The magnitude and character of resistance training-induced increase in tendon stiffness at old age is gender specific

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Key words: Elderly, Gender, Tendon properties, Human, Hormones, Cytokine

Word count: 4,437

Abstract

Background- Human tendon mechanical properties are modified with loading. Moreover, there are indications that the training response in the tendon is gender specific. **Aims & Methods-** The aim of the current study was to examine whether *in vivo* patella tendon stiffness (K) differentially alters with training in older males compared with females. We also aimed to identify which endocrine pathway underlies the responses. Maximal knee extensor forces were also monitored to determine the training effect on muscle function. Fourteen healthy, habitually active older persons (7 males aged 74.0 ± 1.2 years (Mean ± SEM) and 7 females aged 76.7 ± 1.2 years) were tested at baseline and after 12 weeks of weekly, progressive resistance training. **Results-** With training, percentage increase in quadriceps maximum voluntary isometric force (MVC) was similar in males (2469.6 ± 168.0 N to 3097.3 ± 261.9 N; +25.3±6.1% ($p<0.01$)) and females (1728.8 ± 136.3 N to 2166.5 ± 135.8 N; +30.4 ± 15.1% ($p<0.05$)) respectively. K increased more in the males (338.0 ± 26.6 N/mm to 616.9 ± 58.7 N/mm; 79.8 ± 4.2% ($p<0.001$)) compared to the females (338.9 ± 31.0 N/mm to 373.2 ± 25.8 N/mm; +13.0 ± 3.7% ($p<0.001$)). Interestingly, a pattern was found whereby below ~40%MVC, the females showed their greatest degree of K changes, whereas the males showed their greatest degree of K change above this relative force level. This gender contrast was also true at a standardised force level (1200 N), with 5.8 ± 0.4% vs. 82.5 ± 1.8% increments in the females (i.e. value change from 380.3 ± 14.1 N/mm to 402.4 ± 13.3 N/mm) and the males (i.e. value change from 317.8 ± 13.8 N/mm to 580.2 ± 30.9 N/mm) respectively ($p<0.001$). Whilst circulating levels of both IGF-I and IL-6 did not alter with training, IGFBP-3 showed a significant training effect (19.1 ± 4.8%, $p<0.001$) and only in the male subgroup ($P=0.038$). **Conclusion-** We show here that with training, *in vivo* older females' tendon is less dramatically modulated than that of males'. We also show that the relative forces, at which the greatest adaptations are exhibited, differ by gender, with a suggestion of endocrine adaptations in males only. We thus propose that both training and rehabilitation regimens should consider gender-specific tendon responsiveness, at least in older persons.

Introduction

In the young, there appears to be gender related differences in the *in vivo* characteristic of connective tissue properties (Onambele et al. 2007; Carroll et al 2008). The study by Carroll et al. (2008) also reported differences between males and females, with ~28% lower values in the young females and ~26% in the older females, in terms of tendon stiffness values, compared to their male age-matched counterparts. In addition, the male tendon fascicle is reported to have a greater modulus (i.e. stiffness normalised for the dimensions (length and cross-sectional area) of the tissue) in comparison to the female, so that the stress-to-failure is less in women than in men (Magnusson et al. 2007). It is also known that young females are more susceptible to connective tissue injury in contrast to males (For a review see Dugan, 2005), and this could in part reflect the aforementioned differences seen in basal tendon mechanical properties. What is more, it is well established that tendon is a malleable tissue that has the ability to adapt to the stimulus presented to it. As with muscle, there are structural and mechanical type responses that optimise the adaptation of the tendon tissue to loading. In vivo, loading of the tendon typically carried out through resistance exercise has been shown to increase the anthropometric markers associated with general growth (i.e. cross sectional area; Kongsgaard et al. 2007) as well as increasing mechanical indices such as stiffness and Young's Modulus (Kubo et al. 2001; Burgess et al. 2007; Kubo et al, 2010). Others have also shown that the level of habitual loading in the young, even other than resistance loading, impacts on tendon mechanical properties. Arampatzis et al. (2007) reported that the triceps surae tendon and aponeurosis showed increased stiffness in sprinters in contrast to endurance athletes and sedentary individuals. However, it has been shown that in the young, there is an effect of gender on the magnitude of change with training or loading (Magnusson et al. 2007). Comparisons of age-matched trained and untrained men and women suggested that men showed increases in tendon size whereas females did not show this adaptation. This was partly explained by the acute reductions in both collagen synthesis rate (Miller et al. 2006) as well as regulatory mRNA expression (Sullivan et al, 2009) seen in females compared to males. This gender effect has been suggested to be as a result of higher circulating oestrogen in females, since this ligand is associated with decreased tendon synthesis (Liu et al, 1997; Yu et al, 1999). There is also evidence that even post-menopausally, oestrogen has a pivotal role to play in terms of its deleterious impact on collagen fibrils size whereby oestrogen

replacement users have smaller fibrils than age-matched non-users (Hansen et al, 2009). However, Carroll et al. (2008) have suggested that any gender related differences seen, may in fact reflect the level of absolute loading (rather than hormonal changes per se) as, when mechanical properties were normalised for force output, the differences between males and females were not apparent. The picture therefore, in terms of gender impact on tendon properties is less than clear when the literature is looked at as a whole.

