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Review

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Thermal degradation of hyaluronic acid dermal fillers

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Abstract

Hyaluronic acid (HA) dermal fillers are extensively used for facial volume enhancement. Despite their widespread use, HA fillers are prone to degradation due to various factors, including enzymatic activity, pH changes, ultrasound exposure, temperature variations, oxidative stress, and ultraviolet (UV) radiation. To mitigate these issues, manufacturers have developed cross-linking techniques to improve the stability of HA fillers. Energy-based devices (EBDs) are increasingly utilized for purposes such as skin tightening, collagen stimulation, and fat reduction. However, the interaction between EBDs and HA fillers is complex and requires further investigation. Recent research has examined the effects of EBDs on HA fillers, yielding mixed results. Some studies suggest that early EBD treatment may lead to the degradation of HA fillers, while others find no significant impact. The timing between filler injection and EBD treatment appears to be crucial, with delayed treatment potentially reducing the risk of degradation. Histological examinations have demonstrated that the interactions between EBDs and HA fillers are intricate, influenced by factors such as the location of the filler and the timing of the treatment. The relationship between EBDs and HA fillers is multifaceted and affected by numerous variables, including the type of EBD, energy levels, filler characteristics, and the timing of the treatment. Further research involving diverse participant groups, various types of HA fillers, and different EBD technologies is necessary to develop comprehensive guidelines for optimal treatment intervals.

Keywords: Dermal fillers, hyaluronic acid, energy-based devices, multi-wavelength diode laser, high intensity focused ultrasound, radiofrequency

INTRODUCTION

Hyaluronic acid (HA) dermal fillers are essential in aesthetic medicine, providing effective options for facial volume enhancement, contouring, and lifting[1-3]. Categorized as temporary, semi-permanent, or permanent, HA fillers are the most frequently used temporary fillers due to their biocompatibility, versatility, and safety profile[4]. HA is a naturally occurring polysaccharide found abundantly in the dermis and various tissues, easily synthesized and degraded by the body. However, its breakdown can be accelerated by factors such as enzymatic activity from hyaluronidase, pH fluctuations, ultrasound waves, temperature shifts, oxidative stress, and ultraviolet (UV) radiation[5-7]. Manufacturers have employed cross-linking techniques to improve the stability of HA fillers, extending their longevity and maintaining their structural integrity[8,9].

Energy-based devices (EBDs), which generate heat within tissues, are widely used in cosmetic applications to achieve skin tightening, fat reduction, and collagen stimulation. The optimal temperature for EBD treatments varies according to specific clinical goals. Generally, fibroblast activation and neocollagenesis occur at approximately 47 °C, while collagen contraction is triggered at around 60 °C, and adipocytolysis begins at approximately 70 °C in subcutaneous tissues. Temperatures exceeding 85 °C can cause irreversible tissue and nerve damage. As heat accelerates HA degradation, physicians often avoid using heat-generating treatments immediately after HA filler injections[Figure 1]. However, the optimal interval between filler injection and EBD treatments remains uncertain, and current studies on the effects of EBD-induced thermal exposure on HA fillers show mixed results[10-16].

In particular, multi-wavelength diode lasers (MWDL) have gained prominence in South Korea for their capability to target deep skin layers with minimal downtime by delivering heat at specific tissue depths while cooling the skin surface. Research by Choi *et al*. demonstrated that wavelengths of 755 and 810 nm can induce carbonization in hair follicles, while the 1,064 nm wavelength penetrates more deeply[17]. These findings underscore the potential for combining these technologies with fillers in aesthetic treatments. This highlights a growing need to understand how EBDs, especially those with high thermal output, affect the integrity and longevity of HA fillers.

A consensus has emerged among experts that laser and EBD treatments should be applied before administering HA fillers to minimize degradation risk[18]. When EBDs are used after filler injections, caution is necessary, especially with deeply penetrating devices or lasers exceeding 1,000 nm, as these can interact with HA fillers placed within deeper tissue layers, potentially compromising filler effectiveness.

