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Burn Scar Biomechanics Following Pressure Garment Therapy

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Abstract

Background—The current standard of care for the prevention and treatment of scarring following burn injury is pressure garment therapy (PGT). Although this therapy has been used clinically for many years, controversy remains regarding its efficacy. The purpose of this study was to evaluate the efficacy of PGT in a female Red Duroc pig (fRDP) burn model where wound depth could be tightly controlled.

Methods—Full-thickness burn wounds were generated on fRDPs. At day 28 post-burn, PGT was applied to half of the wounds (10 mmHg), with control wounds covered with garments exerting no compression. Scar area, perfusion, hardness, and elasticity were quantified at days 0, 28, 42, 56, and 72 using computerized planimetry, Laser Doppler and torsional ballistometry. Scar morphology was assessed at days 28, 56 and 76 using histology, immunohistochemistry and transmission electron microscopy.

Results—Pressure garment therapy significantly hindered scar contraction with control scars contracting to 64.6 + 13.9% original area at day 72 while PGT scars contracted to 82.7 + 17.9% original area. PGT significantly reduced skin hardness and increased skin strength by 1.3X. No

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difference in perfusion or blood vessel density was observed. Average collagen fiber diameter was greater in control burns than PGT.

Conclusions—PGT was effective at reducing scar contraction and improving biomechanics compared to control scars. These results confirm the efficacy of pressure garments and highlight the need to further investigate the role of pressure magnitude and time of therapy application to enhance their efficacy for optimal biomechanics and patient mobility.

Introduction

Burns account for roughly 1.25 million injuries in the United States annually[1,2]. Scarring is the most common form of morbidity for burn survivors. This exaggerated proliferative response to wound healing results in rapid growth of connective tissue and excessive contraction[3-5]greatly reducing skin pliability and quality of life for patients. The current standard of care for the prevention and treatment of scarring following a burn injury is the use of pressure garments. These garments exert static compression on skin[6-12] and this pressure is hypothesized to limit blood flow, nutrient and oxygen supply to the scar tissue, reducing collagen synthesis[10,13-17].

With little modification from the original, custom-fitted Jobst garments, pressure garment therapy (PGT) remains the preferred treatment modality for the prevention and treatment of burn scars[18-21]. Although this therapy has been used clinically for over 40 years, controversy remains regarding its efficacy[22]. Prior clinical studies reported outcomes with pressure garment therapy ranging from no evidenced-based benefit[23] to significant increases in scar pliability[24]. A systematic review of four randomized controlled trials showed a trend towards decreased scar height in PGT-treated scars[22]. Significant reductions in scar redness and thickness were also observed in scars receiving PGT[25]. Because pressure garments are often used in conjunction with other forms of therapy, and due to the high incidence of patient non-compliance, the efficacy of PGT has been difficult to evaluate and neither the efficacy nor the optimal protocol for delivery have been scientifically established[,7,26-27].

Complicating the study of pressure garment therapy is the inherent variation of burn depth and location found in human clinical trials and the variation in actual levels of pressure delivered by garments based on manufacturer and anatomical site. One clinical study used a low flow transducer to directly measure the cutaneous pressures generated by a pressure garment on various body parts[27]. The results showed an increase in subdermal pressures in the range of 9-90 mm Hg depending on the anatomical site[27]. Garments over soft sites, such as the medial and posterior mid-calf, exerted pressures ranging from 9 to 33 mm Hg with a mean of 21 mm Hg. Subdermal readings taken over bony prominences showed an increase, ranging from 47 to 90 mm Hg[27]. In one study, the clinical effectiveness of compressive bandages was observed on 210 separate anatomic burn sites, which included sites in the head/neck, trunk, upper extremities, hands, lower extremities, and feet[28]. The study found that a critical factor in determining the effectiveness of pressure therapy was the anatomic area of the scar. Scars present on flat areas, such as the foot, exhibited the best improvement in contracture while the trunk region showed intermediate results and treatment of the hand and neck were unsuccessful[28]. As outcomes are so closely linked with anatomical location and initial degree of injury, an animal model is needed where burn site and depth can be controlled.

