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Therapeutic Promise of Hyaluronidase in Systemic Sclerosis: A Systematic Review

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ABSTRACT

Introduction: Systemic sclerosis, also known as scleroderma, is a chronic disease marked by autoimmune-mediated damage to connective tissues leading to vascular damage, tissue injury, and fibrosis. Effective treatment for this condition has remained difficult; however, a promising therapeutic option for patients with systemic sclerosis has emerged as hyaluronidase.

Objectives: We conducted a systemic review of the available literature to describe the therapeutic usage of hyaluronidase in systemic sclerosis.

Methods: We conducted a comprehensive review on PubMed and Embase, using the terms: "hyaluronidase" AND "scleroderma," as well as "hyaluronidase" AND "systemic sclerosis." Our criteria for inclusion were English-written articles published between 2013 and 2023. Only studies conducted on human subjects or *in vitro* on human cell lines were included. We excluded articles that did not discuss therapeutic use as well as articles that focused on medical conditions other than systemic sclerosis.

Results: Ten articles were included in our review. Overall, intradermal hyaluronidase showed improvement in systemic sclerosis-associated microstomia via increased oral aperture with minimal side effects. Treatment protocol and outcome measured differed per case, however, multiple rounds of injections were necessary in all treatment courses. In some studies, a plateauing effect for hyaluronidase was seen after 3-5 months of injections.

Conclusions: Case studies and case series have demonstrated hyaluronidase effectiveness in treating systemic sclerosis-associated microstomia, however, more research using larger sample sizes, standardized protocols, and specific outcomes such be conducted.

Introduction

Systemic sclerosis (SSc), also known as scleroderma, is a rare autoimmune connective tissue disorder with a very complex and poorly understood pathogenesis, presenting a challenge to both patients and physicians. Scleroderma can manifest in two principal forms: limited SSc, formerly known as CREST syndrome, or diffuse SSc depending on the combination of both clinical and serological criteria [1]. Among the numerous complications associated with SSc, the development of microstomia, characterized by progressive narrowing of the oral orifice due to perioral soft tissue fibrosis, is recognized as a particularly distressing one [2]. True microstomia affects approximately 30% of these patients and may have a profound negative impact on a patient overall quality of life, for example, restricted mouth opening may impair eating, speech, or oral hygiene [3-5].

In search of therapeutic interventions to address this complication, one avenue currently being investigated holds potential: hyaluronidase injections. Hyaluronidase plays a crucial role in degrading hyaluronic acid (HA) within the extracellular matrix (ECM), thus offering a potential therapeutic option for alleviating the fibrosis and stiffness associated with microstomia in these patients [6].

Objectives

The purpose of this paper is to thoroughly explore and evaluate the potential of hyaluronidase in the context of SSc, particularly in the management of microstomia. We aim to systematically synthesize and analyze the current literature to better understand the extent of hyaluronidase effectiveness, as well as the potential advantages and limitations it holds. We hope to facilitate more informed decision-making by physicians when considering the use of hyaluronidase to manage this complication in SSc patients. Ultimately, our goal is to advance evidence-based therapies and enhance the overall quality of life of SSc patients by offering practical insights and evidence-based recommendations in addressing the multifaceted challenges presented by SSc.

Methods

This systematic review was conducted in adherence to the standards outlined in the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement. This section outlines our search strategy as well as our inclusion and exclusion criteria that were used to identify and select pertinent articles for our investigation, all in accordance with the PRISMA guidelines.

We conducted a comprehensive search, initially on PubMed, using the following search terms: "hyaluronidase" AND "scleroderma," as well as "hyaluronidase" AND "systemic sclerosis" which yielded 43 relevant articles. After duplicate articles were removed, we assessed the title, abstract, and full-text of each article. Seven articles following the predetermined criteria remained which prompted us to proceed with an additional search on a different database. This supplementary search was conducted on Embase using the same search terms yielding 96 articles and 53 articles, respectively. After applying the predetermined criteria, three articles remained. After ensuring the articles met our criteria, a total of 10 articles were used in this review.