This review focuses on HA fillers due to their central role in aesthetic medicine and the substantial research validating their efficacy and outcomes. HA fillers are the most widely used dermal fillers globally, with distinct susceptibility to thermal and enzymatic degradation, making them particularly important to study in relation to EBDs[19,20]. While alternative fillers such as Poly-L-lactic acid (PLLA), calcium hydroxylapatite (CaOH), and polycaprolactone are available, concentrating on HA fillers enables an in-depth exploration of their unique challenges and facilitates the development of tailored guidelines for their safe, effective use.

The primary objective of this review is to synthesize current knowledge on the thermal degradation of HA fillers, particularly regarding their interaction with EBDs. By focusing on HA fillers, this review aims to offer clinicians evidence-based guidelines to optimize treatment protocols, thereby enhancing the durability and efficacy of HA fillers when used in combination with EBDs.

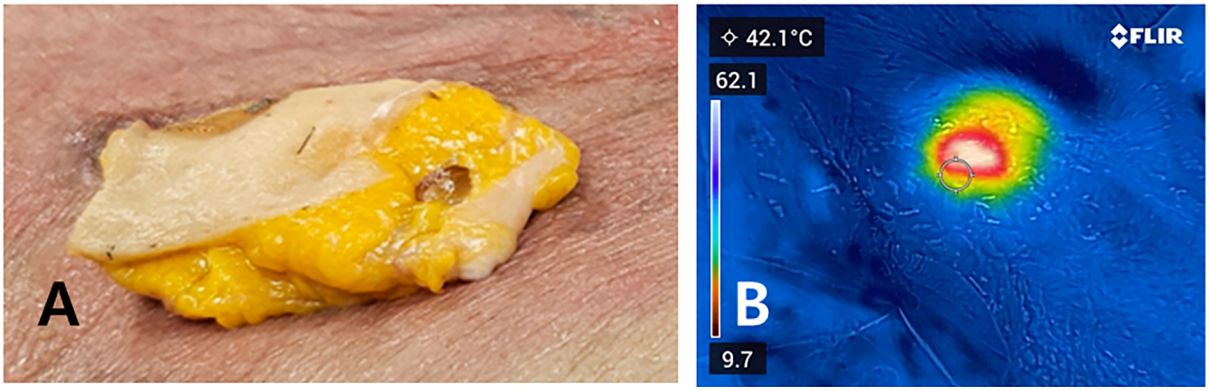

Figure 1. (A) Hyaluronic acid filler dissected from fat tissue, showing the effects of thermal exposure; (B) Thermal imaging camera used to monitor and confirm areas of thermal damage in the HA filler. HA: Hyaluronic acid.

MATERIAL AND METHODS

Keywords including "Poly-lactic acid", "Hyaluronic acid", "Energy-based devices" "Radiofrequency", "Temperature", "Clinical use", and "Dermatology" were searched in the MEDLINE, PubMed and Ovid databases for relevant published studies on clinical trials, diagnosis and treatment. Some papers were further reviewed using a double-blinding approach, sample size, control usage, randomization usage, and objective endpoint measurements. All studies were classified according to the Oxford Center for Evidence-Based Medicine evidence hierarchy.

RESULT

Rheological and thermal degradation studies

HA fillers are susceptible to degradation due to various external and physiological factors, with temperature playing a significant role. Rheological studies have consistently shown that HA solutions exhibit decreased viscosity with rising temperatures[21]. Bothner *et al.* investigated high-molar-mass HA samples and reported substantial degradation at 128 °C in autoclave conditions, revealing a marked decrease in molar mass[22]. This degradation was characterized by a random-scission mechanism as determined through laser light scattering and limiting viscosity measurements. Reháková *et al.* further confirmed that HA samples exposed to 60-90 °C for 1 h demonstrated minor degradation with slight increases in polydispersity, suggesting a temperature sensitivity that has clinical relevance for HA fillers[6]. These findings emphasize the importance of controlling thermal exposure to maintain HA integrity.

Historically, the cross-linking process for HA fillers was achieved by heating the cross-linking agent at 45 °C for over 4 h, leading to the creation of the filler. However, this process has evolved, and most fillers today undergo drying at room temperature. Despite this shift, cross-link detection in fillers often still involves autoclaving at approximately 120 °C for about 20 min, followed by an assessment of the point at which the filler liquefies. Given the potential for EBDs to produce significant temperature shifts, the effects of thermal exposure on cross-linked HA fillers merit ongoing investigation [Table 1].

