# Electrochemical treatment of ex vivo human abdominal skin and potential use in scar management: A pilot study

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## Abstract

**Introduction:** Scar treatments aim to address pathologic collagen deposition; however, they can be expensive or difficult to control. Electrochemical therapy (ECT) offers a simple alternative treatment. The purpose of this study is to examine the acid-base and histological changes in ex vivo human abdominal skin following ECT.

**Methods:** Forty-two ex vivo human panniculus tissue sections collected from six individuals were tumesced with normal saline. ECT was performed by inserting two platinum needle electrodes connected to a DC power supply into each specimen. Voltage was varied (3–6 V) and applied for 5 minutes. Each specimen was sectioned across both electrode insertion sites and immediately stained with pH sensitive dye. The width of dye color change for each dosimetry pair was calculated. Hematoxylin and eosin staining was used to evaluate samples.

**Results and Discussion:** ECT caused a spatially localised and dose-dependent increased area of acidic and basic pH around the anode and cathode, respectively. A significantly greater mean width of pH change was generated at the cathode compared to the anode in all treatment groups. Histological evaluation displayed broad condensation and hyalinisation of dermal collagen.

**Conclusion:** ECT triggered dermal pH alterations and changed the underlying structural framework of the specimen. This technology may serve as a low-cost, minimally invasive local soft-tissue remodeling technique with potential application in scar management.

**Level of Evidence: 5**

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**Lay Summary**

Electrochemical therapy is a novel treatment that causes spatially selective dermal injury in areas of interest. This study measures the effects of electrochemical therapy when applied to abdominal skin. Electrochemical therapy appears to have beneficial effects by causing a highly localised reduction in collagen content or local softening of tissue, which is consistent with other studies on scar therapies, including chemexfoliation, radiofrequency technologies, and lasers. However, electrochemical therapy can be performed at a fraction of the costs of these aforementioned modalities.

## Introduction

The cutaneous wound healing response varies from scarless recovery to pathological hypertrophic and keloid scarring.[1] Unlike normal skin, scar tissue exhibits characteristic features such as collagen fiber misalignment, excessive dermal fibrosis, and disruption of skin texture.[2,3] Dermal scarring can cause significant physical and psychological distress for patients, and treatment is inexact and complicated.[4–6] There remains a need for new methods to treat cutaneous scars beyond the current therapeutic armamentarium.

There is little evidence on the efficacy of dermal scarring treatments for abdominal tissue compared to that which exists for the face. Abdominal skin differs from facial tissue in terms of blood supply, dermal thickness and active tensile forces.[7,8] Contemporary minimally invasive scar treatments include surgical scar revision, strain release mechanisms, silicone sheeting, pulsed dye or fractionated laser ablation, chemexfoliation, pressure therapy, microneedling and intralesional injection of platelet-rich plasma (PRP), steroids, 5-FU, bleomycin or verapamil.[7,9–14] The common therapeutic objective underlying these technologies is to address pathologic collagen deposition. However, some of these modalities require the use of expensive devices and can be difficult to control in skin, which is heterogeneous by nature. As such, there is a need for an inexpensive, minimally invasive, and simple-to-use scar therapy. One potential solution is electrochemical therapy (ECT).

ECT initiates oxidation-reduction (redox) reactions in tissue through the insertion of two passivated electrodes into a saline laden (tumescent) surgical field followed by the application of an electrical potential from a DC power supply.[15] Electrical energy is converted into chemical energy through hydrolysis at the electrodes, with paired redox reactions occurring within the tissue: reduction of water at the cathode and oxidation at the anode. Accordingly, this reaction generates pH gradients within the tissue through the production of hydroxide ions at the cathode and hydrogen ions at the anode, leading to spatially localised biophysical alterations. The potential of electrochemical therapy to reshape cartilage, lyse adipocytes and modify collagen in facial skin has been previously described.[15–21]

This study is the first to characterise the redox-induced alterations to ex vivo human abdominal skin. Specifically, we aim to identify structural changes that occur after these electrochemical reactions through pH landscape mapping and histopathologic analysis. We hypothesise that ECT will alter the abdominal dermal pH to stimulate innate wound healing processes and aid in collagen fiber reorganisation (Figure 1). The results of this preliminary ex vivo study may support the potential therapeutic role of ECT to treat human scar tissue through collagen remodeling.

