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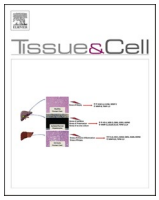

Evaluation of the tissue repair process and immunomodulatory action of Platelet-Rich Plasma (PRP) in the treatment of abdominal stretch marks

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ABSTRACT

The aims of this study were to characterize and to compare the structural alterations of collagen and elastic fibers in the abdominal stretch marks of patients submitted to intralesional and per quadrant (region close to stretch marks) Platelet-Rich Plasma (PRP) treatment, as well as, to establish the possible mechanisms of action of this treatment involving toll-like receptors (TLRs) signaling pathways and growth factors. Incisional biopsies were collected from abdominal stretch marks with a 2 mm diameter punch in female patients, at the beginning of treatment, after 6 and 12 weeks of treatment, and submitted to morphological analyzes of elastic and collagen fibers, and immunohistochemistry for TLRs signaling pathways and growth factors. Our results demonstrated PRP per quadrant treatment was most effective in reducing the area of the abdominal stretch marks, with consequent stimulation of the synthesis and remodeling of collagen and elastic fibers. Also, PRP per quadrant treatment promoted an increase in TLR2 and TLR4 immunoreactivities, with consequent increase in TNF-α, VEGF and IGF-1. Based on the current findings, PRP constitutes a promising therapeutic approach in patients with stretch marks, since it promoted modulation of inflammatory cytokines and growth factors, with consequent remodeling of extracellular matrix, culminating with tissue improvement.

1. Introduction

Stretch marks, skin patches, cellulite, esthetically, can be unpleasant and cause some disorders that hinder the well-being of individuals, especially women. Stretch marks are common skin lesions resulting from stretching or distension of the skin, due to the rupture of elastic and collagen fibers (Cordeiro and Moraes, 2009). Its structure is divided into two layers: epidermis and dermis. The epidermis is the most superficial layer of the skin, formed by stratified and avascular epithelial tissue. It rests on the dermal papillae, and right below, is the dermis, the deepest layer, formed by dense connective tissue, where defense cells, blood vessels, and a tangle of collagen and elastic fibers are found, providing support, strength and elasticity to the skin (Oakley and Patel, 2021; MacGregor and Wesley, 2021).

Stretch marks manifest as linear, atrophic plaques, initially present as slightly flattened or raised pink or red scars (*stria rubrae*) and later becoming clear, flat and permanent (*stria albae*) (Stamatas et al., 2014). Stretch marks are formed due to the rupture of the elastic fibers that support the intermediate layer of the skin, which is formed by collagen and elastin, which are responsible for the skin's tonicity and elasticity and considered by MacGregor and Wesley (2021) as an acquired integumentary atrophy occurring in different sites of the body during adolescence or pregnancy. Although the vast majority is associated with pregnancy, puberty and obesity, they are also described in association with Cushing's Syndrome, short and long-term administration of corticosteroids, in the topical or systemic form, and other drugs such as antiretroviral therapy, chemotherapy, neuroleptics, oral contraceptives and tuberculostatics (MacGregor and Wesley, 2021).

Among the theories for etiopathogenesis, one can mention inadequate skin development, especially of elastic and collagen fibers, skin stretching (Al-shandawely et al., 2021) and hormonal disturbances (Cordeiro and Moraes, 2009). The pathophysiological mechanism of

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streaks involves an inflammatory reaction and elastolysis, resulting from the release of elastase by mast cells (Mitts et al. 2005; Stamatas et al., 2014). Connective tissue in skin types with less relaxin is looser and thus has a greater risk of structural breakage of the elastic fiber during stretching, compared to skin that contains more relaxin. Similar to what occurs in keloids and scleroderma, pathologies associated with extracellular matrix expression gene disorders, and streaks can also present this change (Wang et al. 2017).

The disposition of elastic, elaunin and oxitalanic fibers in the upper dermis of human skin is well known (Sherratt, 2019). It was observed, in histological sections that in the deepest plane there are elastic fibers, which continue with the plexus of elaunin fibers, located in the papillary dermis. From this plexus depart the thinner oxitalan fibers that reach the dermo-epidermal junction. Oxithalanic fibers, also called elastofibrils or bonding fibers, are considered to belong to the elastic system and seem to be precursors of elastic and elaunin fibers. Davey (2010) divided the abdominal area into four parts and scored each part from 0 to 2 and the total score was 0–8. This scoring system considered the different *striae gravidarum* areas, but only one parameter was scored. In the study on the clinical effect of gold microneedle radio frequency, Chen et al. (2019) evaluated the elasticity of skin at *striae gravidarum* at 2 months after the last treatment. The elasticity was an objective parameter, but it could not be observed directly (Dai et al., 2021).

There are several therapeutic modalities for stretch marks such as topical medications, radiofrequency (Lu et al., 2020), pulsed light, laser (Lokhande and Mysore, 2019), microdermabrasion and carboxytherapy. However, none of them are sufficiently effective and with minimal adverse effects. On the other hand, comparative studies using non-ablative fractional lasers (LFNA) at 1410, 1540 and 1550 nm demonstrated a significant improvement in the appearance of streaks (Wang et al., 2016).

Most topical products claim to improve the appearance of stretch marks by stimulating collagen production to increase skin elasticity; however they have not demonstrated this efficiency in systematic studies (Ud-Din et al., 2016). In other direction, there is growing evidence that Platelet-Rich Plasma (PRP) injections can play an important role in the treatment of stretch marks, through the release of growth factors that induce the proliferation of fibroblasts, responsible for tissue repair (Hausauer and Humphrey, 2020).

Given the above, it can be observed that the treatment of stretch marks is considered a great challenge for professionals, and its results are not always satisfactory, and may have side effects. In this sense, it is important to study new therapeutic modalities for the treatment of stretch marks and improve the quality of life of patients. In this direction, PRP is a blood-derived product obtained by centrifugation, which, in turn, allows a high concentration of platelets - three to five times greater than the basal level - in a small portion of the plasma. This procedure allows for the degranulation of the platelet α granules and the release of several important growth factors, such as the platelet-derived growth factor isomers ([PDGF-αα] [PDGF-αβ] [PDGF-ββ]), β-factor vascular endothelial growth (VEGF), two isomers of transforming growth factor-β ([TGF-β1] [TGF-β2]) and epithelial growth factor (EGF) (Luzo et al., 2020). PRP can also release various other growth factors and active ingredients, such as platelet-rich growth factors (PRGF), concentrate growth factor (CGF) and platelet-rich fibrin matrix (PRF), among others (Durán et al., 2020; Luzo et al., 2020).

The term PRP was created by hematologists in the 1970 s to describe plasma with platelet levels higher than peripheral blood. In addition to the hemostatic properties capable of inducing fibrin generation, new properties of PRP were discovered in recent years; among them are its anti-inflammatory and immunomodulatory properties, as well as its cell proliferation capacity (Durán et al., 2020; Luzo et al., 2020). Platelets are cellular fragments (approximate diameter = 2 μm) of megakaryocytes produced in the bone marrow (Durán et al., 2020; Luzo et al., 2020). They have large amounts of bioactive proteins that play a key role in tissue healing or hemostasis (Ali et al., 2015; Durán et al., 2020). Growth Factors (FCs) are essential for wound healing processes; as well as blood proteins such as fibronectin, fibrin and vitronectin, known as cell adhesion molecules (Durán et al., 2020).

The method used to prepare PRP involves centrifugation, which can induce platelet activation, releasing PRGF into the plasma, and the disposal of this portion with the PRGF, can promote a decrease in the effectiveness of PRP. Several methods of obtaining the PRP are available, but caution is required (Perez et al., 2013; Durán et al., 2020). Hoeferlin et al. (2014) demonstrate that the peptide-free lipid fraction of PRP can be pro-migratory and pro-mitogenic, and crucial to overcoming the arrest of proliferative growth of chronic wound fluid related to adult human dermal fibroblasts.

PRP associated to ascorbic acid have been used for the treatment of *striae distensae* (SD) with promising results (Ibrahim et al., 2015; Hersant et al., 2016). Ibrahim et al. (2015) performed a prospective study on 68 patients, complaining of SD (*albae* and *rubrae*). Each patient underwent two to six PRP injection sessions at 2-week interval. Authors observed a clinical improvement in SD in all the patients with an increase in dermis collagen and elastic fibers at the end of treatment.

Very recently, a study analyzed stretch marks-derived fibroblasts (SMF), the differences between *striae rubrae* (SR)- and *striae albae* (SA)-derived fibroblasts (SRF, SAF), testing two treatments in vitro (*ex-vivo*; conventional abdominoplasty procedure) (sodium ascorbate and PRP) on SAF. Significant increase in alpha smooth muscle actin (SMA) was observed in SRF. SAF treated with PRP and sodium ascorbate showed a resumption of their metabolic activity by an increase in collagen type I production and cell proliferation. Data showed that a biologically mediated improvement in SMF metabolic activity is possible (La Padula et al., 2021).

Platelets contribute to immune regulation (Kanikarla-Marie et al., 2018), participating in adaptive and innate immune functions (Ali et al., 2015). The role of the innate immune system is to identify, nonspecifically, invading microorganisms or tissue fragments and encourage their elimination (Newton and Dixit, 2012). Interestingly, platelets also express several immunomodulatory receptor molecules on their surface and in the cytoplasm, such as P-selectin, transmembrane protein ligand CD40 (CD40L), cytokines (e.g., IL-1β, TGF-β) and platelet-specific toll-like receptors (TLRs) (Cognasse et al., 2019). Therefore, platelets can interact with various immune cells (Lood et al., 2016; Clarck et al., 2016).

Since so far there is not fully effective and minimally invasive treatment for stretch marks caused by the process of mechanical distension or by the use of medications, new therapeutic approaches are needed. Then, the aims of this study were to characterize and to compare the structural alterations of collagen and elastic fibers in the abdominal stretch marks of patients submitted to intralesional and per quadrant (region close to stretch marks) PRP treatment, as well as, to establish the possible mechanisms of action of this treatment involving immune system receptors (TLRs) signaling pathways and growth factors.

