Tendon hierarchy and structure health and social care essay

Introduction

Tendon Hierarchy and Structure

The tendon has a dry weight composition of approximately 65-80% collagen and 1-2% elastin (1). The mature tendon has a backbone of collagen which has a random scattering of tenocytes throughout. The tenocytes are specialised fibroblasts which contain actin and myosin and as such in some cases can undertake active contraction and relaxation (2). The smallest sized part of the tendon at 1. 5nm is the collagen molecule, this is mostly collagen type 1 (1). This is created by cross-links which are formed between soluble tropocollagen molecules to create insoluble collagen molecules these then aggregate to form collagen fibrils (3). A number of these form a fibril combine to form a structure 50-500nm in size. These fibrils are attached to each other by fibril-associated proteoglycans (decorin, fibromodulin). Many fibrils are interspersed with cells form a fascicle sized 50-300µm and many fascicles make up a whole tendon which is approximately 1-10mm. The fascicles are also surrounded by the epitenon and are arranged along the long axis of the tendon (3). The whole tendon is also encapsulated by epitenon, however the whole tendon has a further layer surrounding it and the epitenon, which is called the paratenon. This is separated from the epitenon by a thin layer of fluid (proteoglycan- water matrix) (1); this allows the tendon to move with reduced friction (4). The tenocytes is also responsible for the degradation of the ECM of the cartilage this is why it has key clinical importance in the pathology of the tendon (34). The tensile loads are transmitted through the cells of the tendon during mechanical loading. There is an unequal strain response exhibited throughout the matrix and

variability between different samples. Local strains within the tendon were a lot smaller than the force that had been applied. However large compressive forces were recorded in a perpendicular direction to that, in which, the force was applied. Rotation of the grid and sliding between the collagen fibres were also recorded (41). To aid the understanding between structure and mechanical properties x-ray scattering and tensile tests have been carried out. Intermolecular cross-links are thought to greatly affect the mechanical behaviour of collagen. X-ray diffraction was used to examine the effect of load on the elongation of the collagen fibrils. It was again shown that the strain within the fibrils was smaller than the overall strain placed on the tendon (42).

Functional adaptations

The extensor tendons tend to be more flattened in nature which helps to avoid subluxation of the joint whereas the flexor tendons tend to be more rounded (3). The fibrils have a unique structure which is adapted to help transmit force to the bone. They are arranged within one collagen fibre longitudinally, transversely and horizontally. The longitudinal fibres are special in that they not only run parallel to each other but also cross each other in order to form spirals. This helps transmit the energy released from the muscles to the bone and the aids the tendon in the many different aspects of movement they are exposed to including longitudinal, transversal and rotational motion. Tendons main mechanical function is to convert muscular contractions from the muscles to the bone. Tendon also has the ability to passively store and release energy converted to it from the muscles, from the joint-loading cycle, this ultimately results in more efficient

movement of the bone (4). Due to tendon’s high tensile strength (5) and viscoelastic nature the tendon also dissipates energy as heat this has positive and negative effects on the musculoskeletal system. It helps prevent damage to the muscle and bone; however the tendon giving off heat affects different aspects of the joint these will be discussed later in this essay (4). Tendon properties seem to be altered by altered by movement. It is not certain how the tendon tissue alters in response to the mechanical loading of the tendons this can lead to an increase in stiffness and could be due to a change in the cross sectional area. Tendons appear to adapt to acute exercise and loading by increasing collagen synthesis (39). Collagen fibre sliding is thought to facilitate the tendon extension. This viscoelastic property of the tendon helps it adapt for its primary role i. e. transferring force from the muscle to enable movement of the bone, whilst reducing injury caused to the tendon (43).

Tendon Injury Importance and Rehabilitation

The SDFT in the horse and the Achilles tendon in humans are both high energy storage systems which are prone to damage due to the high amount of strain they are exposed to during regular high speed locomotion (44). During healing flexor tendons require motion in order to prevent adhesion formation although excessive mechanical loading and movement can cause more harm and lead to gaps within the tendon and a weaker repair. Comparison with anterior ligament healing could provide a valuable insight which could help in the healing of tendons. Immobilisation in anterior cruciate ligament (ACL) graft led to a decrease in the amount of phagocytic macrophages that are within the structure. There was also an improved

bone-to-tendon integration (20). Deep digital flexor (DDF) tendinopathy is a common injury in horses and prognosis is poor, only 26% had an excellent outcome with the rest having and average or a poor outcome (24%). 74% of horses thus never returned to the work that they were undertaking before the injury. This makes tendon damage a significant injury for equine. A study was carried out on horses with DDF tendinopathy. They tested the healing of the tendon with MRI (magnetic resonance imaging). This imaging could help adjust the rehabilitation of the horse to hopefully aid healing. However at this moment in time it is hard to know for sure what rehabilitation is effective in aiding the tendon repair. It was found that horses that were rested and were not treated did not have a significantly worse outcome (32). It has been found that using MRI and rehabilitation combined is the most cost effective way of treating tendon injury when being compared to surgery (35).

