JDHAB

Journal of Digital Health and Advanced Biomaterials
Vol. 1, No. 1, 2026
ISSN 3086-5972 (Online)
Open access - peer reviewed

REVIEW ARTICLE

Hyaluronic acid fillers as injectable biomaterials: relationships among network architecture, rheology, and hyaluronidase response

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Received 18 March 2026
Accepted 28 March 2026
DOI 10.67463/b9ekmt47

Revised 28 March 2026
Published 29 March 2026
Article type Review article

ABSTRACT

Objective: To critically reinterpret contemporary evidence on hyaluronic acid fillers through a biomaterials framework linking network architecture, rheology, and hyaluronidase response.

Data sources: Comparative degradation studies, material characterization papers, and platform-level experimental investigations published between 2018 and 2026 were prioritized, with emphasis on studies that enabled interpretable comparison among filler technologies.

Eligibility criteria: Studies were retained when they clarified how network architecture, viscoelastic behavior, physicochemical attributes, or enzymatic conditions influenced comparative performance or hyaluronidase-mediated degradation. Greater interpretive weight was given to studies with explicit reporting of enzyme formulation, dose, dilution, exposure time, and readout method.

Methods of synthesis: This narrative review applied a structure-property-processing performance framework and read the literature comparatively rather than descriptively. Priority was assigned to studies reporting analytically useful rheological or microstructural attributes, standardized degradation conditions, or material features capable of supporting platform-level interpretation.

Main findings: Current evidence consistently shows that HA fillers are materially heterogeneous. Differences in crosslinking strategy, molecular-weight composition, gel-phase organization, cohesivity, and viscoelastic behavior translate into non-equivalent dissolution patterns under exposure to hyaluronidase. Dynamic rheology, especially amplitude sweeps, linear viscoelastic range analysis, and frequency sweeps, provides a more diagnostic account of network architecture than static G' values alone. Comparative interpretation is further conditioned by enzyme formulation, endpoint definition, and the transparency of the analytical workflow used to assess degradation.

Conclusion: The literature supports a materially explicit reading of filler performance and argues against treating enzymatic reversibility as a generic class property. Further progress will depend on standardized and auditable comparative designs integrating advanced rheology, microstructural characterization, digitally assisted metrology, and, where prospectively validated, computational approaches that improve traceability, reduce observer dependence, and strengthen platform-level comparison within translational biomaterials research.

KEYWORDS
hyaluronic acid; biomaterials; hyaluronidase; rheology; physicochemical characterization; injectable fillers.

How to cite: Nemer MRM. Hyaluronic acid fillers as injectable biomaterials: relationships among network architecture, rheology, and hyaluronidase response. J Digit Health Adv Biomater. 2026;1(1):14-24. doi: https://doi.org/10.67463/b9ekmt47

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Introduction

Hyaluronic acid (HA) fillers are established injectable biomaterials in aesthetic medicine because they are biocompatible, adaptable to different tissue planes, and susceptible to enzymatic reversal.[1,2] They are not materially uniform, however. Crosslinking chemistry, HA concentration, molecular-weight profile, manufacturing strategy, and gel-phase organization shape how these products behave clinically and experimentally.[2–6] This matters because fillers marketed for similar indications may differ substantially in cohesivity, projection, tissue integration, and response to hyaluronidase.

Comparisons among HA fillers are therefore more informative when they follow a structure-property-processing-performance logic rather than relying on brand identity or isolated descriptors. Rheological parameters such as storage modulus (G'), loss modulus (G''), tan delta, complex modulus, and the linear viscoelastic range (LVE) only become analytically meaningful when interpreted alongside microstructure, cohesivity, and the processing choices that generated the final network.[3–6] Rankings based on a single parameter tend to obscure the biomaterial logic that actually governs performance.

Susceptibility to hyaluronidase is especially relevant because it links physicochemical characterization to functional performance and safety. In practice, reversibility influences adverse-event management, predictability of correction, and material selection in anatomically sensitive regions. Within this framework, the relevance of digital health is methodological rather than rhetorical. As biomaterial evaluation becomes increasingly dependent on quantitative imaging, digital metrology, traceable analytical workflows, and reproducible comparative assays, digital tools may help standardize how network architecture and degradation are measured and interpreted across studies.

Review rationale and objective

Much of the current discussion still relies on simplified comparisons based on nominal rheological values, commercial categories, or broad claims of tissue integration. That framing is analytically weak. Hyaluronidase response is a property of a material system shaped by crosslinking chemistry, molecular-weight composition, cohesivity, water-binding behavior, and network architecture rather than by category labels alone.[2–6]

The aim of this review is not simply to summarize comparative degradation studies, but to reinterpret them through a biomaterials framework that connects material architecture, rheology, and enzymatic reversibility. More specifically, it asks which aspects of network architecture are most relevant for comparative interpretation, which rheological measurements are genuinely diagnostic of that architecture, and what differential response to hyaluronidase reveals about translational safety, reversibility, and rational biomaterial selection.