More recently, female, red Duroc pigs (FRDPs) have been proposed as a model for studying excessive scarring[29-31]. Studies have confirmed that scars on FRDPs from deep wounds are red, thick, firm, and lack hair,[30-31]. In addition, the timescale for wound healing and scar development in FRDP correlates with that of deep dermal wounds in humans[30-31] and the expression of transforming growth factor β1 (TGF-β1), insulin-like growth factor 1 (IGF-1), decorin, and versican in FRDP displayed similar changes following deep wounds in humans [30-35]. The similarities in skin structure, wound healing and scar development between female Red Duroc pigs and humans provide an ideal model for the study of PGT efficacy.

The current study examines the efficacy of pressure garment therapy on scar prevention in a Red Duroc pig full-thickness burn wound model. Burn wounds were created on the dorsum of each pig and treated with PGT or treated with garments without compression. Scar contraction, biomechanics, blood flow, vascularization and extracellular matrix production and structure were evaluated at multiple time points over the 78 day study to investigate PGT's ability to maintain skin pliability and to identify possible mechanisms of action.

Materials and Methods

Burn Wound Generation

All experiments and data collection were performed following The Ohio State University Institutional Laboratory Animal Care and Use Committee (ILACUC) approved protocols. Female Red Duroc pigs (n=8, 60 lb; Isler Genetics Inc., Prospect, OH) were anesthetized with Telazol followed by isoflurane and the dorsal trunk shaved and surgically prepared with alternating chlorhexidine 2% and alcohol 70% scrubs (Butler Schein, Columbus, OH). Full-thickness wounds were induced by heating a 1 x 1 inch stainless steel stylus to 200 ± 6 °C and applying to the skin for 30 seconds. Eight total wounds were generated per pig, 4 control and 4 receiving PGT (see Supplementary Figure 1A-B, Photograph of female Red Duroc pig immediately after burn wound generation. After wounds heal for 28 days, compression garments were applied at a reduction in circumference of 10% for the treatment group and 0% for the control group, INSERT LINK, total of 32 PGT treated burns and 32 control burns). Wounds were covered with non-stick gauze pads (Curad) and Elastikon™ (3M). A fentanyl patch (NOVAPLUS patch, Watson Laboratories Inc, 100 mcg) was placed in the pig ear pinna and removed three days post wounding. Animals received a single intramuscular injection of Buprenorphine (Buprenex, Reckitt Benckiser Healthcare, 0.3 mg/ml) during recovery from anesthesia. Animals were maintained on standard chow *ad libitum*, fasted overnight before the procedures, and were housed individually. Animals were euthanized following the completion of experiments.

Pressure Garment Therapy and Pressure Quantification

Compression vests (The Marena Group Inc., Lawrenceville, GA) were modified for pig use. Two sets of adjustable, wrap-style garments with Velcro closures were fabricated for each pig to accommodate body circumferences ranging from 20-35 inches (Supplementary Figure 1B, INSERT LINK). At 28 days post-burn, pig circumference was measured and compression garments applied at a 10% reduction in circumference (Supplementary Figure 1B). Vests with no reduction in circumference were placed over control burns (Supplementary Figure 1B). To evaluate the magnitude of pressure exerted by the compression garments, compression garment fabric was wrapped around a load cell of a mechanical tester (TestResources; Shakopee, MN) at 10% reduction in circumference and pressure was tracked continuously for 12 hours. A representative plot of pressure versus time was reported (See Supplementary Figure 1C, quantification of pressure generated by a compression garment tailored to a 10% reduction in circumference, INSERT LINK.).

Scar Contraction

Photographs of the scars were taken at days 0, 7, 28, 42, 56 and 78. Each photograph of the scars (n=16 per group days 0-56, n = 14 per group at day 78) was taken with a scale in the field of view for scar area quantification. Scar contraction was quantified using computer planimetry (Image J[36-39]) and defined as total scar area, including hyperpigmented border, at a specific time point divided by original scar area (at day 28, time of therapy application) x 100. Data are presented as percent original area (mean ± standard error of the mean (SEM)).

Laser Doppler

The MoorLDI-Mark 2 laser Doppler blood perfusion imager (Moor Instruments Ltd., UK) used a visible red laser beam (633 nm) to map tissue blood flow using in control and PGT scars immediately after garment removal at days 28, 56 and 78 (n=16, day 78 n=14).

