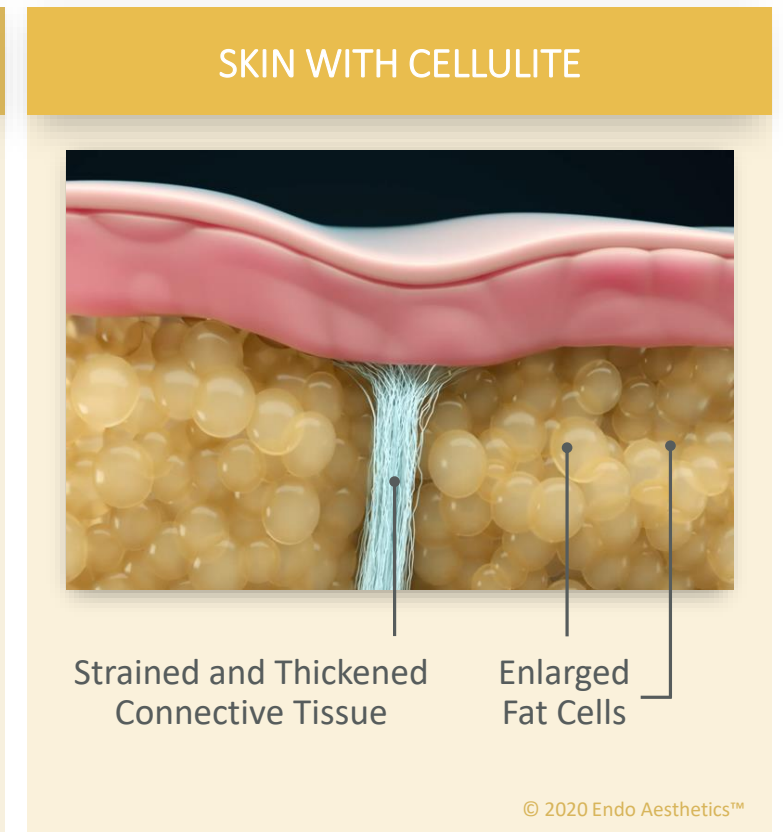
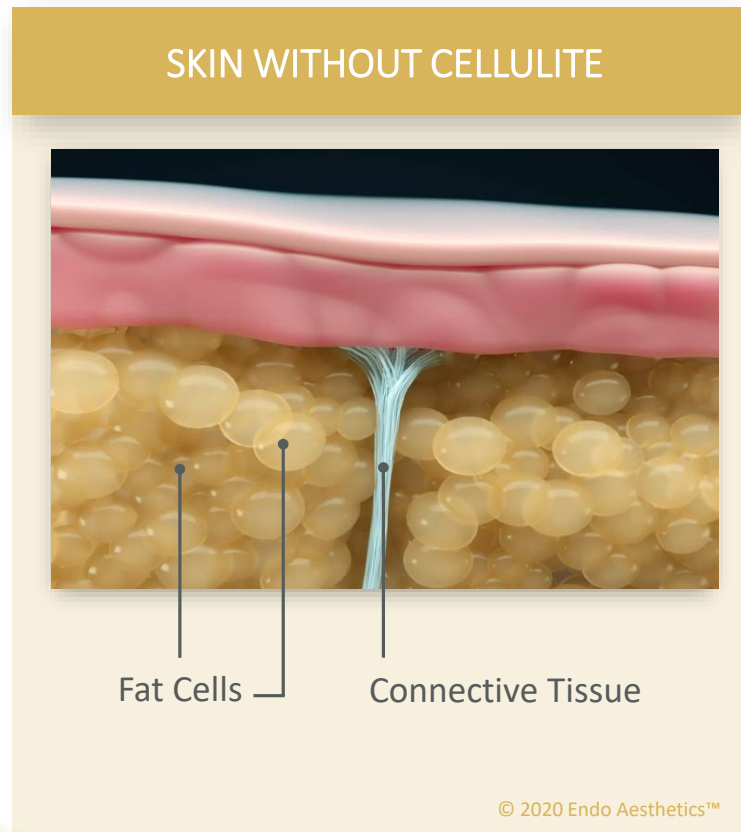


CELLULITE OVERVIEW



WHAT IS CELLULITE?

