabolic and nutritional perturbations, suggesting a potential role for nutritional supplements in altering the impaired tendon environment in tendinopathy. However, there has been a paucity of research into the effects of nutritional supplements in the clinical management of tendinopathies, despite findings from preclinical studies suggesting beneficial effects of nutraceuticals on tendons (Fusini et al. 2016, Loiacono et al. 2019). Therefore, the objective of this scoping review is to evaluate current research on the use of nutritional supplements for treating tendon injuries. The scoping review will be guided by addressing the following review questions on specific aspects of nutritional supplement interventions within tendon rehabilitation: 1. What nutritional supplement interventions for tendon injuries have been used in studies? What intervention parameters and outcome measures have been used for nutritional supplement interventions for tendon injuries in published studies? 3. What outcomes have been reported for nutritional supplement interventions for tendon injuries? 4. What physiological mechanisms explaining effects of nutritional supplement interventions for tendon injuries have been reported in published studies?

METHODS

Due to the exploratory nature of the research questions of this review, a scoping review was conducted as they are recommended for mapping key concepts, evidence gaps and types of evidence within a particular field and can help guide future research and the possibility of conducting systematic reviews on the topic (Tricco et al. 2018). The scoping review is reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-analysis extension for Scoping reviews (PRISMA-ScR) (Tricco et al. 2018).

Inclusion criteria

The inclusion criteria for the scoping review were guided by a modified PICO, which includes population, concept, and context (PCoCo) as recommended for scoping reviews (Peters et al. 2020). The review considered participants of any age with a diagnosis of any tendinopathy for any time duration. Any tendon condition characterised by common tendinopathy symptoms, in the absence of a full thickness tendon rupture was considered for inclusion. A clinician's diagnosis based on symptoms including pain location and a symptom altering response to palpation or tendon loading with specific tendinopathy tests were accepted for inclusion. The concept of interest is any form of nutritional supplement intervention for tendinopathy. The intervention may be delivered in isolation or combined with other interventions. The context considered for inclusion included any setting in which nutritional supplement interventions for tendinopathy have been provided. This scoping review considered both experimental and quasi-experimental study designs including randomized controlled trials and non-randomized controlled. In addition, prospective and retrospective cohort studies, case series and case reports were considered for inclusion. Unpublished studies, reviews or reports were not considered for inclusion.

Search strategy

A 3-step search strategy was implemented in this scoping review. It incorporated the following: 1) a limited search of MEDLINE and CINAHL using initial keywords, followed by analysis of the text words in the title/abstract and those used to describe articles to develop a full search strategy; 2) The full search strategy was adapted to each database and applied to MEDLINE, CINAHL, AMED, EMBase, SPORTDiscus, Cochrane library (Controlled trials, Systematic reviews), JBI Evidence Synthesis, and PEDro. The following trial registries were searched: ClinicalTrials.gov, ISRCTN, The Research Registry, EU-CTR (European Union Clinical Trials Registry), ANZCTR (Australia and New Zealand Clinical trials Registry). Databases were searched from inception to March 20th, 2022. The search for grey literature included Open Grey, MedNar, Cochrane central register of controlled trials (CENTRAL), EThOS, CORE, and Google Scholar. 3) For each article located in steps 1 and 2, a search of cited and citing articles using Scopus and hand-searching where necessary, was conducted. Studies published in a language other than English were only considered if a translation was available as translation services were not available to the authors.

