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„Collagen and collagen supplements and their influence on body composition, strength and the musculoskeletal tissue: A systematic review "

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Abstract

Introduction: In recent years, interest in collagens as food supplements has been steadily increasing. It is known that due to their composition collagens have an anabolic effect on muscles, ligaments and tendons. The following systematic review wants to examine whether collagen supplements have an influence on body composition, strength or the musculoskeletal tissue, like muscles, tendon and ligaments.

Methods: A systematic literature search was conducted in PubMed and WebofScience. Included in the systematic review were those studies that addressed the long-term effects of collagen supplements on body composition, physical performance or musculoskeletal system. Only human studies conducted in healthy people were included. Another inclusion criterion was the simultaneous implementation of an exercise intervention. The risk of bias was assessed using the PEDro scale. The synthesis of results was conducted qualitatively.

Results: Nine studies were included in the systematic literature review. A total number of 313 participants took part in the included studies and the interventions lasted from three days to 12 weeks. Not all studies examined every aspect of the research question. Therefore, the analysis of the results was split in four parts. Concerning the effects of collagen supplementation and exercise on body composition, the studies revealed a higher increase in fat-free mass in the collagen supplementation group. Regarding the effects on performance, the six studies, which addressed this outcome, reported higher increases over the study period, without any further benefits from the collagen supplementation. The effects on musculoskeletal tissue and the amino acids concentrations were controversy. Other than that, the supplementation with collagen peptides resulted in an increase in the hydroxyproline concentration measured in the blood.

Conclusion: Chronic supplementation with collagen peptides and concurrent exercise intervention tends to lead to improved body composition, a slight improvement in physical performance and slightly accelerated recovery compared to a placebo. Compared to a higher-quality protein, collagen peptides perform worse in terms of muscle protein synthesis. Further studies are needed to investigate the mechanism of action of collagen peptides.

Zusammenfassung

Einleitung: In den letzten Jahren nahm das Interesse an Kollagenen als Nahrungsergänzungsmittel stetig zu. Es ist bekannt, dass Kollagene aufgrund ihrer Zusammensetzung eine anabole Wirkung auf Muskeln, Bänder und Sehnen haben. In der folgenden systematischen Übersichtsarbeit soll untersucht werden, ob Kollagenpeptide einen Einfluss auf die Körperzusammensetzung, die Kraft oder das muskuloskelettale Gewebe, wie Muskeln, Sehnen und Bänder, haben.

Methoden: Es wurde eine systematische Literaturrecherche in PubMed und WebofScience durchgeführt. In die systematische Überprüfung wurden jene Studien einbezogen, die sich mit den langfristigen Auswirkungen von Kollagenpräparaten auf die Körperzusammensetzung, die körperliche Leistungsfähigkeit oder den Bewegungsapparat befassten. Es wurden nur Humanstudien, die an gesunden Menschen durchgeführt wurden, berücksichtigt. Ein weiteres Einschlusskriterium war die gleichzeitige Durchführung einer Trainingsintervention. Das Risiko einer Verzerrung wurde anhand der PEDro-Skala bewertet. Die Synthese der Ergebnisse wurde qualitativ durchgeführt.

Ergebnisse: Neun Studien wurden in die systematische Literaturübersicht aufgenommen. An den einbezogenen Studien nahmen insgesamt 313 Personen teil, und die Interventionen dauerten zwischen drei Tagen und 12 Wochen. Nicht alle Studien untersuchten jeden Aspekt der Forschungsfrage. Daher wurde die Analyse der Ergebnisse in vier Teile aufgeteilt. Was die Auswirkungen von Kollagenpeptiden und Bewegung auf die Körperzusammensetzung betrifft, so ergaben die Studien eine höhere Zunahme der fettfreien Masse in der Gruppe, die Kollagenpeptide zuführte. Was die Auswirkungen auf die Leistungsfähigkeit betrifft, so berichteten die sechs Studien, die sich mit diesem Ergebnis befassten, einen Anstieg während des Studienzeitraums, ohne dass die Kollagenpeptide weitere Vorteile mit sich brachten. Die Auswirkungen auf das Muskel-Skelett-Gewebe und die Aminosäurekonzentrationen waren umstritten. Abgesehen davon führte die Supplementierung mit Kollagenpeptiden zu einem Anstieg der im Blut gemessenen Hydroxyprolin-Konzentration.

Schlussfolgerung: Eine chronische Supplementierung mit kollagenen Peptiden bei gleichzeitiger sportlicher Betätigung führt tendenziell zu einer verbesserten Körperzusammensetzung, einer leichten Verbesserung der körperlichen Leistungsfähigkeit und einer leicht beschleunigten Erholung im Vergleich zu einem Placebo. Im Vergleich zu einem höherwertigen Protein schneiden kollagene Peptide in Bezug auf die Muskelproteinsynthese schlechter ab. Weitere Studien sind erforderlich, um den Wirkmechanismus von Kollagenpeptiden zu untersuchen.

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1 Introduction

The goal of everyone who is somehow active in sports is to get the best out of themselves day after day, to improve - be it in performance or health - and to perform at their individual best (Lukaski, 2004). To achieve this, the close interaction between nutrition and training must be well coordinated. Due to the increasing awareness of this, it is therefore not surprising that the interest in nutritional or dietary supplements has increased rapidly in recent years (Knapik et al., 2016).

A dietary supplement is a commercially available product that is taken as a supplement to normal meals. This includes vitamins, minerals, herbs, amino acids, and several other products. The marketing of those products promises improved health or physical and mental performance, increased energy, loss of unnecessary weight, accelerated recovery, and more (Knapik et al., 2016). Supplements are widely used by athletes of all ages and from various sports. It is primarily hoped that they increase performance and accelerate recovery (Hurst et al., 2017).

Collagen peptides are also among the dietary supplements. They are derived from enzymatic hydrolyses of collagens. Therefore, they are consisting mainly of glycine, proline and hydroxyproline (Walrand et al., 2008; Watanabe-Kamiyama et al., 2010). They are recognized as safe by the European Food Safety Authority (Administration, 2005). In some animal studies it has been found, that the collagen peptides are rapidly absorbed in the small intestine and transferred into the blood because of their high proportion in proline and hydroxyproline (Walrand et al., 2008; Watanabe-Kamiyama et al., 2010). This is also the case in humans (Iwai et al., 2005). Because of their antimicrobial and antioxidant characteristics collagen peptides are commonly used as an ingredient in functional food supplements (Gómez-Guillén et al., 2011). The bioavailability for the human body is good due to their ability to bind Ca^{+} ions (Guo et al., 2015).

Collagen plays a crucial role in the human body, participating not only in the development of organs, but also in wound healing. It also helps maintain bones and blood vessels. Furthermore, it is needed in the cell for some important functions, such as proliferation, cell survival and differentiation. It is therefore important to note that collagens are present everywhere in the body - in bones, tendons, ligaments, skin, and muscles (León-López et al., 2019). Nutritional supplements that affect the skeletal muscle tissue are of great interest for nutritional and

sports sciences. In detail nutritional interventions, which benefits the connective tissue proteins, such as proline, hydroxyproline or hydroxylysine, are valuable not only for elite sports but also for recreational sports (Rawson et al., 2018).

Injuries of the soft tissue, like muscles, tendons, and ligaments, are extremely abundant in all levels of sports. This circumstance is unfavourable not only for elite athletes who finance their lives through sports, but also for risk groups who want to prolong their lives and avoid concomitant diseases through sports. Therefore, it is important to devote attention to the prevention of these injuries (Baar, 2017).

The effectiveness of supplements for the healing of skeletal muscle injuries has already been sufficiently studied depending on the type of injury and the muscles involved. For tendons and ligaments there is not so many data so far. Because of their similar structure, tendons and ligaments are often grouped into one category. The basic distinction between the two is that tendons connect a soft tissue to a rigid tissue, for example a muscle to a bone, and ligaments are the connections between rigid tissues, i.e. bones (Baar, 2017).

There is some evidence that glycine, proline, lysine, hydroxylysine and hydroxyproline have an influence on the collagen synthesis and therefore also on the soft tissue, like tendons and ligaments, because these amino acids are the main components of collagen (Baar, 2017). In a randomised controlled double-blind crossover trial, the acute effects of gelatine supplementation have been studied. A dose of 15 g gelatine one hour before a rope-jumping exercise was able to double collagen synthesis (Shaw et al., 2017).

However, the present review aims to investigate not only the effects of collagen supplements on the musculoskeletal system, but also on functional parameters such as strength or body composition. Especially in older individuals, where muscle mass, strength and function are already declining, supplementation with collagen peptides could play a role in preventing orthopaedic complaints and the development of a metabolic syndrome (Cruz-Jentoft et al., 2010; Stephen & Janssen, 2009). To date, there have been many studies examining the effects of different protein supplements on muscle strength (Li & Liu, 2019), but how collagen peptides affect strength has not been studied as often. This review will therefore summarize these studies for the first time.

1.1 Collagens

The extracellular matrix (ECM) of connective tissue is a very complex conglomerate of different representatives of several protein families and has varying physiological functions. Fibrillar elements, microfibrillar networks and soluble proteins and glycoproteins define its characteristics (Gelse, 2003). In the following pages the most abundant protein of the extracellular matrix, the collagens, will be discussed. Afterwards a brief description of the extracellular matrix and its function as well as the extracellular matrix of the skeletal muscle will be given.

Collagens belong to the group of proteins, are widely distributed and their distinctive feature is a simple, repetitive sequence of amino acids (Prockop, 2004). They are fibrous proteins found in all multicellular animals and up to 25% of the total protein content in mammals are collagens. Figure 1 shows the typical triple-stranded helical structure of collagens, which all of them have in common. Three chains of collagen peptides, the so called α-chains, are organised in a superhelix to build a cordlike collagen molecule (Gelse, 2003; Gordon & Hahn, 2010; Kadler et al., 2007; Teti, 1992). The long triple helices can be formed into large fibrils, while the shorter tripe helices supply rigidity (Prockop, 2004; Riso et al., 2016).

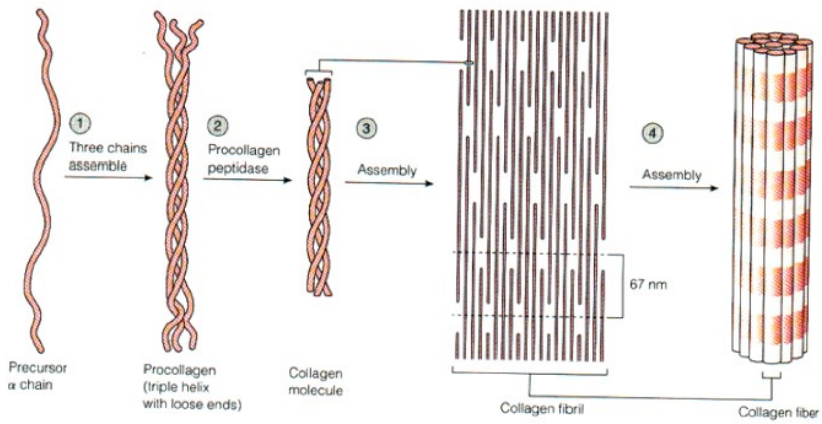

Figure 1 Formation process of fibrillar collagen (from Riso et al., 2016, p. 47)

Collagens are the major structural element of all connective tissue and can also be found in the interstitial tissue of all parenchymal organs, where they ensure stability and structural integrity (Gelse, 2003).

1.1.1 The unique sequence of collagens

Even though the collagens differ highly in their function depending on where they sit, all members of the collagen-family are characterized by their unique sequence (Gelse, 2003; Prockop,

2004; Teti, 1992). Every third amino acid in the sequence is a glycine. The compilation of the α-chains is around a central axis with the glycine residues in the centre of the triple helix. The more massive side chains of the other amino acids are seated on the outer positions (Gelse, 2003; Gordon & Hahn, 2010; Kadler et al., 2007).

In the most common cases the following amino acids are proline and hydroxyproline. Therefore the sequence is often illustrated as $(Gly\text{-}X\text{-}Y)_n$. As mentioned before head the X is often proline and the Y hydroxyproline. Three of these (Gly-X-Y) chains form the three-stranded helix that is special for collagens (Gordon & Hahn, 2010; Kadler et al., 2007; Prockop, 2004). In the fibril-forming collagens the triple helixes could be up to 300 nm long, which means that about 1000 amino acids are needed (Gelse, 2003).

The small amino acid glycine and its hydrogens on the α-carbon makes it possible to form hydrogen bonds across the chains. Proline and hydroxyproline have a closed-ring structure, which hinder rotation and makes the structure rigid. The amino acids in the sequence, which are charged, point out from the centre of the triple helix. The task of these charged groups is to form slat bridges to bind the monomers to each other. Further, covalent bounds between aldehydes and the monomers are formed through a deamination of the terminal amino group on lysine residues (Prockop, 2004).

Every triple helix is flanked by non-collagenous domains, the so-called C- and N-domains, which also have some important structural functions (Gordon & Hahn, 2010). The C-propeptide initiates the triple helix formation and the N-propeptide regulates the fibril diameter. The short non-helical telopeptides between the helix and the terminals play a role in the cross-linking of the collagen molecules and with other molecular structures (Gelse, 2003).

To come to a point the signature $(Gly\text{-}X\text{-}Y)_n$ have everything what it needs to spontaneously assemble into ordered fibrils and fibres, that withstand high forces and can be several cm long (Prockop, 2004).

1.1.2 The collagen superfamily

To date 28 different members of the collagen superfamily are known (Csapo et al., 2020; Kadler et al., 2007).

Depending on their structure and supramolecular organization, they can be clustered in to seven different groups according to Gelse (2003) or Kadler et al. (2007):

- fibril-forming collagens
- fibril-associated collagens (FACIT)
- network-forming collagens
- anchoring fibrils
- transmembrane collagens
- basement membrane collagens
- others with unique functions.

The different collagen types differ in their complex and multifaceted structure, their splice variants, the presence of non-helical domains and their function. The fibril-forming collagens are making up to 90% of the total collagen (Gelse, 2003).

A detailed table of most of the collagens as well as their basic tissue distribution is given in table 1.