To ensure the relevance and quality of the selected articles, we imposed specific criteria that required the inclusion of English-written articles relating to this topic published between 2013 and 2023. This timeframe was chosen to encompass the most recent and up-to-date research on hyaluronidase in the context of SSc. Studies conducted on human subjects or *in vitro* on human cell lines were included as well. We also applied exclusion criteria to eliminate articles that did not align with our specific research goals. Articles outside the defined publication date range or published in languages other than English were excluded to maintain timeliness and accessibility of the data. Articles that did not discuss therapeutic use, or had results based on animal models were excluded. Moreover, we excluded articles that focused on conditions such as externally-induced morphea, scleredema, scleromyxedema, mixed connective tissue disease (MTCD), or oral submucous fibrosis if they were unrelated to the underlying SSc. Studies that evaluated hylaronidase in a mixed cohort of diseases were only included if the majority of patients recruited (≥ 75%) had SSc-related microstomia.

Bias in our search included selection, language, and publication bias. Our results were limited to articles found in PubMed and Embase, however, these databases were used due to their focus on clinical studies. Only English articles were included which limited our results. English translations of studies first published in other languages were retrieved when possible. Lastly, we acknowledge publication bias may have limited the number of searches we found in both databases. Bias was assessed in the studies by identifying biases due to randomization bias, bias from missing outcome data, and biases in outcome measurement.

Results

In this section, we present the findings obtained from our data analysis, providing a thorough review of each study outcomes to highlight the potential advantages of hyaluronidase injections to address the discomforting symptoms of SSc, particularly microstomia. Our findings consistently suggest that hyaluronidase administration leads to a simultaneous improvement of skin elasticity and reduction in dermal

thickness, thereby contributing to a significant reduction in some of the more distressing aspects of the condition. Notably, no consistent formulation of hyaluronidase or method of injection was seen throughout therapeutic reports. A summary of key findings and methodology from all cases assessed in our review is provided in Table 1.

In Vitro

A 2015 study by Kilic et al analyzed the levels of hyaluronan and hyaluronidase activation in dermal tissue of patients with SSc [7]. Hyaluronan is a glycosaminoglycan, a major component of the extracellular matrix, and is involved in initiating the inflammatory process and remodeling after tissue damage. The enzyme hyaluronan synthase is responsible for building this polymer, while hyaluronidase degrades it. The study found significantly increased levels and density of hyaluronan in SSc patients with cutaneous involvement. The authors noted patients with SSc had increased activity levels of hyaluronan synthase-2 and decreased activity of hyaluronidase-2 in patients versus healthy controls [7].

Case Reports

Three recent case reports were published detailing the therapeutic use of hyaluronidase in SSc. In one case report involving a 30 year-old female patient with diffuse SSc, hyaluronidase injections proved to be successful in improving discomfort and overall self-image [9]. She presented with increased tautness in the perioral and periocular regions, along with functional impairments in mastication, phonation, and sleep. Despite her ongoing treatment regimen with mycophenolate mofetil, hydroxychloroquine, sildenafil, nintedanib, and prednisone, she experienced no relief from her microstomia and therefore decided to undergo a trial of intradermal hyaluronidase. Following the administration of 150 units of recombinant human hyaluronidase (0.1 mL per injection), she experienced an improvement in daily function and cosmetic appearance. After three months, her oral aperture had expanded to 15.2 cm from 13.7 cm prior to the injections [9].

The use of hyaluronidase to address microstomia in this patient population is further supported by two cases, advocating for its recognition as a desirable alternative when conventional treatments are refractory. In the first case, a 45-year-old female with scleroderma and a year-long complaint of microstomia received 4mg of dexamethasone sodium phosphate in combination with 1,500 units of intradermal hyaluronidase periorally for 5 months, increasing her interincisal distance by 13 mm over that duration [10]. The second case describes a 53-year-old female who experienced a mild improvement in the Mouth Handicap in Systemic Sclerosis (MHISS) score after receiving 470 units of intradermal hyaluronidase in her lips over 7 months [11].

