# Stimulation of Collagen Synthesis in Human Skin Following Ultherapy®

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## INTRODUCTION

- Collagen synthesis occurs through a highly-regulated process by which newly-synthesized collagen molecules are secreted and then stabilized within the existing extracellular matrix by intermolecular crosslinking[1].
- Ultherapy® (microfocused ultrasound with visualization, MFU-V; Merz North America, Inc.) is the only non-invasive procedure FDA-cleared to lift, not just tighten, the skin on the neck and brow, and under the chin[2].
- Ultherapy triggers the natural healing process resulting in gradual collagen and elastin production[1-2]
- Ultherapy is an energy modality that can be focused to penetrate deeper into the tissue and cause discrete zones of thermal coagulation, avoiding the undesirable post-treatment effects observed with treatment modalities unable to avoid the superficial layers.
  - Optimally focused thermocoagulation points stimulate neocollagenesis
  - Ultherapy reaches ideal temperatures for enhanced rejuvenation while preserving the skin's integrity
- Ultherapy uses real-time ultrasound visualization to deliver energy precisely and accurately[2-3], and is the only technology that treats at isolated depths to target specific foundational tissues where laxity begins[2-3]

**Figure 1. Dual Modality Ultrasound**

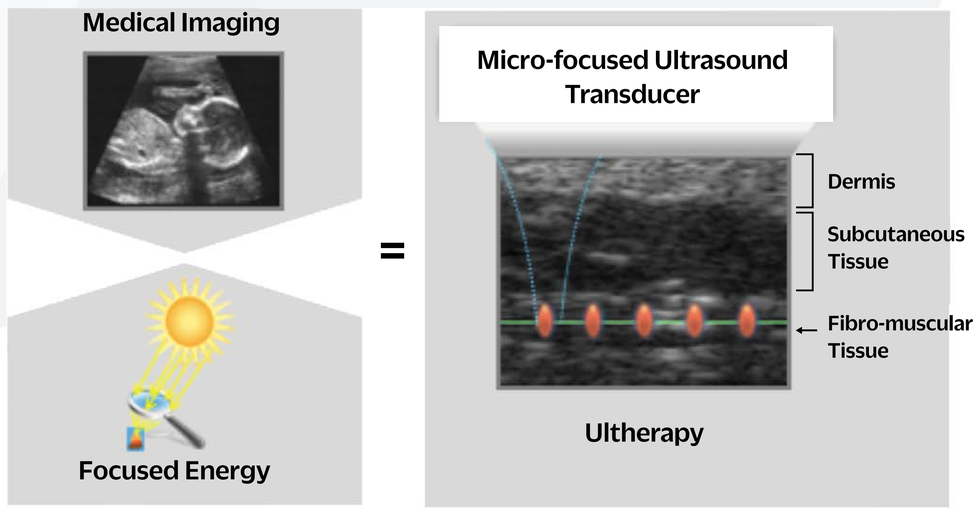
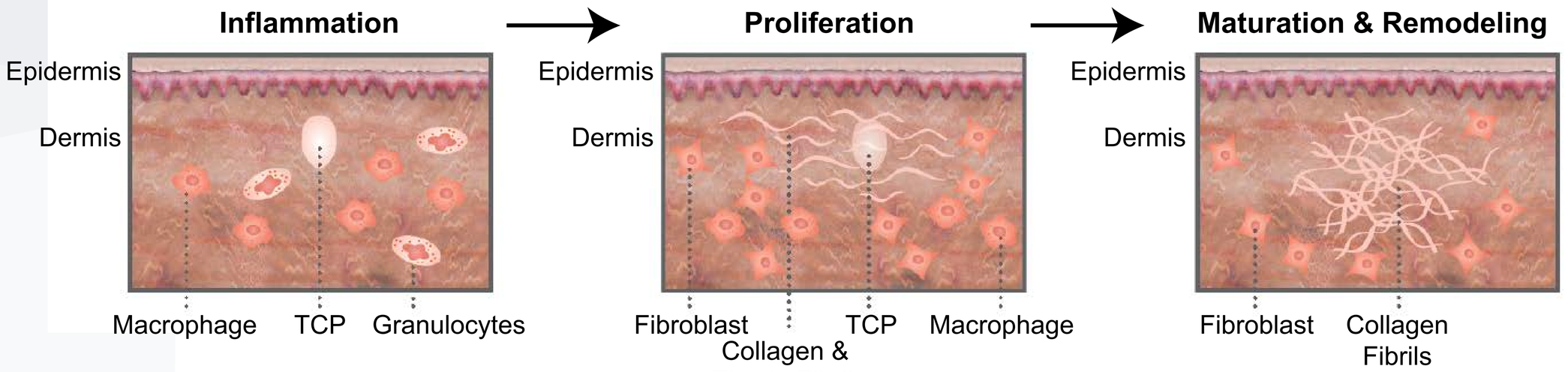