Table 1 Various collagens type and their tissue distribution (modified, see Gelse, 2003, p. 1533; Kadler et al., 2007, p. 1955; Kjeld & Karsdal, 2016)

Type	tissue distribution
fibril-forming collagens	
I	bone, dermis, tendon, ligaments, cornea
II	cartilage, vitreous body, nucleus pulposus
III	skin, vessel wall, reticular fibres of most tissues (lungs, liver, spleen, etc.)
V	lung, cornea, bone, fetal membranes; together with type I collagen
XI	cartilage, vitreous body
XXIV	cornea and bone
XXVII	embryonic cartilage, developing dermis, cornea, inner membrane of the retina, major arteries of the heart, adult cartilage
fibril-associated collagens (FACIT)	
IX	cartilage, vitreous humor, cornea
XII	perichondrium, ligaments, tendon
XIV	dermis, tendon, vessel wall, placenta, lungs, liver
XVI	fibroblasts, amnion, keratinocytes
XIX	human rhabdomyosarcoma
XX	corneal epithelium, embryonic skin, sternal cartilage, tendon
XXI	blood vessel wall

XXII	tissue junctions, heart, skeletal muscle

network-forming collagens

VIII	endothelial cells, Descemet's membrane
X	hypertrophic cartilage

anchoring fibrils

VII	skin, dermal–epidermal junctions; oral mucosa, cervix

transmembrane collagens

XIII	epidermis, hair follicle, endomysium, intestine, chondrocytes, lungs, liver
XVII	dermal–epidermal junctions
XXIII	heart, retina, metastatic prostate cancer cells
XXV	brain of patients with Alzheimer

basement membrane collagens

IV	basement membranes

others

Microfibrillar collagen:	
VI	widespread; dermis, cartilage, placenta, lungs, vessel wall, intervertebral disc
XXVI	testis and ovary of adult tissue, reproductive tissue of neonates
XXVIII	peripheral nerves, skin, lungs
Multiplexins:	
XV	fibroblasts, smooth muscle cells, kidney, pancreas
XVIII	lungs, liver

1.1.2.1 Fibril forming collagens

Collagen types I, II, III, V, XI, XXIV and XXVII count as fibril forming collagens. Their special feature is their ability to build supramolecular aggregates with fibrils with diameters between 25 and 400 nm (Gelse, 2003; Kadler et al., 2007).

The fibril forming collagens consist of long and uninterrupted $(Gly\text{-}X\text{-}Y)_n$ sequences. In nature they count to the most abundant protein. Each fibril forming collagen is made up of three α-chains with approximately 330 Gly-X-Y triplets. These α-chains assemble into monomers and the monomers into fibrils (Prockop, 2004).

Type I collagens represent the largest proportion of collagens in the body, and they account for over 50% of the dry weight of ligaments, tendons and demineralized bones. Depending on their location their formation is different. For example, in ligaments and tendons type I collagen fibrils are assembled as parallel bundles of thick fibres (Prockop, 2004), where they procure tensile stiffness (Gelse, 2003).

Type II collagens are very similar to type I but are found almost only in cartilage, but also partly in the nucleus pulposus of intervertebral discs or the notochord (Gelse, 2003). Very thin fibrils of type II catch charged proteoglycans and water, so the structure of cartilage becomes able to withstand compression (Prockop, 2004).

Type III collagens are again very similar to type I and it can be found in large amounts in the aorta (Prockop, 2004). Type III is everywhere in tissue where type I is present expect in bones. In the reticular fibres of the interstitial tissue of lungs, liver, spleen, dermis and vessels it also plays an important role (Gelse, 2003).

Type V and XI are a subgroup of the fibril forming collagens and they appear in various tissues. Even though they are clustered as a subgroup, they have something in common regarding their functions. Type V makes up heterofibrils with type I and III and is part of the organic bone matrix and the interstitial matrix of muscle, liver, lungs and placenta. Type XI works together with type II to stabilize articular cartilage (Gelse, 2003).

Collagen type XXIV is predominantly found in the formation of bone, but also in the brain or muscle and a few other organs. In mice it is known as a marker for osteoblast differentiation and bone formation. In humans it is elevated during squamous cell carcinoma of the head and neck (Bechshøft et al., 2016).

The triple helix domain of type XXVII is shorter than from his other colleagues of the group of fibrils forming collagens. It also has two untypical interruptions and no N-terminal telopeptide region. It can be found in cartilage and plays a key role in the development (Genovese & Karsdal, 2016) .

1.1.2.2 Fibril-associated collagens (FACIT)

Types IX, XII, XIV, XVI, XIX, XX, XXI and XXII belong to the FACIT collagens. Typically, the triple helix of FACIT collagen is interrupted by a non-collagenous sequence. The non-collagenous sequences differ in structure and function and may account for flexibility and proteolytic cleavage (Gelse, 2003; Gordon & Hahn, 2010; Kadler et al., 2007).

Type IX collagen is a short non-fibril collagen which is disconnected by two non-collagenous sequences. It can bind to the fibrils of type II collagen and proteoglycans to make up the arcade-like structure of cartilage (Gelse, 2003; Gordon & Hahn, 2010; Kadler et al., 2007; Prockop, 2004).

Type XII and XIV have a similar structure and collude with type I or II in for example skin, perichondrium, tendons, lung and liver (Gelse, 2003; Gordon & Hahn, 2010). Type XVI helps in organizing and stabilizing the ECM through stabilizing the collagen fibrils (Bechshøft et al., 2016). Collagen type XXI serves as a molecular bridge in the ECM and can be found in heart, placenta, stomach and a few other regions. Its role in blood vessel assembly is under discussion (Kehlet & Karsdal, 2016). Type XXII can be found in the myotendinous junctions, where it binds to integrins and stabilizes the mechanical functions (Kehlet & Karsdal, 2016).

1.1.2.3 Network-forming collagens

Collagen types X and VIII belong to the short-chain collagens and have a similar structure. Type X plays a crucial role in hypertrophic cartilage and eventually in endochondral ossification or matrix calcification. As for its role in the cartilage it is connected to type II collagen. Collagen type VIII is produced in endothelial cells and is arranged into hexagonal lattices, for example in the cornea (Gelse, 2003).

1.1.2.4 Anchoring fibrils

Collagen type VII is a major structural component of anchoring fibrils (Sakai et al., 1986). It could bind to collagen fibres, microfibrils and other components of the ECM. They provide an additional adhesion of the lamina densa to the stroma (Keene et al., 1987).

1.1.2.5 Transmembrane collagens

Type XIII, XVII, XXIII and XXV are transmembrane collagens. They have cell adhesive properties and can also be found in malignant cells. Transmembrane collagens have important roles for example in the neural function and the eye development (Banyard et al., 2003; Gordon & Hahn, 2010; Kadler et al., 2007).

1.1.2.6 Basement membrane collagen

Type IV collagen is a nonfibrillar collagen and an important constituent of basement membranes, where it plays an important role in molecular filtration (Kadler et al., 2007). It contains multiple $(Gly\text{-}X\text{-}Y)_n$ sequences which are interrupted by non-collagen sequences and at both

ends globular domains are attached. Not only the non-collagen sequences but also the globular domains make the collagen flexible and able to form networks which can bind other proteins. By that the network connects epithelial cells and form barriers to defend the organism from the external environment (Gordon & Hahn, 2010; Prockop, 2004).

1.1.2.7 Microfibrillar collagen

The collagen type VI is secreted into the ECM and builds up a microfibrillar network in nearly all tissues except bones (Gelse, 2003; Gordon & Hahn, 2010). The type XXVI collagen has collagenous domains and forms trimers. It is present in testis and ovary of adult tissue and to high rates in reproductive tissue of neonates. For that it plays an important role in the early development of testis and ovary (Kjeld & Karsdal, 2016). Type XXVIII is important in the peripheral nervous system and it may be involved in damage repair processes (Arvanitidis & Karsdal, 2016).

1.1.2.8 Multiplexins

Collagen type XV is a molecule consisting of collagen and proteoglycan with mainly chondroitin sulphate chains. It has some roles in physiological and pathological contexts. It has also some mechanical functions, like the protection from over-stretching of collagen fibrils (Bretaud et al., 2020).

1.1.3 Biosynthesis of collagens

As the biosynthesis of collagen type I is best described in literature, the following section focuses on this collagen type.

The synthesis and secretion of collagen is made by Fibroblasts. About 44 genes are associated with collagen formation. The biosynthesis starts with the transcription of the genes in the nucleus. In from of mRNA the information goes from the nucleus to the rough endoplasmic reticulum, where it will be encoded into pre-pro-collagen, which is made up of repetitions of Gly-X-Y (Gelse, 2003; McCormick, 1994).

The pre-pro-peptide moves into the endoplasmic reticulum and the following modification processes happen (Gelse, 2003; Sorushanova et al., 2019):

- The hydroxylation of lysine and proline on the propeptide takes place with the help of the enzymes “prolyl hydroxylase” and “lysyl hydroxylase”.
- The glycosylation adds glucose or galactose monomers onto the hydroxyl groups.

- With hydrogen and disulphide bonds, the three hydroxylated and glycosylated propeptides twist into a triple helix forming procollagen, where the ends are still unwound.

The new formed procollagen is packed into vesicles in the Golgi compartment and transported into the extracellular space. The ends of the procollagen are cleaved off in the extracellular space. The new formed collagen is called tropocollagen (Gelse, 2003).

The final step is the cross-linking between the tropocollagens. They self-assemble with covalent bonds into collagen (Sorushanova et al., 2019).

1.2 Extracellular matrix (ECM)

All tissues and organs of the human body are surrounded by the so-called extracellular matrix (ECM). The ECM plays an important role not only by holding up the cellular scaffolding but also in many important biochemical and biomechanical processes, such as tissue morphogenesis, differentiation and homeostasis (Frantz et al., 2010; Rozario & Desimone, 2010; Teti, 1992). It forms a complex, three-dimensional network among cells of different tissues and is specific for every organ. In the beginning it was assumed that the ECM is an inactive, space-filling material that only would offer mechanical strength for tissues and organs. Nowadays we know that the ECM is a dynamic structure, which plays an important role in the interaction with cells and controlling the behaviour of cells through generating signals (Järveläinen et al., 2009). In some tissues, like the epithelium or muscle, cells are connected tightly and the space between them is very limited. Therefore, there is less ECM and the cells could also be mechanically or functionally coupled by specific cell junctions. In connective tissue there is plenteous ECM and cells are sparsely distributed within it (Teti, 1992).

Basically, the ECM is made up of water, proteins and polysaccharides, but every tissue has its own ECM with a unique composition and topology. Throughout the tissue development the ECM evolves by a dynamic biochemical and biophysical dialogue between the various cellular components, e.g. epithelial, fibroblasts, adipocytes and endothelial elements, and the protein environment. So, the composition of the ECM is quite tissue-specific and heterogeneous (Frantz et al., 2010). The molecules of the ECM are exclusively organised and even minor alterations led to several changes. The substitution of a single amino acid in a single ECM component can lead to altered physiochemical properties of the tissue and to changes in the phenotype and in cell-matrix interactions. The sum of these changes can precede into the development of a disease (Järveläinen et al., 2009).

1.2.1 Molecular composition of the ECM

The composition of the ECM is highly dynamic and is constantly remodelled by enzymatic or non-enzymatic processes. Therefore, its molecular components are going through a lot of posttranslational modifications. This process is necessary so that the ECM can make up the specific biochemical and mechanical characteristics for every organ (Frantz et al., 2010).

The ECM is arranged of two main classes of macromolecules, the proteoglycans and the fibrous proteins (Frantz et al., 2010; Rozario & Desimone, 2010). The ECM components are classified into fibre-forming and non-fibre-forming molecules. Collagen and elastin count as fibre-forming molecules while the proteoglycans or the fibronectin are regarded as non-fibre-forming molecules (Järveläinen et al., 2009).

1.2.1.1 Proteoglycans

Proteoglycans are biological molecules, that consists of a glycosaminoglycan (GAG) that is covalently attached to a core protein. (Olson & Esko, 2004). GAG and proteoglycans form a highly hydrated gel. This is like a ground substance where the fibrous proteins are diffused. Proteoglycans are different in protein content, molecular weight and number and types of GAG per molecule (Teti, 1992). So, every proteoglycan can interact with different ligands, like growth factors, chemokines and enzymes, depending on their GAG chains (Olson & Esko, 2004). When the proteoglycan is not linked to the plasma membrane, the core protein is connected to hyaluronic acid which can retain a large amount of water und ions. Consequently, it gives the connective tissue its ability to resist compression (Teti, 1992). An example for this is aggrecan, the most present proteoglycan in cartilage. It has a large number of GAG chains and is linked to hyaluronic acid in the ECM, where it attracts water to the cartilage. By that the cartilage becomes resistant against compressive forces (Olson & Esko, 2004).

GAGs are linear, sulphated, negatively charged polymers of repeating disaccharides, which are composed of a hexosamine, e.g. galactosamine or glucosamine, and a uronic acid (Rozario & Desimone, 2010). Fundamentally they can be divided into two classes based on their name. There are sulphated GAGs - chondroitin sulphate and dermatan sulphate or heparan sulphate and heparin or keratan sulphate - and non-sulphated GAGs such as hyaluronan, which is not bound to a protein core (Olson & Esko, 2004; Schaefer & Schaefer, 2010). Depending on their carboxyl, hydroxyl and sulphate groups they have different physical properties. They could be defined as polyanionic molecules with osmotically active characteristics (Rozario & Desimone, 2010).

There are more than 25 known proteoglycans found in mammalians, which differ in their GAGs. While some of them carry only a single type of GAG, there are also proteoglycans that carry heparin and chondroitin sulphate or chondroitin and keratan sulphate or also proteoglycans that carry other types of glycans. Likewise, the molecular masses are ranging from 10 kDa to 400 kDa (Olson & Esko, 2004).

1.2.1.2 Fibrous proteins

The main fibrous proteins are collagens, elastin, fibronectins and laminins, whereas collagen is the most abundant fibrous protein within the ECM and it constitutes up to 30% of the total protein mass. Collagens give the ECM its structure and provide tensile strength, regulate the cell adhesion, support chemotaxis and migration and lead the tissue development. Fibroblasts, which are located in the stroma or are recruited to it from neighbouring tissue, transcribe and secrete the majority of the interstitial collagen (De Wever et al., 2008). Because the fibroblasts bring tension on the matrix, they can organise the collagen fibres into sheets and cables and can by that extremely influence the alignment of the fibres. Although the collagen in various tissue is heterogenic, there is always one type predominating (Frantz et al., 2010) .

Another fibrous protein is elastin, a very hydrophobic, non-glycosylated protein, which is rich in proline and glycine (Teti, 1992). If a tissue undergoes repeated stretch, elastin fibres provide recoil to tissue (Frantz et al., 2010). The fact that the elastin is closely associated with collagen fibrils limits the elastin stretch. The precursor of elastin is secreted tropoelastin, which assembles into fibres and become crosslinked by lysine residues through specific enzymes (Wise & Weiss, 2009). Elastic fibres are especially present in skin, blood vessels and lungs, where they ensure elasticity (Teti, 1992).

The third important fibrous protein is fibronectin (FN), a large glycoprotein. It is involved in the organisation of the interstitial ECM, cell attachment and -function. Through cellular traction forces it could be stretched several times over its resting length. When it comes to such a force-dependent unfolding of FN integrin-binding sites will be exposed and by that the cellular behaviour changes and implicate FN as an extracellular mechano-regulator. It also plays an important role in cell migration during development and is linked to cardiovascular disease and tumour metastasis (Smith et al., 2013).

1.2.2 Functions of the ECM

The ECM is accomplishing widespread functions and influences several biochemical and mechanical processes simultaneously. As mentioned above the ECM is highly dynamic and it can be modified by the cells, which come into contact with it (Rozario & Desimone, 2010).

In certain connective tissues, e.g. tendons, cartilage and bones, the ECM has a mechanical function. In the tendons for instance the fibrous proteins have to be organised in order to become resistant to stretch. In cartilage and bones the main task is to resist stretch and compression (Teti, 1992).

