Use of autologous growth factors in aging tendon and chronic tendinopathy

Geoffroy Nourissat1,2,3, Xavier Houard1, Jeremie Sellam1,4, Delphine Duprez5, Francis Berenbaum1,4

1 UR4 Aging, Stress and Inflammation Laboratory, University Pierre and Marie Curie University, 7, quai St-Bernard, 75252 Paris cedex 5, France, 2 Clinique des Maussins, Groupe Maussin, 67 rue de romainville, 75019 Paris, France, 3 Health for Health Foundation, Paris, France, 4 Department of Rheumatology, Saint-Antoine Hospital, AP–HP, Pierre and Marie Curie University, 184, rue du Faubourg-Saint-Antoine, 75012 Paris, France, 5 CNRS, UMR7622, Pierre and Marie Curie University, 9 Quai St Bernard, Bat. C, 6E, Case 24, 75252 Paris Cedex 05, France

TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Tendon
   3.1. Normal tendon
   3.2. Aging tendon
       3.2.1. Cellular changes
       3.2.2. Matrix and molecular changes
   3.3. Chronic tendinopathy
       3.3.1. Physiopathology
       3.3.2. Histological findings
       3.3.3. Molecular findings
       3.3.4. Factors influencing tendinopathy
4. Healing process of tendon lesions and tendinopathy
5. From clinical disorders to rational use of autologous growth factors
   4.1. TGF-β
   4.2. PDGF
   5.3. VEGF
6. Clinical issues
   6.1. Injection of growth factors in chronic tendinopathy
   6.2. Injection of growth factors and aging tendon healing
7. Conclusions
8. References

1. ABSTRACT

Aging tendons or chronic tendinopathy are frequent conditions responsible for handicap in middle-aged and aging populations. Current therapies fail to relieve handicap. Medical treatment can sometimes be efficient, but surgical procedures often fail to restore tendon function. Cell therapy with platelets, based on tendon histological modifications and the capacity of such tissue to respond to growth factors, is an ever-expanding field of clinical research. In the current review, we compare the histological properties of normal tendons, aging tendons and chronic tendinopathy. We explain the natural healing process of such tendons and the rationale for using, or not, autologous growth factors. We review current clinical studies exploring the effect of concentrated autologous growth factor injection in chronic lesions and attempt to explain why, to date, all clinical studies have demonstrated no effect of such therapies.

2. INTRODUCTION

In industrialized countries, the global aging of the population is leading to an increased prevalence of age-related comorbidities that affect quality of life. Chronic tendinopathy is at the forefront of locomotor handicap and chronic pain with aging, reducing day-to-day activities and increasing sedentarism, a well-known critical risk factor for cardiovascular events. However, with aging tendons or chronic tendinopathy, current therapies fail to relieve handicap. Unfortunately, surgical procedures, the curative procedures, are not adapted to older adults because of tissue fragility. Aging tendons have lower capacities to heal when torn. Adjuvant therapies, based on autologous growth factors, are useful in acute tendinopathy or to promote healing of healthy tendons and may theoretically be a way to enhance the natural ability of the body to heal. Cell therapy with platelets, based on tendon histological modifications and the capacity of such tissue to respond to growth factors,
Growth factor use in tendon disorder

Figure 1. Structural changes of tendons through ageing and chronic tendinopathy. Normal tendon is a well-organized network of collagen fibrils. Collagen is arranged in hierarchical levels of increasing complexity, beginning with tropocollagen, a triple-helix polypeptide chain, which unites into fibrils, fibers (primary bundles), fascicles (secondary bundles), tertiary bundles and the tendon itself. The ECM is dense, with a fibrillar network of predominantly parallel-aligned collagen fibers, principally consisting of 95% type I collagen. The ECM is composed of proteoglycans, glycosaminoglycans and glycoproteins. The synthesis of the tendon ECM is under the control of two main growth factors: TGF-β and FGF. Blood supply is necessary for nutrition and healing of the tendon and is coming from two places. The first source of blood supply is the extremity of the tendon; the second source is the peripheral zone of the tendon, called the peritendon and synovial sheath. With ageing, tenocytes decrease in volume, becoming longer, slender, with an increased nucleus to cytoplasm ratio, and produce less ECM, but with increase in type I collagen volume density (mostly by less degradation). Deposit of lipid is routinely seen in ageing tendon. TGF-β receptors disappear from tenocytes membranes. Tendon blood flow decreases with increasing age. In chronic tendinopathy, histological examination shows intra-tendinous collagen degeneration with fiber disorientation and glycosaminoglycans accumulation in between thinning fibrils without inflammatory cells or inflammatory signs. Tenocytes look normal but decrease in number. Hyper vascularization is frequently found.