Scar Biomechanics

Hardness and elasticity of the upper regions of the skin (to a depth of approximately 0.75 mm) was measured using torsional ballistometry (Torsional Ballisometer, Dia-Stron Limited, Broomall, PA) at post-burn days 28, 42, 56 and 78 (n=16 per group, n =14 at day 78). Hardness was reported as average indentation (mm) ± SEM and elasticity reported as elasticity coefficient ± SEM. Elasticity coefficient, α, is inversely proportional to the elasticity of the tissue. Additionally, failure biomechanics were assessed at day 78. Strips of tissue were removed from the pig parallel to the circumference of the pig. Dogbone shaped samples were cut from the tissue with the scar centered within the length of the sample[40]. Skin thickness was measured and strained at 2 mm/sec until failure (TestResources, Shakopee, MN). Ultimate tensile strength and linear stiffness were reported as mean ± SEM (n=12 per group).

Immunohistochemistry

Biopsies were taken from control and PGT scars at post-burn days 7, 28, 42, 56 and 78 for histology (n=4 per group for days 7, 28, 42 and 56, n = 6 for day 78, no scars were biopsied more than once). The biopsies were embedded in OCT resin, frozen, and stored at -80°C until sectioning. Sections were stained with hematoxylin and eosin or immunostained to visualize general anatomy. To visualize blood vessels, sections were immunostained with von Willebrand factor protein (VWF, Santa Cruz Biotechnology) and DAPI. The stained sections were imaged using an Olympus FV1000 Multi-Photon confocal microscope. Quantitative analysis for VWF positive cells in the dermis was performed by calculating the percent area of the total field of view that was positive for VWF (n = 6 per group).

Transmission Electron Microscopy

On day 78, biopsies (n = 6 per group) were fixed in 2.5% glutaraldehyde in 0.1M phosphate buffer (pH=7.4) overnight at 4°C. Skin was post-fixed with a 1% osmium tetroxide. En block staining was performed using 2% uranyl acetate in 10% ethanol followed by dehydration in a graded ethanol series and embedding in Eponate 12 epoxy resin (Ted Pella, Redding, CA). Ultrathin sections were cut (Leica Microsystems), collected on copper grids and stained with lead citrate and uranyl acetate. Images were acquired with an FEI Tecnai G2 Spirit (FEI; Hillsboro, OR) transmission electron microscope. A minimum of 50 collagen fiber diameters were measured (Image J) from each sample (n = 6 per group) and plotted as a histogram for each sample type.

Statistics

Statistical analyses were performed using SigmaStat (Systat Software, Inc., San Jose, CA). Statistically significant differences were detected using either student's t-test or a One Way ANOVA with a *posthoc* test of Tukey. Statistical significance was considered at $p<0.05$.

Results

Full-thickness Wound Generation and Pressure Garment Fabrication

Application of a 200 °C burn stylus to the skin for 30 seconds resulted in a full-thickness burn injury as evidenced by the complete damage of the epidermis and dermis of the skin (see Supplementary Figure 1D, histological section of burn wound 7 days after initial thermal injury, INSERT LINK). Wounds were allowed to heal naturally for 28 days until the majority of wounds had fully re-epithelialized. The PGT group's garments were manufactured to be 10% reduction in circumference (Supplementary Figure 1B) resulting in an initial pressure of 10.1 mm Hg (Supplementary Figure 1C) which slowly decreased to 9.5 mm Hg after 12 hours. Garments were repositioned on the pigs daily to maintain an average pressure of 10 mm Hg.

Scar Morphology and Contraction

Immediately after thermal injury, the affected area appeared dry with linear wound margins (Supplementary Figure 1A). Scars were hairless and hypopigmented in the center with a thin line of hyperpigmentation outlining the scar. Small areas of epidermal damage near the center of the scars were observed at day 28 in 6 of the 64 scars. This was not observed past day 28 (Figure 1). Scars contracted with time, becoming more star-shaped (Figure 1). Quantitative analysis of scar area showed a significant decrease in scar area from 42 days to 56 days post injury (Figure 2). At day 56, PGT scars were 88.1 ± 3.5% original area as compared to the control, which were 73.8 ± 4.8% original area (Figure 2). By day 78, scar contraction plateaued in the PGT group with no statistical difference between average scar area at days 56 and 78 (Figure 2). In contrast, control scars contracted an additional 8.5% from day 56 to 78 (Figure 2).