Impact of EBDs on HA fillers

Studies show that the interaction between EBDs and HA fillers is influenced by specific device settings, timing intervals, and filler properties, notably cross-linking density[13-16].

Table 1. Summary of studies on energy-based devices in combination with hyaluronic acid filler injections

Author(s)	Summary
Bothner *et al.*[22]	Investigated high-molar-mass HA samples and found significant degradation at 128 °C in an autoclave setting.
Reháková *et al.*[6]	Exposed various HA samples to 60-90 °C for 1 h, resulting in minor degradation and a slight increase in polydispersity.
Jurairattanaporn *et al.*[27]	Utilized a monopolar RF device at 42 °C. Immediate RF treatment post-HA injection showed a 36% reduction in HA levels, whereas delaying RF treatment for over 14 days resulted in only a 7% HA loss.
Mochizuki *et al.*[24]	Found that HA filler injections led to increased fibroblast activity and collagen production over 8 weeks, providing some protection against RF degradation.
Yi *et al.*[12]	Observed a risk of burn injury when there is subcutaneous bleeding post-injection followed by laser treatment, as thermal imaging showed energy absorption by the dye.
Alam *et al.*[25]	Injected HA into the dermal layer and performed RF treatment 2 weeks later, showing no significant HA degradation.
England *et al.*[26]	Compared biphasic HA filler injection alone to a combination with RF treatment immediately post-injection, found no significant difference in HA degradation after two months.
Hsu *et al.*[28]	Noticed histological changes after concurrent fractional laser and RF treatments with pre-injected intradermal HA fillers, with heat-related HA degradation along microneedle paths.
Vachiramon *et al.*[29]	Conducted a pilot study on HIFU post-HA injection, finding it generally safe but noting significant HA loss when HIFU was performed within two weeks of injection.

HA: Hyaluronic acid; RF: radiofrequency; HIFU: high-intensity focused ultrasound.

Radiofrequency

Radiofrequency (RF) devices typically generate temperatures ranging from 47 to 70 °C, which can accelerate HA degradation if applied immediately after injection. Immediate RF treatment following HA filler injection has been shown to lead to significant filler degradation. However, delaying RF treatment by two weeks or more has been found to mitigate this effect, highlighting timing as a crucial factor for preserving filler stability[5-7,23].

Multi-wavelength diode laser

MWDL devices operate across multiple wavelengths, allowing deep tissue penetration. Research suggests that the choice of wavelength significantly impacts HA degradation, with 1,064 nm laser settings affecting HA fillers more profoundly due to deeper penetration. While specific energy and wavelength settings may influence the extent of filler degradation, combining these with RF has been shown to exacerbate degradation, underscoring the need for cautious parameter selection[13].

High-intensity focused ultrasound

High-intensity focused ultrasound (HIFU) devices generate rapid heating at targeted depths, which can exceed the protein denaturation threshold. This intense heat can lead to the degradation of HA fillers if the treatment is conducted too soon after filler injection[13]. However, delaying HIFU treatment may reduce the risk of filler degradation, though further research is required to establish optimal timing guidelines.

Impact of specific energy-based device treatments on HA fillers

EBDs are increasingly popular in cosmetic applications for their ability to generate heat within tissues, achieving effects such as skin tightening, fat reduction, and collagen stimulation. Optimal temperatures vary based on treatment goals: fibroblast stimulation and neocollagenesis begin around 47 °C, collagen contraction at 60 °C, and adipocytolysis at approximately 70 °C. However, temperatures exceeding 85 °C can cause irreversible damage to tissues and nerves[23]. This understanding of temperature-dependent effects has informed the practice of scheduling EBD treatments separately from HA filler injections to mitigate the risk of rapid filler degradation[5-7,23]. Despite this precaution, studies exploring the effects of combining HA fillers with EBDs have yielded mixed results, although interval spacing between treatments has shown

potential benefits for filler preservation[24-26].