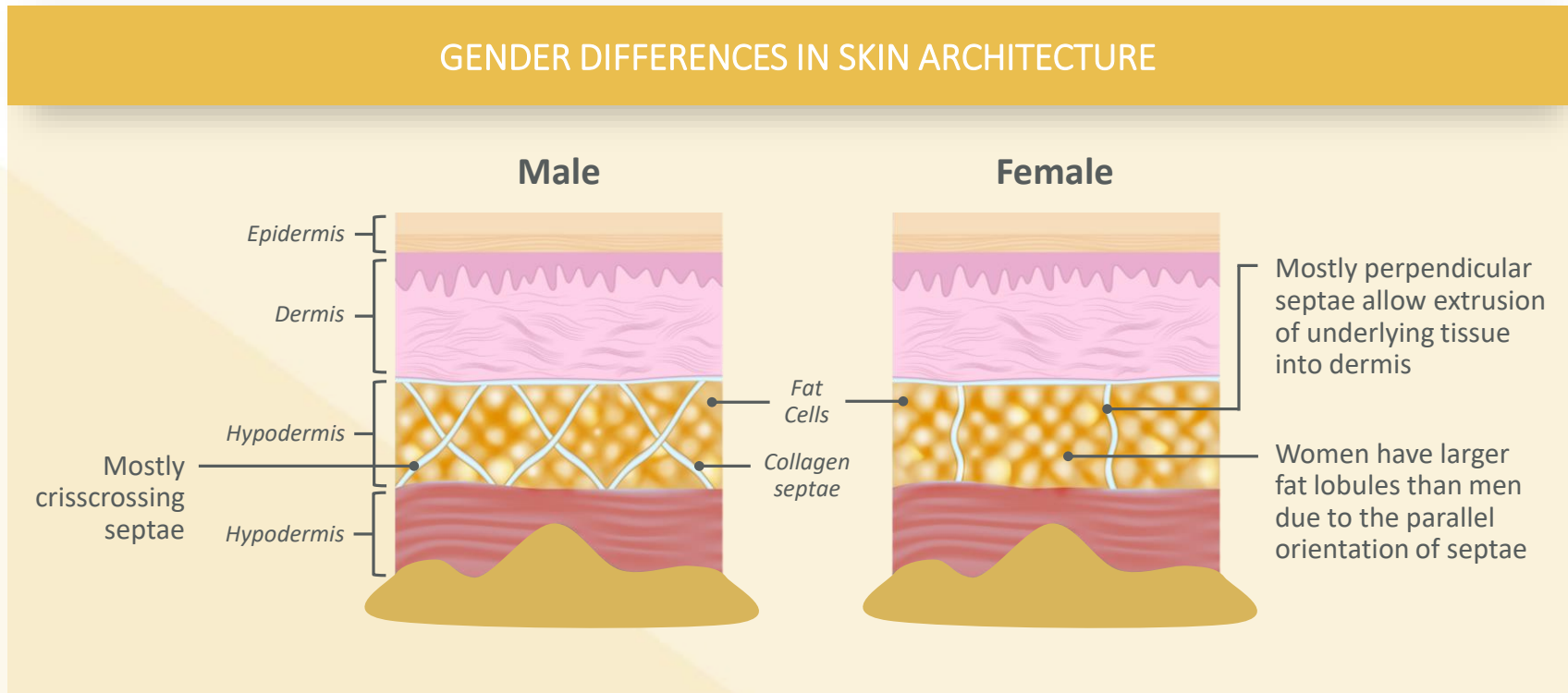
- Cellulite is an alteration in skin topography¹
- It is ubiquitous in postpubescent women, affecting 85% to 98%²
- Cellulite causes a dimpled appearance of the affected skin, primarily affecting the thighs and buttocks²
- Cellulite is a multifactorial condition³



References: 1. Friedmann DP, et al. *Clin Cosmet Investig Dermatol*. 2017;10:17-23. 2. Avram MM. *J Cosmet Laser Ther*. 2005;6(4):181-185. 3. Sadick N. *Int J Womens Dermatol*. 2019;5(1):68-72.