Case Series

The first case series on hyaluronidase in SSc microstomia was recently published by Min et al, who reported 4 patients with autoimmune sclerosing disease, 3 with SSc and one with MCTD [12]. Primary outcomes included improvements in mouth opening capacity (MOC), measured vertically in centimeters from upper to lower vermillion border, and MHISS. This study involved a total of four patients with various forms of scleroderma: two with limited SSc, one with diffuse SSc, and one with mixed connective tissue disease with sclero-dermoid features. All patients experienced significant oral microstomia at the start of the study with a baseline MOC ranging from 4.4 to 5.2 cm (mean 4.8 cm) and MHISS scores from 24 to 37 (mean 31). Treatment was standardized: all patients received an initial treatment of 200 IU hyaluronidase diluted in 6mL saline, injected 1 cm apart in 2 rows all around the lip. Monthly follow-up treatments were provided, of which duration varied per patient. All patients showed improvements in both MOC and MHISS scores. On average, MOC increased by 0.9 cm (19.1% increase), ranging from 0.5 to 1.6 cm (11.1-36.3% increase). MHISS scores decreased by an average of 19.3 (61.9% decrease), ranging from 17 to 24 (48.4 to 70.8% decrease). Additionally, perioral skin softening was observed in all patients. Researchers noted benefits plateaued after 3-5 months of injections. These benefits and overall symptomatic improvement were maintained for at least six months post-treatment with no occurrence of serious adverse events [12].

Cohort

One survey study on 20 children with juvenile scleroderma noted the therapeutic use of helium-neon laser in combination with intramuscular or electrophoresis hyaluronidase in areas of skin damage in a rehabilitation center. However, this abstract was limited by its lack of detailed administration methodology and numeric results [13].

Review

One review noted the use of iontophoretic hyaluronidase in SSc. Iontophoresis is a form of drug delivery in which the charged molecule (drug) is delivered trans-dermally via a low-voltage electric current [14]. The first review noted iontophoretic hyaluronidase was used to decrease tissue stiffness and cold sensitivity in SSc patients, with therapeutic benefit lasting around 3 months after treatment, citing a 1951 case series by Popkin [14,15]. The patient was treated with 40 applications of hyaluronidase over 3 months, with a reduction in sclerodactyly, microstomia, cold intolerance and general cutaneous stiffness throughout the body. Improvement of microstomia was measured by increased teeth opening from 2.0 cm to 2.3 cm, whereas mouth opening increased

Table 1. Overview of Key Case Report Findings of Hyaluronidase in Microstomia

Study Authors	Publication Year	Diagnosis	Delivery Method	Total Units Used (IU)	Unit Sequence	Degree of Improvement (% or mm)	Outcome Measurement	Time to secondary injection	Adverse Side Effects
Abbas et al [8]	2019	Pansclerotic morphea	Intradermal injection	435 IU	Right jawline: • 80 IU x2 50 IU Left jawline: • 35 IU x2 • 50 IU • 15 IU Chin: • 35 IU x2 • 20 IU	+30 mm	+30 mm	2 weeks	Mild discomfort at injection site
Chopra et al [9]	2022	Diffuse systemic scleroderma	Intradermal injection	300 IU	150 IU x2	+ 15 mm	Oral aperture - circumference	6 months	None reported
Kumar et al [10]	2016	Limited systemic scleroderma	Intradermal injection	1500 IU	Unknown	+13 mm	Oral aperture- vertical	2 weeks	Gastritis secondary to dexamethasone sodium phosphate co-administration
Melvin et al [11]	2019	Limited systemic scleroderma	Intradermal injection	470 IU	20 IU, 50 IU, 200 IU x2	+11%	MHISS	2 months	Mild bruising at injection site
Min et al [12]	2023	Limited systemic scleroderma (n=2), diffuse systemic scleroderma (n=1)	Intradermal injection	200 IU	200 IU x 2-7, depending on patient	On average over 4 patients: MOC: +9 mm MHISS: +61.9%	MOC, MHISS	1 month	Transient bruising and pain at injection site
Popkin (Patient 1)	1951	Generalized scleroderma	Iontophoresis	311 IU	0.1 IU, 1 IU, 10 IU, 20 IU x 15	+3 mm; +15 mm	Oral aperture - interincisional; oral aperture - lips	2 weeks	None reported
Popkin (Patient 2)	1951	Severe generalized scleroderma	Iontophoresis	611 IU	0.1 IU, 1 IU, 10 IU, 20 IU x 30	N/A	N/A	2 weeks	None reported

