39 Gold-Induced Autologous Cytokine Treatment in Achilles Tendinopathy

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39.1 Introduction

In the last two decades, there has been a huge amount of clinical and scientific interest in the application of regenerative-based therapies to improve treatments for acute and chronic tendon lesions. The rationale has been to improve the quality of repair in injured tendons more towards actual tendon tissue regeneration and away from scar tissue repair that theoretically leads to a superior outcome and decreased chance of reinjury. Such therapies have had a rapid rise in clinical popularity, and while having an excellent scientific rationale, clinical evidence supporting their use has frequently been inadequate (Zhou and Wang 2016).

Most described techniques have used either cell therapy (Adams et al. 2014; Bruder et al. 1994; Chong et al. 2007, 34) and/or the administration of regenerative growth factors, sourced endogenously or exogenously (Aspenberg 2007; Cummings et al. 2012; Daher et al. 2011; Jonge et al. 2011; Gholami et al. 2016). A variety of cellular products have been created, sourced most commonly from the peripheral blood, bone marrow, and/or adipose tissue. Additionally, embryonic stem cells and induced pluripotent stem cell (iPS) products have also been described for possible clinical use (Beattie et al. 2009; Prockop 1997; Tetta et al. 2012).

In 2014, the first clinical results of a new procedure using specially designed gold particles to stimulate the expansion, a myriad of protective and regenerative proteins found naturally in a

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patient's own blood (GOLDIC®) was published. In this article, the underlying research and the effects of tendon healing will be demonstrated.

39.2 GOLDIC® Procedure

The GOLDIC® procedure was developed to enhance the therapeutic effects of gold on the cellular level in combination with the advantages of an autologous blood therapy. Extensive basic science investigation was completed to establish the most effective cultivation protocol, the best substantial gold composition, and the most promising application modality for this procedure. The primary aim of this approach was to decrease the risk of side effects.

39.3 Biological Effects of GOLDIC® Procedure on the Cellular Level

In vitro testing was initially carried out to validate the effectiveness of this novel platform. Human venous blood was incubated in GOLDIC containers for 24 hours at 37 °C. Initial analyzed serum and the control serum (incubation in non-gold-enriched containers) were analyzed by a new spectroscopic method (AquaSpec).

AquaSpec™ Technology is a unique and full-automated method for the measurement of the proteomic pattern in biological fluids like serum, plasma, urine, or synovial fluid. The methodology is based on mid-infrared spectroscopy (spectral range from 4000 to 400 cm^{-1}) that is sensitive to all chemical bonds and functional groups in molecules. This technique is suitable to print a physiological snapshot of all ingredients that reflects the composition in biological fluids. Compared to many other techniques in proteomic pattern diagnostics (e.g., MALDI-TOF), the native state of the biofluid can be accurately investigated and detects the unique proteomic pattern similar to a "fingerprint." Differences in biological samples can be considered in total, and chemometric models allow for the classification and identification of compounds present. Moreover, since the spectroscopic absorbance is linear to the concentration of a compound, the kinetics and the decay of the substrate can be quantified (Fig. 39.1).