With age the tendon properties have often been shown to alter, older individuals having lower values of tendon stiffness properties (both absolute and normalised for size, i.e. Young's modulus) compared to their younger counterparts. Patellar tendon stiffness in older subjects has been reported to range from approximately 800 - 2411 Nmm^{-1} (Burgess et al. 2009; Carroll et al 2008), whilst in the young values approximate 2552 – 3487 Nmm^{-1} (Carroll et al 2008; Kongsgaard et al. 2010). Although older individuals have previously been shown to retain the ability to adapt to increased loading, reflected by increased tendon stiffness (Reeves et al 2003, Onambele et al. 2008), to our knowledge no study to date has examined the effect of gender in older persons with respect to the tendon responses to loading. As females go past the menopause they have a significant reduction in circulating oestrogen. As mentioned above, in the young, oestrogen has been suggested to in part explain gender related differences in the loading responses of tendon. Interestingly however, the documented gender differences in tendon properties in the young even in the absence of training, disappear in the older persons (Burgess et al, 2009; Carroll et al 2008). The above observations are in contrast to studies by Ochala et al. (2004; 2007) that suggested the existence of a gender difference in 'musculoarticular stiffness' in older persons. This latter parameter however, does not distinguish between the muscular and tendinous contribution to the reported stiffness. In view of the literature therefore it is evident that further questions need to be answered in terms of whether with age, loading adaptations in the two genders will be similar. In summary, tendon response to resistance training with gender, especially in the older person has not been well documented.

In light of the above we aimed to determine whether older men and women would show similar adaptations of the tendon to increased resistance loading. In view of the fact that ageing has a detrimental effect on the

tendon stiffness of both genders, we hypothesised that following a period of exercise training, both genders would show incremented tendon stiffness. We also hypothesised that owing to the gender differential tendon metabolism response to training (with previous reports demonstrating that collagen synthesis rate following acute exercise loading, varies between the genders (Magnusson et al. 2007)), the degree of tendon chronic response to training would differ by gender. We hypothesised that this effect would be linked to endocrine markers which have previously been shown to impact on tendon metabolism including insulin-like growth factor 1 (IGF-I), insulin-like growth factor binding protein 3 (IGFBP-3) and interleukin-6 (IL-6) changes. Indeed IGF-I and its binding proteins plus IL-6 have been linked to collagen synthesis and repair responses (Døssing & Kjær, 2005; Abrahamsson, 1997; Kurtz et al., 1999). We hypothesised that any gender differences in the in vivo expression of tendon structural and mechanical properties would therefore be associated with specific magnitude of endocrine responses, hence providing *in vitro* markers for the potential status of tendon metabolism.

Method

Subjects

Fourteen healthy, habitually active older individuals were recruited to take part in this study (7 males aged 74.0 ± 1.2 yrs; body mass 78.1 ± 4.2 kg; height 171.4 ± 1.2 cm and 7 females aged 76.7 ± 1.2 yrs; body mass 70.0 ± 4.9 kg; height 159.7± 2.5 cm, (Mean ± SEM)). All subjects were familiarised with the training and testing apparatus prior to starting the experiment. All were tested at baseline and after 12 weeks of progressive resistance training. The local Ethics committee approved this study and subjects gave written informed consent. The study conformed to the declaration of Helsinki.

Strength measurement

Maximal isometric knee extension torque was measured with the knee at 70° angle (full knee extension = 0°) on the right leg of all participants. After a series of warm up trials consisting of ten isokinetic contractions at $60°s^{-1}$ at 50-75% maximal effort, participants were instructed to rapidly exert maximal

isometric force against the dynamometer (Cybex NORM, NY) lever arm. Participants were given both verbal and visual encouragement/feedback throughout their effort. Joint torque data were displayed on the screen of a Macintosh G4 computer (Apple Computer, Cupertino, CA, USA), which was interfaced with an A/D system (Acknowledge, Biopac Systems, Santa Barbara, CA, USA) with a sample frequency of 500 Hz. Isometric contractions were held for ~2 s at the plateau with a 90 s rest period between contractions. Peak torque was expressed as the average of data points over a 500 ms period at the plateau phase (i.e. 250 ms either side of the instantaneous peak torque). The peak torque of three extensions was used as the measure of strength in each participant

Tendon properties

Tendon elongation was determined using B mode ultrasound (7.5-MHz, 40-mm linear array, B-mode ultrasound probe (AU5, Esaote Biomedica, Italy)) set to a depth resolution of 49.3 mm, and placed over the apex of the patella in the sagittal plane with the knee fixed at 90^0. Forces were simultaneously determined by the measured external torque applied to the dynamometer with the addition of the estimated co-contraction torque from the antagonistic muscles by utilising electromyography (EMG).

The method for applying this technique has been detailed previously (Pearson and Onambele, 2006), but briefly, an echo-absorptive marker was placed between the probe and the skin to act as a fixed reference from which relative measures of displacement could be made. The idea of the whole technique revolves around the fact that the shadow cast by the echo-absorptive marker delineates the position of the skin and the underlying tissue at the start of the contraction. By the end of the contraction, what is recorded is the distance between the original position of the tissue under the skin, relative to the new position of the tissue. The position of the shadow also doubles up as a control for any movement of the probe relative to the skin. Essentially, the data acquisition is only considered successful where the location of the shadow on the ultrasound screen (which has a precise scale grid) does not move from resting to contracted positions. The technique has been used in numerous papers both by ourselves (e.g. Burgess et al. 2007; Pearson and Onambele, 2006) as well as other researchers (e.g. Kubo et al 2001b; Reeves et al, 2003) and is considered to be very reliable.

