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Review

The effect of estrogen on tendon and ligament metabolism and function

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ABSTRACT

Tendons and ligaments are crucial structures inside the musculoskeletal system. Still many issues in the treatment of tendon diseases and injuries have yet not been resolved sufficiently. In particular, the role of estrogen-like compound (ELC) in tendon biology has received until now little attention in modern research, despite ELC being a well-studied and important factor in the physiology of other parts of the musculoskeletal system. In this review we attempt to summarize the available information on this topic and to determine many open questions in this field.

1. Introduction

For a long time estrogens have been known as a regulating factor of the metabolism in many connective tissues, like bone [1], muscle [2] and cartilage [3]. The group of steroid hormones primarily influences the development, maturation and function of the female reproductive tract, but is involved in developmental processes like bone formation and various diseases like breast cancer or rheumatoid arthritis. The three major forms of estrogens in humans are estradiol, estrone and estriol, with estriol being the predominant one. All forms of estrogens are derived from cholesterol. The main sources of estrogens are the ovaries and the placenta, but small amounts are also produced by the male testes, the adrenal glands and via intracrine synthesis by several peripheral cells and tissues [4].

Since in many studies it is not defined which form of estrogen, or natural or chemical synthetic compound imitating estrogen, is used, we will use the term estrogen-like compound (ELC) throughout this article to cover all substance variances implicated in research. Research has been conducted especially with regards to possible treatments of diseases in these tissues by the means of hormone replacement therapy (HRT) and by treatment with selective estrogen receptor modulators (SERM). HRT in this case refers to the supplementary treatment of women with estrogen alone or in a combination with other sex hormones mostly progestins usually as a remedy against conditions common in the *peri-* and post-menopause like hot flushes, osteoporosis and urogenital atrophy [5,6]. While HRT has been practised since the 40′s it has in recent years often been criticised due to an associated increase in the risk of cardio-vascular events, breast- and endometrial-cancer as well as thromboembolic events [7]. SERMs are a class of drugs defined by their ability to target the same receptors as estrogen while differing in their preference towards the various receptor-subtypes and their exact selectivity on various tissues. They play an important role in the treatment of a variety of mostly gynaecological diseases like endometriosis, breast cancer and osteoporosis in females, whilst also being discussed as an alternative in HRT to traditional hormones [8,9]. In comparison, only a few studies have been aimed at uncovering the role of ELC in tendon biology, even though it has been shown for a while that gender specific differences exist in the prevalence of tendon diseases and −injuries [10–12]. In particular, in the athletic field where the injury rate of the anterior cruciate ligament is believed to be between two and eight times higher in women than in men [13–15]. A discrepancy in the risk of tendon-injuries can be also observed between pre- and post-menopausal women, with the risk of tendon injury being higher for pre-menopausal women [16], with some data even suggesting, that the occurrence of tendon-injuries in female athletes might differ in different phases of the menstrual cycle [17,15]. A meta-analysis of studies concerning the effects of the menstrual cycle on knee laxity concluded that the laxity in the knee of women peaks between ovulation and post-ovulation, meaning at times of declining estrogen levels [18]. In contrast, a positive coherence between Achilles tendinopathy and HRT as well as oral contraceptives was found [19]. This is of particular interest given the potentially disabling consequences of tendon injuries [20,21]. These contradictions bring into prominence, the need for further research investigating the effects of estrogen on

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tendon composition and strength as well as inflammation and neovascularization, which are typical signs of tendinitis [22].

The expression of estrogen receptors (ER) in tendon tissue has been demonstrated for the first time for the ER-α in 1996 by Liu et al. using an immunoperoxid assay on anterior cruciate ligaments obtained from female and male humans [23], while a relation between tendons and ELC can be traced as far back as the year 77 CE, when roman scholar Plinius the elder described the application of the Silphium plant, a known phytoestrogen, for the attenuation of tendons in pain in his *Naturalis Historia* [24]. Modern day research has until now seen only little progress as far as our understanding of the interactions between ELC and tendon-biology is concerned.

Many estrogen sensitive cells are expressing aromatase themselves and are therefore capable of synthesising certain amounts of estrogen, even if they are independent of the gonads, like for example osteoblasts, adipocytes and endothelial cells [25–27]. Estrogens are thereby able to initiate their influence in several different ways: endocrine, paracrine and autocrine [28]. At the moment, there are two known classes of receptors which act as signalling-targets for estrogens: two intracellular hormone receptors and a rhodopsin-like G protein-coupled receptor that is localized at the endoplasmic reticulum [29]. The term ER traditionally refers solely to the nuclear receptors, whilst the G protein-coupled receptor is usually called GPER1 or GPR30 [30]. Two intracellular receptors representing two individual genes with distinct chromosomal localizations are known to exist, being named ER-α and ER-β. Both are members of the nuclear receptor superfamily [31]. In many of the estrogen sensitive tissues both receptors can be found. Yet, in most cases, they are unevenly distributed between different organs and tissues. On the one hand, the ER-α is predominantly found in mammary gland, uterus, theca cells of the ovary, bone, male reproductive system, liver, and adipose tissue, while on the other hand the ER-β is found for the most part in the bladder, granulosa cells of the ovary, colon, adipose tissue, and immune system [6]. Both receptors are prevalent in neuronal as well as non-neuronal brain-tissue, although again differing in their respective patterns of distribution within the brain [32].

As mentioned above the existence of the ER-α has been proposed for the first time in 1962 with the evidence of its expression in ligament tissue following many years later in 1996 [33,23].