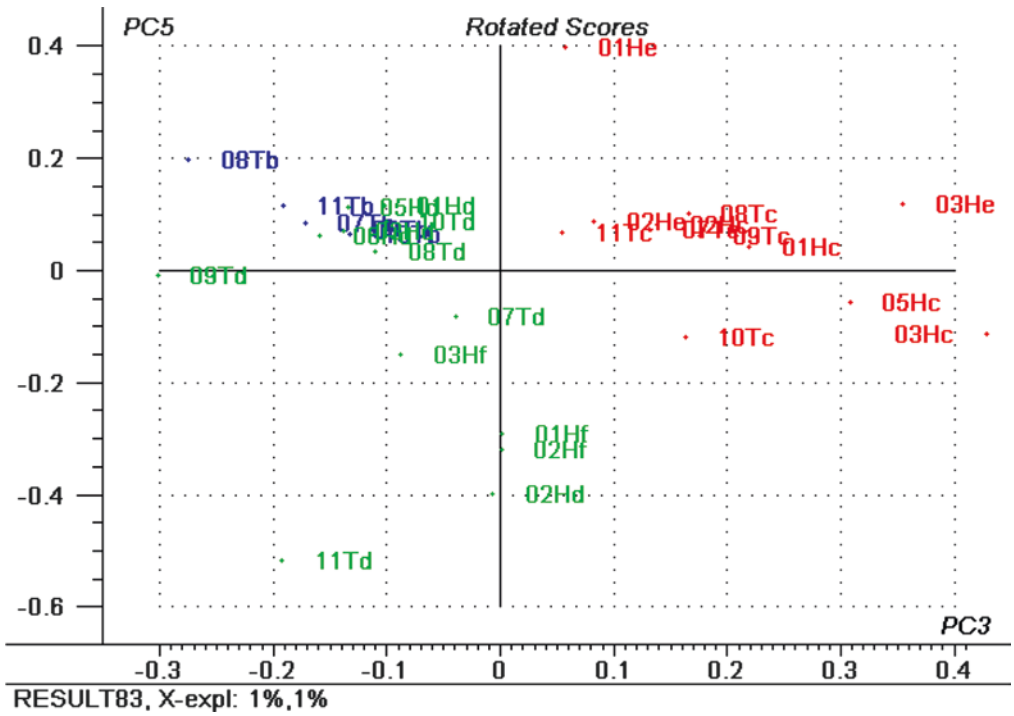

Fig. 39.1 Aqua spec analysis of 11 donors after GOLDIC® incubation: *blue*, T0; *green*, T24 GOLDIC; *red*, T24 control

Based on Aquaspec analysis, the GOLDIC® procedure leads to a significant change of protein quantities and overall composition and highlights individual differences between the different blood samples/patients.

39.4 Protein Analyses of GOLDIC®-Treated Human Serum

Using Elisa and Bioplex assays, protein levels were measured of several important cytokines/chemokines before and 24 h after treatment with the GOLDIC® procedure.

The major effect of the GOLDIC process is indicated by the significant increase of the gelsolin concentration in human serum. Gelsolin is a highly conserved, multifunctional actin-binding protein with an extracellular isoform, plasma gelsolin, for which there is not yet a clearly defined function. The secreted form of gelsolin has been implicated in a number of processes such as the extracellular actin scavenging system and the presentation of lysophosphatidic acid and other inflammatory mediators to their receptors. Additionally, gelsolin functions as a substrate for extracellular matrix-mediating enzymes (Wen et al. 1996; Spinardi and Witke 2007; Li et al. 2012) (Fig. 39.2).

Upon GOLDIC® treatment, the highest increase could be found in the following proteins, p-Gelsolin and granulocyte colony-stimulating factor (G-CSF); the following proteins were upregulated also: IL-8, macrophage chemotactic protein (MCP-3), stromal-derived protein (SDF-alpha), tumor necrosis factor-alpha (TNF-alpha), leukemia inhibitory factor (LIF), IL-10, macrophage inflammatory protein (MIP-1alpha), and MIP-1ß. Macrophage colony-stimulating factor (M-CSF), IL-15, IL-17, granulocyte-macrophage colony-stimulating factor (GM-CFS), hepatocyte growth factor (HGF), IL-2Ra, IL-12p40, chemokine (C-C motif) ligand 11 (Eotaxin/CCL11), fibroblast growth factor-basic (bFGF), and interferon-gamma (IFN-g)

GOLDIC treatment failed to induce differential expression of IL-2, IL-3, IL-4, IL-5, IL-7, IL-9, IL-13, IL-18, C-C chemokine receptor type 10 (CCR10), and interferon alpha 2 (IFN-a2).

39.5 First Clinical Results After GOLDIC® Treatment

39.5.1 Clinical Studies in Horses

The aim of the first clinical study was to determine the effectiveness of GOLDIC injections in horses with different lameness-associated diseases. In a