Scar Biomechanics

Non-destructive mechanical analysis of scars revealed that hardness of PGT treated skin was lower than that of the controls at day 78 with an average indentation (lower depth of indentation = higher hardness) of 0.27 ± 0.08 mm in control scars and 0.42 ± 0.06 mm in the PGT group. Additionally, elasticity coefficient, α, which is inversely related to elasticity, was significantly lower in the PGT group (α = 0.033 ± 0.0071) than the controls (α = 0.052 ± 0.009) and approached normal pig skin values (α = 0.026 ± 0.0056) by day 78 (Figure 3C). Tensile testing of excised scar tissue showed that the ultimate tensile strength of the scars with PGT was significantly stronger than that of control scars (Figure 3A). Additionally, PGT increased linear stiffness of scars compared to control (Figure 3B).

Scar Perfusion and Blood Vessel Density

Laser Doppler imaging of control and PGT treated scars showed no differences in perfusion at any time point (Figure 4A). Immunohistochemistry showed no observable change in blood vessel density between the control and PGT group at day 78. A quantitative analysis of blood vessel density within the dermis of PGT and control scars confirmed this observation (Figure 4B).

Scar Structure and Collagen Organization

At day 42, both control and PGT scars had completely epithelialized and a uniform epidermis was visible (Figure 5 A&B). The junction between the epidermis and dermis in the control burns contained few rete ridges whereas a greater number of rete ridges were seen in the PGT group. Dense, cellular infiltration was apparent in both groups (Figure 5 A&B). By day 78, thick bands of collagen formed in the dermis of both the control and PGT groups with no gross difference in organization (Figure 5 C&D). Depth and number of rete ridges was greater in the PGT group compared to control.

Collagen organization was examined in greater detail using transmission electron microscopy. Collagen fibrils in control burns were larger and less tightly-packed than in PGT treated scars, with approximately 27% less free space between fibers in the PGT group compared to controls. Collagen fibril diameter distribution ranged slightly larger in the control scars with an average of 17 nm greater fibril diameter than in PGT treated scars (Figure 6).

Discussion

In this study, the female red Duroc pig model was used to study the efficacy of PGT following burn injury. Advantages of this model over human clinical trials, such as uniformity of burn depth and body site, and ability to collect tissue biopsies for analysis, enabled a detailed evaluation of the effects of PGT on scar formation. Though control scars were thick and raised at day 78, their thickness and excess erythema was not believed to be significant enough to categorized the scars as hypertrophic in the current injury model. Significant differences in scar contraction were observed between scars receiving PGT and control burns that received no pressure. Pressure garments exert compressive forces normal to the scar and also parallel to the surface of scar. These forces act to oppose the direction of contracture[41]. It has been recently proposed that wound tension acts upon integrins by stretching them, which leads to increased phosphorylation of focal adhesion kinase (FAK) and downstream upregulation of smooth muscle actin (SMA) and collagen production[42]. When a compressive force was applied to incisional wounds in an opposite direction to the wound tension, it was shown that scars did not form[43]. These data suggest that the mechanical forces applied to the scar can assist in reducing differentiation of fibroblasts to myofibroblasts, ultimately decreasing scar contraction and collagen deposition. It is likely that the reduced scar contraction observed in the current study was, in part, a result of reducing the strain state within the scar, which subsequently abates myofibroblast differentiation and excessive collagen deposition.

Scar strength was improved with PGT compared to controls with a 34% increase in ultimate tensile strength. In addition to improvements in strength, PGT altered collagen deposition in the dermis with PGT scars comprised of smaller, more densely packed collagen fibers. Correlations between compression, tissue mechanics and collagen structure have previously been reported. Human scars treated with pressure via elastic bandages resulted in thinner reticular collagen fibers that resemble that of normal skin[44]. A direct relationship between collagen fiber diameter and tensile strength was previously observed, with small diameter collagen fibers found in low strength wounds in the proliferative phase of healing, and large diameter fibers comprising high strength wounds in the remodeling phase of healing[45]. In the current study, control collagen fiber diameter was ~1.2-fold greater than collagen in PGT treated scars, thus it is unlikely that collagen fiber diameter was a dominant factor in controlling tissue mechanics. The difference in collagen fiber density was more dramatic. The decrease in interfiber free space likely inhibited fiber-fiber motion during deformation and led to increases in tissue strength and stiffness.