Ultrasound images were recorded in real-time and captured onto PC at 25 Hz. The ultrasound output was synchronized (using an electronic square wave signal generator) to allow temporal alignment with the torque and EMG data. Tendon displacements were determined at intervals of 10% of the maximal force (from 10 to 100%) using image J (National Institutes of Health, Bethesda, Maryland, USA). Three efforts ramped to maximum over 6 seconds, were recorded for each individual.

Patellar tendon moment arm length was estimated from MRI (0.2T MRI scanner (E-scan, Esaote Biomedica, Genoa, Italy) sagittal scans (TI HF protocol; matrix 256 × 256 pixels; TR of 420 ms, TE of 18 ms, slice thickness of 4 mm with 0.6 mm inter-slice gap), as the perpendicular distance from the patellar tendon to the midpoint of the distance between the tibio-femoral contact points in the lateral and medial femoral condyles (Baltzopoulos, 1995; Tsaopoulos et al, 2006). Due to constraints in the MRI scanner configuration, moment arm scans could only be performed with the knee fully extended. Then the moment arm at 90° of knee flexion was determined using previously reported ratios at 90° to 0^0 (Baltzopoulos, 1995). Tendon forces were then calculated as: Measured Torque (corrected for antagonist co-activation) / Patella Moment Arm. The plotted force–elongation relationship was fitted with a second-order polynomial function, forced through zero. Tendon stiffness (K in $N \cdot mm^{-1}$ or N/mm) was calculated from the slope of the tangents at 10% force intervals. Tendon stiffness was also calculated at a standardised force level (1200N), which corresponded to just under the maximum baseline force value of the weakest person. Patellar tendon cross-sectional area (PTCSA) and resting length (PTL) was assessed with the knee joint in 90 degrees of flexion. PTCSA was determined from a transverse plane ultrasound image taken at 50% PTL. PTL was measured from the inferior pole of the patellar to the superior aspect of the tibial tuberosity as determined from sagittal-plane ultrasound images. Young's modulus was calculated as the product of stiffness and the ratio between PTL to PTCSA. Tendon strain (%) was calculated as the ratio of tendon elongation to the PTL. Tendon stress was calculated by dividing force in the tendon by PTCSA.

Training protocol

Resistance exercise was carried out on a twice a week basis (once supervised, once home based) for a total of 12 weeks. The home based training (total time ~1h-1h20 mins) was given through information detailed in an instruction manual, which was provided to each participant and consisted of a combination of i) a 10-15 mins warm-up including 12 exercises performed in the seated position; ii) an aerobic component which included a 20 mins walk (to be progressively built up to 40 mins); iii) a strength training component which consisted of 8 exercises performed with rubber band exercises (Therabands) in the seated position, and 4 exercises performed standing, with the use of a chair for support; iv) a 10 mins cool down component which involved repeating 7 of the warm-up exercises, as well as stretches.

Lab-Gym based training was supervised at all times by two researchers who checked for correct technique and gave verbal encouragement, throughout the sessions. During these supervised sessions, prior to the main resistance exercises, a warm up was carried out (10-15 minutes) which consisted of low impact aerobic exercises to music. Resistance exercises utilised cable weight machines (leg press, knee extensors, calf raise machine, and hip extensor; Technogym, Gambettola, Italy) and targeted the lower limb muscles (i.e. quadriceps, hamstrings, triceps surae and gluteus). In addition, the same resistance exercise as those carried out for the home based sessions using therabands, were included. Each exercise was carried out in 2 sets of eight repetitions at 8 RM (maximum load the participant could lift correctly 8 times), with the 8RM loads being revised every 4 weeks. A cool down (~10 minutes) was also incorporated at the end of each exercise session, consisting of a tai chi and stretch routine.

Endocrine profiling

At the onset and end of the training intervention and following an overnight fasting period (~10 hours for all participants), participants reported to the laboratory. A 21-gauge 1-inch ultra thin wall needle (Terumo Medical Corporation, New Jersey, USA) was inserted into the antecubital vein of the forearm. Using a vacutainer assembly and serum separator tubes (Monovette, Sarstedt, Numbrecht, Germany), 5 mL blood samples were collected. After being kept on an ice bed for up to 2-hours, the sample was then centrifuged at 2-5°C for 5 min at 4,000 rpm, with the supernatant being removed and stored in eppendorfs at −20° Celsius

for later analyses. IGF-I (Biocode-Hycel, Liege, Belgium. Sensitivity of 4.9 ng/ml; intra-assay variability of 8.0%, manufacturers' data), IGFBP-3 (Biocode-Hycel, Liege, Belgium. Sensitivity of 10.5 ng/ml; intra-assay variability of 6.5%, manufacturers' data) and interleukin-6 (IL-6; Diaclone, Besancon Cedex, France. Sensitivity <0.8 pg/ml; intra-assay variability of 3.3%, manufacturers' data) were analysed using standard enzyme-linked immuno-sorbent assay procedures.

