

Pneumatic Delivery of Hyaluronan for Skin Remodeling: A Comparative Review

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ABSTRACT

Jet Volumetric Remodeling (JVR) utilizes the principle of superficial soft tissue delivery of fluids, such as hyaluronic acid (HA) and other therapeutic materials. Dermal delivery of HA activates fibroblasts increasing collagen and elastin synthesis with a long-lasting dermal remodeling and thickening effect. JVR-injected HA causes immediate and diffuse skin hydration resulting in an aesthetically pleasing aspect. JVR technology is able to target different layers during the same treatment with only minor side effects. The article reviews JVR delivery of hyaluronan in comparison to current skin remodeling treatment modalities.

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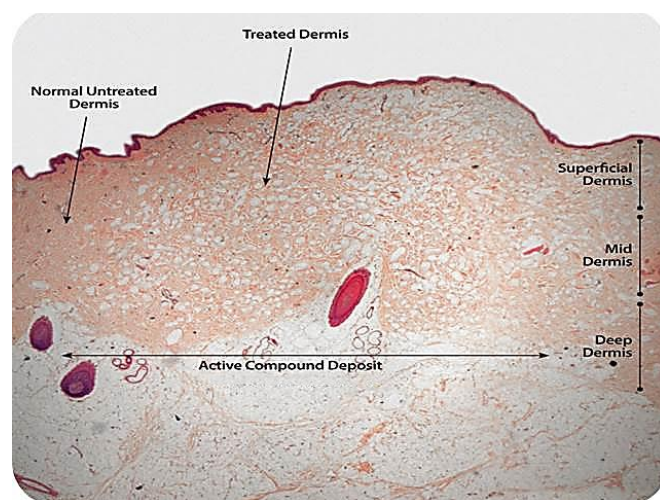
INTRODUCTION

M Aging visibly affects the skin appearance and is due to two main factors: environmental (extrinsic) and genetic (intrinsic), resulting in decreased dermal thickness and diminished fibroblast activity of the aging skin. UV exposure specifically reduces collagen synthesis and causes its degeneration.^{1,59}

Therefore, the main goal for correction of the skin thickening is to successfully stimulate collagen and elastin synthesis in the dermis. Various energy-base devices (EBD) (thermal, light, infrared, radio-frequency) can stimulate collagen synthesis and tightening leading to thicker and firmer skin, whilst restoring elastin with the EBD has not been definitely demonstrated yet. Micro-needling, dermal fillers, dermal threads and platelet rich plasma have been also reported as effective for wrinkles reduction and tightening effect.¹⁻³

Jet Volumetric Remodeling (JVR) utilizes the principle of superficial soft tissue delivery of fluids, such as hyaluronic acid and other therapeutic materials. A pneumatically accelerated jet penetrates the epidermis through a small entry point and immediately disperses the fluid in a 3-D way.^{4,42} The accelerated dispersion of the fluid particles creates multiple nano-traumas to the surrounding tissues fibers (Figure 1). An activated repair results in dermal thickening and strengthening over time.⁵ JVR technology (EnerJet, PerfAction Technologies, Rehovot, Israel) accurately controls depth and volume of the delivery allowing for optimal penetration and distribution as needed through the treatment.

FIGURE 1. Intradermal distribution of JVR-injected hyaluronic acid (HA). Focal vacuolization presents dispersion of HA without a mechanical separation of the collagen bundles (Courtesy of Dr. E. Loeb).



There are a growing number of publications describing clinical efficacy of JVR method in skin thickening and other aesthetic indications. The aim of this paper is to review JVR delivery of hyaluronan in comparison to current skin remodeling treatment modalities.

Biological Effect

Progressive degrading of collagen and elastin fibers results in gradual reduction in dermis thickness and reduced density of retinacula cutis.^{6,7} EBDs promote collagen remodeling through

TABLE 1.