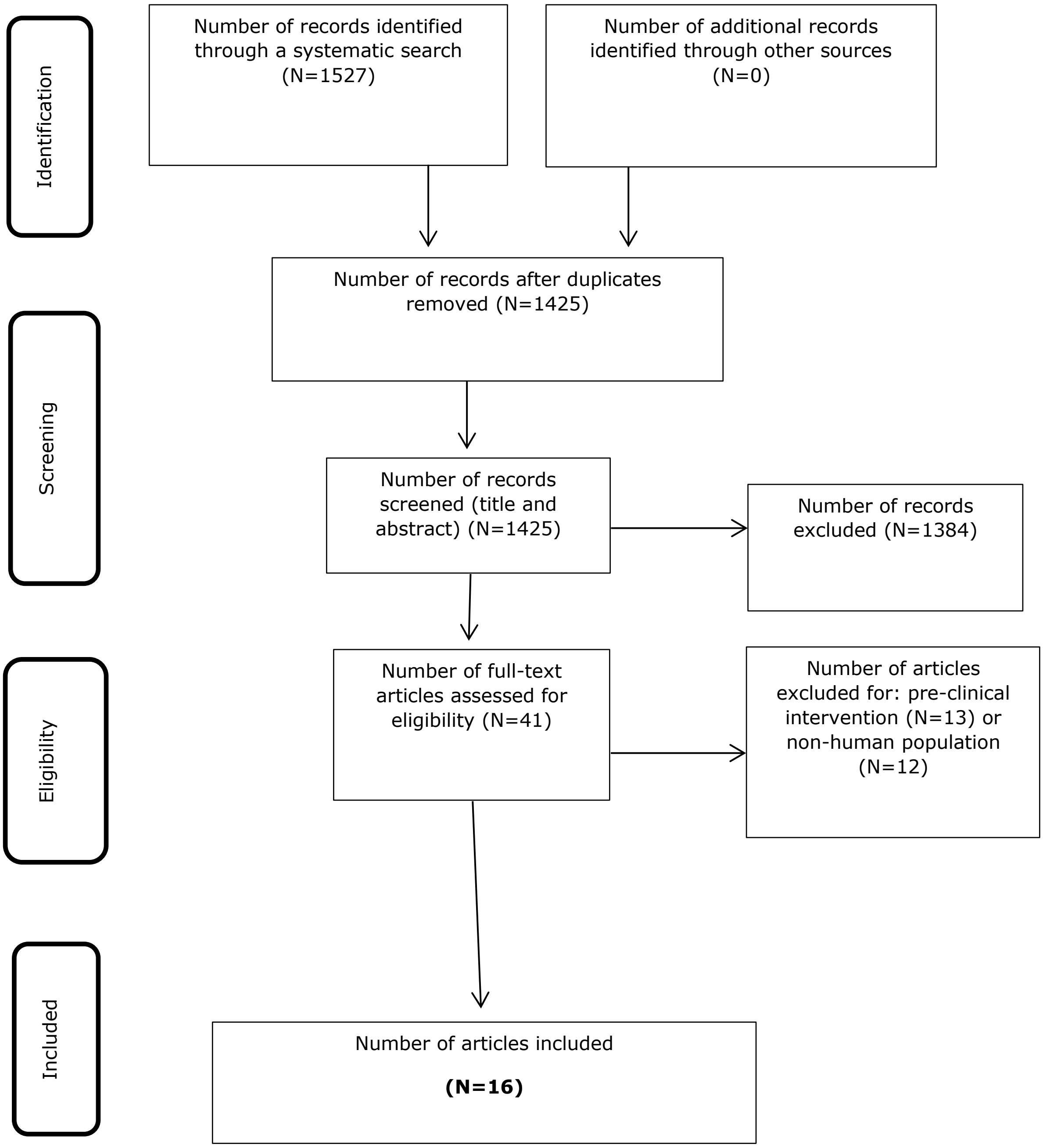
Study selection

Following the search, all identified citations were collated and uploaded into RefWorks and duplicates removed. Titles and abstracts were screened by two independent reviewers (IB and AM) and assessed against the review inclusion criteria. Potentially relevant studies were retrieved in full, with their details imported into Covidence software (Veritas Health Innovation, Melbourne, Australia). Two independent reviewers (IB and AM) assessed the full text of selected articles in detail against the review inclusion criteria. Any disagreements that arose at any stage of the study selection process were resolved through discussion. The results of the search are reported in accordance with the PRISMA-ScR (Figure 1). In accordance with guidance on conducting scoping reviews, critical appraisal was not conducted (Peters et al. 2020).

Data extraction and analysis

Data were extracted from sources included in the scoping review by one reviewer (IB), with independent data extraction by a second reviewer (AM) for 10% of studies. The data extracted included dimensions such as study type, purpose, population & sample size, methods, details of intervention, outcome measures used and clinical outcomes. Interventions details included type, dosage, intervention parameters, and any methods used for progression and monitoring compliance. The extracted data are presented in Table 1 with a narrative synthesis accompanying the tabulated results. The extracted data were analysed using descriptive statistics, with findings presented in tabular form as tables and figures, along with a narrative synthesis.

FIGURE 1: PRISMA study flow diagram



RESULTS

Included study characteristics

The literature search yielded 1527 articles, reduced to 1425 after removing duplicates, of which 16 met the inclusion criteria and were included in the review. The search results are summarised in the PRISMA flow chart (Figure 1). An overview of the characteristics, intervention parameters and outcomes of the included studies are provided in Table 1. The included studies consisted of 12 randomised controlled trials (RCTs), one comparative study, one open-label non controlled observational study, one open-label non-comparative study and one case report. The sample sizes of included studies ranged from 1-670 and intervention duration ranged from 4-78 weeks, with 12 weeks (5 studies) and 4 weeks (5 studies) most common. Follow-up periods ranged from 4-78 weeks, with most studies having follow-up length between 12-52 weeks. Various tendinopathies were included in 4 studies, Achilles tendinopathy in 4 studies, rotator cuff tendinopathy or tendon repair in 4 studies, patellar tendinopathy in 2 studies, plantar heel pain in 1 study, and flexor hallucis longus tendinopathy in 1 study. Studies investigated a range of nutritional supplements in the clinical management of various tendinopathies, including several commercially available proprietary blends of several ingredients. TendoActive (Mucopolysaccharides, type-1 collagen & vitamin C) was used in two studies (Balius et al. 2016, Arquer et al. 2014). TENDISULFUR supplement (MSM, hydrolysed collagen, L-arginine, L-lysine, Vitamin C, Bromelain, Chondroitin, Glucosamine, Boswellia, & Myrrh) was used in three studies (Merolla et al. 2015, Vitali et al. 2019, Notarnicola et al. 2021). Tenosan supplement (Arginine-L-alpha ketoglutarate, hydrolysed collagen type-1, MSM, vitamin C, and bromelain, vinitrox) was used in two studies (Gumina et al. 2012, Notarnicola et al. 2012). Collagen peptides were used in 2 studies (Choudhary et al. 2012, Praet et al. 2019), with omega 3 fatty acids (Sandford), gelatin (Baar), combined fatty acids and antioxidants (Mavrogenis 2004), bioptimized turmeric rhizome (Henrotin), HMB (sanchez-gomez), Vitamin C (Martel 2022) and creatine (Juhasz) investigated in one study each. Supplements were prescribed with various dosages and delivery methods such as tablets, capsules and sachets mixed with fluids. Several studies investigated nutritional supplements combined with other interventions, such as various forms of exercise (7) and ESWT (4), while 4 studies used supplements in isolation.

