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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].