## Methods

This ex vivo pilot study was approved by the University of California, Irvine Institutional Review Board (IRB). An IRB Waiver of Consent was granted for this protocol.

### Tissue preparation

Large (20 × 12 × 7 cm) specimens of non-identifiable, discarded human skin and adipose tissue were obtained from six patients after abdominoplasty procedures. Specimens were wrapped in phosphate buffered sodium-soaked gauze for up to four hours prior to processing to ensure freshness. Each specimen was further cut with a razor blade to obtain smaller sections with standard dimensions of 1 × 2 × 1.5 cm. Tumescence was achieved through the administration of 3 mL of normal saline (0.9% sodium chloride) over six injections via a 27-gauge needle, providing a medium for hydrolysis and more turgid tissue to facilitate electrode insertion.
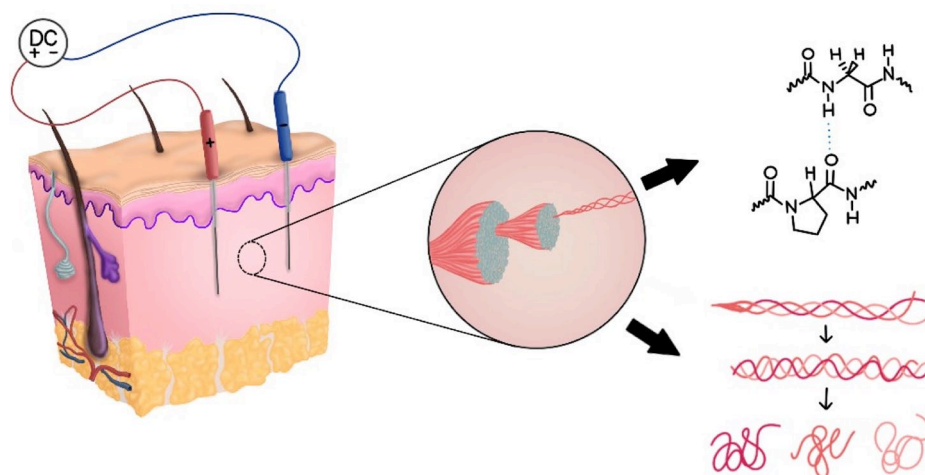
**Figure 1.** Hypothesised model of electrochemical therapy reaction within ex vivo human skin. (a) Insertion of electrodes into dermis with application of electrical potential converts electrical energy to chemical energy, generating hydrogen and hydroxide ions. (b) Triple helical structure of collagen fibers and (c) molecular structure of collagen stabilised by hydrogen bonds. (d) Proposed mechanism of electrochemical therapy, including alteration of hydrogen bonding and subsequent triple helical structure, and (e) nucleic acid and protein degradation. Original image.
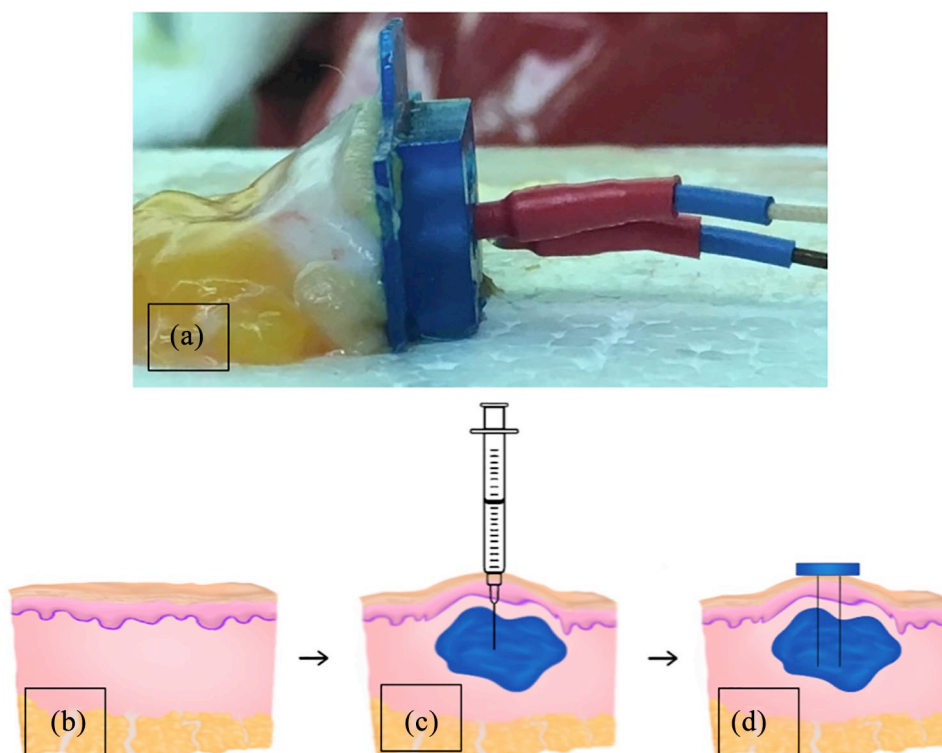