MHISS = Mouth Handicap in Systemic Sclerosis; MOC = mouth opening capacity; N/A = not available

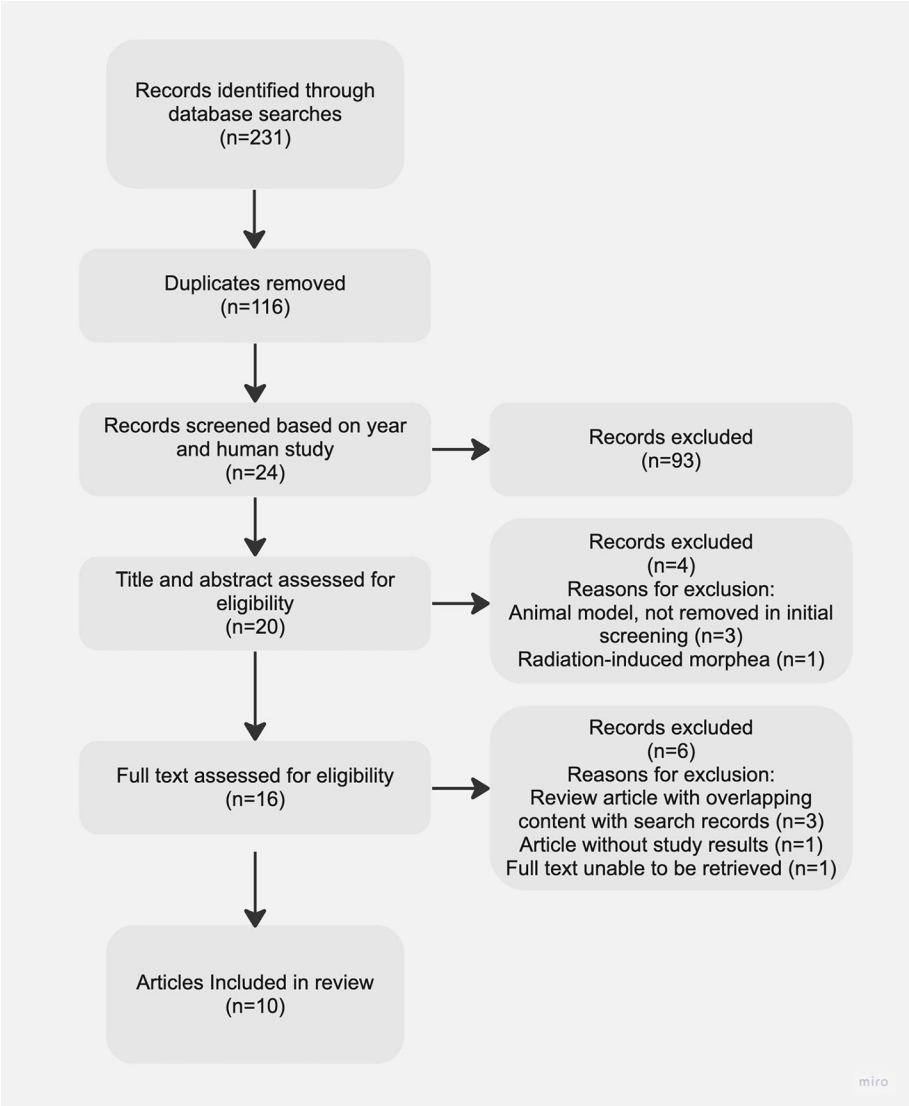

Figure 1. The PRISMA flow diagram for the systematic review detailing database search, number of title and abstract screens, full text screens, reasons for exclusion, and total number of articles included in the review.

from 3.0 cm to 4.5 cm. In the second case, the SSc patients received 33 treatments over 3 months, resulting in 9 months of improvement in skin stiffness, color, and cold intolerance related to their Raynaud syndrome. The author noted after 3 months, the therapeutic benefit of hyaluronidase appeared to decrease, however, changing the application site seemed to improve this finding. Even after treatment cessation, the severity of Raynaud experienced by each patient remained lower than before starting hyaluronidase treatment [14].