During development the ECM plays a crucial role in cell proliferation, differentiation and migration (Teti, 1992). In addition, the ECM controls essentials morphological and physiological functions by binding growth factors and interacting with cell-surface-receptors to induce signal transduction and regulate gene transcription. It must be stated that the numerous features of the ECM could differ extremely from one tissue to another or even within a tissue but even from one physiological state to another (Frantz et al., 2010).

Other processes regulated by the ECM are filtration and blood clotting. Thereby, the basal laminae of the endothelium and the glomerular cells are part of the glomerular filtration. This is a network from ECM constitutes that blocks blood cells and plasma proteins but allows the filtration of low-molecular weight molecules. During the blood clotting the platelets interacts with the connective tissue and blood ECM constituents (Teti, 1992).

As discussed in the first part, the ECM has diverse compositions and functions. Since it is important for the present work how the extracellular matrix around the skeletal muscle is composed or how it behaves, this will be discussed in the next section.

1.2.3 Skeletal Muscle Extracellular Matrix

Skeletal muscles in humans are not only important for holding the body in an upright position and the production of movement, they also play a role in many other physiological processes, like for metabolism or thermogenesis (Baskin et al., 2015; Rowland et al., 2015). In men more than 40% and in women more than 30% of the total body mass are composed of muscle mass. For this reason, the progress and the maintenance of skeletal muscle health are of vital importance, whereby physical activity is still the most effective way to achieve this goal (Csapo et al., 2020). In this setting, the ECM of tendon tissue and muscles guarantees a functional link between skeletal muscle cells and the bone (Kjaer, 2004).

1.2.3.1 Structure of the skeletal muscle ECM

As mentioned above, also muscle fibres are nestled in an ECM. When it comes to the muscular context the ECM has different roles for example in the development, the growth or in the repair of muscle tissue. The ECM also plays an important role by the transmission of contractile force. The composition of the ECM of skeletal muscle is basically the same as described above (Csapo et al., 2020; Gillies & Lieber, 2011).

The collagens, which are the central fibrous components of the ECM, make up the so called intramuscular connective tissue (IMCT). Simplified, the IMCT is structured in three layers:

- the endomysium or basal lamina, which is the innermost layer surrounding single muscle fibres
- the perimysium, which is pooling groups of muscle fibres and
- the epimysium, which surrounds the whole muscle (Gillies & Lieber, 2011; Purslow, 2020).

The IMCT accounts for 1-10% of the skeletal muscle, but varies from muscle to muscle. The endomysium is a random arrangement of collagen fibrils, that encounter movement during the contraction. The perimysium runs transversely to the fibres and keeps them in place. The epimysium is formed of two layers of wavy collagen fibrils so that a sheet like structure at the surface is build (Kjaer, 2004; Purslow, 2020).

In figure 2 the three layers of the IMCT and their components are shown (Zhang et al., 2021).

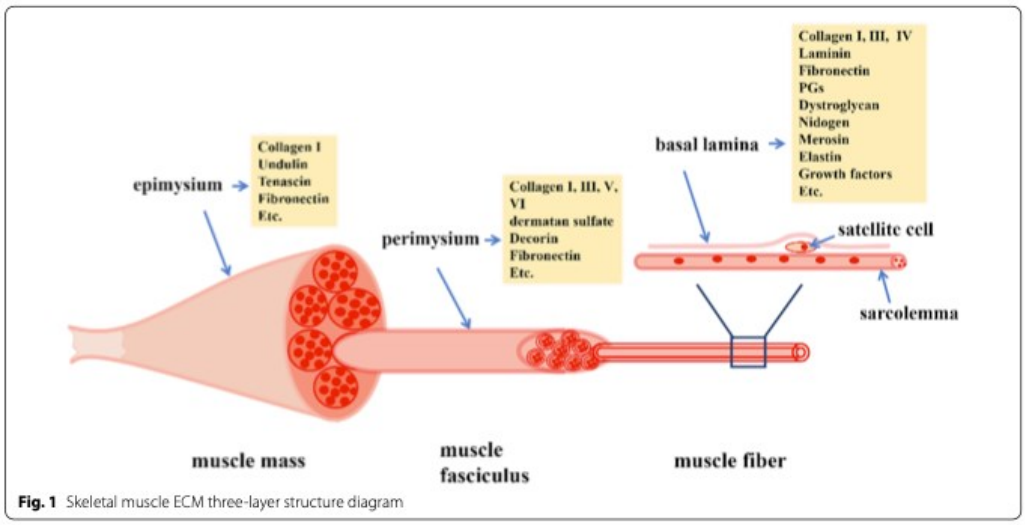

Figure 2 Layers of the IMCT including its components (from Zhang et al., 2021, p. 3)

In figure 3 the different structures of the IMCT are shown by scanning electron myographs after removal of skeletal muscle protein (Kjaer, 2004).

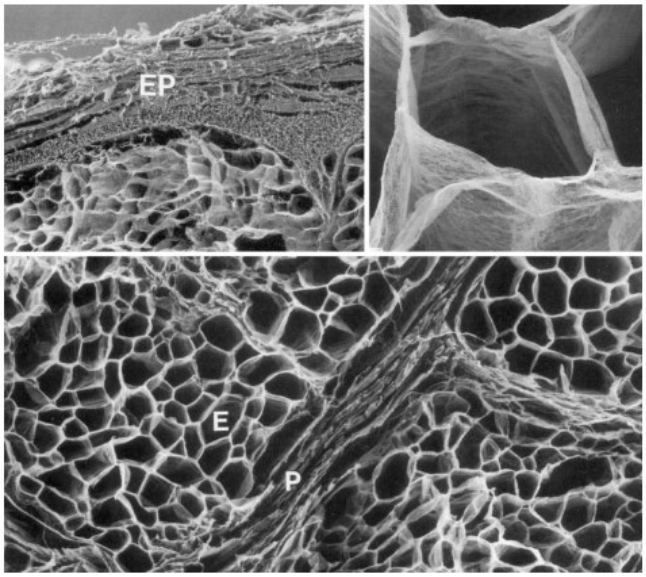

Figure 3 Epimysium (top left, E), perimysium (bottom picture, P) and endomysium (top right) (from Kjaer, 2004, p. 656)

1.2.3.2 ECM and skeletal muscle force

Not only the interaction of actin and myosin but also the interaction with other sarcomeric proteins results in the shortening of muscle fibres. In biomechanical models, the forces being generated through fibre shortening, go along the muscle fibre and are then transferred on the tendon longitudinally via the myotendinous junction. The myotendinous junction has a finger-like form and connects the tendon with the muscle tissue. By that from, the surface available for force transmission becomes bigger. The force is transmitted from the muscle filaments to the collagen fibres of the tendon tissue (Knudsen et al., 2015).Collagens which play a role in this process are of type XXII, that form an inner layer, and of types III, VI, XII and XIV, which lie further away from the muscle fibre membrane (Jakobsen et al., 2017). It seems that, collagen XXII can only be found in in the myotendinous junction. It could be possible, that this collagen should maintain the structural integrity and stabilize the myotendinous junction (Csapo et al., 2020; Jakobsen et al., 2017).

Because a big part of fibres in long muscles do not reach a tendon directly, it has to be acknowledged, that the myotendinous junction is not the only way to achieve force transmission. Those interfascicular terminating fibres have to work together with a parallel arranged medium to

transmit their forces onto the passive components of the locomotor system (Sheard, 2000). The IMCT transfers the lateral force through contractile proteins across costameres (protein complexes that transmit forces from the sarcomere to the ECM) to the endomysium and onto the perimysium, which finally merges in aponeuroses and tendons (Passerieux et al., 2007; Street, 1983). To sum up, the lateral transmission of force should also be considered as a biomechanical need to further improve the contraction efficiency. It spreads the contractile forces all over the surface of myofibers, which reduces the mechanical stress and protects the fibres from over tension (Csapo et al., 2020; Kjaer, 2004). Further, the lateral force transmission helps in keeping up the integrity of the muscle by bridging fibres that are not contracting simultaneously or to an unequal extent. The IMCT and the muscle fibres can provide a direct force transmission through the translaminar shear linkage (Purslow, 2002).

Besides the lateral transfer of force, the ECM can also affect the muscle fibre shortening. When the muscle fibres contract, they expand in their radius. If the radial expansion is limited through a physical barrier, the muscle shortening is limited. So, the IMCT, in which muscle fibres are embedded, can directly influence the contractility of the skeletal muscle (Csapo et al., 2020).

To sum up, it is now clear, that the force transmission takes not only place via myotendinous junctions but also via lateral transmission between neighbouring fibres and fascicles within a muscle (Kjaer, 2004).

1.2.3.3 ECM in skeletal muscle and muscle development

The ECM of the skeletal muscle is not only transmitting force but also has some functional tasks. For example, it offers mechanical support for the muscle fibres, nerves and blood vessels or ensures the passive elastic response of the muscle (Kjaer, 2004).

Furthermore, the interaction between myoblasts, muscle fibres and the ECM is of crucial importance for the development from embryonic stage until senescence (Csapo et al., 2020; Thorsteinsdóttir et al., 2011; Zhang et al., 2021). There are some complex regulatory processes involved in the development which are not going to be further discussed.

To adapt and regenerate throughout their lifecycle the skeletal muscles depend on satellite cells. These adult stem cells are located in niches between the sarcolemma of the muscle fibres and their basement membranes. The ECM plays a role in sending signals to protect the quiescent state of the stem cells or to activate, proliferate or differentiate them. To sum up, the ECM is important to keep up the quiescent state from satellite cells and by that to maintain the

physiological function of them (Csapo et al., 2020; Fry et al., 2017; Grzelkowska-Kowalczyk, 2016; Thorsteinsdóttir et al., 2011; Zhang et al., 2021).

Furthermore, several collagens, proteoglycans and fibronectin influence the stem cell division. These components maintain the balance between differentiation and renewal and by that influence the maintenance and regenerative capacity of skeletal muscle. The ECM acts upon different processes that activate and differentiate satellite cells to myoblasts to get over muscle trauma (Csapo et al., 2020; Zhang et al., 2021). To conclude, the ECM and its changes can influence the development and the regenerative capacity of the muscle (Thorsteinsdóttir et al., 2011).

The ECM is a very complex and highly developed structure. Its components are synthesized and secreted by many types of cells. The ECM of the skeletal muscle is not only involved in development and maintenance of muscle morphology and its contraction, but also regulate some physiological functions like signal transmission or regeneration after injury (Csapo et al., 2020; Zhang et al., 2021).

1.3 Collagen peptides

Collagen peptides are also known as collagen hydrolysates or hydrolysed collagen. Hydrolysed collagen consists of small peptides, which are produced from native collagen. Collagen peptides are mainly obtained from beef (Ferraro et al., 2017). The extraction can be done from different tissues, like bones, tendons or connective tissue. Another source is pork. There are also some alternative sources for extraction like tendon and skin from sheep, bones, skin and scales from fishes or chicken, duck and rabbit skin (León-López et al., 2019; Sibilla et al., 2015).

When the collagen is heated above 40°C, the chains are separated by proteolytic enzyme and the end product is hydrolysed collagen. It is made up of small peptides with a low molecular weight from three to six kilodalton. The solubility and the functional activity depend on the type and degree of hydrolysis and the enzymes that are used in the process (León-López et al., 2019; Sibilla et al., 2015). The hydrolysis can also be made with the use of chemical products in acidic or alkaline environment (Moskowitz, 2000).

A schematic denaturation of the native collagen into smaller peptides is shown in figure 4.

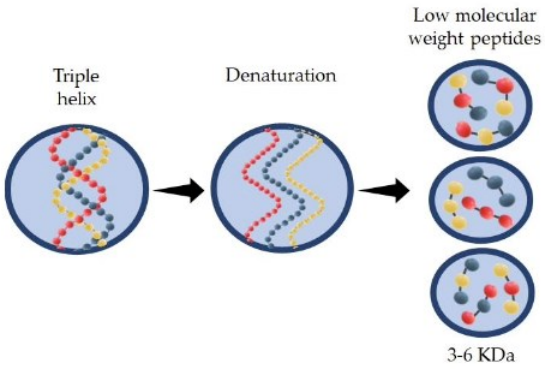

Figure 4 Collagen denaturation (from León-López et al., 2019, p. 3)

Hydrolysed collagens are very soluble in water (Moskowitz, 2000) and have some advantages towards native collagen. For example, no multistep extraction is required, they are highly digestible and easily absorbed and distributed in the human body (León-López et al., 2019; Sibilla et al., 2015).

Because of its composition collagen peptides have a low biological value. They contain large amounts of glycine, proline and hydroxyproline. They do not have tryptophan and cysteine can only be found in small amounts. Additionally, they do not contain all essential amino acids. But it is yet thought to be a valuable nutritional component because of his excellent digestibility (Moskowitz, 2000; Sibilla et al., 2015).

Due to their small molecule size and the high amounts of proline and hydroxyproline hydrolysed collagens are more resistant to peptidases. They are almost completely resorbed in the small intestine and absorbed into the blood stream in the form of collagen peptides and free amino acids (Iwai et al., 2005; Sibilla et al., 2015).

Products from collagens are recognized as safe by the European Food and Drug Administration (Administration, 2005; Bello & Oesser, 2006).

2 Research question

There are already some studies, which investigate the influence of different types of collagen supplementation on body composition, strength, muscle, tendons, ligaments and cartilage in the context of sports and physical activity.

The effects of long-term collagen supplementation on musculoskeletal system, strength and body composition are gaining interest in the past few years. Therefore, this review wants to elaborate the consequences of chronic collagen supplementation combined with an exercise intervention on muscles, tendons, ligaments, strength, performance and the body composition. As can be seen from the above introduction, collagen peptides have an impact on tissue and muscle strength due to their composition. The combination of amino acids glycine, proline and hydroxyproline have a signalling effect in anabolic processes in musculoskeletal tissue (Oesser & Seifert, 2003; Schunck & Oesser, 2013). The aim is to systematically collect data from randomised controlled trials in healthy individuals.

Hereinafter, a research question according to PICO (population, intervention, comparator, and outcome (Methley et al., 2014)) was developed: “Is there a effect of chronic collagen supplementation on musculoskeletal system, body composition and strength and performance in healthy individuals compared to placebo or other control?”.

As such this systematic review aims to identify whether collagen supplements provide any benefits on musculoskeletal system, body composition and strength in healthy active people and if so, what mechanisms are responsible for this.

3 Methods

In order to answer the research questions, the methods of the systematic review will be discussed in the following part. The reporting will be presented in accordance with the Preferred reporting items for systematic review and meta-analyses (PRISMA) statement for reporting systematic reviews (Moher et al., 2009; Page et al., 2021).

3.1 Eligibility criteria

Since collagen supplementation and its effects on body composition, strength and the musculoskeletal system is a topic of increasing interest, the publication date was not restricted to any year.