Outcome measures

Of the 16 included studies, all assessed pain and or function as a main outcome measure of the intervention, using measures such as the visual analogue scale (VAS) (11), Victorian Institute of Sport Assessment – Achilles (VISA-A))4) Victorian Institute of Sport Assessment – Patellar (VISA-P) (2), Roles and Maudsley score (2), simple shoulder test (3), and the Constant Murley score for shoulder function (3). Other outcome measures included tendon properties assessed by ultrasound (4), MRI (2) or oximetry (1), global rating of change (GRoC) (2), measures of strength (2), and quality of life (1).

Outcomes

Most of the studies included in this review found positive clinical outcomes, such as improvements in pain, function and tendon structure following nutritional supplement intervention. The TendoActive supplement was found to enhance clinical outcomes when combined with eccentric training for Achilles tendinopathy (Balius 2016), and significantly improve pain, function and tendon structure when delivered in isolation for Achilles, patellar, lateral elbow tendinopathy (Arquer et al. 2014). Three studies found clinical improvement following supplementation with TENDISULFUR, with the supplement being superior to placebo following rotator cuff tendon repair (Merolla 2015), and efficacy being higher when combined with ESWT for various tendinopathies (Notarnicola 2021, Vitali 2019). Supplementation with Tenosan was also found to be superior for pain improvement following rotator cuff tendon repair versus control (Gumina et al. 2012), with increased efficacy when combined with ESWT versus ESWT alone for Achilles tendinopathy (Notarnicola 2012). Collagen peptide supplementation was found to be superior for improving pain and function in Achilles tendinopathy versus diclofenac (Choudhary 2021) and when combined with eccentric training versus eccentric training alone (Praet et al. 2019). However, both studies found non-significant changes in tendon structure, despite clinical improvement. Omega-3 fatty acid supplementation combined with exercise was found to have a small improvement in pain and function in rotator cuff tendinopathy versus exercise alone (Sandford). However, combined supplementation with omega-3 fatty acids and antioxidants was found to significantly improve pain and function for various tendinopathies in another study (Mavrogenis et al. 2004). Combined supplementation with turmeric (C. longa) and Boswellia serrata was found to significantly improve pain for various tendinopathies when delivered in isolation (Henrotin et al. 2020). Creatine monohydrate supplementation combined with rehabilitation was found to be superior for improving pain and physical performance compared to rehabilitation alone in swimmers with flexor hallucis longus tendinopathy (Juhasz et al. 2018). Vitamin C supplementation combined with exercise was found to be superior to exercise only for improving pain, function and tendon healing rates following rotator cuff tendon repair (Martel et al. 2022). Supplementation with HMB Combined with rehabilitation consisting of ESWT and eccentric training was not found to be superior for pain improvement versus rehabilitation alone for patellar tendinopathy, but was superior for improving muscle power, strength, and physical performance outcomes (Sanchez-Gomez et al. 2022).Gelatin and Vitamin C supplementation combined with strength training was found to lead to normalised tendon structure, improved pain and function after long-term follow up of 78 weeks in a case study (Baar et al. 2019).

DISCUSSION

Nutritional supplements, either in isolation or combined with traditional tendinopathy rehabilitation methods, such as exercise, may serve to improve pain and function in patents via several mechanisms. Inflammatory changes are known to occur in tendons with tendinopathy, with several inflammatory cytokines and molecules implicated in the pathogenesis of tendinopathy (Legerlotz et al. 2012). The main mechanisms by which nutritional supplements may improve tendinopathy symptoms, could be there ability to affect inflammation and augment inflammatory processes and cells, reducing pain (Ronchetti et al. 2017). Many of the supplement interventions included in this review are known to have anti-inflammatory properties and may be capable of downregulating inflammatory processes in tendinopathy. The supplement blend Tendisulfur (MSM, hydrolysed collagen, L-arginine, L-lysine, Vitamin C, Bromelain, Chondroitin, Glucosamine, Boswellia), was found to improve pain in serval studies in this review, with the authors postulating this improvement may be due to downregulation of the NF-Kb signaling pathway and decreased inflammatory mediators and cytokines such as TNF-a, and IL-6 (Merolla et al. 2015, Vitali et al. 2019, Notarnicola et al. 2021). The supplement TendoActive (Mucopolysaccharides, type-1 collagen & vitamin C) was also found to be effective for improving pain and function in a variety of upper and lower limb tendinopathies (Arquer et al. 2014), with this effect potentiated when combined with eccentric training for Achilles tendinopathy (Balius et al. 2016). TendoActive has been shown to have the potential to inhibit the NF-Kb mediated IL-1B catabolic signaling pathway in human tenocytes, resulting in downregulation of COX-2, MMP-1 and activated caspase-3, while preventing the downregulation of collagen type-1 (Shakibaei et al. 2011). The supplement Tenosan (Arginine-L-alpha ketoglutarate, hydrolysed collagen type-1, MSM, vitamin C, and bromelain) was also found to reduce pain, and improve function and tendon repair (Notarnicola et al. 2012), which may be due to its ability to inhibit the generation of bradykinin and catabolic signaling pathways in tenocytes (Gumina et al. 2012).