In general ER-β, as a separate receptor of its own, was described for the first time also in June 1996 by Kuiper GG et al. by cloning from rat prostate and ovary [34]. A month later, Mosselman et al. described its presence in human tissue for the first time, using the method of cloning, whilst applying a degenerate PCR primer on human thymus, spleen, ovary and testis [35].

Yet by comparison, the ER-β has only recently in 2010 been shown to be prevalent in the tissue of tendons and ligaments (T/L) as well [36]. Research suggests that the ER-β is capable of influencing the cell biology even in absence of its ligand, an ability its closest relative the ER-α is disputed to possess [37].

Each receptor has several known isoforms. In humans so far two isoforms of the gene product relating to ER-α and six isoforms of the gene product relating to ER-β are known, although only the variations of the ER-β concern coding regions of the respective gene [38]. It should be noted, that the total number of variations does differ in other species [39].

Estrogen receptors following activation through binding with a susceptible ligand, (most commonly estradiol itself but also SERMs or phytoestrogens) are able to change the cell signalling via the means of three possible interactions of which they are capable: [37] (Fig. 1): (i) the capacity as a ligand dependent transcription factor, (ii) the direct influence on cytosolic target proteins, (iii) tethering mechanisms through other transcription factors besides itself.

Both estrogen receptors encompass six different domains with varying homology between the ER-α and the ER-β (Fig. 2). While the DNA binding sites C show homology of up to 98% between the two receptor subtypes, the ligand binding domains E correlate only in 54% of their respective sequences and the activation sites A/B, responsible for the interaction with non-DNA targets, correspond to another even less in just about 24% in the level of transcribed amino acids. So while both receptors are quite similar in their immediate genomic signalling, they appear to differ for the most part in their non-genomic signalling as well as in their indirect genomic signalling via different transcription factors [40].

With the tissue of tendons and ligaments being an often neglected subject in science, despite its obvious clinical relevance, this review article is designed:

(1) To briefly summarize the known basic principles of different signalling pathways of the know ER.
(2) To provide information on the multiple ways, through which ELC is believed to have an effect on connective tissues besides tendon.
(3) To present the current literature on the relation between ELC and tendons and ligaments. Special attention will be given towards the specific properties of these tissues including their healing properties and how they might be affected by estrogens.
(4) To provide motivation for conducting further research into the role of ELC in tendons in the light of their potential clinical relevance.

2. Aging and estrogen-loss in musculoskeletal tissues

The physiological process of aging in the musculoskeletal system sets on, in most cases, a few years after the end of puberty and increases in momentum after the age of 50 [41]. Aging does contain changes concerning the average estrogen levels in females, predominantly a decrease thereof after puberty, with the most rapid changes during the per-imenopause, as well as changes in the expression of the estrogen receptors over time varying between different tissues independent of changing ELC-levels [42–44].

In this part of the article we attempt to provide a short summary of the various effects ELC is known to have on different elements of the musculoskeletal system, namely bone, muscle and cartilage. For further reading we would like to refer to the excellent review articles linked to this section. The intent is to grant the necessary background for the actual motivation in writing this review and to highlight the scientific advances in the other musculoskeletal elements in comparison to tendons and ligaments, which will be discussed later in greater detail.

The focus of research with regards to the role of ELC in the aging-process of musculoskeletal tissues has mostly been on the subject of bone, due to the discovery of the relation between declining estrogen levels and the prevalence of osteoporosis [45]. Since then, a tremendous amount of evidence has been generated towards the conclusion that ELC is one of the leading factors in bone metabolism in females as well as in males [46].

It is important to note that while ELC maintains bone homeostasis and prevents bone loss on the overall bone mass of an individual [45], it is also responsible for an increase in the structural turnover of bone extra cellular matrix (ECM) and inorganic bone mass, allowing it to adapt more quickly to changes in mechanical loading by rearranging its formation according to the overall direction of applicated forces [47,48]. This is achieved by ELC, through direct and indirect stimulation of various pathways in ECM-resorbing osteoclasts, as well as in ECM-forming osteoblasts, while the balance of the entire process is favourable towards a gain of ECM-mass [40–50]. ELC also appears to affect the linear growth of bones in pubertal years directly by influencing estrogen receptors in the human growth plate as well as indirectly by stimulating the secretion of GH-insulin-like growth factor-I [51].

A study conducted in mice suggests that the two known ELC receptors play different roles in bone physiology. While in males and females the ER-α appears to have an upregulating effect on the cortical and trabecular bone mass, the ER-β accounts for a modulation of the ER-α which predominantly affects females [52].