The PICO (Methley et al., 2014) for the following review were determined as follows:

- *Patients*: healthy active adults
- *Intervention*: collagen supplementation and physical activity
- *Control*: placebo
- *Outcome*: effects on body composition, strength, performance, muscles, tendons and ligaments

All studies were selected for eligibility if they met the following criteria:

- intervention studies (randomised controlled trials)
- studies in humans without any diseases or orthopaedic complaints
- studies with chronic collagen supplementation (minimum 3 days supplementation)
- studies including any type of physical activity or exercise intervention (lasting minimum 3 days)
- studies which analysed body composition, strength, performance or musculoskeletal system as an outcome
- studies in German or English

The exclusion criteria were defined as the following:

- observational studies, reviews, meta-analysis, …
- animal studies

- studies in humans with any disease
- acute or no collagen supplementation
- no exercise intervention
- studies in other language than German or English

3.2 Information sources and search strategy

The computer databases PubMed (*PubMed*) and Web of Science (*Web of Science Core Collection*) were searched up until 7th of July 2021 to carry out the review. Since there is the possibility that one database neglects relevant research, the two mentioned databases were used to ensure that all relevant studies are included.

PubMed including MEDLINE is known as a database of references and abstracts on life sciences and biomedical topics. Web of Science is recognised for his access to several databases that provide citation data for several different disciplines.

The search string was created similarly to Bramer et al. (2018). The keyword used for the search string were “collagen supplementation”, “body composition”, “muscle strength”, “musculoskeletal system” and “physical activity”. The original search string for PubMed was the following: (((collagen) OR (collagen supplement) OR (collagen peptides) OR (collagen derivates) OR (collagen hydrolysate)) AND ((body composition) OR (muscle strength) OR (muscles) OR (ligament) OR (tendon) OR (cartilage)) AND ((physical activity) OR (resistance training) OR (exercise)) AND (humans)) AND (randomized controlled trial). The search string for Web of Science looked like this: (TS=(collagen* AND supplementation* AND exercise*)) NOT (DT==("REVIEW")).

There were no further articles found by hand search which was based on the screening of the reference lists of the selected articles. No limitation occurred during the search.

3.3 Selection and data collection process

The screening process did take place with the help of the web-based systematic review software “Covidence” (https://www.covidence.org/). Both the citations from PubMed and the ones from Web of Science were exported to an appropriate file to insert them into Covidence. The duplicates were automatically removed by Covidence. A two-step procedure to screen for the predefined inclusion and exclusion criteria was applied. In the first step the literature was screened by title and abstract to assess eligibility. The remaining articles were chosen for the

full-text analysis, read in detail and either excluded or included. The Prisma flow chart in the result section gives an overview about the process and shows the reasons for exclusion. Only one reviewer (the master student) screened the records and extracted relevant information from the included articles.

From each included study the following information was selected.

General characteristics:

- Name of the authors
- Country
- Study design
- Study setting
- Enrolled and completed study samples
- Duration of the intervention

Sample characteristics:

- Sample number
- Sex
- Age
- Fitness level
- Baseline subject characteristics

Intervention characteristics:

- Type of exercise
- Exercise duration
- Exercise frequency
- Exercise intensity

Supplement characteristics:

- Type of collagen peptide
- Amount
- Timepoint

- Duration
- Type and amount of control (placebo)

Outcome:

- Changes in muscle mass
- Strength or performance changes
- Body composition changes
- Changes in collagen synthesis
- Changes in function and cross-sectional area of muscles, tendons and ligaments
- Changes in amino acid concentrations

If missing or unclear information appeared it was discussed between the student and the supervisor. When results where only presented in figures, WebPlotDigitizer (version 4.4 for Windows 10) was used to quantify the outcomes. When standard deviation (SD) or standard error of the mean (SEM) were not clear it was declared as not reported. If not described otherwise mean ± SD are reported.

3.4 Risk of bias assessment

For the assessment of risk of bias, the PEDro scale was used. The included studies were searched in the Physiotherapy Evidence Database. The tool consists of eleven items and scores can range from two to eleven. Depending on the score the studies can be clustered into low methodological quality (less than or equal to three points), moderate quality (four to six points) and high methodological quality (more than or equal seven points) (De Morton, 2009).

4 Results

In the next chapter the results of the literature search of the systematic review are presented. The flow diagram (figure 5) shows the selection process. Subsequently, the characteristics of the studies are presented. In detail, study characteristics, participant characteristics, exercise protocols, and collagen supplementation characteristics are listed for each study. The main outcomes are also presented in table 6 to 9.

4.1 Study selection

A total of 220 studies has been found based on the database search with the respective search string. The search in PubMed resulted in 113 papers, whereas the search in Web of Science produced 107 citations. Covidence identified and removed 22 duplicates, which resulted in 198 records for the title and abstract screening. Thereof, 180 articles did not meet the eligibility criteria during title and abstract screening. The remaining 18 articles were read in full text. Figure 5 shows the PRISMA flow chart of the study selection process and the reasons for exclusion (Page et al., 2021).

There are a few studies which met many but no all inclusion criteria. In the study of Hays et al. (2009) the effects of whey and fortified collagen hydrolysate protein supplements on nitrogen balance and body composition was studied in older women. The crossover study consisted of a 15-day diet with a one week wash out period. The subjects did receive a collagen supplementation but they did not undergo any exercise intervention. The same exclusion reason counts for Lugo et al. (2013) and Mertz et al. (2021). Another near-miss was the study from (Zdzieblik, Brame, et al., 2021). The working group examined the influence of collagen peptides on knee joint discomfort in young physically active adults. The study was excluded from the review because of the predefined study population.

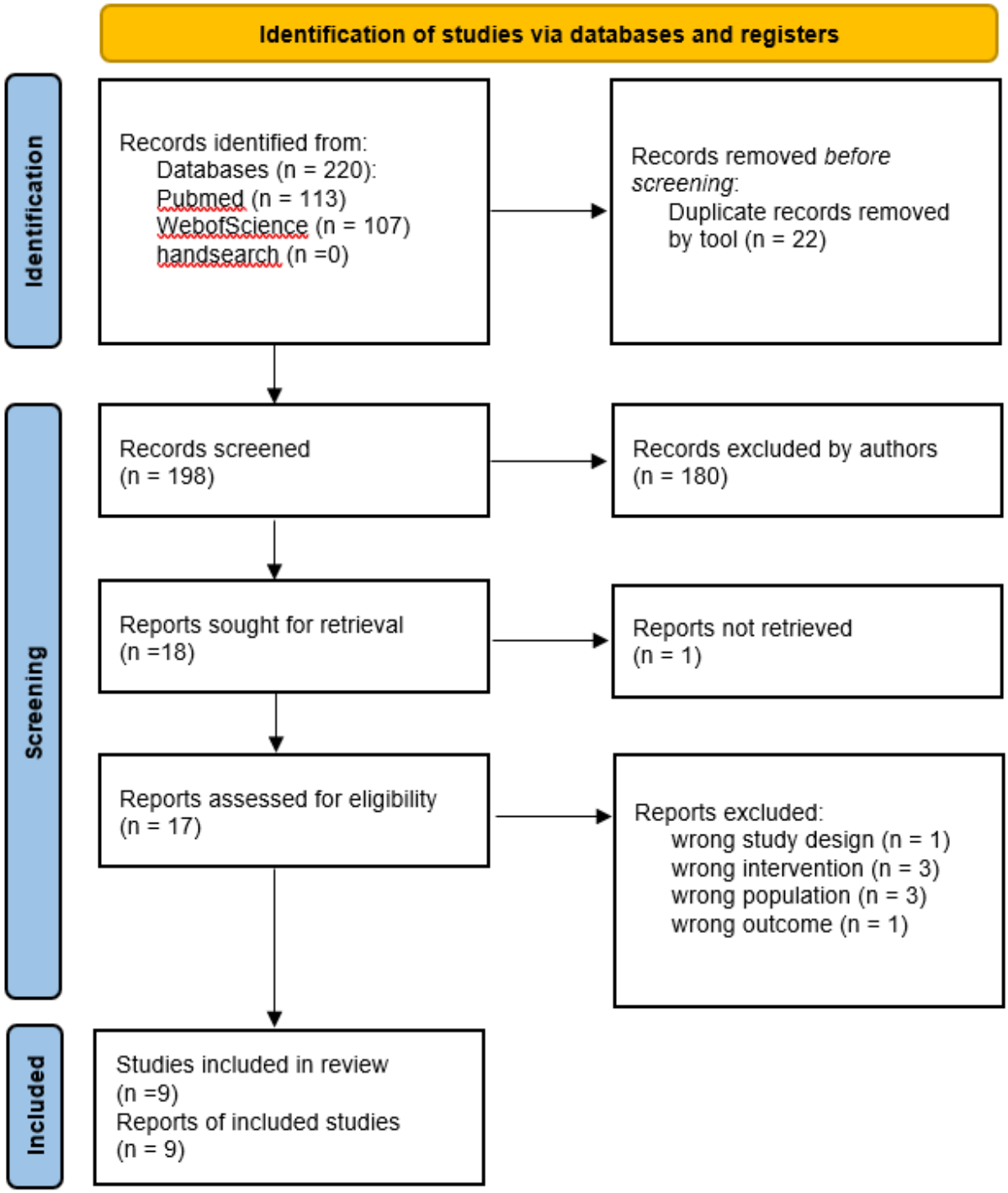

Figure 5 PRISMA flow chart

4.2 Study characteristics

The nine included studies were published between 2017 and 2020. The subjects were recruited from Germany, United Kingdom, Canada and Australia. As defined in the eligibility criteria all of the subjects were healthy and without any diseases or orthopaedic complaints. The enrolled number of participants ranged from a minimum of eight subjects to the maximum of 90 subjects. The intervention lasted from three days to 12 weeks. All of the included studies were prospective intervention studies. Except from Oikawa, Macinnis, et al. (2020), which used a crossover design, all the studies were conducted in a parallel group design. Table 2 shows the general characteristics of the included studies.

Table 2 Study characteristics of the included studies (n = 9)

Authors	Year	Country	Study design	Study population	Duration
Centner et al.	2019	Germany	randomized, placebo-controlled, double-blinded study	healthy older men	8 weeks
Clifford et al.	2019	United Kingdom	randomized, placebo-controlled, double-blinded study	recreationally active	9 days
Jendricke et al.	2019	Germany	randomized, placebo-controlled, double-blinded study	untrained premenopausal women	12 weeks
Jendricke et al.	2020	Germany	randomized, placebo-controlled, double-blinded study	healthy women	12 weeks
Kirmse et al.	2019	Germany	randomized, placebo-controlled, double-blinded study	moderately trained men	12 weeks
Oertzen-Hagemann et al.	2019	Germany	randomized, placebo-controlled, double-blinded study	healthy sport students	12 weeks
Oikawa, MacInnis et al.	2020	Canada	double-blinded, randomized cross-over study	healthy men and women	3 days
Oikawa, Kamal et al.	2020	Canada	double-blinded, parallel group, randomized controlled trial	healthy older women	9 days
Shaw et al.	2017	Australia	randomized, placebo-controlled, double-blinded study	recreational active men	3 days

A summary of included participants and those finalizing the respective studies is shown in figure 6. The number of drop-outs differed between the studies. The longer the duration of the study, the more drop-outs could be observed.

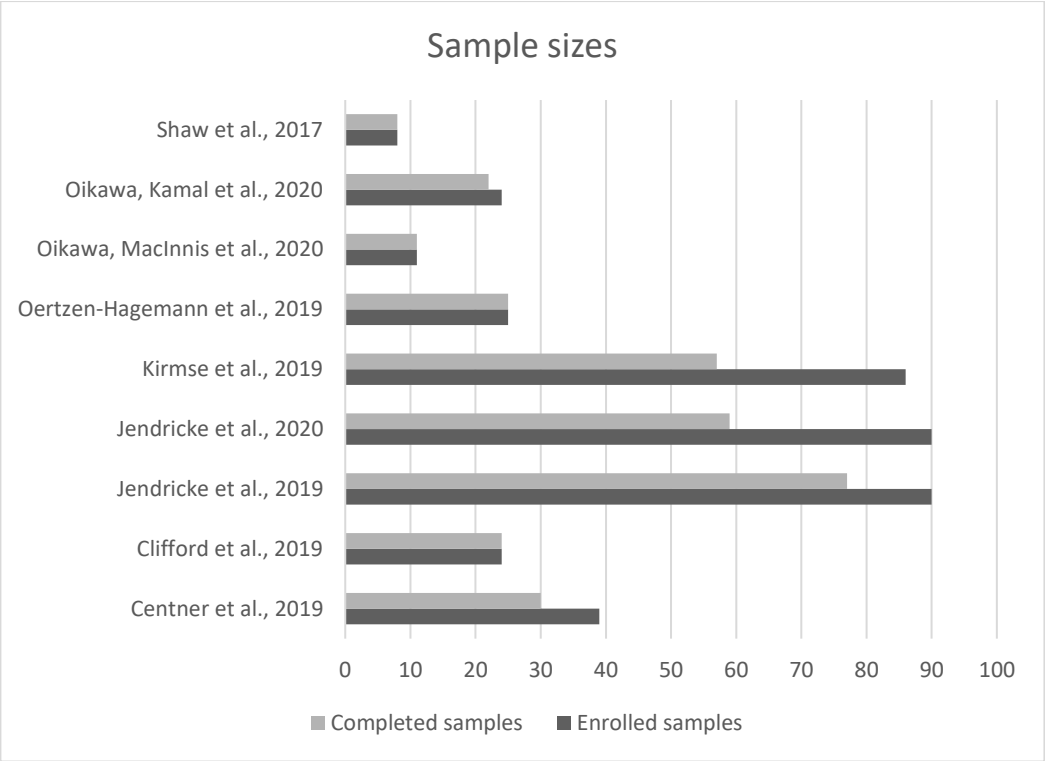

Figure 6 Enrolled and completed samples of the studies

Due to the fact, that all studies investigated healthy and more or less active adults, the comparability between the studies is warranted. Over all studies 313 subjects where investigated, whereby 149 of them were males (47,6%) and 164 females (52,4%). Figure 7 show the distribution of the participants.

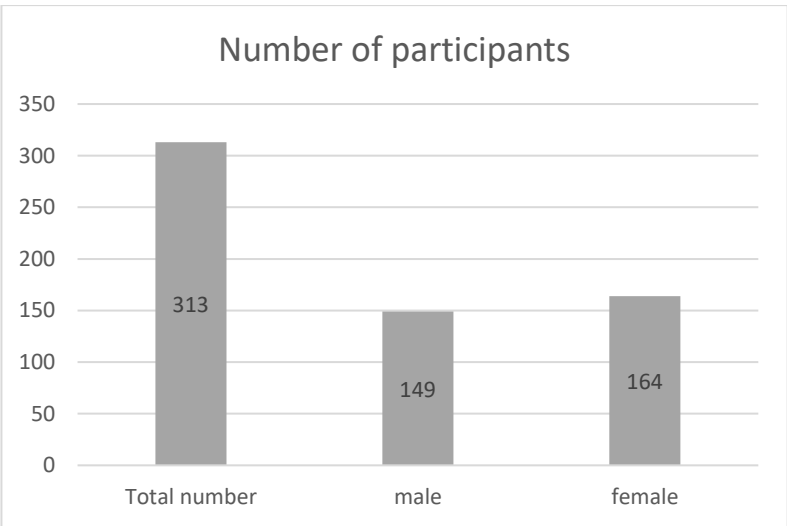

Figure 7 Sex distribution of the included subjects

The average age of the objects from the studies was 35,3 years with a range from 24 to 69 years. Only Centner et al. (2019) and Oikawa, Kamal, et al. (2020) examined the effects of collagen supplementation in older men and women. Table 3 summarises the general characteristics of the study population. Average BMI was, if not reported, calculated based on the information from the included studies.