**Figure 2.** Experiment design. (a) Electrodes inserted into composite specimen held by three-dimensional printed jig on Styrofoam block. (b) Ex vivo human tissue. (c) Saline injected into tissue to achieve tumescence. (d) Electrodes inserted into tumesced tissue.

## Electrochemical therapy

Two platinum needle electrodes (13 mm in length) were inserted perpendicular to the dermal surface. A custom three-dimensional printed acrylic jig was placed along the dermal surface to space the electrodes 3 mm apart from one another and to secure them during experimentation (Figure 2). ECT was initiated in the experimental groups using current drawn from a DC

power supply (Agilent, Santa Clara, CA, USA) at dosimetry parameters of 3–6 V exposed over 5 minutes. These voltage and time parameters were chosen based on previous work demonstrating the therapeutic potential of ECT in ex vivo human facial skin and porcine skin.[18,19]

At minimum, at least five sections were studied per donor sample (one for each ECT treatment parameter). The maximum number of sections included per donor sample was limited both by time constraints impacting freshness of the tissue and experimenter error in sectioning the tissue precisely through the electrode insertion sites after ECT. Samples that were not sectioned precisely through the center points of the electrode insertion sites were excluded from the study.

### pH mapping

Specimens were sectioned with a razor blade through a sagittal midline across both anode and cathode electrode insertion sites. A single drop of halochromic pH sensitive dye (Micro Essential Lab, Brooklyn, NY, USA) was applied to the fresh-cut surface. The immediate color change was photographed with a digital single-lens reflex camera (Rebel XS EOS; Canon USA Inc., Melville, NY, USA), with the focus set between the electrode sites. An LED lantern shining through white fabric achieved standardised diffuse illumination of all samples. Both pH calibration and ruled scales were included in each photograph.

A custom MATLAB algorithm was developed to quantify the width of pH perturbations at both electrode sites in each photograph as previously described.[20] Briefly, photographs were processed using CIELAB, a color space designed to be perceptually uniform to human color vision. A custom algorithm allows users to define the region of interest (ROI) of a select color for semi-automatic segmentation. The mean ROI value and the Euclidean distances between each pixel within the ROI and the mean are then calculated. Images are segmented based on the boundary created by pixel values that are three standard deviations away from the calculated mean distance. A hole-filling technique removes any discontinuities. Finally, the averaged horizontal widths are outputted for further analysis. A two-tailed paired t-test compared the mean width of pH alteration differences between anode and cathode sites at each treatment voltage. Statistical significance was assigned to $P < 0.05$.

### Histology

ECT-treated and control samples of composite skin were fixed in 10% formalin in a 20:1 solvent-to-tissue volume ratio for at least one week. Fixed specimens then underwent automated processing (Tissue-Tek VIP 6-A1, Sakura) according to the standard large breast tissue schedule at the University of California, Irvine Medical Center.

Sectioning was performed with a rotary microtome (Swerdlick systems, HM 340 E) and disposable knife blade. Section thickness was in the range of 6–10 µm. Whole-mount sections were stained with hematoxylin and eosin (H&E). A light microscope at 2× magnification captured representative images of ECT-treated sites and controls.

Original figures were created with Autodesk Sketchbook on iPad. Statistical analysis was performed utilising Microsoft Excel.

## Results

Between five and ten small sections from each of the six large human donor specimens were used constituting a total of 42 small sections included in the study (control: n = 6, 3V-5min: n = 7, 4V-5min: n = 10, 5V-5min: n = 11, 6V-5min: n = 8).