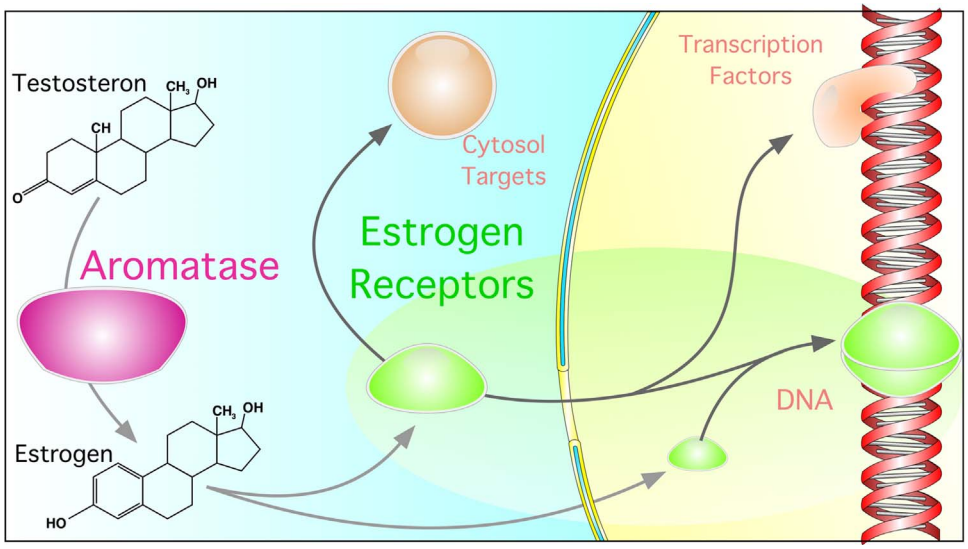

Fig. 1. A scematic drawing showing the chemical reaction of testosteron to estrogen katalysed by aromatase [182] and the subsequent ways in which the activated estrogen receptor is able to influence the cell biology. The estrogen receptor is in a monomeric form capable of influencing target proteins in the cytosol as well other transcription factors inside the nucleus. Besides that the estrogen receptor can in a dimerized form work as a transcription factor of its own and in this directly alter the reading of the cell's DNA [38].

Though the mechanisms responsible are highly complex, it is safe to say that overall ELC has an overwhelmingly well documented positive effect on bone physiology in females and males. In applying this ELC and related substances play an important role in the current treatment of bone related diseases in particular of osteoporosis.

In view of the aim of this review we would like to focus exclusively on the interaction between skeletal muscle and ELC given its relevance for the overall subject of this review.

Sarcopenia, the degenerative loss of muscle mass and strength is an issue of the aging human body, affecting up to 30% of the population above the age of 60 [2,53]. While both sexes are afflicted with this problem, it is known to increase particularly in females during the *peri*-menopause [11]. Though testosterone may, particularly in males, be the more dominant factor, ELC has been shown to have a stimulating effect on the recruitment of satellite cells, the progenitor cells of the adult muscle, capable of adding themselves to, or differentiating themselves into functioning myocytes [54,55]. Studies have demonstrated a positive effect of HRT on the contractile muscle-force in postmenopausal individuals as well as a preventing effect on post-menopausal Sarcopenia [56–58].

In studies using muscle tissue gained from ovariectomized rats ER-β is suggested to facilitate an increase in muscle mass as well as in its regenerative capacity [59,60]. A further study conducted on male rats supplemented with phytoectysteroid ecdysterone suggested, that ER-β mediates an anabolic effect on the skeletal muscle mass [61].

Still several other effects in muscle have been linked to ELC, such as an upregulating effect on the otherwise insulin-related uptake of glucose into the muscle fibres [62] and it enhances the overall metabolism of myofibre-mitochondria [63].

In general it can be said that while the relationship between ELC and skeletal muscle might differ from the one observed in bone, it is still an important factor in the sustainment and metabolism of muscle tissue.

Cartilage, with regards towards its relation to ELC, has for the longest time been given almost as little attention as tendon. Though this has changed in recent years after the discovery of the possible applications of SERMs in the treatment of osteoarthritis [64,65].

The climacteric transition is, like with the aforementioned parts of the musculoskeletal system, a factor often linked to the occurrence of degenerative diseases in cartilage, in particular osteoarthritis [66,67,65]. Being a rheumatic disease of the joints tied to an inflammatory pathophysiology, HRT as well as the application of SERMs have been shown to have a positive effect on the overall process as well as the cartilage tissue in particular [64,65,68]. On a cellular level this connection could be explained by the fact that treatment with post- or pre-menopausal concentrations of estrogen leads to telomere shortening in human chondrocytes, hence entry in cell senescence, which could contribute to the degenerative effects in cartilage [69]. On a molecular level ELC appears to counter the degradation of collagen type II, which is the predominant form of collagen in articular cartilage [70]. Therefore, it would be of interest to test if higher levels of ELC are chondro-protective.

In contrast, it was shown that administration of estradiol to human mesenchymal stem cells inhibits their chondrogenic differentiation, hinting at the possibility that high estradiol concentrations can exert negative effects in cell-based regenerative therapy of osteoarthritis in females [71].

It should also be noted that the aforementioned influence of ELC on linear bone growth is mediated through pathways in growth plate cartilage, an effect connecting those two types of tissue [51,72].

3. Role of ELC in the physiology of tendons and ligaments

In the musculoskeletal system, tendons transfer the contractile energy from muscle to the bone [73] and, due to their elastic properties, store some of that energy in a way similar to a spring [74,75].