Supplementation with curcuminoids and Boswellia serrata in isolation (also found in Tendisulfur) was found to reduce pain in several tendinopathies, which may also be associated with inhibition of the NF-kB pathway (Henrotin et al. 2020). Curcumin is a compound derived from curcuma longa and is a powerful antioxidant which has been shown to have many beneficial effects on wound healing, tissue regeneration, tenocyte survival and tendon structure, and reductions in neovascularization, apoptosis, and inflammation in tendons (Jiang et al. 2016, Peddada et al. 2015, Pari et al. 2007, Buhrmann et al. 2011). The positive effects of Boswellic acid on pain reduction is thought to be caused by inhibition of elastase and 5-lipoxygenase which leads to suppressed leukotriene formation and migration, and reductions in inflammatory cytokines (Abdel-Tawab et al. 2011, Ammon 2010, Roy et al. 2006). Bromelain is a compound derived from pineapples which is included in Tenosan, which has been shown to have ant-inflammatory properties and may reduce levels of oxidative stress, edema and lymphocytes and increase immunosuppression and tenoblast proliferation in tendons (Muhammad et al. 2017, Golezar et al. 2016, Aiyegbusi et al. 2011, Fitzhugh et al. 2008). Glucosamine and chondroitin sulfate are included in Tendisulfur and have shown beneficial effects on tendons in both in vivo and in vitro studies, including increased collagen synthesis, improved collagen structural organization, reduced inflammation and improved tendon tensile strength and biomechanical properties (Taskesen et al. 2015, Oryan et al. 2011, Lippiello et al. 2007, Ozer et al. 2011). Methylsulfonylmethane (MSM) is included in both Tendisulfur and Tenosan and has been shown to have analgesic and anti-inflammatory effects and can reduce pain in tendon disorders through permeating cell membranes and altering inflammatory and oxidative stress processes (Gumina et al. 2012, Oliva et al. 2020, Usha and Naidu 2004). Supplementation with Omega-3 fatty acids have also been suggested to have anti-inflammatory effects on tendons (Lewis and Sandford 2009, Calder 2011). Two studies found improvement in pain, function and return to sport rate following omega-3 fatty acid supplementation for a variety of upper and lower limb tendinopathies (Mavrogenis et al. 2004, Sandford et al. 2018).

Vitamin C was included in nine of the studies in this review, and is a component of the supplement blends Tendisulfur, TendoActive and Tenosan. Vitamin C delivered as an isolated supplement intervention was found to improve pain, function and tendon healing rate compared to no supplementation following rotator cuff tendon repair (Martel et al. 2022). Vitamin C combined with gelatin and strength training was also shown to improve pain, strength, and tendon structure in a case report on patellar tendinopathy (Baar 2019). Vitamin C is known for its antioxidant and anti-inflammatory properties and ability to reduce oxidative stress and as a cofactor in key stages of collagen synthesis such as hydroxyproline synthesis of procollagen in tendon cells (Molnar et al. 2014, Mertens et al. 2011). Supplementation with Vitamin C enriched gelatin has been shown to stimulate increased collagen synthesis when taken as a supplement prior to exercise (Shaw et al. 2017). Therefore, Vitamin C deficiency could reduce levels of collagen synthesis and be a potential risk factor for musculoskeletal pathologies (DePhillipo et al. 2018). Following tendon injury or repeated microtrauma from exercise, Vitamin C requirements may increase for adequate collagen synthesis and tendon healing to occur (Kipp et al. 1996, Omeroglu et al. 2009). Despite a lack of research into the effects of ingestion of hydrolyzed collagen peptides on tendons, studies have demonstrated their ability to affect the size of collagen fibrils, glycosaminoglycan composition and mechanical properties of the Achilles tendon (Minaguchi et al. 2005). The combined supplement of collagen peptides, chondroitin, sodium hyaluronate and vitamin C reduced Achilles tendinopathy pain, with the supplement being known to improve glycosaminoglycan composition and tendon collagen synthesis (Choudhary et al. 2021). Hydrolyzed collagen peptides (Tendoforte) combined with eccentric training was found to be more effective for improving pain, function and tendon vascularity compared to eccentric training and placebo for Achilles tendinopathy (Praet et al. 2019).

Amino acids are an essential requirement for protein synthesis, with the amino acids leucine and glycine also identified as having a key role in collagen synthesis, with lysine, proline and cysteine important factors in collagen synthesis and integration, suggesting amino acids could play a role in tendon injury and healing (Barbosa et al. 2012, Vieira et al. 2015, 2015b, Meijer et al. 2015). L-arginine is an essential amino acid found in both Tenosan and Tendisulfur, which is required by the enzyme nitric oxide synthases (NOS) in the production of nitric oxide (NO), which is considered a crucial factor in tendon healing (Murrell 2007,2007b, Bokhari and Murrell 2012). Reductions in availability of NO can lead to impaired tendon healing and collagen synthesis, through increases in Transforming Growth Factor B (TGF-B), which can lead to chronic inflammation and fibrosis development (Moraes et al. 2013, Xia et al. 2006, Darmani et al. 2004). B-Hydroxy B-methylbutyric (HMB) is a metabolite of the essential amino acid leucine, which has been extensively studied as an ergogenic sports supplement for improving performance and increasing lean body mass. HMB has been shown to preserve or improve muscle mass in the elderly including in the treatment of sarcopenic obesity (Rossi et al. 2017, Oktaviana et al. 2019, Sanchez-Martinez et al. 2018, Holland et al. 2022, McIntosh et al. 2018). Although there is no direct evidence for effects on tendons, HMB was found to potentiate strength and functional performance improvement when combined with eccentric training and ESWT in patellar tendinopathy (Sanchez-Gomez et al. 2022).

