Prolotherapy for Podiatrists - part 1, understanding dense connective tissue

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Introduction
Prolotherapy is an injection technique which may be effective for promoting repair of ligament sprains and treating the pain and joint dysfunctions caused by damaged peri-articular Dense Connective Tissues (DCT) subsequent to injury. It can also be applied to other slow-healing DCT structures such as damaged tendons and entheseal and some sources suggest it may be of value in helping to address cartilage damage in conditions such as osteoarthritis. Prolotherapy seeks to stimulate the bodies production of growth factors (also called cytokines) which are chemical messenger proteins that control the immune response to injury or damage[1,2].

The practice of prolotherapy in the foot, ankle and knee by suitably qualified podiatrists opens a broad vista of possibilities for safe extended practice in podiatric rheumatology, sports medicine and our pharmacological management of musculoskeletal pathologies.

The Institute of Chiropodists and Podiatrists has recently added prolotherapy to its list of insurable modalities, subject to the holding of a current local anaesthesia certificate, resuscitation certificate and evidence of theoretical and practical training in prolotherapy.

In the first part of this article it is proposed to examine the mechanisms of injury and repair in general and dense connective tissue. The second part will examine prolotherapy itself and its methods of application.

Anatomy and healing of Dense and other Connective Tissue
In order to subsequently discuss the mechanism of action of prolotherapy it is necessary to briefly consider the comparative anatomy and physiology of Dense and other Connective Tissue. DCT is differentiated from other body tissue by its structure and function. Structurally, it is rich in the protein collagen which makes up the bulk of its extra cellular matrix (ECM). The collagen occurs in the form of strands embedded in an amorphous ground substance. In ligaments and tendons the strands and their subsequent organisational structures lie longitudinally along the axis of tension. The basic structural unit of collagen strands is tropocollagen; this is a helical construct consisting of three polypeptide chains, each chain is composed of about a thousand amino acids, coiled around each other to form a spiral and stabilised by inter- and intrachain covalent bonds. DCT can be sub-typed as regular, irregular or elastic, ie. lung tissue is primarily elastic DCT.

Ligaments and tendons are mainly regular DCT. The tropocollagen strands are cross bonded to adjacent strands by disulphide compounds. So in a tendon, for example, the structure would be as follows: tropocollagen strands bundle together to form micro - fibrils, these bundle together to form sub - fibrils which bundle together to form fibrils, these bundle together to form fascicles which then bundle together to comprise the gross organisational structure of the tendon[3].

Ligaments and tendons have the highest collagen content of all regular DCT - up to 70% in the Achilles tendon[4]. Such animal body parts were traditionally boiled to produce glue. (Colla = glue[5]).

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growth factor beta (fibroblasts) and Transforming Growth Factors including transforming sequentially secreted by a variety of immune cells, such cytokines include; should ultimately repair the damage. There are numerous cytokines inflammatory response - release / receptor bonding events which stimulate further immune cell normally external to the cell. This process provokes additional various GF release / receptor bonding events which stimulate further immune cell activities, which results, ideally, in a structured healing cascade (the classic inflammatory response - rubor, tumor, calor, dolor and functio laesa) that should ultimately repair the damage. There are numerous cytokines sequentially secreted by a variety of immune cells, such cytokines include ; Interleukins (ie. IL-1 is secreted by macrophages and is a primary mediator of inflammation), Interferons (ie. beta interferon boosts the action of fibroblasts) and Transforming Growth Factors including transforming growth factor beta (TGF-β) which plays a pivotal role in cell production, growth and apoptosis (apoptosis is programmed cell death which is an integral component of homeostasis). Immune cells include; platelets, monocytes, neutrophils, macrophages, lymphocytes and fibroblasts(11)(12).

To simplify a complex sequence of events; the usual distinct phases of healing are; haemostasis, inflammation, proliferation and remodelling. It is important to consider that even in an ideal situation although the majority of healing should occupy around 10 days the entire process can exceed 12 months dependent upon location and circumstances, especially the maturation of collagen that has been secreted into the damaged ECM.

The situation above may be contrasted with that which can exist in DCT which may be composed of up to 70% collagen with correspondingly less room for other structural components. This can mean DCT has a low fibroblast population and relative avascularity when compared to other tissue types. When the damage shown in picture 2 occurs in DCT, although there is considerable disorganisation of the structure there may be little haemorrhage or cell damage. Thus although DCT may have its structure (and therefore function) seriously compromised and may also be very painful due to nociceptor stimulation, it is possible that there may be little in the way of a healing cascade initiated due to lack of cellular and vascular structures to provide cytokine release or production. This may account for the chronicity of peri articular DCT injuries which, in turn, can compromise joint functions due to persistent ligament laxity which allows the joint to articulate outside its physiological Range Of Movement (ROM). Aberrant joint movement can cause severe cartilage and other articular damage(13).