Review method and interpretive strategy

This manuscript was developed as a critical narrative review organized around a structure-property-processing-performance framework. The goal was interpretive integration rather than pooled effect estimation. For that reason, inclusion was concept-driven rather than statistical: evidence was retained when it clarified how network architecture, viscoelastic behavior, physicochemical attributes, or enzymatic conditions influenced comparative filler performance or hyaluronidase-mediated degradation. Priority was assigned to comparative studies, material characterization papers, and experimental investigations published from 2018 to 2026 that allowed platform-level interpretation, reported analytically meaningful material attributes, or tested degradation under explicit and reproducible conditions.[7-15]

Greater interpretive weight was given to studies that controlled enzyme dose, dilution, exposure time, gel volume, and readout strategy, because those variables affect the meaning of any conclusion about relative degradability. By contrast, studies reporting only generic claims of softness, integration, or longevity without adequate analytical context were considered of limited comparative value. The review also distinguished between evidence that is merely descriptive and evidence that is analytically interpretable. Papers focused primarily on handling impressions, product positioning, or undifferentiated statements of integration were not treated as equivalent to studies reporting rheology, microscopy, or controlled degradation behavior.

Likewise, not every comparison among fillers was considered equally informative. A head-to-head study becomes materially meaningful only when it clarifies what is being compared: technological platform, network organization, dose-response to enzyme, or a defined physicochemical property. This distinction is central to the present review because the field is crowded with nominal comparisons that are easy to cite but difficult to translate into mechanisms or practice.

The interpretive strategy was comparative and hierarchical. First, studies were read in relation to technological platforms rather than brand reputation alone. Second, results were weighed according to the degree of methodological transparency regarding enzyme formulation, unit definition, dilution, exposure interval, and scoring or measurement endpoint. Third, rheological and physicochemical data were valued when they could plausibly be linked to network behavior rather than treated as detached descriptors.

This is particularly important in filler literature, where nominal G' values are often reported as if they were self-sufficient proxies for architecture, despite the fact that they only become informative when embedded in a broader rheological and microstructural description.

The decision to prioritize platform-level interpretation also reflects a practical editorial concern. Reviews that merely enumerate products or brand families tend to age quickly and add little analytical value, especially in a field where formulations evolve, naming conventions shift, and commercial positioning changes faster than mechanistic understanding. By contrast, a review organized around architecture, rheology, and degradation remains useful even as individual products are updated, because it clarifies the principles by which new formulations should be interpreted. That durability is one reason why a biomaterials framework is preferable to a cataloguing approach for a journal seeking long-term scientific relevance.

Because this is a narrative review, it does not claim exhaustive retrieval, formal risk-of-bias scoring, or quantitative synthesis. That is a limitation, but it is also consistent with the manuscript's purpose. The current degradation literature is methodologically heterogeneous to a degree that makes naive pooling less illuminating than disciplined comparative reading. Under such conditions, a narrative design can still be rigorous if its inclusion logic, interpretive criteria, and limitations are made explicit. A further implication of that position is that digitally interpretable outputs, including rheological curves, microscopy-derived metrics, and standardized scoring workflows, may improve future comparability when acquisition and analysis are prospectively standardized.

Thematic synthesis of the literature

Available studies consistently show that HA fillers are heterogeneous in network architecture, gel-phase organization, and viscoelastic behavior. Distinctions among biphasic particulate gels, cohesive polydensified matrix (CPM) systems, compact monophasic systems, Vycross-based formulations, and preserved network technology (PNT) architectures are not mere commercial labels. They encode manufacturing decisions regarding crosslink density, phase continuity, particle organization, and molecular-weight blending that influence elasticity, cohesivity, projection, and susceptibility to enzymatic attack.[2,4–6]

At the platform level, the relevant issue is less whether one family is globally better than another than whether particular processing strategies generate networks with different structural logic. Biphasic particulate systems, for example, combine discrete crosslinked particles with a carrier phase, whereas more continuous or polydensified networks may distribute material density differently across the gel. Likewise, differences between BDDE- and PEGDE-linked systems are not reducible to brand identity; they may alter swelling behavior, chain mobility, cohesion, and the way the network resists or yields under load.[4–6] From a biomaterials standpoint, these distinctions should be read as hypotheses about performance rather than as marketing language.

Cohesivity deserves special emphasis within this framework because it occupies the practical boundary between microstructure and tissue behavior. Highly cohesive gels may better preserve continuity after placement, whereas less cohesive systems may spread more readily or fragment differently under stress. Yet cohesivity is not a free-floating handling impression; it emerges from the way HA chains, crosslinks, and water are organized across the network. This is why cohesivity, swelling behavior, and phase organization should be read together rather than separated into independent commercial talking points. A filler can appear clinically smooth or supportive for very different material reasons, and those reasons may also influence how enzymatic access propagates through the network during dissolution.[3–6]

That is why G' alone is an incomplete explanation of gel behavior. Storage modulus captures one dimension of the elastic response, but it cannot by itself specify whether a network is broad or narrow in its deformation tolerance, whether it loses structure abruptly or gradually under increasing strain, or whether it behaves similarly across changing deformation timescales. A more credible interpretation requires joint consideration of cohesivity, tan delta, the linear viscoelastic range, gel content, fibrillar appearance, and crosslink distribution.[3–6] These parameters do not simply add descriptive detail; together they help reconstruct the internal organization that static modulus values flatten.