Further studies on EBD treatments illustrate their varied effects on HA fillers. For example, Jurairattanaporn *et al.* used a monopolar RF device at a surface temperature of 42 °C[27]. They found a 36% reduction in HA levels when RF treatment was applied immediately following HA injection. However, when RF treatment was delayed by more than 14 days, only a 7% loss in HA levels was observed, underscoring timing as a pivotal factor for preserving filler integrity. In contrast, Mochizuki *et al.* found that HA injections could stimulate fibroblast activity and collagen production over an eight-week period[24]. This increase in surrounding collagen may offer some protective effect against RF-induced degradation, highlighting the complex interplay between HA fillers and the body's natural regenerative processes. Additionally, Yi *et al.* documented risks associated with combining EBDs with fillers, especially in cases involving subcutaneous bleeding or the use of other fillers such as polycaprolactone or CaOH[12]. In their experiments, injecting a blood-like dye into cadaveric tissue and subsequently applying laser treatment led to concentrated energy absorption at the dye sites, which did not penetrate deeply but intensified local heating. This suggests that, in clinical practice, unaddressed subcutaneous bleeding may elevate the risk of burn injuries when EBDs are used post-injection, emphasizing the importance of careful consideration of tissue conditions prior to treatment.

Histological and clinical implications

Alam *et al.*, explored the effects of RF treatment on HA fillers by injecting HA into the dermal layer and performing RF treatment two weeks later[25]. Their findings indicated no significant HA degradation when RF treatment was applied two weeks after filler injection. This suggests that a careful timing strategy may allow for the safe use of EBDs without compromising filler integrity.

Similarly, England *et al.* compared the outcomes of HA filler injections with and without immediate RF treatment[26]. Skin biopsies taken two months post-injection revealed no significant differences in HA degradation between the two groups, further supporting the idea that appropriate timing can mitigate the risks associated with EBD treatments.

Hsu *et al.* reported histological changes following fractional laser and RF treatments administered concurrently with pre-injected intradermal HA fillers[28]. Fractional microneedle RF instruments caused heat-related damage to HA fillers along the paths of microneedles, contrasting with the surrounding regions. The researchers noted that the targeted temperature of fractional RF devices typically ranges between 60 and 75 °C, a level deemed sufficient to prompt HA filler degradation.

Vachiramon *et al.* conducted a pilot study on the use of HIFU following HA filler injection[29]. Fourteen subjects underwent intradermal HA injection at four abdominal sites, with one site serving as a control. HIFU treatment using a 1.5 mm transducer was administered at varying intervals after injection. Biopsies were taken at baseline and on Day 56 to evaluate HA retention. The results indicated that while HIFU treatment was generally safe, significant HA loss occurred when HIFU was performed within two weeks of HA injection. This study underscores the importance of considering both the type of EBD and the timing of its application relative to filler injection.

DISCUSSION

The integration of HA fillers with EBDs in aesthetic practice offers both promising outcomes and significant challenges. HA fillers are widely valued for their biocompatibility, safety, and efficacy in facial rejuvenation; however, their susceptibility to thermal degradation under heat-generating EBDs demands precise planning

and caution in clinical applications.

The reviewed studies suggest that the timing of EBD application plays a crucial role in managing HA degradation risks. For example, immediate application of RF treatment after HA injection has been associated with significant filler degradation, whereas delaying RF treatment appears to mitigate this effect. Besides timing, the molecular structure and cross-linking characteristics of HA fillers substantially influence their thermal stability. Cross-linking involves chemically bonding HA molecules to enhance structural resistance to enzymatic and thermal degradation, increasing the filler's durability. Different cross-linking techniques, including stabilizing agents and synthetic cross-linkers, affect the thermal resilience of HA fillers, creating varying degradation profiles under EBD exposure. Recognizing these distinctions in filler composition is essential for clinicians who need to select fillers based on degradation characteristics, particularly when planning treatments involving heat-generating EBDs.