Table 3 Population characteristics (SD= standard deviation, SEM = standard error of the mean)

Author	n	age (mean ± SD)	height in cm (mean ± SD)	weight in kg (mean ± SD)	Mean BMI in kg/m²
Centner et al., 2019	30	61,7 ± 5,5	177 ± 7	84,9 ± 13,5	27
Clifford et al., 2019	24	24,1 ±4,3	178 ± 4	79,6 ± 7,5	25
Jendricke et al., 2019	77	38,3 ± 8,7	167 ± 6	73,5 ± 10,7	26
Jendricke et al., 2020	59	25,4 ± 4,2	167 ± 7	62,5 ± 8,6	22
Kirmse et al., 2019	57	24 ± 2	184 ± 6	79,3 ± 8,4	23
Oertzen-Hagemann et al., 2019	25	24,4 ± 2,3	186 ± 5	81,4 ± 6,6	24
Oikawa, MacInnis et al., 2020	11	24 ± 4	171 ± 9	68,8 ± 10,6	24
Oikawa, Kamal et al., 2020	22	69 ± 4	160 ± 3	70,6 ± 17,1	28
Shaw et al., 2017	8	27 ± SEM: 6	not reported	79,6 ± SEM: 12,0	not reported

The exercise interventions differed between the studies. From the nine included studies, five conducted a resistance training intervention (Centner et al., 2019; Jendricke et al., 2020; Kirmse et al., 2019; Oertzen-Hagemann et al., 2019; Oikawa, Kamal, et al., 2020). Only Centner et al. (2019) used a blood flow restriction training with an accordingly low exercise intensity to examine the effect of collagen supplements on muscle mass and strength. A protocol to induce muscle damage by the help of drop jumps was applied by Clifford et al. (2019). Furthermore, a concurrent training intervention was investigated by Jendricke et al. (2020). In the intervention phase of the study from Oikawa, Macinnis, et al. (2020) the subjects completed brief daily periods of intense endurance exercise for the timespan of the study (3 days). Shaw et al. (2017) implemented a rope skipping protocol to study the collagen synthesis. An overview over the characteristics of the exercise interventions could be found in the table 4.

Table 4 Exercise intervention characteristics (1RM = one repetition maximum, RT = resistance training, END = endurance training, PPO = peak power output)

Author	type of exercise	muscle groups	exercise frequency	exercise intensity
Centner et al., 2019	blood flow restriction	lower extremity	3 days/week	20-30% 1RM
Clifford et al., 2019	drop jump protocol	lower extremity	once per intervention	150 drop jumps from 60cm box
Jendricke et al., 2019	resistance training	full body	3 days/week for 60 mins	adjusted individually according to repetitions
Jendricke et al., 2020	concurrent training	full body	3 days/week (RT+END)	adjusted individually according to repetitions
Kirmse et al., 2019	resistance training	full body	3 days/week	70% 1RM
Oertzen-Hagemann et al., 2019	hypertrophy resistance training	full body	3 days/week	70% 1RM
Oikawa, MacInnis et al., 2020	HIIT	full body	daily	4x4 min intervals with 70% PPO
Oikawa, Kamal et al., 2020	unilateral resistance exercise	leg	two times per intervention	60% 1RM
Shaw et al., 2017	rope skipping	full body	three sessions per day	

The amount of collagen supplementation was quite similar between the studies with an amount between 15 and 30 g/day being most common one. Only (Oikawa, Kamal, et al., 2020) used a supplementation of 60 g/day, whereby 20 g were consumed post-exercise and 40 g before going to sleep. Concerning the control/placebo silicon dioxide was used in five studies (Centner et al., 2019; Jendricke et al., 2019; Jendricke et al., 2020; Kirmse et al., 2019; Oertzen-Hagemann et al., 2019), maltodextrin in two studies (Clifford et al., 2019; Shaw et al., 2017) and in another two studies another protein source was supplemented (Oikawa, Kamal, et al., 2020; Oikawa, Macinnis, et al., 2020). Table 5 outlines the type of collagen, the amount and the timepoint of the supplements and respectively controls.

Table 5 Supplementation characteristics

Author	type of collagen	amount	timepoint	control
Centner et al., 2019	collagen hydrolysate	15 g/day	within 60 mins after training or at the same time when no training	silicon dioxide
Clifford et al., 2019	collagen peptides	20 g/day	twice per day, 10g in the morning and 10g in the evening	maltodextrin
Jendricke et al., 2019	collagen peptides	15 g/day	within 60 mins after training or at the same time when no training	silicon dioxide

Jendricke et al., 2020	collagen peptides	15 g/day	7,5g 2h before training and 7,5g after training, the same schedule when no training	silicon dioxide
Kirmse et al., 2019	collagen peptides	15 g/day	immediately after training or 24h after previous ingestion	silicon dioxide
Oertzen-Hagemann et al., 2019	collagen hydrolysate	15 g/day	immediately after training or at the same time when no training	silicon dioxide
Oikawa, MacInnis et al., 2020	hydrolysed collagen peptides	60 g/day	20g post-exercise and 40g pre-sleep	lactalbumin
Oikawa, Kamal et al., 2020	hydrolysed collagen peptides	30 g/day	twice per day	whey protein
Shaw et al., 2017	gelatine + vitamin C	5 or 15 g/day	1h before training (9x)	maltodextrin

Regarding the outcomes the change in body composition was examined in four studies (Jendricke et al., 2019; Jendricke et al., 2020; Kirmse et al., 2019; Oertzen-Hagemann et al., 2019). All studies used a bioelectrical impedance analysis to asses changes in body composition and body weight.

The effects of collagen supplementation on strength and performance was investigated in a total of six studies (Centner et al., 2019; Clifford et al., 2019; Jendricke et al., 2019; Jendricke et al., 2020; Kirmse et al., 2019; Oertzen-Hagemann et al., 2019). If the maximal voluntary isometric contraction was measured, it was done using a 90° leg press (Centner et al., 2019; Jendricke et al., 2019; Jendricke et al., 2020), a portable strain gauge (Clifford et al., 2019) or a dynamometer (Kirmse et al., 2019; Oertzen-Hagemann et al., 2019). Changes in a muscle endurance test, a one hour running time trial, an incremental test and in one repetition maximum of back squat were used to determine the effects of collagen supplementation and concurrent training on performance in Jendricke et al. (2020). The one repetition maximum of squat, bench press, deadlift or rowing was used to measure muscle strength in Kirmse et al. (2019) and Oertzen-Hagemann et al. (2019) intervention study.

Four studies assayed the effects of collagen peptides on the musculoskeletal system (Centner et al., 2019; Clifford et al., 2019; Kirmse et al., 2019; Shaw et al., 2017). The muscle cross-sectional area was assessed through magnetic resonance imaging (Centner et al., 2019), muscle biopsies (Kirmse et al., 2019) and in Shaw et al. (2017) observation the cross-sectional are was obtained via digital callipers in the engineered ligament, which was formed from human anterior cruciate ligament. In these engineered ligaments also the collagen content, the collagen dry mass and the maximal tensile load was measured. The PINP concentration was measured in blood samples. Kirmse et al. (2019) additionally measured muscle thickness via

a b-mode ultrasound system and the fibre distribution via the muscle biopsies. Clifford et al. (2019) wanted to examine the influence of collagen peptides on parameters for muscle damage. They used the visual analogue scale (VAS) and the pressure pain threshold (PPT), both subjective markers for muscle soreness.

The amino acid concentrations and the muscle protein synthesis were assessed in a total of five studies (Kirmse et al., 2019; Oertzen-Hagemann et al., 2019; Oikawa, Kamal, et al., 2020; Oikawa, Macinnis, et al., 2020; Shaw et al., 2017). For determination of amino acid concentrations blood samples (Kirmse et al., 2019; Oikawa, Kamal, et al., 2020; Oikawa, Macinnis, et al., 2020; Shaw et al., 2017) or muscle biopsies (Oertzen-Hagemann et al., 2019) were used. To label the newly synthesized myofibrillar proteins $^{2}H_2O$ was used in Oikawa, Kamal, et al. (2020) and Oikawa, Macinnis, et al. (2020).

4.3 Results of individual studies

For a better overview, the results are presented summarized by research question. The outcome for every individual study could be found in detail in the Appendix section.

4.3.1 Effects on body weight and body composition

From the included nine studies, four studies examined changes in body weight and body composition with a bioelectrical impedance analysis at the begin and the end of the intervention (Jendricke et al., 2019; Jendricke et al., 2020; Kirmse et al., 2019; Oertzen-Hagemann et al., 2019). The body weight remained unchanged in the untrained premenopausal women from Jendricke et al. (2019) and in the healthy women, who underwent a concurrent training intervention (Jendricke et al., 2020). The subjects body weight increased over the intervention period in the study from Kirmse et al. (2019) as well as in the study from Oertzen-Hagemann et al. (2019). In the healthy sport student sample from Oertzen-Hagemann et al. (2019) a higher increase in the collagen peptide group was observed (81,4 ± 6,6 kg vs. 84,4 ± 6,3 kg in CP and 77,9 ± 4,1 kg vs. 79,4 ± 5,1 kg in PLA; p = 0,035).

Concerning the fat-free mass all four studies reported an increase in both groups with a significant higher increase in the CP group. The results are summarised in table 6.

The results in the changes of fat mass did differ between the studies. Jendricke et al. (2019) observed a decrease in fat mass in both groups with a higher decline in the CP group. Also in the concurrent training intervention a decrease in fat mass was observed but no difference

between the groups was detected (Jendricke et al., 2020). The intervention from Kirmse et al. (2019) resulted in an increase in fat mass in the PLA group whereas the CP showed no differences. Nearly the same outcome was observed in the study from Oertzen-Hagemann et al. (2019), with the difference that the fat mass increased over time in both groups.

Additionally, to these parameters, Jendricke et al. (2020) reported skeletal muscle mass, total body water and extra- and intracellular water. The skeletal muscle mass increased over the 12-week period (21,0 ± 2,80 kg vs. 21,6 ± 2,85 kg in CP and 21,8 ± 2,58 kg vs. 22,1 ± 2,62 kg in PLA) with a trend to a higher increase in the CP group ($p = 0,052$). The total body water increased over time (32,8 ± 3,54 L vs. 33,4 ± 3,51 L in CP and 33,7 ± 3,30 L vs. 33,9 ± 3,51 L in PLA) with a significant higher increase in CP ($p = 0,041$). Additionally, the extracellular water increased over the study period (14,0 ± 1,54 L vs. 14,3 ± 1,65 L in CP and 14,3 ± 1,49 L vs. 14,5 ± 1,48 L in PLA) but without a difference between the groups. Lastly, the intracellular water did not differ between pre and post, but revealed a statistically significant interaction effect (increase in CP: 0,3 ± 0,5 L, no increase in PLA, $p = 0,011$).

Table 6 Effects on body weight and body composition (CP = collagen peptides, PLA = placebo; values are mean ± SD)

Reference	sample size	population	study length	exercise intervention	outcomes			
					body weight (in kg)	fat-free mass	fat mass	skeletal muscle mass
Jendricke et al., 2019	77	untrained premenopausal women	12 weeks	resistance training	no significant difference	increased in both groups, with a higher increase in CP *pre vs. post:* **CP**: 62,6 ± 6,0 vs. 64,4 ± 6,2% **PLA**: 63,8 ± 6,0 vs. 64,7 ± 6,0%	decreased in both groups, with a higher decline in CP *pre vs. post:* **CP**: 37,4 ± 6,0 vs. 35,6 ± 6,1% **PLA**: 36,2 ± 6,0 vs. 35,3 ± 6,1%	
Jendricke et al., 2020	59	healthy women	12 weeks	concurrent training	no significant difference	increased in both groups, with a higher increase in CP *pre vs. post:* **CP**: 44,6 ± 4,69 vs. 45,4 ± 4,60 kg **PLA**: 45,6 ± 4,33 vs. 45,9 ± 4,36 kg	decreased over time, but no difference between groups	increased over time, but no difference between groups
Kirmse et al., 2019	57	moderately trained men	12 weeks	resistance training	increased over time, but no difference between groups	increased in both groups, with a higher increase in CP *pre vs. post:* **CP**: 70,1 ± 6,7 vs. 72,1 ± 6,6 kg **PLA**: 69,4 ± 6,2 vs. 70,1 ± 5,9 kg	increased only in PLA *pre vs. post:* **CP**: 9,2 ± 3,8 vs. 9,2 ± 3,9 kg **PLA**: 8,8 ± 3,2 vs. 9,5 ± 3,0 kg	
Oertzen-Hagemann et al., 2019	25	healthy sport students	12 weeks	resistance training	increased in both groups, with a higher increase in CP *pre vs. post:* **CP**: 81,4 ± 6,6 vs. 84,4 ± 6,3 kg **PLA**: 77,9 ± 4,1 vs. 79,4 ± 5,1 kg	increased in both groups, with a higher increase in CP *pre vs. post:* **CP**: 71,2 ± 5,7 vs. 73,8 ± 5,3 kg **PLA**: 69,6 ± 4,0 vs. 70,3 ± 4,3 kg	increased over time, but no difference between groups	

4.3.2 Effects on strength and performance parameters

Six studies examined the effect of an exercise intervention and a collagen supplementation on different performance parameters (Centner et al., 2019; Clifford et al., 2019; Jendricke et al., 2019; Jendricke et al., 2020; Kirmse et al., 2019; Oertzen-Hagemann et al., 2019). The maximal isometric voluntary contraction (MIVC) was measured in all six studies. Results are summarized in table 7. Except from Clifford et al. (2019), who reported a decrease in both groups, and Centner et al. (2019), who did not report the outcome, the studies observed an increase in MIVC without a difference between the collagen supplement or the placebo (Jendricke et al., 2019; Jendricke et al., 2020; Kirmse et al., 2019; Oertzen-Hagemann et al., 2019).

The leg strength was measured by Centner et al. (2019) and Clifford et al. (2019). Only the change in 1RM leg press strength was reported in the paper from Centner et al. (2019). No significant difference was detected between the experimental and the placebo group. The increases were 10,2 ± 2,8 % and 4,8 ± 11,4 % respectively. In the study from Clifford et al. (2019) the countermovement jump (CMJ) was used as an indirect measure of muscle power. After exercise the CMJ height decreased in both group ($p = 0,001$), whereas the recovery was faster with CP (group*time effect; $p = 0,040$).