2. Materials and methods

We used tissue samples of abdominal stretch marks from 12 patients from the *Hospital Municipal "Dr. Mario Gatti"*, Campinas-SP, Brazil. This was a basic, prospective and randomized study, through clinical and histopathological follow-up. The patients were randomly divided into four experimental groups (n = 3 patients per group): **a) Group 1:** patients received 1 weekly intralesional application (along the entire stretch mark) of 4 mL physiological solution 0,9% over 12 weeks; **b) Group 2:** patients received 1 weekly intralesional application (along the entire stretch mark) of 4 mL PRP over 12 weeks; **c) Group 3:** patients received 1 weekly subcutaneous application (region near the stretch marks) of 4 mL physiological solution 0.9% over 12 weeks; **d) Group 4:** patients received 1 weekly subcutaneous application (region near the stretch marks) of 4 mL PRP over 12 weeks.

The patients were followed up as outpatients for 12 weeks. The

abdominal region of each patient in the study was divided into quadrants and the lower left quadrant (infraumbilical region) was used for the analysis of abdominal stretch marks. All patients involved underwent incisional biopsy of the abdominal stretch marks with 2 mm punch at three different moments: before the beginning of the study, 6 weeks after the beginning of applications, and at 12 weeks, coinciding with the end of treatment.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee. This study was approved by the Research Ethics Committee from University of Campinas (***CAAE number: 69189017.5.0000.5404***). Each subject provided written informed consent before participating in the study.

2.1. Inclusion criteria

Female patients, Caucasian, aged between 19 and 35 years old, postadolescent, post-gestational, overweight, and with a body mass index (BMI) between 35 and 38.

2.2. Exclusion criteria

African American/Black patients, due to the increased risk of occurrence of keloids or hypertrophic scars during treatment; Asian patients; above 35 years of age; adolescents using growth hormone (GH), patients with diabetes mellitus (DM), types 1 and 2, patients with autoimmune diseases or using corticotherapy.

2.3. Platelet-Rich Plasma (PRP) preparation and treatment

The peripheral blood from all patients 6 patients (Groups 2 and 4) was collected to obtain PRP according to protocol described by Amable et al. (2013). Each patient did not use drugs within 72 h prior to collection in order to avoid the influence of drugs on the individual's platelet production. A total of 10 mL of blood was collected and transferred it to specific collection tubes (ACD tubes) containing 3.2% sodium citrate anticoagulant at a ratio of 9:1 respectively. After, the blood was centrifuged at 300 g for 5 min at 20 °C (Routine 380 R, Hettich Zentrifugen, Munich, Germany). After centrifugation, it was observed the separation of the blood into three layers: top, middle and bottom. The middle layer ("buffy coat"), which has the highest concentration in platelets, was collected with a 200 μL micropipette and transferred to a sterile 15 mL Falcon-type centrifuge tube, which was centrifuged at 700 g for 17 min at 20 °C (Amable et al., 2013). From the final volume obtained, around 80% was aspirated with a sterile pipette and disposed, since it is the Platelet-Poor Plasma (PPP). The remaining 20%, which constitute the PRP (platelet-rich plasma) were slowly homogenized with a sterile Pasteur pipette and aliquoted in a 2.0 mL eppendorf tube and kept on ice until the moment of administration to the patients.

2.4. Macroscopic and histopathological analyses

We measured the dimensions of stretch marks (length and thickness) at the beginning, middle, and end of treatment, with the aid of a digital pachymeter (Mitutoyo Corporation, Japan). These measurements were taken in millimeters and tabulated according to the period of measurement. From the measurements of length and width, we obtained the areas of the stretch marks in mm^2.

For histopathological analysis, samples of stretch marks (n = 3 per group) were fixed in 10% buffered formalin for 12 h and then washed in 70% ethanol, dehydrated in an increasing series of alcohols, cleared in xylene for 2 h and embedded in plastic polymer (Paraplast Plus, St. Louis, MO, USA). Subsequently, 5-μm thick sections were cut on a rotary microtome (Slee CUT5062 RM 2165; Slee Mainz, Mainz, Germany), stained with hematoxylin-eosin and photographed with a Leica DM2500 photomicroscope (DM2500 Leica, Munich, Germany).

2.5. Quantitative evaluation of collagen and elastic fibers

The same samples used in the histopathological analysis were submitted to quantitative evaluation of collagen and elastic fibers. For each sample, 10 sections with a thickness of 5 μm were obtained. Half of the sections were stained using Weigert's iron hematoxylin and Weigert's resorcin-fuchsin, allowing the visualization of the elastin system components. The other half was stained by Masson's trichrome, which highlights the collagen fibers. Images from stretch marks were captured using a photomicroscope (DM2500 Leica, Munich, Germany) and morphometric analyses were performed using Image ProPlus 6.0 software. The elastic fibers ratio was estimated by counting 1000 points (per patient), projected onto random fields at 400x magnification on Weigert-stained slides. Collagen fiber height was obtained by randomly measuring 10 sections in random fields per patient on the slides stained by Masson's trichrome.

2.6. Immunohistochemistry of TLRs signaling pathway (TLR2, TLR4, MyD88, TRIF, IRF3 and IFN-γ) and growth factors (VEGF, IGF-1)

The same tissue samples (n = 3 per group) used for histopathological analysis were used for immunolabelings. The samples were cut into 5-μm thick sections and antigen was retrieved by boiling the sections in a 10 mM citrate buffer, pH 6.0, three times for 5 min each in a conventional microwave oven. The sections were subsequently incubated in peroxidase blocker (EasyPath EP12–20523, Sao Paulo, Brazil) with subsequent incubation in 5% Goat Serum blocking solution (EP-12–20532) for 10 min at room temperature. The primary rabbit polyclonal anti-TLR2 (RRID:AB_2303458; 1:100), mouse monoclonal anti-TLR4 (RRID:AB_10611320; 1:100), rabbit polyclonal anti-MyD88 (RRID:AB_2146724; 1:100), rabbit polyclonal anti-TRIF (RRID: AB_2255834; 1:50), rabbit polyclonal anti-IRF3 (RRID:AB_218160; 1:50), mouse monoclonal anti-IFN-γ (RRID:AB_315493; 1:50) rabbit polyclonal anti-VEGF (RRID:AB_2212642; 1:100) and mouse monoclonal anti-IGF-1 (RRID: AB_1124693) were diluted in 1% BSA and applied to the sections overnight at 4 °C. Bound antibody was detected with an EasyLink One kit (EasyPath EP-12–20504, Sao Paulo, Brazil). The sections were lightly counterstained with Harris' hematoxylin and photographed with a photomicroscope (DM2500 Leica).

In order to evaluate the intensity of antigen immunoreactivity from regions of the biopsied stretch marks, the percentage of positive-staining cells and/or fibrillar elements was examined in ten fields for each antibody under high magnification (400 ×). The Image J software (https://imagej.nih.gov/ij/) was employed for this analysis. We evaluated quantitative data in two ways: Total Immunoreactivity and Intensity of Immunoreactivity. Total immunoreactivity was obtained as the result of the negative percentage of cells and/or fibrillar elements of the extracellular matrix for a given antibody subtracted from 100%, i.e., the values represent the total number of cells and/or fibrillar elements of the extracellular matrix in the field that showed immunoreaction for the antibody evaluated. The analysis of the intensity of immunoreactivity was performed by categorizing the occurring immunoreactivity in cells and/or fibrillar elements of the extracellular matrix by intensity criteria. The categories were defined in the Image J software on a scale of 0–3, and expressed as: 0: (no immunoreactivity), 0% of positive cells and/or fibrillar elements of the extracellular matrix; 1: (weak immunoreactivity), 1 – 35% of positive cells and/or fibrillar elements of the extracellular matrix; 2: (moderate immunoreactivity), 36 – 70% of positive cells and/or fibrillary elements of the extracellular matrix; and 3: (intense immunoreactivity), > 70% of positive cells and/or fibrillar elements of the extracellular matrix (Reis et al., 2022).

2.7. Statistical analyses

Quantitative results were expressed as the mean ± standard deviation and evaluated it using the ANOVA parametric analysis of variance,

complemented with Tukey's test, when they presented normality and homoscedasticity. In cases of absence of normality, the Kruskal-Wallis non-parametric analysis of variance was used, complemented with the Dunn's test or the Student-Newman-Keuls test. We used the software GraphPad Prism, version 7.00 (GraphPad Software Inc., San Diego, California, USA) and BioEstat 5.0 (Sociedade Civil Mamiraua/CNPq, Belem, PA, Brazil). Analyses were performed with a statistical significance level of 5% ($p < 0.05$).

Immunohistochemistry results were compared with a proportion test. The difference between the two proportions was tested using test of proportion with a type-I error of 5%.

3. Results

3.1. PRP therapy was safe and reduced the area of abdominal stretch marks

The PRP treatment presented a relatively low operational cost since it, as an autologous product, showed highly satisfactory results. So far, no other adverse effects have been observed, except for slight pain during application and local erythema.

The measurements of the stretch marks were compared between the groups of patients who received treatment with PRP and saline solution. The first measurement was taken before treatment, and the second at the end of treatment (Table 1).

Regarding the patients who received intralesional PRP treatment, there was a 53.66% reduction in the area (mm^2) of stretch marks when comparing the initial and final measurements for PRP therapy per quadrant (Fig. 1**A-B**). However, statistically, this result was not significant ($p = 0.1625$), which can be explained by the small number of samples ($n = 3$).

The images in Fig. 2 are representative of the PRP, intralesional and per quadrant treatment groups, at pre- and post-treatment.

The histopathological analysis of striae-stained showed disruption of dermal fibers and structural disarray of collagen fibers in groups that received saline, both intralesional (Group 1) and in the quadrant (Group 3). However, the groups that received intralesional PRP treatment (Group 2) and in the quadrant (Group 4) showed a more organized structural arrangement of collagen fibers when compared to the groups that received physiological solution 0.9%. The results can be seen in Fig. 3.

Table 1
Averages of the measurements (length, width, and area) of abdominal stretch marks at the beginning and the end of the intralesional treatment and per quadrant treatments with saline.