Emerging evidence suggests that creatine supplementation has anti-inflammatory and anti-catabolic properties can decrease markers of inflammation and measures of muscle protein catabolism and bone resorption when combined with resistance training (Cordingley et al. 2022, Forbes et al. 2022, Bassit et al. 2008). Furthermore, creatine supplementation has been reported to have antioxidative, neuroprotective, anti-lactatic, and calcium-homoeostatic effects, having a direct impact on cellular bioenergetics and improving mitochondrial dysfunction, muscle strength and physical function in chronic injuries and diseases (Marshall et al. 2022, Harmon et al. 2021, Smith et al. 2014, Nomura et al. 2003, Gualano et al. 2012, Lanhers et al. 2017, Farshidfar et al. 2017). Recently, evidence of altered creatine signalling in tendinopathy has been identified, suggesting that creatine supplementation may have a beneficial role in tendon healing (Sikes et al 2021). Muscle and myotendinous junction studies have identified associations between creatine kinase activity and tendon elongation during exercise (Hicks et al. 2017, Pirog et al. 2010, Koch et al. 2014, Sahlin 2014). The only study that used creatine supplementation in this review, found it led to significantly faster improvements in pain and function and lower levels of creatine kinase when combined with rehabilitation compared to rehabilitation alone for flexor hallucis longus tendinopathy in swimmers (Juhasz et al. 2018).

The ability of anti-inflammatory supplements to reduce or halt the inflammation process by mechanisms such as inhibition of COX-2 and suppressing prostaglandin E2 (PGE2) production can impair tendon healing by altering matrix remodeling and adaptive increases in collagen synthesis following exercise (Shahnazi et al. 2018, Bauge et al. 2015, Sauerschnig et al. 2018, Christensen et al. 2010, 2011). These mechanisms of action appear like non-steroidal anti-inflammatory drugs (NSAIDS) which have been shown to not be effective for long-term management of tendinopathy any may be associated with more adverse side effects such as gastrointestinal disturbances, than nutritional supplements (Astrom et al. 1992, Pattanittum et al. 2013). The clinical management of tendinopathies with nutritional supplements is a relatively recent approach, with only a few RCTs available, showing pain relieving benefits of supplements when delivered in isolation. While nutritional supplements may be able to reduce pain in tendinopathy through there anti-inflammatory properties and mechanisms, it is less clear if they are able to improve physical function outcomes when delivered in isolation. Therefore, combining supplements with known interventions that improve physical function and capacity in tendinopathy, such as resistance training, may be the optimal approach (Praet et al. 2019). The analgesic effects of nutritional supplements may allow for early pain reduction to allow concomitant commencement of progressive resistance training interventions, without the increased risk for adverse side effects associated with NSAIDS and analgesic medications. Several nutritional supplements have also been shown to be capable of improving tendon structure alongside pain reduction and may help to potentiate the beneficial tendon adaptations derived from progressive resistance training in tendon rehabilitation. Despite appearing to have a good safety profile and the potential for less serious side effects compared to analgesic medications, nutritional supplements are not without risk, and have the potential for abuse leading to deleterious consequences, particularly for athletes who are subject to banned substances testing (Maughan 2018). The potential effects of ingestion of high doses of supplements, and their potential interactions with other compounds, dietary factors and chronic diseases are largely undetermined, so caution is advised when prescribing or advising patients on their use, with appropriate education an essential prerequisite (Maughan 2018). Several nutritional compounds and vitamins with potential benefits for tendons have yet to be investigated, despite having a potential rationale for beneficial effects. Vitamin D is well known for its role in regulating bone metabolism, but studies have shown it also directly acts on collagen synthesis in tendons, and can reduce reactive oxygen species, oxidative stress, MMPs and calcification development in tendons, with deficiency a potential risk factor for tendon pathology (Scott and Nordin 2016, Angeline et al. 2014, Dougherty et al. 2016). Quercetin, a flavonoid phenolic compound derived from plants has been shown to have anti-inflammatory, antioxidant, antiapoptotic and antiautophagic effects in tendinopathy in rats (Semis et al. 2021) and has been found to improve clinical outcomes for carpal tunnel syndrome (Notarnicola et al. 2015). However no clinical studies have investigated Vitamin D or quercetin supplementation in tendinopathies.