As mentioned before changes in ELC levels can be related to a higher occurrence of injuries in T/L structures [10–12]. Besides these, other diseases in T/L have been linked to the same changes. The climacteric transition in particular appears to be a turning point for the prevalence of tendon related diseases, like for example carpal tunnel

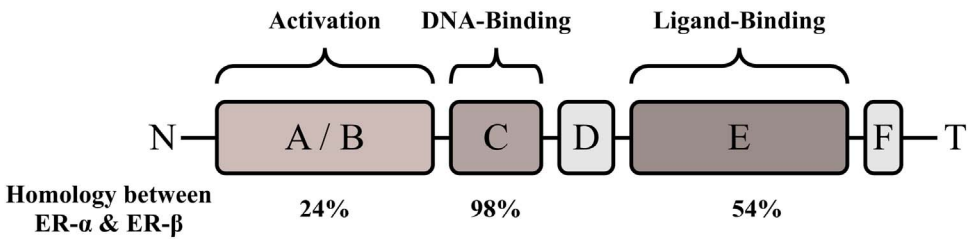

Fig. 2. A simplified sketch showing the alignment of the different domains of the ER with their predominant function, while also illustrating the amount of homology in between the amino acid sequences of the ER-α and the ER-β.

syndrome or tenosynovitis de Quervain [76–78]. The carpal tunnel syndrome is of particular interest since it has already been shown to be induced by inhibitors of aromatase [79], whilst also improving under HRT [80,81]. A further link between estrogen and T/L diseases might be forged by investigating the coherences between obesity, hormonal status and disease progression. Achilles tendinopathy is significantly correlated with obesity in women and men [19]. Interestingly, research has suggested that obesity can be triggered in men, at least partially, by estrogenic effects [82].

The scientific literature on the interactions of tendon tissue and ELC has up to today been rather scarce when compared with the amount of attention given to the role of ELC in the regulation of function of other kinds of tissue. An online-search, conducted on PubMed [http://www.ncbi.nlm.nih.gov/pubmed] during the process of writing this review, provided only 84 results in total, by applying the parameters: (tendon OR tenocytes) AND (estrogen OR estradiol OR aromatase). By comparison, a search using the terms 'bone' and osteocytes' instead of 'tendon' and 'tenocytes' yielded 16,717 results. A similar search referring to 'muscle' and 'myocytes' provided us with 8838 results and even the terms 'cartilage' and chondrocyte' led to 735 results in total. For the purpose of this review, we have focused on those publications dealing with the imminent effect of ELC on certain traits of T/L (Table 1). The most of the articles listed in Table 1 will be discussed in detail throughout chapter 3.

Despite the number of articles being comparably low, there are in several instances findings being contradictory to one another. One issue contributing to this might be that most of the research on this subject has been conducted in the form of clinical studies or case reports with human participants. While this information is without any doubt the most relevant and closest to possible applications, it also provides the problem that the influence of other correlating factors is difficult to eradicate from any final conclusion [83], such as for example multiple hormonal changes during the per-imenopause [84], interactions with different cell types [85], as well as rather small sample sizes [86]. Additionally, it should be noted, that most of the scientific research on this subject has focussed on only three different anatomical structures: the anterior cruciate ligament, the Achilles tendon and in fewer cases, the patellar tendon (Table 1). The anterior cruciate ligament is the structure most studied due to its prominent role in knee injuries [87], as well as the known gender difference in the occurrence of knee injuries, with women being significantly more affected than men [13,14].

By far the largest part of research conducted on the effect of ELC on

Table 1
Overview of the effects of ELC on tendon features.

Effect	Experimental Model	Tendon	Type of study	Species	Finding	Ref.
Collagen Type I levels		AT	In vivo	Human	No effect after exercise	[107]
		ACL	Cell culture	Rabbit	Synthesis decreases with lower estrogen beginning at sub-physiological levels	[105]
		ACL	Engineered tissue	Human	Increased synthesis	[103]
		ACL	Cell culture	Pig	Increased synthesis	[104]
		ACL	Cell culture	Human	Decreased synthesis attenuated after a short time after increased estrogen substitution	[106]
		AT	In vivo	Human	Higher number of fibrils after postmenopausal estrogen supplementation	[110]
	Postmenopause	PT	In vivo	Human	Higher synthesis in combination with exercise	[107]
	Gonadectomy; Substitution	ACL	In vitro	Rabbit (male)	Lower concentration with higher fibre diameter after 21 days	[183]
		PT	In vivo	Human	Decreased synthesis in postmenopausal females after HRT	[184]
Stiffness		ACL; PT	In vitro	Monkey	No effect after 2 years ovariectomy in undamaged tendon	[127]
		ACL	In vitro	Rat	No difference in between different stages of the estrous cycle	[129]
		ACL	In vitro	Sheep	No difference 6 month after ovariectomy or SERM-Treatment	[128]
		PT	In vitro	Rat	Estrogen up regulates mRNA- and protein expression of relaxin receptor isoforms in tendon	[185]
		ACL	In vivo	Human	Elasticity is higher during ovulation	[147]
		ACL	In vivo	Human	Laxity, measured through ant. tibial translation, increases with estrogen levels during pregnancy	[148]
		PT	In vivo	Human	No changes in between menstrual cycle phases	[150]
		AT	In vivo	Human	No changes in between menstrual cycle phases	[149,151]
		ACL	Engineered tissue	Human	Decreases by inhibiting lysyl oxidase	[103]
		AT	In vivo	Human	Decreases after long-term exposure in users of oral contraception in comparison to non-users	[152]
Failure load		ACL; PT	In vitro	Monkey	No effect 2 years after ovariectomy in undamaged tendon	[127]
		ACL	In vitro	Rat	No difference in between different stages of the estrous cycle	[129]
		ACL	In vitro	Sheep	No difference 6 month after ovariectomy or SEM-Treatment	[128]
		ACL	In vitro	Rabbit	Reduced 30 days after ovariectomy in comparison to ovariectomy plus estrogen supplement	[153]
Healing		AT	In vivo	Rat	Improved	[173]
	Ovariectomy	AT	Cell culture	Rat	Decreases with age and estrogen deficiency	[172]
	Ovariectomy	MCL	In vitro	Rabbit	Ovariectomy had no effect on mechanical properties in comparison to non-ovariectomized animals	[174]
	Substitution	UCL	Cell culture	Human	Higher fibroblast proliferation and collagen synthesis in damaged tissue	[175,176]
Size		AT	In vivo	Human	Smaller diameter in active postmenopausal women	[178]
		ACL; PT	In vitro	Monkey	No difference in cross-sectional area or length 2 years after ovariectomy	[127]
		AT	In vivo	Human	No changes in between menstrual cycle phases	[149]
Proteoglycans		AT	In vitro	Rabbit	Lower mRNA-Expression after ovariectomy	[181]
Apoptosis	Ovariectomy	AT	In vitro	Rat	Higher rates after ovariectomy	[174]