Application type	Treatment	Measurements	Length (mm)	Width (mm)	Area (mm^2)
Intralesional	**Physiological solution 0.9% (Group 1)**	**Initial**	47.7 ± 5.7	2.7 ± 0.8	131.3 ± 41.3
		Final	47.7 ± 5.7	2.8 ± 0.7	134.1 ± 37.8
	PRP (Group 2)	**Initial**	36.0 ± 8.2	3.5 ± 1.1	147.0 ± 97.7
		Final	30.7 ± 21.1	1.5 ± 0.8	60.7 ± 42.2
Per quadrant	**Physiological solution 0.9% (Group 3)**	**Initial**	40.3 ± 4.4	5.4 ± 0.1	269.3 ± 30.1
		Final	33.2 ± 6.0	6.2 ± 0.2	275.3 ± 6.7
	PRP (GRUPO 4)	**Initial**	25.4 ± 0.9	4,0 ± 0.6	104,2 ± 8.7
		Final	20,6 ± 1,2	2,2 ± 0,3	48,3 ± 6,2

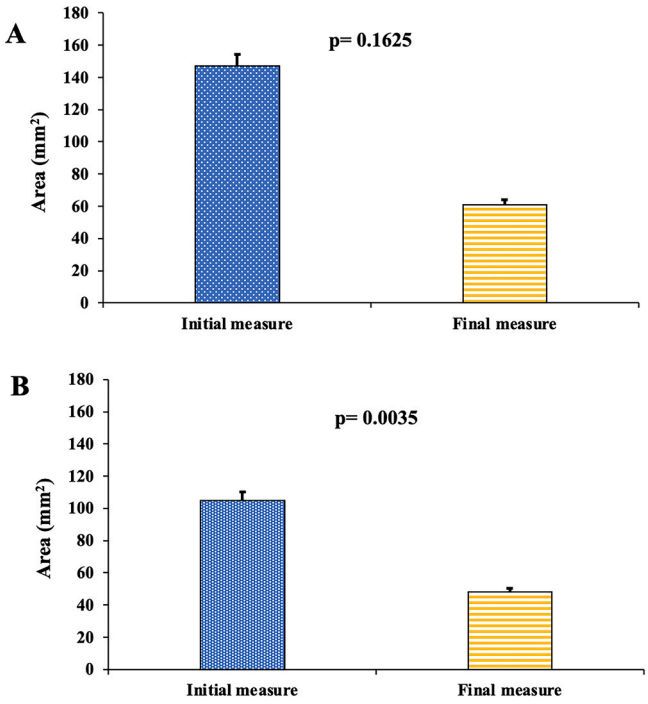

Fig. 1. : Comparison of the average area (mm^2) between the initial and final measurements of the stretch marks treated with intralesional (A) and per quadrant (B) PRP.

3.2. PRP treatment per quadrant stimulated the synthesis of collagen and elastic fibers

Histomorphometric analyses demonstrated that the group treated with PRP per quadrant showed an increase in the height of collagen fibers after 6 and 12 weeks of treatment, suggesting increased synthesis of these fibers. Histological analysis also showed a greater organization of these fibers after 6 and 12 weeks of treatment. The ratio of elastic fibers also showed an increase when compared to the beginning of treatment, suggesting that PRP treatment also stimulated the synthesis of this type of fiber.

Nevertheless, intralesional PRP treatment promoted the opposite effect, decreasing the height of collagen fibers, as well as the ratio of elastic fibers, suggesting less synthesis of these fibers after intralesional application. The results described above are confirmed by Table 2 analysis, which shows the measures of collagen fibers and the proportions of elastic fibers in each group and by treatment, and Figs. 4 and 5 confirm the organization of these fibers.

3.3. PRP therapy modulated tlrs 2 and 4 signaling pathways, leading to increased TNF-α immunoreactivity

TLR2, TLR4, IRF3, IFN-γ immunoreactivities were moderate in both intralesional and per quadrant physiological solution 0.9% treatment (Figs. 6**A, B, C, D,** 7**A, B, C, D;** Table 3). In the intralesional PRP group, TLR2 immunoreactivities were weak in both at the beginning and after 6 weeks of treatment (Fig. 6**F, K;** Table 3). After 12 weeks of PRP intralesional treatment, TLR2 immunoreactivities were significantly moderate (Fig. 6**P;** Table 3). Regarding the PRP per quadrant group, TLR2 immunoreactivities were weak at the beginning (Fig. 7**F;** Table 3), moderate after 6 weeks (Fig. 7**K;** Table 3) and significantly intense at after 12 weeks (final) of treatment (Fig. 7**P;** Table 3).

TLR4 immunoreactivities were moderate at the beginning and after 6 weeks of PRP intralesional treatment (Fig. 6**G, L;** Table 3). After 12

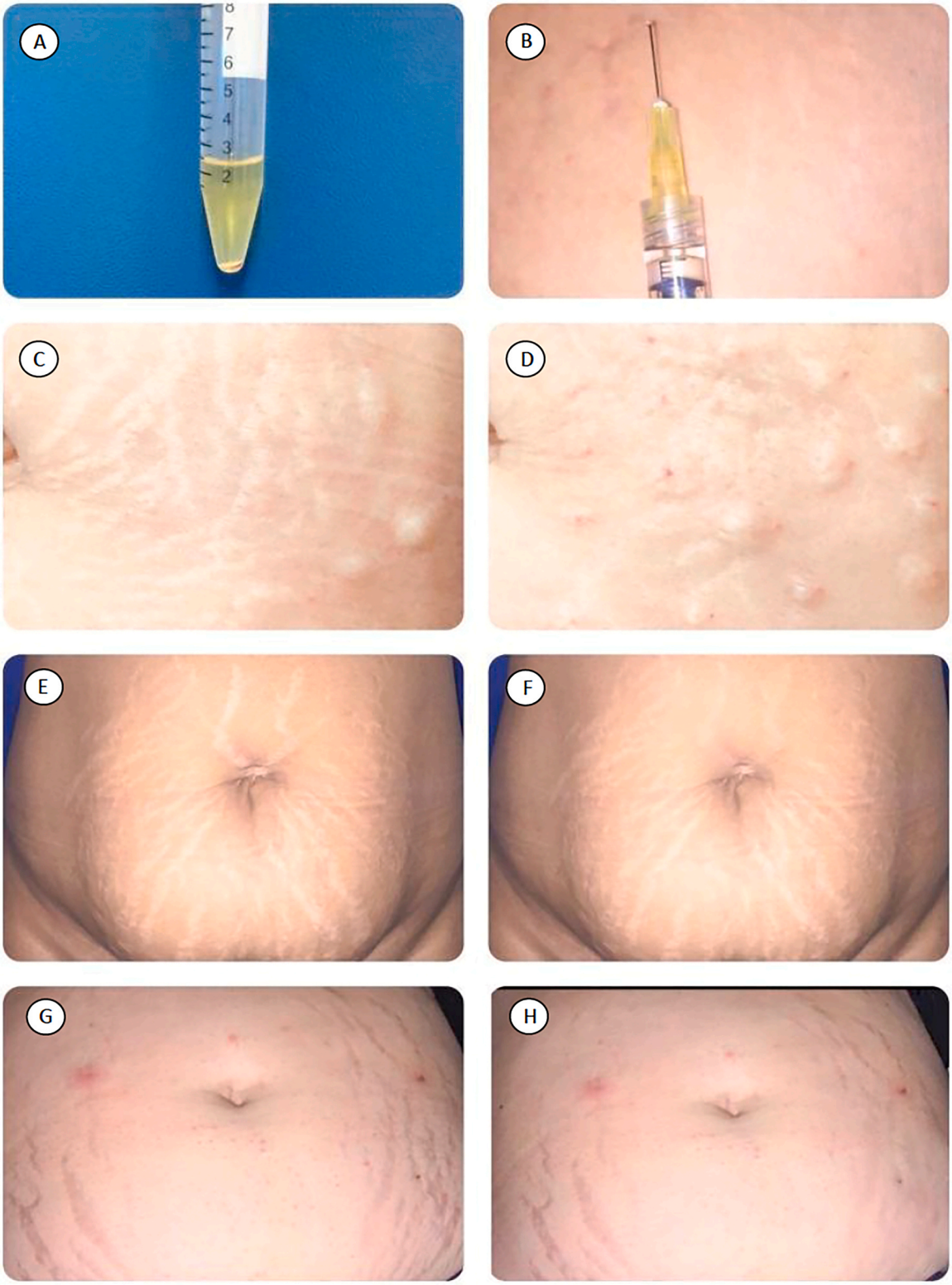

Fig. 2. (A – H): Representative images of PRP-treated patients in Groups 2 and 4. PRP preparation, after centrifugation (A). PRP in the syringe (B) before intralesional and per quadrant applications. Immediate intralesional (C) and per quadrant (D) applications. Before (E) and after 12 weeks (F) of intralesional PRP treatment. Before (G) and after 12 weeks (H) of PRP application per quadrant.

weeks of PRP intralesional treatment, TLR4 immunoreactivities were significantly intense (Fig. 6**Q;** Table 3). In the PRP per quadrant group, TLR4 immunoreactivities were weak at the beginning (Fig. 7**G;** Table 3) and significantly intense after 6 and 12 (final) weeks of treatment (Fig. 7**L, Q;** Table 3).

IRF3 (Fig. 6**H, M, R,** 7**H, M, R**) and IFN-γ (Figs. 6**I, N, S,** 7**I, N, S**) immunoreactivities were moderate (Table 3) in both intralesional and per quadrant PRP groups.