Dynamic rheological testing is especially important because it moves the analysis from nominal stiffness toward network behavior. Amplitude sweeps define the linear viscoelastic range (LVE), that is, the deformation interval within which the gel maintains proportional viscoelastic behavior and yields interpretable material data. A narrow LVE may suggest earlier structural destabilization under strain, whereas a broader LVE indicates that the network tolerates deformation before nonlinear behavior dominates. In practical terms, this matters because fillers are not used under perfectly static conditions. They are injected, compressed, molded, and subjected to repeated facial movement. A gel's ability to maintain structural coherence within and beyond the LVE is therefore more informative than a single small-strain modulus considered in isolation.

Frequency sweeps add a second diagnostic layer by showing how elastic and viscous components shift across deformation timescales. Two fillers with similar G' at one measurement frequency may diverge substantially when their behavior is interrogated across a broader frequency spectrum. One may preserve a predominantly elastic signature over a wider range, whereas another may reveal a more time-dependent viscous contribution. In that sense, amplitude and frequency sweeps function as dynamic rheological fingerprints of HA fillers. They provide a more diagnostic view of network architecture than static G' values because they expose how the network behaves when mechanically challenged rather than merely how it performs under one predefined condition.[3–6]

A second translational implication is that dissolution should not be interpreted as the opposite of performance, but as part of it. A filler with slower degradation under standardized enzyme exposure may be advantageous in one clinical context and disadvantageous in another. Likewise, a platform that is readily reversible may offer greater corrective flexibility without implying weak performance in routine use. The clinically relevant question is therefore not which filler is globally most resistant, but which profile of architecture, mechanics, integration, and reversibility best matches the treatment objective and risk tolerance of the anatomical site. The biomaterial literature becomes more useful when it helps answer that question rather than when it merely ranks products.

Microstructural interpretation further sharpens this point. Fibrillar appearance, phase continuity, particle boundaries, and apparent network density are frequently described qualitatively in the filler literature, but these descriptors matter because they suggest how the gel stores water, distributes load, and presents accessible substrate to enzymatic degradation. Microscopy alone does not solve the interpretive problem, yet when read together with rheology it helps distinguish a merely firm gel from one whose internal organization may genuinely resist fragmentation or dilution. A recurring weakness of the literature is that microstructure is often shown as illustration rather than integrated as evidence. A more mature biomaterials reading treats microscopy as part of the causal chain linking processing to performance.

This point has direct translational value. Products occupying similar clinical niches may differ substantially in the material attributes that govern correction, molding, integration, and reversibility. A static ranking of G' can therefore mislead clinicians into assuming mechanical equivalence where none exists. A filler selected for projection in one context may also be a filler whose network is less easily reversed, or whose deformation profile under repeated movement differs from what its nominal modulus suggests. The literature reviewed here repeatedly indicates that the rheological language most useful to clinicians is not the language of isolated modulus values, but the language of network behavior.

Across standardized dissolution experiments, resistance to hyaluronidase differs by product and by technological platform. Under comparable conditions, several Vycross-based formulations tend to be relatively more resistant, whereas cohesive polydensified matrix architectures and some non-animal stabilized hyaluronic acid (NASHA) products tend to dissolve more readily in selected models.[7–15] The important analytical point, however, is not to build a commercial hierarchy. Hyaluronidase response does not map linearly onto a single descriptor. It emerges from the interaction among network architecture, molecular-weight composition, cohesivity, crosslink density and distribution, gel concentration, and enzyme-related variables.

Degradation kinetics should therefore be read as the result of both enzyme action and network accessibility. A more crosslinked or more densely organized platform may resist early dissolution not simply because it is “stronger,” but because the enzyme encounters a differently organized substrate, with different diffusion pathways, hydration behavior, and local chain accessibility. Conversely, a product that dissolves more readily may do so because its network becomes structurally unstable sooner under comparable enzymatic conditions, not because it is globally inferior as a filler. These distinctions are easy to lose when degradation is reduced to a binary of reversible versus resistant. What matters analytically is the pattern, rate, and context of dissolution, and what that pattern reveals about the material system.

Table 1 is useful precisely because it reframes these platforms through structure-property-processing-performance logic rather than through market positioning. When viewed in that way, technological families become comparative material systems with distinct processing assumptions, not interchangeable commercial categories. Table 2 performs a complementary function: it shows that apparent differences in degradability can only be interpreted responsibly when enzyme formulation, dose, dilution, exposure time, gel volume, and readout method are explicit. In other words, the tables are not simple summaries; they are part of the argument that comparability is earned through design transparency, not assumed from product naming.

Methodologically, these findings discourage claims based solely on nominal G' values, soft-versus-firm language, or brand family identity. Comparative interpretation is only defensible when the experimental context is explicit and when material characterization is sufficiently rich to support mechanistic inference. The principal implication is that reversibility should be treated as a measured functional property of the biomaterial system rather than an assumed class characteristic.