Statistical analyses

Mixed-design ANOVAs (analyses of variance) were used to determine the presence of significant changes in the variables of interest. Here the within factor was phase of training (pre- vs. post-training) and the between factor was gender (males vs. females). Correlation analyses were used to determine any relationships between the changes in stiffness and strength for both groups. Where data was non-parametric, appropriate tests were carried out. Unless otherwise stated, data are exhibited as means ± S.E.M.

Results

Muscle Strength

With training, percentage increase in quadriceps maximum voluntary isometric force was similar in males (2469.6 ± 168.0 N to 3097.3 ± 261.9 N, a 25.3±6.1% increment ($p<0.01$)) and in females (1728.8 ± 136.3 N to 2166.5 ± 135.8 N, a 30.4±15.1% increment ($p<0.01$)). It was however also found that there was a significant difference in strength at baseline between males and females ($P= 0.0049$) and that the change in MVC was significantly correlated with the baseline MVC ($r = 0.772$, $P <0.001$). Therefore an ANCOVA was run with baseline strength as the covariate. This showed that after accounting for the baseline strength differences between men and women, the change in MVC between the two genders was not in fact significant ($P > 0.05$). In other words, the difference that existed between the genders at baseline still existed to a similar degree after training.

Tendon Size and Stiffness

With training, the dimensions of the tendon did not alter significantly in either males or females. Briefly, pre to post PTL in the males were 4.6 ± 0.2 cm and 4.3 ± 0.4 cm (P>0.05), whereas pre to post PTL in the females were 4.5 ± 0.2 cm and 4.6 ± 0.3 cm (P>0.05). Similarly, pre to post PTCSA in the males were 83.7 ± 29.5 mm^2 and 82.8 ± 29.2 mm^2 (P>0.05), whereas PTCSA in the females were 73.4 ± 3.3 mm^2 and 73.4 ± 3.5 mm^2 (P>0.05).

Patella tendon stiffness showed a mean increase, across all relative force levels (10-100% MVC - see figure 1), which was greater in the males (338.0 ± 26.6 N/mm to 616.9 ± 58.7 N/mm ($p<0.001$) for average stiffness at each 10% force increment from 10% MVC) compared to that in the females (338.9 ± 31.0 N/mm to 373.2 ± 25.8 N/mm ($p<0.001$)). To confirm that the above gender-specific responses were independent of the forces at which stiffness was estimated, we also measured this characteristic at a standardised force level (1200 N). The changes at this standardised force level were 5.8 ± 0.4% vs. 82.5 ± 1.8% increments in the females (i.e. value change from 380.3 ± 14.1 N/mm to 402.4 ± 13.3 N/mm) and the males (i.e. value change from 317.8 ± 13.8 N/mm to 580.2 ± 30.9 N/mm) respectively ($p<0.001$). The changes in tendon stress, strain and Young's Modulus very much mirrored those seen in tendon stiffness and are summarised in table 1.

→ [*Figure 1 near here*]

→ [*Table 1 near here*]

Interestingly, a 'cut-off point' (~40%MVC) was identified which related to a gender-specific pattern in the changes in tendon stiffness (see Figure 2). Below this force level, females exhibited their highest tendon stiffness increases whereas above this point tendon adaptations were minimal. On the other hand, the males exhibited their highest tendon stiffness increases above this point.

→ [*Figure 2 near here*]

Association between intrinsic physiology and tendon stiffness changes

Probable factors affecting changes in tendon stiffness were investigated to try and separate the gender effects from any other obvious intrinsic differences between genders. A multiple correlation revealed no correlation between strength and stiffness regardless of whether absolute values, or relative changes were taken into consideration. Thus, the relationship between baseline strength & baseline K gave non-significant correlation coefficients ($r = 0.113$ and $r = 0.070$ for stiffness taken at MVC and 1200 N respectively). Similarly, strength (whether at baseline or training-induced changes) was not related to either post-training K nor training-induced changes in K (r values ranged between 0.017 and 0.355, $P>0.05$). Finally, baseline K was not a significant indicator of the post-training K (r values ranged from 0.180 and 0.305, $P>0.05$). These lack of associations therefore confirmed that the gender differences in terms of training responses was not due to the intrinsic muscle strength and/or tendon stiffness differences between the two genders.

Endocrine profiles

The coefficients of variation of the endocrine assays, which were run in duplicates, were comparable with those published by the manufacturers with intra-assay values of 7.1%, 2.6% and 4.9 % for IGF-I, IGFBP3 and IL-6, respectively. Endocrine data are summarised in Table 2. Circulating levels of IL-6 were equivalent for the two genders at baseline (3.4 ± 1.0 pg/ml vs. 2.3 ± 0.4 pg/ml in males and females, respectively; $P>0.05$) and did not change significantly with training ($P>0.05$).

→ [*Table 2 near here*]

At baseline circulating IGF-I levels in the males (350.3 ± 28.7 ng/ml) did not significantly differ from that of females (336.4 ± 24.7 ng/ml). With training neither the females nor the males, showed any significant changes in IGF-I levels (324.9 ± 26.8 ng/ml and 308.9 ± 21.2 ng/ml post-training values for females and males respectively, ($P>0.05$)).