Weak TNF-α immunoreactivities (Table 3) were found in the groups of patients receiving intralesional (Fig. 6**E**) and per quadrant (Fig. 7**E**)

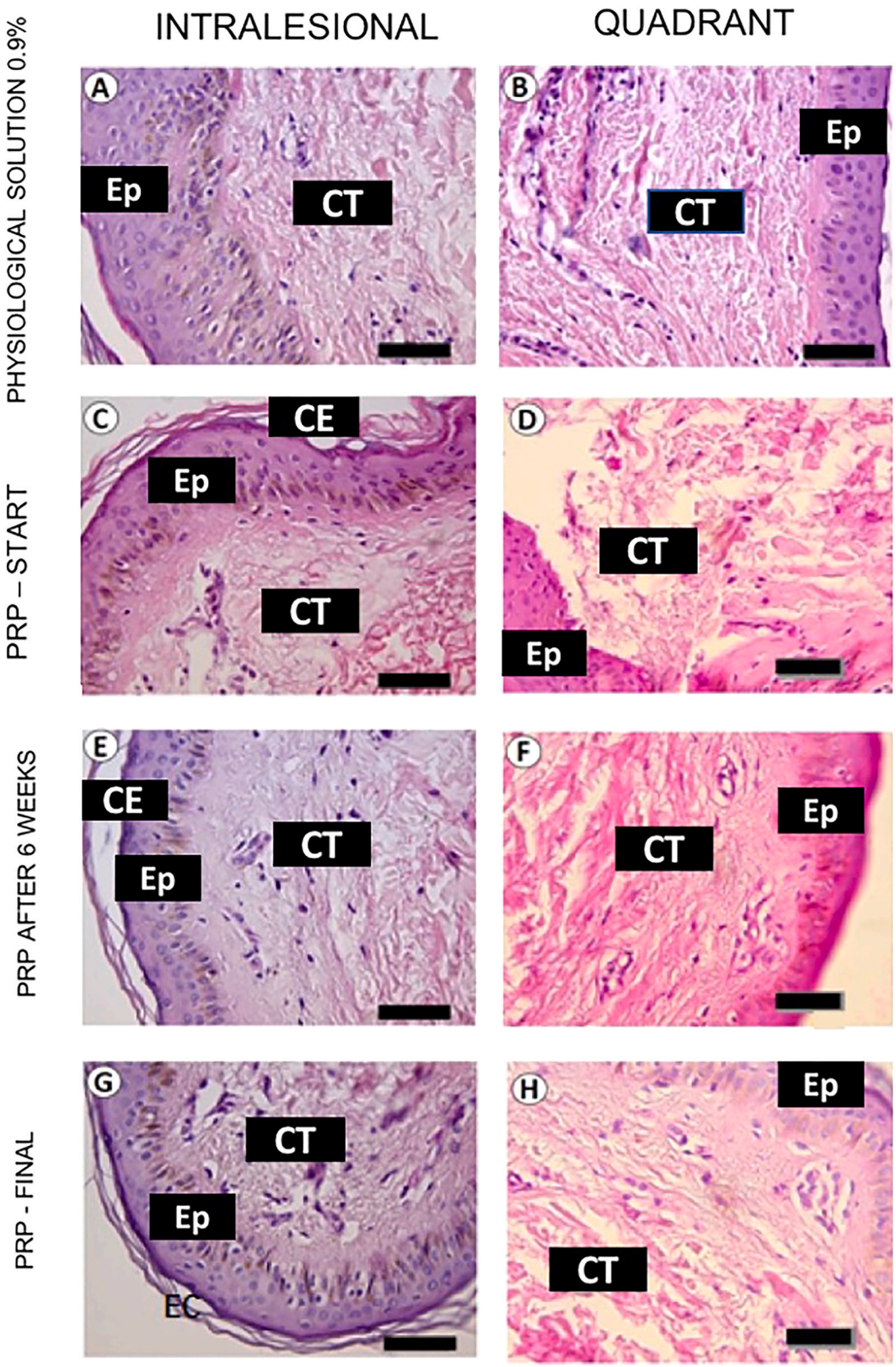

Fig. 3. (A – H): Representative photomicrographs of histological analyses from abdominal stretch marks at the beginning and after 6 and 12 (final) weeks of intralesional and per quadrant physiological solution 0.9% and PRP treatments. Intralesional (A) and per quadrant (B) physiological solution 0.9% treatment. PRP intralesional (C) and per quadrant (D) applications at the beginning of treatment. PRP intralesional (E) and per quadrant (F) applications after 6 weeks of treatment. PRP intralesional (G) and per quadrant (H) applications after 12 weeks of treatment. Hematoxylin & Eosin (HE) stain. In **A – H**: CE = stratum corneum of the epidermis; Ep = Epidermis; CT = connective tissue of the dermis. Scale bar = 50 μm.

Table 2
Measures (μm) of collagen fibers and proportion (%) of elastic fibers comparing the evaluated groups.

Application type	Treatment	Collagen fiber measurements (μm)		Elastic fibers ratio (%)
INTRALESIONAL	**Physiological solution 0.9% (Group 1)**		119.8 ± 38.50	23,4%
	PRP (Group 2)	**Initial**	112.5 ± 38.2	20.8%
		6 Weeks	71.7 ± 51.9 *	13,0%
		12 Weeks	108,3 ± 30.9	14.7%
PER QUADRANT	**Physiological solution 0.9% (Group 3)**		126.7 ± 25.9	24.3%
	PRP (Group 4)	**Initial**	93.9 ± 612	205%
		6 Weeks	123.3 ± 42.6	24.8%
		12 Weeks	138.5 ± 36.9 *	28.5%*

Values correspond to mean and standard deviation. Values followed by * are statistically significant ($p < 0.05$).

physiological solution 0.9%, as well as, at the beginning of intralesional (Fig. 6**J**) and per quadrant (Fig. 7**J**) PRP treatments. In both intralesional (Fig. 6**O, T**) and per quadrant (Fig. 7**O, T**) RP groups, TNF-α immunoreactivities for were significantly moderate after 6 and 12 weeks (Table 3).

3.4. PRP per quadrant treatment increased VEGF and IGF-1 immunoreactivities, culminating to tissue improvement

Moderate VEGF and IGF-1 immunoreactivities were found in the patients that received intralesional (Fig. 8**A, B**) and per quadrant (Fig. 9**A, B**) physiological solution 0.9% (Table 3). Similarly, at the beginning and after 6 and 12 weeks of intralesional PRP treatment, VEGF and IGF-1 immunoreactivities were moderate (Fig. 8**C, D, E, F, G, H;** Table 3).

In contrast, in the per quadrant PRP group, VEGF and IGF-1 immunoreactivities were weak at the beginning of treatment (Fig. 9**C, D;** Table 3). After 6 and 12 weeks of per quadrant PRP treatment, VEGF and IGF-1 immunoreactivities were significantly moderate (Fig. 9**E, F, G, H;** Table 3).

4. Discussion

The treatment of stretch marks is quite challenging, and its main objective is to replace fibrous tissue with new cells, promoting tissue repair and returning elasticity and healthy skin appearance. The process of tissue repair is very complex and involves interactions between various molecules and cells, and can occur in two ways: through regeneration, which restores tissue activity and functionality; or by the recovery of homeostasis. In general, therapies for tissue repair aim to stimulate the production of extracellular matrix components by promoting a local inflammatory process.

Currently, there are several therapeutic modalities available for the treatment of stretch marks, but none of them has demonstrated high scientific evidence in the eradication of this skin disease. Different therapeutic modalities such as carboxytherapy, phototherapy, radiofrequency and PRP have been successfully used (Lokhande and Mysore, 2019; Mendes et al., 2022). Carboxytherapy stimulates blood circulation, increasing the release of oxygen (Lokhande and Mysore, 2019), which activates the synthesis of collagenase, elastin and hyaluronic acid, and has been shown to decrease the size of stretch marks (Lokhande and Mysore, 2019). However, it is considered painful and uncomfortable and therefore a controversial therapy (Mendes et al., 2022). Treatments based on the emission of high-intensity light are moderately effective (Mendes et al., 2022). One study using a high-intensity light device emitting UVB and UVA1 with peak wavelengths at 313, 360, and 420 nm reported improvements of more than 51% in stretch mark pigmentation after 10-week phototherapy sessions, although cases of hyperpigmentation transient have been reported (Sadick et al., 2007). Intense pulsed light (IPL) appears to lead to moderate improvement in stretch marks; however, the presence of erythema and post-inflammatory hyperpigmentation complicate this treatment (Al-Dhalimi and Nasyria, 2013). Bipolar radiofrequency also showed clinical and histological improvements in distended striae, while tripolar radiofrequency resulted in a 25–75% improvement in just one week of treatment (Manuskiatti et al., 2009). Needle therapy has also shown significant improvements in stretch marks (Nassar et al., 2016) compared to microdermabrasion, although the latter is only effective for red stretch marks (Abdel-Latij and Elbendary, 2008).

PRP administration is a promising approach to enable tissue repair since it possesses cytokines and growth factors, capable of enabling stem cell proliferation and differentiation (Spartalis et al., 2017; Syllaios et al., 2019; Luzo et al., 2020). PRP controls several biological processes, such as angiogenesis, inflammation, cell proliferation, cell migration, as well as extracellular matrix synthesis and remodeling processes (Luzo et al., 2020). Kim et al. (2012) studied, through a clinical trial, the treatment of stretch marks with the use of autologous PRP associated with intradermal radiofrequency through a special device. The treatment was performed in 19 patients of Asian origins, with three sessions administered in four-week intervals. The patients were evaluated by the researchers, and by themselves, four weeks after the end of the treatment. One patient (5.3% of the total) showed excellent improvement; seven (36.8%), remarkable improvement; six (31.6%), moderate improvement; and five (26.3%), minimal improvement after evaluation by the researchers. About the self-evaluation of the participating patients, three (15.8%) were very satisfied, nine (47.4%) were satisfied, five (26.3%) were slightly satisfied, and two (10.5%) were dissatisfied. There were no significant differences according to the anatomical site of the stretch marks and the results were similar, considering the two forms of evaluation. Suh et al. (2012) studied, in 18 female patients, the treatment of stretch marks with PRP and ultrasound after radiofrequency sessions. The results were evaluated by the researchers and the participating patients in the study through photos and biopsies. Two months after the last treatment, the average width of the stretch marks decreased from 0.75 mm to 0.27 mm. In the researchers' objective evaluation through photos, six (33%) of the patients were classified as "excellent" result (75–100% improvement); seven (38.9%) as "very good" (50–74% improvement); four (22.4%) as "good" (25–49% improvement); and one patient (5.6%) as "mild" result (1–24% improvement). In the subjective evaluation, 72.2% reported the treatment as "good" or "very good." In three patients who underwent a biopsy, there was a significant increase in collagen and elastic fibers in the papillary and reticular dermis.