is an ever-expanding field of clinical research. In the current work, we compare the histological properties of normal tendons, aging tendons and chronic tendinopathy. We explain the natural healing process of such tendons and the rationale for using, or not, autologous growth factors and describe the results of current studies involving clinical data and basic knowledge.

3. TENDON

3.1. Normal tendon

The tendon is a well-organized network of collagen fibrils. Collagen is arranged in hierarchical levels of increasing complexity, beginning with tropocollagen, a triple-helix polypeptide chain, which unites into fibrils, fibers (primary bundles), fascicles (secondary bundles), tertiary bundles and the tendon itself, whose anatomy varies with location and function (Figure 1) (1). The extracellular matrix (ECM) is dense, with a fibrillar network of predominantly parallel-aligned collagen fibers, principally consisting of type I collagen (2). About 95% of collagen in tendons is type I collagen; 3% is other collagens (3) such as FACIT collagens (types XII and XIV). Besides collagen, the ECM is composed of proteoglycans, glycosaminoglycans, glycoproteins, and small leucine-rich proteoglycans (4). Proteoglycans, such as in cartilage and other tissues, play an important role in tissue hydration. In tendons, decorin, containing chondroitin sulfate, is mostly present as proteoglycans; fibromodulin and lumican, containing keratane sulfate, are less present (5). The glycoproteins fibronectin and thrombospondin are involved in tendon repair. Tenascin-C action is modulated by biomechanical stress and is involved in 3D organization of collagen, influencing the elasticity of tendons (6). Elastin, thought to make up less than 2% of the tendon dry weight, is a component of the elastic fibers responsible for the elastic properties of the ECM (7).

The synthesis of the tendon ECM is under the control of growth factors. Transforming growth factor (TGF-β) and fibroblast growth factor (FGF) signaling
pathways are the 2 main pathways identified as being involved in tendon formation during pre- and post-natal development and in adult tendon physiology (8, 9). Downstream of TGF-β, the basic helix-loop-helix transcription factor Scleraxis is a specific marker for tendon cells, regulating the expression of types I and XIV collagen and tenomodulin (10). Recently, 2 other DNA binding proteins were shown to regulate the production of type I collagen in tendons (11-13).

Cells are composed of tenoblasts and tenocytes, which are fibroblast-like cells, producing the ECM. Tenoblasts are spindle-shaped immature tenocytes (4) that have numerous cytoplasmic organelles, which reflects their very high metabolic activity. During maturation, tenoblasts become elongated and transform into tenocytes. Another small contingent of cells consists of peripheral cells around the tendon, which are vascular cells bringing blood to the tendon, and synovial cells, forming the sheath of the tendon.

Recently, tendon stem cells have been identified in mice and human tendons (14), although their recruitment and precise functions during aging and chronic tendinopathy need to be clarified.

The tendon has a particular function; during prolonged biomechanical solicitation, it has very low oxygen requirements for resistance. This adaptation to function impairs its ability to heal lesions (15). Blood supply is necessary for nutrition and healing tendons and has 2 sources: tendon extremities, at the myotendinous and osteotendinous junction; and the peripheral zone, the peritendon and synovial sheath (16, 17). From this surrounding network, which varies by tendon location and function in the body, a complex network of small vessels penetrates the tendon to provide vascularization (18, 19).