Stress, strain curve

Whole Tendon

If stretch is continued past the stage of un-crimping the fibrils then the tendon enters a linear relationship between stress/ load and strain. When this happens the load is taken up by the collagen fibrils and the amount of stress-strain the tendon can undertake without failure is determined by the collagen fibrils properties (9). Fig. 1. Graph taken from Rees et al 2006 (9) shows all of the keys phases that a tendon goes through from beginning to stretch to eventual failure of the tendon. The ‘ Toe phase’, is where the fibrils are crimped still and are starting to be stretched out straight. The linear phase is where the collagen fibrils are being stretching within their physiological limits. The partial failure phase is where the collagen fibrils are

reaching the top of their physiological limits are getting partly damaged. The complete rupture phase is when the tendon fails as too much force/ stress is being applied and the percentage strain gets too high.

Elastic, energy-storing, adaptation

Tendons may be categorised by function as either positional or energy storage. Positional tendons experience lower stress and are used for intricate movements and in force transmission and are relatively extensible (7). Energy storage tendons store the energy transmitted to them from muscles and can release during locomotion (6), they act like springs and undergo stretch and recoil, which ensures efficient return of energy. They have to be more extensible and have a higher failure strain and a lower modulus and failure strain (24). Usually flexor tendons are high stress and energy storage tendons and extensor tendons are low stress tendons (5). Elastic modulus of the porcine digital extensor tendon 0. 76+/- 0. 12 and of the porcine digital flexor tendon 1. 66+/-0. 16 and is significant to p <0. 01 (6). Energy is lost in locomotion as kinetic and potential energy and it can be stored as elastic strain which is immediately released as elastic recoil energy. The tendons seem to act in the same way as springs (7). The human Achilles tendon is estimated to store 35% as strain energy (7). Sliding between fascicles prior to fascicle extension in SDFT might allow the SDFT to store energy and allow the large extensions required of energy-storage tendons without causing damage to the fascicles (24).

How the tendon gets damaged

In vivo strains of up to 16. 6% have been recorded for equine superficial digital flexor tendon (SDFT) during strenuous exercise; at gallop. (STEPHENS

ET AL 1989!! FIND (8). In vitro failure measurements for the SDFT range between 12. 5-17. 3%. This shows that tendons work very close to their margins (35). This suggests that they are being loaded beyond their elastic region and thus undergo micro-trauma/ damage during strenuous activity (8). Conversely the equine common digital extensor tendon (CDET) can experience maximum strains of 2. 5% in vivo (40) (and BROWN ET 2003), however their maximum strain capacity is up to 9. 7% which is relatively similar to that of energy storing tendons (40). This leads to the assumption that the energy storing tendons would have a greater demand for matrix turnover to help repair the micro-damage, formed during use, than the positional tendons which are functioning way below their threshold and still comfortably within the elastic region of the stress strain curve. Mechanically induced micro-damage (i. e. due to over-use, prolonged or repetitive) has been proposed as a mechanism prior to tendon failure/ rupture. This theory would help to explain why there is such a high incidence of injury within the SDFT and the Achilles tendon (9).

What happens when tendon is damaged?

Basic Function of Tenocyte during injury

Following injury of tendons the repair process forms tissue that is different from the original tendon tissue. The tenocyte is thought to have a major role in causing the matrix degradation, which may occur before clinical disease. The tenocyte is also thought to be the cause of the inadequate repair after injury as it helps create fibro-cartilagenous repair tissue. This subsequently leads to tendinopathy (34). More knowledge as to what mechanism causes the tenocyte to lay down this fibro-cartilagenous tissue would be useful as it

would provide a target for future treatment. Within degenerating supraspinatus and subscapularis tendons there was a reduced collagen content. The changes in collagen composition are thought to be caused by new matrix synthesis in tendinitis (38).

