SYNCHRONIZED RF & HIFEM: MULTI-CENTER ABDOMINAL ULTRASOUND STUDY

RADIOFREQUENCY HEATING AND HIFEM DELIVERED SIMULTANEOUSLY - THE FIRST SHAM-CONTROLLED RANDOMIZED TRIAL

Bruce Katz MD[1], Robert Weiss MD[2], Julene B. Samuels MD[3] F.A.C.S

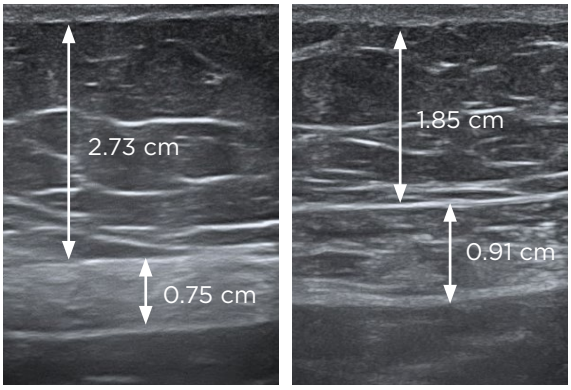
1. Juva Skin and Laser Center, Manhattan, NY, USA; 2. Maryland Laser Skin & Vein Institute, Hunt Valley, MD, USA; 3. Julene B Samuels MD. F.A.C.S, Louisville, KY, USA

Presented at the Annual Meeting of the American Society for Dermatologic Surgery, 2020 Virtual Meeting.

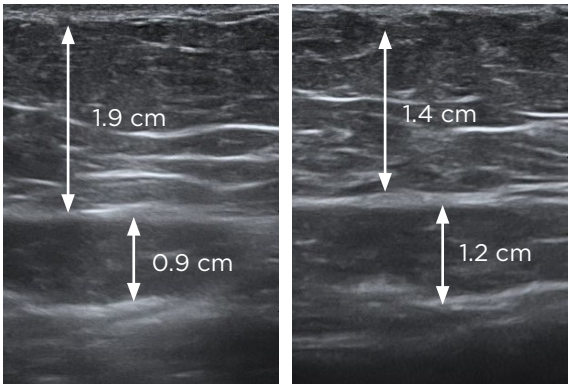
HIGHLIGHTS

- A total of 72 subjects allocated into two groups (Active: N=48, **BMI of 25.8 kg/m2)**; Sham: N=24, **BMI of 25.6 kg/m2)**.
- Active group showed **28.3% reduction in subcutaneous fat** at **3-month** follow-up visit.
- **Muscle thickness** increased by **24.2%** at **3-months** post-treatment in **active group**.
- At 3 months **38/40 patients** showed fat reduction **higher than 20%**.

A 64-YEAR OLD FEMALE



A 51-YEAR OLD FEMALE



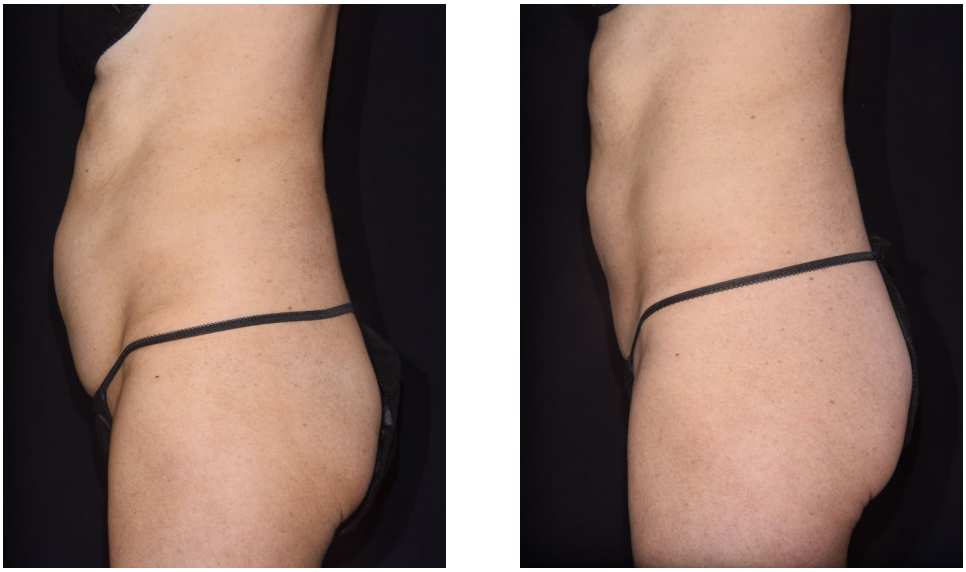
Ultrasound images of patients in active group taken before (left) and 1 month after (right) the treatments.

STUDY DESIGN

- Both groups received three 30-minute treatments on abdomen (active: maximum tolerable intensities, sham: intensities of 5%).
- Ultrasound images were taken at baseline, 1M and 3M after the last treatment.
- Evaluation included measurements of subcutaneous fat and muscle mass thickness.

CONCLUSION

- **Dual field technology** showed **high efficacy** for subcutaneous **fat reduction** and thickening of **rectus abdominis muscle**.
- **93.9%** of patients reported satisfaction with the results.
- **Sham treatments did not induce** any **significant changes**.
- **The procedure** combining HIFEM and RF energy **was safe** and did not cause any adverse events.



Digital photographs of a 55-year old female, taken before (left) and 3 months after (right) the treatments.

SYNCHRONIZED RF & HIFEM: FAT HISTOLOGY & SCANNING ELECTRON MICROSCOPY STUDY

SIMULTANEOUS APPLICATION OF HIFEM AND SYNCHRONIZED RADIOFREQUENCY FOR FAT DISRUPTION: HISTOLOGICAL AND ELECTRON MICROSCOPY PORCINE MODEL STUDY

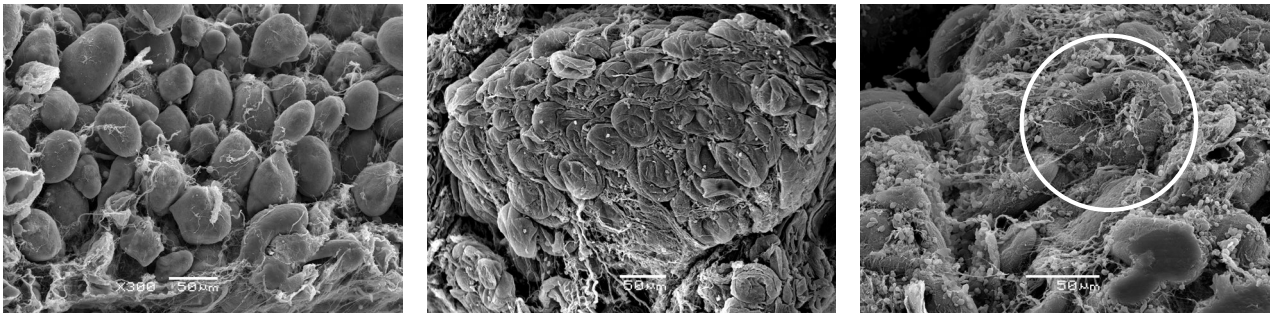
Robert A. Weiss MD, FAAD[1], MVDr. Jan Bernardy Ph.D.[2], Prof. MVDr. Frantisek Tichy, CSc[3]

1. Maryland Laser Skin & Vein Institute, Hunt Valley, MD, USA; 2. Veterinary Research Institute, Brno, CZ
3. Department of Anatomy and Histology, University of Veterinary and Pharmaceutical Sciences Brno, CZ

Presented at the Annual Meeting of the American Society for Dermatologic Surgery, 2020 Virtual Meeting.

HIGHLIGHTS

- Both **histology** and **scanning electron microscopy** showed **damaged adipocytes** post-treatment due to apoptosis and lipolysis.
- **Adipocyte size** was **decreased by 31.1%** at 2 weeks post-treatment.
- The **temperature** in fat tissue was maintained **just below 45°C** for the entire treatment.
- **No necrosis** was seen in the tissue.



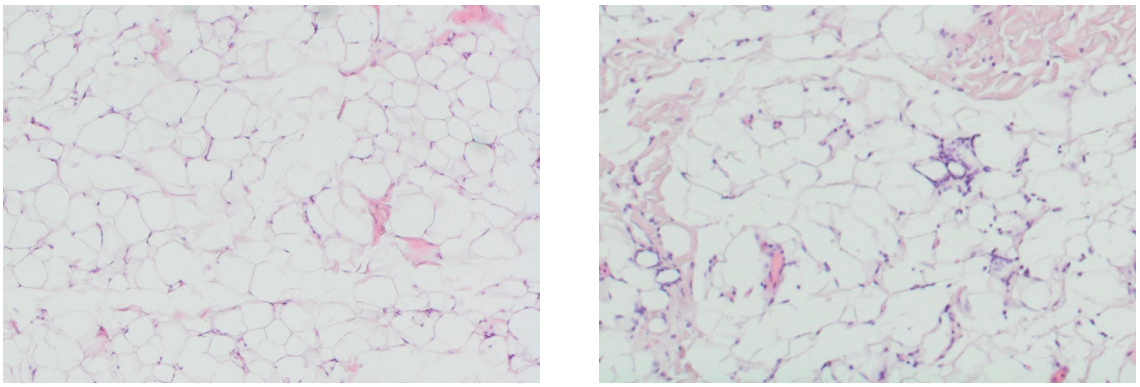
Healthy fat cells with well-defined shape at the baseline (left); shrunk adipocytes with noticeable membrane ruptures occurred at 4 days (center); disrupted adipocytes with extrusion of lipid droplets at two weeks (right)

STUDY DESIGN

- 7 Large White pigs (approximately 6 months old).
- All animals received three 30-minute treatments applied to abdomen.
- Biopsy specimens of fat tissue were collected at baseline, 4 days, 2 weeks, 1 month and 2 months post-treatment for each animal.
- Control specimens were collected from the site opposite to the treatment site.
- Evaluation included scanning electron microscopy and histology.

CONCLUSION

- The procedure elevates the **temperature** in subcutaneous fat to levels **necessary** for **apoptosis induction**.
- **Efficacy** of the procedure for **disruption of adipocytes** was documented in **252** analyzed tissue slices.
- Mild inflammatory response was present to promote the **apoptotic death cells removal**.
- The procedure was **safe, no burns, no necrosis** or other adverse events were documented.



Baseline histology (left) showed adipocytes without any damage. At 2 weeks (right), flattened adipocytes with delaminated membranes are seen along with immune cells clearing the damaged tissue.

SYNCHRONIZED RF & HIFEM: HISTOLOGICAL EVALUATION OF THE EFFECT ON FAT IN HUMANS

HISTOLOGICAL EVALUATION OF THE SIMULTANEOUS RF AND HIFEM TREATMENTS ON HUMAN FAT TISSUE

Radina Denkova MD.

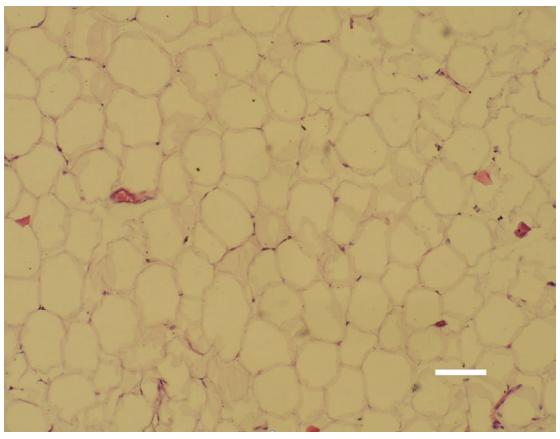
1. Aesthetic Clinic Beauty, Sofia, BG

Source: U.S. Food and Drug Administration. 510(k) Premarket Notification: K192224.Published online December 5, 2019.

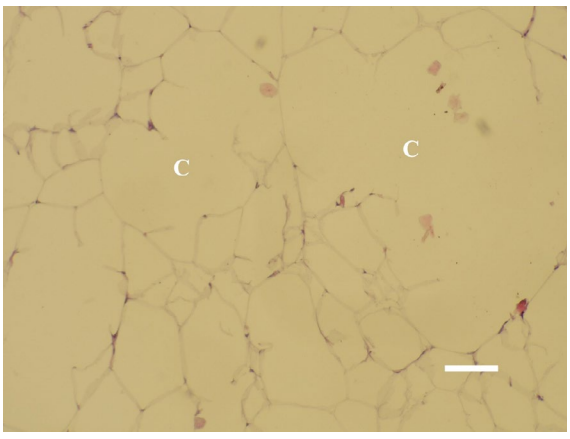
HIGHLIGHTS

- **Intensive fat cell disruption peaking at 20 days post-treatment**.
- **Non-invasive lipolysis** seen in the **first 10 days** post-treatment.
- Investigated device was found to be effective for **elimination of fat cells**.
- **No damage** to skin, sweat glands and sebaceous glands was observed, ensuring procedural safety.
- **Deformed nucleus** and pyknotic nucleus indicating **cell death**.

BASELINE



20 DAYS AFTER



Normal subcutaneous tissue morphology with typical uniform size of adipocytes at the left; bar = 40 micrometers. Intensive fat cell disruption (C) and alternation of adipocytes shape 20 days post-treatment at the right; bar = 30 micrometers.

SYNCHRONIZED RF & HIFEM: ULTRASOUND EVALUATION OF FAT TISSUE

ULTRASOUND EVALUATION OF THE SIMULTANEOUS RF AND HIFEM TREATMENTS ON HUMAN FAT TISSUE

Radina Denkova MD[1]

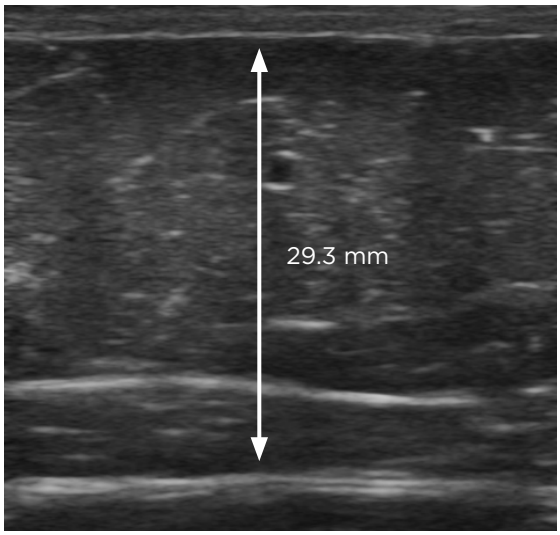
1. Aesthetic Clinic Beauty, Sofia, BG

Source: U.S. Food and Drug Administration. 510(k) Premarket Notification: K192224.Published online December 5, 2019.

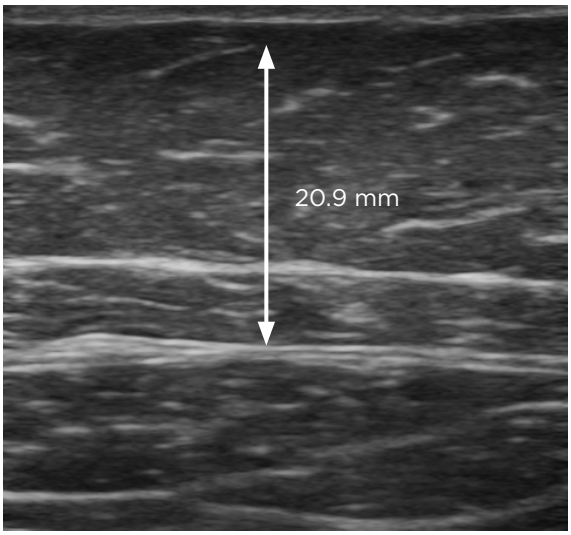
HIGHLIGHTS

- **Reduction** in **subcutaneous fat thickness** at 3 months was **29.8%**.
- A total of **88.1%** of patients **were satisfied** with treatment outcomes.
- **92.9%** of patients found the treatments **comfortable**.
- Waist **circumference** was **reduced** on average **by 3.2 cm**.

BASELINE



3 MONTHS AFTER



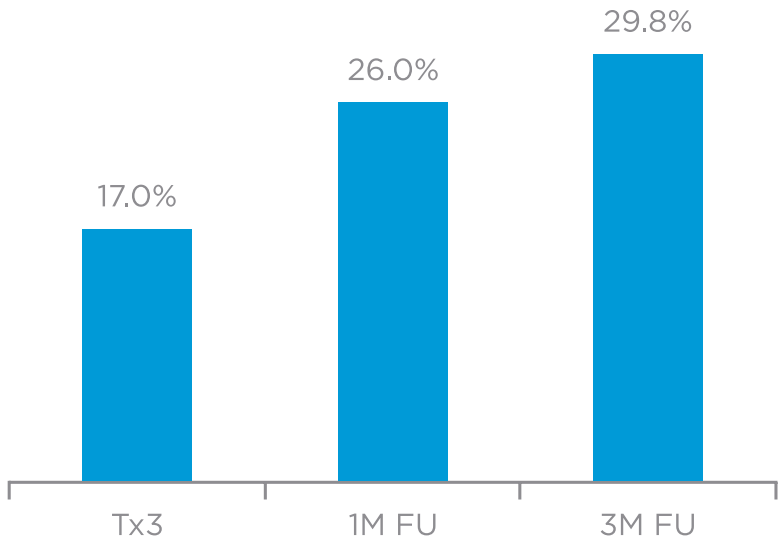
Ultrasound images of a 42-year old female, who also showed a 4-cm reduction in waist circumference.

STUDY DESIGN

- 42 subjects (29 females, 13 males).
- Three 30-minute treatments on abdomen.
- Evaluation by ultrasound imaging.

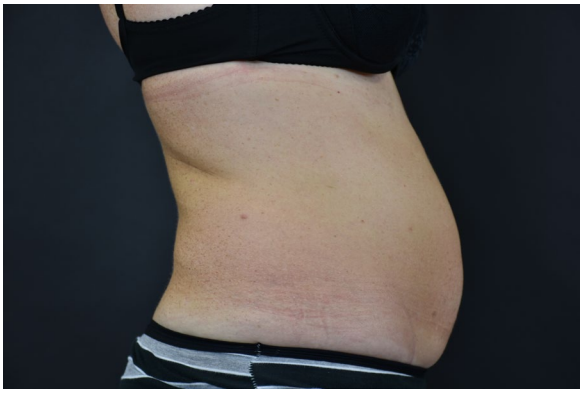
RESULTS

- Results showed continuous improvement over time.

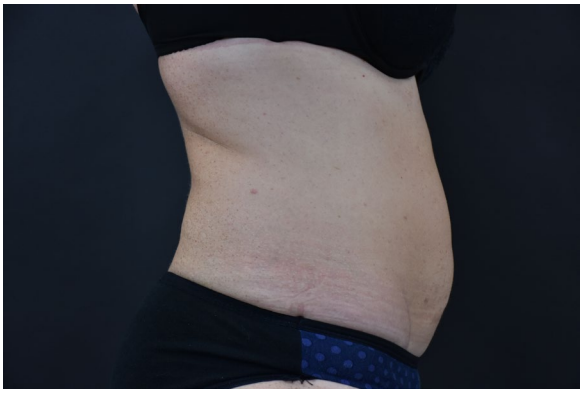


The chart showing continuous improvement in the fat reduction over time.

BASELINE



3 MONTHS AFTER



A 49-year old female at baseline and 3 months post-treatment showing 4.5 cm waist circumference reduction and 29.2% reduction in abdominal fat layer.

SYNCHRONIZED RF & HIFEM: HUMAN FAT HISTOLOGY & TEMPERATURE MEASUREMENT

ADIPOCYTE APOPTOSIS INDUCED BY SYNCHRONIZED RADIOFREQUENCY WITH HIFEM PROCEDURE: HUMAN HISTOLOGICAL STUDY

David J. Goldberg MD, JD[1]

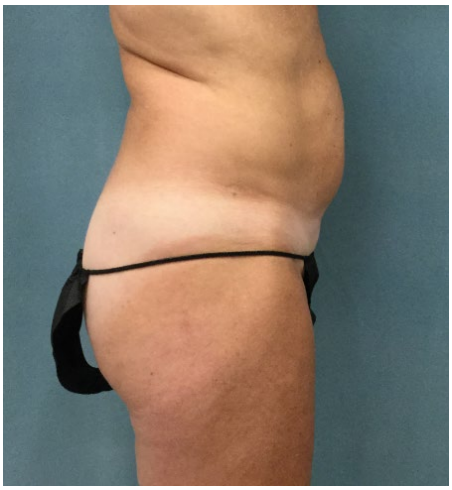
1. Skin Laser & Surgery Specialist, New York, NY, USA

Presented at the Annual Meeting of the American Society for Dermatologic Surgery, 2020 Virtual Meeting.

