

The mystery of female connective tissue

Females and males differ in many ways – also physiologically, and the fact that some types of connective tissue injuries (e.g. ligament ruptures and bone stress fractures) are more frequent in females than in males remains a puzzle. Estrogen receptors are known to be present in fibroblasts of tendon and ligaments. However, the effect of estrogen on anterior cruciate ligament collagen turnover is still debated. *In vitro* studies have reported both an inhibiting, no effect, and a stimulating effect on fibroblast proliferation and collagen synthesis (Lee et al 2004). Nevertheless, animal findings and *in vitro* testing of human tendon fascicles indicate that estradiol have a weakening effect on the tissue (Slauterbeck et al 1999). In humans it has been shown that females demonstrate a lower collagen synthesis response to exercise than males, and that also the basal values for tendon collagen synthesis were lower in females compared to males (Miller et al 2007). This is suggestive for - but not any proof - that sex hormones could play an regulatory role on collagen formation in tendon, collagen being the most important load bearing tissue in the matrix, and the most abundant protein in the human body.

In this issue of Journal of Applied Physiology an interesting observation is made in humans, that females who receive oral contraceptives with synthetic estrogen and gestagens demonstrate stiffer Achilles tendons, as compared to matched women with normal fluctuations in endogenous sex hormones (Bryant et al 2008). In the control group no variation in strain behaviour of the tendon was found with acute menstrual cycle fluctuations in hormones. This indicates that long term exposure to hormonal changes alters the tissue structure and function, whereas short term variations do not. While not studied in the present study, these findings may imply that the tendons of females receiving oral contraceptives have a thicker tendon fibril diameter, which provides better ability for increased amounts of intra-fibrillar cross bindings and thus will result in an increased stiffness of the tendon.

The paper by Bryant et al (2008) therefore is suggestive for an influence of female ovary hormones e.g. estradiol upon the collagen turnover of ligament and tendon tissue in humans. This finding fits nicely with a recent observation that oral contraceptives given to young women result in a reduced response of exercise-induced tendon collagen synthesis (Hansen et al. 2008), and thereby indicates an inhibiting effect of oral contraceptives containing synthetic estradiol. In that study long-term administration of oral contraceptives was not associated with any change in tendon diameter, suggesting that structural changes in the tendon as a result of oral contraceptives is occurring in the absence of any change in gross magnitude of the tendon. Interestingly, the latter observation might be linked to cross-sectional data, which have not shown any difference in gross magnitude of Achilles and patellar tendons between trained and untrained females, an observation that differ from findings in males, where trained individuals demonstrate larger tendons than untrained (Westh et al 2008, Magnusson et al. 2008). These observations further indicate a gender specific adaptation of tendon tissue, and suggestive for estradiol playing an important role.

Recently, also studies from our laboratory have shown an impaired tendon collagen synthesis response to exercise when estrogen was raised in elderly women by estrogen replacement therapy, but that estrogen in the resting state if anything had a stimulating effect upon basal tendon collagen synthesis (unpublished observations). Similarly, in young women a positive association between endogenous estradiol and tendon collagen synthesis at rest have been observed. For the resting state, this is in some contrast to the overall suppressing effect that oral contraceptives have, and may suggest that endogenous estrogen has a “homeostatic effect” upon collagen synthesis – by having a

pivotal role in stimulating collagen synthesis at rest but diminishing the exercise response. Oral contraceptives on the other hand, may have an overall depressing effect upon collagen synthesis. Whereas, these findings could implicate that women adapt slower than males to training and therefore should take this into account in designing their training programs in order not to gain injuries, it could be very likely that in the reverse situation – during inactivity or bedrest – women are more resistant to lose too much of their supportive structure during periods with lack of activity. By maintaining homeostasis women may be more robust towards detrimental perturbations, ensuring that vital female functions like pregnancy and birth can be carried out without problems due to pronounced changes in connective tissue properties.

The final question still remains to be solved, and that is the mechanism by which gender differences in collagen tissue adaptations occur, and while estrogen is one likely candidate, its still not proven as to whether this effect is a direct one or rather mediated via other factors. Interestingly, it has in recent studies been shown that administration of synthetic estradiol is inversely related to the bioavailability of free IGF-I in the peritendinous fluid surrounding the tendon (Hansen et al, 2008) and low estradiol may via elevated IGF-I stimulate collagen formation in tendon. Local IGF-I is able to stimulate connective tissue formation, and it is very likely that female sex hormones play important roles in the interplay between growth factor in order to interact with mechanical loading, and thereby to regulate collagen synthesis and to optimize the adaptation of tendon tissue in humans with the major goal to avoid sports injury and allow for optimal performance in both genders.

References:

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