It is widely believed that pressure exerted by compression garments limits blood, nutrient and oxygen supply to the scar tissue limiting collagen synthesis[6,10,13-15]. In the current study, no difference in scar perfusion or blood vessel density were observed between the PGT group and the controls (Figure 4). A possible reason for equivalent levels of scar perfusion and blood vessel density may have been the magnitude of pressure applied. Garments manufactured to a 10% reduction in circumference resulted in approximately 10 mm Hg on the scar. This level of pressure is considered to be in the low range, and has been shown previously to result in increased redness and vascularity in scar tissue compared to high pressure (20-25 mm Hg)[25]. Prior clinical studies have also shown no difference in scar vascularity between pressure garment treatment groups and controls[22].

Limitations to the current study include maintenance of pressure magnitude and duration of garment wear. Though garments were repositioned daily, the pigs were able to shift the position of the garments, relieving some pressure. Shifting of garment position by the pig was observed zero to two times per week, effectively reducing the total duration of compression. The maintenance of pressure magnitude for 23 hours of daily wear, which is currently the standard of care for burn patients, is challenging and a problem for all garment materials. Measurement of pressure exerted by the garments over a 12 hour period showed that pressure was reduced from 10 to 9.45 mm Hg in this time frame, and likely reduced further in the following 11 hours. As a result, the total effect of pressure garment therapy may have been moderately suppressed by challenges with garment position and pressure maintenance.

Conclusions

The Red Duroc burn scar model provides the ability to probe the efficacy of a variety of treatments with internal controls and greater ability to control patient compliance. Pressure garment therapy at 10 mm Hg was found to be effective at reducing scar contraction. Modest improvements to scar biomechanics and structure also resulted from PGT use. While the current study indicated the efficacy of pressure garments, improvements to the therapy to provide greater benefit to skin biomechanics are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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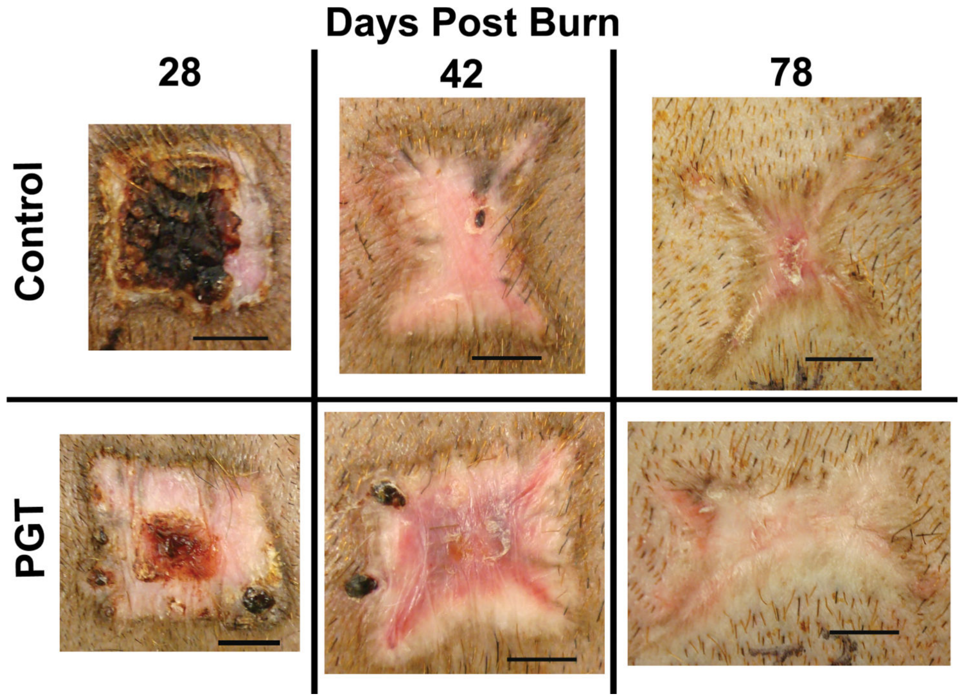

Figure 1.

Representative photographs of the scars 28-78 days post burn. Compression garments were applied at day 28.