Critical appraisal of the field

The available literature is now sufficient to reject the idea that HA fillers behave as a homogeneous class with respect to enzymatic reversibility. Yet the same literature remains difficult to compare rigorously because methodological heterogeneity persists at nearly every analytical stage. Studies differ not only in filler selection but also in enzyme formulation, dose, dilution, exposure time, gel volume, incubation conditions, sampling intervals, and endpoint definition.[7–15] Some report visual dissolution grades, others volumetric reduction, rheological change, or gross structural loss. These are not trivial methodological differences; they shape the phenomenon being measured.

Endpoint selection is another source of interpretive distortion. Visual disappearance, reduction in volume, change in rheological profile, and microscopy-derived structural loss do not measure the same thing, even when all are loosely described as “degradation.”A gel may lose macroscopic volume before it fully loses viscoelastic identity, or it may show marked structural fragmentation while still retaining enough continuity to resist complete collapse. Without clarity about the endpoint, the meaning of relative resistance becomes unstable. This is why a field that wants platform-level comparison needs not only standardized enzyme conditions, but also clearer agreement

about what counts as meaningful degradation and which outputs best capture it.

A related problem is that network descriptors and degradation endpoints are often reported in parallel rather than in an integrated manner. One paper may provide useful rheology but limited enzymatic detail, another may compare dissolution kinetics but without sufficiently informative physicochemical characterization, and another may offer microscopy without a framework for translating visual pattern into network-level interpretation. The result is an evidence base in which the question most worth asking, why a given platform degrades as it does, often cannot be answered with full analytical confidence.

Another underappreciated issue is that product family names can create a false sense of comparability. Even within the same commercial platform, HA concentration, rheological behavior, intended tissue plane, and formulation-specific processing choices may still differ enough to affect dissolution pattern and minimum effective dose. Platform-level tendencies are therefore useful as interpretive scaffolds, but they do not eliminate the need for product-specific reading of the evidence. Comparative studies are strongest when they preserve both levels of analysis at once: technological family and individual formulation. That distinction becomes especially important when clinicians extrapolate bench findings to site-specific treatment planning directly.

Methodological heterogeneity also extends to the enzymatic agent itself. Comparative interpretation becomes stronger when studies specify whether hyaluronidase is bovine- or ovine-derived or instead recombinant human hyaluronidase, because these formulations are not analytically interchangeable.[13–15] Recombinant human hyaluronidase offers a more standardized and traceable comparator in cross-study designs, whereas animal-derived preparations may introduce additional variability related to formulation source and biological activity. Recent comparative work further suggests that filler response depends not only on enzyme source but also on dilution scheme and liquid-to-solid ratio; in one in vitro model, no further gain was observed beyond a 3:1 dilution ratio, and ovine hyaluronidase performed similarly to recombinant human hyaluronidase when adequate fluid volume was provided.[14] The critical issue is therefore not only pharmacologic potency, but analytical comparability.

There is also room for computational standardization at the level of nomenclature and comparative mapping. One persistent difficulty in the filler field is that similar material behaviors are often described with inconsistent terminology across manufacturers, clinicians, and laboratory studies. Computationally assisted mapping of descriptors, readouts, and platform characteristics could help create more stable comparative language for future reviews and consensus work. This would not replace material testing, but it could reduce semantic drift and improve how evidence is aggregated across otherwise heterogeneous studies.

Even when enzyme source is reported, unit equivalence is not always conceptually stable across studies. Dose alone does not solve the problem if dilution, gel volume, exposure interval, and endpoint definition differ materially. A nominally higher dose in a short exposure window may not be analytically comparable to a lower dose assessed over longer incubation, just as a visually scored endpoint is not automatically equivalent to a quantitative volumetric or rheological one. The degradation literature therefore suffers from a recurring problem of pseudo-comparability: studies appear similar enough to be juxtaposed, yet differ in ways that alter the meaning of the comparison.

Traceability is especially important when enzyme formulations are compared across studies or across laboratories. Lot information, formulation source, unit definition, reconstitution method, and storage conditions are rarely discussed at the same level of detail as filler brand names, yet they may exert equal or greater influence on the observed result. A study that carefully distinguishes bovine, ovine, and recombinant human hyaluronidase is analytically stronger not because it sounds more technical, but because it reduces ambiguity about the comparator. In a field increasingly interested in reproducibility, that level of reporting should be treated as part of study quality rather than as optional detail.

These problems also affect translational interpretation. In vivo behavior cannot be inferred directly from in vitro dissolution without caution, because tissue confinement, injection plane, mechanical loading, hydration conditions, and host response may modify how the gel behaves after placement.8–10 That does not diminish the value of standardized in vitro testing; rather, it clarifies its role. In vitro studies are most informative when treated as controlled comparative models of biomaterial behavior, not as literal reproductions of the clinical field. Their value lies in isolating differences among platforms under defined conditions and generating interpretable hypotheses for practice.

Recent experimental work also highlights a neglected source of variability: the physical context in which hyaluronidase is delivered. Studies using fixed 0.2-mL aliquots, no stirring, and explicit liquid-to-solid ratios suggest that degradation is shaped not only by enzyme units, but also by whether sufficient fluid volume is available to reach and permeate the gel.[14] That point is methodologically important because many comparative claims are framed as dose-response observations when they may in fact reflect a combined effect of enzyme source, concentration, dilution, and local diffusion conditions. A study that reports units without reporting delivery volume or dilution therefore leaves a substantial part of the experimental meaning unspecified.