### pH mapping

ECT induced acid-base chemical reactions at the anode and cathode sites, respectively, visualised as pH perturbation (Figure 3). Acidic pH (red) was noted bordering the anode insertion site, and basic pH (blue) surrounding the cathode insertion site, consistent with hydrolysis and generation of hydrogen and hydroxide ions at the respective electrodes. This effect was dose-dependent and spatially localised.

A custom automated computer software quantified the spatial extent (mm) of pH perturbation surrounding the electrode insertion sites at each treatment voltage. The average width of pH alteration (mm) at both electrode sites expectedly increased with increasing voltage (Figure 4). Data analysis demonstrated a statistically significant ($P < 0.05$) greater width of pH change at the cathode compared to the anode in in all treatment voltages (Table 1).

### Histology

Representative histological images of samples are shown, demonstrating morphology of
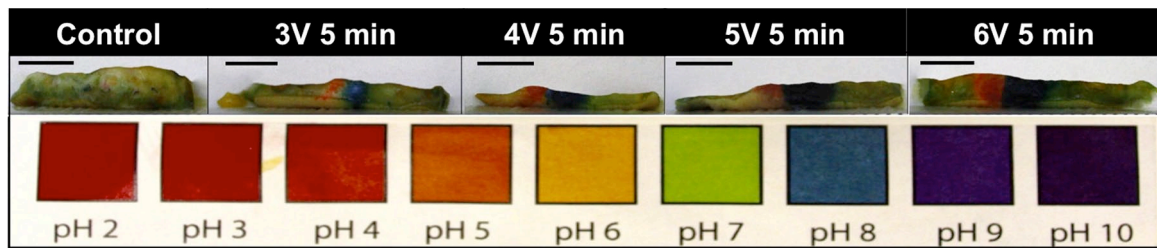
**Figure 3.** Effect of electrochemical therapy on composite human dermis with increasing voltage (V) and constant time (5 min), visualised as pH perturbation in hemisected samples. Samples are oriented with the surface of insertion site (epidermis) along the bottom. Alteration of pH is seen as color change at anode (red) and cathode (blue) sites. Universal pH indicator included for reference. Scale = 0.5 cm.
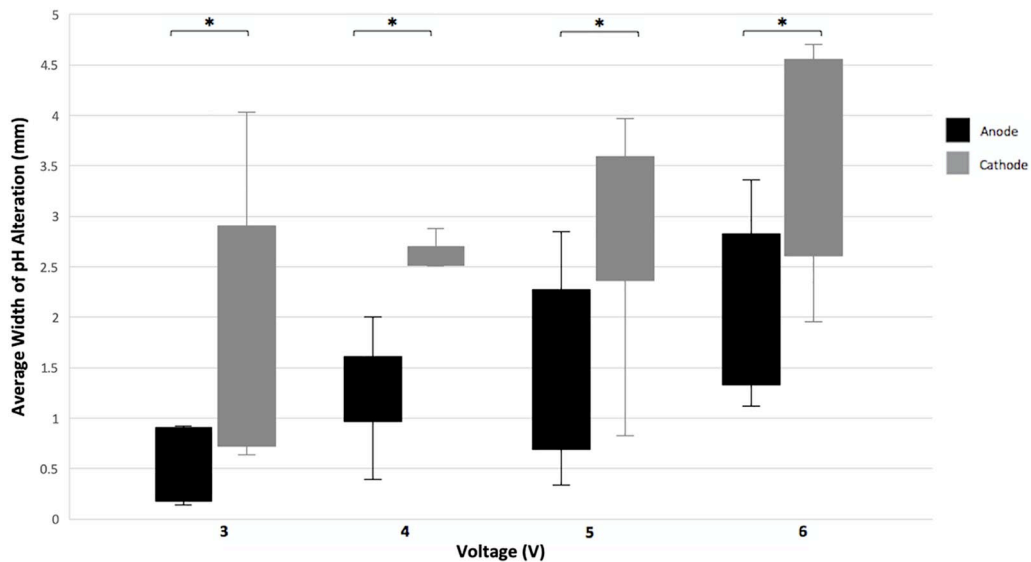


**Figure 4.** Effect of electrochemical therapy (mm) on human abdominal dermis at constant time (5 min) and increasing voltage (3V-5 min: n = 7, 4V-5 min: n = 10, 5V-5 min: n = 11, 6V-5 min: n = 8). There was a significantly greater width of pH change at the cathode compared to the anode in all treatment groups ($P < 0.05$).