3.2. Aging tendon
3.2.1. Cellular changes
With aging, many reports note a decrease in the volume density of tenocytes and tenoblasts in association with the modification of cell phenotype. Cells become longer and slender, with an increase in nucleus-to-cytoplasm ratio until the main body of the cell is almost completely occupied by the nucleus (figure) (20). Just like for any kind of cell, with aging, cells decrease their ability to produce ECM and to respond to surrounding stimuli but do not decrease their number (21).

In general, tendon blood flow decreases with increasing age and mechanical loading (figure) (18). This decreased vascularisation is involved in the pathogenesis of several conditions such as mucoid or lipoid degeneration and hypoxic or calcifying tendinopathy (20, 22). This decreased blood flow reduces nutrition, metabolic supply and oxygen delivery (23). With aging, metabolic pathways shift from aerobic to more anaerobic energy production (23, 24).

3.2.2. Matrix and molecular changes
Studies exploring the effect of aging on biomechanical properties of tendons show inconsistent modifications. No difference is noted in many biomechanical parameters, but stiffness is probably reduced with aging (25). Modifications of the shape and mechanical properties are closely related to cross linking of collagen, considered the best biomarker of tendon aging (26).

Aging of tendons is associated with an increase in type I collagen volume density and total amount, despite the reduced capacity of aging cells to produce ECM components. This situation is explained by decreased collagen turnover and natural occurrence of deposition of lipids inside the tendon matrix with aging (27, 28). Because aging reduces the production of enzymes necessary for collagen production, spontaneous healing of tendons after injury is delayed and decreased (29).

Senescence of tendon is characterized by a decrease in hydration and mucopolysaccharide content (figure) (30), pronounced during maturation and continuing to a lesser degree during the remainder of life; as well, matrix production is genetically defined over the lifetime (31).

Independently of any tendinopathy, many health conditions frequently affecting older patients modulate biological and mechanical properties of tendons. Thyroidectomy, corticosteroid treatment, insulin, testosterone or estrogen variations affect collagen production. Global diet or a vitamin C-deficient diet decreases connective tissue maturation. (32-34). Type II diabetes or ciprofloxacin exposure can also adversely influence tendon structure with time (35, 36).

One of the main factors preventing weak natural tendon aging is physical exercise. Long-term exercise increases the tendon-tissue mass, collagen content, cross-sectional area, ultimate tensile strength, weight-to-length ratio, and load to failure (31, 37).

3.3. Chronic tendinopathy
3.3.1. Physiopathology
Chronic tendinopathies, also called tendinosis, are complex and multifactorial entities. Both intrinsic and extrinsic factors participate in the process. Excessive load, ischemia, hyperthermia, hypoxia, and oxidative stress are involved at several steps and several levels (1). These factors can act as one single factor or together to induce structural changes. They are secondary to a long history of tendinopathy and thus result from 3 elements: aging, chronic local inflammatory response of surrounding tissues, and mechanical stress (38). Apoptosis and hypoxia are associated with chronic tendinopathy, well demonstrated at the shoulder cuff (39, 40), Achilles tendon (23) or patellar tendon (41). This apoptosis is naturally programmed in tendon cells (38) but can also be induced in tenocytes by mechanical or oxidative stress (42, 43).

Tendon rupture cannot occur without an existing chronic tendinopathy (23, 44). The same experimental and clinical reports show hypervascularisation of the normally poorly vascularised tendon during degenerative tendon disease (figure). Vascular endothelial growth factor
(VEGF) might stimulate endothelial cells and vessels to invade hypovascularized tendon areas, participating in tendinopathy genesis (88). Color Doppler with ultrasonography revealed a strong association of neovascularization and tendon changes that could be correlated with pain in chronic, mid-portion Achilles tendinosis (45).