The next methodological step will likely require multicenter discipline rather than isolated methodological ingenuity. If several laboratories were to adopt comparable rheological protocols, imaging standards, and degradation endpoints, the field could move from attractive but local comparisons

toward reproducible platform-level evidence. This is precisely the kind of transition in which digital workflows, shared templates, and computational support may have outsized value: not because they replace material science, but because they help laboratories measure the same phenomenon in the same language.

One way to improve this situation would be the adoption of a minimal comparative reporting framework for filler degradation studies. Such a framework could specify a small set of required descriptors: technological platform, lot or batch information when available, enzyme type and unit basis, dilution protocol, gel volume, timepoints, endpoint definition, and at least one quantitative readout aligned with the stated conclusion. The field does not yet require a rigid universal protocol to become more interpretable; it requires a shared understanding that relative resistance claims are only as strong as the design features that make them comparable.

Knowledge gaps and translational implications

Important gaps remain. Few studies integrate advanced rheology, network microstructure, microscopy, quantitative degradation metrics, and clinically relevant reversal scenarios within the same experimental design. Cross-study comparison is further constrained by heterogeneity in hyaluronidase source, dose, dilution, exposure time, gel volume, and analytical readout. Future comparative work would be substantially strengthened by pairing dynamic rheology with more quantitative microstructural assessment rather than treating these as parallel but disconnected domains.

Future studies would also benefit from separating descriptors that are directly measured from those that remain inferential. Terms such as cohesivity, firmness, spreadability, or support may be clinically meaningful, but they become analytically stronger only when paired with explicit rheological curves, microscopy-based descriptors, and clearly defined degradation endpoints. Without that bridge, the literature risks reproducing the same semantic instability it seeks to overcome, especially when commercial language is allowed to stand in for material characterization.

Finally, the field remains vulnerable to overgeneralization because the space of clinically used fillers is broader than the space of rigorously compared fillers. A review can only interpret what has been studied with sufficient transparency. Some conclusions are therefore stronger at the level of principle than at the level of universal product classification. The present manuscript argues with confidence against the idea of uniform class behavior, but it does not claim that every platform family has already been characterized with equal depth. That distinction should be kept in mind when translating comparative evidence into broader editorial or clinical narratives.

A practical consequence is that future studies should be designed as integrated measurement workflows rather than as isolated assays.

A robust comparative design would ideally report platform identity, gel concentration, crosslinking strategy where known, amplitude- and frequency-sweep behavior, a defined microstructural readout, explicit enzyme formulation and dosing conditions, and a reproducible degradation endpoint. Even if every laboratory cannot report every variable, the field would benefit from converging toward a core analytical set. Digital health becomes relevant here because shared digital outputs and standardized measurement pipelines can help laboratories compare like with like instead of relying on narrative equivalence.

That requirement creates a natural point of contact with digital health. In this field, digital health should not be understood as a vague thematic label, but as the use of digital metrology, traceable workflows, and computational support to make biomaterial characterization more reproducible and less observer-dependent. Microscopy-based descriptions of network density, fibrillar arrangement, heterogeneity, and dissolution-related structural change are still often reported qualitatively. A more mature analytical framework would seek standardized digital readouts that convert those visual impressions into reproducible metrics.

When feasible, digitally assisted analysis of scanning electron microscopy or confocal microscopy images may help generate more standardized and auditable estimates of network density, heterogeneity indices, fragmentation patterns, or dissolution-related structural change. In this context, computational or AI-driven image segmentation should be framed as analytical support rather than as a substitute for material interpretation.Its value lies in reducing observer dependence, increasing traceability, and allowing image-derived descriptors to be compared across studies when acquisition parameters, annotation rules, and analytical pipelines are prospectively standardized and transparently validated. That is the sense in which digital health becomes relevant to advanced biomaterials characterization.

Computational support should likewise be interpreted cautiously but constructively. Model-building in this context does not mean replacing experiment with software. It means using computational approaches to integrate descriptors that are already being generated—network density estimates, amplitude-sweep profiles, frequency-dependent viscoelastic behavior, and dose-response degradation data—so that platform-level comparison becomes more explicit and more reproducible. Properly validated models may help identify which combinations of descriptors most strongly predict resistant, intermediate, or readily reversible behavior. Their value would lie in analytical discipline, not in algorithmic spectacle.

A similar logic applies to rheology. Static summary values are easy to report but difficult to audit. By contrast, shareable primary outputs such as amplitude-sweep and frequency-sweep curves provide a richer and more transparent basis for interpretation. In the future, prospectively validated computational models linking network descriptors, rheological fingerprints, and degradation kinetics may help support platform-level comparison and prediction. The point is not to promise algorithmic certainty, but to move the field toward more comparable, less impressionistic evidence.

