Reduction of scar tissue formation in tendon using Hyaluronic Acid

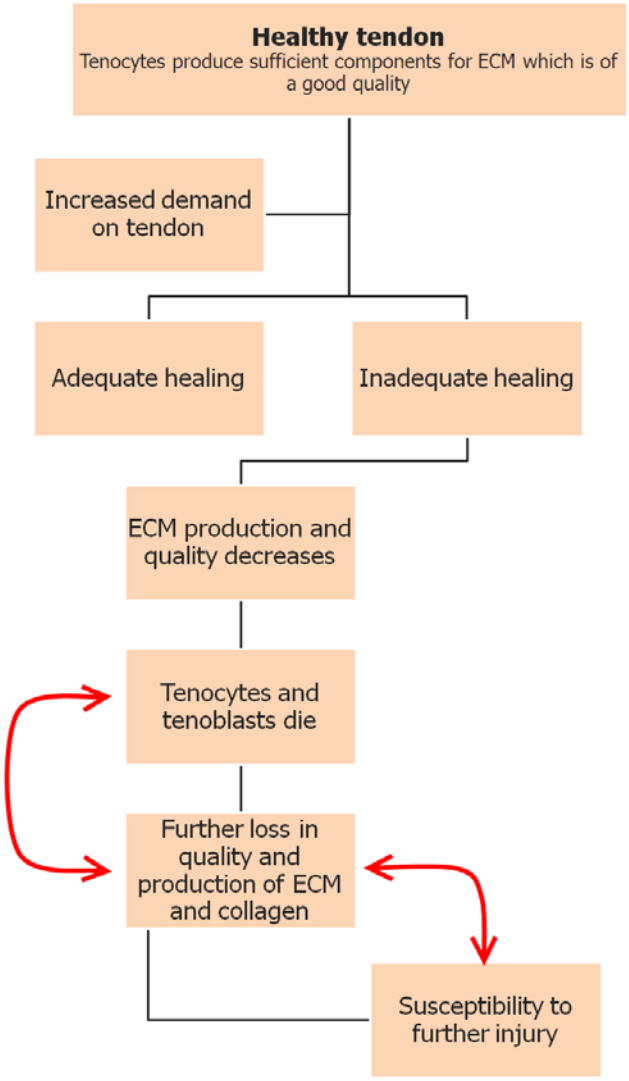
The function of normal tendon fibres function is to enable the transfer of energy from muscle to bone. After an injury, the restoration of normal tendon function requires the **re-establishment** of tendon fibres; the gliding mechanism between the tendon and its surrounding structures.

Repair of a tendon

The initial repair stage involves the formation of scar tissue which provides continuity at the injury site. Lack of mechanical stimulus on the tendon causes proliferation of scar tissue and subsequently, adhesions that are undesirable and harmful because they impede normal tendon function[1]. Repair of an injured tendon proceeds as described below[4].

1. Intrinsic healing – tenocytes (which represent the majority of resident cells in tendons) proliferate and organise the ECM.
2. Extrinsic healing – Invasion of cells from the tendon's environment (e.g. from the tendon sheath, tendosynovium and facsia).

The key to good healing is dependent on the relationship between tenocytes and ECM since tenocytes and ECM have a relationship which is almost symbiotic[5].