**Figure 2. Ultherapy® Mechanism of Action: Neocollagenesis**



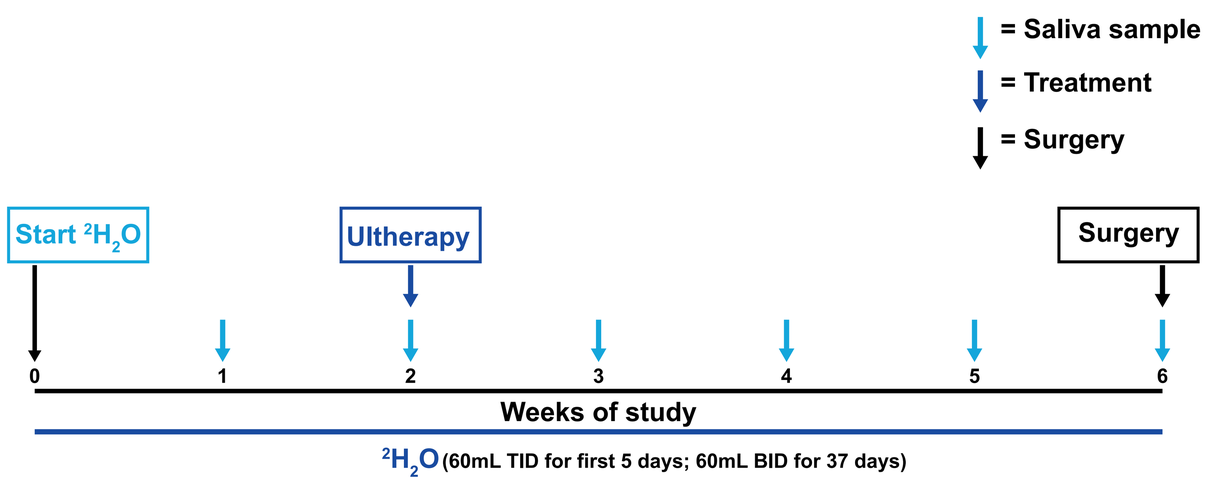

## METHODS

- Prospective, single-center, single-blinded, non-randomized study
- **Primary Endpoint:** The rate of collagen synthesis in tissue treated with Ultherapy compared to non-treated tissue.

**Heavy water**

- Using a stable isotope labeling method[4], the synthesis rate *in vivo* of slow turn-over proteins, e.g., collagen, can be determined by measuring the incorporation of deuterium ($^2H$) from heavy water ($^2H_2O$) into the stable C-H bonds of hydroxyproline in the newly synthesized protein.
- $^2H_2O$ is a safe, non-toxic, non-radioactive isotope safe for use in clinical studies.
- The objective was to assess the effect of Ultherapy treatment on the rates of synthesis and deposition of dermal and subcutaneous tissue collagen.
- A tissue labeling model was used via the consumption of the stable isotope, deuterated water (heavy water).
- The consumption of heavy water and collection of saliva over the course of the study period, and the resection of Ultherapy treated and control tissue at the end of the study period allowed for a direct kinetic measure of in vivo collagen synthesis.