3.3.2. Histological findings
Histological examination of tendinopathy reveals disorders, intra-tendinous collagen degeneration with fiber disorientation and glycosaminoglycan accumulation between thinning fibrils without inflammatory cells or inflammatory signs (figure). Hypercellularity with scattered vascular ingrowth is seen (11). Typical pathological changes in tendinopathy include reduced numbers and rounding of tenocytes; increased content of proteoglycans, glycosaminoglycans and water (by 10%); hypervascularization (with nerve ingrowth involved in the pain); and disorganized collagen fibrils (figure). Local presence of substance-P in nerve fibers and adrenergic receptors in injured but not healthy tissue may explain symptomatic tendinopathy (46, 47). Some cases show local accumulation of tenocytes that seem to be active in some places of the tendon than in other parts without any cells (48). Glycosaminoglycan accumulation, lipid accumulation and calcification can be seen in normal tendons but are generally less severe than in tendinosis. They eventually become pathological, participating in lipoid or mucoid degeneration, fibrosis or fibrocartilaginous metaplasia, which are commonly seen during degenerative changes (49, 50). These modifications of the histologic features are frequent but not necessarily associated with clinical symptoms. All these modes of degeneration can be seen in the same tendon, even inside a partial tear. Tendon rupture is always seen on histology, mostly without any inflammation (23, 51).

3.3.3. Molecular findings
Regarding the matrix composition of tendonitis, studies report an increase in type I and III collagen content. Fibronectin, Tenasin-C, aggrecan and biglycan secretions are all increased. Levels of matrix metalloproteinase 1 (MMP-1), -2, -23, a disintegrin and metalloproteinase protein 12 (ADAM-12) and a disintegrin and metalloproteinase protein with thrombospondin motifs 2 (ADAM-TS2) and -TS3 are increased, whereas those of MMP-3, -10, -12 and -27 are decreased (2). Levels of TGF-β, insulin-like growth factor 1 (IGF-I), and VEGF are increased, along with cyclooxygenase 2, substance P and glutamate. Prostaglandin E2 (PGE2) seems to be stable during tendinopathy (2). Furthermore, levels of platelet-derived growth factor (PDGF) receptors are increased and those of TGF-β receptors decreased.

Surprisingly, few studies have explored biochemical modification in chronic tendinopathy. Shoulder cuff tear exhibits a small but real decrease in total collagen content in the tendon, with an increase in content of type III relative to type I. This collagen usually exhibits a high content of hydroxylysine (52). With time, type III collagen produced by self-repair of the tendinopathy integrates inside the tendon, which is responsible for tendon weakness and can proceed to tendon rupture (53).

3.3.4. Factors influencing tendinopathy
Tendons mostly affected by tendinopathy share some common criteria: they are highly stressed (supraspinatus or long head of the biceps, medial and lateral tendon of the elbow, patellar tendon, Achilles tendon and posterior tibialis tendon) and are often exposed to repeated strain, with poor vascularization and thus capacity to heal after repeated stress (2, 54).

Animal studies demonstrated that prolonged mechanical stimuli induce the production of inflammatory cytokines and prostaglandins (PGE2, interleukin 1β (IL-1β) and IL-6) and modulate levels of MMP-1 and MMP-3, which may mediate tendinopathy genesis, onset and chronicity (55-59). Histological analysis of human samples demonstrated a change in levels of MMP-1, MMP-2 and MMP-3 (60). Mechanical modulation of MMP levels is a natural process for the adaptation of the matrix to mechanical stress and solicitation, but excess stress induces variations in secretion of MMPs responsible for matrix degradation (60).

4. HEALING PROCESS OF TENDON LESIONS AND TENDINOPATHY

Knowledge of the healing process of tendons is based on animal models of tendon transection. Thus, we cannot be certain about the clinically relevant issues in aging tendons and chronic tendinopathy. Basically, the healing process is a succession of 3 steps. In the initial step, or inflammatory phase, cells migrate to clean the area and prepare for repair. Macrophages and neutrophils migrate to the injured area and phagocyte the necrotic tissues. The local conditions needed to allow this cell migration include vascular proliferation, vascular permeability, and angiogenesis. Tenocytes migrate to the wound, and type III collagen starts to be produced for the scar. At this early step, the collagen production is mainly initiated by the release of the local growth factor TGF-β by macrophages (61, 62).