ACL: Ant. cruciate lig.; AT: Achilles tendon; PT: Patellar tendon; UCL: Uterin cardinal ligament; MCL: Medial collateral ligament.

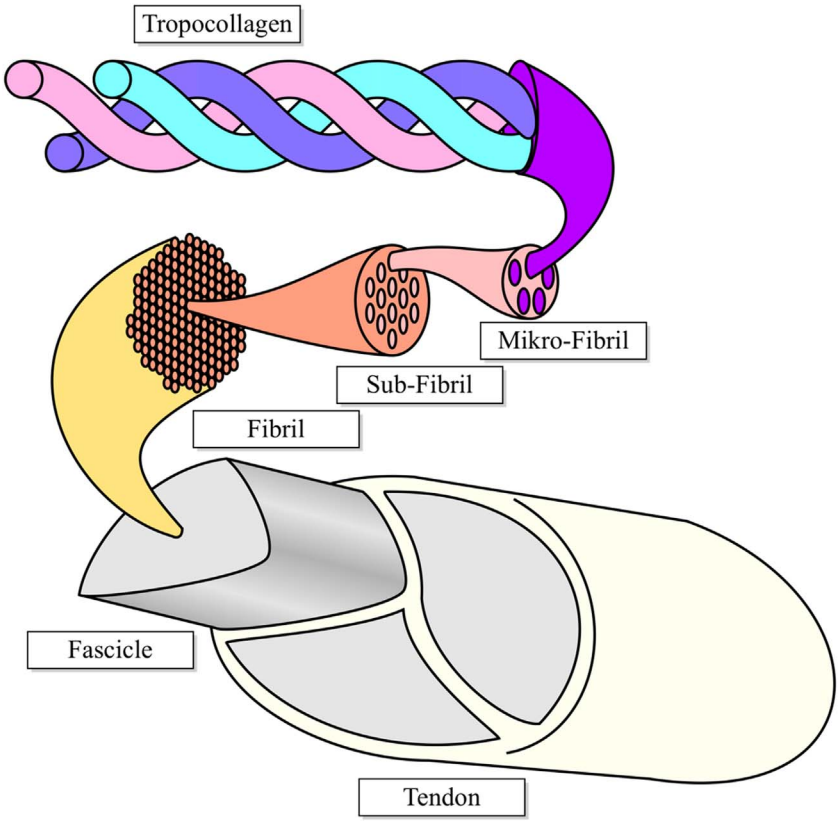

Fig. 3. A schematic presentation of the hierarchy of collagen fibers in tendons. Collagen chains align as a triple-helix to tropocollagen, which organizes in several steps towards fibrils. Together with other elements of the ECM fibrils form the functional unit of a tendon fascicle, which than with a surrounding of peritendineum and other fascicles forms a tendon.

tendon and ligament tissue can be divided into four groups, each defined by a different trait the publication aimed its attention at: content of collagen type I, stiffness, failure load and healing.

3.1. Collagen type I

In tendon tissue; collagen constitutes for approximately 60–85% of the dry mass of the extracellular matrix [88], whilst about 95% of collagen in tendon is attributed to type I [89]. Collagen fibrils in tendon accumulate to form functional fibres, whose purpose is the transmission of force between muscle and bone (Fig. 3) [90,91]. Research on the relation between ELC and collagen, in particular collagen type I, has mostly been directed at the effect on the collagen content of the skin [92,77]. The results imply a connection between declining estrogen levels and age-related skin conditions as well as cellulite, notably in post-menopausal women [93,94]. It has also been shown that hormone replacement therapy as well as therapy using SERM can have a positive effect on skin aging [95–97]. Several other studies have linked the loss of ELC with the prolapse of pelvic organs [98,99], a process highly associated with the pelvic ligaments and the collagen content of the surrounding tissue [100–102].

In engineered tendon tissue based on cells derived from humans, as well as in cell culture using pig cells, it has been shown that an increase in or addition of ELC had a positive effect on the overall collagen synthesis [103,104], while in accordance, a cell culture experiment using cells derived from rabbit showed a decrease in the synthesis of collagen fibres as a result of estrogen being below the physiological levels of < 0.025 ng/ml [105]. Contrary to the above findings, a different cell culture experiment using human derived cells did result in an initial dose dependent decrease in typ I procollagen synthesis after estrogen treatment, even though this decrease in synthesis was attenuated after a week [106].

