What causes changes to the Extracelluar Matrix (ECM)?

With aging or during an injury, there are changes in the ECM both qualitatively and quantitatively[1]. This affects the healing and recovery process from tendinopathy. ECMs are generally remodelled during an individual's life, but for tendons/ligaments this occurs at a slow rate. Parameters such as slow turnover, long-term post-translational modifications and extensive cell–matrix interactions are three aspects of ECM biology. Overuse and/or aging of tendon/ligament are major problems as this affects the mobility and with often slow rate of repair[1-3,4,5].

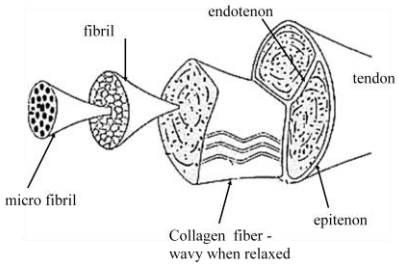
The oxygen consumption of tendons and ligaments is 7.5 times lower than that of skeletal muscles. The low metabolic rate and well-developed anaerobic energy-generation capacity are essential to carry loads and maintain tension for long periods, reducing the risk of ischemia and subsequent necrosis. However, a low metabolic rate results in slow healing after injury[4].

Injecting into a tendon – penetrating a tendon sheath

What is a tendon sheath?

The entire tendon is covered by the epitenon, a fine, loose connective tissue sheath containing the vascular, lymphatic and nerve supply. More superficially, the epitenon is surrounded by paratenon, a loose areolar connective tissue consisting essentially of type I and type III collagen fibrils, some elastic fibrils, and an inner lining of synovial cells.
Together, the paratenon and epitenon are sometimes called the peritendon[3].

The epitenon is a white fibrous sheath surrounding a tendon. The sheath helps to reduce friction and provides structural support to the tendon. The fibrous consistency of the epitenon might create a form of resistance for an injection into the sheath. The epitenon contains a few fibroblast-like cells, blood and lymphatic vessels and a nerve supply. That is why injecting **into** a tendon sheath might result in pain.



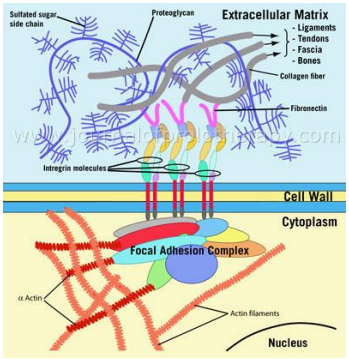
Risk of rupture

There is a certain risk of causing further damage to the tendon when injecting into its sheath as this could result in tendon rupture[6-8]. The mechanics of such rupture could be associated with the sudden increase in volume in that small area, technique of injection, etc.

Why would an injection outside tendon sheath work?

The tendon and its sheath are surrounded by ECM which provides nutrients as well as support[3]. The tendon cells are embedded in a great amount of ECM which is secreted by the cells. It consists of protein fibres embedded in an amorphous mixture of huge protein-polysaccharide ("**proteoglycan**") molecules[9,10].

The contents of the ECM are dynamic and are able to flow freely between the tendon and the tendon sheath[1,10]. Therefore, a peri-tendinous injection along the tendon sheath will be effective without causing the pain of penetrating the sheath[11]. "The 'ground substance' of extracellular matrix is an amorphous gelatinous material. It is transparent, colourless, and fills the spaces between fibres and cells. It actually consists of large molecules called glycosoaminoglycans (GAGs) which link together to form even larger molecules called proteoglycans. These molecules are very good at absorbing water, rather like a sponge, such that 90% of the extracellular matrix is made up of water. This means that the ECM is very good at resisting compressive forces."[9,12].



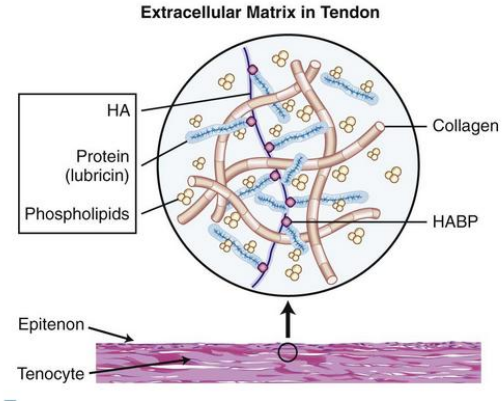
How does healing occur?

When a tendon is injured, it will naturally try to heal albeit slowly. This is known as the proliferative stage.

Proliferative Stage

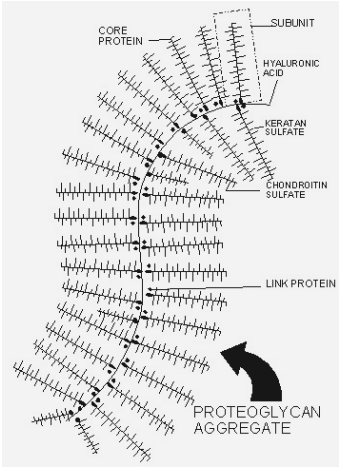
The continued recruitment of fibroblasts and their rapid proliferation at the wound site are responsible for the synthesis of collagens, **proteoglycans**, and other components of the ECM. These components are initially arranged in a random manner within the ECM, which at this point is composed largely of type III collagen[2,9]. An extensive blood vessel network is present, and the wound has a scar-like appearance. At the end of the proliferative stage, the repair tissue is highly cellular and contains relatively large amounts of water and an abundance of ECM components[2]. Collagen type-III is gradually replaced by type-I collagen as the scar tissue matures[1,11].

Collagens and **proteoglycans** are components of the ECM critical to tendinogenesis[1,12].



Proteoglycans and Hyaluronic Acid

Proteoglycans are proteins that are heavily glycosylated. The basic proteoglycan unit consists of a "core protein" with one or more covalently attached glycosaminoglycan (GAG) chain(s). The backbone of a proteoglycan aggregate is a naturally occurring polymer called **Hyaluronic Acid (HA)**[1,12].



HA can also be found in the ECM. HA plays several important organizational roles in the ECM by binding with cells and other components through specific and nonspecific interactions. HA-binding proteins are constituents of the extracellular matrix, and stabilise its integrity[13].

HA plays a fundamental role in the healing of an injured tendon.

How does STABHA work?

STABHA is a specifically manufactured soft tissue adapted biocompatible Hyaluronic Acid for soft tissue injuries (i.e. tendons and ligaments). STABHA is patented and is the only HA available for both the use in ligaments and tendons. Due to its superior purity and biocompatibility, STABHA is able to work efficiently without cause to worry for adverse effects that might be seen with other HA products.

STABHA is the supplementation of biocompatible HA to the injury site. This supplementation

ensures a "localised" delivery (via injection) to the injury site where HA is necessary in aiding the healing process.

Why more injections might be helpful?

The total normal turnover of HA in a human is 10-100mg/day[13]. Therefore, with one injection, it can be assumed that within 24 hours STABHA will be naturally eliminated by the body. Hence it is recommended for all three indications that there is a second injection of STABHA to ensure maintenance of biocompatible HA content at the injury site. It could be considered at more injections might be beneficial due to the rate of turnover during the recovery phase of the injury especially in older patients or patients with chronic tendinopathy.

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