On the subject of the sometimes substantial pain felt from damaged ligaments, it is worth considering that ‘pain wind up syndrome’ may occur. Pain is a complex subject but nociceptive pain (Latin nocere = to injure) originates in muscles and tendons etc and the peripheral nerves themselves. This type of pain may be thought of as peripheral nerves transmitting information to the central nervous system (CNS). Neuropathic pain, on the other hand occurs where structural and/or functional nervous system adaptations have taken place subsequent to injury. Such changes can take place in either, and/or, the peripheral or CNS(14). The ‘wind up syndrome’ can occur when the dorsal horn connections of the nerves to the spinal cord become sensitised by continual stimulation. Structural changes can take place in the secondary neurons that arise in the dorsal horn (ie: the spinothalamic or spino reticular neurons). This can cause reorganisation of the connections in the dorsal horn junction and can result in hyperalgesia (increased sensitivity to pain). The originating factor of the pain does not become worse but this is often assumed to be happening by the sufferer(15).

Conventional treatments of musculoskeletal pathologies

In the western world there is an ‘epidemic’ of musculoskeletal pathology. While it is outside the remit of this document to speculate as to its cause, it is acknowledged in publications such as; The musculoskeletal services framework - a joint responsibility: doing it differently (2006 UK DoH publication). This substantial report identifies the fact that musculoskeletal pathologies account for some 30% of all GP consultations in the UK.

In primary care, the most commonly resorted to treatments for both self and prescribed use are Non-steroidal Anti Inflammatory Drugs (NSAID’s) and Steroids(16). Both of these groups of agents are aimed at suppressing an inflammatory reaction. The description of DCT injury given previously, identifies the fact that in many cases there may be no true inflammation - just pain and loss of function. This has been repeatedly documented in research articles, publications and even a 2002 editorial of the British Medical Journal(17). Thus these treatments may be of little or no value in addressing the pain or loss of function. At best they may be useless, at worst they may be fatal; Tramer et al,(18), writing in Pain (2000), identified the following in Patients > age 60 years taking prescribed NSAID’s orally for > 2 months:

1 in 5 : Endoscopic Ulcer
1 in 70: Symptomatic Ulcer
1 in 150 : Bleeding Ulcer
1 in 1200 : Death from a bleeding ulcer.

Many prescribers now recognise the potential morbidity inherent in the long term use of NSAID’s and concurrently prescribe proton pump inhibitors (PPI) such as lansoperazole and omperazole to moderate stomach acid whilst on the treatments. However, NSAID’s are primarily palliative as opposed to curative agents , as are corticosteroids, so they do not in many instances offer a cure, they simply mask the underlying problem. Sometimes the body will manage to heal the underlying problem while such masking takes place, but as we often encounter in podiatric and other branches of medicine this is in many instances not the case.

Regarding the use of steroids, these are powerful synthetic analogues of neuro-chemicals. They can be highly effective at masking and reducing inflammation when correctly used but are necessarily immunosuppressant. This feature, allied with their potential for inducing pathological tissue changes and even psychoses, in admittedly rare instances, perhaps makes it reasonable to suggest that their use should be limited to instances when they are unavoidably necessary.

It is for the foregoing reasons that prolotherapy may be a valuable alternative to consider, because it aims to proactively stimulate a cure of the underlying pathology rather than merely hide its symptoms and the available evidence highlights it as being intrinsically safe when used correctly.

Its mechanisms of action and use will be explored in part 2.
References and Bibliography

5. “Purified glue (Colla) prepared by boiling gelatious animal tissues in water, evaporating and drying the product in the air” - *King’s American Dispensatory*. Harvey Wickes Felter, M.D., and John Uri Lloyd, Phr. M., Ph.D., 1898.
17. “Most currently practising general practitioners were taught, and many still believe, that patients who present with overuse tendinitis have a largely inflammatory condition and will benefit from anti-inflammatory medication. Unfortunately this dogma is deeply entrenched. Ten of 11 readily available sports medicine texts specifically recommend non-steroidal anti-inflammatory drugs for treating painful conditions like Achilles and patellar tendinitis despite the lack of a biological rationale or clinical evidence for this approach.”
   Time to abandon the tendinitis myth. Editorial *BMJ* 2002;324:626-627