Similar to the results presented by Kim et al. (2012) and Suh et al. (2012), our study demonstrated that PRP therapy, particularly the per quadrant application, was effective in reducing the area of abdominal stretch marks, with consequent stimulation of synthesis and remodeling of collagen and elastic fibers. Also, patients were very satisfied with the effectiveness of PRP treatment, mainly because it was an autologous product and with low operational cost. During the entire treatment, no serious adverse reactions were observed, except for slight pain during application and local erythema. Such reactions ceased in a few minutes without causing any harm to patient.

Inflammation plays an essential role in the process of tissue repair, including the wound healing process. Concerning skin tissue repair, keratinocytes can be cited as the main constituents of the epidermis,

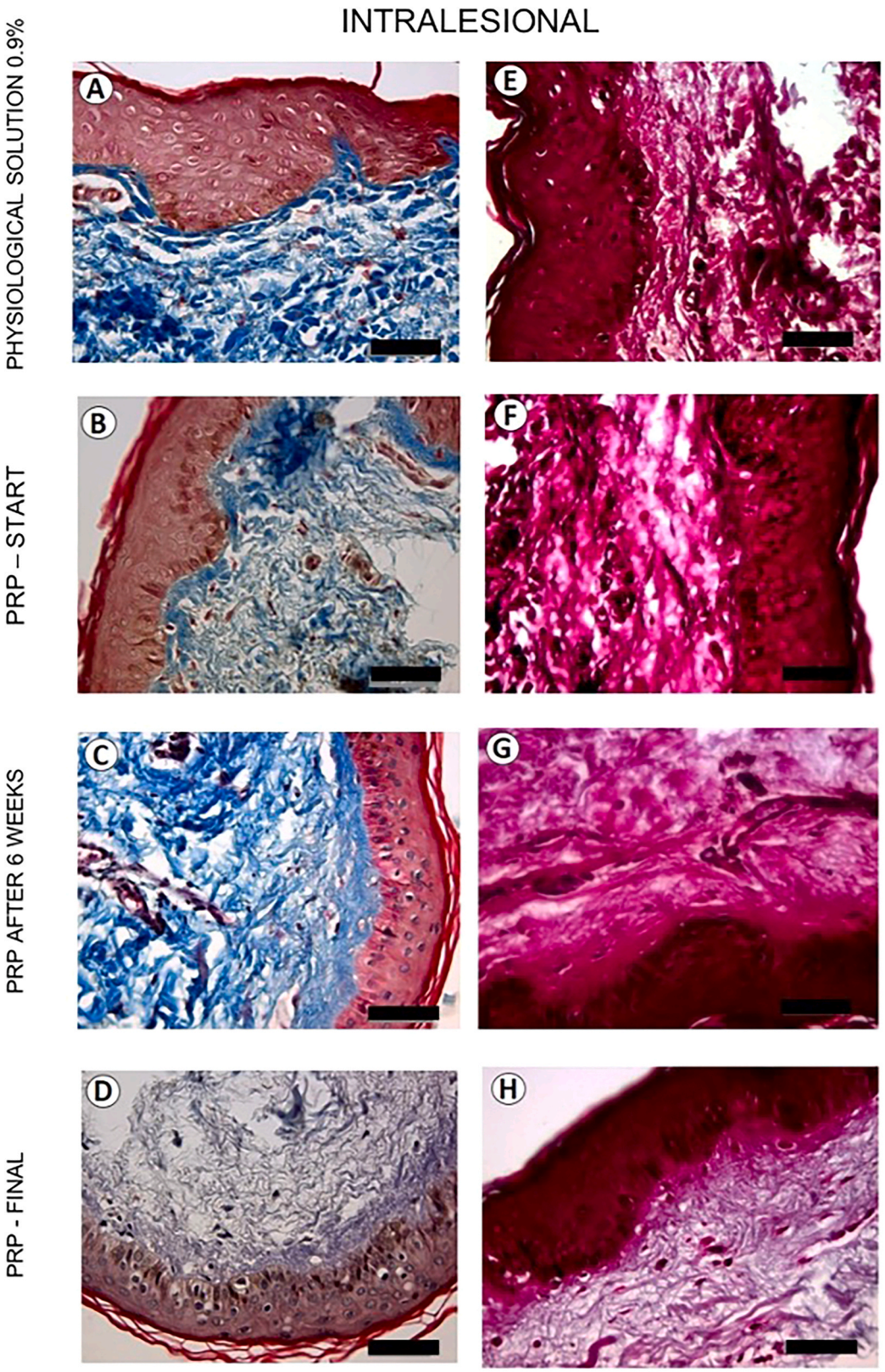

Fig. 4. (A – H): Representative photomicrographs of groups treated with physiological solution 0.9% (A, E) and PRP (B, C, D, F, G, H) intralesional. Masson's trichrome staining showing collagen fibers in blue and epithelial cells in red, in the physiological solution group (A). Masson's trichrome showing collagen fibers in blue and epithelial cells in red at the beginning (B) and after 6 (C) and 12 (D) weeks of PRP intralesional treatment. Weigert's resorcin-fuchsin showing elastic fibers in black/dark blue, in the physiological solution group (E). Weigert's resorcin-fuchsin showing elastic fibers in black/dark blue at the beginning (F) and after 6 (G) and 12 (H) weeks of PRP intralesional treatment. Scale bar = 50 μm.

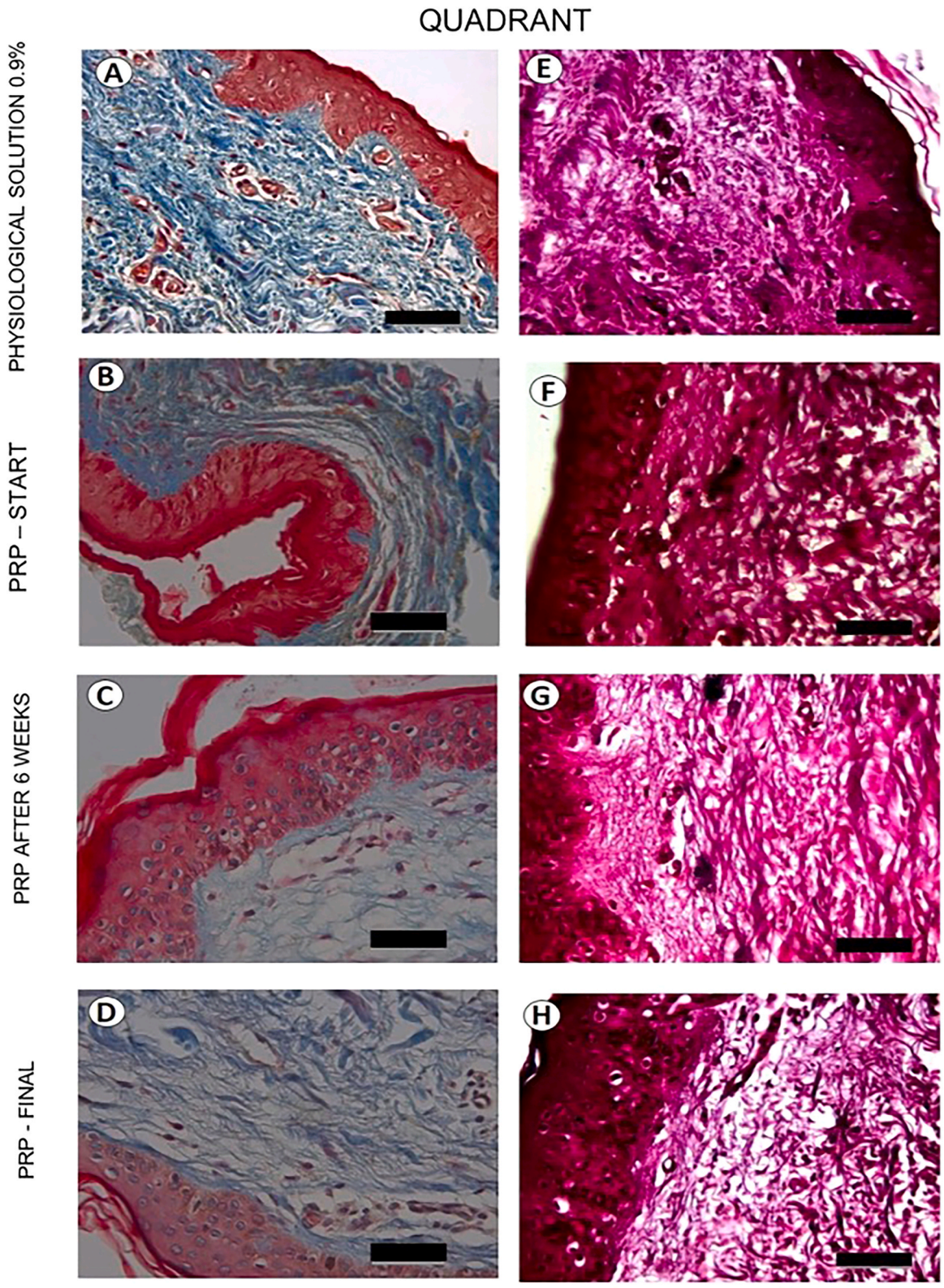

Fig. 5. (A – H): Representative photomicrographs of groups treated with physiological solution 0.9% (A, E) and PRP (B, C, D, F, G, H) per quadrant. Masson's trichrome staining showing collagen fibers in blue and epithelial cells in red, in the physiological solution group (A). Masson's trichrome showing collagen fibers in blue and epithelial cells in red at the beginning (B) and after 6 (C) and 12 (D) weeks of PRP per quadrant treatment. Weigert's resorcin-fuchsin showing elastic fibers in black/dark blue, in the physiological solution group (E). Weigert's resorcin-fuchsin showing elastic fibers in black/dark blue at the beginning (F) and after 6 (G) and 12 (H) weeks of PRP per quadrant treatment. Scale bar = 50 μm.