Comparative Histopathology Data on Dermal Remodeling Effects								
Biological process	JVR	Non-ablative lasers	Ablative lasers	IPL	RF	US	Fillers	Micro-needling
Fibroblast stimulation	↑ ^{5,11}	↑ ¹²⁻¹⁶	↑ ^{13,18}	↑ ¹⁹	↑ ²⁰	↑ ²⁷	↑ ³⁰⁻³²	↑ ^{1,3,33}
Collagen remodeling/contraction	↑ ⁵	↑ ^{13,17}	↑ ^{13,18}	↑ ^{13,19}	↑ ²⁰⁻²⁶	↑ ²⁷⁻²⁹	n/a	n/a
Skin hydration	↑ ^{5,11}	n/a	n/a	n/a	n/a	n/a	↑ ³¹	n/a

↑ - indicates presence; JVR – Jet Volumetric Remodeling; IPL – Intensive Pulsed Light; RF – Radio Frequency; US - ultrasound

activation of the heat-shock protein mechanism and/or by direct damage to the skin inducing inflammatory healing repair.

However, the naturally occurring mechanism of the strengthening mesenchymal tissues is different. In muscles correct exercise causes micro-tears in the myosin fibers inducing a repairing mechanism leading to significant strengthening of the muscle without inflammation. JVR technology provides a similar kind of nanoscopic tears to the dermal matrix, well below the threshold of the inflammatory healing response, avoiding the side effects associated with inflammation unlike most EBDs. JVR-induced dermal remodeling and thickening was demonstrated in the human skin samples after administration of hyaluronan.⁹ In-vitro studies indicated 48% increase of collagen synthesis by dermal fibroblasts after JVR treatment of the UV-aged human skin.¹⁰ The effect also increased collagen level in the superficial-to-middle dermis. A comparative summary of the different histology findings is visible in Table 1, including fibroblast stimulation, collagen remodeling and skin hydration.

Dermal delivery of HA by JVR activates fibroblasts increasing collagen and elastin synthesis with a long-lasting dermal thickening effect.¹¹ HA particles dispersed through the dermis by the pneumatic force also improve skin hydration. Glycosaminoglycans (GAGs) are increased with further improvement of collagen elastin and moisture retention.¹⁰ Biochemical analysis of GAG content showed a 57% increase after a single JVR delivery of hyaluronan to the UV-aged skin sample (Figure 2).

FIGURE 2. Histological analysis of dermal glycosaminoglycans (GAGs) after JVR-injected HA (Hale-staining). (A) Untreated skin: blue staining indicates GAGs in dermis; (B) UV-aged skin: decrease of GAGs in dermis; (C) UV-treated skin after JVR: increase of GAGs in dermis (Boisnic 2009).

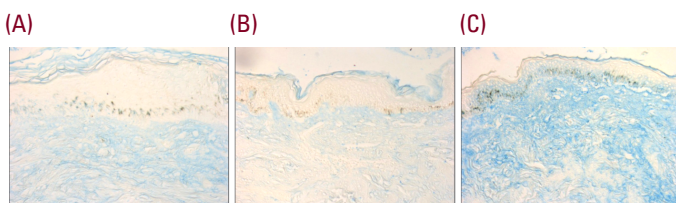
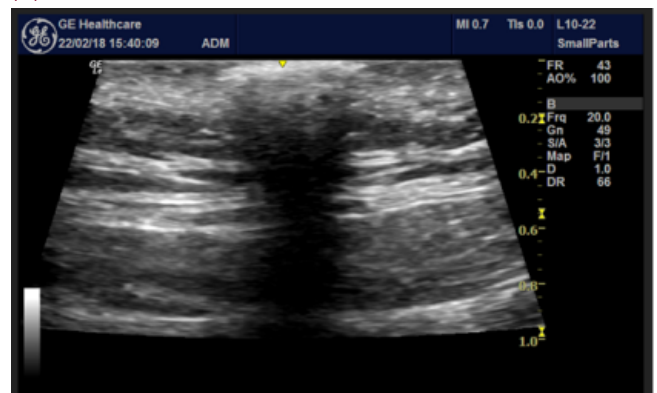
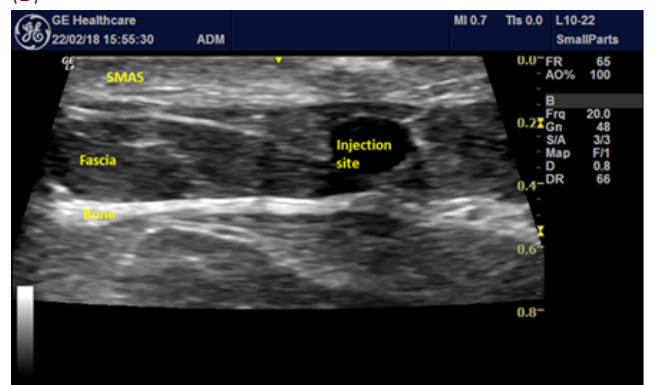


FIGURE 3. US images of JVR-injected normal saline (NS).