There is a significant body of preclinical studies demonstrating the beneficial physiological effects of various nutritional supplements on tendon function and healing, particularly regarding anti-inflammatory mechanisms in tendon pathology. Despite the paucity of clinical interventions studies of nutritional supplements in tendinopathy management, the number of studies and compounds investigated has increased in recent years, with most finding beneficial effects on clinical outcomes in tendinopathy, which is encouraging. However, further high quality RCTs with large sample sizes investigating nutritional supplements in isolation and combined with traditional management options such as resistance training are required before definitive recommendations on their widespread clinical use can be made. This scoping review is not without limitations. The review has included a range of study designs from RCTs to individual case reports, so there is therefore vast heterogeneity throughout included studies, and findings should be interpreted with caution. However, determining effectiveness was not the objective of the review, with the objective being elucidating what interventions and outcomes have been found for nutritional supplements in the clinical management of tendinopathies. Only studies available in English language were included, which may introduce language bias. Although all primary research designs were considered for inclusion, this review did not consider review papers or clinical practice guidelines, which may have included detailed information on nutritional supplement interventions in tendinopathy management.

CONCLUSION

Preclinical studies have identified a plethora of beneficial responses from nutritional supplements in healthy and pathological tendons, such as increased potential for collagen synthesis, tendon healing and activation of anti-inflammatory mechanisms. Despite a paucity of studies to date on nutritional supplements in the clinical management of tendinopathies, findings from this review suggest that several nutritional compounds, either delivered in isolation or in combined formulas, may be beneficial in the clinical management of tendinopathies. Several studies have shown that nutritional supplements can potentiate the beneficial effects of standard tendinopathy treatments such as exercise and ESWT, compared to either alone. The potential role for nutritional supplements in tendinopathy management could be as an adjunctive method to standard and accepted treatment methods such as progressive resistance training, where their pain relieving, anti-inflammatory, and structural tendon effects may augment the positive functional outcomes gained from progressive exercise rehabilitation.

Table 1: Overview of included studies

Author, study design, sample size	Tendinopathy	Intervention groups & Duration	Outcome measures	F-U - wks	Outcomes/ results
Balius et al. 2016, RCT, n=59	Achilles	1. ECCT 2. ECCT + TendoActive Supplement (Mucopolysaccharides, type-1 collagen & vitamin C) 3 capsules 1/d 3. Supplement + stretching. 12 wks	Pain (VAS), function (VISA-A), Tendon structure (US)	12	VISA-A and VAS significantly improved in all groups at 12 wks, with no between group effect (P > 0.1). VISA-A improvement was 56% for group 3, 44% for group 2 % 30% for group 1 (P = 0.154). Reduction in pain at rest was greater in the groups who took the supplement than in the ECCT alone group (P < 0.05). No significant variation was found in the tendon bilateral thickness among treatments (P > 0.1).
Praet et al. 2019, RCT, n=20	Achilles	1. ECCT + TENDOFORTE supplement (hydrolysed specific collagen peptides, 2.5g x 2/d). 2.ECCT + placebo. 12 wks	Pain, function (VISA-A), Tendon structure (US)	26	VISA-A increased significantly in supplement group by 12.6 (9.7; 15.5), while in placebo group VISA-A increased only by 5.3 (2.3; 8.3) points at 12 weeks. After crossing over group 1 and 2 showed subsequently a significant increase in VISA-A of, respectively, 5.9 (2.8; 9.0) and 17.7 (14.6;20.7). Microvascularity decreased to a similar level in both groups.
Notarnicola et al. 2021, crossover RCT, n=44	Plantar	1. ESWT 2. ESWT + TENDISULFUR supplement (MSM, hydrolysed collagen, L-arginine, L-lysine, Vitamin C, Bromelain, Chondroitin, Glucosamine, Boswellia, & Myrrh). 1 sachet 2/d for 30 days, 1/d for 60 days. 12 wks	Pain (VAS), Function (FFI, AOFAS, RMS)	26	Statistically significant improvement in pain and function occurred in both groups at Months 3 and 6. The time-group interaction analysis confirmed the best efficacy of the combination treatment with ESWT and supplement, demonstrating a positive therapeutic effect of the combination.
Notarnicola et al. 2012, RCT, n=64	Achilles	1. ESWT 2. ESWT + Tenosan supplement (Arginine-L-alpha ketoglutarate, hydrolysed collagen type-1, MSM, vitamin C, and bromelain, vinitrox), 2 sachets x 1/d. 8 wks.	Pain (VAS), Function (AOFAS, RMS), tissue oximetry	26	There was no statistically significant difference in VAS between groups at 2 months (3.9 vs. 5.1; *P* = 0.07), at 6 months the value was significantly lower in the combined group (2.0 vs. 2.9; *P* = 0.04). AOFAS score at 2 and 6 months was significantly in favour of the combined group (2 months: 85.4 vs. 72.1; *P* = 0.0035; 6 months: 92.4 vs. 76.5; *P* = 0.0002). The RMS also showed a statistically significant difference in favour of the combined group (at 2 months: 1.7 vs. 2.8; *P* < 0.0001; at 6 months: 1.5 vs. 2.3; *P* < 0.001). At 6 months a significantly lower oximetry value observed in the combined group versus controls (60.2 vs. 66.0; *P* = 0.007).
Choudhary et al. 2021, RCT, n=40	Achilles	1. Oral diclofenac sodium 2. Supplement (collagen peptide type-1, chondroitin sulphate, sodium hyaluronate, & vitamin C), 1 tablet 3/d.	Pain (VAS), tendon thickness (US)	12	Both groups reduced pain, with the supplement group having a significantly better VAS outcome (40 v 20-point improvement) in reducing pain at 12 wks (P=0.031). Both interventions reduced Achilles tendon thickness at 12 weeks. Although there was no absolute significant intergroup difference (P = 0.025), the percentage change was more in the nutraceutical group in the case of anteroposterior thickness (12% vs 7.6%).
Sandford et al. 2018, RCT, n=73	Rotator cuff	1. Long chain omega-3 polyunsaturated fatty acids (2.57g 1/d) + exercise 2. Placebo + exercise. 8 wks	Pain & Function (NRS, OSS, SPADI, PSFS,	52	Both groups had a significant reduction in disability measured by the OSS. There was on average a 25% reduction in disability (95% CI 15.3 to 34.6; mean difference=8.2) in the placebo group and 25% reduction (95% CI 13.5 to 36.2; mean difference=6.7) in the intervention group at 2 months. Difference in the change in the OSS between groups was −0.1 (95% CI −2.6