dermis (Figure 5) in control and ECT-treated tissue. In control dermis (Figure 5a, f), well organised collagen fibres are present. In the 3V-5min treatment group, hyalinisation of dermal collagen is noted at the anode site (Figure 5b), with smudging along the electrode tract showing sclerotic changes with loss of normal collagen configuration. At the cathode site (Figure 5g), similar dermal change is seen with the additional loss of the deep dermal layer and detachment from the subcutaneous layer. In the 4V-5min treatment group, a wide area of homogenised denaturation of dermal collagen is appreciated at both the anode (Figure 5c) and cathode (Figure 5h) sites. The 5V-5min anode sample displayed broad denatured areas of dermal collagen with minor loss of the epidermis, and a cleft appearing to be made from electrode insertion (Figure 5d). Interestingly,

change implying desiccation is observed surrounding the cleft made by the anode. The cathode sample showed similar denaturation of dermal collagen (Figure 5i). Both anode and cathode sites in the 6V-5min samples display completely disorganised dermis in shreds (Figure 5e, j), with some focally homogenised collagen along the path of the anode.

## Discussion

The application of a chemical substance to create superficial dermal injury and trigger regeneration and remodeling is a widely accepted treatment for many dermatologic conditions, though most widely used for rejuvenation (e.g. chemical peels). ECT generates localised hydrogen and hydroxide ions at the anode and cathode sites where they contact the skin, respectively,

**Table 1.** t-test results comparing mean ECT effect (mm) at anode and cathode for each treatment voltage.

| Treatment | | Mean width (mm) | SD | n (%) | t | P value |
|---|---|---|---|---|---|---|
| Control | Anode | 0 | 0 | 6 (14.3) | – | – |
| | Cathode | 0 | 0 | | | |
| 3V-5min | Anode | 0.504 | 0.3 | 7 (16.7) | −2.45 | 0.031* |
| | Cathode | 1.729 | 1.3 | | | |
| 4V-5min | Anode | 1.339 | 0.7 | 10 (23.8) | −5.31 | <0.001* |
| | Cathode | 2.542 | 0.3 | | | |
| 5V-5min | Anode | 1.419 | 0.9 | 11 (26.2) | −3.28 | 0.004* |
| | Cathode | 2.712 | 1.0 | | | |
| 6V-5min | Anode | 2.056 | 0.8 | 8 (19.0) | −3.56 | 0.003* |
| | Cathode | 3.746 | 1.1 | | | |

*denotes statistical significance.
ECT, electrochemical therapy; SD, standard deviation.
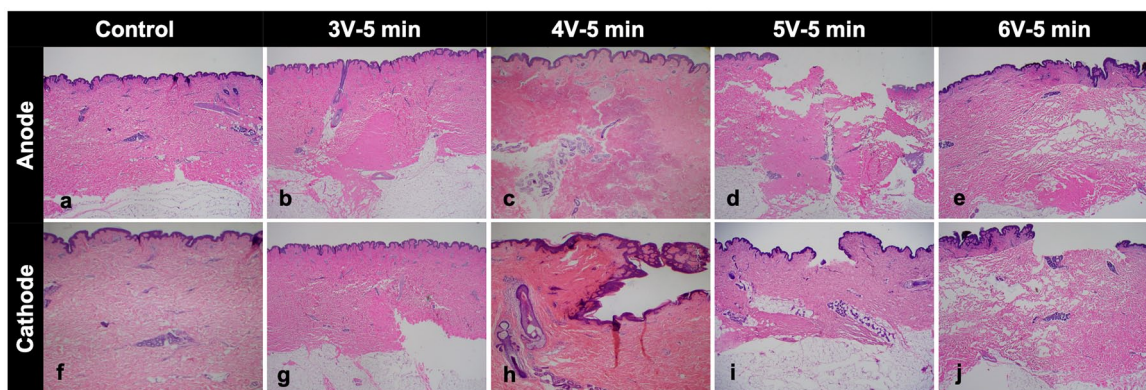


**Figure 5.** H&E staining of dermis. ECT was performed at increasing voltage over a constant duration of 5 min. Representative microscopic fields of untreated control (a, f); anode sites of 3V-5min (b), 4V-5min (c), 5V-5min (d), 6V-5min (e); and cathode sites of 3V-5min (g), 4V-5min (h), 5V-5min (i), and 6V-5min (j) are depicted. Images are shown at 2× magnification. ECT, electrochemical therapy; H&E, hematoxylin and eosin.

through water hydrolysis. Through a series of preliminary studies on ex vivo porcine skin, we have demonstrated with optical coherence tomography, high-frequency ultrasound, and optical coherence elastography that ECT alters the tissue collagen matrix, presumably due to pH perturbations.[18,19] Here, we demonstrated the efficacy of ECT on cutaneous abdominal skin freshly obtained from individuals who have undergone abdominoplasty.