An in vivo study conducted in humans measured the effect of transdermal estrogen application on the collagen turnover in muscle- and tendon-tissue, through assessment of procollagen type I NH(2)-terminal propeptide (PINP), a marker of collagen synthesis, in dialysate collected close the site of the transdermal patch. The study with post-menopausal female participants was able to show an increase in PINP on days following physical exercise in dialysate acquired from muscle tissue but not from tendon tissue, which would indicate a higher collagen synthesis in muscle after transdermal estrogen supplementation but not in tendon. Researchers acknowledge that the content of estrogen itself in the tendon dialysate being below the limit of detection in opposite to the dialysate gained from the muscle. So it is a possibility that a potential reaction in tendon tissue might not even occur under the conditions of this experiment or, as the authors discuss, that the attempt to administer estrogen to the tendon was ineffective [107]. Additionally it is known, that the turnover of collagen in undamaged tendon tissue is very low, with the inner tissue being almost consistent after the age of maturity in humans [108] as well as in mice [109]. However, the duration of the study in question contained a time frame of only two weeks [107]. With this in mind one has to question whether this experiment provides an appropriate approach to justify conclusions on the relationship between ELC and collagen.

A different study conducted also on post-menopausal women, but this time applying an oral estrogen replacement therapy (ERT), compared dialysate levels of a study group and a control group as well, but also took a look at additional parameters of tendon physiology. It showed a higher ratio of medium-sized fibrils compared to large sized fibrils in ERT users compared to the control group [110].

A possible explanation for the effect of ELC on collagen in tendon tissue lies with the known influence of ELC on the expression of matrix metalloproteases (MMPs) [111]. This has to be viewed separately from possible changes to the explicit synthesis of collagen. MMPs are a group of zinc- and calcium-dependent endopeptidases charged primarily with the lysis of ECM-proteins in numerous tissues [112–114]. Different subtypes of MMPs have been linked to estrogen-related collagen degradation, like MMP-8, and MMP-15 being upregulated in ER-knockout-mice [115]. In contrast to these findings, MMP-13, which is also responsible for collagen degradation, has been shown in a rat-

model to be upregulated in the presence of the SERM Raloxifen as well as in that of estrogen [116].

It should be noted that with the limited amount of data from the few studies conducted on this topic, many of the observed differences could be attributed to differences between the experimental models themselves. For instance, different species and sample types, varying form of estrogens, as well as different forms of application, as well as non-standardized protocols. ELC appears in several cases to have a positive effect on collagen type I synthesis in T/L. Still, additional research would be necessary to affirm this conclusion.

3.2. Stiffness

The term of stiffness is used in general to describe the amount of force necessary to achieve a certain amount of deformation in a given object or structure [117]. Due to the purpose of tendon in transmitting as well as storing energy [73–75], stiffness is a crucial trait in regards to both of these abilities in that it can have a positive effect on both, as long as it does not exceed a certain range of value on either end [118,119]. In a similar way, it is also known to affect the maximum load before failure of a tendon [73]. Short-term changes in ligament stiffness are also a crucial and well documented necessity, e.g. during pregnancy [120].

It has been shown that stiffness is on average, considerably lower in female knee ligaments compared to males [121,122]. This condition has often been related to the higher occurrence of knee injuries in female athletes [123,14,15]. Other studies on the stiffness of tendons of the angular joint have been conflicting in contrast to previously mentioned findings [124,125]. In general, besides the implication of gender-specific differences in stiffness, it has been noted that also the adaptation of tendon stiffness in reaction to physical exercise appears to differ between women and men at least in older age [126].

Several studies in animal models have been unable to identify a change in tendon stiffness in reaction to ovariectomy even after months or years after surgery [127,128]. Similarly, a study conducted in rats found no variations in tendon stiffness between different phases of the estrous cycle [129].

All the while, one experiment did conclude higher levels of mRNA and protein expression of relaxin-receptor isoforms RXFP1 and RXFP2 in patellar tendon tissue as a reaction to estrogen treatment [126]. Relaxin is a peptide hormone produced in females in the corpus luteum and thereby following the estrous cycle [130]. Besides other effects, relaxin has been shown to be responsible for a necessary decrease of stiffness in the pelvic ligament system, particularly during pregnancy [131], an effect attributed to changes in the expression of matrix metalloproteases [132]. Relaxin-receptors are present in various tendons and ligaments of several different origins, studies observing the reaction of human tendon tissue to different levels of relaxin concluded that some structures, like for example the patellar tendon or the anterior cruciate ligament, did in fact exhibit a lower stiffness, whilst other tendons, like the aforementioned Achilles tendon, did not [133–137].

Another factor contributing to tendon stiffness resides with the copper dependent ECM enzyme lysyl oxidase [138]. Lysl oxidase mediates the formation of cross links between different ECM fibrils, through oxidation of lysin in collagen and elastin [139–142]. A reduction of these crosslinks by means of reduced levels of lysyl oxidase has successfully been linked to a decrease in tendon stiffness, whilst maintaining an unchanged content of collagen fibrils in total [143]. It has been shown that the amount of lysyl oxidase present is influenced by the levels of estrogen administered [144,99,145,146]. Still only one study attempted to observe this effect in tendon tissue. By using engineered tissue, built with cells derived from the anterior cruciate ligament, researchers concluded that levels of lysyl oxidase did in fact correlate with the applied estrogen and thereby changed the stiffness of the tissue [103].

In vivo studies discerning changes in human tendon and ligament tissue over the course of the menstrual cycle drew different conclusions, according to the exact structure being studied. In the anterior cruciate ligament elasticity, has been shown to be significantly higher during ovulation as well as during phases of higher estrogen levels due to pregnancy [147,148]. On the contrary, the patellar tendon as well as the Achilles tendon appear to be unaffected with regards to stiffness by changing hormone levels during the menstrual cycle [149–151]. However, long-term hormone exposure via oral contraception has been suggested to decrease the strain also in the human Achilles tendon in comparison to non-users of oral contraceptives [152].