HIGHLIGHTS

- Documented **disrupted** adipocytes due to **elevated apoptosis**.
- **Elimination** of adipocytes and **significant reduction in size** of fat cells resulting in **overall reduction** of fat tissue.
- **Effective temperature** needed for apoptotic processes was reached in **4 minutes**.
- Waist **circumference decreased** on average by **2.2 cm (maximum of 5.4 cm)**.
- Procedure was **safe and comfortable** with high satisfaction.

BASELINE

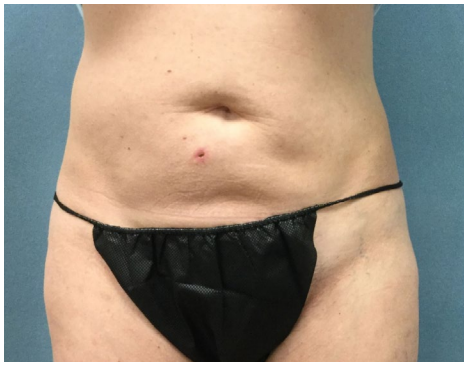


1 MONTH AFTER

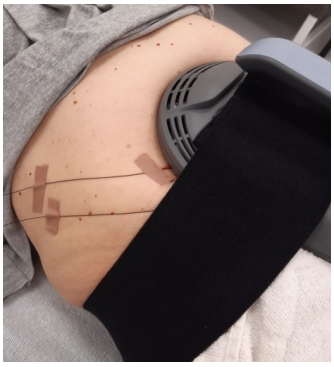
A 57-year old female at baseline and 1 month post-treatment showing prominent aesthetic improvement.

STUDY DESIGN

- Four treated subjects, fifth received sham treatments and served as a control.
- Three 30-minute treatments on abdomen.
- Collected biopsy specimens were histologically examined.
- Evaluation was performed at baseline, 1 week and 1 month post-treatment.



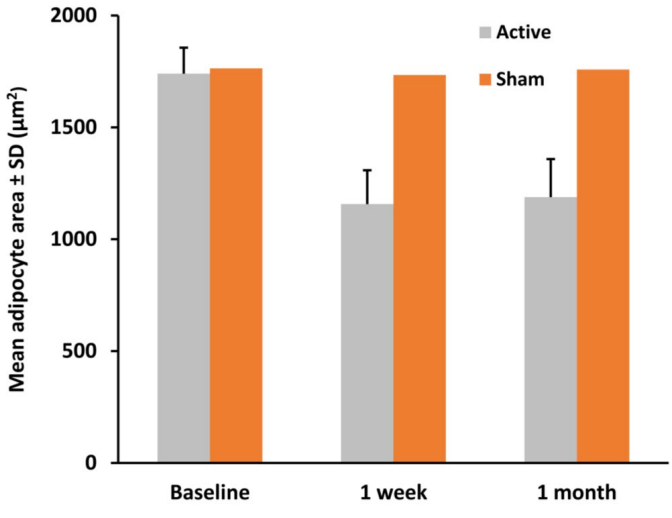
Punch biopsies (Ø 6mm) were taken from the treated area, sectioned to 5-10 µm thick slices and stained by H&E.



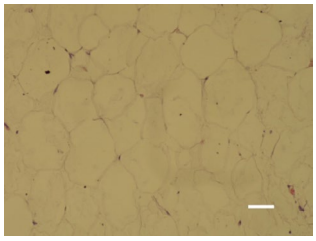
Optical probes were inserted into the subcutaneous layer under ultrasound guidance for in-vivo monitoring of temperature during the 30-minute.

RESULTS

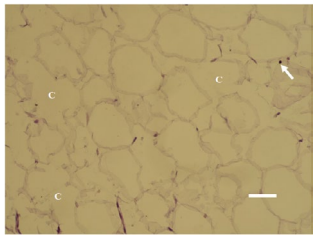
- Adipocyte size was reduced by up to **33.5% at 1 week post-treatment**.
- **Baseline** and **control (sham)** samples **did not** show any **changes** in fat tissue.



Adipocyte size measurement



Baseline histology, bar = 40 µm



1 month, bar = 40 µm; Apoptotic nuclei (arrow) and cystic spaces due to the membrane rupture (C).

SYNCHRONIZED RF & HIFEM: MULTI-CENTER ABDOMINAL MRI STUDY

EFFICACY AND SAFETY OF SIMULTANEOUS APPLICATION OF HIFEM AND SYNCHRONIZED RADIOFREQUENCY FOR ABDOMINAL FAT REDUCTION AND MUSCLE TONING: A MULTI-CENTER MRI EVALUATION STUDY

Carolyn Jacob MD[1], David Kent MD[2]

1. Chicago Cosmetic Surgery and Dermatology, Chicago, IL, USA; 2. Skin Care Physicians of Georgia, Macon, GA, USA

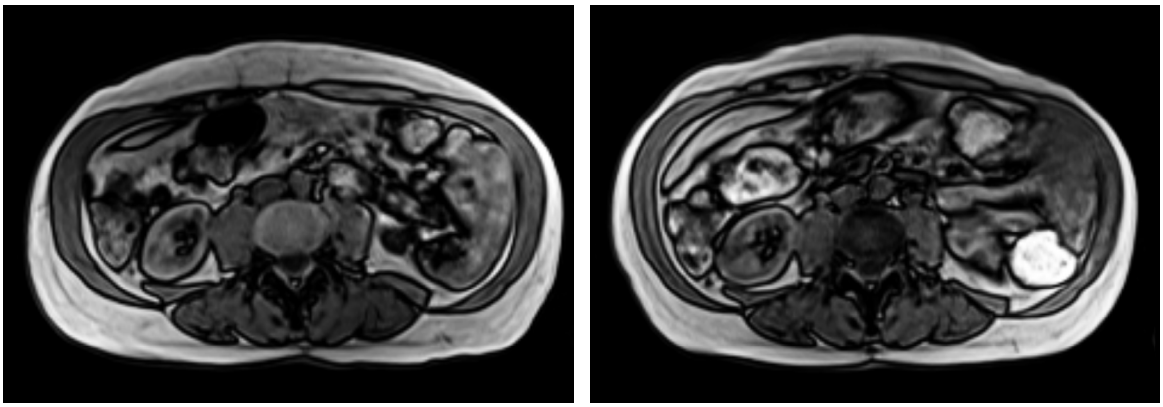
Presented at the Annual Meeting of the American Society for Dermatologic Surgery, 2020 Virtual Meeting.

HIGHLIGHTS

- Study included 41 subjects (average age 39.1).
- MRI assessment showed **30.8% reduction** in **subcutaneous fat** and **26.1% increase** in **muscle thickness at 3 months**.
- **Abdominal separation decreased** by **18.8% at 3 months**.
- **Waist circumference** was **reduced** by **5.9 cm at 3 months**.

BASELINE

3 MONTHS AFTER



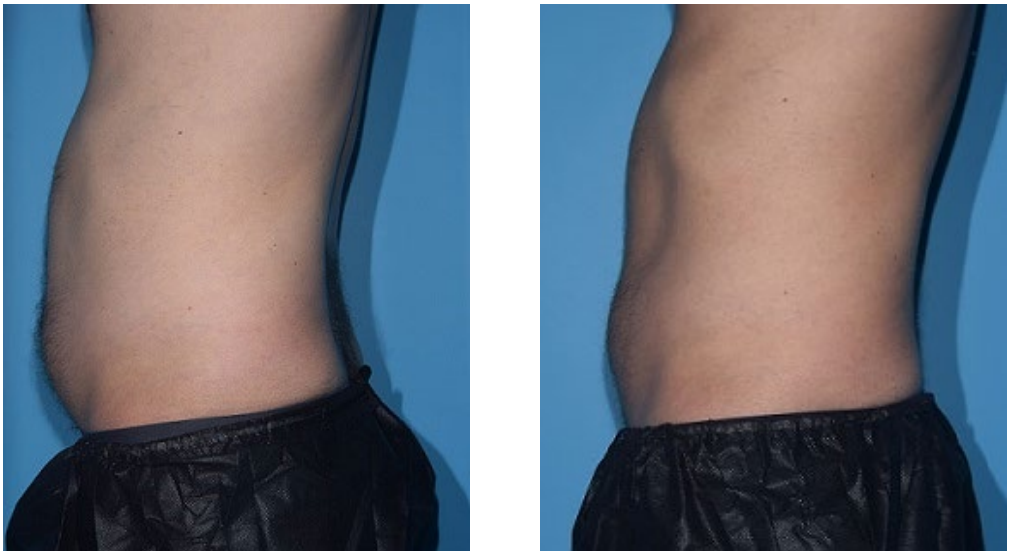
MRI scans of a 62-year old female showing 30% muscle thickening, 16.5% reduction in abdominal separation, 40.8% fat reduction and 6 cm reduction in waist circumference.

STUDY DESIGN

- All subjects received three 30-minute treatments on abdomen.
- MRI images were taken at baseline, 1M and 3M post-treatment.
- Subject satisfaction and therapy comfort were assessed using questionnaires.

CONCLUSION

- **Simultaneous application** of RF and HIFEM **enhances** the **fat reduction** and **boosts up the muscle thickening** effect.
- **Simultaneous application is more effective than using only HIFEM energy**.
- **The treatments were safe and comfortable**.
- **All** of the **patients** were **satisfied with** the **treatment results**.



Digital photographs of a 34-year old male, taken before (left) and after (right) the treatment.

SYNCHRONIZED RF & HIFEM: ACTIVATION OF MYOSATELLITE CELLS

ACTIVATION OF SKELETAL MUSCLE SATELLITE CELLS BY A DEVICE SIMULTANEOUSLY APPLYING HIFEM AND NOVEL SYNCHRONIZED RF TECHNOLOGY: FLUORESCENT MICROSCOPY FACILITATED DETECTION OF NCAM/CD56

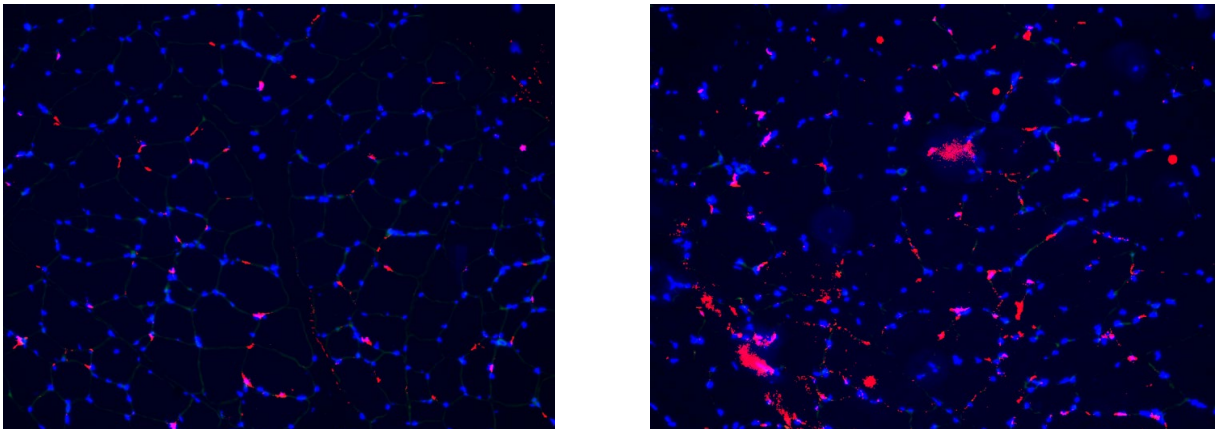
Yael Halaas MD[1], Diane Duncan MD, F.A.C.S[2], MVDr. Jan Bernardy Ph.D.[3], MVDr. Petra Ondrackova Ph.D.[3], Ivan Dinev DVM, Ph.D., DSc[4]

1. Facial Plastic and Reconstructive Surgery, New York, NY, USA; 2. Plastic Surgical Associates, Fort Collins CO, USA; 3. Veterinary Research Institute, Brno, CZ; 4. General and Clinical Pathology, Faculty of Veterinary Medicine, Trakia University, Stara Zagora, BG

Accepted for Oral Presentation at the Annual Meeting of the American Society for Laser Medicine and Surgery, 2020 Phoenix, AZ.

HIGHLIGHTS

- The levels of **satellite cells** increased by **30.2%** at 2 weeks post-treatment indicating muscle fiber growth and formation of new muscle fibers.
- Histological images showed **hypertrophic fibers** and signs of **newly formed myofibers**.
- The **muscle temperature** was between **40 - 41°C** during the whole treatment.
- The observed **results** are equivalent to **12-16 week** exercise programs.



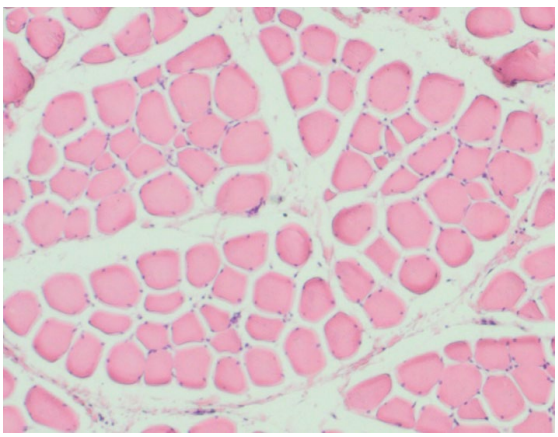
Immunofluorescence images captured at baseline (left) and 2 weeks post-treatment (right) showing an increase in the satellite cell levels. The satellite cells are stained by red color. Blue color represents the myonucleus.

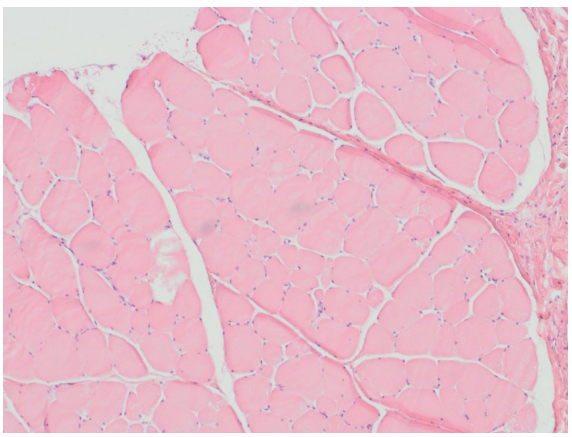
STUDY DESIGN

- 5 Large White pigs (approximately 6 months old).
- All animals received three 30-minute treatments applied to abdomen (1 tx per week).
- Biopsies were collected at baseline, 4 days, 2 weeks and 1 month post-treatment. The **opposite site** of the abdomen was used as a **control area**.
- A total of **275 histological** slices were processed.
- Evaluation included monitoring of satellite cells levels (immunofluorescence), structural changes (histology) and muscle temperature (in-vivo thermal probe measurement).

CONCLUSION

- **Dual field therapy** significantly **increases** the levels of labeled **satellite cells**.
- The satellite cells appear to **form new muscle fibers** and incorporate into the existing muscle fibers to **create new myonuclei**.
- **Procedure** based on stimulating and heating muscle tissue **is safe and does not cause any muscle damage**.





Tissue images collected 1 month after treatments (right) showing pronounced thickening of muscle fibers and increased density of muscle tissue when compared to baseline (left).

SYNCHRONIZED RF & HIFEM: FAT HISTOLOGY & SCANNING ELECTRON MICROSCOPY STUDY

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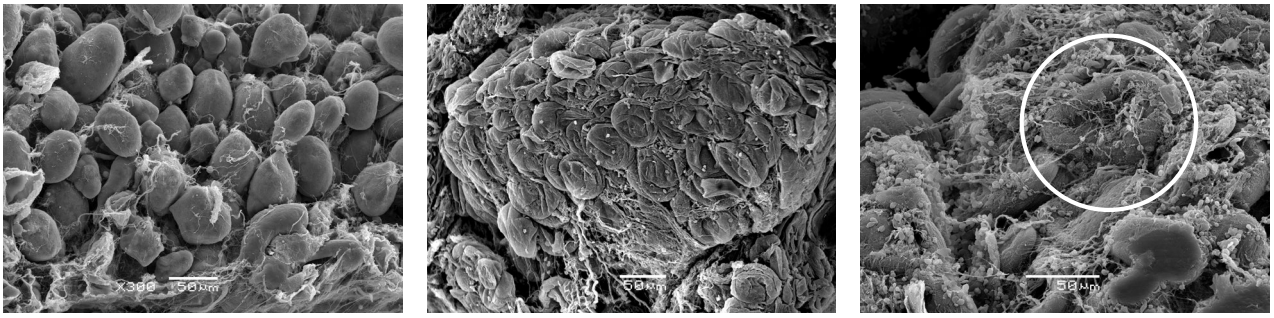
1. Maryland Laser Skin & Vein Institute, Hunt Valley, MD, USA; 2. Veterinary Research Institute, Brno, CZ
3. Department of Anatomy and Histology, University of Veterinary and Pharmaceutical Sciences Brno, CZ

Presented at the Annual Meeting of the American Society for Dermatologic Surgery, 2020 Virtual Meeting.

HIGHLIGHTS

- Both **histology** and **scanning electron microscopy** showed **damaged adipocytes** post-treatment due to apoptosis and lipolysis.
- **Adipocyte size** was **decreased by 31.1%** at 2 weeks post-treatment.
- The **temperature** in fat tissue was maintained **just below 45°C** for the entire treatment.
- **No necrosis** was seen in the tissue.



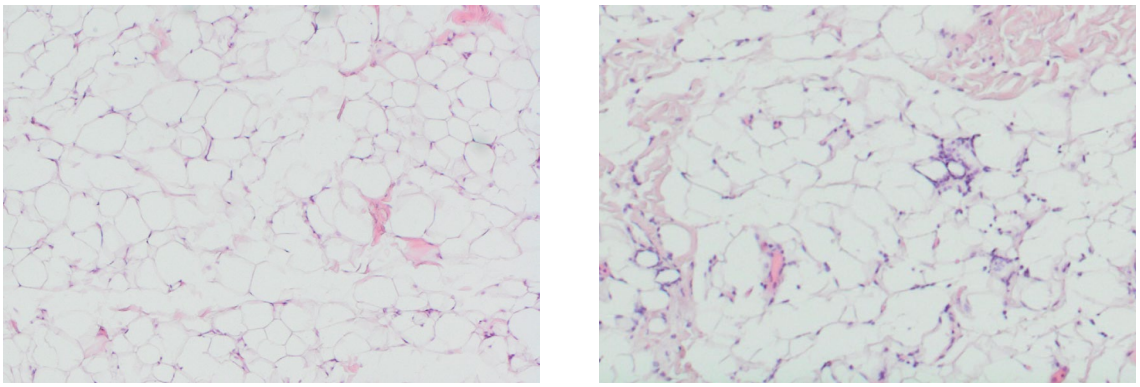
Healthy fat cells with well-defined shape at the baseline (left); shrunk adipocytes with noticeable membrane ruptures occurred at 4 days (center); disrupted adipocytes with extrusion of lipid droplets at two weeks (right)

STUDY DESIGN

- 7 Large White pigs (approximately 6 months old).
- All animals received three 30-minute treatments applied to abdomen.
- Biopsy specimens of fat tissue were collected at baseline, 4 days, 2 weeks, 1 month and 2 months post-treatment for each animal.
- Control specimens were collected from the site opposite to the treatment site.
- Evaluation included scanning electron microscopy and histology.

CONCLUSION

- The procedure elevates the **temperature** in subcutaneous fat to levels **necessary** for **apoptosis induction**.
- **Efficacy** of the procedure for **disruption of adipocytes** was documented in **252** analyzed tissue slices.
- Mild inflammatory response was present to promote the **apoptotic death cells removal**.
- The procedure was **safe, no burns, no necrosis** or other adverse events were documented.