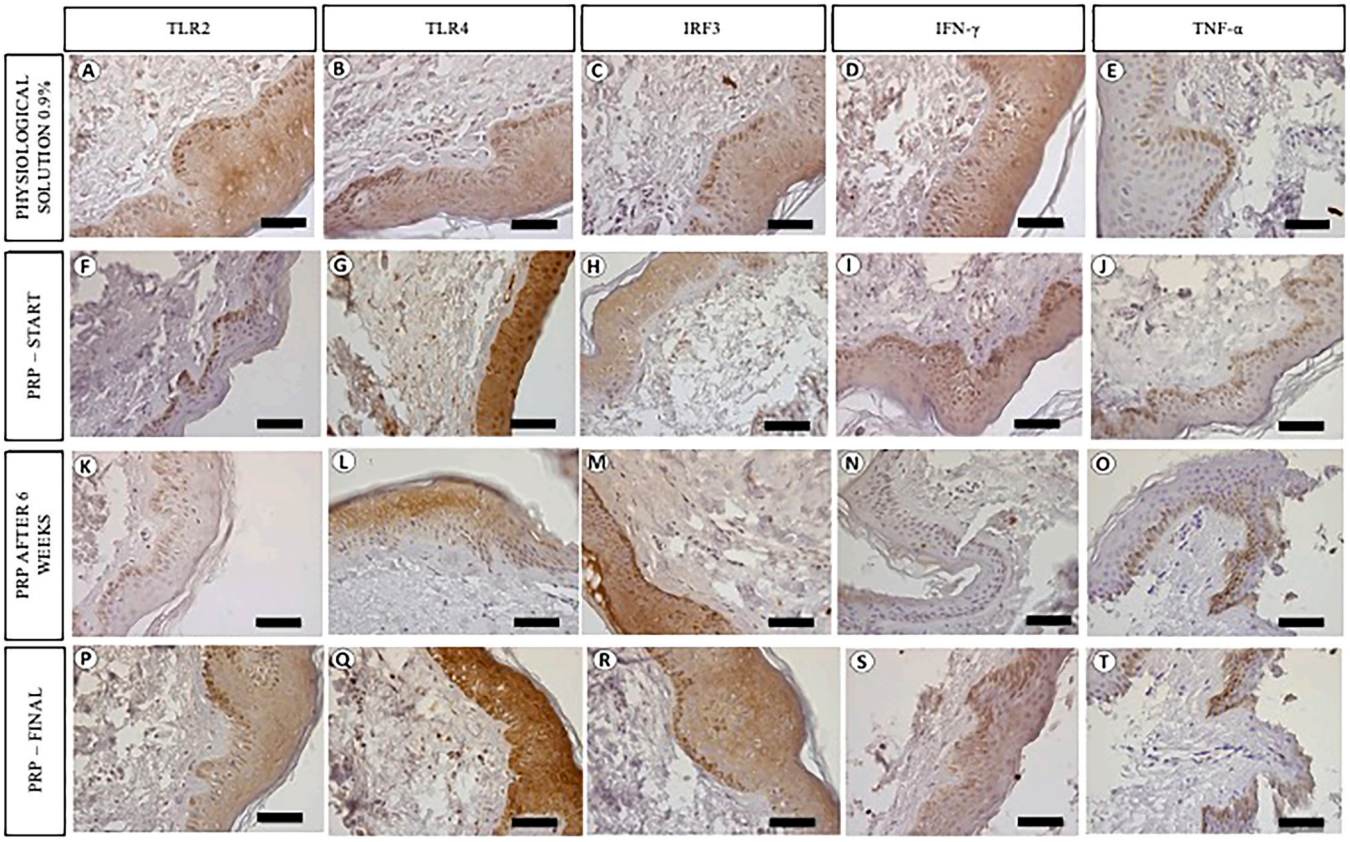

Fig. 6. (A – T): Immunolabelled antigen intensities of the abdominal stretch marks at the beginning and after 6 and 12 weeks of intralesional physiological solution 0.9% and PRP treatments. (A), (F), (K), (P) TLR2 immunoreactivities. (B), (G), (L), (Q) TLR4 immunoreactivities. (C), (H), (M), (R) IRF3 immunoreactivities. (D), (I), (N), (S) IFN-γ immunoreactivities. (E), (J), (O), (T) TNF-α immunoreactivities. Scale bar = 50 μm.

playing a critical role in wound healing. Re-epithelialization begins a few hours after the injury and continues into the proliferation phase. Studies show that keratinocytes contribute significantly to the production of cytokines in the epidermis. Many of the cytokines currently identified in wounds, such as IL-1α and β, IL-6, IL-8, IL-10, IL-12, IL-20, IL-24, and TNF-α, can be produced by keratinocytes (Chen et al., 2013).

Macrophages become the predominant cell type in the wound as the neutrophil content decreases. These cells have two main roles in the regeneration process: involvement of necrotic or apoptotic neutrophils, providing an important clearance mechanism; production of cytokines, chemokines, and growth factors, which stimulate the inflammatory reaction, helping to recruit more inflammatory cells and promoting the proliferative phase of repair, including angiogenesis and tissue growth (Willenborg et al., 2012). Studies show that macrophages play an indispensable role in wound healing. However, macrophages are known for exhibiting heterogeneous phenotypes within wounds. Macrophages in early wounds produce more proinflammatory cytokines (TNF-α and IL-6) and fewer TGF-β, while the opposite is observed in the later stage of wound healing (Daley et al., 2010). Thus, wound macrophages share the characteristics of both classically and alternatively activated macrophages (M1 and M2, respectively) (Daley et al., 2010; Bainbridge, 2013). Macrophages express all TLRs, but predominantly express TLRs 1, 2, 4, 5, 8, and 13 (Zarember and Godowski, 2002). TLRs ligand stimulation in macrophages induces the production of pro-inflammatory cytokines and the antimicrobial peptide cathelicidin and leads to increased phagocytosis.

Recent studies show that TLR activation is a key element to initiate and mediate inflammation after injury. Targeting TLRs or their signaling pathways may provide new therapeutic strategies for the treatment of chronic or difficult-to-heal wounds (Munir et al., 2020). Skin wound healing was significantly delayed in knockout mice for TLR2 and TLR4, or double knockout for TLR2 / TLR4, with decreased neutrophil and macrophage infiltration (Suga et al., 2014). The numbers of macrophages expressing TGF-β and keratinocytes expressing CCL5 in the wounds of these mice were also negatively regulated compared to wild-type animals. Topical administration of TGF-β and CCL5 markedly improved wound healing in knockout mice for TLR2 and TLR4, or double knockout for TLR2/ TLR4 (Suga et al., 2014). TLR4 is mainly expressed in keratinocytes at the wound edge after day 3 of injury (Chen et al., 2013). Wound repair in TLR4 knockout mice was significantly impaired from day 1 to day 5 after injury compared to wild-type mice (Chen et al., 2013). Temporal increases in macrophages, neutrophils, and lymphocytes, as well as decreased expression of inflammatory cytokines (IL-1β and IL-6), were observed in wounds from knockout mice for TLR4. Cytokine production by injured normal human epidermal keratinocytes has been shown to be stimulated through the TLR4-p38 and JNK MAPK signaling pathway (Chen et al., 2013). Hence, TLR4 is an important regulator of the tissue repair process.

Following literature studies involving the role of TLRs in tissue repair, especially the canonical TLR2 and TLR4 signaling pathways, this study demonstrated that PRP per quadrant treatment promoted increased TLR2 and TLR4 immunoreactivities, with consequent increase in TNF-α immunoreactivity. On the other hand, mediators of the MyD88-independent pathway (non-canonical pathway of TLRs), IRF3 and IFN-γ, showed no significant changes in their immunoreactivity patterns throughout the treatment period, indicating that PRP treatment acted directly on the modulation of the canonical pathway of TLRs 2 and 4 for the production of inflammatory cytokines. Thus, we can conclude that the stimulation of the canonical signaling pathway of TLRs 2 and 4 for the production of acute inflammatory cytokines, modulated by treatment with PRP, played an important role in tissue repair, promoting increased synthesis and greater reorganization of collagen and elastic