The study from Jendricke et al. (2019) additionally tested the maximal isometric grip strength using a hand dynamometer. The hand grip strength increased in both groups (31,7 ± 3,5 kg vs. 34,4 ± 3,8 kg in the CP group and 32,7 ± 6,0 kg vs. 34,0 ± 5,5 kg in the placebo group), with a significantly higher increase in the collagen group ($p < 0,05$).

In the other study from Jendricke et al. (2020) the effects of a concurrent training and collagen supplementation were investigated. The performance was analysed using a 1RM test for back squat, a muscular endurance testing, an incremental running test and a one hour running time trial. The CP group had a greater increase in running distance in the time trial than the PLA group (8572 ± 1224 m vs. 9606 ± 927 m in the CP group and 8929 ± 1399 m vs. 9632 ± 1354 m in the PLA; $p = 0,016$). Concerning the results of the incremental running test, an increase in the velocity at the lactate threshold was observed in both groups (6,75 ± 0,76 km/h vs. 7,46 ± 0,98 km/h in CP and 6,91 ± 0,86 km/h vs. 7,48 ± 0,99 km/h in PLA), with no difference between the groups ($p = 0,459$). Similarly, with the velocity at the individual anaerobic threshold, where the velocity improved with time (9,39 ± 1,12 km/h vs. 10,25 ± 1,18 km/h in CP and 9,55 ± 1,30 km/h vs. 10,32 ± 1,19 km/h in PLA) but no group effect was detected ($p = 0,562$). The results from the strength testing look quite similar. The 1RM back squat improved in both groups equally (55,2 ± 11,2 kg vs. 60,2 ± 9,92 kg in CP and 54,7 ± 13,1 kg vs. 61,3 ± 12,9 kg

in PLA). The muscle endurance testing improved over time (22,3± 7,85 kg vs. 30,4 ± 8,99 kg in CP and 23,6 ± 9,67 kg vs. 28,7 ± 10,1 kg in PLA) but did not differ between groups (p = 0,126).

The studies from Kirmse et al. (2019) and Oertzen-Hagemann et al. (2019) examined the effects of a resistance training and collagen supplementation on performance through one repetition maximum (1RM) tests in squat, bench press, deadlift and rowing. All outcomes show a significant increase in all strength tests in all groups. Additionally, the CP group of Oertzen-Hagemann et al. (2019) had a higher increase in rowing 1RM than the PLA group (85,0 ± 11,3 kg vs. 98,3 ± 12,6 kg in CP and 91,2 ± 8,9 kg vs. 97,3 ± 8,1 kg in PLA; interaction: p = 0,025).

Table 7 Effects on strength and performance parameters (CP = collagen peptides; PLA = placebo; 1RM = one repetition maximum; MIVC = maximum voluntary contraction; values are mean ± SD, except Centner et al.: mean ± SEM)

Reference	sample size	population	study length	exercise intervention	outcomes					
					leg strength	MIVC	1 RM squat	1 RM bench press	1 RM deadlift	1 RM row
Centner et al., 2019	30	healthy older men	8 weeks	blood flow restriction training	only change in 1RM leg press reported no significant change between groups	not reported				
Clifford et al., 2019	24	recreationally active	9 days	drop jump protocol	CMJ height decreased in both groups faster recovery in CP *CP vS. PLA:* **pre**: 31,1 ± 1,6 vs. 32,9 ± 2,0 cm **post**: 28,0 ± 2,9 vs. 29,0 ± 4,2 cm **48h post**: 29,2 ± 4,2 vs. 25,4 ± 4,6 cm	decreased over time, but no difference between groups				
Jendricke et al., 2019	77	untrained premenopausal women	12 weeks	resistance training		increased in both groups, but no difference between groups				

Jendricke et al., 2020	59	healthy women	12 weeks	concurrent training		increased in both groups, but no difference between groups	increased in both groups, but no difference between groups			
Kirmse et al., 2019	57	moderately trained men	12 weeks	resistance training		increased in both groups, but no difference between groups	increased in both groups, but no difference between groups	increased in both groups, but no difference between groups	increased in both groups, but no difference between groups	increased in both groups, but no difference between groups
Oertzen-Hagemann et al., 2019	25	healthy sport students	12 weeks	resistance training		increased in both groups, but no difference between groups	increased in both groups, but no difference between groups	increased in both groups, but no difference between groups	increased in both groups, but no difference between groups	increased in both groups, with a higher increase in CP *pre vs. post:* **CP**: 85,0 ± 11,3 vs. 98,3 ± 12,6 kg **PLA**: 91,2 ± 8,9 vs. 97,3 ± 8,1 kg

4.3.3 Effects on musculoskeletal system

The effects of collagen peptides combined with an exercise intervention on muscles, tendons and ligaments were examined in four studies (Centner et al., 2019; Clifford et al., 2019; Kirmse et al., 2019; Shaw et al., 2017).

The muscle cross sectional area was observed in three studies and the results are shown in table 8. In the study of Centner et al. (2019) the cross-sectional area (CSA) of the thigh muscle was investigated through MRI scanning. The blood flow restriction training led to a significant increase in CSA from 6,7 ± 3,2 % ($p < 0,001$) in the experimental group and 5,7 ± 2,7 % ($p < 0,001$) in the control group. There was an additional control group, which only received collagen supplementation without a training intervention and this group had no change in CSA (1,1 ± 1,7%; $p = 0,124$). The study from Kirmse et al. (2019) measured the CSA in muscle biopsies, that were obtained from 21 subjects. The fCSA of type II muscle fibres increased significantly over time in the whole cohort in equal measure (7258 ± 1444 μm^2 vs. 8330 ± 2076 μm^2 in CP and 7501 ± 1604 μm^2 vs. 8484 ± 1812 μm^2 in PLA). The increase in fCSA of type I fibres did not reach statistical significance (6544 ± 1462 μm^2 vs. 6883 ± 1650 μm^2 in CP and 6419 ± 1094 μm^2 vs. 6886 ± 1120 μm^2 in PLA). Concerning the changes in CSA from the engineered ligaments in the study from Shaw et al. (2019), the CSA did not change (Pre vs. PLA vs. 5g vs. 15g: 0,8 ± 0,1 vs. 0,8 ± 0,1 vs. 0,8 ± 0,1 vs. 0,8 ± 0,1 mm^2).

Apart from that, the changes in muscle soreness after the drop jump protocol used by Clifford et al. (2019) were recorded subjectively through the visual analogue scale (VAS) and objectively through the pain pressure threshold (PPT). The muscle soreness increased with time in both groups, but no group effect could be detected. There was a trend for lower muscle soreness in the collagen peptide group but this trend did not reach statistical significance ($p = 0,071$). The exercise protocol decreased PPT, but no group effect was present.

In the study from Kirmse et al. (2019) changes in muscle thickness were quantified through a b-mode ultrasound system. All the measured parameters improved over time with no further improvement with CP supplementation. The muscle biopsies revealed no changes within and between the groups in fibre distribution.

To determine the effect of gelatine on collagen synthesis the working group from Shaw et al. (2017) treated engineered ligaments with serum samples. The outcomes are reported as mean ± SEM. After six days the ligaments showed a significant increase in collagen content (Pre vs. PLA vs. 5g vs. 15g: 41,1 ± 3,0 vs. 42,0 ± 4,6 vs. 54,4 ± 2,5 vs. 65,4 ± 8,9 µg) and collagen dry

mass (Pre vs. PLA vs. 5g vs. 15g: 2,9 ± 0,2 vs. 3,0 ± 0,4 vs. 4,0 ± 0,3 vs. 4,4 ± 0,3%). The maximal tensile load did increase significantly in all groups (Pre vs. PLA vs. 5g vs. 15g: 0,11 ± 0,01 vs. 0,19 ± 0,01 vs. 0,17 ± 0,01 vs. 0,19 ± 0,01 N). After the in vitro also in vivo experiments were conducted. The procollagen type I C-propeptide (PINP) increased in all groups after exercise, but only stayed elevated in the 15g group. Calculating the area under the curve for all groups and PINP concentrations, the supplementation with 15 g resulted in a significant treatment effect (PLA vs. 5g vs. 15g: 41,7 ± 19,3 vs. 47,5 ± 17,7 vs. 114,6 ± 19,0 ng/mL*hr).

Table 8 Effects on musculoskeletal system (CP = collagen peptides; PLA = placebo; CSA = cross sectional area; values are mean ± SD, expect for Shaw et al., 2017: mean ± SEM)

Reference	**sample size**	**population**	**study length**	**exercise intervention**	**outcome**
					CSA
Centner et al., 2019	30	healthy older men	8 weeks	blood flow restriction training	significant increase in both groups **CP**: 6,7% (SEM: 3,2) **PLA**: 5,7% (SEM: 2,7)
Clifford et al., 2019	24	recreationally active	9 days	drop jump protocol	
Kirmse et al., 2019	21	moderately trained men	12 weeks	resistance training	no changes in type I fibres significant increase in type II fibres in both groups
Shaw et al., 2017	8	recreational active men	3 days	rope skipping	no changes in treated ligaments

4.3.4 Effects on amino acid concentration and muscle protein synthesis

Five of the included studies examined and reported changes in amino acid concentration and muscle protein synthesis (Kirmse et al., 2019; Oertzen-Hagemann et al., 2019; Oikawa, Kamal, et al., 2020; Oikawa, Macinnis, et al., 2020; Shaw et al., 2017). The essential amino acid and leucine concentration was measured at the beginning and the end of the intervention by Oikawa, Kamal, et al. (2020), Oikawa, Macinnis, et al. (2020) and Shaw et al. (2017), whereas Oikawa, Macinnis, et al. (2020) additionally measured tryptophan concentration and Shaw et al. (2017) only the leucine concentration. The supplementation with LA in the study from Oikawa, Macinnis, et al. (2020) resulted in a significant increase in the sum of essential amino acids (pre vs. 1h after ingestion: 1582 vs. 2959 µM), whereas with the CP supplementation the EAA did not increase significantly (pre vs. 1h after ingestion: 1614 vs. 2025 µM). Also, leucine and tryptophan increased to a greater extent in LA. In the other study from (Oikawa, Kamal, et al., 2020) whey protein (WP) and a collagen supplement were compared. In response to the supplementation the summed total amino acid concentration also increased in both groups to the same extent. The maximal concentration of essential amino acids (WP vs. CP: 5733 ± 2368 µM vs. 2869 ± 1604 µM) and leucine (WP vs. CP: 645 ± 206 µM vs. 223 ± 117 µM), were as in the previous discussed study, significant higher after the WP intake than in CP. In the study from Shaw et al. (2017) leucine decreased significantly over time without any differences between the groups.

The hydroxyproline concentration was tested in a venous blood sample at Kirmse et al. (2019), Oertzen-Hagemann et al. (2019) and Shaw et al. (2017). In the first two studies the CP group showed a significant increase in hydroxyproline levels after ingestion while no change in PLA could be detected (Kirmse et al., 2019; Oertzen-Hagemann et al., 2019). Shaw et al. (2017) additionally found, that the most common amino acids found in collagen, like glycine, proline, hydroxyproline and hydroxylysine, increased in a dose-dependent manner with a peak one hour after ingestion.

In the study from Oikawa, Kamal, et al. (2020) and Oikawa, Macinnis, et al. (2020) the effects of protein quality on muscle protein synthesis were examined. The acute myofibrillar muscle protein synthesis (MyoPS) significantly increased with WP (baseline vs. rest vs. exercise: 0,02 vs. 0,04 vs. 0,05 %/h) and stayed the same with CP (0,02 vs. 0,03 vs. 0,03 %/h). With LA supplementation the acute MyoPS increased in both groups with a significant higher increase in LA (CP vs. LA vs. washout: 1,4 vs. 1,6 vs. 1,1 %/d).

The integrated MyoPS was additionally examined in Oikawa, Kamal, et al. (2020) and they reported a significant increase from baseline to rest and exercise only in WP (baseline vs. rest vs. exercise: 1,45 vs. 1,50 vs. 1,61 %/d). The values of integrated MyoPS in CP did not elevate above baseline values in rest or exercise (1,47 vs. 1,47 vs. 1,46 %/d, respectively). There were no group differences between muscular collagen protein synthesis (MCPS), but it did increase significantly over time. Also, no significant differences in total amino acid concentration was found (Oikawa, Kamal, et al., 2020).

Table 9 Effects on amino acids and muscle protein synthesis (CP = collagen peptides; PLA = placebo; MyoPS = myofibrillar muscle protein synthesis; values are mean ± SD, expect for Shaw et al., 2017: mean ± SEM is reported)

Reference	sample size	population	study length	exercise intervention	outcomes			
					essential amino acids	**leucine**	**hydroxyproline**	**acute MyoPS**
Kirmse et al., 2019	57	moderately trained men	12 weeks	resistance training			significant higher levels in CP *CP vs. PLA:* 31,1 ± 16,4 vs. 14,7 ± 6,4 µmol/L	
Oertzen-Hagemann et al., 2019	25	healthy sport students	12 weeks	resistance training			significant higher levels in CP *CP vs. PLA:* 33,3 ± 19,7 vs. 14,4 ± 6,4 µmol/L	
Oikawa, MacInnis et al., 2020	11	healthy men and women	3 days	HIIT	significant increase in LA and no increase in CP *pre vs. 1h after ingestion:* **CP**: 1614 vs. 2025 µM **LA**: 1582 vs. 2959 µM	significant increase in LA and no increase in CP *pre vs. 1h after ingestion:* **CP**: 148 vs. 184 µM **LA**: 131 vs. 413 µM		increased in both groups significantly higher in LA *CP vs. LA vs. washout:* 1,4 vs. 1,6 vs. 1,1 %/d
Oikawa, Kamal et al., 2020	24	healthy older women	9 days	resistance training	significant higher maximal concentration in WP *WP vs. CP:* 5733 ± 2368 vs. 2869 ± 1604 µM	significant higher maximal concentration in WP *WP vs. CP:* 645 ± 206 vs. 223 ± 117 µM		significantly increased in WP *baseline vs. rest vs. exercise:* 0,02 vs. 0,04 vs. 0,05 %/h no increase in CP *baseline vs. rest vs. exercise*: 0,02 vs. 0,03 vs. 0,03 %/h
Shaw et al., 2017	8	recreational active men	3 days			no difference between groups decreased over time	significantly increased in a dose-dependent manner with peak 1h after ingestion	

4.4 Risk of bias

PEDro score was only found for one of the nine studies (Centner et al., 2019). This study scored with eight, which refers to a high methodological quality. The other studies were rated by the master student. All of them scored very well, with a mean score of 9, suggesting that all studies are of very good quality and there is little risk of bias. The ratings can be seen in the figure 8.

The subjects counted as blinded if they did not know which treatment, collagen or control supplement, they received. The exercise intervention was done by every subject regardless the supplementation.