Discussion

The ECM of the skin constitutes an array of macromolecules, functioning not only as the structural scaffold but also as an important regulator of several cellular processes such as proliferation, adhesion, migration, and gene expression [16]. It is primarily comprised of collagen, elastin, and proteoglycans to which glycosaminoglycans (GAG) attach [17]. Notably, hyaluronic acid (HA), a linear GAG composed of alternating units of N-acetyl-D-glucosamine and D-glucuronic acid, is the predominant GAG in the dermis due to its significant hydrophilic properties, contributing largely to the cutaneous viscoelastic properties [17,18]. However, in the context of cutaneous sclerosing conditions such as SSc, an abnormal accumulation of HA and collagen within the ECM occurs, ultimately resulting in fibrosis and scarring [19]. To address this underlying pathological process, treatment with hyaluronidase has been proposed due to its ability to hydrolyze disaccharides at hexosaminidase linkages, subsequently degrading ECM components, improving dermal fibrosis, and creating a more favorable environment for tissue remodeling and repair [20]. It is crucial to understand that the underlying mechanism of action of hyaluronidase in the context of improving fibrosis in SSc patients is multifactorial as it

triggers various downstream effects upon breaking down hyaluronic acid. The disruption of the HA barrier plays a pivotal role in facilitating the delivery of therapeutic agents into affected tissues [21]. Furthermore, hyaluronidase capacity to degrade HA also acts as a potential modulator of the immune system, contributing to inflammation reduction. Through the alteration of the proinflammatory environment within affected tissues, it can effectively regulate immune cell activity and cytokine production, potentially reducing the severity of the condition [22].

Limited contraindications exist for the use of hyaluronidase in SSc, however, hypersensitivity to the material or other injection ingredients can occur in some patients [23]. Some research suggests hyalornidase can be pro-thrombogenic, and therefore cautionary use is recommended in patients with hypercoagulable conditions [23]. Risk in pregnancy has not been well-elucidated.

Numerous case reports have demonstrated hyaluronidase efficacy in enhancing overall quality of life for SSc patients by enhancing both the aesthetic appearance and associated functional impairments such as microstomia. While a thorough exploration of various aspects of quality of life was not explicitly detailed in all case reports, it is well-established that microstomia significantly impacts everyday functioning: mastication, speech, oral hygiene practices [3,5]. In some cases reviewed in this article, decreased quality of life due to difficulty eating, talking, sleeping, and poor self-image was reported [9,11]. The improvement of patients oral function and appearance through hyaluronidase injections positively impacting a patient quality of life was subsequently documented in the results. Therefore, it is important to note that symptomatic improvement of this microstomia can have profound outcomes not fully measured by increased oral aperture, such as improved nutrition and increased ability to socialize.

Although many studies do suggest promising results for various SSc manifestations, including morphea and microstomia, these are isolated case reports and standardized trials. Therefore, these studies lack strength to validate its use as a first-line treatment option for symptoms associated with SSc. However, one can reasonably conclude that hyaluronidase may serve as a valuable alternative when conventional approaches prove ineffective, offering hope to these patients. Additionally, the flexibility in dosing and administration allows for individualized treatment plans tailored to each patient unique clinical presentation.

The limitations of these studies include the variation in their administration and formulation of hyaluronidase, lack of clear improvement metrics, and small cohort size, as previously shown in Table 1. Most of the studies were case reports on the use of hyaluronidase in microstomia that mentioned improvement in oral aperture as a therapeutic endpoint. However, measurement varied between oral aperture (inter-incisional opening versus circumferential) or the MHISS. In addition, each study varied in the volume of hyaluronidase used per injection, number of injections per session, and potential additives—such as one case that mixed hyaluronidase with dexamethasone.