Although this review primarily focuses on HA fillers, understanding differences in thermal degradation susceptibility among alternative fillers is essential for comprehensive patient care. PLLA and CaOH fillers exhibit distinct thermal resilience profiles due to their unique compositions. PLLA fillers, for instance, tend to offer prolonged collagen stimulation but may degrade differently under thermal stress, while CaOH fillers are mineral-based and demonstrate inherent stability at varied temperatures[30-32]. Such comparative insights underscore the necessity of filler selection tailored to treatment goals and thermal exposure risks.

Expanding on the molecular mechanisms involved, HA fillers react to thermal stress depending on factors such as molecular weight, degree of cross-linking, and stabilizer content. HA's polysaccharide structure consists of repeating disaccharide units that are prone to depolymerization under heat, with thermal exposure accelerating this process by breaking HA chains and reducing filler viscosity. High-energy EBDs that cause rapid heating can destabilize cross-linked structures, leading to reduced volumizing effects and overall filler integrity. These insights underscore the importance of controlling thermal exposure in clinical settings to preserve filler properties.

Recent studies have highlighted a heightened risk of hypersensitivity reactions at HA filler sites in patients who have received COVID-19 vaccinations, particularly when EBDs are also used. These cases show an increase in swelling, inflammation, and delayed-type hypersensitivity reactions, likely due to immune responses triggered by vaccine adjuvants, such as lipid nanoparticles and polyethylene glycol, interacting with HA fillers. While the exact mechanisms are still being studied, it is suspected that these vaccine components may activate immune pathways that enhance filler-related inflammation, especially when fillers are subsequently exposed to thermal effects from EBDs[33,34]. Clinicians are therefore advised to obtain comprehensive patient histories, including recent vaccination status, to anticipate potential hypersensitivity reactions. This is particularly crucial for practices integrating EBDs with HA fillers, as heightened immune responses could compromise filler stability and patient safety. By carefully screening and monitoring these patients, practitioners can better manage and mitigate these risks, ultimately improving patient outcomes in aesthetic treatments.

Histological findings suggest that the body's natural regenerative responses, such as fibroblast activity and collagen production, may partially shield HA fillers from thermal degradation. This interplay between HA fillers and the body's repair processes highlights the complexity of combining EBDs with filler treatments, as these biological processes might offer a level of resilience against filler degradation over time. Additionally, the sequencing of EBD and filler treatments is pivotal. Administering EBD treatments prior to filler injections is generally recommended to avoid exposing fillers to immediate thermal stress, thus improving

filler longevity. Evidence indicates that performing EBD treatments before HA filler injection minimizes degradation risks, offering a safer approach for patients requiring both interventions.

In clinical settings, the combination of EBD and filler treatments necessitates informed consent processes that explicitly address the risks of thermal degradation and hypersensitivity. Patients should be informed of potential interactions between EBD treatments and fillers, particularly in the context of recent COVID-19 vaccinations, which have been linked to delayed hypersensitivity reactions. Ensuring patients are fully aware of these risks not only supports ethical practice but also mitigates medicolegal risks by enhancing patient understanding and consent.

To optimize the use of HA fillers in conjunction with EBDs, further research is essential across several domains. Firstly, establishing optimal time intervals between filler injections and EBD treatments will aid in minimizing degradation risks. Research should involve diverse participant groups and consider variables such as skin type, filler depth, and the specific characteristics of each EBD. Long-term studies are needed to assess the cumulative effects of repeated EBD applications on HA fillers, as this would provide insights into the long-term safety and efficacy of combined treatments. Such studies could also investigate whether and how the body's regenerative processes might enhance filler longevity, thereby supporting more effective treatment protocols.

Developing personalized treatment protocols that account for individual patient characteristics, including skin type, aesthetic goals, and treatment history, would enable clinicians to optimize outcomes and reduce the risk of complications when using HA fillers alongside EBDs.

In conclusion, the interaction between EBDs and HA dermal fillers is complex and requires thorough consideration in clinical practice. While HA fillers are prone to thermal degradation, this degradation is modulated by factors including the type of EBD, energy settings, treatment timing, and the specific cross-linking characteristics of the filler. This review highlights the need for further research to develop comprehensive, evidence-based guidelines that support the safe and effective use of HA fillers with EBDs, ultimately enhancing patient outcomes.

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Ethical approval and consent to participate

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Consent for publication

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