A regulating effect of ELC on stiffness has for the most part been observed in humans, whilst experiments conducted on animals have been futile in this aim. Due to stiffness being an important factor particularly in injuries of T/L, this subject matter might prove to be of high relevance in future treatment and prevention of these injuries.

3.3. Failure load

Failure load refers to the force necessary to break a certain object or structure under usage of a given application. In tendons and ligaments, this usually refers to a linear pull, which is sufficiently powerful to rip the structure apart [110,153]. Even though studies on the subject of failure load are quite often performed using samples gained from human cadavers [154–157], there have been, to the knowledge of the authors, up to this point no other studies, which observed the influence of ELC on the failure load of tendons and ligaments in human tissue. So far, all research has been performed using exclusively animal models.

One study using a rat model found no differences in failure load in samples harvested from animals in accordance to the different phases of the estrous cycle [129]. Two studies examining the failure load of the ligaments in question after ovariectomy in comparison with animals still bearing their gonads, also found no differences between groups [127,128]. However, a different publication using ovariectomized rabbits in both groups with one of the groups receiving estrogen supplementation, describes a reduction in failure load in the group with hormone substitution, which would imply that T/L under ELC influence could rupture at a lower applied force [153].

With only four publications in total, directly assessing the failure load of tendon and ligament tissue, little can be said conclusively whether or not ELC does have an influence on this subject. Other studies in general suggest a close connection between tendon failure load and the aforementioned traits of stiffness and collagen due to the numerous factors contributing to failure load [158–161], thus a significant effect is a realistic possibility.

3.4. Healing

Finding new approaches for improving the healing capacities of tendons and ligaments are amongst the most essential challenges in modern day traumatology [162,163]. Firstly tendon injuries are a common occurrence in sports [13–15] but with age related changes in the demographics of society, issues of the aging musculoskeletal system including tendons and ligaments have gained more attention as well [164].

The natural healing process in tendons and ligaments has been described according to three overlapping phases: inflammation, proliferation and matrix remodelling [165]. Yet, distinct variation between different ligamentary structures can be observed. Following, the initial injury, a proliferation of fibroblasts, inflammatory cells and vascular cells set in, triggered by various factors like the stretching of the tissue [166–168]. The next step involves creating a new initially less organised ECM, which afterwards is rearranged, over the course of months and years towards a closer resemblance of the initial tissue, by resident tendon cells. Still, a recognisable difference in structure and function compared to undamaged tendon tissue remains usually for the rest of the patient's life [169].

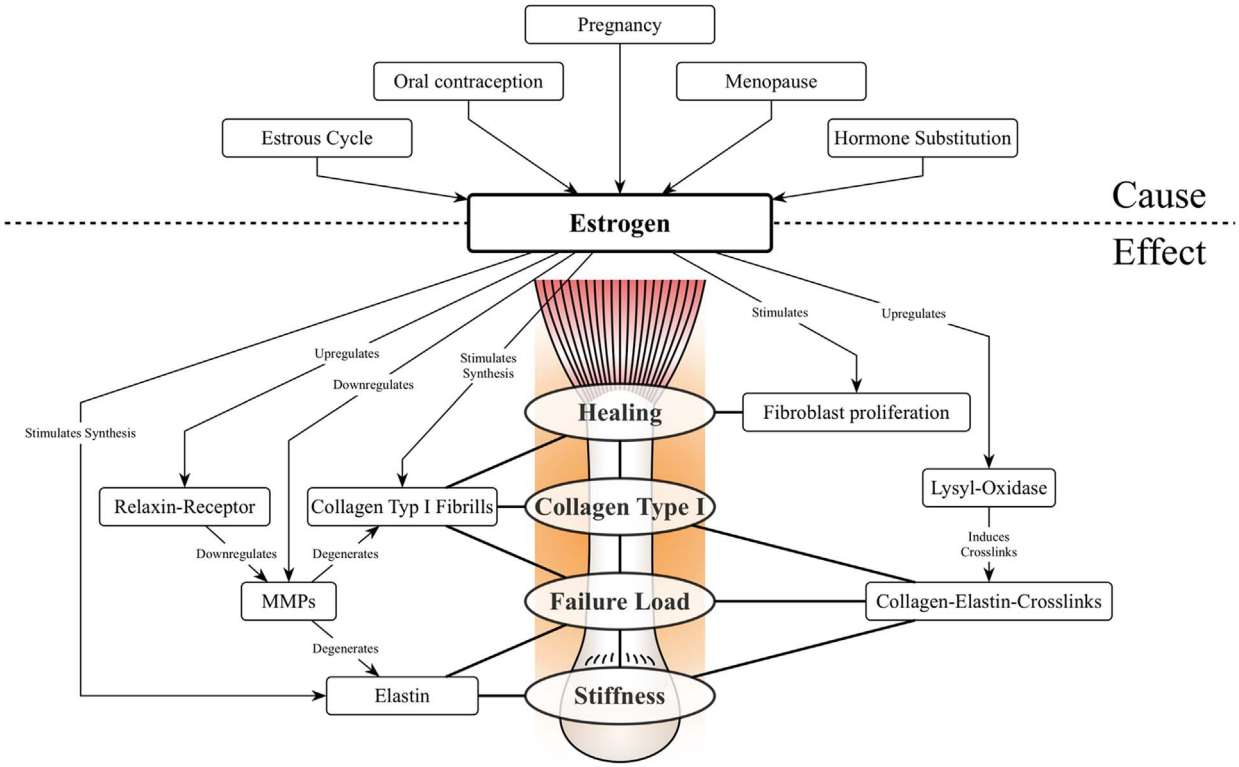

Fig. 4. A schematic of possible modes of interaction between estrogen and T/L tissue suggested by the literature mentioned in this review. It also names common causes of changes in estrogen levels during the life of a woman. These mechanisms might affect different traits of tendon biology in diverse ways, thereby facilitating the changes observed in clinical studies.