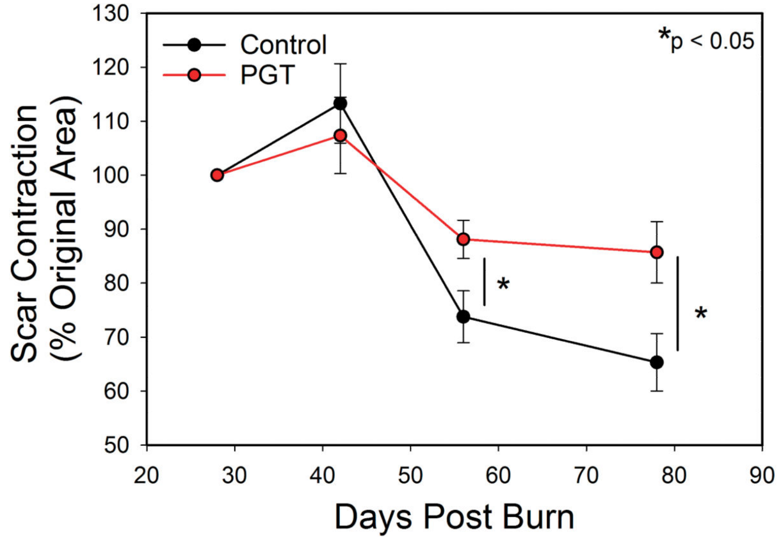

Figure 2.

Scar contraction, presented as percent of original area, as a function of time and treatment. As compression garments were applied at day 28, all area measurements are normalized to the scar area at this time point. After 28 days of garment application (56 days post burn), compression garment treated scars were significantly less contracted than control scars.

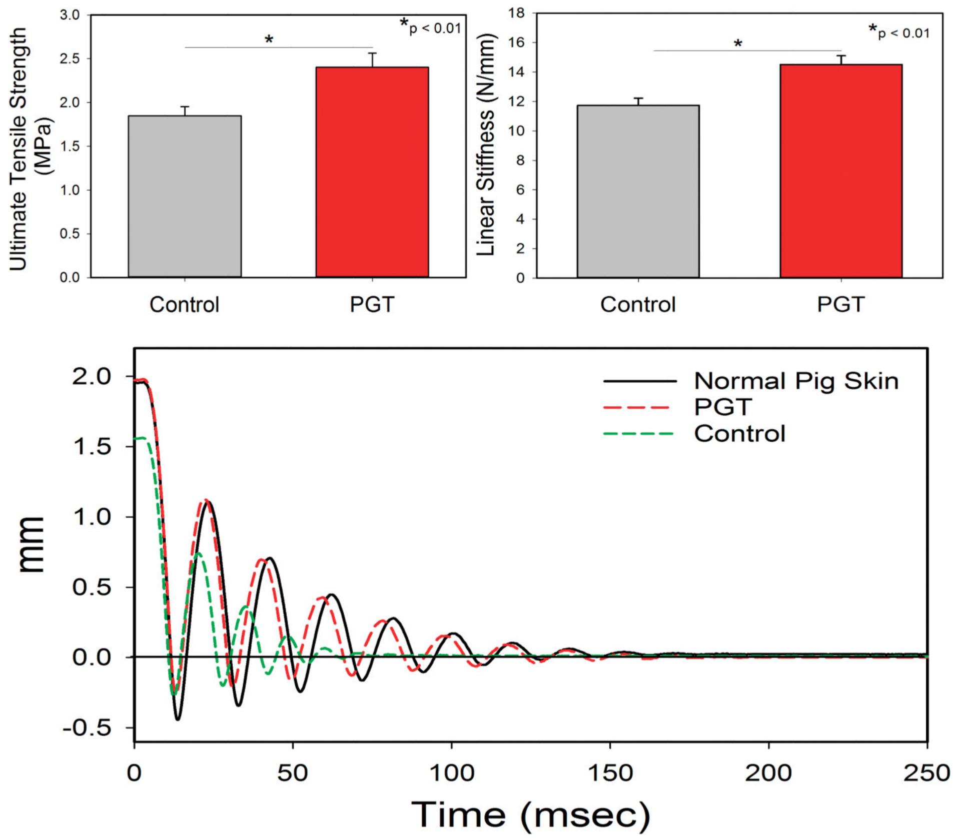

Figure 3.

Scar mechanics at day 78 post burn. A) Ultimate tensile strength and B) linear stiffness of compression garment treated wounds were significantly higher than control wounds. C) Torsional ballistometry of control scars, PGT treated scars and normal pig skin showed an increase in probe indentation and elasticity compared to control scars.