Baseline histology (left) showed adipocytes without any damage. At 2 weeks (right), flattened adipocytes with delaminated membranes are seen along with immune cells clearing the damaged tissue.

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Radina Denkova MD.

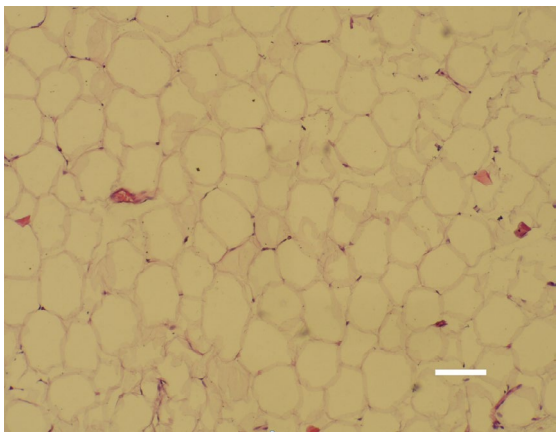
1. Aesthetic Clinic Beauty, Sofia, BG

Source: U.S. Food and Drug Administration. 510(k) Premarket Notification: K192224.Published online December 5, 2019.

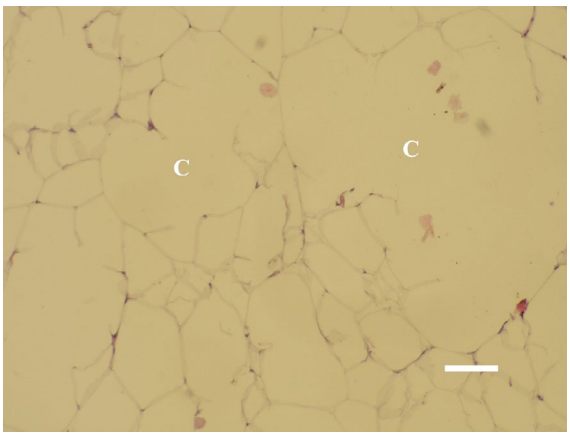
HIGHLIGHTS

- **Intensive fat cell disruption peaking at 20 days post-treatment**.
- **Non-invasive lipolysis** seen in the **first 10 days** post-treatment.
- Investigated device was found to be effective for **elimination of fat cells**.
- **No damage** to skin, sweat glands and sebaceous glands was observed, ensuring procedural safety.
- **Deformed nucleus** and pyknotic nucleus indicating **cell death**.

BASELINE



20 DAYS AFTER



Normal subcutaneous tissue morphology with typical uniform size of adipocytes at the left; bar = 40 micrometers. Intensive fat cell disruption (C) and alternation of adipocytes shape 20 days post-treatment at the right; bar = 30 micrometers.

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Radina Denkova MD[1]

1. Aesthetic Clinic Beauty, Sofia, BG

Source: U.S. Food and Drug Administration. 510(k) Premarket Notification: K192224.Published online December 5, 2019.

HIGHLIGHTS

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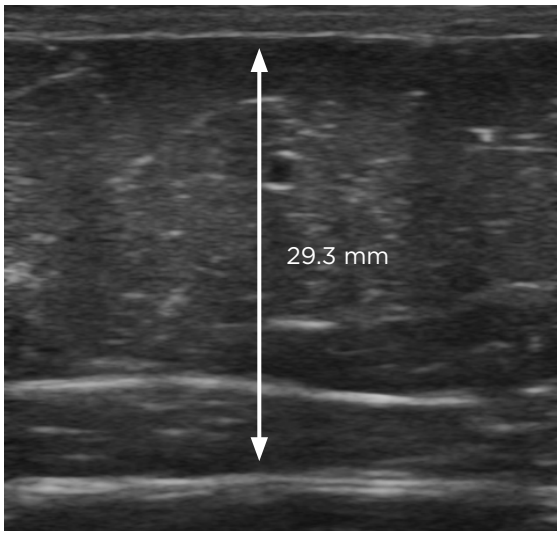
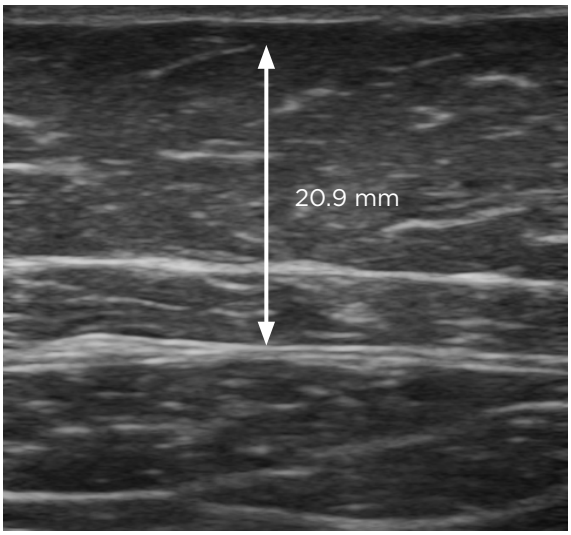
- A total of **88.1%** of patients **were satisfied** with treatment outcomes.
- **92.9%** of patients found the treatments **comfortable**.
- Waist **circumference** was **reduced** on average **by 3.2 cm**.

BASELINE



3 MONTHS AFTER



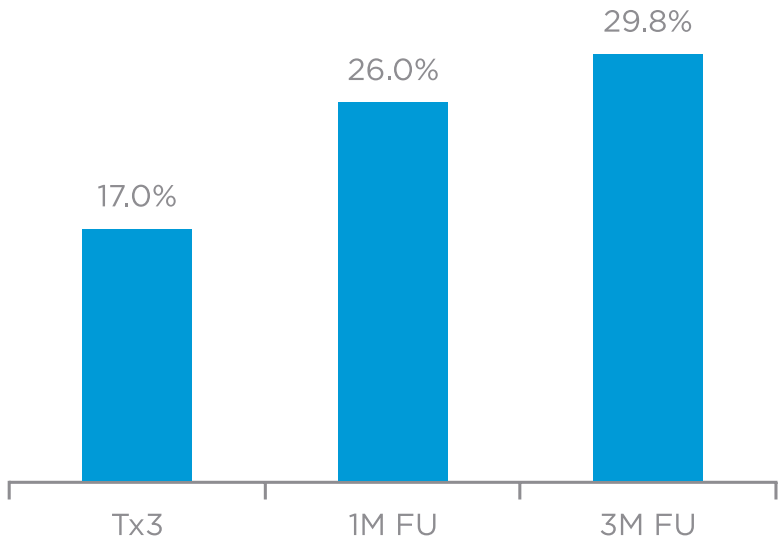
Ultrasound images of a 42-year old female, who also showed a 4-cm reduction in waist circumference.

STUDY DESIGN

- 42 subjects (29 females, 13 males).
- Three 30-minute treatments on abdomen.
- Evaluation by ultrasound imaging.

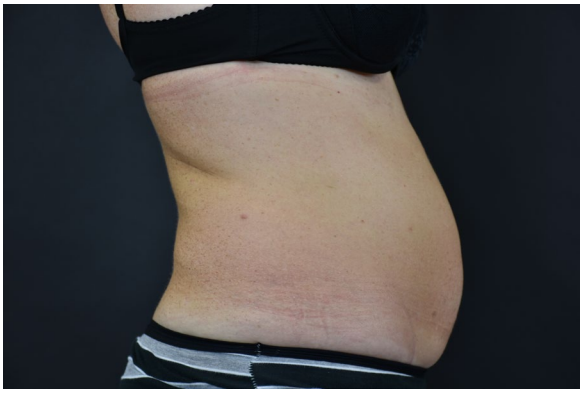
RESULTS

- Results showed continuous improvement over time.



The chart showing continuous improvement in the fat reduction over time.

BASELINE



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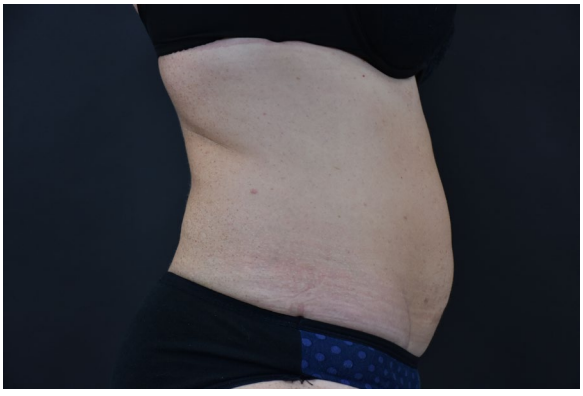


A 49-year old female at baseline and 3 months post-treatment showing 4.5 cm waist circumference reduction and 29.2% reduction in abdominal fat layer.

SYNCHRONIZED RF & HIFEM: HUMAN FAT HISTOLOGY & TEMPERATURE MEASUREMENT

ADIPOCYTE APOPTOSIS INDUCED BY SYNCHRONIZED RADIOFREQUENCY WITH HIFEM PROCEDURE: HUMAN HISTOLOGICAL STUDY

David J. Goldberg MD, JD[1]

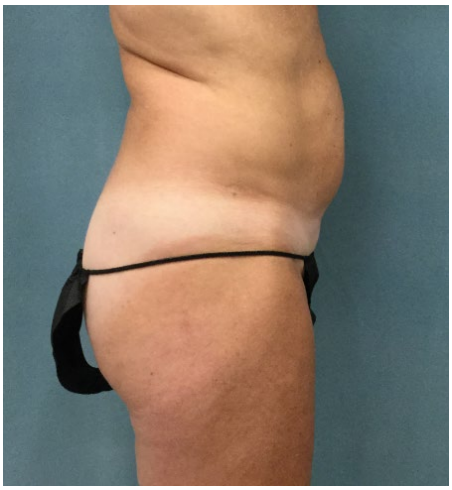
1. Skin Laser & Surgery Specialist, New York, NY, USA

Presented at the Annual Meeting of the American Society for Dermatologic Surgery, 2020 Virtual Meeting.

HIGHLIGHTS

- Documented **disrupted** adipocytes due to **elevated apoptosis**.
- **Elimination** of adipocytes and **significant reduction in size** of fat cells resulting in **overall reduction** of fat tissue.
- **Effective temperature** needed for apoptotic processes was reached in **4 minutes**.
- Waist **circumference decreased** on average by **2.2 cm (maximum of 5.4 cm)**.
- Procedure was **safe and comfortable** with high satisfaction.

BASELINE

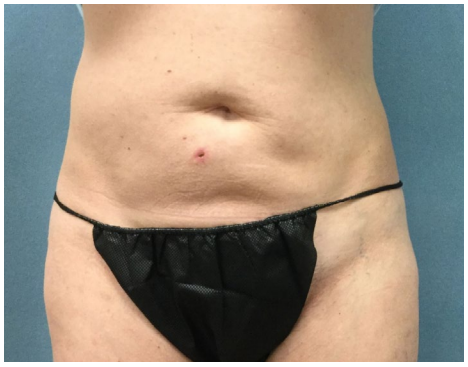


1 MONTH AFTER

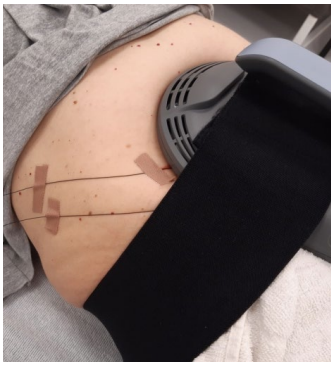
A 57-year old female at baseline and 1 month post-treatment showing prominent aesthetic improvement.

STUDY DESIGN

- Four treated subjects, fifth received sham treatments and served as a control.
- Three 30-minute treatments on abdomen.
- Collected biopsy specimens were histologically examined.
- Evaluation was performed at baseline, 1 week and 1 month post-treatment.



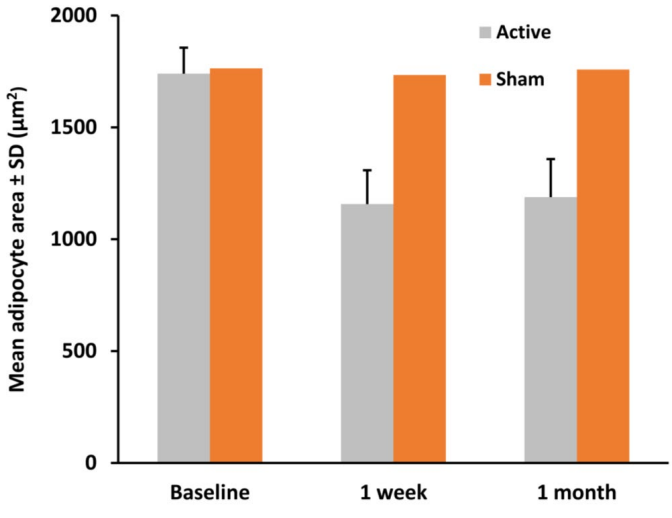
Punch biopsies (Ø 6mm) were taken from the treated area, sectioned to 5-10 µm thick slices and stained by H&E.



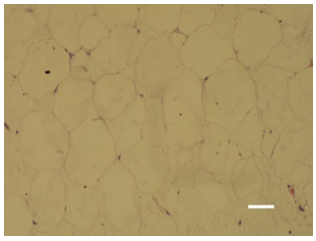
Optical probes were inserted into the subcutaneous layer under ultrasound guidance for in-vivo monitoring of temperature during the 30-minute.

RESULTS

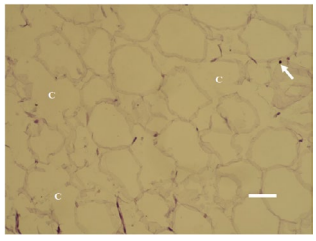
- Adipocyte size was reduced by up to **33.5% at 1 week post-treatment**.
- **Baseline** and **control (sham)** samples **did not** show any **changes** in fat tissue.



Adipocyte size measurement



Baseline histology, bar = 40 µm



1 month, bar = 40 µm; Apoptotic nuclei (arrow) and cystic spaces due to the membrane rupture (C).

SYNCHRONIZED RF & HIFEM: MULTI-CENTER ABDOMINAL MRI STUDY

EFFICACY AND SAFETY OF SIMULTANEOUS APPLICATION OF HIFEM AND SYNCHRONIZED RADIOFREQUENCY FOR ABDOMINAL FAT REDUCTION AND MUSCLE TONING: A MULTI-CENTER MRI EVALUATION STUDY

Carolyn Jacob MD[1], David Kent MD[2]

1. Chicago Cosmetic Surgery and Dermatology, Chicago, IL, USA; 2. Skin Care Physicians of Georgia, Macon, GA, USA

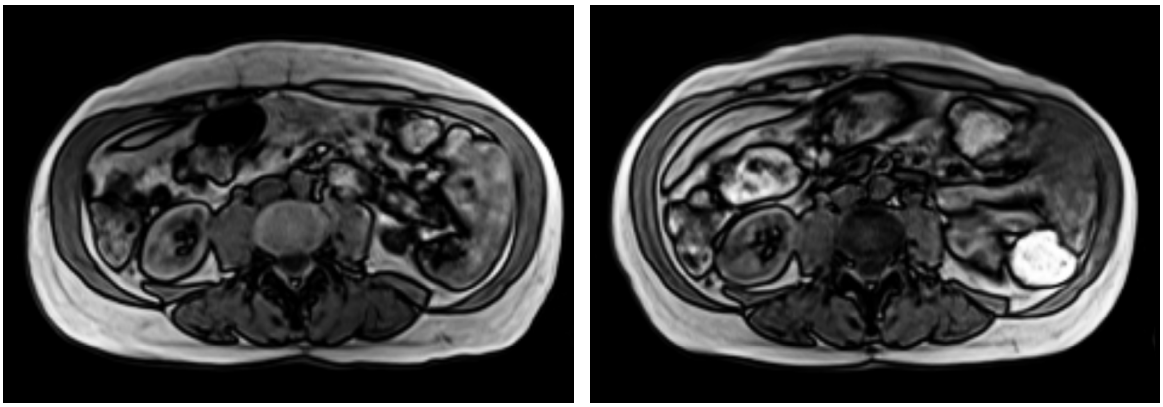
Presented at the Annual Meeting of the American Society for Dermatologic Surgery, 2020 Virtual Meeting.

HIGHLIGHTS

- Study included 41 subjects (average age 39.1).
- MRI assessment showed **30.8% reduction** in **subcutaneous fat** and **26.1% increase** in **muscle thickness at 3 months**.
- **Abdominal separation decreased** by **18.8% at 3 months**.
- **Waist circumference** was **reduced** by **5.9 cm at 3 months**.

BASELINE

3 MONTHS AFTER



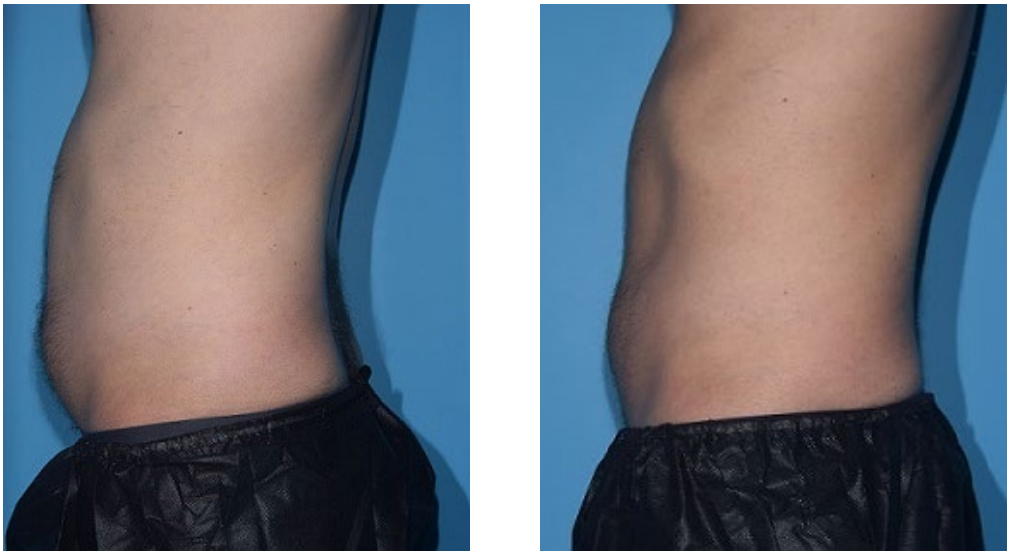
MRI scans of a 62-year old female showing 30% muscle thickening, 16.5% reduction in abdominal separation, 40.8% fat reduction and 6 cm reduction in waist circumference.

STUDY DESIGN

- All subjects received three 30-minute treatments on abdomen.
- MRI images were taken at baseline, 1M and 3M post-treatment.
- Subject satisfaction and therapy comfort were assessed using questionnaires.

CONCLUSION

- **Simultaneous application** of RF and HIFEM **enhances** the **fat reduction** and **boosts up the muscle thickening** effect.
- **Simultaneous application is more effective than using only HIFEM energy**.
- **The treatments were safe and comfortable**.
- **All** of the **patients** were **satisfied with** the **treatment results**.



Digital photographs of a 34-year old male, taken before (left) and after (right) the treatment.