The acute alteration of tissue collagen found in this study supports anticipated future work focused on ECT as a means to target the dermis in scar tissue. While speculative, spatially selective dermal injury may lead to a highly localised

reduction in collagen content or local softening of tissue which, in turn, may facilitate the injection of agents such as steroids.

Histological evaluation of human abdominal dermis in our ECT-treated samples displayed broad condensation and hyalinisation of dermal collagen, indicated by a smooth, granular layer in the superficial dermis. Clefting was also evident within the dermal layer of samples treated with ECT at higher voltages, likely due to degeneration. These alterations to tissue collagen are consistent with other studies on scar therapies including chemexfoliation, radiofrequency technologies, and lasers.[22–25] However, whereas radiofrequency and laser-based technologies cause

heat-based collagen denaturation, ECT presumably acts through in situ electrochemistry. Notably, although we did not directly measure dermal heat in this study, only minimal temperature elevation far below the denaturation threshold has been identified in other ECT studies using cartilage or porcine skin.[18,26]

At each voltage, the area of pH change at the cathode (base site) was consistently larger than the anode (acid site). The greater effect of ECT at the cathode compared to the anode has been previously demonstrated in prior studies and was expected.[19,20,22] pH mapping revealed an increase in effect area with increasing voltage, suggesting that dosimetry parameters (along with electrode geometry) may be adjusted to treat a precise area and depth of cutaneous tissue. This direct acid base dose-response relationship is consistent with previous works on ECT and is likely due to the generation and migration of chemical species down both their concentration and electropotential gradients.[17,19,27] With this in mind, investigations are currently underway to develop non-invasive methods of topical ECT application. Such technology would permit spatially controlled epidermal injury that would mimic a superficial chemical peel.

This pilot study is an important first step to describe the fundamental electrochemical and histologic effects of the ECT process in human abdominal skin. While our preliminary results demonstrate the potential efficacy of ECT to promote tissue regeneration, we tacitly acknowledge several important limitations. Due to the ex vivo nature of our study, we are unable to describe any long-term effects of the dermal homogenisation induced by ECT. In vivo animal studies are ongoing to evaluate the evolution of any potential inflammatory infiltrate following ECT-induced collagen disruption. Additionally, specimens were collected from a heterogeneous patient population who differ in age, prior abdominal surgeries or other dermatologic irregularities at the time of surgery. Each of these factors alter skin integrity and can thus influence the therapeutic effect of ECT.[28]

## Conclusion

This pilot study examined the acute electrochemical and histopathologic effects of ECT on ex vivo human abdominal skin and is a stepping-stone to future studies. ECT is a low-cost, simple to use technology that may serve as a novel minimally invasive outpatient scar revision therapy. This technology has potential future applications as an adjunct or solo therapeutic option for scars, including those in the abdominal wall (e.g. stretch marks, cesarean section or any other post-operative scars). The target therapeutic goal of ECT is to correct aberrant fibrotic collagen matrix through tissue remodeling and restructuring. Additionally, we postulate ECT may serve as an adjunct to the intralesional injection of wound healing modulators by softening the dense tissue matrix to make the dermis more amenable to drug delivery. However, the study of ECT in in vivo animal skin models, and subsequently in in vivo human models, is needed to further characterise the effects and limitations of the technology. Future studies are required to optimise needle placement, investigate the chronic effects of ECT and better understand the potential therapeutic value of ECT between heterogeneous cutaneous tissues. Work in in vivo animal studies as well as needle electrode design is ongoing and will offer further insight into the potential clinical application of ECT.

ECT at the studied dosimetry parameters induced acid and base changes in human dermis leading to alterations of the underlying collagen matrix. Its dose-dependent and spatially localised effects make it an attractive low-cost alternative to current surgical and pharmaceutical scar revision therapies.

## Declaration of conflicting interests

## Funding

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