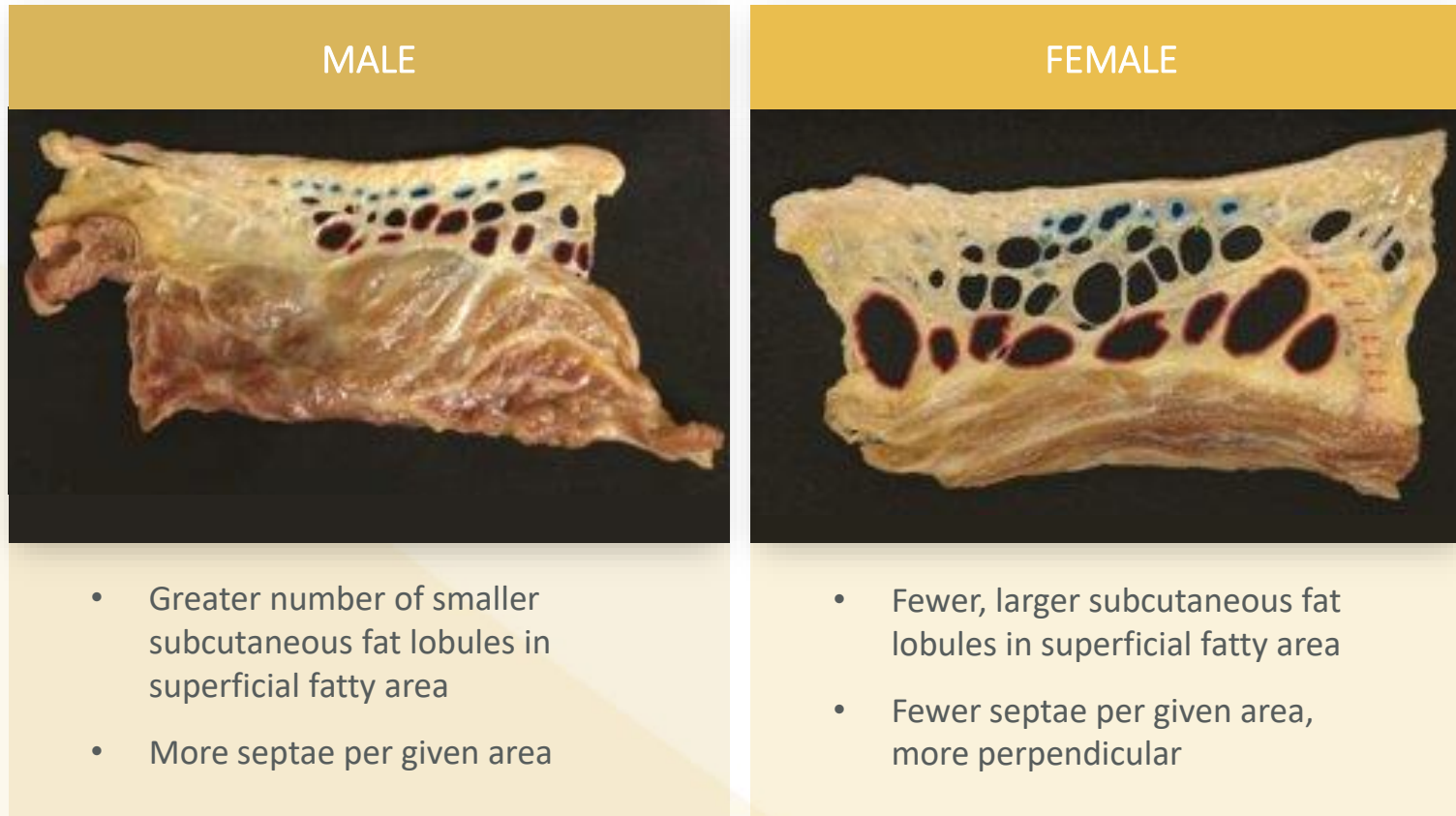
ARCHITECTURE OF SUBCUTANEOUS CONNECTIVE TISSUE DIFFERS BETWEEN GENDERS^{1,2}

In women, a greater percentage of fibrous septae are oriented perpendicular to the skin surface



References: 1. Nürnberger F, Müller G. *J Dermatol Surg Oncol*. 1978;4(3):221-229. 2. Gonzaga de Cunha M, et al. *Surg Cosmet Dermatol*. 2014;6(4):355-359.

ARCHITECTURE OF SUBCUTANEOUS CONNECTIVE TISSUE DIFFERS BETWEEN GENDERS



Images of a longitudinal slice from an 80-year-old male cadaver and a 72-year-old female cadaver.

Reference: 1. Rudolph C, et al. *Plast Reconstr Surg.* 2019;143(4):1077-1086.

CELLULITE: A DISPARITY BETWEEN CONTAINMENT AND EXTRUSION FORCES AT THE SUBDERMAL JUNCTION

1. Decreased dermal thickness with age¹

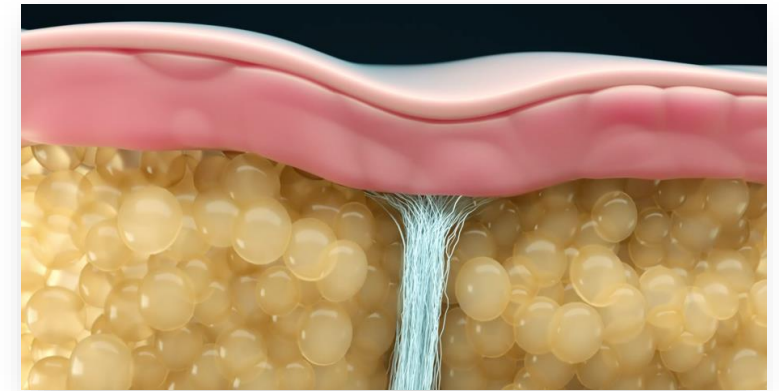
- Gender- and BMI-independent dermal thinning by 0.3% per year
- Less support to contain the underlying fatty layers
- Women can lose 30% of dermal collagen in the 5 years after menopause, further contributing to dermal thinning and loss of structural support²

2. Increased height of superficial fat lobules¹

- In the superficial layer, fat lobule height is significantly higher in females than males

3. Septal morphology¹

- Males have a higher number of smaller subcutaneous fat lobules per given area and a greater number of septae
- Males require a significantly greater force to disrupt the fibrous connections



“Women at any age and with any body mass index are inherently at greater risk for developing cellulite than men because of their reduced septal number and increased superficial fat lobule height.”¹

References: 1. Rudolph C, et al. *Plast Reconstr Surg.* 2019;143(4):1077-1086. 2. Archer DF. *Gynecol Endocrinol.* 2012;28(Suppl 2):2-6.

SUMMARY OF DIFFERENCES BETWEEN GENDERS

In comparison with males, females have:

GREATER	LESS
<ul style="list-style-type: none">• Greater fat lobule height• Greater fat lobule width	<ul style="list-style-type: none">• Lower number of septal connections• Fewer fat lobules• Less force required to cause septal breakage

Reference: Rudolph C, et al. *Plast Reconstr Surg.* 2019;143(4):1077-1086.