SYNCHRONIZED RF & HIFEM: ACTIVATION OF MYOSATELLITE CELLS

ACTIVATION OF SKELETAL MUSCLE SATELLITE CELLS BY A DEVICE SIMULTANEOUSLY APPLYING HIFEM AND NOVEL SYNCHRONIZED RF TECHNOLOGY: FLUORESCENT MICROSCOPY FACILITATED DETECTION OF NCAM/CD56

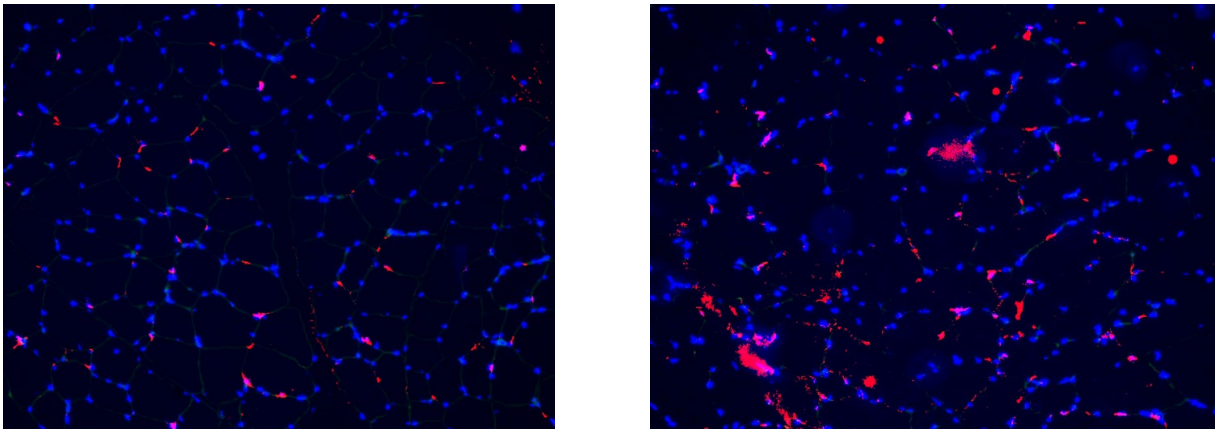
Yael Halaas MD[1], Diane Duncan MD, F.A.C.S[2], MVDr. Jan Bernardy Ph.D.[3], MVDr. Petra Ondrackova Ph.D.[3], Ivan Dinev DVM, Ph.D., DSc[4]

1. Facial Plastic and Reconstructive Surgery, New York, NY, USA; 2. Plastic Surgical Associates, Fort Collins CO, USA; 3. Veterinary Research Institute, Brno, CZ; 4. General and Clinical Pathology, Faculty of Veterinary Medicine, Trakia University, Stara Zagora, BG

Accepted for Oral Presentation at the Annual Meeting of the American Society for Laser Medicine and Surgery, 2020 Phoenix, AZ.

HIGHLIGHTS

- The levels of **satellite cells** increased by **30.2%** at 2 weeks post-treatment indicating muscle fiber growth and formation of new muscle fibers.
- Histological images showed **hypertrophic fibers** and signs of **newly formed myofibers**.
- The **muscle temperature** was between **40 - 41°C** during the whole treatment.
- The observed **results** are equivalent to **12-16 week** exercise programs.



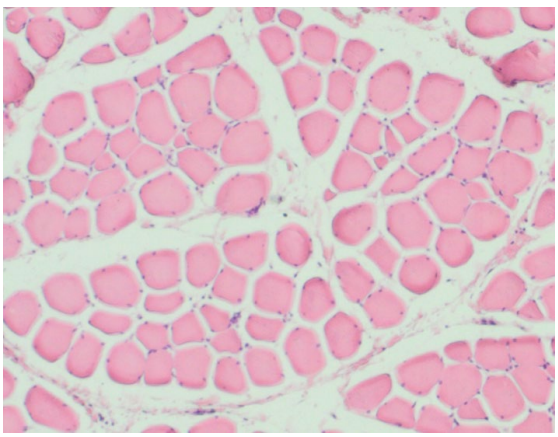
Immunofluorescence images captured at baseline (left) and 2 weeks post-treatment (right) showing an increase in the satellite cell levels. The satellite cells are stained by red color. Blue color represents the myonucleus.

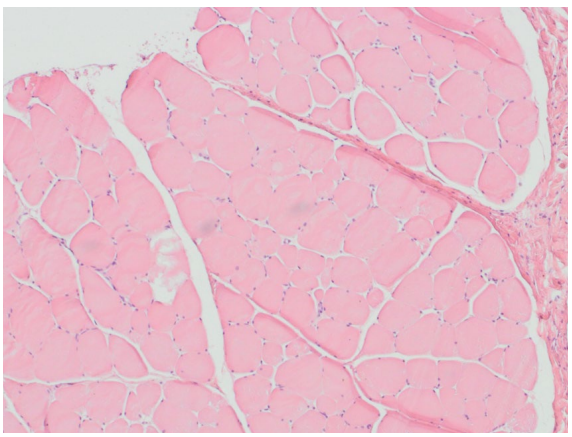
STUDY DESIGN

- 5 Large White pigs (approximately 6 months old).
- All animals received three 30-minute treatments applied to abdomen (1 tx per week).
- Biopsies were collected at baseline, 4 days, 2 weeks and 1 month post-treatment. The **opposite site** of the abdomen was used as a **control area**.
- A total of **275 histological** slices were processed.
- Evaluation included monitoring of satellite cells levels (immunofluorescence), structural changes (histology) and muscle temperature (in-vivo thermal probe measurement).

CONCLUSION

- **Dual field therapy** significantly **increases** the levels of labeled **satellite cells**.
- The satellite cells appear to **form new muscle fibers** and incorporate into the existing muscle fibers to **create new myonuclei**.
- **Procedure** based on stimulating and heating muscle tissue **is safe and does not cause any muscle damage**.





Tissue images collected 1 month after treatments (right) showing pronounced thickening of muscle fibers and increased density of muscle tissue when compared to baseline (left).

SYNCHRONIZED RF & HIFEM: MULTI-CENTER ABDOMINAL ULTRASOUND STUDY

RADIOFREQUENCY HEATING AND HIFEM DELIVERED SIMULTANEOUSLY - THE FIRST SHAM-CONTROLLED RANDOMIZED TRIAL

Bruce Katz MD[1], Robert Weiss MD[2], Julene B. Samuels MD[3] F.A.C.S

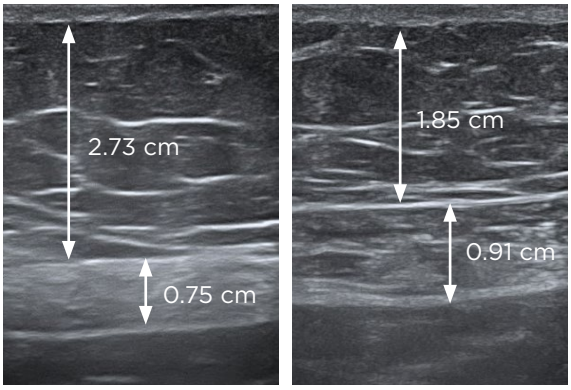
1. Juva Skin and Laser Center, Manhattan, NY, USA; 2. Maryland Laser Skin & Vein Institute, Hunt Valley, MD, USA; 3. Julene B Samuels MD. F.A.C.S, Louisville, KY, USA

Presented at the Annual Meeting of the American Society for Dermatologic Surgery, 2020 Virtual Meeting.

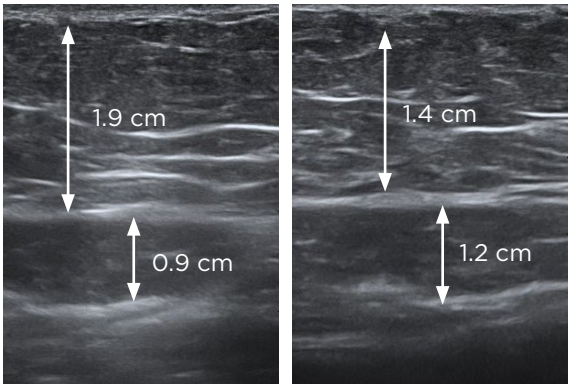
HIGHLIGHTS

- A total of 72 subjects allocated into two groups (Active: N=48, **BMI of 25.8 kg/m2)**; Sham: N=24, **BMI of 25.6 kg/m2)**.
- Active group showed **28.3% reduction in subcutaneous fat** at **3-month** follow-up visit.
- **Muscle thickness** increased by **24.2%** at **3-months** post-treatment in **active group**.
- At 3 months **38/40 patients** showed fat reduction **higher than 20%**.

A 64-YEAR OLD FEMALE



A 51-YEAR OLD FEMALE



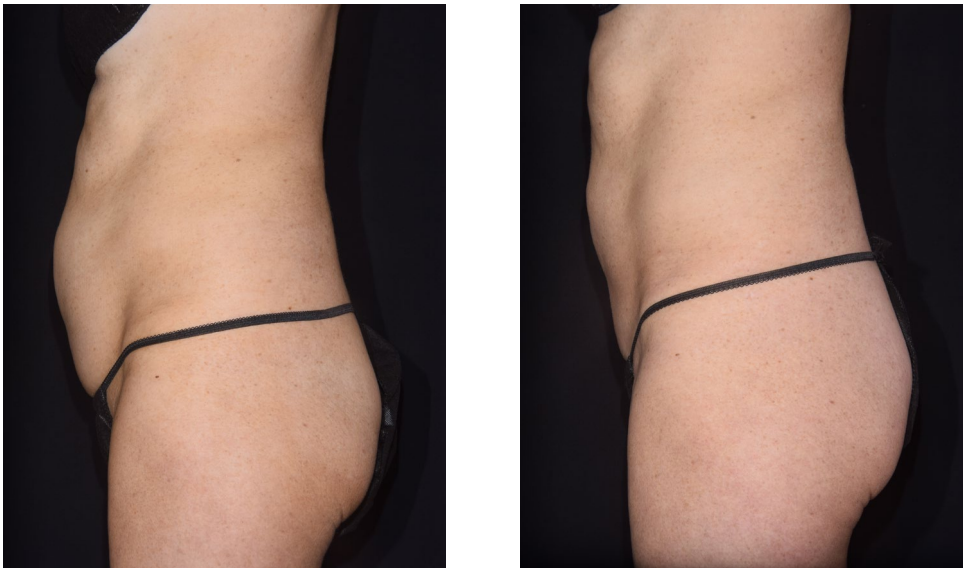
Ultrasound images of patients in active group taken before (left) and 1 month after (right) the treatments.

STUDY DESIGN

- Both groups received three 30-minute treatments on abdomen (active: maximum tolerable intensities, sham: intensities of 5%).
- Ultrasound images were taken at baseline, 1M and 3M after the last treatment.
- Evaluation included measurements of subcutaneous fat and muscle mass thickness.

CONCLUSION

- **Dual field technology** showed **high efficacy** for subcutaneous **fat reduction** and thickening of **rectus abdominis muscle**.
- **93.9%** of patients reported satisfaction with the results.
- **Sham treatments did not induce** any **significant changes**.
- **The procedure** combining HIFEM and RF energy **was safe** and did not cause any adverse events.



Digital photographs of a 55-year old female, taken before (left) and 3 months after (right) the treatments.

SYNCHRONIZED RF & HIFEM: MULTI-CENTER OUTER THIGH MRI STUDY

SIMULTANEOUS EMISSION OF SYNCHRONIZED RADIOFREQUENCY AND HIFEM ENERGY FOR TREATMENT OF LATERAL THIGHS: INTERIM RESULTS OF THE MRI MULTICENTRE STUDY

Melanie Palm M.D., MBA[1]; Brian Kinney M.D., FACS, MSME[2]; Yael Halaas M.D., FACS[3]

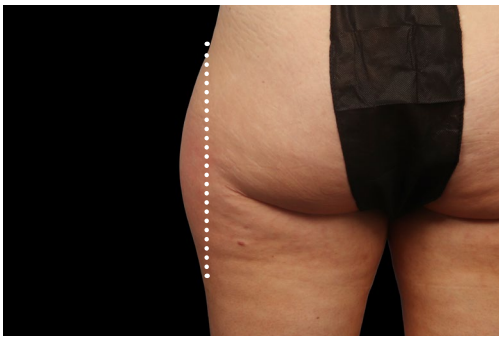
1. Art of Skin M.D., Solana Beach, CA, USA
2. Brian M. Kinney M.D., Beverly Hills, CA, USA
3. Yael Halaas M.D., New York, NY, USA

Presented at the Annual Meeting of the American Society for Laser Medicine and Surgery, 2021.

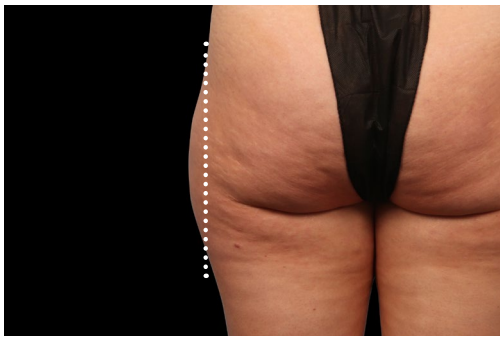
HIGHLIGHTS

- **30 subjects** (29-65 y/o, 19.0-34.5 kg/m^2) received four 30-minute treatments of lateral thighs delivered once per week.
- MRI assessment revealed **average reduction of fat** thickness by **1.4 cm** in saddlebag region **at 1 month**.
- Average **hip circumference decreased by 3.0 cm**.
- There were **no non-responders**.

BASELINE

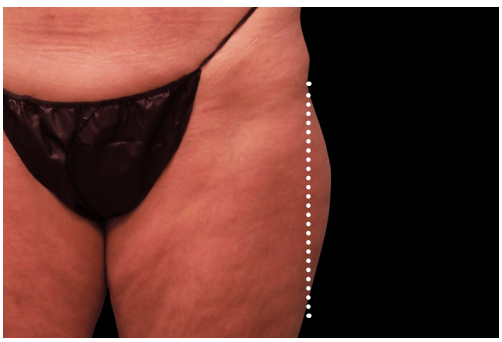


AFTER THE LAST TREATMENT



COURTESY OF: MELANIE PALM, M.D.

BASELINE



1-MONTH FOLLOW-UP

COURTESY OF: BRIAN KINNEY, M.D.

EMSCULPT NEO
Simultaneous emission of novel Synchronized Radiofrequency and HIFEM (magnetic fields) in a single applicator for fat elimination and muscle building

Robert Weiss MD[1], Brian Kinney MD[2], Carolyn Jacob MD[3]

***Abstract*—EMSCULPT NEO is a device that delivers HIFEM and Synchronized RF energies simultaneously through a single applicator. The combined technology induces supramaximal muscle contractions and heating in the treated fat & muscle tissues. This simultaneous combination of two energies has synergistic effects that drastically enhance the results when compared to the individual treatments. RF heating during HIFEM muscle contractions increases activation of proteins stimulating muscle synthesis and enhances the hypertrophic effect. RF heating of fat tissue results in lipolytic and apoptotic processes leading to the permanent elimination of fat cells while being supported by increased metabolic activity due to the HIFEM contractions. Multiple clinical studies on this device documented results superior to any standalone or consecutive treatment regimens, which places the device far ahead of any devices currently used for body contouring.**

***Keywords* — HIFEM, Radiofrequency, Simultaneous, Application, Supramaximal, Contraction, Muscle, Fat, Reduction, Hypertrophy**

I. Introduction

Radiofrequency (RF) and HIFEM technologies are currently used extensively in aesthetic medicine for body shaping. The effect of RF technology is based on differential elevation of temperature in response to selective transformation of radiofrequency energy into heat in targeted tissues. Utilizing specific frequencies of the RF spectrum allows for selective heating, due to the difference in properties between the tissues in the targeted area of treatment. As such, RF is often used for fat reduction, skin tightening, or cellulite reduction. HIFEM technology, on the other hand, uses alternating magnetic fields to induce powerful skeletal muscle contractions via stimulation of the nerve pathways without significant, or even noticeable, elevation of temperature. HIFEM induced, supramaximal contractions are greater than voluntary contractions thanks to the specific stimulation patterns and frequencies. With repetition and over time, there is a tissue healing response that leads to increasing the muscle mass via amplified muscle fiber size.

EMSCULPT NEO is the first of its kind medical device combining novel Synchronized RF and HIFEM that are both emitted simultaneously using specially designed and patented dual-field applicators. The RF component enhances local blood circulation and delivers heat to underlying structures; skin, fat, and muscle, while HIFEM induces supramaximal muscle contractions at the same time. This unique combination has multiple synergistic effects and has been shown to make the simultaneous treatment more effective than any standalone or consecutive application. Studies have shown that the radiofrequency heating supports HIFEM's effects on muscles, while HIFEM enhances the radiofrequency's effects on fat.

II. The Effect in Adipose Tissue

The dual-energy application by EMSCULPT NEO has demonstrated uniform heating of adipose tissue above physiological levels, reaching 43-45°C (See **Figure 1**). The essential temperature of 42°C was achieved in fat in-vivo at approximately 4 minutes[1,2], while thermal imaging measurements showed safe values on the skin throughout the treatment thereby avoiding risks of epidermal damage. Temperature elevation in the fat has been shown to benefit fat reduction in two ways.

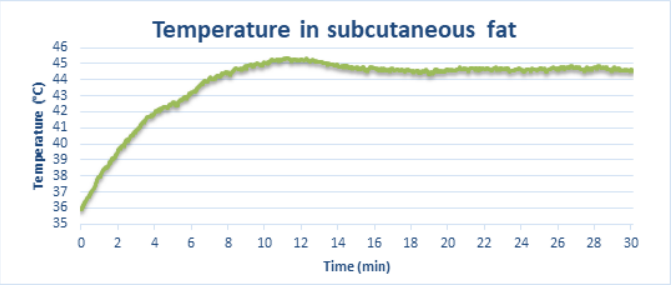


Fig. 1. Fat tissue temperature over time. The temperature is rapidly increased during the first few minutes and then oscillates just below 45°C for the rest of the treatment. Source: Weiss et al.

[1]Maryland Dermatology Laser Skin &Vein Institute, Hunt Valley, MD
[2]Plastic Surgery Excellence, Beverly Hills, CA
[3]Chicago Cosmetic Surgery and Dermatology, Chicago, IL

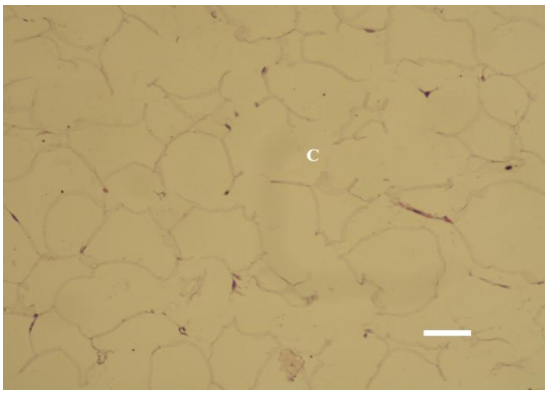


Fig. 2. Adipose tissue showing noticeable shape alternations at 2 weeks post-treatment, some cells are flattened of a smaller size. Numerous adipocytes show membrane ruptures. Source: Goldberg et al.

Initially, the elevated temperature results in increased blood flow and acceleration of metabolic activity. In response, the lipids stored in the fat cells, in the form of triglycerides, are broken down (hydrolyzed) into free fatty acids and glycerol; the two products are subsequently slowly and safely released into the bloodstream. As seen in **Figure 2**, the diameter of affected fat cells is smaller, and the overall response is exhibited as a nondestructive reduction of adipocyte volume aka lipolysis[3,4]. This phenomenon is further enhanced during the intense localized muscle work provided by HIFEM. The muscle load significantly increases the body's need for energy supply, resulting in an induced metabolic stress[5,6]. As such, applying RF and HIFEM at the same time brings the key synergy in the form of a significantly enhanced fat breakdown process.

The other direct effect of fat heating occurs when the elevated temperature is sustained for a sufficient period of time. Adipocytes exposed to temperatures of 43-45°C for several minutes lose their cellular integrity/viability, and a portion will be forced to enter into the apoptotic process, i.e., natural and permanent cell death and resorption[7–10]. The apoptotic cells subsequently lose their membrane integrity and are ultimately digested by macrophages (occasionally accompanied by other immune cells), responsible for clearing the degraded cells and the debris to maintain tissue homeostasis[11–13].

The efficacy of this novel dual-energy device for fat reduction has already been documented through clinical investigation. Histological examinations performed by Goldberg[1] and Weiss et al.[2] consistently revealed noticeable shape alternations of adipocytes after the treatments, including their flattening, shrinkage, and membrane ruptures. The release of intracellular content, due to the lipolysis led to a 33% decrease in the size of adipocytes. In addition, the ongoing apoptotic process was observed in the examined tissue through an increased presence of the adipocyte's pyknotic nuclei. These histological findings coincided with the scanning electron microscopy (SEM), which revealed smaller and deformed adipocytes, with ruptured membranes and noticeable extrusion of lipid droplets outside the cells. See **Figure 3.**

Multiple additional studies have further confirmed the histological observations. A study submitted to the FDA as part of the technology's clearance process evaluated 42 test subjects by ultrasound imaging and showed a reduction in abdominal fat by 29.8% at 3-months post-treatment[14]. Another study, by Jacob and Kent[15] used magnetic resonance imaging (MRI) to conclude a significant reduction of abdominal fat thickness by 30.8% at 3 months after the dual-energy treatments. Similarly, another study performed by Katz et al.[16] used an ultrasonographic examination and demonstrated an average decrease in fat thickness by 20.5% at 1 month. Results further improved to 28.3% at 3 months post-treatment. When compared to the previous HIFEM studies, the scale of documented improved results on fat reduction strongly suggests the beneficial effects of combined treatments.