The population exhibited a non-statistical difference in group data at baseline in terms of circulating levels of IGFBP3 ($P>0.05$). With training however, the males incremented significantly by 19.1 ± 4.8 % (i.e. from 3567.6 ± 252.0 ng/ml to 4245.7 ± 307.4 ng/ml $P<0.001$). The pre to post values for the females were not

significantly different (i.e. from 3946.1 ± 298.7 ng/ml to 4195.0 ± 435.6 ng/ml P>0.05). Further analyses (the data set being non-parametric, a One-tailed Mann-Whitney test was run to compare the changes relative to baseline between the two genders) revealed the gender effect to be significant (P = 0.039).

Association between muscle-tendon properties and IGFBP-3 levels

At baseline there was no association between muscle strength (r = 0.013; p>0.05) or tendon stiffness (r = 0.178; p>0.05) against IGFBP-3 levels. Following the training intervention, the associations between these parameters were still not significant (r = 0.325 and r = 0.028 for muscle strength and tendon stiffness respectively; p>0.05). There was also no correlation between relative changes in IGFBP-3 and relative changes in either muscle strength or tendon properties. Interestingly however, the change in IGFBP-3 was significantly associated with post-training strength (r = 0.566; p<0.05) and tendon stress (r = 0.518; p<0.05) values, but not with post-training tendon stiffness (r = 0.028; p>0.05), strain (r = 0.206; p>0.05) or Young's modulus (r = 0.028; p>0.05) values.

Discussion

To the authors' knowledge this is the first study to determine a gender-related differential resistance training response in tendon in an older population. It was hypothesised that following a period of exercise training, owing to the previously reported differential tendon metabolic profiles/responses between males and females, the degree of response would differ by gender, also that both genders would show incremented tendon stiffness in view of the expected low baseline values. Finally we explored a link between endocrine markers in terms of three potential markers of tendon metabolism mirroring the *in vivo* observations. Our findings have partly supported our hypotheses. Indeed whilst the relative changes in muscle strength were equivalent for both genders, tendon adaptations were vastly different with males showing the greatest degree of stiffness increment. Further analysis revealed that the region of the tendon force-elongation curve with the greatest response to training also differed by gender, females responding optimally at the lower forces (≤40% MVC) and the males responding at their optimal level at the highest forces (≥40% MVC). Based on the previously documented effect of IGFBPs on tendon metabolism (Abrahamsson et al, 1996; Hansson et al

1988; Kjaer, 2004), IGFBP-3 was also found to be a strong candidate for a marker of tendon tensile adaptation to training since changes in this ligand reflected those seen in tendon stiffness. Having observed significantly increased muscle strength, tendon stiffness and IGFBP-3 levels in the males whereas a similar relative strength increment was coupled with lower tendon stiffness increase and no change in IGFBP-3 serum concentration in the females, it became opportune to quantify any correlation between muscle-tendon properties and the protein levels. Thus, it was observed that only post-training muscle strength and tendon stress values were significantly associated with alterations in IGFBP-3 levels.

Resistance training is well documented as being able to improve muscle strength and power. Previous work has established that relative adaptation in response to resistance exercise in older skeletal muscle can be equivalent to that of their younger counterparts (Frontera et al. 2003). This may be surprising in that it is known that certain anabolic hormonal responses are suggested to be somewhat blunted in the older adult (Craig et al. 1989). In this regard Moritani & deVries (1980) reported that increments in strength of the old were primarily due to neural adaptation in contrast to muscle hypertrophic responses seen in the younger adults. This is not always in agreement with others (Ivey et al, 2000), who showed that muscle hypertrophy in the elderly was equivalent to that in younger subjects, when given a similar resistance training stimulus. These reported differences in the literature may be due to heterogeneous subject groups, methods of assessment and variability in the training protocols. Previous authors have reported the optimal knee joint angle in older individuals to be 70° knee flexion and to change to 60° following 12 weeks of resistance training (Reeves et al. 2003). At face value, the fact that in the present study strength was only measured at a knee angle of 70°, may have resulted in an underestimation of an increase in strength following the training intervention, if indeed knee optimal angle does change with training (a possibility which is yet to be confirmed as there may have been an issue with noise in the data of Reeves et al. (2003) with the control population also showing a shift in optimal knee angle in the space of 14 weeks). To further counter this argument, it should be considered that optimal angle differs between individuals. It is not unreasonable therefore, to suggest that in the current study, although true maximal torque may not have been determined,

there is no reason to suggest relative changes were not similar between individuals showing change with training, nor is there any evidence to suggest females' optimal angle would change differently to males'.

Although 'trainability' of the muscle has been examined previously with respect to gender (Ivey et al, 2000), similar investigations in the tendon had not been reported prior to the current study. Here it may be suggested that the tendon shows a similar response to resistance exercise as that of muscle in that not only is this unit modulated by training, but also there is a gender specific response. In general, although differences exist in the ability to generate forces between older males and females, with age the observations are also that, hormonal differences between the genders are reduced, and generally the anabolic responses are blunted. Certainly the results in the current study are supported by the findings of Ochala et al. (2007) who first suggested that gender differences existed in musculoarticular stiffness changes following training in an older population. This latter observation, together with the present finding of different magnitude of tendon training responses are suggestive of intrinsic differential tendon sensitivities to increased loading by gender. This observation is further supported by our previous research which showed, in the absence of a training stimulus, a lack of any statistically significant gender difference in the *in vivo* biomechanical properties of the tendon in this age group (Burgess et al, 2009).