Digital metrology also opens the possibility of more explicit data sharing. Even when full raw datasets cannot be made public, studies could increasingly provide representative rheological traces, image-analysis scripts, segmentation rules, or summary descriptors generated from predefined workflows. Such practices would not only improve reproducibility; they would also help distinguish materially grounded studies from those that remain dependent on opaque analytical choices. For a journal positioned at the interface of digital health and advanced biomaterials, this is a strategic opportunity: the digital contribution lies in strengthening measurement discipline, not in merely appending computational language to conventional characterization.

From a translational perspective, enzymatic reversibility should inform biomaterial selection before complications arise, not only after the need for correction becomes obvious. In high-risk anatomical regions, in patients likely to require staged adjustment, or whenever precision and reversibility materially affect treatment planning, the relevant question is not simply whether a product can be degraded, but how predictably, under what enzymatic conditions, and with what relationship to its mechanical and structural profile. Under that view, safety is part of biomaterial performance rather than an external add-on. A framework linking structure, rheology, and degradability is therefore more useful than one centered on commercial taxonomy alone.

A clinically useful next step would be the development of reversal-oriented comparative models that distinguish urgent rescue scenarios from elective correction scenarios. The amount, dilution, and spatial distribution of hyaluronidase required for acute vascular compromise management are not analytically identical to those required for contour adjustment or delayed refinement. A more mature evidence base should therefore move beyond asking whether a filler is reversible and instead specify under what conditions, at what pace, and with what degree of predictability a given product can be modulated.

Future work should move toward standardized and auditable comparative designs that integrate microstructural characterization, dynamic rheological profiling, network parameters, and reproducible degradation assays.

In this context, auditable refers to analytically transparent and traceable workflows in which enzyme source and formulation, dose, dilution, exposure conditions, and readout strategy are explicitly documented, and in which primary outputs such as rheological curves, microscopy-derived metrics, or standardized digital scoring procedures can be independently interpreted. Studies built on that logic are more likely to yield evidence that is technically comparable, clinically interpretable, and relevant to both biomaterials science and digitally enabled translational assessment.

Operationally, an auditable comparative study could report a core minimum dataset: filler platform and lot, enzyme formulation and source, unit definition, dilution scheme, gel volume, exposure intervals, raw or shareable rheological curves, a predefined degradation endpoint, and, when imaging is used, a clearly documented acquisition and analysis workflow. Not every paper will report all of these elements immediately, but the closer the field moves toward this standard, the less dependent it will remain on subjective judgment and brand-centered inference. In that sense, auditability is not a bureaucratic burden; it is a scientific upgrade.

Limitations of the review

This review is narrative and interpretive rather than systematic. It does not claim exhaustive retrieval, formal risk-of-bias assessment, or pooled effect estimation, and its conclusions therefore remain dependent on the quality and reporting completeness of the comparative literature considered. That limitation is important, particularly in a field where laboratory protocols and outcome definitions vary enough to complicate direct synthesis.

The underlying evidence base also has important structural limits. Only a small subset of studies combines advanced rheological characterization, explicit microstructural description, and directly comparable enzymatic degradation protocols. [3–6,11–15] The number of products assessed per study is often limited, and cross-study equivalence is further weakened by differences in enzyme formulation, dose, dilution, gel volume, and readout method. These constraints restrict the strength of any platform-wide conclusion, especially when extrapolating from controlled in vitro conditions to clinical behavior.

Publication bias may also shape the available literature. Comparative filler research is especially vulnerable to selective emphasis on favorable platform behavior, on descriptive rather than mechanistic conclusions, or on endpoints that are easier to communicate commercially than analytically. This does not invalidate the literature reviewed here, but it reinforces the need for methodological caution. A narrative review in this setting must remain alert to the difference between studies that clarify mechanism and studies that mainly reinforce pre-existing market categories.

A further limitation is conceptual: the literature often describes fillers with mixed vocabularies drawn from marketing, rheology, microscopy, and clinical handling without fully reconciling these levels of analysis. That fragmentation can tempt overinterpretation. The purpose of the present review is therefore disciplined rather than expansive. It does not claim to resolve every uncertainty, but to clarify which comparisons are materially defensible, which claims remain premature, and which methodological upgrades are most likely to improve the evidence base.