Besides enhanced lipolysis, the simultaneous dual-energy application contributes to an even heat distribution. Localized accumulation of heat is often associated with thermal only treatments, and the so-called "*hot-spots*" can lead to various complications. In EMSCULPT NEO, the muscle contractions work as a natural massage and through an accelerated blood circulation[4,17] help distribute the heat homogeneously across the entire treated area.

III. The Effects on Muscle Tissue

The use of in-vivo temperature probes revealed that while fat is heated during the treatment, two simultaneous modalities also affect muscle tissue. Due to the relatively high thermal conductivity, the muscle tissue does not retain the same temperature profile that can be seen in the fat due to its lower

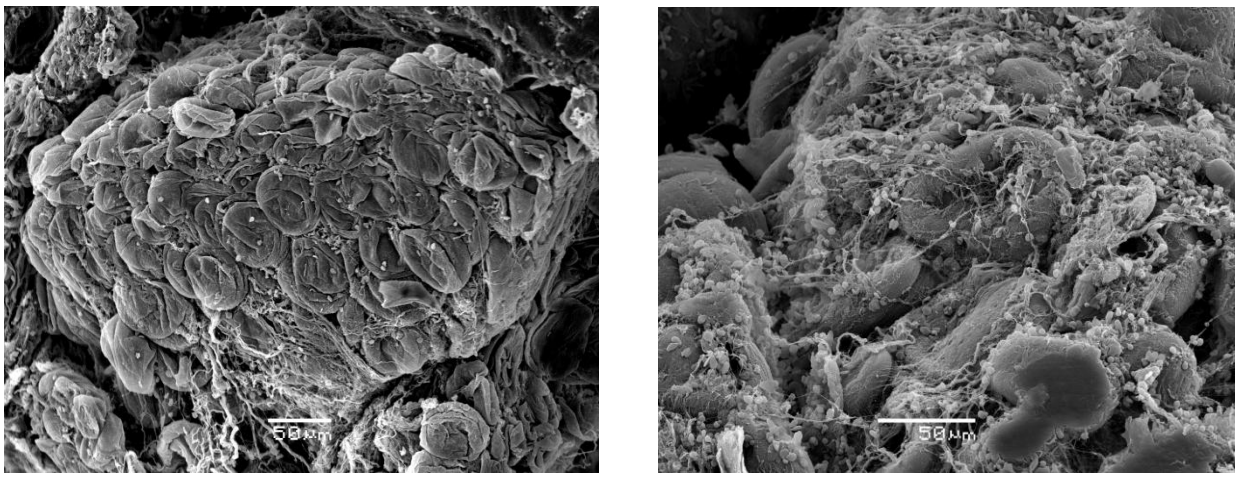


Fig. 3. SEM evidence of the fat cell shrinkage due to lipolysis which occurs 4 days after treatment (left) and fat cell destruction due to apoptosis seen 2 weeks after the last treatment (right). Source: Weiss et al.

thermal conductivity and higher thermal capacitance. The muscle is heated to temperatures ranging from 40-41°C, which is a combined result of the heat directly induced by RF, the heat produced by the muscle during supramaximal contractions, and the heat that physiologically spreads from the adjacent fat tissues. The muscle temperature over time can be seen in **Figure 4**.

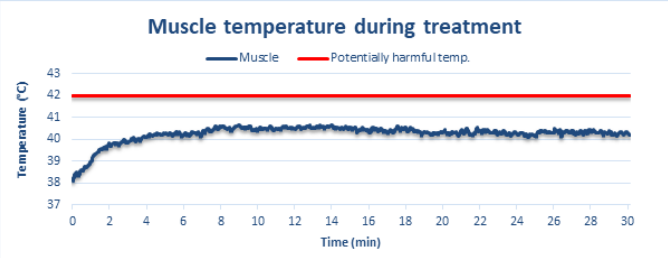


Fig. 4. During the first 2 minutes, the muscle temperature reached 40°C and was maintained between 40 and 41°C for the rest of the treatment. Safe temperature levels were sustained without any risks for the muscle tissue for the entire treatment. Adopted from Halaas et al.

Scientifically, it is well documented that muscle heating provides many physiological benefits. We intuitively warm up shortly before doing any strenuous weightlifting or other types of exercise to protect the muscles from injury for a reason.[19] Studies have shown that heating of the muscle tissue during contractions positively affects the muscle response in several ways:

Muscle heating causes vasodilatation, i.e., increased blood flow into the active tissue, which significantly increases the delivery of oxygen and nutrients to the strained muscle fibers.[20] The oxygen levels are directly affected by heating through dissociation of oxygen from hemoglobin at higher plasma oxygen concentrations, thus providing more oxygen to working muscles.[19,21] An increased oxygenation and nutrient supplementation promotes the anabolic processes and are necessary for faster muscle fiber regeneration and growth.[22]

Increased blood flow is also accompanied by a faster removal of toxic waste products (e.g., lactic and carbonic acid)[20]. Lactic and carbonic acids are by-products of the metabolic process that produce energy for the muscles during intensive muscle work.[23] High levels of these acids within the tissue are associated with muscle soreness and muscle

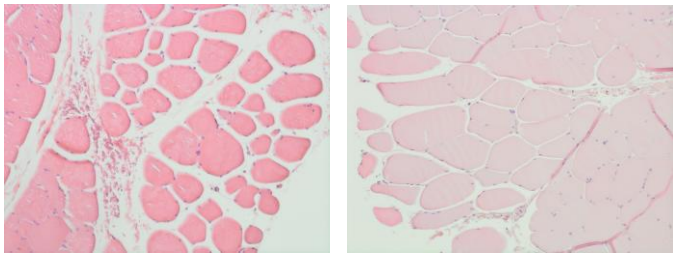


Fig. 5. Images of histological slices of muscle tissue collected at baseline (left) and 2 weeks after the last dual-energy treatment (right). The volume of individual muscle fibers is noticeably increased after the treatment. Adopted from Halaas et al.

fatigue.[24] A faster flush out of the waste leads to an attenuation of muscle soreness and muscle fatigue. This can be experienced the day after the treatment.[25] Furthermore, heated muscle contractions were described as “better”, “easier”, “stronger” and “less fatiguing” than muscle contractions in normal room conditions.[26] Heating thus increases the already high levels of patient’s treatment and post-treatment comfort.

Although all of the benefits mentioned above significantly contribute to the patients’ overall treatment experience, the main synergistic effect of the simultaneous delivery of RF and HIFEM lies in **the enhancement of muscle strengthening by hypertrophy**.

The HIFEM-induced supramaximal contractions produce a strong response, triggering muscle tissue hypertrophy[27]. During intense contractions, muscle fibers are stretched and relaxed, similar to resistance exercise, but with a higher intensity. Muscle workload of a sufficient intensity leads to micro-ruptures in muscle fibers.[28,29] This causes signaling molecules to be released to activate a regenerative process and muscle growth in order to strengthen the muscle and prepare it for another workload.[29] **Heat shock proteins (HSP)** are a family of such signaling molecules that play a crucial role in **muscle hypertrophy** through the **promotion of muscle protein synthesis**.[30,31]

Heat shock proteins may be activated by mechanical stress, such as intense muscle contractions, and heat stress. Several studies have documented increases in HSP levels and increased muscle protein synthesis in the muscle tissue after an application of heat at 40-41°C[30–34]. Goto et al.[33] compared the HSP expression following heat stress, mechanical stress,

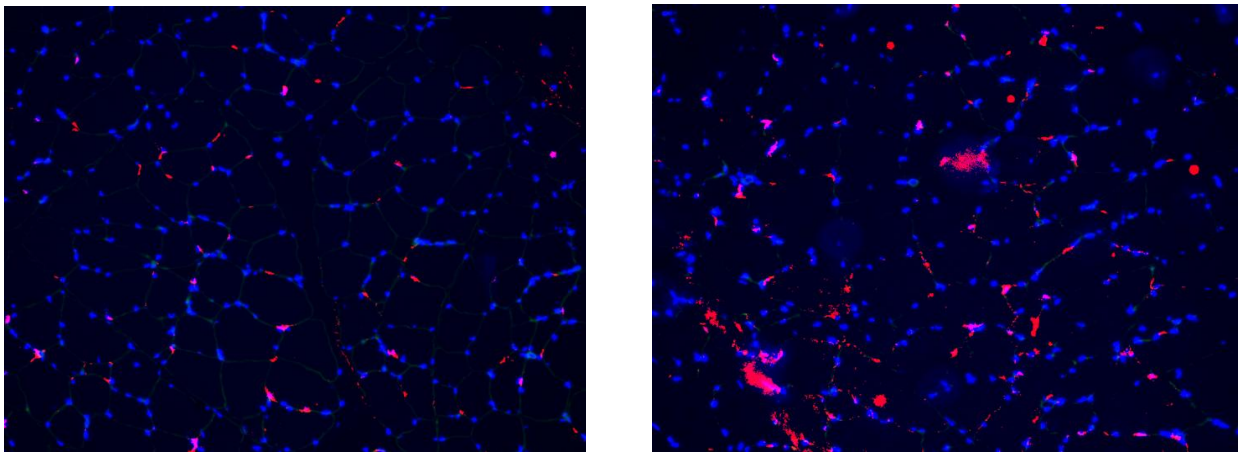


Fig. 6. Images of histological slices of muscle tissue collected at baseline (left) and 2 weeks after the last dual-energy treatment (right). The volume of individual muscle fibers is noticeably increased after the treatment. Adopted from Halaas et al

and simultaneous application of heat and mechanical stress. **The simultaneous application** showed a **significantly higher increase** in the expression of **HSPs** when compared to either heat or mechanical stress alone, which only confirms the synergistic effects of the two energies for muscle hypertrophy.

Another important element in muscle hypertrophy is the so-called satellite cells (SC). SC are muscle-derived stem cells, responsible for **myofiber development and renewal**.[35] In a resting state, the SC remain in a quiescent state, ready to be activated, enter differentiation to provide new myonuclei to existing muscle fibers, or to generate new muscle fibers.[36,37] They can be activated by an intense muscle exercise as a response to **regenerate and strengthen the existing muscle fibers**.[38] However, heat was also found to trigger activation of satellite cells[39]. Simultaneous application of heat and mechanical stress is presumed to result in magnification of the muscle strengthening and hypertrophy. Increased levels of the satellite cell pool after a set of dual-energy treatments have been documented in a study by Halaas et al.[18] The increased SC levels (See **Figure 6**.) were accompanied by histological observation of muscle hypertrophy and even newly formed myoblasts.

Satellite cells and heat shock proteins are not the only muscle bulk enhancing aspect. The increased tolerance of the contractions allows physicians to apply higher HIFEM intensities much earlier in the treatment process, and to use protocols with more intense muscle stimulation patterns.

The first clinical trials[15,16] on this novel dual-energy technology showed significantly more prominent muscle hypertrophy compared to previous studies investigating a standalone HIFEM procedure[40,41]. The average growth in muscle thickness was oscillating around 24-26%, while without the heating effects, the muscle thickening effects averaged at 16%. See **Figure 7** for illustrative MRI images.

One might presume that a consecutive application of RF and HIFEM delivered immediately following each other, would yield similar benefits as a simultaneous application. However, this was shown not to be the case. Muscle tissue, being rich in blood vessels, can dissipate the excessive heat accumulation as soon as it exceeds the blood temperature (appx. 37°C)[42]. Without continuous heat delivery, it is impossible to maintain the proper therapeutic temperature elevation in the targeted tissue, which is essential to achieve all the synergistic effects. This dual-field modality technology thus provides a unique solution that cannot be fully clinically substituted by any combination of two standalone applications.

IV. Concluding comments

Procedures primarily addressing fat and muscles non-invasively have been two separate worlds since their inception. This is due to the clinical as well as technical interferences of the two different concepts. EMSCULPT NEO represents the first-ever technology that, from an engineering standpoint, allows to simultaneously apply RF heating and HIFEM energies to the same targeted body area. This represents a breakthrough approach to non-surgical body

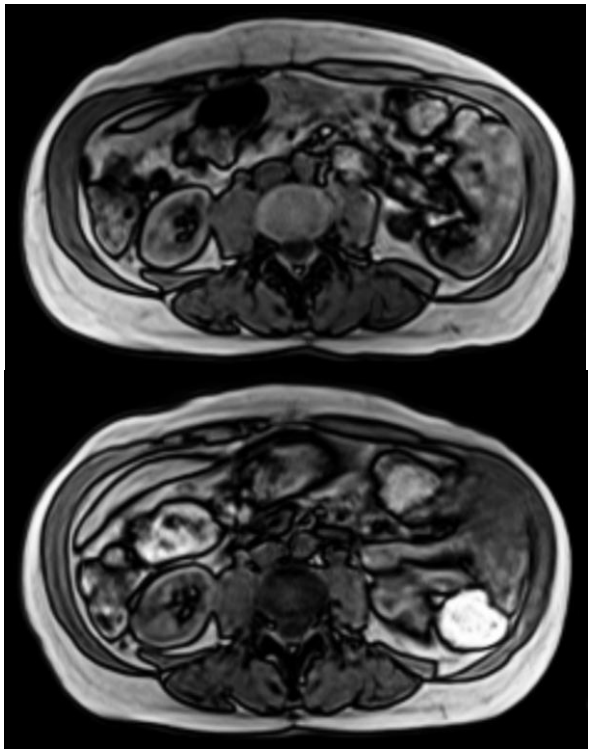


Fig. 7. MRI images of a male patient taken at baseline (left) and 3 month post-treatment (right). The images illustrate significant fat reduction and muscle thickening as a result of the dual field treatment. Adapted from Jacob et al.

shaping that allows us to clinically combine RF-induced fat elimination and HIFEM-induced muscle building in a wide range of patients, varying from trained athletes to sedentary or high-BMI individuals.

This new approach unlocks the various synergistic benefits that can only be seen when the energies are emitted at the same time. The fat-reducing effects of standalone radiofrequency are elevated by the aid of HIFEM and its side effects on fat metabolism. At the same time, the muscle-building effects of HIFEM are delivered on muscles that are pre-heated by the radiofrequency. These synergistic effects of the dual simultaneous delivery have been confirmed by multiple clinical studies documenting efficacy superior to any other standalone or consecutive treatment regimens. EMSCULPT NEO represents a new class of device far ahead of any devices currently in the marketplace for body contouring. Treatments are faster, safer and more effective than ever before.

V. References

1. Goldberg DJ. Adipocyte Apoptosis Induced by the Novel Radiofrequency Device Accompanied with HIFEM procedure: Human Histological Study. Presented at the Annual Meeting of the American Society for Dermatologic Surgery, 2020 Virtual Meeting.
2. Weiss RA, Bernardy J, Tichy F. Radiofrequency Treatment Used in Combination with HIFEM therapy: Histological Analysis including Scanning Electron Microscopy of Adipocytes. Presented at the Annual Meeting of the American Society for Dermatologic Surgery, 2020 Virtual Meeting.
3. Berg J, Tymoczko J, Stryer L. *Biochemistry*. 5th edition. New York: W H Freeman; 2002.