			SF-36), GRoC, EQ-5D		to 2.5, p=0.95). A statistically significant reduction in pain was reported by both groups with NRS (p<0.01) and SF-36 (p<0.01). At 2 months, the placebo group demonstrated a 2.2-point reduction (95% CI 1.2 to 3.1), and the omega-3 PUFA group demonstrated a 2.1-point reduction (95% CI 0.04 to 2.3) in the NRS. Omega-3 supplementation may have a modest effect on disability and pain for rotator cuff pain.
Juhasz et al. 2018, RCT, n=18	Flexor hallucis longus	1. Micronized Creatine monohydrate + rehabilitation. 20g (4x5g) for first 5 days (loading), 5g 1/d for next 37 days (maintenance) 2. Placebo + rehabilitation. 6 wks (2 wk immobilization, 4 wk rehabilitation)	Pain (NRS-P), lean mass, PF peak torque, CK levels	6	Both groups reduced pain, with a significantly faster decrease found in NRS-P of CR versus PL group during treatment (CR vs PL; wk 2- wk 6; 94.4 ± 16.7% vs. 75 ± 20.4%; p < 0.02). After 4 wks lean mass significantly increased in both groups (CR by 5.5% vs. PL by 3.8%; p < 0.01). CK levels were significantly lower in the CR group compared to the PL group. Results indicate that Cr supplementation is beneficial when combined with rehabilitation for tendinopathy.
Sanchez-Gomez et al. 2022, Pilot RCT, n=8	Patellar	1. ECCT, ESWT + Placebo 2. ECCT, ESWT + HMB supplement. 3g per day prior to exercise. 4 wks	Pain & function (VISA-P) lean mass, power & strength tests	4	No changes were noted on body composition or pain (p > 0.05). The combination of ECCT, ESWT & HMB increased concentric muscular power and strength after 4 weeks more than without HMB, without changes in body lean mass or pain. HMB supplementation enhanced muscular performance, optimizing the intervention adaptations.
Mavrogenis et al. 2004, RCT, n=31	Patellar, rotator cuff, lateral elbow, biceps	1. Essential omega-3 fatty acids & antioxidants supplement (EPA, DHA and GLA. selenium, zinc, vitamin A, vitamin B6, vitamin C and vitamin E) + US 2. Placebo + US. 4 wks	Pain (VAS), sports activity	4	Both groups had a reduction in pain scores. In the treatment group there was a significant reduction of pain compared with the placebo group (P<0.001) after 32 days.12 out of 17 (71%) subjects in the supplement group recorded no pain at the end of treatment. There was a mean decrease in pain of 99% in the treatment group compared to 31% in the placebo group. Sport activity increased by 53% in the treatment group and by 11% in the placebo group.
Martel et al. 2022, RCT, n=98	Rotator cuff tendon repair	1. Vitamin C supplement (500 mg/d) + exercise. 2. No supplement + exercise. 45 days	Tendon healing (US – Sugaya scale), Function (CMS, SSV)	26	In the supplement group, functional scores improved significantly, the average SSV was 39% preoperatively and 88% at last follow-up (*p* = 0.001). The mean CMS score improved from 50 to 71.8 points at 6 months (*p* = 0.001).In the control group, the average SSV improved significantly from 44.7% to 83% at 6.3 months (5.5–10) (*p* = 0.001). The mean CMS score also significantly improved from 49.4 to 72.5 points (*p* = 0.001). No significant difference was noted in functional outcomes when the two groups were compared. At 6.3 months, the overall rate non-healing was 17% (*n* = 15). This rate was lower for patients in the supplement group (*n* = 5; 11%) than for those in the control group (*n* = 10; 23%) (*p* = 0.2).
Gumina et al. 2012, RCT, n=90	Rotator cuff tendon repair	1. Tenosan supplement (arginine L-alpha-ketoglutarate, MSM, hydrolysed type-1 collagen & bromelain) 2/d sachets. 2. Control. 12 wks	Pain (VAS), function (CMS, SST), repair integrity (MRI)	52	No statistically significant differences were identified between the two groups for each outcome, except pain (6 months) and repair integrity (12 months). Pain was lower in the Group I patients (p<0.001). Percentage of patients with a better repair integrity result was significantly higher in group I than Group II. The use of the supplement for 3 months after cuff repair decreases shoulder post-operative pain and leads to a slight improvement in repair integrity. This improvement does not seem to correlate with a better objective functional outcome.
Merolla et al. 2015, RCT, n=100	Rotator cuff tendon repair	1. Analgesic medication + TENDISULFUR supplement (Boswellia serrata and Curcuma	Pain (VAS), function (CMS, SST), GRoC	24	The overall pain scores of group T showed a significant reduction at all time points (P < 0.05), however differences in pain improvement were not significant between groups (p > 0.05). The CMS and SST were significantly different compared with baseline at either time point (12 weeks, p = 0.00023