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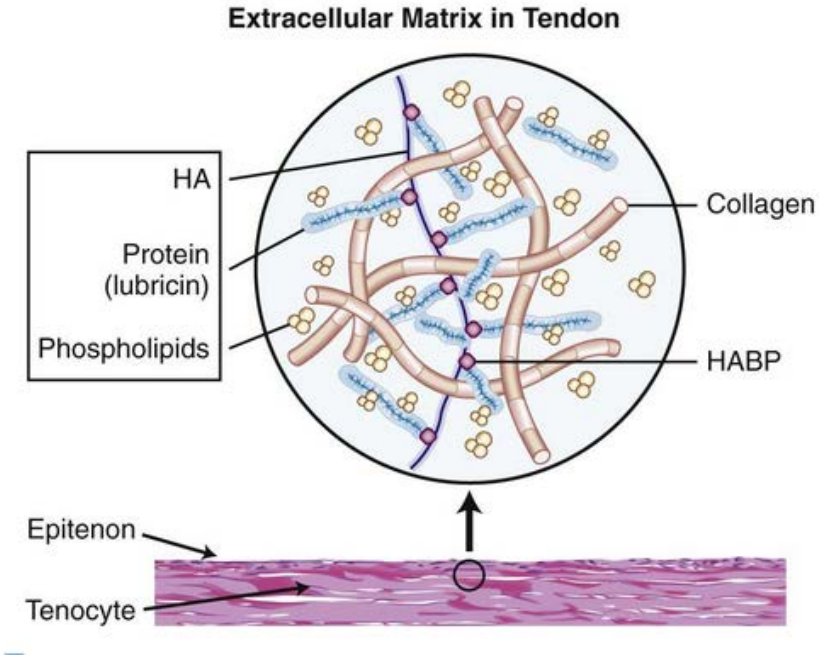
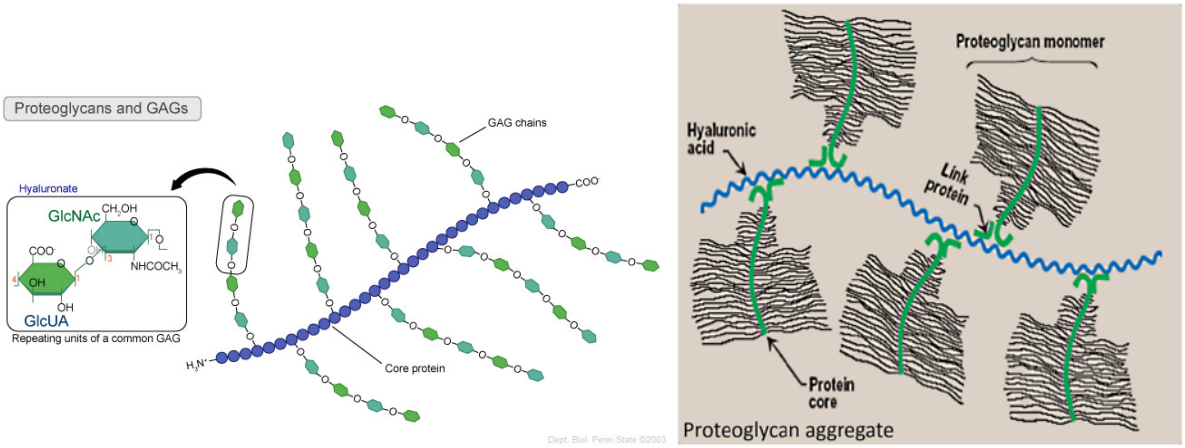
Important components of a tendon

The tendon is composed predominately of collagen fibres and rod- or spindle-shaped fibroblast-like cells (tenocytes) within a well-ordered extracellular matrix[1] (ECM). The ECM provides nutrients for tenocytes to be healthy. The healthy tenocytes are then able to produce both components necessary for a good quality of ECM and collagen for repair and maintenance of a healthy tendon[4,5].



The ECM plays an important role in wound healing as it helps in regulating growth factors and cytokines, and alters cell behaviour.

Three key components of the ECM are Hyaluronic Acid (HA), glycosaminglycans (GAGs) and proteoglycans (PGs). GAGs and PGs both contain HA[6,7].



Foetal healing versus adult healing

Foetal healing is well known for the quality of healing, often resulting in what is known as **scarless** healing. It has been demonstrated that foetal wounds have increased levels of glyosaminoglycans such as hyaluronic acid (HA) found on the cells' surfaces or in the ECM[2].