(A)



(B)



(C)

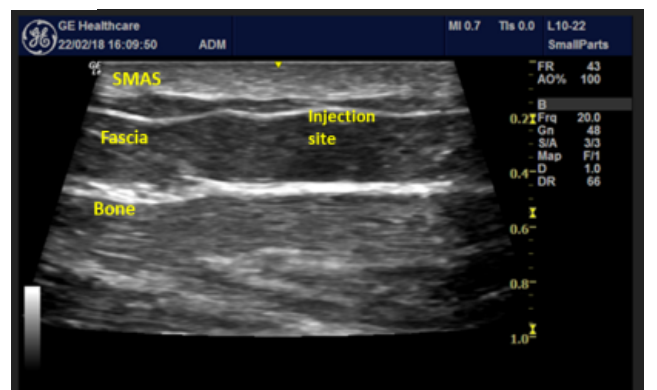


TABLE 2.

Comparative Data on the Penetration Depth									
Technology	JVR	Non-ablative lasers*	Ablative lasers*	IPL*	RF	Fractional RF	Fractional RF needles*	US	Micro-needling*
Penetration depth	1-5 mm ⁹	0.1-2 mm ^{13,17,38}	0.05-0.5 mm ^{13,37}	1-5 mm ²⁵	1-3 mm ²⁰ 3-6 mm ²⁵	0.6 mm ²⁶	0.5-3.5 mm ⁵⁰	1.5-7.8 mm ^{27,28}	up to 3 mm ³

*depends on the light wavelength; **depends on the needle length

Depth of Penetration

Lasers' and light-sources' penetration through the skin is limited by many factors: energy density, skin type, scattering, pulse diameter et al, while radio-frequency devices depend greatly on the tissue hydration and impedance.

For JVR, the depth of penetration is directly related to pneumatic pressure generating delivery of liquid into the tissue. Published evidence shows penetration of the injected fluid down to 5 mm of depth and distributing it across the different skin layers.^{10,35} However, the latest generation of this technology allows even deeper penetration -- through the superficial skin, subcutaneous fat layer and fascia -- as being demonstrated by ultrasound (US) (Figure 3).

In comparison to JVR, ablative lasers and subablative radio frequency (RF) (Table 2) usually do not penetrate the deeper dermis. Non-ablative RFs can heat up skin and subcutaneous layers but their impact is limited.²⁵ High-intensity focused ultrasound (HIFU) penetrates below the skin but its action is destructive, causing scarring rather than regeneration.²⁷ Furthermore, once RF and HIFU are in proximity of the bony surfaces, the pain can be intolerable and limits the treatment efficacy.

Assessment of Thickening Effect

Several recent studies have shown that skin thicknesses, as well as the dermal density is important indicators of the regeneration process associated with the energy-based aesthetic technologies.

Histology Assessment

Quantitative assessment of skin thickening after JVR has been measured by histology, showing focal thickening of collagen fibers, increase in the number of dermal fibroblasts and focal upturn of elastin fibers.²¹

The ability to remodel skin and increase dermal thickness was proven for the following modalities - Er:YAG laser,¹³ pulsed dye laser,¹⁴ 1320 nm Nd:YAG laser,³⁷ intense pulse light (IPL),³⁶ fractional RF needles,⁵² poly-L-lactic acid filler,³⁰ and calcium hydroxyapatite.³² Abdominal skin therapy with 1064 nm Nd:YAG laser demonstrated thickening and reorganization of collagen fibers within the laser-exposed lower reticulum and fibro-septal system.⁴¹ Use of 1440 nm Nd:YAG laser for the neck contouring resulted in average 31% increase in skin thickness 3 months

after a single session. Histopathology examination following several TriPollar RF treatments in periorbital and perioral areas revealed 49% increase in dermal thickening. The increase appears to be due to focal thickening of collagen fibers.^{21,38} As for HIFU, histometric analysis of the skin samples two months after the treatment showed 23%-thickness increase of the dermis.²⁷ Dermal fillers, such as poly-L-lactic acid, HA, and calcium hydroxyapatite can increase collagen production.³⁰⁻³² In these publications, the comparison was done between treated and untreated skin from non-specified sites. In our series, the skin from the same area was compared before and after treatment and results revealed positive effect on the dermal thickness.