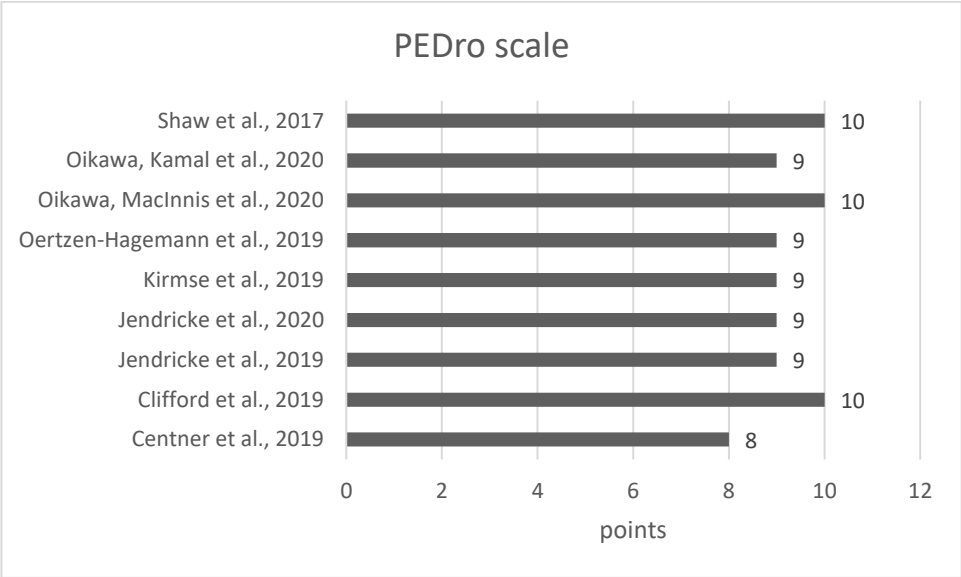

Figure 8 Scores of the PEDro scale

5 Discussion

The aim of the current systematic review was to examine the effects of collagen supplementation on various aspects of body composition, musculoskeletal system and strength or performance. Firstly, a suitable search string was searched. Secondly, a systematic literature search was carried out, which identified nine studies. The included study did not examine every aspect of the research question, so they were clustered according to their outcomes. In general, the findings suggest possible effects on strength and performance or body composition. Regarding the effect on the musculoskeletal system, which was only examined by four of the included studies, it is not possible to make a final statement. Details of the outcomes will again be discussed divided into the different aspects of the research question.

5.1 Effects on body composition

The four invention studies, which examined the effect of collagen supplementation on body composition, lasted for 12 weeks and used some sort of resistance training or a concurrent training as an exercise intervention. It can therefore be said that there is a high degree of comparability between the studies. To summarise the various results, it can be said that supplementation with collagen peptides acted additive to the positive effects of physical activity. Thus, in all studies there was an increase in fat-free mass.

That there is a synergistic effect of resistance training and protein supplementation, has already been stated in an earlier meta-analyses (Cermak et al., 2012). The composition of collagen peptides is much debated, because of its low content of essential amino acids, especially of leucine. The changes in muscle mass induced by resistance training are stimulated by the mechanistic target of rapamycin (mTOR) signalling pathway. mTOR is activated by different nutrients and growth factors and coordinates cell growth and metabolism. It controls the balance between anabolism and catabolism and therefore also plays an important role in muscle growth. It has been shown that the branched chain amino acids, i.e. valine, leucine and isoleucine, trigger this signalling pathway. But also, arginine and glutamine have an influence on the activation of mTOR (Saxton & Sabatini, 2017). It is assumed that the collagen peptides can stimulate the mTOR signalling pathway through their arginine content. In an animal experiment it has been shown, that the 7-day feeding with arginine led to an increase in signalling activity of mTOR in skeletal muscles of piglets and therefore promoted weight gain (Yao et al., 2008). Proline is another amino acid which can be found in collagen peptide in rather high amounts. Proline acts together with arginine und glutamine to enhance protein synthesis in

cells and tissues, like the skeletal muscle, via the mTOR pathway (Wu et al., 2011). So, it seems that the amino acids of collagen peptides have a signalling effect on mTOR and therefore on muscle growth. Moreover, it has been found that the dipeptide of hydroxyproline and glycine, found in collagen hydrolysates, can induce myogenic differentiation and myotube hypertrophy by activating the mTOR signalling pathway (Kitakaze et al., 2016).

With the supplementation of collagen peptides, the collagen content of the intramuscular connective tissue rises. As already stated in the introduction of this thesis approximately 10% of the human skeletal muscle is collagen. Collagen is a major factor when it comes down to operating principles and the biochemical structure of skeletal muscles. Specific collagen peptides have the ability to stimulate the synthesis of collagen and therefore promote increase in muscle mass (Ng et al., 2007; Oesser & Seifert, 2003).

The findings on the changes in fat mass are divers. Both studies from the working group of Jendricke found a decrease in fat mass in both intervention groups (Jendricke et al., 2019; Jendricke et al., 2020). The study from Oertzen-Hagemann et al. (2019) on the opposite found an increase in fat mass and Kirmse et al. (2019) only found an increase in the placebo group. The decrease could be explained because of the higher increase in fat free mass and therefore a higher energy demand (Jendricke et al., 2019; Jendricke et al., 2020). The body fat mass in Kirmse et al. (2019) increased only in the placebo group due to the fact that also the bodyweight increased over the 12 weeks. In Oertzen-Hagemann et al. (2019) the fat mass increased also because of the same reasons mentioned above. To sum up, collagen peptides in combination with physical activity may promote the decrease in fat mas as a result of pronounced adaptions in fat-free mass and the effects of collagen peptides on the connective tissue.

5.2 Effects on strength and performance

The effects on strength and performance can be partly explained by the changes in body composition. With the rise in fat free mass and the exercise intervention also the performance in strength testing raised (Centner et al., 2019; Jendricke et al., 2019; Jendricke et al., 2020; Kirmse et al., 2019; Oertzen-Hagemann et al., 2019). After the intervention the increases in fitness were pronounced in both groups, but there is a small tendency that the increase is higher with the additional supplementation of collagen peptides. The passive tissue components adapted to the training as a physiological reaction (Kjaer et al., 2006; Mackey et al., 2008) and collagen tends to accelerate this process. Not only the ECM of tendons but also the ECM of skeletal muscle tissue reacts to mechanical loading and increases collagen synthesis.

It therefore stands to reason that collagen peptides can improve adaptations to strength training (Kjaer et al., 2006). As in most of the studies a one repetition maximum test was used to assess the effects on strength enhancement, this might not be representative for the effects of collagen supplementation on performance. As already said collagen peptides accelerate the adaptions of passive connective tissue in the muscle-tendon system, this could possibly have a higher impact on fast and reactive movements more than on slow movements, like the 1RM testing. The results of Clifford et al. (2019) underline this hypothesis, as a faster recovery in counter movement jumps after a drop jump protocol was only observed in the CP group. This consideration will also be part of the next section.

Before moving on with the effects on musculoskeletal system the outcomes of Jendricke et al. (2020) should be discussed. This study was the only one which examined the effects of protein supplementation on concurrent training adaptions. Collagen supplementation improved endurance performance by an improved aerobic metabolism. The effects of protein supplementation on endurance performance respectively cardiometabolic parameters are largely unknown. It has been shown that the co-ingestion of carbohydrate and whey protein was able to enhance PGC-1α mRNA expression and thereby enhance adaptions to endurance exercise (Hill et al., 2013). PGC-1α is known for having signalling effect in fat metabolism. Further, peroxisome proliferator-activated receptors (PPAR) are also increased in response to exercise. In a study in mice it has been shown, that the feeding with collagen peptides results in a significant increase in PPAR and fatty acid metabolism (Tometsuka et al., 2017; Woo et al., 2018). Further studies, especially human studies, are needed to confirm these observations. The improvement in performance could also be attributed to the improved biochemical properties of the muscle-tendon system. The additional strength training improves the force-generating capacity of the in running involved muscle groups and thereby improve running economy (Trowell et al., 2020). The supplementation with collagen might represent a strategy to improve tendons and muscular properties to enhance running performance.

5.3 Effects on musculoskeletal system

Collagen supplementation seems to have no significant effects on cross-sectional area of different muscles or ligaments (Centner et al., 2019; Kirmse et al., 2019; Shaw et al., 2017). Supplementation with collagen peptides in combination with physical activity leads to a rise in the appearance of the amino acid components of collagen. This rise is responsible for an increase in collagen and the improvement of mechanical properties of the engineered ligaments (Shaw et al., 2017). This improvements are partly due to the fact that gelatine improves the connective tissue and structure (McAlindon et al., 2011).

Shaw et al. (2017) did additionally observe an increase in procollagen type I C-propeptide (PINP) concentration after exercise. This rise is normal because exercise is known to increase collagen synthesis and the production of PINP in tendons (Kjaer et al., 2006; Langberg et al., 2001). Measured in the blood PINP is used as a marker for bone metabolism (Hale et al., 2007). Because of the short duration of the rope skipping exercise the PINP concentration increased. This increase was supported by the supplementation with collagen peptides.

To sum up, because of its influence on the structure of muscles, tendons and ligaments collagen supplements might have a positive impact in regards to injury prevention and tissue repair, but further research is necessary to state scientifically substantiated statements.

5.4 Effects on amino acids and muscle protein synthesis

In the last part the influence of collagen peptides on amino acid levels on muscle protein synthesis will be discussed. In both studies from Oikawa et al. it was observed that compared to whey protein or lactalbumin collagen supplementation resulted in a lower myofibrillar muscle protein synthesis (myoPS). The difference in leucine concentration may explain this fact. Leucine has been shown to be a key stimulus to increase rates of MPS through the activation of mTOR (Devries et al., 2018; Dickinson et al., 2011).

Concerning the protein quality collagen peptides do not perform well because of their low amount of essential amino acids. The protein digestibility corrected amino acid score (PDCAA) is an indicator for the quality of a protein. Also, the digestible indispensable amino acid score (DIAAS) could be used to determine the quality of a protein (Phillips, 2017). Both scores are “0” for collagen peptides. Not only lactalbumin but also whey protein increased myoPS after exercise, which is necessary for muscle recovery and performance adaptions (Moore et al., 2014), whereas collagen peptides failed to improve muscle protein synthesis. Therefore, intake of low-quality protein may limit training adaptions or the maintenance of skeletal muscle mass (Oikawa, Kamal, et al., 2020; Oikawa, Macinnis, et al., 2020).

5.5 Other considerations

In the study from Clifford et al. (2019) the collagen peptide supplementation did not only lead to an accelerated recovery but also a small effect of CP on reduced inflammation could be found. The parameters were only measured in blood and a small reduction in inflammation could be observed. More research is necessary and especially the measurement of inflammation markers in muscle biopsies should be aimed for. The reduction in muscle soreness after

ingestion of CP might only reflect the faster remodelling of the affected tissue. This also support the thesis from Kirmse et al. (2019) that the collagen peptides do not affect the muscle cell per so but the structural components of the tissue surrounding the cells. They came to this conclusion because in their observations the increase in fat-free mass was not reflected in an increased cross-sectional-area.

To quantify the influence of collagen peptides on up- and downregulation of proteins, Oertzen-Hagemann et al. (2019) used muscle biopsies. The found a higher number of upregulated proteins in the samples from the CP group. The upregulated proteins are responsible for processes related to skeletal muscle and protein modifications. In PLA other proteins were upregulated. These proteins were relevant for more general categories, like catalytic activity or coenzyme binding. The authors observed differences in the protein response to the same training protocol but with and without collagen supplementation. Regarding the upregulation of pathways, the CP group showed significantly more pathways associated with resistance training. An additional supplementation with collagen peptides might according to that enhance effects of strength training on the skeletal muscle proteome. In contrast to this the enhancements in strength testing were not as clear. Reasons for this discrepancy have already been discussed in earlier parts.

For the sake of completeness, the effects of collagen peptides on several diseases, as sarcopenia or tendinopathy, will shortly be discussed. Especially the results from Shaw et al. (2019) promise helpful hints to accelerate injury recovery or tissue repair. Thinking of obese patients, which get injured quite easily because of obvious reasons, a strategy to hasten recovery to quickly return to physical therapy would be helpful not only for the patients themselves but also for the broader population (Levine & Violet, 2017). In older patients with sarcopenia the above discussed effects on body composition and strength could be game-changing. Collagen peptide supplementation in combination with resistance training was shown to increase fat-free mass and muscle strength and counteract the loss in life quality for sarcopenic patients (Zdzieblik, Jendricke, et al., 2021; Zdzieblik et al., 2015). In postmenopausal women collagen peptides increased the bone mineral density and reduced bone degradation (König et al., 2018). These results could be important in the treatment of osteoporosis, which is a widespread disease especially in older women and results in chronic pain, inactivity and invalidity (Hernlund et al., 2013). Beneficial effects of collagen peptides on reducing joint pain and improving joint function has been shown in some studies (Clark et al., 2008; Zdzieblik, Brame, et al., 2021). The increase in collagen type I, II and IV, proteoglycans and elastin synthesis after chronic supplementation with collagen peptides may reduce the tissue damage and decrease

pain (Oesser & Seifert, 2003). The supplementation also aids formation of the ECM and therefore leads to an increased firmness of the connective tissue (Schunck & Oesser, 2013). In regard to the effects of collagen supplements on Achilles tendinopathy, it has been observed that the benefits of a calf-strengthening program could be supported with the supplementation of collagen peptides (Praet et al., 2019).

5.6 Strength and limitations

The topic covered by this systematic review is a very new one. All included studies were published between 2017 and 2020. A limitation of this review is therefore the small number of included studies. However, it again shows that the topic still has a lot of research to be done and that not all of it is known and mature.

Another limitation is that not all studies examined the same outcomes. In addition, each study used a slightly different study design, supplementation protocol or sports intervention, but this did not harm the comparability too much. All studies observed the subjects' diet and were of good methodological quality overall. On top, the interpretation of the results is difficult because not much data is available for the mechanistic effect of collagen peptides. It also stays unclear whether the source, for example bovine or pig, has an influence on certain effects of collagen peptides. Overall there is a mixed consensus and more controlled studies with precise outcomes such as engineered human ligaments or muscle biopsies are required (Khatri et al., 2021). Future research faces a lot of questions.

Collagen has the potential to reduce joint pain and improve joint functionality. To date it seems to be important that the supplementation period is longer than three months. An acute supplementation might not bring the expected effects. As stated in a systematic review, which was published at the same time, when finishing this master thesis, amounts between 15 and 30g/d seem to be the optimal dose to reach beneficial effects (Khatri et al., 2021).

Next steps in the research on collagen peptide supplementation could be the following:

- examining different kind of collagen peptides,
- comparing the results from the effects on body composition to a high-quality protein,
- examining the underlying mechanisms of mode of action of collagen peptides,
- examining differences between gender due to various hormone statuses and
- examining the effect in elite athletes.

6 Conclusion

The influence of specific collagen peptides on body composition and strength or endurance performance has recently gained a lot of interest. Because of their low-quality collagen peptides have not been given too much consideration so far. Some studies showed promising results in body composition or strength gains. Especially the increase in collagen content of muscle or ligaments holds bright chances for healing joint disorders or to prevent diseases associated with a loss in muscle mass and function, like sarcopenia. Also, the ability to increase gains in fat free mass might bring promising options to counteract the increasing obesity.