However, cases consistently showed positive results regarding either increased oral aperture or MHISS, with reported side effects limited to temporary injection site reactions. This makes hyaluronidase a promising treatment for SSc-related microstomia. The most common volume of injection seen was 0.1cc/mL of hyaluronidase, in multiple injection points in sclerotic lesions around the mouth, not entering the lip border. Most clinicians opted to have multiple rounds of injections with a few weeks of interval in between to confirm no adverse side effects and clinical improvement. The recent case series published by Min et al. demonstrating a standard protocol of hyaluronidase injection for 3 patients with SSc microstomia provides a useful template for clinicians and researchers to build upon [13].

Yet, the potential for hyaluronidase in SSc-related symptoms likely extends beyond microstomia. This was earlier demonstrated in 1951, where SSc patients treated with iontophoretic hyaluronidase noted improvement in sclerodactyly, Raynaud syndrome, and general skin stiffness in addition to microstomia [15]. One consideration noted from the 1951 Popkin case series was the perceived decreased efficacy of hyaluronidase usage over time, in which after 3 months the clinician halted treatments due to diminishing returns [15]. This plateau effect was also seen by Min et al, who noticed diminished returns after 3-5 rounds of monthly injections. Despite this, the patients described maintained greater oral aperture for at least 6-9 months after their last injection [13,15]. While other studies did not notice diminishing returns from increased injections at the time of publication, the investigators in those studies did not establish plateau effect as an endpoint.

Despite this promising feature, the literature regarding hyaluronidase and SSc has been sparse. In our initial PubMed search over all years, only 43 studies presented with the search terms “hyaluronidase” AND “scleroderma.” Notably, none of these studies were classified as a randomized control trial. In addition, some studies such as that from Min et al. combines the results of hyaluronidase in SSc with other sclerosing diseases, making it difficult to accurately appreciate the effect within SSc. Similarly, no identified randomized control trial was seen in the Embase search over all years. In addition, all recent reports only consider the use of hyaluronidase in microstomia. While one cohort study considered its use in general SSc skin damage, this was a conference abstract without definitive results provided. This indicates a significant lack of research in this potential treatment

modality for a product that has become increasingly cheap and available. Beyond case reports, well-designed clinical trials are necessary and should be pursued to establish the safety, efficacy, and long-term outcomes of hyaluronidase treatment in larger SSc patient populations.

An important consideration to advancing this therapeutic option is standardization of outcome measurements and initiation of randomized control trials (RCTs) for high-quality evidence. The protocol initiated by Min et al. provides two objective measurements that clinicians can use in future trials: MOC and MHISS. Durometry or ultrasound to measure skin thickness can be considered as an additional outcome measurement for hylauronidase in SSc. An RCT for hyalornidase in SSc microstomia could involve placebo injections versus hylaronidase over 1 year, a longer time course than most of the studies mentioned in this review. A longer time course will allow better observation of any plateau or adverse effect of hylauronidase outside of the treatment period.

All in all, a multidisciplinary approach involving collaboration among various specialists, including dermatologists and rheumatologists is imperative when considering this approach to SSc symptom management. Moreover, it is essential to acknowledge the limited scope of the case reports discussed, highlighting the need for standardized, large-scale research to establish the safety and effectiveness of hyaluronidase in these patients. While physicians should adhere to current evidence-based treatment guidelines to manage SSc symptoms, it is important to be open-minded about exploring alternative therapeutic approaches when needed.

Conclusions

Overall, the use of hyaluronidase in SSc is under-researched. Case reports have shown hyaluronidase efficacy in treating microstomia in SSc. However, limited research has shown this treatment modality used in the setting of randomized control trials, case-control trials, or cohort studies with standardized outcome measures. The duration of symptom improvement and potential long-term effects should be further investigated in hyaluronidase as a promising therapeutic option for scleroderma patients.

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