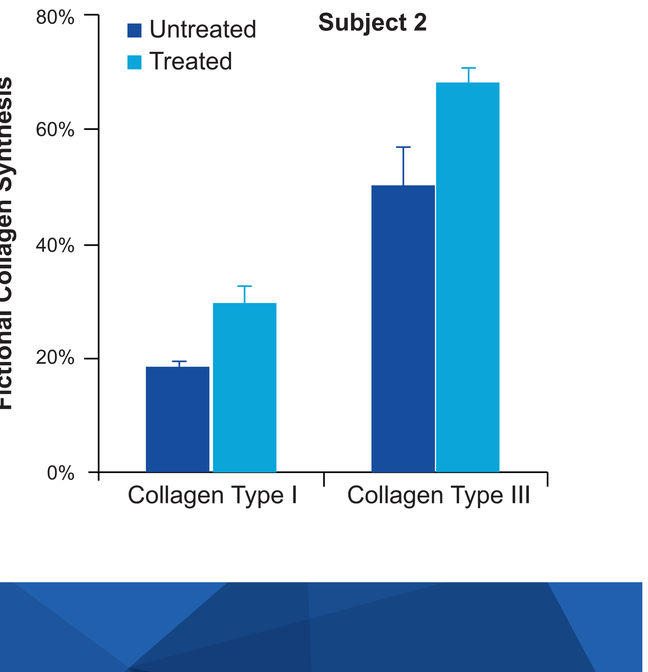
**Figure 3. Study Design**




**Overview**

- 2 female subjects scheduled to undergo a rhytidectomy were administered heavy water for a total of 6 weeks prior to surgery to label newly-synthesized proteins with heavy hydrogen
- At study onset, subjects began drinking heavy water daily
- Starting at Week 1, saliva samples were taken weekly to ensure subject compliance
  - Two weeks later, the preauricular area of one side of the face was treated with a dual density treatment (30 lines using the 7-3.0mm transducer and 30 lines using the 4-4.5mm)
- Subjects continued to drink heavy water daily for 4 more weeks until the time of surgery
- Skin samples were taken from the left and right side after unilateral Ultherapy treatment
- Isolated collagen (Types I and III) proteins were analyzed for isotopic labeling by liquid chromatography/mass spectrometry to determine new collagen synthesis.
- Several tissue samples from each side of the face were analyzed in blinded fashion.
- Collagen was extracted with guanidine & analyzed for isotopic labeling by isotope ratio mass spectrometry (IRMS) to determine the new collagen synthesis over 6 weeks

**Figure 4. The preauricular area treated with triple density Ultherapy and subsequently excised during rhytidectomy.**




## RESULTS

**Safety and Efficacy**

- No adverse events were reported
- In both subjects, the induction of a dermal and subdermal repair response by Ultherapy increased the proportion of recently-synthesized collagen.
- Type I and Type III collagen synthesis was 8.4% and 16.8% higher respectively, on the treated side compared to control tissue.
- Type I collagen synthesis increased 5.5% to 21% in Subject 1 and 11.2% to 30% in Subject 2. (**Figure 5**)
- Type III collagen synthesis increased 15.7% to 52% in Subject 1 and 17.8% to 68% in Subject 2. (**Figure 5**)
- Synthesis of Type I collagen increased by 26% on average
- Synthesis of Type III collagen increased by 60% on average

**Figure 5. Mean change in soluble Type I and Type III collagen synthesis 4 weeks after Ultherapy treatment.**




Standard deviations of replicate measurements are represented by error bars.

## CONCLUSIONS

- **Collagen (Types I and III) synthesis rate was increased 1.5-fold after the Ultherapy treatment**
- **After only 4 weeks post-treatment:**
  - **Type I collagen synthesis increased an average of 26% on the treated side**
  - **Type III collagen synthesis increase an average of 60% on the treated side**
- **On average, the rate of collagen production on the Ultherapy-treated side was 42% higher compared to the untreated side.**

**References:** 1. Hulmes DJS. Collagen Diversity, Synthesis and Assembly. In, Fratzl P. (ed.), Collagen:Structure and Mechanics. Springer Science+Business Media, LLC. 2008. 2. Ulthera Instructions For Use. 3. White WM, Makin IRS, Barthe PG, et al. Selective creation of thermal injury zones in the superficial musculoaponeurotic system using intense ultrasound therapy. *Arch Facial Plast Surg*. 2007;9(1):22-29. 4. Dobke MK, et al. Tissue Restructuring by Energy-Based Surgical Tools. *Clin Plastic Surg*. 2012;39:399–408.

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