THE DEVELOPMENT OF CELLULITE IS MULTIFACTORIAL

DERMIS	Inflammatory¹ <ul style="list-style-type: none">• Chronic low-grade inflammation that results in dermal atrophy
SEPTAE & CONNECTIVE TISSUE	Genetic² <ul style="list-style-type: none">• Differences in 2 genes: ACE and HIF1A
FAT, MUSCLES, DERMIS	Hormonal^{3,4} <ul style="list-style-type: none">• Estrogen, insulin, prolactin• Increased lipogenesis• Vascular changes
VASCULATURE	Vascular³ <ul style="list-style-type: none">• Water retention/edema• Restricted blood flow

References: 1. Khan MH, et al. *J Am Acad Dermatol.* 2010;62(3):361-370. 2. Emanuele E, et al. *J Eur Acad Dermatol Venereol.* 2010;24(8):930-935. 3. Rawlings AV. *Int J Cosmet Sci.* 2006;28(3):175-190. 4. Avram MM. *J Cosmet Laser Ther.* 2004;6(4):181-185.

FIBROUS SEPTAE PLAY A ROLE IN THE DEVELOPMENT OF CELLULITE¹

The septae attach the skin to the underlying muscle or fascia¹

It has been suggested that as the superficial layer of fat beneath the skin pushes upward it can create the dimpling effect¹

The fibrous septae are rich in COLLAGEN TYPE I and COLLAGEN TYPE III, which are resistant to degradation by most common proteases, except collagenolytic proteases²



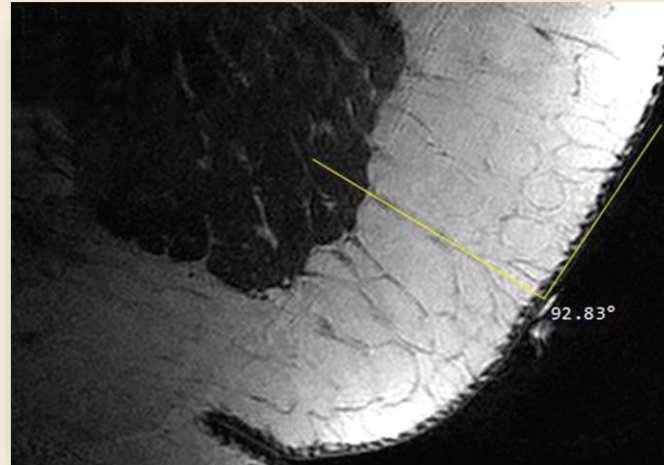
Gjorgiev/Shutterstock.com

References: 1. Rudolph C, et al. *Plast Reconstr Surg.* 2019;14(4):1077-1086. 2. Zhang YZ, et al. *Appl Environ Microbiol.* 2015;81(18):6098-6107.

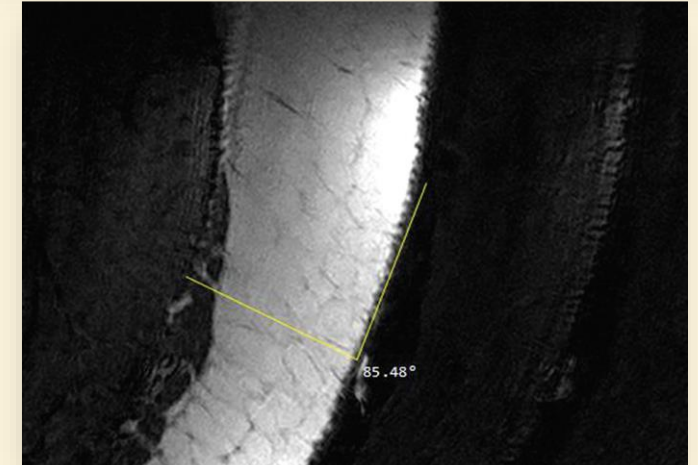
FIBROUS SEPTAE ANGLE VARIES BY $\sim 10^\circ$ IN STANDING AND PRONE POSITIONS

“The appearance and disappearance of the cellulite dimple in the standing and prone positions, respectively, are illustrative of the imbalance of the containment and extrusion forces at the subdermal junction.”