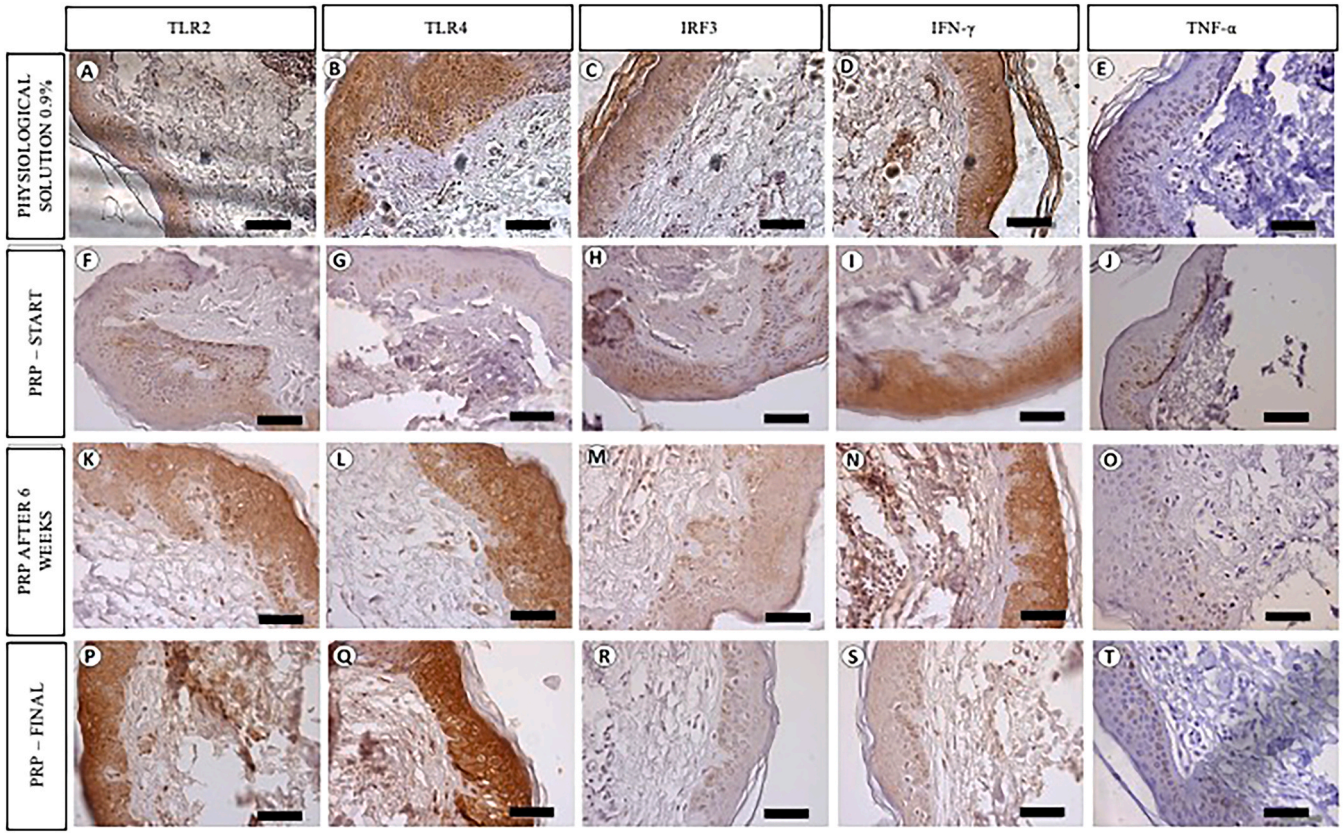

Fig. 7. (A – T): Immunolabelled antigen intensities of the abdominal stretch marks at the beginning and after 6 and 12 weeks of per quadrant physiological solution 0.9% and PRP treatments. (A), (F), (K), (P) TLR2 immunoreactivities. (B), (G), (L), (Q) TLR4 immunoreactivities. (C), (H), (M), (R) IRF3 immunoreactivities. (D), (I), (N), (S) IFN-γ immunoreactivities. (E), (J), (O), (T) TNF-α immunoreactivities. Scale bar = 50 μm.

Table 3
Average of immunolabelled antigen intensities in the different treatments and periods.

Application types	Treatment		TLR2	TLR4	IRF3	IFN-γ	TNF-α	VEGF	IGF-1
INTRALESIONAL	**Physiological solution 0.9% (Group 1)**		2 (42.4%)*	2 (41.2%)	2 (38.9%)	2 (46.1%)	1 (20.1%)	2 (40.4%)	2 (49.2%)
	PRP (Group 2)	**Initial**	1 (19.1%)	2 (66.8%)	2 (41.7%)	2 (47.2%)	1 (35.2%)	2 (43.1%)	2 (49.6%)
		6 Weeks	1 (26.4%)	2 (38.4%)	2 (37.2%)	2 (46.3%)	2 (44.2%)*	2 (46.1%)	2 (39.5%)
		12 Weeks	2 (40.1%)*	3 (86.4%)*	2 (41.3%)	2 (43.8%)	2 (46.1%)*	2 (41.3%)	2 (48.1%)
PER QUADRANT	**Physiological solution 0.9% (Group 3)**		2 (37.8%)	2 (68.9%)	2 (44.0%)	2 (49.2%)	1 (20.4%)	2 (41.2%)*	2 (42.5%)*
	PRP (Group 4)	**Initial**	1 (27.2%)	1 (25.1%)	2 (48.8%)	2 (48.2%)	1 (26.9%)	1 (32.2%)	1 (34.6%)
		6 Weeks	2 (59.4%)	3 (78.6%)*	2 (39.0%)	2 (40.0%)	2 (38.7%)*	2 (41.8%)*	2 (45.8%)*
		12 Weeks	3 (85.5%)*	3 (91.4%)*	2 (40.3%)	2 (44.8%)	2 (42.3%)*	2 (42.7%)*	2 (51.5%)*

0: (no immunoreactivity), 0% of positive cells and/or fibrillar elements of the extracellular matrix; 1: (weak immunoreactivity), 1 – 35% of positive cells and/or fibrillar elements of the extracellular matrix; 2: (moderate immunoreactivity), 36 – 70% of positive cells and/or fibrillary elements of the extracellular matrix; and 3: (intense immunoreactivity), > 70% of positive cells and/or fibrillar elements of the extracellular matrix.

fibers.

In the process of tissue repair, several growth factors are also released: epidermal growth factor (EGF); vascular endothelial cell growth factor (VEGF), which increases vascular permeability; insulin-like growth factor-1 (IGF-1), which stimulates the synthesis of sulfated proteoglycans, collagen synthesis, keratinocyte migration, and fibroblast proliferation - endocrine effects similar to basic growth hormones; and also the fibroblast growth factor (FGF) family, which stimulates keratinocyte migration, angiogenesis, wound contraction, and matrix deposition (Bainbridge, 2013). Macrophages are crucial in modulating processes such as angiogenesis and fibroplasia, producing PDGF, FGF, VEGF, TGF, which are key in the transition between inflammation and granulation tissue formation in the proliferative phase, promoting cell migration, in proliferation and production of extracellular matrix, and enhancing the organization of elastic and collagen fibers (Bainbridge, 2013). In addition to macrophages, fibroblasts are a major cellular component of the dermis. In the proliferation phase, fibroblasts resident in the skin, or fibroblasts that have differentiated from blood-borne fibrocytes, produce extracellular matrix molecules to provide structural support to repair tissue (Bainbridge, 2013). Bainbridge (2013) demonstrated fibroblasts can also participate in the regulation of inflammation, as they can be induced to produce a variety of cytokines and growth factors, such as VEGF, PDGF, FGF2, EGF, TGF-β, matrix metalloproteinases (MMPs), and the inhibitors of tissue MMPs. These molecules can affect the functions of fibroblasts themselves, as well as keratinocytes, macrophages, neutrophils, and mast cells (Bainbridge, 2013). Human skin fibroblasts express TLRs 1–10 (Jang et al., 2012).

Treatment of fibroblasts with ligands for TLRs 2, 3, 4, 5, and 9 with IFN-γ results in the production of CXCL9, CXCL 10, and CXCL 11 molecules, chemokines that are important for the recruitment of T cells and natural killer (NK) cells. Given the large number of fibroblasts in the wound bed area, TLR activation in these cells may play an important role

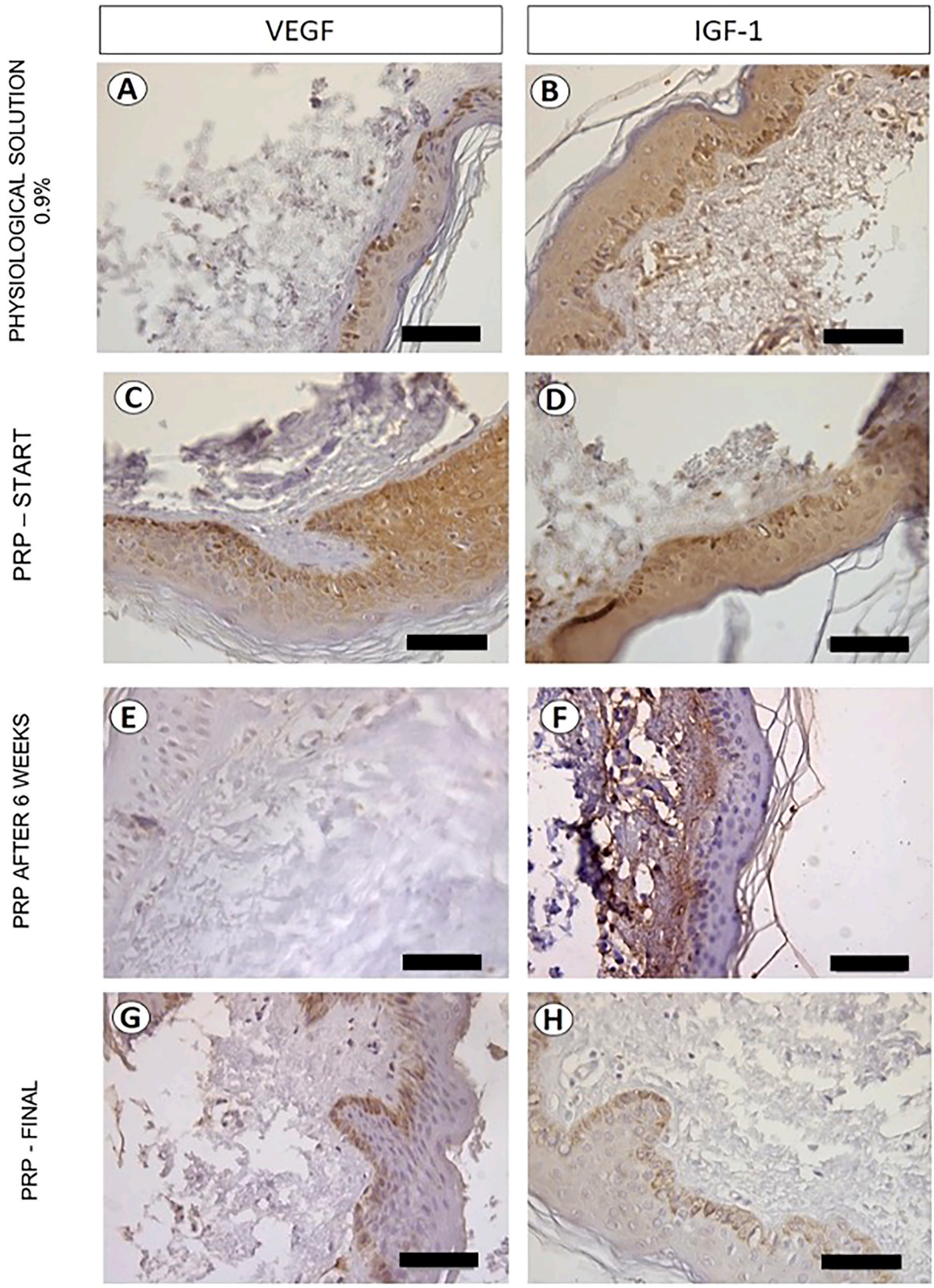

Fig. 8. (A – H): Immunolabelled antigen intensities of the abdominal stretch marks at the beginning and after 6 and 12 weeks of intralesional physiological solution 0.9% and PRP treatments. (A), (C), (E), (G) VEGF immunoreactivities. (B), (D), (F), (H) IGF-1 immunoreactivities. Scale bar = 50 μm.