MMP

Overuse, sudden injuries, repeated movements and ageing can all lead to tendinopathy and eventually tendon rupture. This may or may not occur in conjunction with inflammation or tendinitis. Mechanical loading, tissue damage and the cellular response that goes with these cause changes in the expression of the matrix-degrading enzymes e. g. the collagenases and the interleukins (inflammatory cytokines) (10). Rabbit Achilles tendons were loaded for 11 weeks, 2 hours a day, 3 times a week at an average peak force of 26N. This did not affect the gross morphology or water content of the tendon. An increase in the expression of collagen type III and MMPs was seen, but there was no observable damage. The study concluded that in addition to the mechanical loading other factors may also be needed to cause damage to the tendon i. e. ageing, illness or stress (11). Most studies however are undertaken over an acute period of time and might not be representative over a longer period of time e. g. years of damage. Another study showed that tendinosis in tissues and cultures showed an increase in MMP1 and a decrease in tissue inhibitor of MMP1 (TIMP1). These conditions favour collagen degeneration and thus speed up the tendinosis and degradation, this process is also shown to increase with ageing (14, 29). After injury or tendinosis there was found to be an up-regulation of substance P, is mediated by neurokinin-1 receptor and leads to a

remodelling of the collagen. It was also found that SP stimulation results in significant increase in MMP3 levels within the collagen. This response by the MMP3 is further heightened with the exposure of cyclic loading and unloading (30). Fatigue damage was induced in a rat tendon. An up-regulation of various genes (Collagenase I, III, V, MMP3, MMP13 and TIMP1) was seen with the cyclic loading of the tendon. However at a set point when the damage is deemed too great there was in fact a down regulation of certain genes (Collagenase I, XII, MMP 2 and TINMP 3)(31). This might be an adaptive response from the body to the damage although the true function is not currently known.

Spontaneous rupture

There are numerous reasons for spontaneous tendon rupture; the main reason is thought to be due to the delicate vascular system and a critical area which has a lower blood supply. This area is thought to be where the spontaneous rupture occurs. It may be the case that in conjunction with this hypoxia, genetics, exogenous and local factors can all play a role in the pathological degeneration of the tendon (15).

Ageing, effect on tendon

As the tendons age the attachment between them and the bone degenerates, this usually requires surgery in order to aid joint mobility. However due to the reduced healing mechanisms in the elderly repairing the tendon after the surgery proves to be a problem. A study undertook an experiment on rats to see whether injection of chondrocytes and mesenchymal stem cells aids this healing. It was found that in the control group there was a spontaneous healing rate of 40%. In the chondrocyte and

mesenchymal stem cell injection group this was increased to 69%. A new attachment was formed in the treatment group but not in the controls (21). The racemization of aspartic acid has been used to calculate the age of the collagenous and non-collagenous products of the tendons. Two tendons were tested the high strain SDFT and the low strain CDET from a group of horses. The collagen half-life was found to be higher in SDFT than the CDET. The non-collagenous products the half-life was shown to be lower in the SDFT than the CDET. There was also a build-up of collagen degradation markers in the aged SDFT and this was thought to possibly be linked to the susceptibility of damage in the older horse tendons (22). Covalent crosslinking of collagen fibre increases with animal age and maturity this means that there is less loss of thermal stability than in the younger animals after overloading (23).

Hystresis

Hysteresis was recorded for two mature porcine tendons one flexor and one extensor. The flexor tendon released less heat at 9. 2+/- 2. 4 than the extensor tendon which was 17. 5+/- 5. 2 (5) p <0. 01 significant (6). Overuse tendinosis was measured in vivo at the highest peak strain group of hysteresis % was 39. 92+/-11. 44; this is higher than a lower force for a longer period of time (27). The hysteretic behaviour of tendons is thought to arise from extra cellular matrix (ECM) components the irreversible energy is dissipated in the tensile loading and unloading cycles as heat (28).

Lubrication

The principle lubricants in the tendon are hyaluronic acid, phospholipids and lubricin (glycoprotein) (16). The tendon needs to be lubricated to prevent

damage to the tendons which would otherwise be caused by friction caused by movement.

Surface lubrication

Removing hyaluronic acid from the tendon results in an increase in resistance/ friction (16, 17) whereas adding it to the tendon results in a reduction in friction (18). A study also tried to get rid of the lubricin from the tendon however there was no known protease for this process so trypsin was used this has an effect on collagen and thus is not a 100% reliable experiment to undertake. Despite this it proved that lubricin might be involved in tendon boundary lubrication (16). Kohn MD et al showed that human synoviocyte lubricin functioned as well as bovine synovial fluid lubricin when reducing friction, in vitro, in canine tendon gliding resistance. Lubricin has also been shown to reduce friction and adhesions. It has been shown that there is no species difference in the action of lubricin even though the molecular structures between species are different (26).