In vitro work also supports the suggestion that the tendinous structures of the two genders differ since it is found that, female tendon has ~9.6% lower dry mass, as well as reduced water content compared with males (LeMoine et al, 2009). Interestingly, these authors reported no gender differences in either the cross-linking of collagen, or in collagen content normalised for dry mass (LeMoine et al, 2009). What is more, these authors also report no influence of chronic resistance training on these markers (i.e. collagen cross-linking, dry mass, collagen content). Thus on this basis, it seems unclear what the mechanism for the differential training responses in the current study between the two genders may be. Their findings however are in fact directly opposed to earlier works (Kjaer 2004; Last et al, 1984; Walker et al, 1964) that showed that tendon dry mass, collagen content, and cross-links impact tendon strength and mechanical properties, and also with work that shows increased collagen content of tendon following exercise training in both human (Langberg

et al, 2001; Kjær et al, 2009) and animal (Michna 1984; Woo et al, 1980) models. It is possible that the work of Lemoine et al (2009) differs to other works on the effect of training since Lemoine and colleagues' study population (1) did not follow a given training protocol but were recruited on the basis of self-reported elevated habitual physical activity as opposed to being given a controlled training program, (2) had a different duration of training in the study populations (≥3-4 days per week, for ~10 years, compared with the other studies that were carried out in a matter of days/weeks). Notwithstanding the above discussion, it is still puzzling why the two genders should respond to training differently in the present study, since the presumed blunting effect of oestrogen on the tendon metabolism should not be a factor in a population where the females were all at least 20 years post menopausal. In addition to the above, we would also speculate that time course of tendon responses may be gender linked whereby the females would have the same ultimate capacity for tendon adaptation to training but their tendons may require a longer time period to reach the same stiffness as that of men. Certainly future studies should look into following up the present study, to determine the time-course of tendon adaptations by gender.

Another key finding from the current study is linked to how mechano-transduction works (for an overview see Kjaer, 2004); it may be that the female tendon, through an as yet unidentified mechanism, adjusts to its lowered capacity for adaptation to loads (Kjaer et al, 2006) by predominantly responding to lower compared with higher loading. In fact, any suggestion of intrinsic difference in the propensity to respond to loading is illustrated by the current data showing preferential loads at which the greatest tendon training response was seen. Certainly other work would support this idea as it would indeed seem that there is a dose-response to training in terms of tendon's adaptive responses of collagen to increased stress (Kjær et al, 2009; Barone et al 2009). In this case, the fact that the absolute stresses experienced by the males' tendons were greater than those of the females would explain the greater adaptation in the former group. Also in support of the idea of preferential loads for tendon training responses, it was described that in horse, tendon tissues appear to favour lower stresses in terms of maximising collagen content response (Parry et al, 1978). Similarly, previous work suggest that mechanical loading may set collagen synthesis thresholds (Kjær et al, 2009), which would support the idea that females in the current study being weaker (hence having lower habitual

mechanical loading) than their male counterparts would only require lower forces to produce a tendon adaptation response. Notably also, following training and only in the female sub-group, the increment in muscle strength was accompanied by an increased deformation of said tissue at MVC (maximum tendon elongation increased from 6.4±1.1mm to 7.1±0.6). This effect though not statistically significant (as determined using a one-tailed Wilcoxon Signed Ranks test, $P>0.05$), is suggestive of changes in females which were qualitative in nature and point towards a deleterious impact of high loads on the females' tendon mechanical properties - at least within the time frame of this study.

Whether an elevated net potential for increased synthesis of collagen type I would be transformed into morphologically detectable increase in tendon dimensions was not necessarily expected since previous work has not always associated training-induced incremented tendon stiffness with increased tendon size (Reeves et al, 2003). The tendons of our study populations displayed load-deformation curves that were altered without any detectable changes in tendon volume (length and CSA), suggesting that the mechanical loading resulted in qualitative rather than quantitative changes in tendon characteristics. Our data (see table 1) indeed shows significant changes in tendon Young's Modulus (70.0 ± 3.9% in males vs. 15.0 ± 3.8% in females), which is a measure of the qualitative property of this tissue. This result is very much supported by the literature which more often (Reeves et al, 2003; Viidik 1969) than not (Woo et al, 1981; Kongsgaard et al, 2007), shows the same impact of chronic loading. Admittedly, animal models (Viidik 1969; Woo et al, 1981) may not necessarily be representative of those changes seen in humans. In addition, it must be acknowledged that tendon hypertrophy response to loading may be region specific (Seynnes et al. 2009; Kongsgaard et al. 2007). In the present study the tendon was only measured at 50% of its length. Even so region specific gender hypertrophic changes may not be similar in the elderly. Indeed where comparable resistance training studies have been performed in older persons (e.g. Reeves et al, 2003), no tendon hypertrophy is reported despite the tendon being monitored at 3 sites (proximally, centrally and distally), and the duration of the training program being thrice weekly for 14 weeks (i.e. a much larger training volume than in the present study).