BUTTOCK STANDING; SLICE 3/32

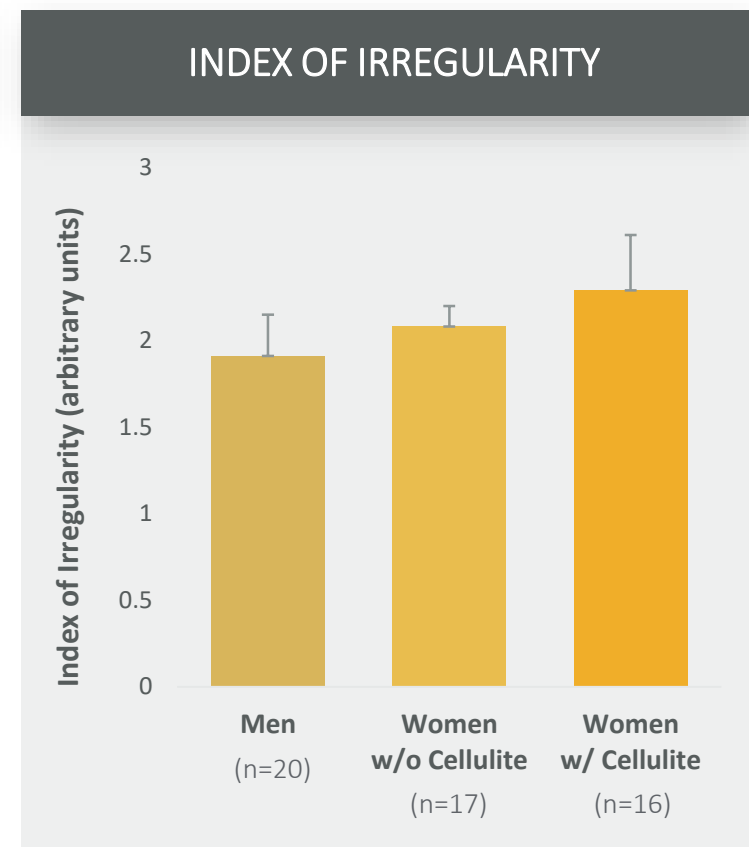
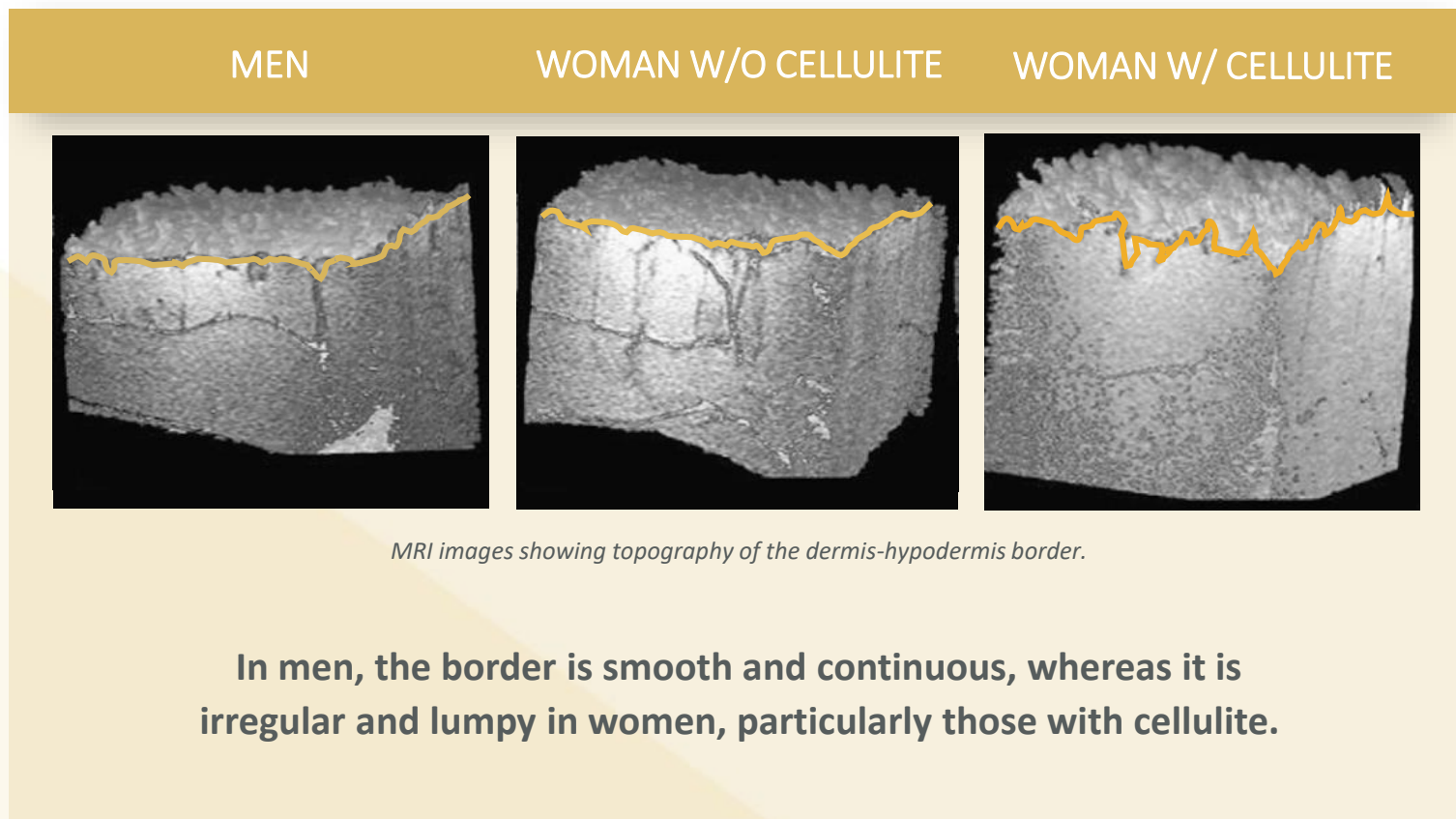