Lubricin within the tendon

A study was carried out into the infraspinatus of goats. Lubricin was found to be present at the bone insertion site. This concluded that lubricin might be involved in the lubrication of the interfascicular movement (25). Another study investigated the role of perifasicular lubricin in 3 different groups of mice; lubricin knockout, heterozygous and wild type mice. It was found that there was a significant difference between peak gliding resistance of the knockout and wild type mice. Individual differences were avoided by comparing the fascicular diameters of those fascicles that were used in the peak gliding resistance experiment. Here there were no significant

differences between any of the groups. There was however no significant difference of peak gliding resistance between the wild type and the heterozygous mice. This leads to the assumption that perhaps it is not the quantity of the lubricin present but the fact that it is present at all that leads to a decrease in the peak gliding resistance within the fascicle. Lubricin's role within the fascicle is still not very well studied and to get a conclusive result of its effect within the fascicle then more work still needs to be undertaken in this area (19).

Treatment

When tendon injury is detected it is difficult to treat. In humans NSAIDs have been used but these can have long term side effects. Low level laser therapy (LLLT) has been shown to significantly (P <0. 05) decrease MMP-3, MMP-9, MMP-13, TNFα and PGE2. It was then concluded that LLLT reduced tendon inflammation and could reduce tendinosis (12). LLLT has previously been used in muscular strains and it has been found that it improves muscle performance, thus this could have positive clinical applications to tendinosis treatment (13). A non-invasive measure that could be used to measure tissue motion and deformation under axial-loading is 2D elastography. A study showed that all elastographic measures of displacement and strain were consistent between repeat loading cycles of similar specimens (16). Botulism toxin A has been used in order to prevent to release of acetyl choline(Ach) from tendons this has been found to have favourable clinical results (20). The reasons why we get micro-damage are still unknown, tendon-specific stem or progenitor cells (TSPCs) have been thought to help repair the tendons. Although TSPCs are unlikely to be involved in full

regeneration of the tendon in Achilles tendon and the superficial digital flexor tendon (SDFT) it may be involved in repairing the micro-damage. The TSPCs are thought to reside within the endotenon and they are progenitor cells which can only divide a limited number of times (44). Another set of cells which have been used to treat tendon damage. Ovine amniotic epithelial cells (oAEC) has been assessed for their use as stem cells when injected into the equine SDF tendon with acute tendon lesions. oAECs were shown to help the healing process by laying down ovine collagen type I among the equine collagen fibres. It was also found that pain on palpitation related to the tendinopathy reduced after the administration of oAECs. 12/15 horses tested returned to full training and competition after this treatment (the other three horses were ruled out of the study for other reasons unrelated to the tendon injury). There was also found to be a process of advanced healing across the injured tendon. This was seen in the post mortem analysis of the tendons (36). Recently there has been the discovery of a scaffold free-tendon tissue has been produced from tendon-derived stem cells. Most biomechanical scaffolds have a poor ability to allow cell proliferation and differentiation of the tenocytes and collagen. Histology, fluorescence, imaging and immunohistology all show that engineered scaffold free tendon tissue (ESFTT) could potentially provide a new treatment for tendon damage and help aid repair and regeneration (37). Optimal repair in equine and human athletes avoids the formation of fragile scar tissue which makes the tendon weaker. A study carried out examined the effect of injecting bone marrow derived stromal stem cells into moderate and severe acute superficial digital flexor (SDF) tendon injuries. Horses were then entered into a 48 week rehabilitation period of ascending amounts of

exercise. Re-injury rate was found to be only 18% whereas when it is compared to previous studies without this treatment there is a 56% chance of re-injury (33). However this treatment is very expensive and its effectiveness is still being debated.

Conclusion and future work

There are many different possible treatments which has studies which prove them to be effective. Most are done on relatively small sample sizes or in vitro, these need to be adapted for different tendons and for different tendon conditions i. e. tendinosis or tendinitis and for a much larger population size although this may be technically difficult to do. An effective rehabilitation method needs to be found for tendon damage and to help aid repair. Also horses and humans need an effective training regime which could help to avoid the occurrence of tendon rupture or damage. I think that the most likely area of success in the short term in to find a way to prevent the tendon injury altogether as managing an injury in a tendon proves to be very tricky and the prognosis even with treatment is not very good.