It may simply be that the duration of training has to be relatively prolonged (Birch et al 1999) or even a life-long habit (Rosager et al, 2002), before any quantitative effect of high loading to become apparent. Admittedly the serum concentrations of the molecules monitored in the current study may not necessarily have been the same as seen in the tissues of interest. For instance, IL-6 would have been up to 100 fold lower in the serum compared with levels in the peritendinous interstitial fluid (Langberg et al, 2002). Nevertheless, our results pointed neither towards a gender, nor a loading impact of this cytokine's-mediated pathway of tendon metabolism. It should nonetheless be pointed out here that the failure to observe a significant cytokine response in the current study might also have been caused by the large between subjects variability in the IL-6 response and as such, a role for cytokines on tendon responses cannot be ruled out as yet. Interestingly however, IGF-I and IGFBP3 have been linked to an enhanced expression of procollagen I (Abrahamsson et al, 1996, Hansson et al 1988). In the current study IGF-I remaining unchanged whilst IGFBP-3 showed a post-training increment in males. Therefore, it may be that the complex which incorporates IGF-I, IGFBP-3 as well as an acid-labile subunit, broke off with increased loading to allow at least one of these components to effect its biological activities related to tendon. We would go so far as to propose that despite the lack of changes in IGF-I (though there was a trend for decreased IGF-I levels in both genders), it is likely that changes occurred in this ligand also (since the IGFBP-3 increased) but the tendon tissue (or even the liver) sequestered the circulating IGF-I too effectively for circulating levels to be seen to alter, all in an attempt to maintain the homeostatic balance of IGF-I in the systemic circulation (Kraemer et al. 1999). It should also be emphasised that since the IGFBP-3 changes were seen (to a significant extent) in the males only, our data is suggestive of a gender effect on tendon responsiveness to loading, at the cellular/endocrine level. The presumed mechanism would be one whereby, IGFBP-3, possibly via IGF-I, causes an increase in tendon collagen synthesis in a dose-dependent manner (as shown in equine flexor tendon by Murphy and Nixon (1997)) thus causing increased material stiffness of this tissue.

Finally, since the data in the current study is of no change in tendon dimensions (however a more complete picture of this would be determined by measurement of the tendon CSA at a number of sites along its length,

in an older population) linked with increases in at least one precursor of tendon metabolism, we would speculate that in older males at least, training initially results in an increased turnover of collagen type I to allow for reorganization of the tissue rather than increased size per se,. Presumably, similar events would occur in the females but only following longer duration exposure to increased loading.

Conclusion: We show here that older females' tendon is less dramatically modulated than that of males' in agreement with previous work on tendon dimensions. The large changes in tendon mechanical properties were accompanied with changes in circulating IGFBP-3 in the males, suggesting an eventual increment in tendon dimensions, has the training duration carried on beyond 12 weeks. We also show that the forces at which the greatest adaptations are exhibited are gender specific. Indeed we have identified a 'cut-off point' (~40%MVC) which was related to a gender-specific pattern in the changes in tendon stiffness. Below this force level, females exhibited their highest tendon stiffness increases whereas above this point tendon adaptations were minimal. On the other hand, the males exhibited their highest tendon stiffness increases above this point. It may be that the female tendon preferentially requires low forces to respond to training whereas the male tendon seems to adapt to all force levels, though preferentially to relatively high forces (≥40% MVC). We thus propose that both training and rehabilitation regimens should consider gender-specific tendon responsiveness.

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Tables

Table 1. Resistance training induced changes in tendon properties as a factor of gender and force level. Avg. denotes the average value across all force levels. Where there was no change from baseline to post-training, N.S. signifies a Non-Significant effect.

Patella Tendon	Older Males			Older Females		
	Pre	Post	**% Change**	Pre	Post	**% Change**
Length (cm)	4.6 ± 0.2	4.3 ± 0.4	**N.S.**	4.5 ± 0.2	4.6 ± 0.3	**N.S.**
CSA (mm^2)	83.7 ± 29.5	82.8 ± 29.2	**N.S.**	73.4 ± 3.3	73.4 ± 3.5	**N.S.**
Avg. Stiffness (N/mm)	338.0 ± 26.6	616.9 ± 58.7	**79.8 ± 4.2**	338.9 ± 31.0	373.2 ± 25.8	**13.0 ± 3.7**
Stiffness at 1200 N (N/mm)	317.8 ± 13.8	580.2 ± 30.9	**82.5 ± 1.8**	380.3 ± 14.1	402.4 ± 13.3	**5.8 ± 0.4**
Avg. Stress (MPa)	16.8± 2.8	20.8 ± 3.5	**21.8 ± 2.2**	13.2 ± 2.3	17.2 ± 2.7	**37.4 ± 5.8**
Avg. Strain (%)	12.6 ± 1.4	10.6 ± 1.2	**-15.5 ± 1.8**	9.7 ± 1.2	10.1 ± 1.2	**5.5 ± 2.7**
Avg. Young's Modulus (GPa)	0.19 ± 0.01	0.32 ± 0.03	**70.0 ± 3.9**	0.21 ± 0.02	0.23 ± 0.02	**15.0 ± 3.8**

Table 2. Endocrine profiles of the study population by gender and phase of training intervention. Data are given as mean ± SEM.