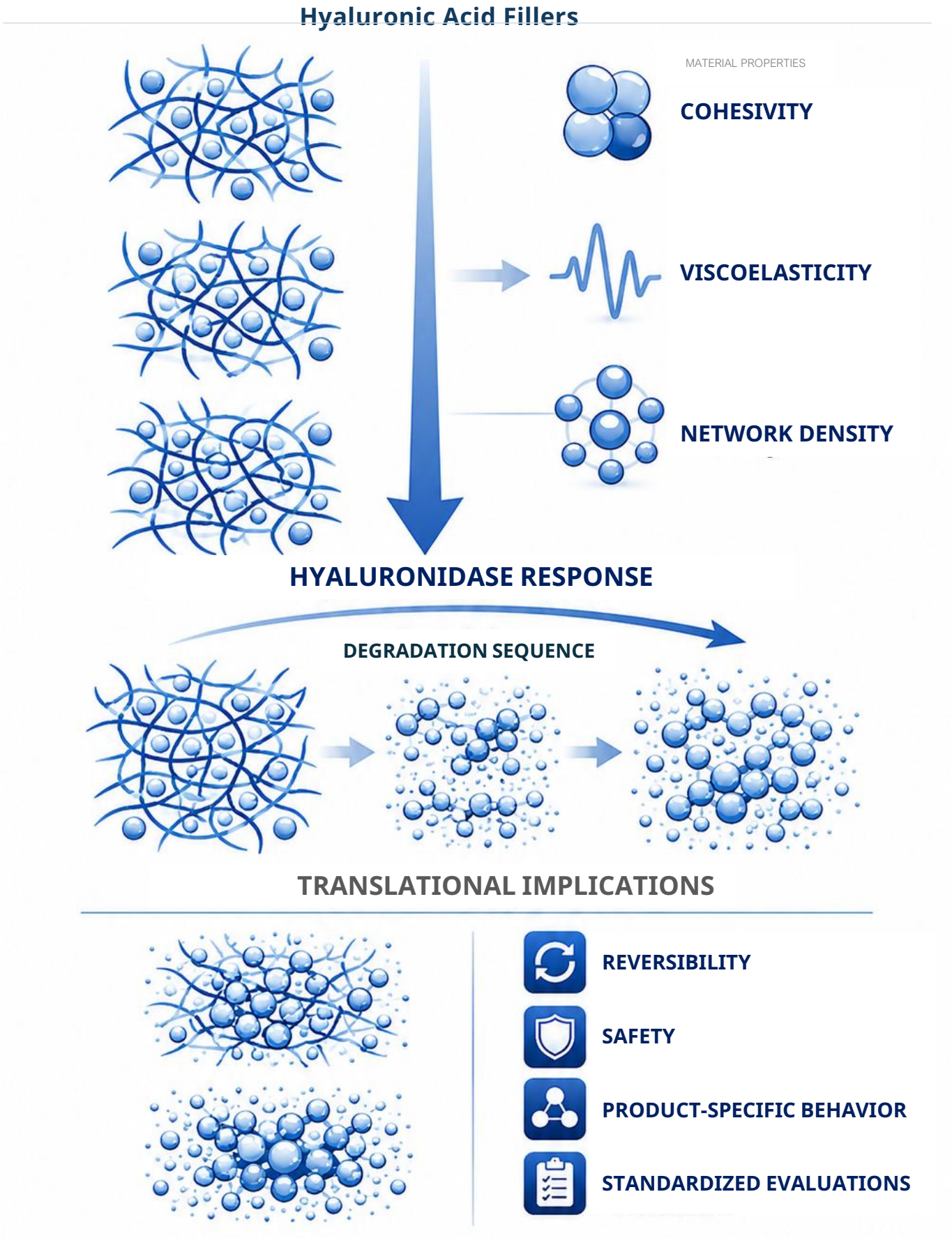

Figure 1. Hyaluronic Acid Fillers. Conceptual overview of the structure-property-processing-performance framework applied to hyaluronic acid fillers. Differences in network architecture, cohesivity, viscoelastic behavior, and network density may influence both hyaluronidase response and translational performance. The scheme highlights the value of standardized analytical readouts for comparative interpretation across studies.

Design logic

The technological platform is not a marketing descriptor; it is a biomaterial design variable.

Differences in crosslinking strategy, network organization, and physicochemical architecture may influence cohesivity, viscoelastic behavior, enzymatic accessibility, and clinical reversibility.

Technological platforms

Table 1. Technological platforms of hyaluronic acid fillers under a structure-property-processing-performance perspective.

PLATFORM / EXAMPLES	PREDOMINANT ARCHITECTURE	RELEVANT PHYSICOCHEMICAL ATTRIBUTES	COMPARATIVE TREND VERSUS HYALURONIDASE	TRANSLATIONAL INTERPRETATION
Non-animal stabilized hyaluronic acid (NASHA) Restylane-L, Lyft, Silk	Biphasic particulate gel	Crosslinked HA particles dispersed in an aqueous phase; relevant elasticity and a defined particulate structure	In several studies, faster response or lower required doses than some more resistant monophasic gels	May widen the reversibility margin in safety-sensitive settings without implying lower clinical usefulness
Cohesive polydensified matrix (CPM) Belotero Balance, Volume	Cohesive polydensified matrix	Heterogeneous distribution of network density; consistency influenced by polydensification	Among the more easily degradable profiles in part of the recent comparative literature	Suggests that network architecture may carry greater interpretive weight than nominal G' alone
Vycross Volbella, Voluma, Volux	Monophasic gel with mixed molecular weights	Compact network, greater cohesivity, and recurring relative resistance	Frequently among the more resistant profiles, requiring more time or higher enzymatic load	Relevant for applications requiring support, but it calls for more deliberate reversal planning
Preserved network technology (PNT) RHA 2-4	Preserved network with emphasis on dynamic resilience	Variable relationship among elasticity, deformability, and consistency	Trend toward progressively greater resistance within the same product family	Reinforces the value of intraplatform comparisons
Experimentally characterized BDDE/PEGDE gels	Microarchitecture dependent on crosslinking agent and formulation	Differences in gel content, fibrillar appearance, cohesivity, and rheological response	The most robust interpretation depends on the integrated attribute set	Refines the structure-property-performance reading applicable across filler families

Comparative tendencies should be interpreted in light of experimental design, enzyme formulation, exposure time, and the readout method adopted in each study. Abbreviations: CPM, cohesive polydensified matrix; NASHA, non-animal stabilized hyaluronic acid; PNT, preserved network technology.