This first step is followed and overlapped by the proliferative phase, of massive production of ECM to produce the new tendon. Local edema occurs because of high water concentration under glycosaminoglycan regulation (61, 62). This second steps stops at around 4 weeks. Tenocytes produce collagen, which is modulated by the type of tendon, biomechanical solicitation, and even the location of the tenocyte inside or outside the tendon (1).

The last step is the remodeling phase, modifying the healed tendon until the structure becomes a scarred tendon. This last step is finished around month 6. It is characterized by a local decrease in cellularity and collagen and glycosaminoglycan synthesis. It can be divided into a consolidation phase and maturation phase (63). The consolidation phase continues for up to 10 weeks. In this period, the repair tissue changes from cellular to fibrous. Tenocyte metabolism remains high, and collagen fibers become aligned in the direction of
stress. A higher proportion of type I collagen is produced during this time, thus allowing for a good-quality tendon, as in the native structure (64). After this step and up to 1 year, the scar tissue matures under local biomechanical conditions.

5. FROM CLINICAL DISORDERS TO RATIONAL USE OF AUTOLOGOUS GROWTH FACTORS

To restore organ integrity, regulation of tissues follows a regular pattern: repair of the matrix requires successive phases of cell activity, including cell recruitment, cell proliferation, matrix synthesis and matrix remodeling. Failure of any one of these activities can induce tendinopathy and explain symptomatic tendon disorders with age (65). Current clinical data report few successes of conventional medical and surgical treatment in managing disabilities related to chronic tendinopathy. Chronic tennis elbows, corresponding to an insertion tendinopathy with damaged tendons, are difficult to treat, and even surgical treatments have poor clinical outcomes (66). Tendon disorders at the shoulder are also difficult to manage. With time, tendon lesions increase, and if caught at an early stage, surgical repair is efficient; re-tears and structural failure are common in chronic lesions (67).

More than aging, those poor clinical outcomes are mostly related to tendinopathy. Many treatments have been proposed to treat chronic tendinopathy. Physiotherapy, corticosteroid injections, topical or oral nonsteroidal anti-inflammatory drugs can be used to treat symptoms. Several prospective randomized trials have involved different types of tendinopathy (Achilles, tennis elbow, shoulder). Evidence of the long-term effect of therapies are unclear (68). Study of surgery has shown, like medical treatment, a high rate of clinical failure and recurrent pain in older patients (69).

The influence of aging on poor clinical outcomes of healing is well defined. For shoulder disorders, acute tear in healthy aged tendons healed better than did chronic tendinopathy in a matched control population (70). Chronicity of the tendinopathy impairs the clinical efficiency of conventional treatment. Thus, current clinical research focuses on adjuvant therapies to increase the efficiency of conventional treatment. Thus, current clinical data report few successes of conventional medical and surgical treatment in managing disabilities related to chronic tendinopathy. Chronic tennis elbows, corresponding to an insertion tendinopathy with damaged tendons, are difficult to treat, and even surgical treatments have poor clinical outcomes (66). Tendon disorders at the shoulder are also difficult to manage. With time, tendon lesions increase, and if caught at an early stage, surgical repair is efficient; re-tears and structural failure are common in chronic lesions (67).

The influence of aging on poor clinical outcomes of healing is well defined. For shoulder disorders, acute tear in healthy aged tendons healed better than did chronic tendinopathy in a matched control population (70). Chronicity of the tendinopathy impairs the clinical efficiency of conventional treatment. Thus, current clinical research focuses on adjuvant therapies to increase the efficiency of conventional treatment. Thus, current clinical data report few successes of conventional medical and surgical treatment in managing disabilities related to chronic tendinopathy. Chronic tennis elbows, corresponding to an insertion tendinopathy with damaged tendons, are difficult to treat, and even surgical treatments have poor clinical outcomes (66). Tendon disorders at the shoulder are also difficult to manage. With time, tendon lesions increase, and if caught at an early stage, surgical repair is efficient; re-tears and structural failure are common in chronic lesions (67).