BUTTOCK PRONE; SLICE 14/32



Reference: Omburo G, et al. Presented at 2019 American Society of Dermatologic Surgery Annual Meeting, Chicago, IL Oct 24-27, 2019.

THE DERMIS-HYPODERMIS BORDER MAY BE A CONTRIBUTING FACTOR OF CELLULITE



Reference: Querleux B, et al. *Skin Res Technol.* 2002;8(2):118-124.

CELLULITE MAY PRESENT WITH OR WITHOUT LAXITY¹



References: 1. Christman MP, et al. *J Drugs Dermatol*. 2017;16(1):58-61. 2. Phase 3 subject images (Data on file).

CELLULITE TREATMENT OPTIONS

THERAPY	DESCRIPTION
ADIPOSE TISSUE	
Liposuction ¹	Invasive procedure for fat removal
Cold-assisted lipolysis ²	Freezes unwanted pockets of fat
Focused ultrasound energy ³	Uses focused ultrasound energy to disrupt fat
Radiofrequency therapy ^{4,5}	Uses radiofrequency energy to heat up fat
DERMIS	
Laser therapy ⁶	Tissue is heated to help increase microcirculation
Acoustic wave therapy ^{7,8}	Helps promote lipolysis, lymphatic drainage, and production of new collagen
Dermal fillers and bio-stimulatory injectables ^{9,10}	Stimulates collagen production
RF microneedling system ^{11,12}	Minimally invasive treatment stimulates the natural production of collagen