HA is found at higher levels and to be present for a longer duration in foetal wounds compared to adult wounds[2]. This increased expression is possibly due to two reasons:

1. Reduced activity of hyaluronidase in the foetus
2. Higher level of CD44 (a HA specific receptor) expressed by foetal fibroblasts compared to adult fibroblast.

In the case of foetal wound healing, the events that follow an increased level of HA result in a **scarless** healing of wounds[2] because increased levels of HA promotes both the proliferation and migration of a number of cell types and HA-rich matrices can bind growth factors and cytokines. (A more detailed discussion on foetal healing can be found at the end of this article.)

The cellular and extracellular events responsible for foetal and adult wound healing are fundamentally different. Adult healing is a fibrotic process in which scar formation replaces normal tissue as a consequence of prominent inflammation, fibroplasia and compact which eventually results in poorly organised collagen deposition[8].

As age progresses, there is a reduced turnover and poorer quality of ECM components[3]. It has also been documented that in chronic tendinopathy there is an even lower turnover of ECM components as the body does not recognise the presence of the disease[3] as well as the fact that tendons are often located in regions where blood supply is poorer. Therefore it has been suggested that with the addition of exogenous HA specifically designed for the soft tissue, since HA is an important component of the ECM, we could "alert" the body to recognise the presence of the disease.

Hence, an exogenous addition of a specifically designed biocompatible soft tissue adapted HA (STHABA™) might help in the reduction of scar tissue formation in adults.

The importance of HA in tendon healing

To conclude, it is crucial to keep in mind that HA plays an important role in:

- The ECM
    - Helps in maintaining a good quality of ECM surrounding the tendon
    - Creates and ideal environment that improves lubrication and nutrition of the cells within the tendon
- Proteoglycans
    - Fundamental structural component in proteoglycans
    - Increases the formation of proteoglycans
- Increasing the production of collagen due to the stimulation of the tenocytes and tenoblasts.
- Stimulating the conversion of collagen type III, i.e. fibrotic tissue, (unhealthy tendon, see image 1) into collagen type I (healthy tendon, see image 2).
    - Image 2 - Collagen fibre bundles are arranged in a parallel alignment with the same diameter demonstrating a healthy tendon that is able to transmit energy from bone to muscle efficiently without stress points within the tendon structure.

Image 1

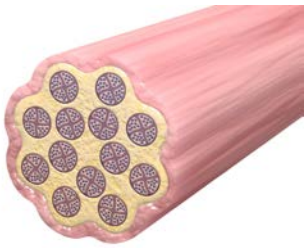


Image 2

These points suggest that if a specific Soft Tissue Biocompatible HA (STABHA) is introduced exogenously, the tendon healing process in an adult could be improved as would help achieve an environment that mimics a foetal-like healing process, eventually resulting in a scarless healing of the injured tendon.

Foetal healing in detail

Glycoproteins, collagen, and proteoglycans are integral components of the ECM, playing a role in cell adherence. Keep in mind as discussed above, the resulting difference seen in foetal versus adult wound is the amount of scar tissue. This is a result of the differences in collagen synthesis respectively. These differences include speed of deposition, variations in collagen ratios and quantity of collagen itself [2].

Studies suggest that foetal fibroblasts not only show increased collagen III expression, but that the new collagen is deposited in a fine reticular or basket weave pattern similar to uninjured skin. Some studies have suggested that the collagen deposited by foetuses is less mature with less cross-linking reducing rigidity but not affecting tensile strength[2]. This

reduced collagen cross-linking may be due to a lower expression of lysyl oxidase, which is known to play a role in both collagen cross-linking and influences collagen architecture.

A study by Chin et al. also showed that foetal fibroblasts have an increased expression of the collagen receptor DDR1 which is thought to be important for both collagen expression and organisation. Though foetuses may show increased collagen production, which might be the reason why their wounds show less scar tissue formation compared to adult wounds, they do not exhibit excessive collagen deposition, and this may be achieved through a more rapid turnover of the ECM components.

References

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