The influence of aging on poor clinical outcomes of healing is well defined. For shoulder disorders, acute tear in healthy aged tendons healed better than did chronic tendinopathy in a matched control population (70). Chronicity of the tendinopathy impairs the clinical efficiency of conventional treatment. Thus, current clinical research focuses on adjuvant therapies to increase the efficiency of conventional treatment. Thus, current clinical data report few successes of conventional medical and surgical treatment in managing disabilities related to chronic tendinopathy. Chronic tennis elbows, corresponding to an insertion tendinopathy with damaged tendons, are difficult to treat, and even surgical treatments have poor clinical outcomes (66). Tendon disorders at the shoulder are also difficult to manage. With time, tendon lesions increase, and if caught at an early stage, surgical repair is efficient; re-tears and structural failure are common in chronic lesions (67).

The influence of aging on poor clinical outcomes of healing is well defined. For shoulder disorders, acute tear in healthy aged tendons healed better than did chronic tendinopathy in a matched control population (70). Chronicity of the tendinopathy impairs the clinical efficiency of conventional treatment. Thus, current clinical research focuses on adjuvant therapies to increase the efficiency of conventional treatment. Thus, current clinical data report few successes of conventional medical and surgical treatment in managing disabilities related to chronic tendinopathy. Chronic tennis elbows, corresponding to an insertion tendinopathy with damaged tendons, are difficult to treat, and even surgical treatments have poor clinical outcomes (66). Tendon disorders at the shoulder are also difficult to manage. With time, tendon lesions increase, and if caught at an early stage, surgical repair is efficient; re-tears and structural failure are common in chronic lesions (67).

5.1. TGF-ß

TGF-ß is probably the first factor released during the healing process of the tendon. Proliferation and matrix synthesis are influenced by the presence of TGFß, but the activation or inhibition effect depends on its interaction with other growth factors (74, 75). The effect of TGF-ß is still present in aged tenocytes (76), and the effect of matrix production is greater in aged tenocytes as compared with the basic production level at each age of cells. Modifications of the concentration of TGF-ß do not modify type I collagen production in human tendons, but the production decreases greatly when PDGF is also present. In vitro, TGF-ß increases type I and III collagen production in cultured tendon fibroblasts (77). Increasing the concentration, in some cases, can be too severe and induce, in animal models, an overproduction of collagen responsible for tendon adherence (78). TGF-ß receptors are upregulated after tendon injury from days 14 to 56 of repair, but no data are available on its regulation during chronic tendinopathy or the aging process (79). In chronic tendinopathy, TGF-ß receptors were not detected in tendon tissue from patients undergoing surgery for chronic Achilles tendinopathy (65); the location of TGF-ß and TGF-ß receptors was explored, and receptors were not detected in aged tendons from a cadaver-matched population. The concentration of cells expressing TGF-ß receptors was higher in lesion sites than in normal or aged tendons. These data suggest that in chronic tendinopathy, the effectors of TGF-ß are not present, and thus the classical pathway is modified. Thus, the local concentration of this growth factor should be increased for action, or the factor may not be effective at all. TGF-ß is the only growth factor among those described above involved in tendon cell differentiation, in addition to its known role in the inflammatory response (80).

5.2. PDGF

PDGF is produced by many cells other than platelets but also by tenocytes (81). It consists of a group of dimeric polypeptide isoforms. The PDGF-B isoform influences cell division and matrix synthesis at different
Growth factor use in tendon disorder

Table 1. Prospective studies using growth factor in treatment of aging tendon disorders or chronic tendinopathy