4. Adatto MA, Adatto-Neilson RM, Morren G. Reduction in adipose tissue volume using a new high-power radiofrequency technology combined with infrared light and mechanical manipulation for body contouring. *Lasers in Medical Science*. 2014;29(5):1627-1631. doi:10.1007/s10103-014-1564-x
5. Halaas Y, Bernardy J. Biochemical perspective of fat physiology after application of HIFEM field technology: additional investigation of fat disruption effects in a porcine study. *Lasers Surg Med*. 2019;51(S31):S4-S15. doi:10.1002/lsm.23067
6. Weiss RA, Bernardy J. Induction of fat apoptosis by a non-thermal device: Mechanism of action of non-invasive high-intensity electromagnetic technology in a porcine model. *Lasers Surg Med*. December 2018. doi:10.1002/lsm.23039
7. Boisnic S, Divaris M, Nelson AA, Gharavi NM, Lask GP. A clinical and biological evaluation of a novel, noninvasive radiofrequency device for the long-term reduction of adipose tissue. *Lasers in Surgery and Medicine*. 2014;46(2):94-103. doi:10.1002/lsm.22223
8. Franco W, Kothare A, Ronan SJ, Grekin RC, McCalmont TH. Hyperthermic injury to adipocyte cells by selective heating of subcutaneous fat with a novel radiofrequency device: Feasibility studies. *Lasers Surg Med*. 2010;42(5):361-370. doi:10.1002/lsm.20925
9. Franco W, Kothare A, Goldberg DJ. Controlled volumetric heating of subcutaneous adipose tissue using a novel radiofrequency technology. *Lasers Surg Med*. 2009;41(10):745-750. doi:10.1002/lsm.20876
10. Weiss R, Weiss M, Beasley K, Vrba J, Bernardy J. Operator Independent Focused High Frequency ISM Band for Fat Reduction: Porcine Model: Focused Field RF For Fat Reduction. *Lasers in Surgery and Medicine*. 2013;45(4):235-239. doi:10.1002/lsm.22134
11. Nikoletopoulou V, Markaki M, Palikaras K, Tavernarakis N. Crosstalk between apoptosis, necrosis and autophagy. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research*. 2013;1833(12):3448-3459. doi:10.1016/j.bbamcr.2013.06.001
12. Prokhorova EA, Kopeina GS, Lavrik IN, Zhivotovsky B. Apoptosis regulation by subcellular relocation of caspases. *Sci Rep*. 2018;8(1):12199. doi:10.1038/s41598-018-30652-x
13. Daisuke Hirayama, Tomoya Iida, Hiroshi Nakase. The Phagocytic Function of Macrophage-Enforcing Innate Immunity and Tissue Homeostasis. *IJMS*. 2017;19(1):92. doi:10.3390/ijms19010092
14. U.S. Food and Drug Administration. 510(k) Premarket Notification. December 2019. https://www.accessdata.fda.gov/cdrh_docs/pdf19/K192224.pdf. Accessed January 20, 2020.
15. Jacob C, Kent DE. Abdominal Toning and Reduction of Subcutaneous Fat with Combination of HIFEM Procedure and Radiofrequency Treatment. Presented at the Annual Meeting of the American Society for Dermatologic Surgery, 2020 Virtual Meeting.
16. Katz BE, Samuels JB, Weiss RA. Novel Radiofrequency Device Used in Combination with HIFEM Procedure for Abdominal Body Shaping: Sham-Controlled Randomized Trial. Presented at the Annual Meeting of the American Society for Dermatologic Surgery, 2020 Virtual Meeting.
17. Joyner MJ, Casey DP. Regulation of Increased Blood Flow (Hyperemia) to Muscles During Exercise: A Hierarchy of Competing Physiological Needs. *Physiol Rev*. 2015;95(2):549-601. doi:10.1152/physrev.00035.2013
18. Halaas Y, Bernardy J, Ondrackova P, Dinev I. The skeletal muscle satellite cell activation by a combination of HIFEM procedure and radiofrequency treatment for body contouring: A first look at the NCAM/CD56 facilitated detection by fluorescent microscopy. In: Pheonix, Arizona, USA: ASLMS; 2020.
19. Shellock FG, Prentice WE. Warming-Up and Stretching for Improved Physical Performance and Prevention of Sports-Related Injuries. *Sports Medicine*. 1985;2(4):267-278. doi:10.2165/00007256-198502040-00004
20. Giombini A, Giovannini V, Cesare AD, et al. Hyperthermia induced by microwave diathermy in the management of muscle and tendon injuries. *Br Med Bull*. 2007;83(1):379-396. doi:10.1093/bmb/ldm020
21. Gogte K, Srivastav P, Miyaru GB. Effect of Passive, Active and Combined Warm up on Lower Limb Muscle Performance and Dynamic Stability in Recreational Sports Players. *J Clin Diagn Res*. 2017;11(3):YC05-YC08. doi:10.7860/JCDR/2017/24766.9595
22. Racinais S, Cocking S, Périard JD. Sports and environmental temperature: From warming-up to heating-up. *Temperature (Austin)*. 2017;4(3):227-257. doi:10.1080/23328940.2017.1356427
23. Cairns SP. Lactic Acid and Exercise Performance. *Sports Med*. 2006;36(4):279-291. doi:10.2165/00007256-200636040-00001
24. Miles MP, Clarkson PM. Exercise-induced muscle pain, soreness, and cramps. *J Sports Med Phys Fitness*. 1994;34(3):203-216.
25. Mayer JM, Mooney V, Matheson LN, et al. Continuous Low-Level Heat Wrap Therapy for the Prevention and Early Phase Treatment of Delayed-Onset Muscle Soreness of the Low Back: A Randomized Controlled Trial. *Archives of Physical Medicine and Rehabilitation*. 2006;87(10):1310-1317. doi:10.1016/j.apmr.2006.07.259
26. Stadnyk AMJ, Rehrer NJ, Handcock PJ, Meredith-Jones KA, Cotter JD. No clear benefit of muscle heating on hypertrophy and strength with resistance training. *Temperature*. 2018;5(2):175-183. doi:10.1080/23328940.2017.1391366
27. Duncan D, Dinev I. Noninvasive Induction of Muscle Fiber Hypertrophy and Hyperplasia: Effects of High-Intensity Focused Electromagnetic Field Evaluated in an In-Vivo Porcine Model: A Pilot Study. *Aesthetic Surgery Journal*. October 2019:sjz244. doi:10.1093/asj/sjz244
28. Brown SJ, Child RB, Day SH, Donnelly AE. Exercise-induced skeletal muscle damage and adaptation following repeated bouts of eccentric muscle contractions. *Journal of Sports Sciences*. 1997;15(2):215-222. doi:10.1080/026404197367498
29. Ebbeling CB, Clarkson PM. Exercise-induced muscle damage and adaptation. *Sports Med*. 1989;7(4):207-234. doi:10.2165/00007256-198907040-00001
30. Kakigi R, Naito H, Ogura Y, et al. Heat stress enhances mTOR signaling after resistance exercise in human skeletal muscle. *J Physiol Sci*. 2011;61(2):131-140. doi:10.1007/s12576-010-0130-y
31. Yoshihara T, Naito H, Kakigi R, et al. Heat stress activates the Akt/mTOR signalling pathway in rat skeletal muscle. *Acta Physiologica*. 2013;207(2):416-426. doi:10.1111/apha.12040
32. Kobayashi T, Goto K, Kojima A, et al. Possible role of calcineurin in heating-related increase of rat muscle mass. *Biochem Biophys Res Commun*. 2005;331(4):1301-1309. doi:10.1016/j.bbrc.2005.04.096
33. Goto K, Okuyama R, Sugiyama H, et al. Effects of heat stress and mechanical stretch on protein expression in cultured skeletal muscle cells. *Pflugers Archiv European Journal of Physiology*. 2003;447(2):247-253. doi:10.1007/s00424-003-1177-x
34. Uehara K, Goto K, Kobayashi T, et al. Heat-stress enhances proliferative potential in rat soleus muscle. *Jpn J Physiol*. 2004;54(3):263-271. doi:10.2170/jjphysiol.54.263
35. Mauro A. Satellite Cells of Skeletal Muscle Fibers. *The Journal of Cell Biology*. 1961;9(2):493-495. doi:10.1083/jcb.9.2.493
36. Schultz E, McCormick KM. Skeletal muscle satellite cells. *Rev Physiol Biochem Pharmacol*. 1994;123:213-257. doi:10.1007/bfb0030904
37. Moss FP, Leblond CP. Satellite cells as the source of nuclei in muscles of growing rats. *Anat Rec*. 1971;170(4):421-435. doi:10.1002/ar.1091700405
38. Hawke TJ, Garry DJ. Myogenic satellite cells: physiology to molecular biology. *J Appl Physiol*. 2001;91(2):534-551. doi:10.1152/jappl.2001.91.2.534
39. Halevy O, Krispin A, Leshem Y, McMurtry JP, Yahav S. Early-age heat exposure affects skeletal muscle satellite cell proliferation and differentiation in chicks. *Am J Physiol Regul Integr Comp Physiol*. 2001;281(1):R302-309. doi:10.1152/ajpregu.2001.281.1.R302
40. Kent DE, Jacob CI. Simultaneous Changes in Abdominal Adipose and Muscle Tissues Following Treatments by High-Intensity Focused Electromagnetic (HIFEM) Technology-Based Device: Computed Tomography Evaluation. *J Drugs Dermatol*. 2019;18(11):1098-1102.
41. Kinney BM, Lozanova P. High intensity focused electromagnetic therapy evaluated by magnetic resonance imaging: Safety and efficacy study of a dual tissue effect based non-invasive abdominal body shaping. *Lasers in Surgery and Medicine*. 0(0). doi:10.1002/lsm.23024
42. Maggiore Q, Pizzarelli F, Sisca S, et al. Blood Temperature and Vascular Stability During Hemodialysis and Hemofiltration. *ASAIO Journal*. 1982;28(1):523.

EMSCULPT NEO – The Mechanism of Action

Simultaneous emission of synchronized radiofrequency and magnetic fields in a single applicator for fat elimination and muscle building

A unique combination of RF and HIFEM®

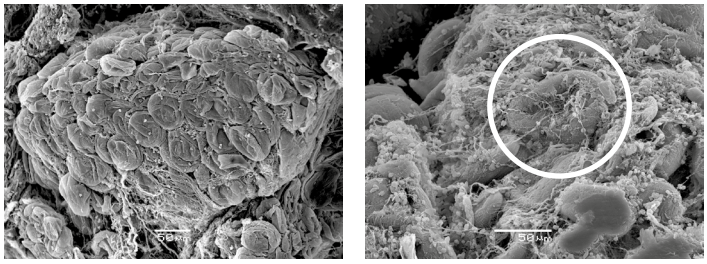
Procedures primarily addressing fat reduction and muscle building non-invasively have been two separate worlds since their inception due to the clinical and technical interferences. EMSCULPT NEO is the first of its kind medical device that generates RF and HIFEM energies simultaneously using dual-field applicators.

The RF component delivers different levels of heat to underlying structures; skin, fat, and muscle. HIFEM is a procedure based on high-intensity magnetic fields that elicit external muscle contractions of supra-physiological nature. The unique combination of muscle contractions and heating by EMSCULPT NEO has multiple synergistic effects making the simultaneous treatment more effective than any standalone or consecutive application.

Effects on adipose tissue

The unique synchronized radiofrequency in EMSCULPT NEO has shown to heat the adipose tissue to 43–45°C uniformly. Adipocytes exposed to temperatures in this range begin to lose their cellular viability and enter into the apoptotic process, i.e., natural and permanent deletion[1]. Consequently, the apoptotic cells lose membrane integrity and are digested by immune cells, which clear the degraded cell debris to maintain tissue homeostasis[2]. As a result, the number of fat cells in the treated area is significantly reduced.

The elevated temperature further results in increased blood flow and acceleration of metabolic activity. In response, the lipids stored in the fat cells are broken down into free fatty acids and glycerol, which are subsequently released to the bloodstream[3]. This directly leads to a shrinkage in the size of the remaining fat cells as they lose a large portion of their contents.



SEM evidence of fat cell shrinkage 4 days after treatment (left) and apoptotic fat cell destruction seen 2 weeks after treatment (right). Source: Weiss et al.

Several veterinary and human trials were conducted to investigate the effects of EMSCULPT NEO on subcutaneous fat tissue. Histological and electron microscopy observations of the adipose tissue revealed extensive disruption of fat cells and lipolytic changes. Noninvasive MRI and ultrasound evaluation demonstrated that the simultaneous treatments result in an average reduction of 28.3% – 30.8% in the subcutaneous fat layer.

The muscle contractions further contribute to an even heat distribution. Localized heat accumulation is often associated with thermal treatments and the so-called *"hot-spots"* can lead to various complications. In EMSCULPT NEO, the muscle contractions work as a natural massager distributing the heat homogeneously across the entire treated area.

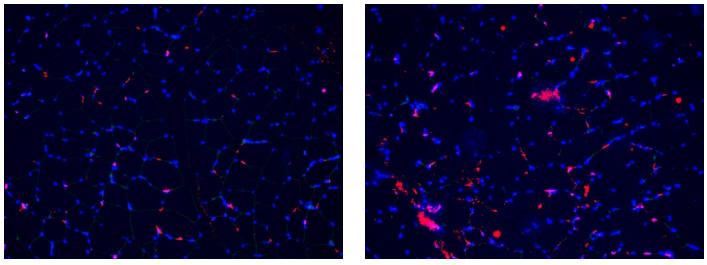
Effect on muscles

Due to the RF, the muscle is heated to 40–41°C, which causes increased blood flow into the

active tissue and thus a significant increase in the oxygen and nutrient delivery to the strained muscle fibers[4]. Increased oxygenation and nutrient supplementation promotes the anabolic processes that take place in an organism and are necessary for faster muscle fiber regeneration and growth.[5]

The HIFEM-induced supramaximal muscle contractions produce a strong response that triggers muscle tissue hypertrophy[6]. During the treatment, muscle fibers are stretched and relaxed with high frequency and intensity, leading to micro-ruptures in the muscle fibers[7,8]. In turn, signaling molecules (heat shock proteins - HSP) are released to activate regenerative and muscle growth processes to strengthen the muscle.[8] Satellite cells (SC), the muscle-derived stem cells responsible for **myofiber development, and renewal**[9] are activated at the same time. When activated the SC's may differentiate to support existing muscle fibers, or to generate new muscle fibers.[10]

Both HSP and SC can be activated by intense muscle exercise, but also by heat. Several studies have documented the ability of muscle heating to alter the levels of HSP as well as SC[11]. Moreover, the simultaneous application of heat and mechanical stress showed the highest levels in the expression of **HSPs** when compared to either heat or mechanical stress alone[12].



Immunofluorescence images. The levels of satellite cells (red) are increased significantly at 2 weeks post-treatment (right) when compared to baseline (left). Adopted from Halaas et al.

Multiple IRB studies have investigated the synergy, and their results have shown a muscle thickening effect of 24–26%. On the other hand, the studies investigating the use of HIFEM without RF heating reported growth in muscle thickness by 16%. This comparison clearly shows that the heat plays an important role in achieving superior clinical efficacy.

Concluding comments

EMSCULPT NEO represents the first-ever technology allowing the application of RF heating and HIFEM energies to the same body area simultaneously. This represents a breakthrough approach to non-surgical body shaping that clinically allows combining RF-induced fat elimination and HIFEM-induced muscle building in a wide range of patients, varying from athletes to high-BMI individuals. This new approach addresses the two biggest patient concerns in a single treatment while unlocking the various synergistic benefits that can only be seen when the energies are emitted at the same time. Multiple clinical studies investigating the synergistic effect of dual emission documented an efficacy superior to any other standalone or consecutive treatment available in aesthetic medicine today.

MRI images taken at baseline (left) and 3 months post-treatment (right). Adopted from Jacob et al.

References:

1. Weiss R, Weiss M, Beasley K, Vrba J, Bernardy J. Operator Independent Focused High Frequency ISM Band for Fat Reduction: Porcine Model: FOCUSED FIELD RF FOR FAT REDUCTION. *Lasers in Surgery and Medicine.* 2013;45(4):235-239.
2. Nikoletopoulou V, Markaki M, Palikaras K, Tavernarakis N. Crosstalk between apoptosis, necrosis and autophagy. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research.* 2013;1833(12):3448-3459.
3. Adatto MA, Adatto-Neilson RM, Morren G. Reduction in adipose tissue volume using a new high-power radiofrequency technology combined with infrared light and mechanical manipulation for body contouring. *Lasers in Medical Science.* 2014;29(5):1627-1631.
4. Giombini A, Giovannini V, Cesare AD, et al. Hyperthermia induced by microwave diathermy in the management of muscle and tendon injuries. *Br Med Bull.* 2007;83(1):379-396.
5. Racinais S, Cocking S, Périard JD. Sports and environmental temperature: From warming-up to heating-up. *Temperature (Austin).* 2017;4(3):227-257.
6. Duncan D, Dinev I. Noninvasive Induction of Muscle Fiber Hypertrophy and Hyperplasia: Effects of High-Intensity Focused Electromagnetic Field Evaluated in an In-Vivo Porcine Model: A Pilot Study. *Aesthetic Surgery Journal.* Published online October 26, 2019:sjz244.
7. Brown SJ, Child RB, Day SH, Donnelly AE. Exercise-induced skeletal muscle damage and adaptation following repeated bouts of eccentric muscle contractions. *Journal of Sports Sciences.* 1997;15(2):215-222.
8. Ebbeling CB, Clarkson PM. Exercise-induced muscle damage and adaptation. *Sports Med.* 1989;7(4):207-234.
9. Mauro A. Satellite Cells of Skeletal Muscle Fibers. *The Journal of Cell Biology.* 1961;9(2):493-495.
10. Schultz E, McCormick KM. Skeletal muscle satellite cells. *Rev Physiol Biochem Pharmacol.* 1994;123:213-257.
11. Kakigi R, Naito H, Ogura Y, et al. Heat stress enhances mTOR signaling after resistance exercise in human skeletal muscle. *J Physiol Sci.* 2011;61(2):131-140.
12. Goto K, Okuyama R, Sugiyama H, et al. Effects of heat stress and mechanical stretch on protein expression in cultured skeletal muscle cells. *Pflugers Archiv European Journal of Physiology.* 2003;447(2):247-253.

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SYNCHRONIZED RF & HIFEM: INTERIM RESULTS OF INNER THIGHS MRI STUDY

EFFICACY AND SAFETY OF SIMULTANEOUS APPLICATION OF HIFEM AND SYNCHRONIZED RADIOFREQUENCY FOR NON-INVASIVE LIPOLYSIS IN INNER THIGHS: PRELIMINARY DATA

Diane Duncan MD, F.A.C.S[1]

1. . Plastic Surgery Associates, Fort Collins CO, USA

Interim data from ongoing clinical study, ClinicalTrials.gov Identifier: NCT04596228

HIGHLIGHTS

- **16 subjects** (24-69 y/o; BMI 21.3-35.0 kg/m^2) received four 30-minute treatments.
- MRI showed an average **fat thickness reduction by 0.84 cm** at 1 month (N=15) and **1.02 cm** at 3 months (N=6), respectively.
- Thigh **circumference decreased** on average by **1.0 cm** at 1 month.
- **94%** of patients reported **satisfaction** with the treatment results.

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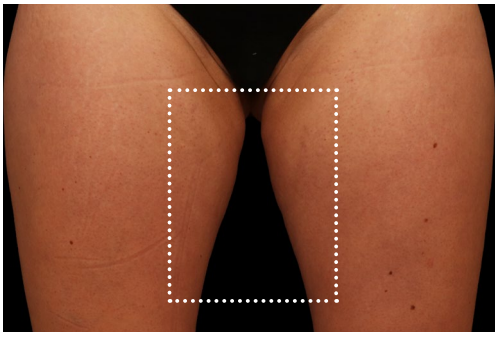
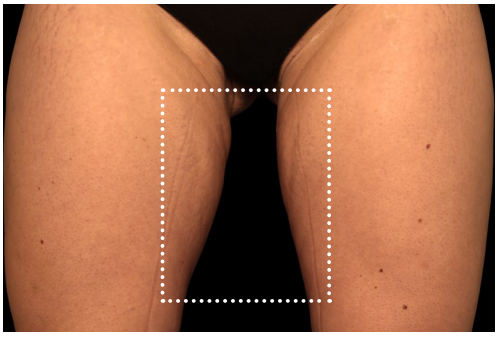


1 MONTH FOLLOW-UP



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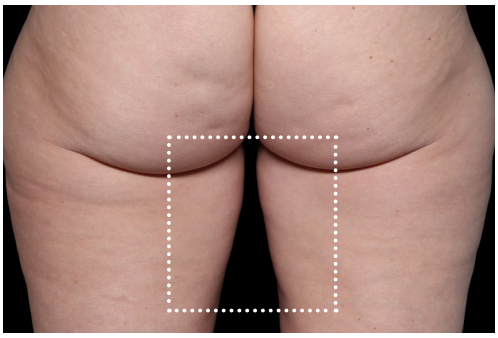
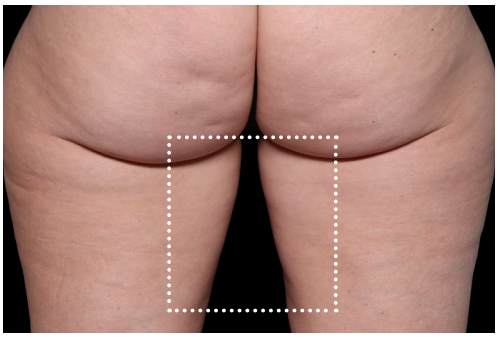


AFTER THE LAST TREATMENT



Courtesy of: Diane Duncan, M.D.

SYNCHRONIZED RF & HIFEM: MULTI-CENTER OUTER THIGH MRI STUDY

SIMULTANEOUS EMISSION OF SYNCHRONIZED RADIOFREQUENCY AND HIFEM ENERGY FOR TREATMENT OF LATERAL THIGHS: INTERIM RESULTS OF THE MRI MULTICENTRE STUDY

Melanie Palm M.D., MBA[1]; Brian Kinney M.D., FACS, MSME[2]; Yael Halaas M.D., FACS[3]

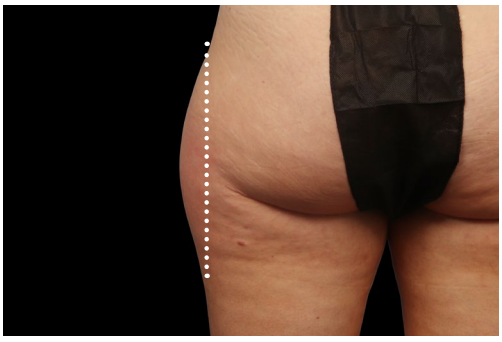
1. Art of Skin M.D., Solana Beach, CA, USA
2. Brian M. Kinney M.D., Beverly Hills, CA, USA
3. Yael Halaas M.D., New York, NY, USA

Presented at the Annual Meeting of the American Society for Laser Medicine and Surgery, 2021.

HIGHLIGHTS

- **30 subjects** (29-65 y/o, 19.0-34.5 kg/m^2) received four 30-minute treatments of lateral thighs delivered once per week.
- MRI assessment revealed **average reduction of fat** thickness by **1.4 cm** in saddlebag region **at 1 month**.
- Average **hip circumference decreased by 3.0 cm**.
- There were **no non-responders**.

BASELINE



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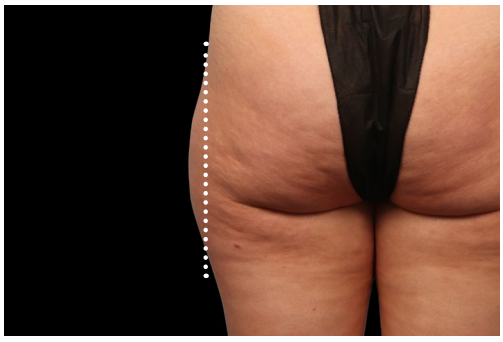
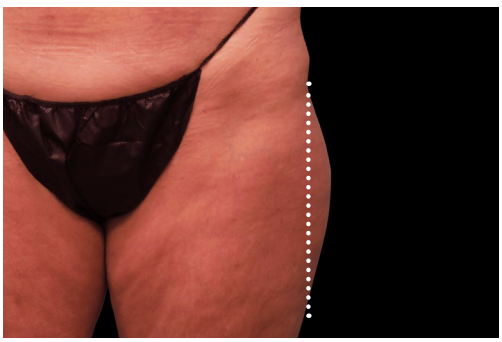


COURTESY OF: MELANIE PALM, M.D.

BASELINE



1-MONTH FOLLOW-UP

COURTESY OF: BRIAN KINNEY, M.D.