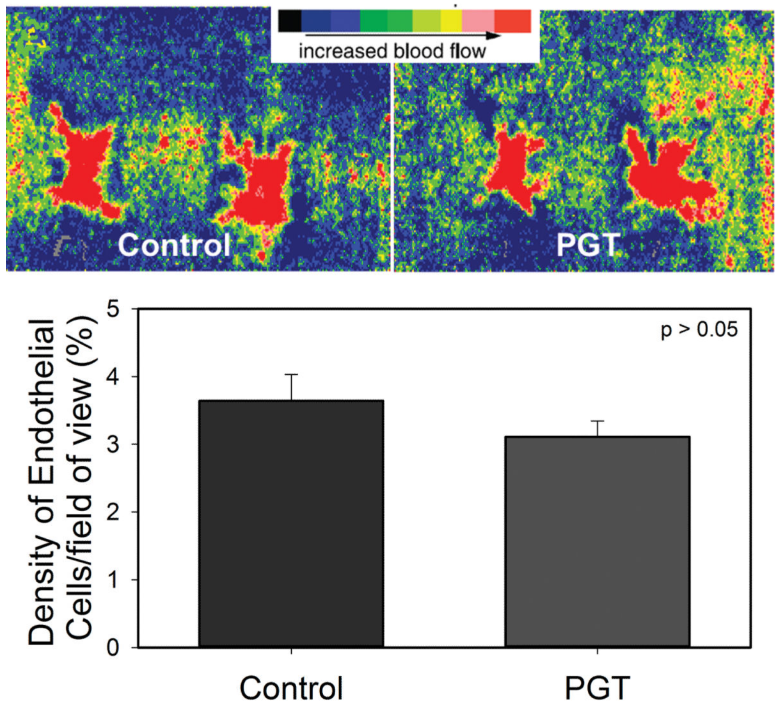

Figure 4.

A) Laser Doppler imaging of scars 78 days post burn showing no difference in blood flow between control and pressure garment treated groups. B) Immunostaining of endothelial cells (VWF) within burn scars at day 78. Quantification of endothelial cells density showed no significant difference in blood vessel density between control and pressure garment treatment.

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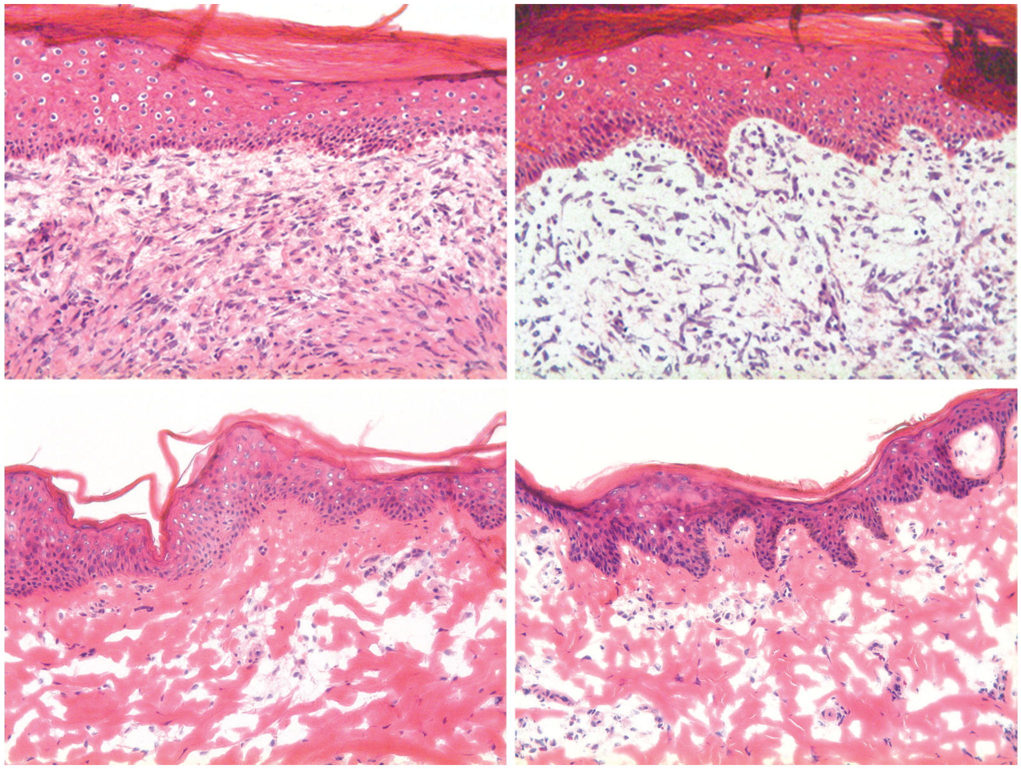

Figure 5.