<table>
<thead>
<tr>
<th>Disorder/Authors</th>
<th>Randomized</th>
<th>Control (injection)</th>
<th>Growth factors</th>
<th>Clinical outcomes</th>
<th>Healing difference</th>
<th>Statistically significant difference</th>
<th>Number of patients</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cuff Tear</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Castricini</td>
<td>Yes</td>
<td>No</td>
<td>PRP</td>
<td>No difference</td>
<td>No difference</td>
<td>No difference</td>
<td>88</td>
<td>99</td>
</tr>
<tr>
<td>Randelli</td>
<td>Yes</td>
<td>No</td>
<td>PRP</td>
<td>No difference</td>
<td>No difference</td>
<td>No difference</td>
<td>53</td>
<td>98</td>
</tr>
<tr>
<td>Jo</td>
<td>No</td>
<td>No</td>
<td>PRP</td>
<td>No difference</td>
<td>Yes (41% vs 27%)</td>
<td>No difference</td>
<td>38</td>
<td>100</td>
</tr>
<tr>
<td>Plantar fasciitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee</td>
<td>Yes</td>
<td>Corticosteroid</td>
<td>Autologous</td>
<td>No difference</td>
<td>No imaging</td>
<td>Yes (for corticosteroid)</td>
<td>64</td>
<td>94</td>
</tr>
<tr>
<td>Kiter</td>
<td>Yes</td>
<td>No</td>
<td>Autologous</td>
<td>No difference</td>
<td>No difference</td>
<td>No difference</td>
<td>44</td>
<td>95</td>
</tr>
<tr>
<td>Achilles tendinopathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Vos</td>
<td>Yes</td>
<td>Saline injection</td>
<td>PRP</td>
<td>No difference</td>
<td>No difference</td>
<td>No difference</td>
<td>54</td>
<td>96</td>
</tr>
</tbody>
</table>

The first 3 studies are exploring influence of PRP on bone tendon healing during rotator cuff repair. No statistically significant difference is seen regarding global clinical outcomes and healing process. The two following studies explore the effect of autologous growth factor injection (not concentrated) on chronic tendinopathy of the foot. No clinical difference is seen. The last study explores, on clinical and on imaging, the effect of concentrated growth factors (PRP) vs corticosteroid injection in chronic Achilles’s tendinopathy. No clinical or imaging difference is reported.

Stages of healing depending on the location of the tenocytes stimulated (82). PDGF is efficient only when acting with specific growth factors such as IGF-1 (83). However, more than working in the same time, the chronology of their action seems to be important. PDGF is probably the first trigger of the healing process, and IGF-1 and bFGF act later on (84). PDGF is suspected to induce the synthesis of IGF-1 and to upregulate IGF receptors (85). Because a large concentration of PDGF is necessary to reproduce the effect on IGF-1, PDGF is probably produced from surrounding platelets (86). The action of PDGF is difficult to analyze, and animal studies demonstrate its action on some specific parts of tendon and not others, which suggests a very sensitive response of some cells under local biomechanical conditions (87, 88). The effect of PDGF-β on matrix production and tendon healing is decreased by the presence of TGF-β in rabbit models (88).

5.3. VEGF

VEGFs are a family of signaling proteins involved in angiogenesis and vasculogenesis (89). During the healing process, vascularization occurs around the tendon, under the influence of cells expressing VEGF (90). VEGF concentration is increased in human Achilles tendon rupture but not in healthy tendons (91). Furthermore, because VEGF can stimulate the expression of MMPs and inhibit the expression of the tissue inhibitors of MMPs in various cell types such as fibroblasts, this growth factor might play a significant role in pathogenesis during degenerative tendon disease (92). In animal models, local injection of VEGF reduced the material properties of the Achilles tendon (92).

6. CLINICAL ISSUES

To date, no prospective study has demonstrated any efficiency of autologous growth-factor injections for chronic tendinopathy or for healing aged tendons (Table 1). The use of autologous growth factors has involved 2 methods: autologous blood injection, without any concentration, used for a long time in clinical practice; and the more recent harvesting of autologous blood, concentrating the blood outside of the patient by several devices and techniques and injecting the concentrated blood in the diseased zone. This last procedure is commonly called injecting PRP. In sports medicine, PRP has been used in 3 different kinds of trials.

One trial type involved enhancing bone tendon healing during anterior cruciate ligament reconstruction. In this case, the reconstruction involves tendons from outside the knee, without any aging phenomena on the tendon structure (the tendon is harvested outside the damaged knee, and patients are young). Thus, we will not discuss clinical outcomes.

The second group of studies involved exploring the effect of PRP and autologous growth factors directly injected at the contact site of the tendinopathy, without additional treatment.