EMSCULPT NEO
Simultaneous emission of novel Synchronized Radiofrequency and HIFEM (magnetic fields) in a single applicator for fat elimination and muscle building

Robert Weiss MD[1], Brian Kinney MD[2], Carolyn Jacob MD[3]

***Abstract*—EMSCULPT NEO is a device that delivers HIFEM and Synchronized RF energies simultaneously through a single applicator. The combined technology induces supramaximal muscle contractions and heating in the treated fat & muscle tissues. This simultaneous combination of two energies has synergistic effects that drastically enhance the results when compared to the individual treatments. RF heating during HIFEM muscle contractions increases activation of proteins stimulating muscle synthesis and enhances the hypertrophic effect. RF heating of fat tissue results in lipolytic and apoptotic processes leading to the permanent elimination of fat cells while being supported by increased metabolic activity due to the HIFEM contractions. Multiple clinical studies on this device documented results superior to any standalone or consecutive treatment regimens, which places the device far ahead of any devices currently used for body contouring.**

***Keywords* — HIFEM, Radiofrequency, Simultaneous, Application, Supramaximal, Contraction, Muscle, Fat, Reduction, Hypertrophy**

I. Introduction

Radiofrequency (RF) and HIFEM technologies are currently used extensively in aesthetic medicine for body shaping. The effect of RF technology is based on differential elevation of temperature in response to selective transformation of radiofrequency energy into heat in targeted tissues. Utilizing specific frequencies of the RF spectrum allows for selective heating, due to the difference in properties between the tissues in the targeted area of treatment. As such, RF is often used for fat reduction, skin tightening, or cellulite reduction. HIFEM technology, on the other hand, uses alternating magnetic fields to induce powerful skeletal muscle contractions via stimulation of the nerve pathways without significant, or even noticeable, elevation of temperature. HIFEM induced, supramaximal contractions are greater than voluntary contractions thanks to the specific stimulation patterns and frequencies. With repetition and over time, there is a tissue healing response that leads to increasing the muscle mass via amplified muscle fiber size.

EMSCULPT NEO is the first of its kind medical device combining novel Synchronized RF and HIFEM that are both emitted simultaneously using specially designed and patented dual-field applicators. The RF component enhances local blood circulation and delivers heat to underlying structures; skin, fat, and muscle, while HIFEM induces supramaximal muscle contractions at the same time. This unique combination has multiple synergistic effects and has been shown to make the simultaneous treatment more effective than any standalone or consecutive application. Studies have shown that the radiofrequency heating supports HIFEM's effects on muscles, while HIFEM enhances the radiofrequency's effects on fat.

II. The Effect in Adipose Tissue

The dual-energy application by EMSCULPT NEO has demonstrated uniform heating of adipose tissue above physiological levels, reaching 43-45°C (See **Figure 1**). The essential temperature of 42°C was achieved in fat in-vivo at approximately 4 minutes[1,2], while thermal imaging measurements showed safe values on the skin throughout the treatment thereby avoiding risks of epidermal damage. Temperature elevation in the fat has been shown to benefit fat reduction in two ways.

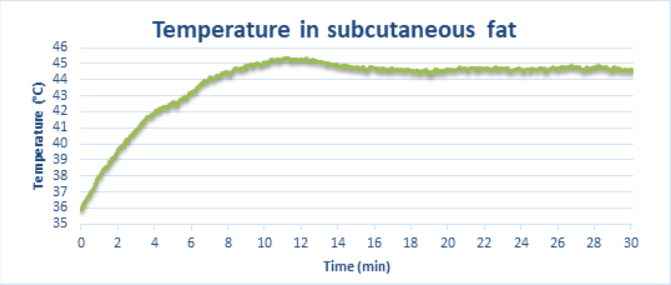


Fig. 1. Fat tissue temperature over time. The temperature is rapidly increased during the first few minutes and then oscillates just below 45°C for the rest of the treatment. Source: Weiss et al.

[1]Maryland Dermatology Laser Skin &Vein Institute, Hunt Valley, MD
[2]Plastic Surgery Excellence, Beverly Hills, CA
[3]Chicago Cosmetic Surgery and Dermatology, Chicago, IL

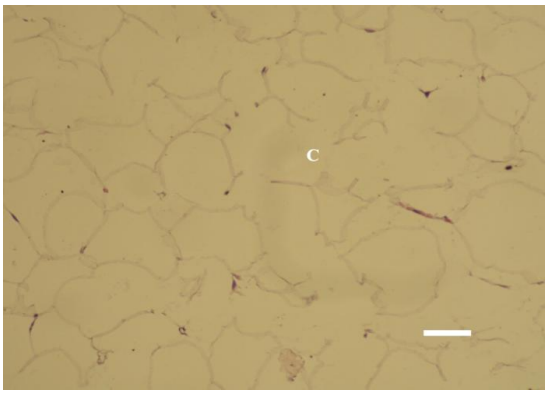


Fig. 2. Adipose tissue showing noticeable shape alternations at 2 weeks post-treatment, some cells are flattened of a smaller size. Numerous adipocytes show membrane ruptures. Source: Goldberg et al.

Initially, the elevated temperature results in increased blood flow and acceleration of metabolic activity. In response, the lipids stored in the fat cells, in the form of triglycerides, are broken down (hydrolyzed) into free fatty acids and glycerol; the two products are subsequently slowly and safely released into the bloodstream. As seen in **Figure 2**, the diameter of affected fat cells is smaller, and the overall response is exhibited as a nondestructive reduction of adipocyte volume aka lipolysis[3,4]. This phenomenon is further enhanced during the intense localized muscle work provided by HIFEM. The muscle load significantly increases the body's need for energy supply, resulting in an induced metabolic stress[5,6]. As such, applying RF and HIFEM at the same time brings the key synergy in the form of a significantly enhanced fat breakdown process.

The other direct effect of fat heating occurs when the elevated temperature is sustained for a sufficient period of time. Adipocytes exposed to temperatures of 43-45°C for several minutes lose their cellular integrity/viability, and a portion will be forced to enter into the apoptotic process, i.e., natural and permanent cell death and resorption[7–10]. The apoptotic cells subsequently lose their membrane integrity and are ultimately digested by macrophages (occasionally accompanied by other immune cells), responsible for clearing the degraded cells and the debris to maintain tissue homeostasis[11–13].

The efficacy of this novel dual-energy device for fat reduction has already been documented through clinical investigation. Histological examinations performed by Goldberg[1] and Weiss et al.[2] consistently revealed noticeable shape alternations of adipocytes after the treatments, including their flattening, shrinkage, and membrane ruptures. The release of intracellular content, due to the lipolysis led to a 33% decrease in the size of adipocytes. In addition, the ongoing apoptotic process was observed in the examined tissue through an increased presence of the adipocyte's pyknotic nuclei. These histological findings coincided with the scanning electron microscopy (SEM), which revealed smaller and deformed adipocytes, with ruptured membranes and noticeable extrusion of lipid droplets outside the cells. See **Figure 3.**

Multiple additional studies have further confirmed the histological observations. A study submitted to the FDA as part of the technology's clearance process evaluated 42 test subjects by ultrasound imaging and showed a reduction in abdominal fat by 29.8% at 3-months post-treatment[14]. Another study, by Jacob and Kent[15] used magnetic resonance imaging (MRI) to conclude a significant reduction of abdominal fat thickness by 30.8% at 3 months after the dual-energy treatments. Similarly, another study performed by Katz et al.[16] used an ultrasonographic examination and demonstrated an average decrease in fat thickness by 20.5% at 1 month. Results further improved to 28.3% at 3 months post-treatment. When compared to the previous HIFEM studies, the scale of documented improved results on fat reduction strongly suggests the beneficial effects of combined treatments.

Besides enhanced lipolysis, the simultaneous dual-energy application contributes to an even heat distribution. Localized accumulation of heat is often associated with thermal only treatments, and the so-called "*hot-spots*" can lead to various complications. In EMSCULPT NEO, the muscle contractions work as a natural massage and through an accelerated blood circulation[4,17] help distribute the heat homogeneously across the entire treated area.

III. The Effects on Muscle Tissue

The use of in-vivo temperature probes revealed that while fat is heated during the treatment, two simultaneous modalities also affect muscle tissue. Due to the relatively high thermal conductivity, the muscle tissue does not retain the same temperature profile that can be seen in the fat due to its lower

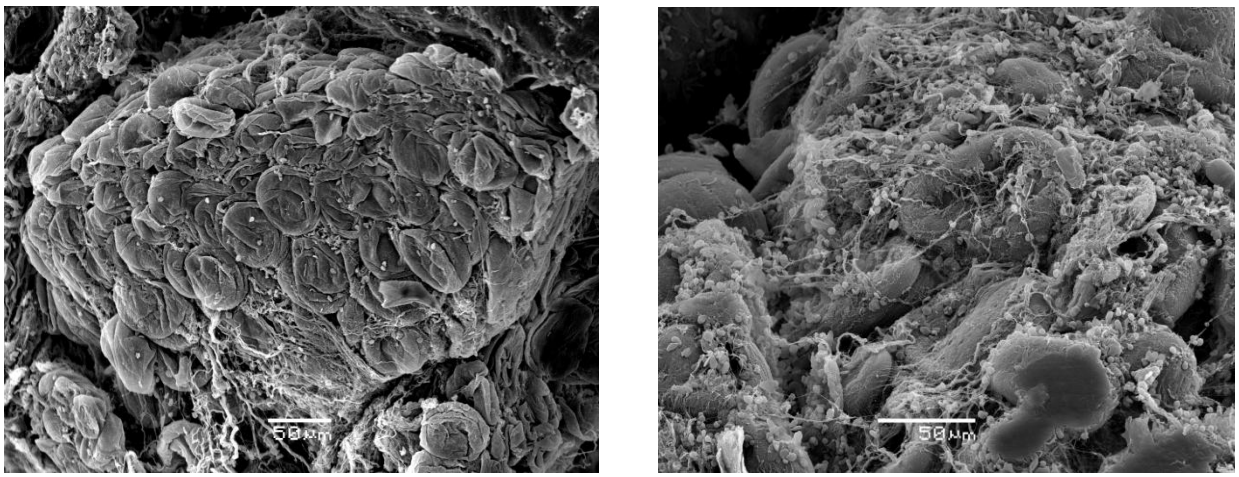


Fig. 3. SEM evidence of the fat cell shrinkage due to lipolysis which occurs 4 days after treatment (left) and fat cell destruction due to apoptosis seen 2 weeks after the last treatment (right). Source: Weiss et al.

thermal conductivity and higher thermal capacitance. The muscle is heated to temperatures ranging from 40-41°C, which is a combined result of the heat directly induced by RF, the heat produced by the muscle during supramaximal contractions, and the heat that physiologically spreads from the adjacent fat tissues. The muscle temperature over time can be seen in **Figure 4**.

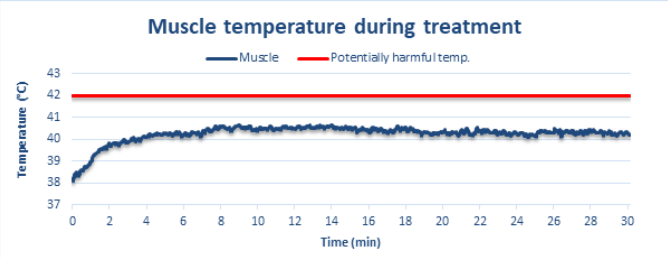


Fig. 4. During the first 2 minutes, the muscle temperature reached 40°C and was maintained between 40 and 41°C for the rest of the treatment. Safe temperature levels were sustained without any risks for the muscle tissue for the entire treatment. Adopted from Halaas et al.

Scientifically, it is well documented that muscle heating provides many physiological benefits. We intuitively warm up shortly before doing any strenuous weightlifting or other types of exercise to protect the muscles from injury for a reason.[19] Studies have shown that heating of the muscle tissue during contractions positively affects the muscle response in several ways:

Muscle heating causes vasodilatation, i.e., increased blood flow into the active tissue, which significantly increases the delivery of oxygen and nutrients to the strained muscle fibers.[20] The oxygen levels are directly affected by heating through dissociation of oxygen from hemoglobin at higher plasma oxygen concentrations, thus providing more oxygen to working muscles.[19,21] An increased oxygenation and nutrient supplementation promotes the anabolic processes and are necessary for faster muscle fiber regeneration and growth.[22]

Increased blood flow is also accompanied by a faster removal of toxic waste products (e.g., lactic and carbonic acid)[20]. Lactic and carbonic acids are by-products of the metabolic process that produce energy for the muscles during intensive muscle work.[23] High levels of these acids within the tissue are associated with muscle soreness and muscle

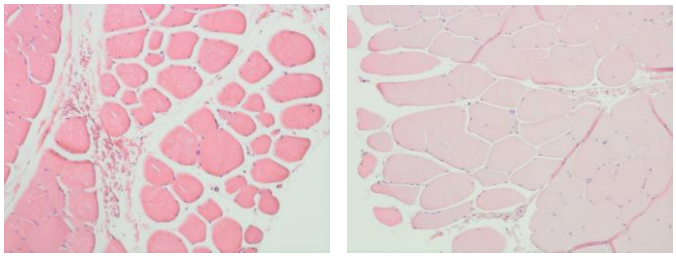


Fig. 5. Images of histological slices of muscle tissue collected at baseline (left) and 2 weeks after the last dual-energy treatment (right). The volume of individual muscle fibers is noticeably increased after the treatment. Adopted from Halaas et al.

fatigue.[24] A faster flush out of the waste leads to an attenuation of muscle soreness and muscle fatigue. This can be experienced the day after the treatment.[25] Furthermore, heated muscle contractions were described as “better”, “easier”, “stronger” and “less fatiguing” than muscle contractions in normal room conditions.[26] Heating thus increases the already high levels of patient’s treatment and post-treatment comfort.

Although all of the benefits mentioned above significantly contribute to the patients’ overall treatment experience, the main synergistic effect of the simultaneous delivery of RF and HIFEM lies in **the enhancement of muscle strengthening by hypertrophy**.

The HIFEM-induced supramaximal contractions produce a strong response, triggering muscle tissue hypertrophy[27]. During intense contractions, muscle fibers are stretched and relaxed, similar to resistance exercise, but with a higher intensity. Muscle workload of a sufficient intensity leads to micro-ruptures in muscle fibers.[28,29] This causes signaling molecules to be released to activate a regenerative process and muscle growth in order to strengthen the muscle and prepare it for another workload.[29] **Heat shock proteins (HSP)** are a family of such signaling molecules that play a crucial role in **muscle hypertrophy** through the **promotion of muscle protein synthesis**.[30,31]

Heat shock proteins may be activated by mechanical stress, such as intense muscle contractions, and heat stress. Several studies have documented increases in HSP levels and increased muscle protein synthesis in the muscle tissue after an application of heat at 40-41°C[30–34]. Goto et al.[33] compared the HSP expression following heat stress, mechanical stress,

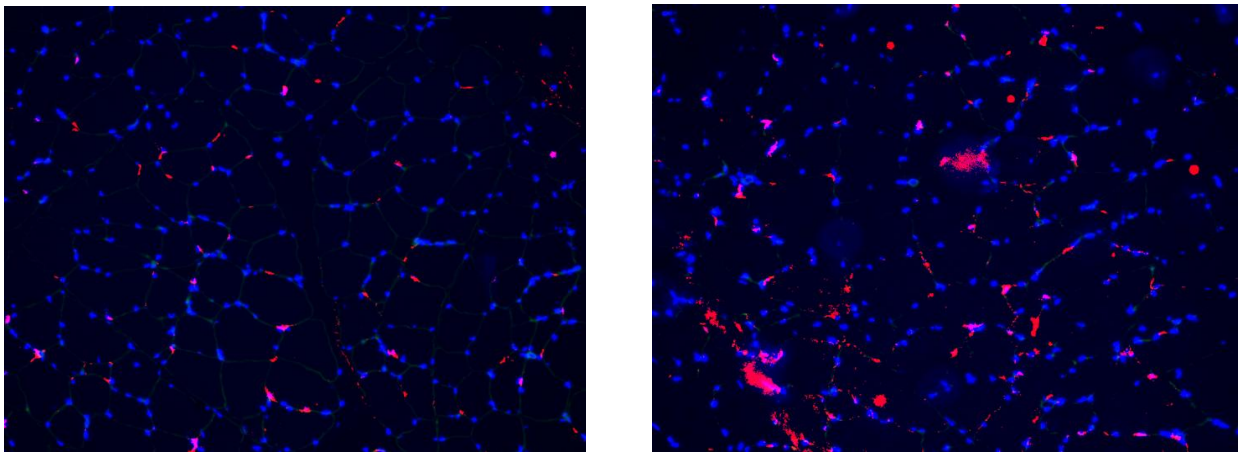


Fig. 6. Images of histological slices of muscle tissue collected at baseline (left) and 2 weeks after the last dual-energy treatment (right). The volume of individual muscle fibers is noticeably increased after the treatment. Adopted from Halaas et al

and simultaneous application of heat and mechanical stress. **The simultaneous application** showed a **significantly higher increase** in the expression of **HSPs** when compared to either heat or mechanical stress alone, which only confirms the synergistic effects of the two energies for muscle hypertrophy.

Another important element in muscle hypertrophy is the so-called satellite cells (SC). SC are muscle-derived stem cells, responsible for **myofiber development and renewal**.[35] In a resting state, the SC remain in a quiescent state, ready to be activated, enter differentiation to provide new myonuclei to existing muscle fibers, or to generate new muscle fibers.[36,37] They can be activated by an intense muscle exercise as a response to **regenerate and strengthen the existing muscle fibers**.[38] However, heat was also found to trigger activation of satellite cells[39]. Simultaneous application of heat and mechanical stress is presumed to result in magnification of the muscle strengthening and hypertrophy. Increased levels of the satellite cell pool after a set of dual-energy treatments have been documented in a study by Halaas et al.[18] The increased SC levels (See **Figure 6**.) were accompanied by histological observation of muscle hypertrophy and even newly formed myoblasts.

Satellite cells and heat shock proteins are not the only muscle bulk enhancing aspect. The increased tolerance of the contractions allows physicians to apply higher HIFEM intensities much earlier in the treatment process, and to use protocols with more intense muscle stimulation patterns.

The first clinical trials[15,16] on this novel dual-energy technology showed significantly more prominent muscle hypertrophy compared to previous studies investigating a standalone HIFEM procedure[40,41]. The average growth in muscle thickness was oscillating around 24-26%, while without the heating effects, the muscle thickening effects averaged at 16%. See **Figure 7** for illustrative MRI images.

One might presume that a consecutive application of RF and HIFEM delivered immediately following each other, would yield similar benefits as a simultaneous application. However, this was shown not to be the case. Muscle tissue, being rich in blood vessels, can dissipate the excessive heat accumulation as soon as it exceeds the blood temperature (appx. 37°C)[42]. Without continuous heat delivery, it is impossible to maintain the proper therapeutic temperature elevation in the targeted tissue, which is essential to achieve all the synergistic effects. This dual-field modality technology thus provides a unique solution that cannot be fully clinically substituted by any combination of two standalone applications.

IV. Concluding comments

Procedures primarily addressing fat and muscles non-invasively have been two separate worlds since their inception. This is due to the clinical as well as technical interferences of the two different concepts. EMSCULPT NEO represents the first-ever technology that, from an engineering standpoint, allows to simultaneously apply RF heating and HIFEM energies to the same targeted body area. This represents a breakthrough approach to non-surgical body

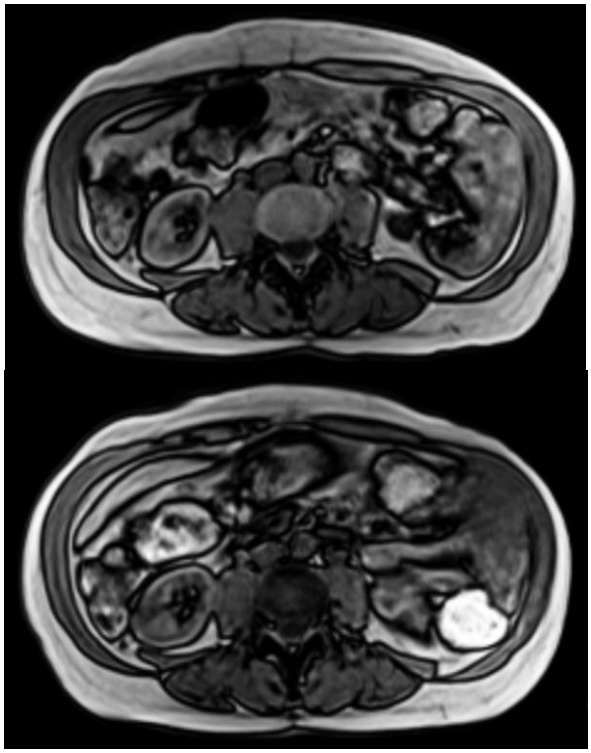


Fig. 7. MRI images of a male patient taken at baseline (left) and 3 month post-treatment (right). The images illustrate significant fat reduction and muscle thickening as a result of the dual field treatment. Adapted from Jacob et al.

shaping that allows us to clinically combine RF-induced fat elimination and HIFEM-induced muscle building in a wide range of patients, varying from trained athletes to sedentary or high-BMI individuals.