For the influence of collagen peptides on recovery further studies are still necessary. To date, no superiority of collagen peptides has been found in comparison to high-quality proteins, because of their higher amounts of essential amino acids.

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Appendix

Centner et al., 2019			
mean (SEM)	CP	PLA	
increase in thigh muscle CSA (%)	6,7 (3,2)	5,7 (2,7)	
maximal isometric leg strength	not reported		
increase in 1RM leg press (%)	10,2 (24,8)	4,8 (11,4)	

Clifford et al., 2019						
mean (SD)		**BL**	**pre**	**post**	**24h post**	**48h post**
MIVC (N)	CP	638,3 (81,1)	625,5 (70,2)	517,0 (63,8)	542,6 (102,1)	561,7 (108,5)
	PLA	588,3 (114,7)	588,3 (47,1)	470,6 (94,1)	453,0 (111,8)	470,6 (111,8)
CMJ (cm)	CP	32,4 (7,9)	32,1 (1,6)	28,2 (2,9)	27,9 (3,9)	29,2 (4,2)
	PLA	32,6 (6,4)	32,9 (2,0)	29,0 (4,2)	25,8 (4,2)	25,4 (4,6)
pressure pain threshold (N)	CP	67,9 (20,4)	73,3 (11,5)	71,3 (86,2)	62,5 (17,7)	61,1 (16,3)
	PLA	72,6 (21,14)	77,0 (14,5)	67,1 (8,7)	60,3 (8,7)	64,6 (8,0)
VAS (mm)	CP	12,2 (10,2)	11,1 (7,7)	79,5 (44,8)	106,0 (44,8)	89,6 (45,3)
	PLA	15,4 (13,3)	16,4 (10,6)	96,9 (59,2)	137,8 (37,1)	125,3 (37,1)

Jendricke et al., 2019			
mean (SD)		**pre**	**post**
body weight (kg)	CP	73,5 (10,7)	73,0 (10,4)
	PLA	72,8 (10,1)	72,4 (10,4)
fat-free mass (%)	CP	62,6 (6,0)	64,4 (6,2)
	PLA	63,8 (6,0)	64,7 (6,0)
fat mass (%)	CP	37,4 (6,0)	35,6 (6,2)
	PLA	36,2 (6,0)	35,33 (6,1)
maximal isometric leg strength (N)	CP	890,2 (246,4)	1141,0 (288,8)
	PLA	939,8 (312,0)	1173,3 (361,9)
hand grip strength (N)	CP	31,7 (3,5)	34,4 (3,8)
	PLA	32,7 (6,0)	34,0 (5,5)

Jendricke et al., 2020			
mean (SD)		**pre**	**post**
1h TT (m)	CP	8572 (1224)	9606 (927)
	PLA	8929 (1399)	9632 (1354)
velocity @ aerobic threshold (km/h)	CP	6,75 (0,76)	7,46 (0,98)
	PLA	6,91 (0,86)	7,48 (0,99)
velocity @ anaerobic threshold (km/h)	CP	9,39 (1,12)	10,25 (1,18)
	PLA	9,55 (1,30)	10,32 (1,19)
heart rate @ aerobic threshold (bpm)	CP	157 (14,29)	149 (12,8)
	PLA	150 (15,5)	148 (12,7)
heart rate @ anaerobic threshold (bpm)	CP	179 (10,5)	171 (13,9)
	PLA	173 (11,1)	172 (8,96)
LT (mmol/l)	CP	1,82 (0,59)	1,79 (0,51)
	PLA	1,78 (0,51)	1,75 (0,66)
IAT (mmol/l)	CP	3,32 (0,59)	3,25 (0,51)
	PLA	3,29 (0,51)	3,25 (0,66)
1RM back squats (kg)	CP	55,2 (11,2)	60,2 (9,92)
	PLA	54,7 (13,1)	61,3 (12,9)
60% 1RM (rep)	CP	22,3 (7,85)	30,4 (8,99)
	PLA	23,6 (9,67)	28,7 (10,1)
body weight (kg)	CP	62,5 (8,60)	62,3 (8,60)
	PLA	63,3 (6,04)	63,0 (6,63)
fat mass (kg)	CP	17,9 (5,19)	16,9 (5,31)
	PLA	17,7 (3,79)	17,1 (4,13)
fat free mass (kg)	CP	44,6 (4,69)	45,4 (4,60)
	PLA	45,6 (4,33)	45,9 (4,36)
skeletal muscle mass (kg)	CO	21,0 (2,8)	21,6 (2,85)
	PLA	21,8 (2,58)	22,1 (2,62)
total body water (l)	CP	32,8 (3,54)	33,4 (3,51)
	PLA	33,7 (3,30)	33,9 (3,51)
extracellular water (l)	CP	14,0 (1,54)	14,3 (1,65)
	PLA	14,3 (1,49)	14,5 (1,48)
intracellular water (l)	CP	18,8 (2,03)	19,1 (1,96)
	PLA	19,4 (1,98)	19,4 (2,01)

Kirmse et al., 2019			
mean (SD)		**pre**	**post**
body water (kg)	CP	79,3 (8,4)	81,3 (8,1)
	PLA	78,2 (6,3)	79,6 (6,0)
fat mass (kg)	CP	9,2 (3,8)	9,2 (3,9)
	PLA	8,8 (3,2)	9,5 (3,0)
fat free mass (kg)	CP	70,1 (6,7)	72,1 (6,6)
	PLA	69,4 (6,2)	70,1 (5,9)
leg circumference (cm)	CP	57,4 (3,8)	58,7 (3,5)
	PLA	57,1 (2,7)	58,0 (2,4)
rectus femoris (mm)	CP	25,45 (3,42)	26,10 (3,09)
	PLA	25,57 (3,15)	26,06 (2,60)
vastus intermedius (mm)	CP	19,31 (3,70)	21,21 (3,89)
	PLA	18,88 (3,37)	19,92 (2,78)
vastus lateralis (mm)	CP	26,10 (3,82)	28,75 (3,35)
	PLA	26,63 (4,37)	28,62 (4,56)
leg extension (N*m)	CP	271,5 (51,4)	299,5 (61,6)
	PLA	261,2 (41,2)	283,7 (45,6)
1 RM squat (kg)	CP	110,9 (16,5)	131,5 (21,4)
	PLA	110,1 (13,2)	124,9 (13,4)
1 RM deadlift (kg)	CP	132,7 (16,2)	154,0 (18,8)
	PLA	129,6 (19,4)	148,9 (16,6)
1 RM bench press (kg)	CP	82,6 (14,0)	95,4 (14,3)
	PLA	81,0 (14,2)	92,9 (11,6)
1 RM bent over row (kg)	CP	88,5 (11,0)	100,6 (11,1)
	PLA	87,6 (9,5)	99,1 (8,9)
MUSCLE BIOPSY (only 21 samples)			
type 1 (%)	CP	40 (10)	37 (11)
	PLA	37 (13)	38 (9)
type 2 (%)	CP	60 (10)	63 (11)
	PLA	63 (13)	62 (9)
type 1 fCSA (µm^2)	CP	6455 (1462)	6883 (1650)
	PLA	6419 (1094)	6886 (1120)
type 2 fCSA (µm^2)	CP	7258 (1444)	8330 (2076)
	PLA	7501 (1604)	8484 (1812)

Oertzen-Hagemann et al., 2019			
mean (SD)		**pre**	**post**
hydroxyproline (µmol/l)	CP	33,3 (19,7)	95,8 (27,1)
	PLA	14,4 (6,4)	14,3 (11,3)
body mass (kg)	CP	81,4 (6,6)	84,4 (6,3)
	PLA	77,9 (4,1)	79,4 (5,1)
fat mass (kg)	CP	10,3 (3,6)	10,9 (4,1)
	PLA	8,4 (2,2)	9,4 (2,4)
fat free mass (kg)	CP	71,2 (5,7)	73,8 (5,3)
	PLA	69,6 (4,0)	70,3 (4,3)
squat test (kg)	CP	114,3 (20,2)	140,8 (24,3)
	PLA	108,7 (8,3)	126,3 (13,9)
dead lift (kg)	CP	131,7 (19,6)	156,3 (21,2)
	PLA	128,0 (15,6)	143,9 (10,6)
bench press (kg)	CP	80,4 (14,0)	94,4 (15,6)
	PLA	84,4 (13,9)	94,2 (10,2)
rowing (kg)	CP	85,0 (11,3)	98,3 (12,6)
	PLA	91,2 (12,6)	97,3 (8,1)
isometric strength testing (nM)	CP	294,3 (56,3)	323,6 (72,1)
	PLA	260,7 (25,0)	275,2 (31,3)

Oikawa, MacInnis et al., 2020			
mean, SD		**pre**	**1h after ingestion**
EEA (µM)	CP	1614	2025
	LA	1582	2959
leucine (µM)	CP	148	184
	LA	131	413
tryothophan (µM)	CP	117	83
	LA	125	281
	CP	**LA**	**washout**
myofibrillar MPS (%/d)	1,4	1,6	1,0
sarcoplasmis MPS (%/d)	1,5	1,6	1,1

Oikawa, Kamal et al., 2020								
mean (SD)		**ingestion**	**30min post**	**45min post**	**1h post**	**2h post**	**2,5h post**	**3h post**
sum TAAS (µM)	WP	4730 (4026)	4553 (982)	8050 (3220)	7094 (2818)	6214 (1736)	5585 (2038)	4679 (2390)
	CP	5409 (2616)	3799 (1308)	6893 (4126)	4780 (1333)	4956 (1384)	4654 (1157)	3849 (956)
sum EAAS (µM)	WP	2728 (2527)	2206 (876)	4648 (2325)	4076 (1701)	3116 (1044)	3015 (1953)	2476 (1869)
	CP	2156 (1887)	1785 (1532)	2189 (808)	1987 (1229)	1987 (1347)	1600 (505)	1549 (589)
leucine (µM)	WP	145 (88)	213 (79)	535 (228)	624 (215)	561 (304)	360 (177)	274 (167)
	CP	123 (32)	187 (74)	229 (151)	205 (127)	195 (169)	175 (117)	127 (30)

		baseline	**rest**	**exercise**
myofibrillar fractional synthetic rate (%/h)	WP	0,02	0,04	0,05
	CP	0,02	0,03	0,03
myofibrillar muscle protein synthesis (%/d)	WP	1,45	1,5	1,61
	CP	1,47	1,47	1,46
muscle collagen protein synthesis (%/d)	WP		0,95	0,96
	CP		0,99	1,00

AA derived variables		
TAA c max (µM)	WP	10041 (4793)
	CP	8808 (5276)
TAA t max (min)	WP	64 (31)
	CP	84 (37
TAA AUC (µmol*min/l)	WP	1431600 (10900)
	CP	1205300 (16900)
EAA c max (µM)	WP	5733 (2368)
	CP	2869 (1604)
EAA t max (min)	WP	50 (10)
	CP	46 (13)
EAA AUC (µmol*min/l)	WP	775000 (12800)
	CP	442900 (10800)
Leucine c max (µM)	WP	645 (206)
	CP	223 (117)
Leucine t max (min)	WP	54 (9)
	CP	62 (31)
Leucine AUC (µmol*min/l)	WP	103800 (17700)
	CP	43600 (10100)

Shaw et al., 2017							
mean (SEM)		**1h pre**	**0,5h pre**	**exercise**	**0,5h post**	**1h post**	**2h post**
glycine (µM)	PLA	315	282,4	282,4	265,2	290,1	288,2
	5g	295,8	387,9 (28,7)	391,7 (28,7)	349,5 (38,4)	328,4 (30,7)	292,0 (24,9)
	15g	292	514,4 (44,1)	706,1 (70,9)	619,8 (55,6)	516,3 (42,0)	462,6 (46,0)
proline (µM)	PLA	244,0 (21,2)	222,8 (25,3)	212,2 (22,0)	209,0 (25,2)	237,5 (23,6)	217,1 (14,7)
	5g	238,3 (19,6)	306,0 (17,1)	278,3 (13,8)	273,4 (13,8)	264,4 (17,9)	233,4 (15,5)
	15g	284,0 (35,8)	409,5 (39,1)	464,1 (43,2)	438,0 (29,4)	398,1 (31,8)	354,1 (30,1)
hydroxyproline (µM)	PLA	11,3	10,8	7,4	5,4	8,4	6,4
	5g	19,7	38,9 (6,4)	44,8 (5,9)	40,8 (7,9)	39,8	33
	15g	8,9	45,7	104,3 (11,8)	95,9 (13,3)	89,5 (7,4)	76,7 (9,4)
lysine (µM)	PLA	240,6	212,1	202,7	196,5	213,7	210,9
	5g	215,2	229,7 (9,8)	203,5	192,2	198 (10,5)	195,7 (10,5)
	15g	216,0 (11,0)	273,8 (14,9)	252,3	223,4 (9,0)	214,5 (10,1)	214,5 (11,3)
hydroxylysine (µM)	PLA	1,12	1,17	1,21	0,73	1,02	1,41
	5g	1,75	9,13	8,74	7,09	6,12	3,4
	15g	2,23	11,75	19,81 (1,74)	16,99	12,14	8,83
leucine (µM)	PLA	192,8 (9,4)	158,4 (7,4)	135,2 (8,8)	130,8	137,6	134,3
	5g	201,0 (15,5)	185,7 (15,6)	152,5 (8,9)	144,6 (8,8)	142,3	145,5
	15g	193,3 (15,9)	213,3 (10,0)	181,0 (8,9)	164,6 (8,5)	152,0 (7,9)	149,3 (7,9)
collagen (µg)	PRE	41,1 (3,0)					
	PLA	42,0 (4,6)					
	5g	54,4 (2,5)					
	15g	65,4 (8,9)					
collagen (% dry mass)	PRE	2,9 (0,2)					
	PLA	3,0 (0,4)					
	5g	4,0 (0,3)					
	15g	4,4 (0,3)					
CSA (mm^2)	PRE	0,8 (0,1)					
	PLA	0,8 (0,1)					
	5g	0,8					
	15g	0,8					
MTL (N)	PRE	0,11 (0,01)					
	PLA	0,19 (0,01)					
	5g	0,17 (0,01)					
	15g	0,19 (0,01)					
modulus (MPa)	PRE	0,97 (0,06)					
	PLA	1,80 (0,19)					
	5g	1,54 (0,14)					
	15g	1,92 (0,17)					
UTS (MPa)	PRE	0,09 (0,01)					
	PLA	0,15 (0,01)					
	5g	0,14 (0,01)					

	15g	0,16 (0,01)				
		ingestion	**post ingestion**	**24h post**	**48h post**	**72h post**
PINP (ng/ml)	PLA	-0,2	16,9	9,2 (3,8)	10,6 (7,0)	6,2 (12,2)
	5g	0,4	19,0 (3,0)	5,6 (4,1)	11,6 (6,8)	12,2 (6,5)
	15g	0	30,7 (6,9)	28,0 (5,7)	27,5 (7,1)	29,6 (6,3)
PINP (ng/ml/hr)	PLA	41,7 (19,3)				
	5g	47,5 (17,7)				
	15g	114,6 (19,0)				