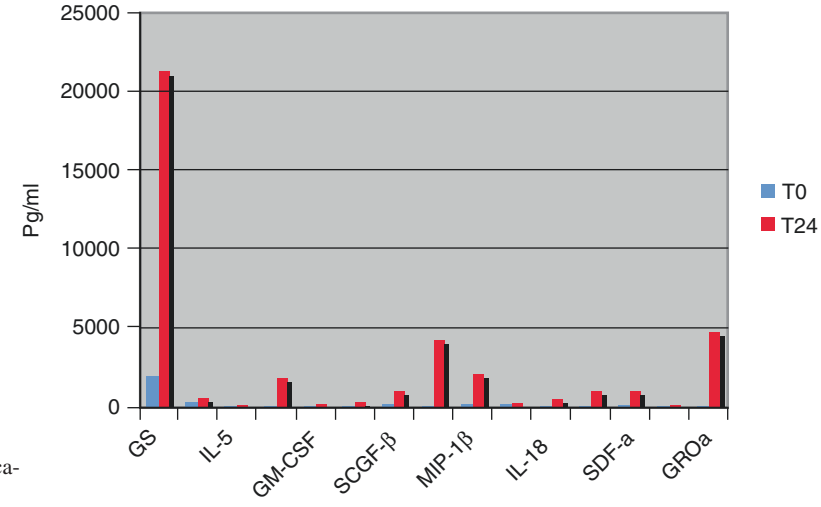

Fig. 39.2 Protein quantification in GOLDIC® serum

case series study, 36 horses (37 cases) with the clinical sign of lameness were included in this study. The causes for lameness was chondromalacia (n = 19) or soft tissue disorders (n = 18). The horses were treated by four injections of gold-induced, autologous-conditioned serum. The conditioning process included the incubation of the autologous serum with solid gold particles over 24 hours (GOLDIC procedure). Twenty-eight subjects had previously undergone therapeutic interventions, whereas nine had not. Horses were assessed for lameness using the AAEP (American Association of Equine Practitioners) grading scale (0 = no lameness, 5 = severe lameness). Swelling and/or effusion were evaluated in an equal scale between 0 and 5 (0 = no swelling/effusion, 5 = severe swelling/effusion). Scores were collected at pretreatment, and after 1, 2, and 3 weeks, and 3 and 6 months posttreatment. AAEP grading scale score was defined as the primary parameter. A P-value of less than 0.05 was considered statistically significant. In all 37 cases, a significant reduction of lameness, effusion (joint group), and swelling (soft tissue disorders group) within 3 weeks after treatment ($p < 0.05$) was found. Up to 3 and 6 months after treatment, all horses were free of symptoms. There were no major side effects noted throughout the study (Schneider and Veith 2013).

In a prospective randomized controlled, two-center clinical trial, 30 horses with arthrogenic lameness were enrolled in this study. The horses were treated by four injections of gold-induced, autologous-conditioned serum GOLDIC® (group B, n = 16) or by a single injection of corticosteroid and hyaluronic acid (group A = 14). Lameness was assessed using the AAEP grading system before and 3, 6, 12, and 36 months after treatment. The AAEP grade was the primary endpoint. Differences were considered significant at $p < 0.05$. Secondary endpoints were the results of the flexion test, degree of joint-effusion, radiographic findings, the ability to return to original performance level, and adverse effects. The GOLDIC®-treated horses showed significantly lower lameness grades at all follow-up examinations compared with the value before treatment ($p < 0.01$). In horses of group A (control HA + steroid), there was no significant decrease in lameness grade during the follow-up period. Horses of group B had significantly lower lameness grades than horses of group A at all follow-up examinations. Severe adverse events did not occur in either group.

The authors concluded that the treatment of arthrogenic lameness in horses using the gold-induced, autologous-conditioned serum (GOLDIC®) method is superior to the conventional treatment with corticosteroids and hyaluronic acid (Widmer et al. 2017).

39.5.2 Clinical Studies in Humans

In a prospective case series study, patients with chronic Achilles tendinopathy were treated with GOLDIC®. All patients received four peritendinous Achilles injections. Pain score ((VAS) visual analog scale) was evaluated at 4, 12, 24, and 52 months follow-up. MRI follow-up could be performed in five patients before and after 1 year. Adverse events were documented using MedDRA version 12.1.

39.5.2.1 Material and Methods

Nineteen patients (10 male, 9 female) were included in this study. The mean age was 44.5 years (range, 32–80). In 12 cases, the right side was affected and in 7 cases, the left side, respectively.

39.5.2.2 Statistical Analysis

Statistical analysis (Sigma Stat 3.5) was performed by an independent statistician. As normality test failed, data were analyzed by Dunn method, reporting p values with a level of >0.05 indicating significance. Data are expressed as medians and interquartile ranges.

39.5.2.3 Results

After a single four injection GOLDIC® series, the median baseline level was at 6.84 points in the VAS and dropped after 4 months down to 4.16. After 12 months, we found a further improvement in the VAS score down to 2.63. After 2 and 5 years, the VAS score further improved to 1.47

(24 months) and 1.17 (52 months), respectively. In all patient groups, a statistically significant improvement could be demonstrated at all time points compared to baseline (Figs. 39.3).