	Older Females		Older Males	
	Pre	Post	Pre	Post
IL-6 (pg/ml)	2.3 ± 0.4	2.3 ± 0.4	3.4 ± 1.0	3.3 ± 0.4
IGF-I (ng/ml)	336.4 ± 24.7	324.9 ± 26.8	350.3 ± 28.7	308.9 ± 21.2
IGFBP-3 (ng/ml)	3946.1 ± 298.7	4195.0 ± 435.6	3567.6 ± 252.0	4245.7 ± 307.4

Figure Legends

Figure 1. Force-elongation relationships in an aged population by gender and phase of a training intervention. It is notable that even though the maximal muscle strength is greater in the older males

(Triangles) than their female counterparts (Circles) at baseline, the tendon properties are in fact very similar. With training, the relative strength increments are similar but the shapes of the tendon force-elongation curves are dissimilar. Horizontal dashed line = standardised force level (1200N) at which the tendons were compared. Data are Means ± SEM.

Figure 2. The characteristic of tendon adaptation by force level is gender dependent in terms both of A) Magnitude B) The characteristic force-region. In Part A) we see that where stiffness changes are expressed relative to baseline values (i.e. K change in % or % K change), both genders show increments in stiffness with training, though the absolute magnitude of increment is greater in the males compared to the females across all the levels of forces. In other words the values of %K changes are higher in males compared with females. In part B) where the % K changes are further normalised for the mean %K change within each gender (in order to highlight how, within each gender, % K changes (at discreet force levels) compared with the average of the whole range of tendon stiffness values changes (mean K at 0-100%MVC)), there is a pattern emerging whereby the female tendon exhibits the greatest average change at low forces (<40% MVC; i.e. a decrease, followed by a stabilisation, of the magnitude of stiffness increment as loading increases), in contrast to males showing a high response pattern at high forces (>40% MVC; i.e. an increase, followed by a stabilisation, of the magnitude of stiffness increment as loading increases). Figures A and B, both represent data from group changes.

Figures

Figure 1

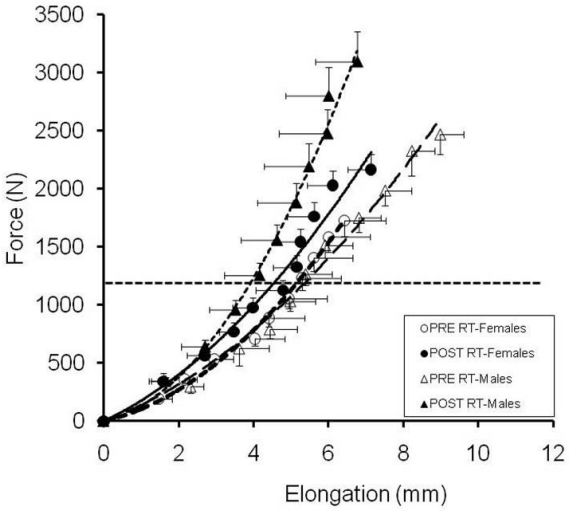
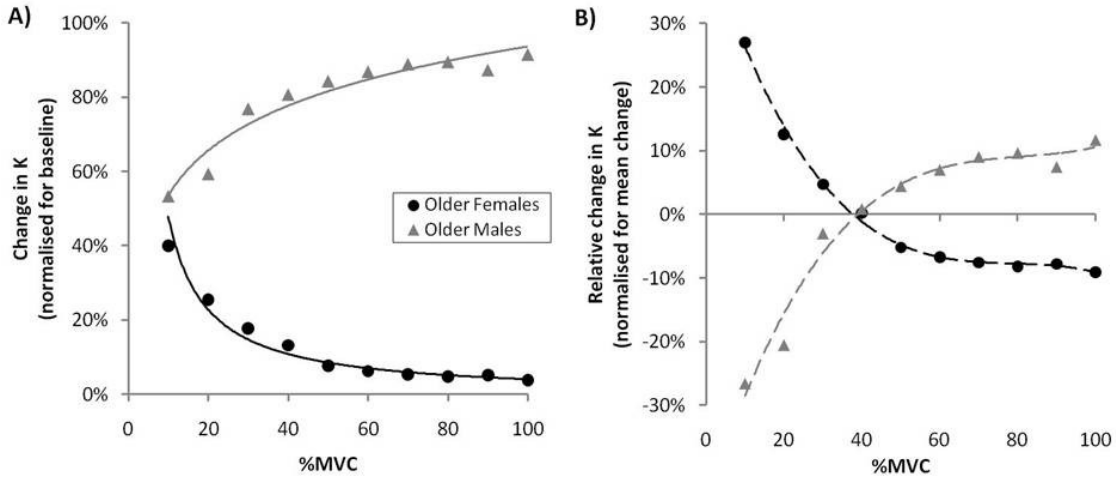

Force (N)
Elongation (mm)
PRE RT-Females
POST RT-Females
PRE RT-Males
POST RT-Males

Figure 2


A)
Change in K
(normalised for baseline)
%MVC
Older Females
Older Males
B)
Relative change in K
(normalised for mean change)
%MVC