H&E stained histological section of control (A&C) and pressure garment treated (PGT) burn scars (B&D) 42 (A&B) and 78 (C&D) days post injury.

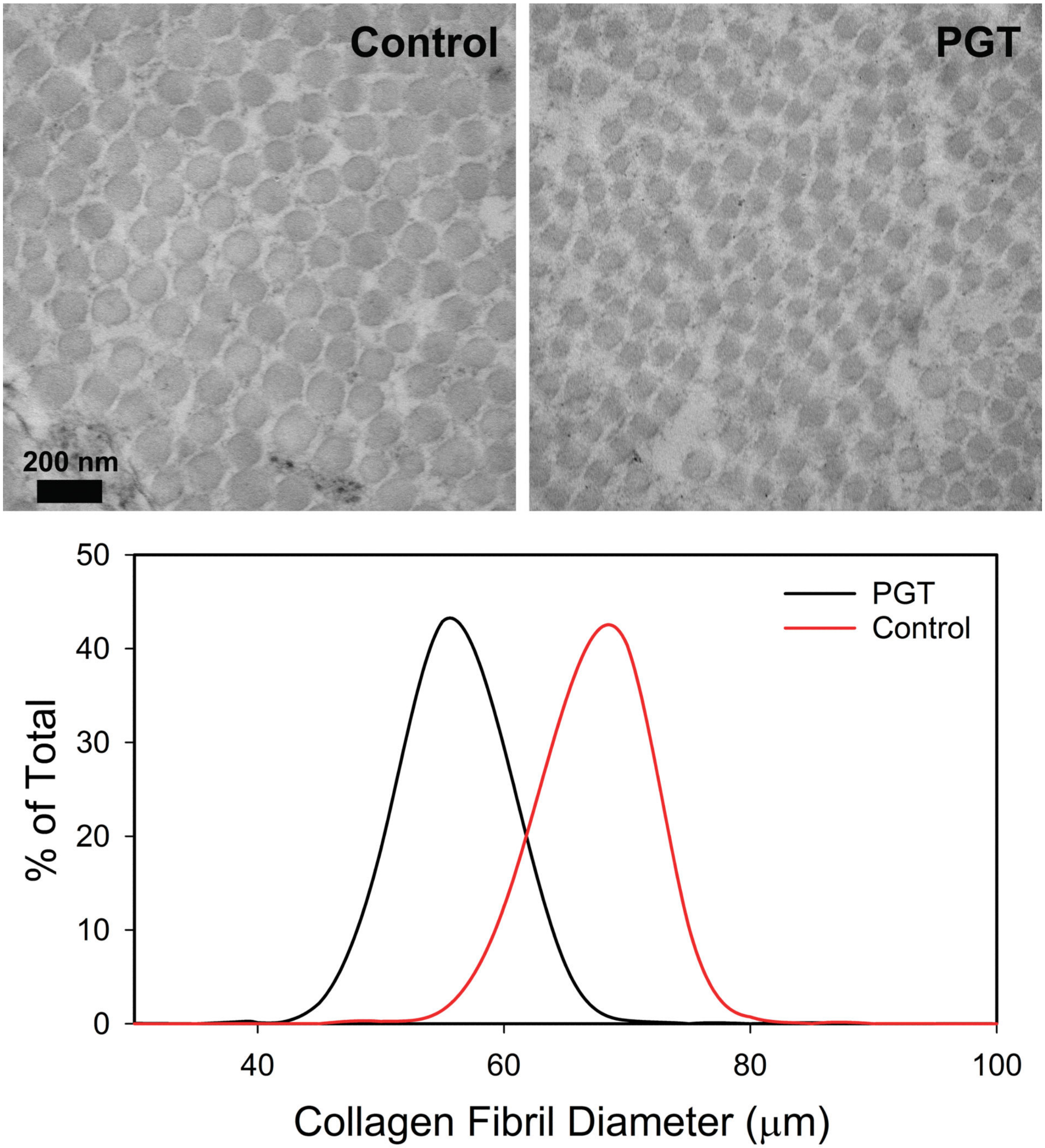

Figure 6.

Transmission electron micrographs of collagen fibers in control and pressure garment treated burns scars 78 days after injury. Scale bar = 100 nm. Control scars contain large, loosely packed collagen fibers whereas PGT scars are more densely packed with smaller diameter collagen fibers. B) Histogram of collagen fiber diameter distribution