All MRIs showed fatty degeneration on the side of the tendinopathy with various sizes. One year after the treatment, all patients showed a complete regeneration of the tendon tissue. This regeneration capacity was not size or age dependent. No severe side effects could be detected (Figs. 39.4 and 39.5).

These results indicate that the treatment with GOLDIC® injections is safe and has the potential to reduce pain and increase quality of live in patients suffering under chronic Achilles tendinopathy. An impressive regenerative capacity could be demonstrated using MRI even in old patients

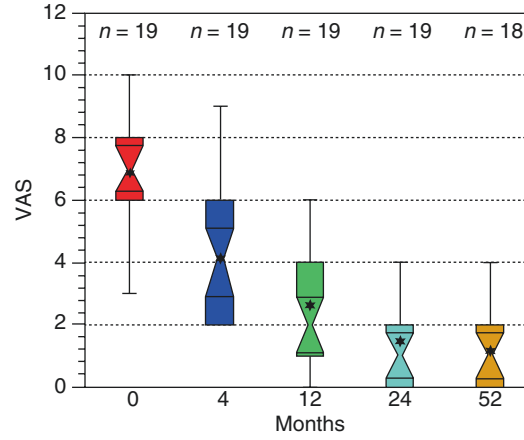

Fig. 39.3 Demonstration of the VAS score after GOLDIC® treatment. A statistically significant improvement ($p < 0.05$) compared to baseline could be demonstrated in all patient groups at all time points

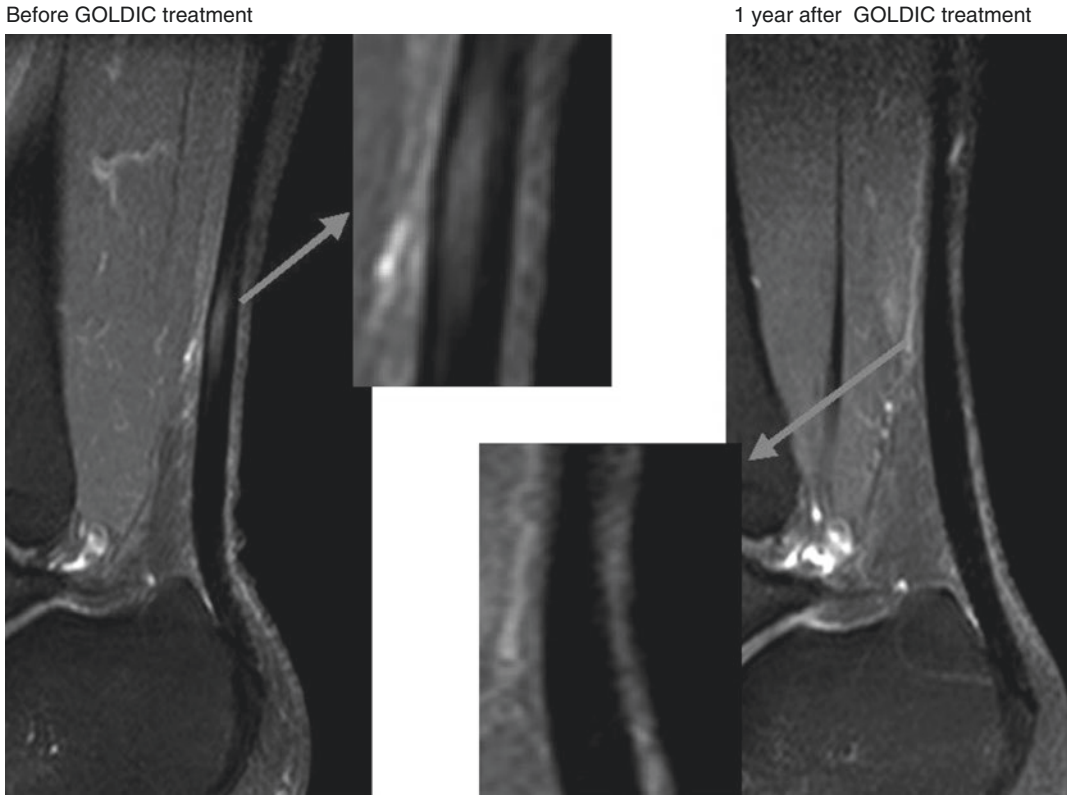

Fig. 39.4 MRI documentation of a 43-year-old female patient with chronic tendinosis of the Achilles tendon before and 1 year after GOLDIC® treatment. The necrotic tissue inside the tendon was replaced completely by original tendon tissue