Comparative degradation evidence

Table 2. Technological platforms of hyaluronic acid fillers under a structure-property-processing-performance perspective.

STUDY	DESIGN	HIGHLIGHTED PRODUCTS / PLATFORMS	CENTRAL ANALYTICAL MESSAGE
Buhren et al., 2018	Standardized in vitro analysis by time-lapse microscopy	Belotero Balance, Emervel, Juvederm Ultra 3	Established a comparable experimental approach and demonstrated detectable differences in degradability
Ryu et al., 2021	In vitro dose-response study in 12 gels	Restylane-L, Lyft, Voluma, Versa, Vollure	Showed a broad dissolution spectrum, with greater susceptibility of some NASHA products and greater resistance of selected monophasic gels
Zhang-Nunes et al., 2021	Prospective in vivo evaluation of 3 gels	Restylane-L, Juvederm Ultra, Voluma	Indicated that reversibility also varies in a biological context, not only on the bench
Faivre et al., 2024	Degradation kinetics study with 16 fillers and 6 technologies	CPM, NASHA, OBT/XpresHAn, PNT, Hylacross, Vycross	Suggested manufacturing technology as a central determinant of relative reversibility
Sudharshan et al., 2025	Minimum single-dose study for dissolution of 22 fillers	Volbella, Vollure, Skinvive, Restylane-L, Lyft, RHA 2-4, Volux, Versa	Documented a wide minimum-dose gradient, reinforcing heterogeneity among platforms
Oliveira et al., 2025; Safran et al., 2025	Comparison of hyaluronidase formulations and sources	Multiple commercial fillers and distinct enzymatic formulations	Suggest that degradation kinetics depend simultaneously on filler characteristics, enzymatic source, dilution strategy, and liquid-to-solid ratio, reinforcing the need for analytically comparable designs.

Relative resistance varies according to gel volume, enzyme formulation and source, dilution, exposure time, and readout method; the categories shown should therefore be interpreted as comparative tendencies rather than absolute equivalences among brands.

Conclusion

Material heterogeneity.

HA fillers should not be interpreted as a homogeneous biomaterial class with respect to enzymatic reversibility. The evidence reviewed here supports a materially explicit framework in which response to hyaluronidase arises from the interaction among network architecture, rheological behavior, composition, and degradation conditions, rather than from commercial taxonomy or any single isolated descriptor. This distinction is not merely semantic; it has direct translational relevance.

Reversibility as performance.

Reversibility should not be reduced to a rescue attribute alone. It is an integral dimension of biomaterial performance and is therefore directly relevant to safety, predictability, and rational product selection, particularly in anatomically sensitive settings. Comparative interpretation is most defensible when fillers are analyzed at the level of technological platforms, measurable physicochemical attributes, dynamic rheological behavior, and explicitly reported degradation conditions.

Future comparative standards.

Further progress in this field will depend on more standardized, analytically transparent, and auditable study designs integrating dynamic rheology, microstructural characterization, and reproducible degradation assays. In this context, auditable refers to methodological traceability: studies should clearly report enzyme formulation and source, dose, dilution, exposure conditions, and readout strategy, while increasingly relying on reproducible primary outputs such as rheological curves, quantitative microscopy, and standardized digital measurements. From this perspective, the contribution of digital health is methodological rather than rhetorical. Its value lies in enabling more consistent, less observer-dependent, and more comparable characterization of injectable HA biomaterials across platforms and studies. Prospectively validated computational models linking network descriptors, rheological fingerprints, and degradation kinetics may further strengthen future platform-level comparison and support a more rigorous translational interpretation of reversibility.

Required statements

Ethics approval: Not applicable.This study is a narrativereview of previ-ouslypublished literatureand did not involve human participants,animals, or identifiablepersonal data.

Consent to participate: Not applicable.

Consent for publication: Not applicable.

Competing interests: The author declares that there are no conflicts of interest related to this work.

Data availability: No new data were generated or analyzed in the preparation of this review.

Funding: This work received no externalfunding.

Code availability: Not applicable.

AI uses disclosure: An AI-assistedimage-generationtool was used exclus-ivelyto prepare Figure 1, which is presented as a conceptual schematic,under direct human supervision.No AI tool was used for data generation,referenceselection,scientific interpretation,or developmentof the manu-scriptconclusions.The author critically reviewed all content and takes full responsibility for the final manuscript.

Author contributions: Mariucha Ramella Marcon Nemer was responsiblefor conceptualization,literaturereview, evidence synthesis,interpretationof findings, original draft preparation, manuscriptreview and editing, and approval of the final version.

Acknowledgements: The author has no acknowledgementsto declare.

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References are set in Vancouver/NLM style and kept compact without breaking the manuscript sequence.

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