Histological findings after multiple JVR treatments with hyaluronic acid showed an increased amount of collagen and increased dermal thickness.⁹ At four months after the treatment, regeneration of dermal structures, "notable augmentation of collagen type III and increased fibroblasts migration" were shown (Figure 4). Overall, there was a 175% increase of the dermis thickness in comparison to baseline.⁹ Clinically the authors reported a full Fitzpatrick-Goldman Wrinkle class reduction in face and neck and palpably thicker and visually more homogeneous skin in the chest and dorsal hands.

Ultrasound Assessment

The importance of ultrasound for dermal assessment is steadily increasing and gains recognition. Unlike histology, the measurements are made on live skin that was not undergone any modification or processing. Therefore, the findings represent

FIGURE 4. Histological findings after intradermal JVR injection of HA. Hematoxylin-eosin-stained specimen of 39-years old male taken at baseline (A) and 4 months after JVR (B) shows increased number and density of collagen fibers. No evidence of inflammatory infiltrate or dermo-epidermal separation is present at treated site (Levenberg 2010).

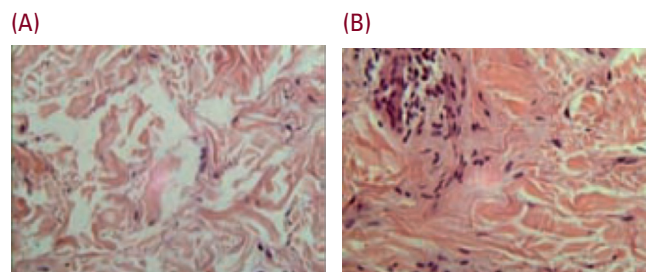


TABLE 3.

Comparative Data on Maximum Increase in Dermal Thickening						
Technology	JVR	Non-ablative lasers	Ablative lasers	RF	US	Fillers
Maximum increase in dermal thickening	250% ^{*5}	17% ^{*40} , 6% ^{*41}	10.3% ^{*39}	23% ^{#27} , 49% ^{#21}	23-25% ^{#27,28}	4% ^{#58}

*assessed by ultrasound methods; #assessed by histopathology analysis

more of a true skin thickness. Furthermore, ultrasound allows for repeated follow-up of the same portion of skin, which obviously cannot be the case with histology.

Ultrasound assessment and quantitative analysis by Kobus⁵ in patients after JVR therapy demonstrated significant ($P<.05$) increase in dermal thickness in different facial regions. The most substantial effect was noted in the upper lip area, where the thickness had increased by an average of 1.3 mm. At the end of the 6-month follow-up, the biggest difference was noted around the eyes, where the skin remained thicker by an average of 0.77 mm over baseline, which represented average 2.5-times increase.

Ablative lasers showed a 10.3% increase in skin thickness three months after single treatment.³⁹ HIFU generated an increase of 23-25% two months after single treatment.^{27,28} Bipolar RF technology showed a 49% increase after 7 treatments.²¹ For Nd:YAG laser, the ultrasound measurements demonstrated a 31% increase after 6 months.⁴³ Comparative changes in the dermal thickness are presented in Table 3.

Safety

Patients seeking aesthetic improvement are concerned by efficacy and safety of the treatment. A low pain and risk profile with minimal chances for side effects is definitely a desirable combination.

Side Effects

American Society for Aesthetic Plastic Surgery emphasizes bruising, redness, and swelling pain as the main risks following the device-based aesthetic procedures.

Side effects associated with JVR are limited to occasional bruising and rare pinpoint post-inflammatory hyperpigmentation.^{9,34} The occurrence rate is operator-related and mainly associated with miscalculated use of excessive injection pressure due to inexperienced operator. Unnecessarily high pressure causes untoward deep penetration, bruising, and pain. Furthermore, it may induce more damage to the dermis than needed, well beyond the threshold that causes inflammation during the healing process. This could increase the risk of pinpoint post-inflammatory hyperpigmentation in sensitive skin types.