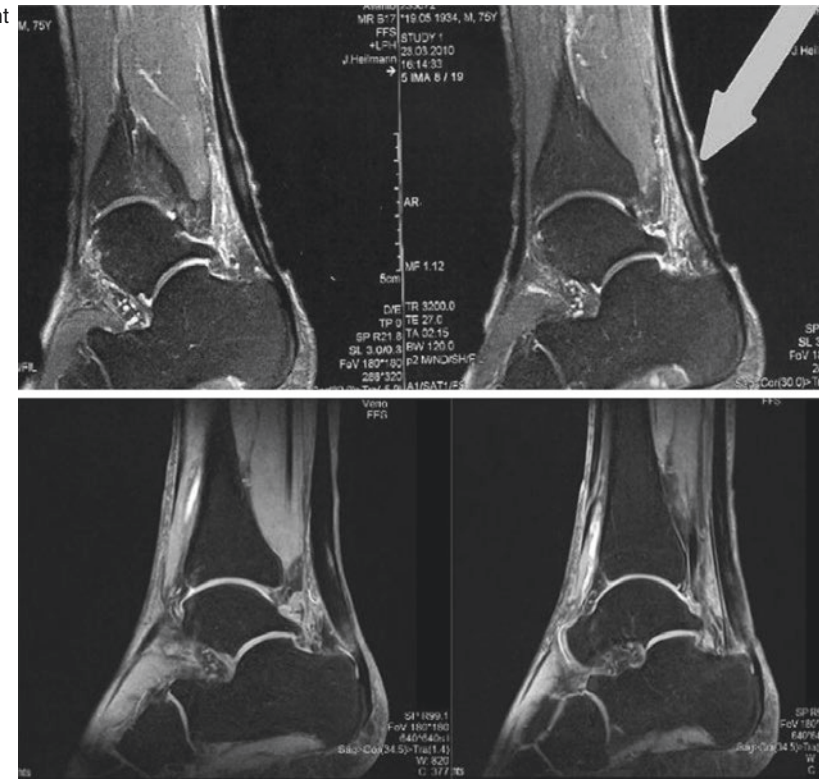

Fig. 39.5 MRI documentation of an 80-year-old male patient with chronic tendinosis and a fatty degeneration of the whole middle part of the Achilles tendon before and 1 year after GOLDIC® treatment

39.6 Discussion

While over the last two decades there has been considerable advances in the treatment of tendon disorders, new developments using cell-based and cell-free approaches are under debate. The use of these potential regenerative-acting procedures is still not fully understood, and the results are not consistent. One major problem is the inconsistency of the preparation and processing methods in the cell-based procedures like PRP. This has translated to great variability in clinical outcome of PRPs demonstrated in the literature (Gholami et al. 2016; Mlynarek et al. 2016; Zhou and Wang 2016; Filardo et al. 2016).

Currently the use of mesenchymal stromal cells (MSC) provides an exceptional alternative to conventional methods of tendinopathy treatment. Based on their proliferative potential and immunosuppressive properties, MSC are increasingly used in veterinarian and human medicine; however, the perfect conditions for an effective induction of tendon healing has not been found (Prockop 1997; Tetta et al. 2012; Huang et al. 2013).

The use of growth factors such as HGF, rhPDGF-BB, IL-6, and TGF-β in Achilles tendon repair has shown promising results (Andersen et al. 2011; Aspenberg 2007; Cui et al. 2011; Hou et al. 2009; Kashiwagi et al. 2004; Kessler et al. 2014; Kim et al. 2007; Shah et al. 2013). Bone morphogenetic proteins such as BMP-12, BMP-2, BMP-7, and BMP-14 have also shown positive results for the biological augmentation of Achilles tendon repair (Bolt et al. 2007; Dines et al. 2007; Jelinsky et al. 2011; Keller et al. 2011; Majewski et al. 2008; Rickert et al. 2005). The further investigation of these techniques in a clinical setting is warranted. Another area of great interest is the use of various scaffold material in augmentation of Achilles rupture and repair; however, these materials alone are