The third group of studies involved the use of PRP to enhance the healing of aged tendons. The best example is the use of PRP in shoulder cuff repair.

6.1. Injection of growth factors in chronic tendinopathy

In a recent systematic review of published results of the effect of growth factor injections in chronic tendinopathies (93), only 2 studies were prospective randomized controlled trials: a prospective randomized trial comparing autologous blood injection versus corticosteroid injection in chronic plantar fasciitis (94) and a randomized prospective comparison of injection modalities for treating plantar heel pain (95). These 2 prospective studies did not involve PRP. Three of the 5 non-randomized studies involved use of PRP. The indication was chronic tendinopathy of the wrist extensor (tennis elbow). All review studies showed an improvement in pain and function scores but no difference in pain score.
improvement as compared with control groups. A qualitative analysis revealed level-one evidence that injections with autologous blood were not of benefit (93). The same author published results of a prospective randomized study evaluating clinical and imaging outcomes of PRP injection for chronic Achilles tendinopathies; for patients who underwent eccentric exercises, PRP injection did not result in greater improvement in pain and activity than saline injection and did not modify the vasculature or structure of the tendon (93, 96). An analysis of the 3 studies involving autologous blood (non-concentrated) for treating plantar fasciitis favored the control group but not significantly (97).

6.2. Injection of growth factors and aging tendon healing

Regarding the effect of PRP on bone tendon healing, in chronic rotator cuff repair, results of few studies have been published. A prospective randomized study showed a difference in postoperative pain with PRP injection but no difference in healing rate of the cuff (98). A larger study of 88 patients with a minimum of 16 months’ follow-up found no significant difference in cuff-healing rate (99). No clinical difference was found for 2 smaller populations, but a higher rate of healing, although not significantly, was found with PRP (100). A small study of 40 patients with massive cuff tears showed a significant difference in healing at 2-year follow-up (60% vs 20%) (101) but no clinical difference.

7. CONCLUSIONS

The present review reports what is known about histological modification of tendons during the frequently seen conditions of aging tendons and chronic tendinopathy. Because current treatment, from physiotherapy to surgery, provides disappointing results in patients with these conditions, new therapies are needed. Injection of autologous growth factor, by re-injecting harvested blood, is a classical treatment of chronic tendinopathies. Concentration of autologous growth factors seems to be a promising opportunity to enhance the natural ability of the body to heal. The rationale is to use an increased concentration of growth factors to promote healing of damaged tissues. For local modifications of tendons during aging or histological lesions induced by chronic tendinopathy, tendons seem to have weak response to growth factors in autologous growth-factor concentrations. Clinical data confirm no beneficial effect of this therapy in such disorders.

8. REFERENCES


Growth factor use in tendon disorder


Growth factor use in tendon disorder


Growth factor use in tendon disorder


Growth factor use in tendon disorder


**Abbreviations:** ADAM: a disintegrin and metalloproteinase protein; ADAM-TS: a disintegrin and metalloproteinase protein with thrombospondin motifs; ECM: extracellular matrix; FGF: fibroblast growth factor; IL: interleukin; IGF-I: insulin-like growth factor 1; L-PRP: leukocytes and platelet-rich plasma; MMP: matrix metalloproteinase; PDGF: platelet-derived growth factor; PGE2: prostaglandin E2; P-PRF: pure platelet-rich fibrin; P-PRP: pure platelet-rich plasma; PRP: platelet-rich plasma; TGF-β: transforming growth factor; VEGF: vascular endothelial growth factor

**Key Words:** Aging Tendon, Chronic Tendinopathy, Platelet-Rich Plasma, Growth Factors, Review

**Send correspondence to:** Geoffroy Nourissat, UR4 Aging, Stress and Inflammation Laboratory, University Pierre and Marie Curie University, 7, quai St-Bernard, 75252 Paris cedex 5, France. Clinique des Maussins, Groupe Maussin, 67 rue de Romainville, 75019 Paris, France, 75019, Tel: 33-1-42034737, Fax:33-1-40031357, E-mail: gnourissat@wanadoo.fr