in wound healing, especially in the remodeling phase. Moreover, for efficient tissue repair, new vessels must also be formed through the proliferation of endothelial cells (Reinke and Sorg, 2012). With neovascularization, there is an increased oxygen supply to the tissue, improving the nutrition of cells during the tissue repair process. VEGF (endothelium growth factor) regulates angiogenesis. Therefore, the results of the present study are in line with the results found in the relevant literature, since treatment with PRP increased immunoreactivities for

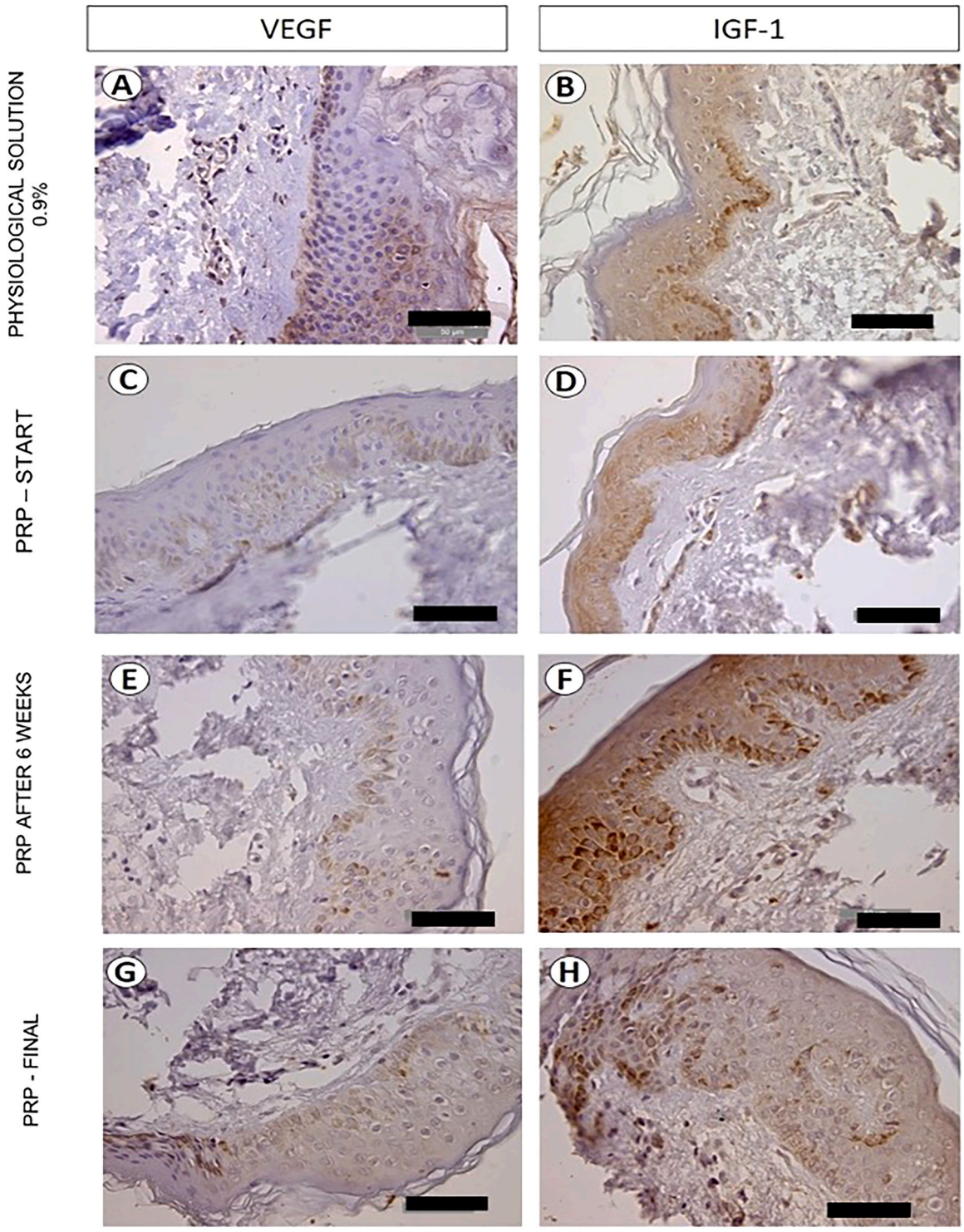

Fig. 9. (A – H): Immunolabelled antigen intensities of the abdominal stretch marks at the beginning and after 6 and 12 weeks of per quadrant physiological solution 0.9% and PRP treatments. (A), (C), (E), (G) VEGF immunoreactivities. (B), (D), (F), (H) IGF-1 immunoreactivities. Scale bar = 50 μm.

VEGF and IGF-1, which were related to tissue improvement.

5. Conclusions

Considering the data together, it can be concluded that the use of PRP in patients with stretch is a promising therapeutic approach, since it promoted the stimulation of inflammatory cytokines and growth factors, with the consequent remodeling of the fibrillar elements of the extracellular matrix, culminating in tissue improvement. However, the use of PRP in abdominal stretch marks needs further investigation in a larger sample of patients to verify the reproducibility of the findings.

Limitations and Perspectives

Stretch mark is a common disfiguring skin disease that affects a large number of patients, predominantly post-pregnant women. The current literature evidence supporting the use of PRP for stretch mark is poor. Furthermore, satisfactory clinical strategies are still lacking.

Important developments in recent years have been observed in medical fields such as cardiac surgery, pediatric surgery, plastic surgery, gynecology, ophthalmology, urology and oncology based on the use of Platelet-Rich Plasma (PRP). Advances in PRP studies have contributed to improving immune regulation. Thus, two themes attracted the attention of the scientific community: the first refers to innate and adaptive immune functions, while the second refers to the role of platelets in the regulation of inflammatory processes. Therefore, innovative studies focused on the investigation of alternative therapies for the treatment of stretch marks need to be developed, and PRP presents itself as a potential therapy.

To date, there is not fully effective and minimally invasive treatment for stretch marks caused by the mechanical distension process or by the use of medications such as corticosteroids, antiretrovirals, chemotherapy drugs, neuroleptics, contraceptives and tuberculostatics. In this sense, new therapeutic approaches are needed and, in this scenario, the use of PRP opens a new perspective for the treatment of stretch marks, since it has important modulation mechanisms of growth factors and immune mechanisms related to tissue repair.

However, investigative studies involving the use of PRP are scarce in approaching the pathogenesis of stretch marks, including studies that relate histopathology, fibrillar elements of the extracellular matrix, growth factors and immune system signaling pathways. The investigation of these factors is fundamental for the formulation of an effective clinical strategy, using PRP alone or in combination with other therapies. Unfortunately, many professionals use PRP indiscriminately in aesthetic medicine, without standardizing the preparation and handling of PRP, and without investigating in depth the cellular and molecular mechanisms of this therapy.

This study has some limitations. The main one is related to number of patients. Therefore, our results are not generalizable to all potential candidates of PRP therapy. The number of patients (n = 12) was estimated taking into account that it was an experimental study, not a clinical one, which detailed the structural alterations of collagen and elastic fibers in abdominal stretch marks and how PRP treatment affects them, as well as explored the possible mechanisms of action of this treatment, including TLRs signaling pathways and growth factors. Additionally, the number of patients used in this study followed the norms of Brazilian legislation through Resolution 2128/2015, which restricted the use of PRP to clinical experimentation, within the protocols of the Ethics Committee system and the National Research Ethics Committee (CEP/CONEP). According to the technical standard, the research activity must "be conducted in duly qualified institutions that meet the Ministry of Health's standards for the handling and experimental use of blood and blood products in Brazil".

Thus, considering this scenario, we chose to carry out an experimental study with a reduced number of patients, since we did not have predictable results, in addition to not violating the legislation in force in the country and not causing any harm to patients.

The other limitation of this study refers to the comparison of PRP treatment with other modalities already used in clinical practice. Combining therapy is currently a hot topic in stretch marks treatment and more combinations can be tried to improve the efficacy, reduce side effects to achieve a better treatment effect and increase patient compliance. Thus, other therapeutic options were not considered since the scope of this study was to analyze the histopathological and immunohistochemical effects of PRP in tissue repair of abdominal stretch marks. Interestingly, our results demonstrated that the subcutaneous application of PRP (per quadrant), region near to stretch marks, was more effective than intralesional application, promoting a greater modulation of inflammatory cytokines and growth factors, with consequent remodeling of extracellular matrix, culminating with tissue improvement.

Considering the promising results of the treatment of abdominal stretch marks with PRP, our research group is conducting a new clinical trial with 25 patients submitted to subcutaneous application (per quadrant) of PRP to verify the reproducibility of the findings.

Ethics approval and consent to participate

Research involving human participants.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Research Ethics Committee from University of Campinas (**CAAE number: 69189017.5.0000.5404**).

Informed consent

Each subject provided written informed consent before participating in the study.

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CRediT authorship contribution statement

Roston JRC: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Reis IB:** Formal analysis, Investigation, Data curation. **Luzo ACM:** Conceptualization, Methodology, Investigation, Validation, Formal analysis, Resources, Data curation. **Roston MO:** Investigation, Data curation. **Durán N:** Formal analysis, Investigation, Data curation. **Fávaro WJ:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare no conflicts of interest.

Data Availability

Data will be made available on request.

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Author statement

We want to declare that the work described was original research that has not been published previously, and not under consideration for publication elsewhere. All the authors listed wish to be considered for publication in **"Tissue and Cell"**. No conflict of interest exists in submitting this manuscript.

Consent to publish

The authors affirm that human research participants provided informed consent for publication of the images in Figs. 2–9.

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