not enough to achieve a sufficient tendon healing. Scaffolds in combination with biologic material may prove useful in order to optimize the benefits (Adams et al. 2014; Barber et al. 2008; Chen et al. 2010; Cummings et al. 2012; Farnebo et al. 2014; Gilbert et al. 2007; Lee 2007; Lee 2008; Lohan et al. 2013; Majewski et al. 2012; Ning et al. 2012; Nirmalanandhan et al. 2008; Pietschmann et al. 2013; Tang et al. 2014; Webb et al. 2013; Wisbeck et al. 2012; Yao et al. 2011; Yin et al. 2013; Zantop et al. 2006).

The GOLDIC® procedure is a completely new approach that is based on the upregulation of several important new proteins that can directly influence the body's own regenerative processes. One of the most important proteins of the GOLDIC procedure is plasma-Gelsolin (p-GSN). p-GSN is the longest known member of a family of actin-binding proteins. p-GSN regulates the integrity of the actin cytoskeletal structure and, therefore, influences on cell migration and proliferation and even ensures cell survival. Extensive research has been done, and more than 2000 papers are available to understand the various functions of this protein in all types of injuries, inflammatory conditions, or degenerative processes. Plasma-GSN is an important protective protein, and it prevents the toxic reaction, which occurs during cell death. Moreover, p-GSN is an important factor initiating healing process. The plasma concentration of GSN decreases during acute injury and inflammation, whereas application of recombinant gelsolin to animals improves recovery after sepsis or burn injuries (Zhang et al. 2011; Li et al. 2012). Osborn et al. showed that low serum levels of GSN correlate with the presence of gelsolin-actin complexes in synovial fluids, suggesting on local consumption of GSN in the inflamed joint. Therefore, one may assume that injection of GSN in the site of injury may improve the healing process, due to stabilization of cellular proliferative activity, and maintain the structural integrity of cells.

A study using fat-derived stem cells cultured with gelsolin and gelsolin combined with nucleotides showed its influence on cell morphology and growth pattern (Marycz et al. 2014). The lack of alteration in actin and vimentin expression after treatment with gelsolin may be a very desirable feature, as these proteins play essential role in governing the solid-like viscoelastic behavior of cells, whereas instability of cytoskeleton structure could be associated with cell disintegration. Translational research is currently addressing whether replenishment of plasma gelsolin could provide an efficacious and well-tolerated therapeutic intervention in several medical conditions.

Another important protein that is upregulated during the GOLDIC procedure is granulocyte colony-stimulating factor (G-CSF). G-CSF, also known as colony-stimulating factor 3 (CSF-3), is a glycoprotein that stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream. Functionally, it is a cytokine and hormone, a type of colony-stimulating factor, and is produced by a number of different tissues. The pharmaceutical analogs of naturally occurring G-CSF are called filgrastim and lenograstim. These pharmaceuticals are used to produce and mobilize stem cells for treatment after chemotherapy. Philpott et al. (1997) showed a significant reduction in the proportion of apoptotic cells in the CD34 + population mobilized by G-CSF compared to CD34 + cells in unstimulated PB (peripheral blood), consistent with the theory that G-CSF is acting, at least in part, by suppressing apoptosis. They also found that G-CSF-mobilized CD34 + cells are less apoptotic than CD34 + cells of unstimulated normal bone marrow, indicating that G-CSF is significantly altering the survival capacity of the mobilized cells. This protein is not detectable under normal conditions in the blood and serum. During the incubation process with gold particles, we found a significant increase in the activated serum. Therefore, G-CSF can be seen as an inductor for an endogenous stem cell treatment. In conjunction with other proteins like p-GSN, this might explain the enormous regenerative capacity of the GOLDIC® procedure.

This first clinical study in humans on tendon healing showed promising clinical results. In comparison with other modern approaches like PRP and MSC transplantation, GOLDIC® is the only procedure that can upregulate p-GSN and G-CSF. These two proteins can play an important role to achieve the highest grade of regeneration. The healing capacity that could be found in the

follow-up MRIs is impressive. To our knowledge, there is no other procedure on the market that shows comparable long-lasting clinical results and a similar regenerative effect. Future comparative clinical studies have to be performed to investigate the potential of this new approach in comparison to other regenerative therapies.

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