ELC and other steroid hormones have a well-documented positive effect on the healing process of the skin through stimulation of local fibroblasts and enhanced synthesis of ECM components [170,171]. Still, the results on whether these findings translate to tendons and ligaments are conflicting.

An in vitro model using rat-tenocyte-based cell cultures determined that ELC deficiency may contribute an important part to the age-related decrease in the healing capacities of the Achilles tendons. The cell proliferation as well as ECM synthesis of cell cultures derived from ovariectomized animals, animals of advanced age and younger specimens have been compared with one another. Factors attributed to healing properties like proliferation rate and collagen type I were lower in both the ovariectomized and the aged animals in comparison to the younger ones, while collagen type III and MMP-13 were significantly higher in ovariectomized animals compared to the younger as well as the older ones [172]. The conclusion of this study, on ELC having a positive effect on tendon healing, has also been held up in biomechanical testing comparing the healing of Achilles tendons in rats after ovariectomy [173]. Yet, a different study observing ovariectomized rabbits was not able to document a significant difference to animals of the control group. This time the study did not evaluate properties of the Achilles tendon but rather of medial collateral ligament of the knee [174]. The only two available studies on this subject using human tissue were performed on samples gained from the uterine cardinal ligament. The researchers associated ELC with an enhancing effect on both cell proliferation and matrix synthesis [175,176].

A first coherence between estrogen and tendinopathies was observed in vivo, in a study positively linking the expression of ERβ in the tenosynovial tissue to the grade of De Quervain's disease. In this disease it is very possible that estrogen increases inflammation and neovascularization via the augmented ERβ expression [177].

As with the other issues discussed in this review, the actual amount of literature is rather limited and not sufficient to provide a final conclusion. Keeping in mind that different tendon structures do have different healing properties in general, ELC may at some point be useful in the treatment of some of these injuries, whilst being of less value in other cases.

3.5. Other traits

Besides stiffness, failure load, healing and collagen properties several other aspects of tendon biology have been looked into though not as thorough. The question of ELC mediated influence on the overall size of tendon has been observed with conflicting results. Given its longitudinal structure changes in size in tendons and ligaments is usually measured by evaluating the cross-sectional area or diameter of the structure in question. A smaller Achilles tendon diameter has been described in active post-menopausal women in comparison to younger individuals [178]. Yet neither have quantifiable changes been recorded over the course of the human menstrual cycle in the Achilles tendon [149], nor did an in vitro study on ovariectomized monkeys present a significant difference in the cross-sectional area of the anterior cruciate ligament or patellar tendon 2 years after the operation [127].

Most of the studies aimed at the influence of ELC on cell proliferation in T/L have been conducted using an injury model. Due to the circumstance that the in vivo cell proliferation in these tissues is of particular importance for the healing process [165]. Still, one study on observing ovariectomized rats describes a higher rate of cell apoptosis in previously undamaged tendon tissue in these animals compared to those which had received no additional surgical procedure [179].

Proteoglycans are, besides collagen, an additional component of the ECM in T/L with high importance for overall function [180]. A study on rabbits described a decrease in proteoglycan-mRNA-expression after ovariectomy in the Achilles tendon of female animals [181].

Like in other known cases of connective tissue ELC appears to affect the biology of T/L in several different ways.

4. Perspectives

In summary, it can be said that the pathways in which ELC interacts

with tendon and ligament tissue are numerous. So far, we know of several possible ways through which ELC might influence the stiffness, failure load, collagen content and fibroblast proliferation in tendons (Fig. 4). However, we only have a limited knowledge of the specific mechanisms by which these are activated. While parts of them are indicated in the publications presented in this review, others may still be unknown, given the various possible pathways, the different types of estrogen receptors are capable of triggering or to interacting with. Contributing to this, is that most of the research conducted focused primarily on aspects observable through biomechanical testing, whilst only a few studies committed themselves to an approach on a molecular level. Especially data from research using a knockout model is till now not available, despite the possibility that a deeper understanding gained in this way may provide approaches towards new methods of treatment, like for example through the utilization of the ever increasing group of SERMs. An example: at the moment it is completely unclear whether ELC could have a specific effect on stem cells in T/L in ways different from those in regular tenocytes. Then again the relevant signalling pathways initiated by ELC in T/L in general, have as of yet not sufficiently been described.

Additionally, it would be of particular interest to see more studies on this topic using injury models given the high occurrence of gender- and age-related injuries in tendons and ligaments. Without these, the healing properties of tendons are quiet challenging to estimate, due to the known low turnover in tendon-ECM in comparison to other musculoskeletal tissues.

As mentioned before the overall literature on the topic of this review is rather limited, leaving more than enough space for possible findings, which hopefully might in the long term affect the lives of many people in a positive way. Due to the limited availability of relevant data in the field we as the authors hope to encourage other researches to join in on this interesting topic.

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