		longa). 2/d sachets for 15/d, 1/d sachets for 45/d 2. Placebo. 8 wks			and p = 0.00012, respectively; 24 weeks, p = 0.00011 and p = 0.00021, respectively). Trends were similar in group P and intergroup CMS and SST differences were not significant, either at 12 (p = 0.884 and p = 0.352, respectively) or at 24 weeks (p = 0.523 and p = 0.292, respectively). PGA scores were good in all subjects. DS alleviated short and partially mid-term pain, while long-term pain was unchanged.
Vitali et al. 2019, comparative, n=90	Achilles, rotator cuff, lateral elbow	1. ESWT 2. ESWT + Tendisulfur Forte supplement (MSM, hydrolysed collagen type-1 & type-2, L-arginine, L-lysine, Vitamin C, Chondroitin, Glucosamine, Curcuma longa, Boswellia serrata, Myrrh. 2/d x 1 month, 1/d x 1 month. 8 wks	Pain (VAS), function (UCLA shoulder score, Mayo elbow score, VISA-A)	8	Patients in the Tendisulfur Forte group had overall better functional and VAS scores for each tendinopathy. UCLA scores showed significant results at 60 days (p=0.0002). Mayo scores was significant at 60 days in the study group (p<0.0001). VISA-A was improved in the study group at 30 days (p<0.0001). VAS scales were significant for each pathology at 60 days (p<0.0001). In addition, NSAIDs consumption was greatly reduced and, in most cases, stopped in the Tendisulfur Forte Groups.
Henrotin et al. 2020, open-lable non-controlled observational, n=670	Various types	1.Biooptimized turmeric rhizome extract (C. longa L.) containing 72mg of curcumin and 120mg of B. serrata extract containing 78mg boswellic acids. 2 tablets X 2/d. 4 wks	Pain (VAS), satisfaction, drug intake	4	After 1-month, pain and functional limitation were significantly improved whatever the cause of tendinopathy, its localization, and the duration of symptoms. VAS decreased from 6.16 ± 1.53 to 2.98 ± 1.64 (p<.0001), yielding a drop of 51.6% and the functional limitation score fell after 1-month from 5.96 ± 1.73 to 2.88 ± 1.67 (p<.0001) corresponding to a drop of 51.6%. The percentage of patients taking at least one concomitant treatment decreased from 81.3% to 61.8% (p<.0001). Only 43 (6.5%) patients reported side effects.
Arquer et al. 2014, open label non-comparative, n=98	Achilles, patellar, lateral elbow	1. Tendoactive - daily dose of 435 mg mucopolysaccharides, 75 mg type-1 collagen and 60 mg vitamin C. 12 wks	Pain (VAS), Function (VISA-A, VISA-P, PRTEE), tendon structure (US)	12	A significant reduction in pain at rest and when active was observed at 12 wks for all three types of tendinopathy. Thus, a 38% improvement in VISA-A, 46% in VISA-P and 77% in PRTEE was observed at 12 wks ($P < .001$). Similarly, a 12% decrease in the thickness of the Achilles tendon, a 10% decrease in the patellar tendon and a 20% decrease in the lateral epicondyle tendon was observed ($P < .05$).
Baar 2019, case report	Patellar	1. Strength training + 15g gelatin supplement, 225mg Vitamin C prior to exercise. 78 wks	Tendon structure (MRI), Pain (VAS), strength - dynamometer	78	On follow-up one and a half years into the program an independent orthopaedic surgeon declared the tendon normal on MRI. Importantly, the improved MRI results were associated with a decrease in pain and improved performance.

Abbreviations: ECCT: eccentric training, ESWT: extracorporeal shockwave therapy, VAS: visual analogue scale, NRS-P: pain numeric rating scale, VISA-A: Victorian Institute of Sport Assessment – Achilles, VISA-P: Victorian Institute of Sport Assessment – Patellar, AOFAS: American orthopaedic foot and ankle score, MRI: magnetic resonance imaging: RMS: Roles and Maudsley score, FFI: foot function index, US: ultrasound, wks: weeks, CK: creatine kinase, CMS: constant murley score, PRTEE: patient rated tennis elbow evaluation, SST: simple shoulder test, GRoC: global rating of change, SSV: subjective shoulder value, SPADI: shoulder pain and disability index, OSS: Oxford shoulder score, SF-36: short-form 36, PF: plantarflexion.

Appendix 1: Search strategy

- Information sources and search strategy.

Databases: MEDLINE (PubMed), CINAHL, AMED, EMBase, SPORTDiscus CENTRAL of Cochrane Library

Search fields: Title, abstract, key words

Search terms (database subject headings)

1. - “tendon” OR “tendinopathy” OR “tendonitis” OR “tendinitis” OR “tendon pain”

2 - “nutrition” OR “supplement” OR “nutraceutical” OR “nutritional”

3. 1 AND 2

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