This new approach unlocks the various synergistic benefits that can only be seen when the energies are emitted at the same time. The fat-reducing effects of standalone radiofrequency are elevated by the aid of HIFEM and its side effects on fat metabolism. At the same time, the muscle-building effects of HIFEM are delivered on muscles that are pre-heated by the radiofrequency. These synergistic effects of the dual simultaneous delivery have been confirmed by multiple clinical studies documenting efficacy superior to any other standalone or consecutive treatment regimens. EMSCULPT NEO represents a new class of device far ahead of any devices currently in the marketplace for body contouring. Treatments are faster, safer and more effective than ever before.

V. References

1. Goldberg DJ. Adipocyte Apoptosis Induced by the Novel Radiofrequency Device Accompanied with HIFEM procedure: Human Histological Study. Presented at the Annual Meeting of the American Society for Dermatologic Surgery, 2020 Virtual Meeting.
2. Weiss RA, Bernardy J, Tichy F. Radiofrequency Treatment Used in Combination with HIFEM therapy: Histological Analysis including Scanning Electron Microscopy of Adipocytes. Presented at the Annual Meeting of the American Society for Dermatologic Surgery, 2020 Virtual Meeting.
3. Berg J, Tymoczko J, Stryer L. *Biochemistry*. 5th edition. New York: W H Freeman; 2002.

4. Adatto MA, Adatto-Neilson RM, Morren G. Reduction in adipose tissue volume using a new high-power radiofrequency technology combined with infrared light and mechanical manipulation for body contouring. *Lasers in Medical Science*. 2014;29(5):1627-1631. doi:10.1007/s10103-014-1564-x
5. Halaas Y, Bernardy J. Biochemical perspective of fat physiology after application of HIFEM field technology: additional investigation of fat disruption effects in a porcine study. *Lasers Surg Med*. 2019;51(S31):S4-S15. doi:10.1002/lsm.23067
6. Weiss RA, Bernardy J. Induction of fat apoptosis by a non-thermal device: Mechanism of action of non-invasive high-intensity electromagnetic technology in a porcine model. *Lasers Surg Med*. December 2018. doi:10.1002/lsm.23039
7. Boisnic S, Divaris M, Nelson AA, Gharavi NM, Lask GP. A clinical and biological evaluation of a novel, noninvasive radiofrequency device for the long-term reduction of adipose tissue. *Lasers in Surgery and Medicine*. 2014;46(2):94-103. doi:10.1002/lsm.22223
8. Franco W, Kothare A, Ronan SJ, Grekin RC, McCalmont TH. Hyperthermic injury to adipocyte cells by selective heating of subcutaneous fat with a novel radiofrequency device: Feasibility studies. *Lasers Surg Med*. 2010;42(5):361-370. doi:10.1002/lsm.20925
9. Franco W, Kothare A, Goldberg DJ. Controlled volumetric heating of subcutaneous adipose tissue using a novel radiofrequency technology. *Lasers Surg Med*. 2009;41(10):745-750. doi:10.1002/lsm.20876
10. Weiss R, Weiss M, Beasley K, Vrba J, Bernardy J. Operator Independent Focused High Frequency ISM Band for Fat Reduction: Porcine Model: Focused Field RF For Fat Reduction. *Lasers in Surgery and Medicine*. 2013;45(4):235-239. doi:10.1002/lsm.22134
11. Nikoletopoulou V, Markaki M, Palikaras K, Tavernarakis N. Crosstalk between apoptosis, necrosis and autophagy. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research*. 2013;1833(12):3448-3459. doi:10.1016/j.bbamcr.2013.06.001
12. Prokhorova EA, Kopeina GS, Lavrik IN, Zhivotovsky B. Apoptosis regulation by subcellular relocation of caspases. *Sci Rep*. 2018;8(1):12199. doi:10.1038/s41598-018-30652-x
13. Daisuke Hirayama, Tomoya Iida, Hiroshi Nakase. The Phagocytic Function of Macrophage-Enforcing Innate Immunity and Tissue Homeostasis. *IJMS*. 2017;19(1):92. doi:10.3390/ijms19010092
14. U.S. Food and Drug Administration. 510(k) Premarket Notification. December 2019. https://www.accessdata.fda.gov/cdrh_docs/pdf19/K192224.pdf. Accessed January 20, 2020.
15. Jacob C, Kent DE. Abdominal Toning and Reduction of Subcutaneous Fat with Combination of HIFEM Procedure and Radiofrequency Treatment. Presented at the Annual Meeting of the American Society for Dermatologic Surgery, 2020 Virtual Meeting.
16. Katz BE, Samuels JB, Weiss RA. Novel Radiofrequency Device Used in Combination with HIFEM Procedure for Abdominal Body Shaping: Sham-Controlled Randomized Trial. Presented at the Annual Meeting of the American Society for Dermatologic Surgery, 2020 Virtual Meeting.
17. Joyner MJ, Casey DP. Regulation of Increased Blood Flow (Hyperemia) to Muscles During Exercise: A Hierarchy of Competing Physiological Needs. *Physiol Rev*. 2015;95(2):549-601. doi:10.1152/physrev.00035.2013
18. Halaas Y, Bernardy J, Ondrackova P, Dinev I. The skeletal muscle satellite cell activation by a combination of HIFEM procedure and radiofrequency treatment for body contouring: A first look at the NCAM/CD56 facilitated detection by fluorescent microscopy. In: Pheonix, Arizona, USA: ASLMS; 2020.
19. Shellock FG, Prentice WE. Warming-Up and Stretching for Improved Physical Performance and Prevention of Sports-Related Injuries. *Sports Medicine*. 1985;2(4):267-278. doi:10.2165/00007256-198502040-00004
20. Giombini A, Giovannini V, Cesare AD, et al. Hyperthermia induced by microwave diathermy in the management of muscle and tendon injuries. *Br Med Bull*. 2007;83(1):379-396. doi:10.1093/bmb/ldm020
21. Gogte K, Srivastav P, Miyaru GB. Effect of Passive, Active and Combined Warm up on Lower Limb Muscle Performance and Dynamic Stability in Recreational Sports Players. *J Clin Diagn Res*. 2017;11(3):YC05-YC08. doi:10.7860/JCDR/2017/24766.9595
22. Racinais S, Cocking S, Périard JD. Sports and environmental temperature: From warming-up to heating-up. *Temperature (Austin)*. 2017;4(3):227-257. doi:10.1080/23328940.2017.1356427
23. Cairns SP. Lactic Acid and Exercise Performance. *Sports Med*. 2006;36(4):279-291. doi:10.2165/00007256-200636040-00001
24. Miles MP, Clarkson PM. Exercise-induced muscle pain, soreness, and cramps. *J Sports Med Phys Fitness*. 1994;34(3):203-216.
25. Mayer JM, Mooney V, Matheson LN, et al. Continuous Low-Level Heat Wrap Therapy for the Prevention and Early Phase Treatment of Delayed-Onset Muscle Soreness of the Low Back: A Randomized Controlled Trial. *Archives of Physical Medicine and Rehabilitation*. 2006;87(10):1310-1317. doi:10.1016/j.apmr.2006.07.259
26. Stadnyk AMJ, Rehrer NJ, Handcock PJ, Meredith-Jones KA, Cotter JD. No clear benefit of muscle heating on hypertrophy and strength with resistance training. *Temperature*. 2018;5(2):175-183. doi:10.1080/23328940.2017.1391366
27. Duncan D, Dinev I. Noninvasive Induction of Muscle Fiber Hypertrophy and Hyperplasia: Effects of High-Intensity Focused Electromagnetic Field Evaluated in an In-Vivo Porcine Model: A Pilot Study. *Aesthetic Surgery Journal*. October 2019:sjz244. doi:10.1093/asj/sjz244
28. Brown SJ, Child RB, Day SH, Donnelly AE. Exercise-induced skeletal muscle damage and adaptation following repeated bouts of eccentric muscle contractions. *Journal of Sports Sciences*. 1997;15(2):215-222. doi:10.1080/026404197367498
29. Ebbeling CB, Clarkson PM. Exercise-induced muscle damage and adaptation. *Sports Med*. 1989;7(4):207-234. doi:10.2165/00007256-198907040-00001
30. Kakigi R, Naito H, Ogura Y, et al. Heat stress enhances mTOR signaling after resistance exercise in human skeletal muscle. *J Physiol Sci*. 2011;61(2):131-140. doi:10.1007/s12576-010-0130-y
31. Yoshihara T, Naito H, Kakigi R, et al. Heat stress activates the Akt/mTOR signalling pathway in rat skeletal muscle. *Acta Physiologica*. 2013;207(2):416-426. doi:10.1111/apha.12040
32. Kobayashi T, Goto K, Kojima A, et al. Possible role of calcineurin in heating-related increase of rat muscle mass. *Biochem Biophys Res Commun*. 2005;331(4):1301-1309. doi:10.1016/j.bbrc.2005.04.096
33. Goto K, Okuyama R, Sugiyama H, et al. Effects of heat stress and mechanical stretch on protein expression in cultured skeletal muscle cells. *Pflugers Archiv European Journal of Physiology*. 2003;447(2):247-253. doi:10.1007/s00424-003-1177-x
34. Uehara K, Goto K, Kobayashi T, et al. Heat-stress enhances proliferative potential in rat soleus muscle. *Jpn J Physiol*. 2004;54(3):263-271. doi:10.2170/jjphysiol.54.263
35. Mauro A. Satellite Cells of Skeletal Muscle Fibers. *The Journal of Cell Biology*. 1961;9(2):493-495. doi:10.1083/jcb.9.2.493
36. Schultz E, McCormick KM. Skeletal muscle satellite cells. *Rev Physiol Biochem Pharmacol*. 1994;123:213-257. doi:10.1007/bfb0030904
37. Moss FP, Leblond CP. Satellite cells as the source of nuclei in muscles of growing rats. *Anat Rec*. 1971;170(4):421-435. doi:10.1002/ar.1091700405
38. Hawke TJ, Garry DJ. Myogenic satellite cells: physiology to molecular biology. *J Appl Physiol*. 2001;91(2):534-551. doi:10.1152/jappl.2001.91.2.534
39. Halevy O, Krispin A, Leshem Y, McMurtry JP, Yahav S. Early-age heat exposure affects skeletal muscle satellite cell proliferation and differentiation in chicks. *Am J Physiol Regul Integr Comp Physiol*. 2001;281(1):R302-309. doi:10.1152/ajpregu.2001.281.1.R302
40. Kent DE, Jacob CI. Simultaneous Changes in Abdominal Adipose and Muscle Tissues Following Treatments by High-Intensity Focused Electromagnetic (HIFEM) Technology-Based Device: Computed Tomography Evaluation. *J Drugs Dermatol*. 2019;18(11):1098-1102.
41. Kinney BM, Lozanova P. High intensity focused electromagnetic therapy evaluated by magnetic resonance imaging: Safety and efficacy study of a dual tissue effect based non-invasive abdominal body shaping. *Lasers in Surgery and Medicine*. 0(0). doi:10.1002/lsm.23024
42. Maggiore Q, Pizzarelli F, Sisca S, et al. Blood Temperature and Vascular Stability During Hemodialysis and Hemofiltration. *ASAIO Journal*. 1982;28(1):523.

EMSCULPT NEO – The Mechanism of Action

Simultaneous emission of synchronized radiofrequency and magnetic fields in a single applicator for fat elimination and muscle building

A unique combination of RF and HIFEM®

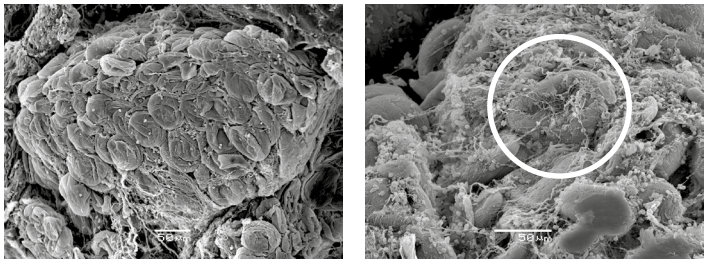
Procedures primarily addressing fat reduction and muscle building non-invasively have been two separate worlds since their inception due to the clinical and technical interferences. EMSCULPT NEO is the first of its kind medical device that generates RF and HIFEM energies simultaneously using dual-field applicators.

The RF component delivers different levels of heat to underlying structures; skin, fat, and muscle. HIFEM is a procedure based on high-intensity magnetic fields that elicit external muscle contractions of supra-physiological nature. The unique combination of muscle contractions and heating by EMSCULPT NEO has multiple synergistic effects making the simultaneous treatment more effective than any standalone or consecutive application.

Effects on adipose tissue

The unique synchronized radiofrequency in EMSCULPT NEO has shown to heat the adipose tissue to 43–45°C uniformly. Adipocytes exposed to temperatures in this range begin to lose their cellular viability and enter into the apoptotic process, i.e., natural and permanent deletion[1]. Consequently, the apoptotic cells lose membrane integrity and are digested by immune cells, which clear the degraded cell debris to maintain tissue homeostasis[2]. As a result, the number of fat cells in the treated area is significantly reduced.

The elevated temperature further results in increased blood flow and acceleration of metabolic activity. In response, the lipids stored in the fat cells are broken down into free fatty acids and glycerol, which are subsequently released to the bloodstream[3]. This directly leads to a shrinkage in the size of the remaining fat cells as they lose a large portion of their contents.



SEM evidence of fat cell shrinkage 4 days after treatment (left) and apoptotic fat cell destruction seen 2 weeks after treatment (right). Source: Weiss et al.

Several veterinary and human trials were conducted to investigate the effects of EMSCULPT NEO on subcutaneous fat tissue. Histological and electron microscopy observations of the adipose tissue revealed extensive disruption of fat cells and lipolytic changes. Noninvasive MRI and ultrasound evaluation demonstrated that the simultaneous treatments result in an average reduction of 28.3% – 30.8% in the subcutaneous fat layer.

The muscle contractions further contribute to an even heat distribution. Localized heat accumulation is often associated with thermal treatments and the so-called *"hot-spots"* can lead to various complications. In EMSCULPT NEO, the muscle contractions work as a natural massager distributing the heat homogeneously across the entire treated area.

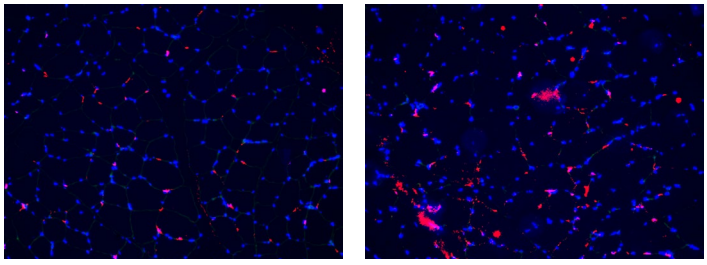
Effect on muscles

Due to the RF, the muscle is heated to 40–41°C, which causes increased blood flow into the

active tissue and thus a significant increase in the oxygen and nutrient delivery to the strained muscle fibers[4]. Increased oxygenation and nutrient supplementation promotes the anabolic processes that take place in an organism and are necessary for faster muscle fiber regeneration and growth.[5]

The HIFEM-induced supramaximal muscle contractions produce a strong response that triggers muscle tissue hypertrophy[6]. During the treatment, muscle fibers are stretched and relaxed with high frequency and intensity, leading to micro-ruptures in the muscle fibers[7,8]. In turn, signaling molecules (heat shock proteins - HSP) are released to activate regenerative and muscle growth processes to strengthen the muscle.[8] Satellite cells (SC), the muscle-derived stem cells responsible for **myofiber development, and renewal**[9] are activated at the same time. When activated the SC's may differentiate to support existing muscle fibers, or to generate new muscle fibers.[10]

Both HSP and SC can be activated by intense muscle exercise, but also by heat. Several studies have documented the ability of muscle heating to alter the levels of HSP as well as SC[11]. Moreover, the simultaneous application of heat and mechanical stress showed the highest levels in the expression of **HSPs** when compared to either heat or mechanical stress alone[12].



Immunofluorescence images. The levels of satellite cells (red) are increased significantly at 2 weeks post-treatment (right) when compared to baseline (left). Adopted from Halaas et al.

Multiple IRB studies have investigated the synergy, and their results have shown a muscle thickening effect of 24–26%. On the other hand, the studies investigating the use of HIFEM without RF heating reported growth in muscle thickness by 16%. This comparison clearly shows that the heat plays an important role in achieving superior clinical efficacy.

Concluding comments

EMSCULPT NEO represents the first-ever technology allowing the application of RF heating and HIFEM energies to the same body area simultaneously. This represents a breakthrough approach to non-surgical body shaping that clinically allows combining RF-induced fat elimination and HIFEM-induced muscle building in a wide range of patients, varying from athletes to high-BMI individuals. This new approach addresses the two biggest patient concerns in a single treatment while unlocking the various synergistic benefits that can only be seen when the energies are emitted at the same time. Multiple clinical studies investigating the synergistic effect of dual emission documented an efficacy superior to any other standalone or consecutive treatment available in aesthetic medicine today.

MRI images taken at baseline (left) and 3 months post-treatment (right). Adopted from Jacob et al.

References:

1. Weiss R, Weiss M, Beasley K, Vrba J, Bernardy J. Operator Independent Focused High Frequency ISM Band for Fat Reduction: Porcine Model: FOCUSED FIELD RF FOR FAT REDUCTION. *Lasers in Surgery and Medicine.* 2013;45(4):235-239.
2. Nikoletopoulou V, Markaki M, Palikaras K, Tavernarakis N. Crosstalk between apoptosis, necrosis and autophagy. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research.* 2013;1833(12):3448-3459.
3. Adatto MA, Adatto-Neilson RM, Morren G. Reduction in adipose tissue volume using a new high-power radiofrequency technology combined with infrared light and mechanical manipulation for body contouring. *Lasers in Medical Science.* 2014;29(5):1627-1631.
4. Giombini A, Giovannini V, Cesare AD, et al. Hyperthermia induced by microwave diathermy in the management of muscle and tendon injuries. *Br Med Bull.* 2007;83(1):379-396.
5. Racinais S, Cocking S, Périard JD. Sports and environmental temperature: From warming-up to heating-up. *Temperature (Austin).* 2017;4(3):227-257.
6. Duncan D, Dinev I. Noninvasive Induction of Muscle Fiber Hypertrophy and Hyperplasia: Effects of High-Intensity Focused Electromagnetic Field Evaluated in an In-Vivo Porcine Model: A Pilot Study. *Aesthetic Surgery Journal.* Published online October 26, 2019:sjz244.
7. Brown SJ, Child RB, Day SH, Donnelly AE. Exercise-induced skeletal muscle damage and adaptation following repeated bouts of eccentric muscle contractions. *Journal of Sports Sciences.* 1997;15(2):215-222.
8. Ebbeling CB, Clarkson PM. Exercise-induced muscle damage and adaptation. *Sports Med.* 1989;7(4):207-234.
9. Mauro A. Satellite Cells of Skeletal Muscle Fibers. *The Journal of Cell Biology.* 1961;9(2):493-495.
10. Schultz E, McCormick KM. Skeletal muscle satellite cells. *Rev Physiol Biochem Pharmacol.* 1994;123:213-257.
11. Kakigi R, Naito H, Ogura Y, et al. Heat stress enhances mTOR signaling after resistance exercise in human skeletal muscle. *J Physiol Sci.* 2011;61(2):131-140.
12. Goto K, Okuyama R, Sugiyama H, et al. Effects of heat stress and mechanical stretch on protein expression in cultured skeletal muscle cells. *Pflugers Archiv European Journal of Physiology.* 2003;447(2):247-253.

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