References: 1. Dhami LD. *Indian J Plast Surg.* 2008;41(Suppl):S27-S40. 2. Data on file. ZELTIQ Aesthetics, Inc. Pleasanton, CA. 2017. (510(k) clearance, K172144). 3. Data on file. Syneron Medical, Ltd. Philadelphia, PA. 2016. (510(k) clearance, K160896). 4. Data on file. BTL Industries, Inc. Waltham, MA. 2016. (510(k) clearance, K152731). 5. Data on file. Solta Medical, Inc. Hayward, CA. 2013. (510(k) clearance, K132431). 6. Data on file. Biocellulase, Inc. Newton, MA. 2005. (510(k) clearance, K053611). 7. Adatto MA, et al. *J Cosmet Laser Ther.* 2011;13(6):291-296. 8. Russe-Wilflingseder K, Russe E. AIP Conference Proceedings. 1226. 10.1063/1.3453782. 9. American Society of Plastic Surgery. Dermal Fillers. Available from: <https://www.plasticsurgery.org/cosmetic-procedures/dermal-fillers/types>. Accessed on 11th Feb 2020. 10. SCULPTRA Aesthetic Instructions for Use. Galderma Laboratories, L.P. Fort Worth, TX. 11. Data on file. Syneron Medical, Ltd. Philadelphia, PA. 2016. (510(k) clearance, K161043). 12. Alexiades M, et al. *Dermatol Surg.* 2018;44(10):1262-1271.

CELLULITE TREATMENT OPTIONS

THERAPY	DESCRIPTION
MUSCLE	
Electromagnetic field therapy ^{1,2}	Uses rapidly changing electrical fields/EM stimulation to cause muscle contraction to stimulate muscle growth and tone area
SEPTAE	
Vacuum-assisted precise tissue release ³	Tissue stabilized-guided subcision system
Subcision ⁴	Manual cutting of the fibrous cords of cellulite
Laser therapy ^{5,6}	Release of bands and stimulation of collagen for increased dermal thickness
Injectable collagenase clostridium histolyticum ⁷	Release of fibrous septae by specifically targeting types I and III collagen
HYBRID DEVICES	
Some devices have additional clearance for the temporary improvement of blood circulation, such as Velashape III. ⁸	

References: 1. Data on file. Zimmer Medizin Systeme GmbH. Stow, MA. 2019. (510(k) clearance, K192940). 2. Data on file. BTL Industries, Inc. Framingham, MA. 2016. (510(k) clearance, K160992). 3. Kaminer MS, et al. *Dermatol Surg.* 2015;41(3):336-347. 4. Friedmann DP. *Clin Cosmet Invest Dermatol.* 2017;10:17-23. 5. Data on file. Cynosure, Inc. Westford, MA. 2012. (510(k) clearance, K102541). 6. DiBernardo BE. *Aesthet Surg J.* 2011;31(3):328-341. 7. Qwo [package insert]. Malvern, PA: Endo Pharmaceuticals, Inc. 8. Data on file. Syneron Medical, Ltd. Israel. 2012. (510(k) clearance, K122579).

FURTHER READING

Archer DF. *Gynecol Endocrinol*. 2012; 28(Suppl 2):2-6.

Avram MM. *J Cosmet Laser Ther*. 2005; 6(4):181-185.

Christman MP, et al. *J Drugs Dermatol*. 2017;16(1):58-61.

Emanuele E, et al. *J Eur Acad Dermatol Venereol*. 2010;24(8):930-935.

Friedmann DP, et al. *Clin Cosmet Investig Dermatol*. 2017;10:17-23.

Gonzaga de Cunha M, et al. *Surg Cosmet Dermatol*. 2014;6(4):355-359.

Khan MH, et al. *J Am Acad Dermatol*. 2010;62(3):361-370.

Nürnberg F, Müller G. *J Dermatol Surg Oncol*. 1978;4(3):221-229.

Oct Omburo G, et al. Presented at 2019 American Society of Dermatologic Surgery Annual Meeting, Chicago, IL 24-27, 2019.

Rudolph C, et al. *Plast Reconstr Surg*. 2019;143(4):1077-1086.

Rawlings AV. *Int J Cosmet Sci*. 2006;28(3):175-190.

Sadick N. *Int J Womens Dermatol*. 2019;5(1):68-72.

Zhang YZ, et al. *Appl Environ Microbiol*. 2015;81(18):6098-6107.