Unlike JVR, lasers have been reported to cause diffuse post-inflammatory hyperpigmentation, scarring, infection, and permanent hypopigmentation.^{40,44} IPL, although considered less harmful due to the filtration of ultraviolet radiation is also linked to blistering, hypo- or hyperpigmentation, and scarring.⁴⁸ Electromagnetic radiation of RF devices (monopolar, bi-polar, and fractional) is converted to thermal energy and may produce erythema, edema, skin breakdown, and scarring.^{8,21} HIFU uses ultrasound beams to induce cellular damage and tissue coagulation which may induce temporary side effects of skin erythema, swelling and bruising.²⁸ Summary of the side effects is presented in Table 4.

Pain Level

JVR treatment procedures produce minimal pain and discomfort for which no pre-treatment medication or local anesthesia required.^{11,34,35,53,54} The fluid jet penetrates the skin in 30 ms (average measurement; unpublished data) possibly explaining the relatively low stimulation of pain receptors. While needle injection produces a uniform vertical damage, the jet disperses immediately after penetrating the epidermis losing pressure

TABLE 4.

Comparative Clinical Data on Side Effects								
Technology	JVR	Non-ablative lasers	Ablative/Fractional lasers	IPL	RF	Fractional RF/Needles	US	Micro-needling
Side effects	Bruising, PIH ^{8-10,21}	PIH, crusting, scaling, blistering ^{20,38,43,45}	PIH, crusting, scarring, dyschromia prolonged discomfort, infection ^{39,40,44,46}	PIH, blistering, burns ^{46,48}	Crusting, scaling, blistering, burns, inflammation ^{8,48}	PIH, crusting, scaling, blistering ⁴⁹⁻⁵²	Bruising, PIH, prolonged discomfort, inflammation ²⁸	Bruising, PIH, scarring ^{3,33}

*depends on the light wavelength; **depends on the needle length

TABLE 5.

Comparative Data on Procedural Pain Level (VAS score)

Technology	JVR	Non-ablative lasers	Ablative lasers	RF	Fractional RF	Fractional RF Needles	US	Micro-needling
Average VAS score	2 ³⁵	2-3 ¹⁶ Fractional: 5.4-6.4 ⁴³	3.6-6.7 ⁵⁵	Bi-polar RF: 1.1 ⁴⁷	6.7 ^{**56} , 3.6 - 4.4 ²³	5.05 ⁵⁰	5.68 - 6.53 ²⁹	2 ³

*with cold air; **after 10% lidocaine cream

while the particles are scattered across the dermis or the deeper layers (Figure1). Therefore, the pain stimulus is much lower than with the traditional injection.

Comparing to JVR, most EBD treatments are more painful and require topical or local anesthesia (Table 5). Ablative lasers and HIFU appeared to be the least tolerable. The pain of CO2 laser is measured up to 6.7 on Visual Analog Scale (VAS), even with skin cooling by cold air.⁵⁵ HIFU and Microfocused Ultrasound (MFU) require pain killers, nerve blocks, pre-treatment local anesthesia, and in some cases, conscious sedation.²⁸ Fractional non-ablative laser is associated with less pain, though it also needs topical and cold air anesthesia.⁹ Pain at fractional RF treatments is reported to range from “moderate” to “intolerable,” which requires the use of anesthesia.^{23,25,56,57} Non-ablative high-energy RF Thermage requires topical lidocaine applied prior to the treatment.⁵⁷ Only IPL reported to have mild transient discomfort during treatment, similar to JVR though with much lower benefit per session.²⁵

CONCLUSION

Since its introduction, JVR has been proven efficacious for dermal remodeling, using kinetic energy generated by the mechanical pressure. JVR is capable of remodeling many superficial soft tissue layers during the same treatment. While other EBD may temporarily improve skin turgor by an immediate edema, the JVR-injected HA solution causes immediate and diffuse skin hydration resulting in an aesthetically pleasing aspect. Review of published data shows that JVR is effective in improving dermal thickness up to two-fold. Fractional devices can be aggressive and effective, but lack capability of treating all superficial soft tissue layers. JVR technology is able to target different layers during the same treatment with only minor side effects if any. JVR's safety profile looks by far more advantageous and causes less concern than EBD.

DISCLOSURES

Drs. Vinshtok and Cassuto are employed by PerfAction Technologies and claim no conflicts of interests. Dr. Belenky claims no conflict of interests.

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