Received: 22 January 2020 | Accepted: 28 May 2020

DOI: 10.1111/jocd.13528

REVIEW ARTICLE

JCD Journal of Cosmetic Dermatology WILEY

Low molecular weight heparan sulfate containing facial skin care for reducing inflammation and restoring aged-skin homeostasis

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Funding information
SENTÉ® Laboratories USA

Abstract

Background: Chronic exposure of the skin to environmental factors, including solar radiation and air pollution, promotes skin aging by inducing inflammation which damages the skin. Heparan sulfate (HS) is one of the glycosaminoglycans, which has a central role in modulating skin repair. In its appearance in the skin, HS is large and highly polar and therefore unable to penetrate the skin. As a component in a topical formulation, the modified to a low molecular weight heparan sulfate analog (LMW-HS) showed biological modulation activity.

Aims: This review discusses the potential role of topical formulations containing LMW-HS in restoring aged-skin homeostasis and skin health.

Methods: An expert panel of dermatologists who regularly treat clinical signs of facial photoaging explored the role of LMW-HS containing formulations for reducing inflammation and facial-aging signs. For this purpose, evidence from the conducted literature searches was used together with expert opinion and experience of the panel.

Results: Extrinsic factors contribute to skin aging through oxidative stress, stimulating inflammation involved in extracellular matrix degradation. Evidence showed that chemokines require heparan sulfate for their full range of functional activities during innate immunity. Studies showed the LMW-HS containing topical formulation to penetrate the skin within 48 hours of once-daily application. LMW-HS used in the periorbital area improved discoloration and wrinkles at Week 2 with continuous improvement up to Week 12.

Conclusion: The LMW-HS containing formulation showed improvements in skin condition when applied on photo-damaged skin, indicating its therapeutic potential.

KEYWORDS

aged skin, Heparan sulfate, inflammation reduction

1 | INTRODUCTION

Skin aging is triggered by the body's response to both internal and external factors such as solar radiation, air pollution, tobacco smoke, and poor nutrition.[1-3] Chronic exposure of the skin to these factors promotes skin aging by enhancing the production of reactive oxygen species (ROS), thereby inducing cellular inflammatory infiltrates, and damaging the dermal extracellular matrix (ECM) and protein structures.[1-3]

Glycosaminoglycans (GAGs) are complex carbohydrates, one of which is heparan sulfate (HS), which plays a central role in modulating

skin repair. In its natural configuration, HS is too large and highly polar to penetrate the skin. Applied to the skin as a cream, low molecular weight heparan sulfate (LMW-HS) analog has been shown to penetrate the skin, thereby delivering its biological modulation activity.

This paper discusses the potential role of an LMW-HS containing cream in restoring aged-skin homeostasis and skin health.[3,4]

2 | METHODS

The authors, who regularly treat clinical signs of facial photoaging, participated in an expert panel of dermatologists exploring the role of an LMW-HS containing cream for reducing inflammation and signs of facial aging. For this purpose, evidence from the conducted literature searches was used together with expert opinion and experience of the panel.

2.1 | Literature searches

Review articles, clinical trials, and other studies on skin aging, inflammation, and topical anti-aging treatment using LMW-HS were identified during the literature searches. Publications were in the English language dating from 2012 to 2019.

Exclusion criteria were no original data, information not specific to topical management of photoaging and inflammation, and publication in a language other than English. The searches yielded fifty-four articles. After removal of duplicates and those that did not meet the inclusion criteria, thirteen articles were included.

A dermatologist and a physician/scientist with extensive experience in the field conducted the literature searches. Two reviewers independently evaluated the results of the searches.

3 | FACTORS INFLUENCING SKIN AGING

The skin barrier function comprises a physical, well-hydrated, antioxidant, anti-microbial, and photo-protective barrier, which may be damaged by the cumulative effects of intrinsic and extrinsic factors.[1,2] Extrinsic or environmental factors that enhance skin inflammation, leading to signs of skin aging, include solar radiation (ultraviolet radiation, visible light, blue light, and infrared radiation), air pollution, tobacco smoke, nutrition, and other factors such as stress and sleep deprivation.[1] These extrinsic factors have been shown to contribute to skin aging through oxidative stress, negatively impacting cellular processes including DNA replication, for example.[1-3] Glycation, which favors oxidation[4] and the pathophysiological changes during menopause that result from a reduction in estrogen levels, also contribute to skin aging.[5] Principal health concerns of menopausal women include vasomotor symptoms, urogenital atrophy, osteoporosis, cardiovascular disease, cancer, psychiatric symptoms, cognitive decline, and sexual problems. The decline in estrogen levels may result in reduced blood flow to the epithelium leading to dry facial skin and signs of facial aging, such as wrinkles.[5]

Dietary habits may also impact facial skin aging, as was shown in a study where a group of patients consuming red meat, fat, and carbohydrates containing snacks were shown to have more facial wrinkles than those following a fruit-rich diet.[6] A higher intake of vegetables, legumes, and olive oil may also protect against actinic damage.

A study that analyzed the skin features of over 4000 women showed, after controlling for other factors, that a diet high in potassium and vitamins A and C correlated with fewer wrinkles.[7]

4 | INFLAMMATION AND THE ROLE OF HS

Among the four identified classes of GAGs, (a) chondroitin sulfate (CS)/dermatan sulfate (DS), (b) heparin/heparan sulfate (HS), (c) keratin sulfate (KS), and (d) hyaluronic acid (HA), only HA is nonsulfated and does not form a part of proteoglycans (Figure 1).[8] Hyaluronic acid is distributed in the ECM of connective tissue, whereas HS is located on cell surfaces, in basement membranes and the ECM (Table 1).[8]

Carbohydrates can be divided into simple sugars and more complex glycans.[9-11] Glycosaminoglycans are large, linear, negatively charged glycans that are components of the ECM and are required for cell viability. Different GAGs play different roles in cellular processes.[8]

Endogenous HS, which amplifies, binds, stores, and preserves secreted factors and is a natural hydration agent, is reduced in mature skin (Figure 2).[8] Moreover, chronic exposure environmental factors that increase ROS is reported to trigger the skin aging process. The skin aging process includes the creation of a pro-inflammatory microenvironment, increased production of multiple matrix metalloproteinases (MMPs), which are involved in ECM breakdown and collagen fibril fragmentation, and reduced production of collagen.[1-3] As a result, the dermal structural and mechanical integrity of the skin is weakened, further leading to inflammation[2] and additional breakdown of the ECM.

Inflammation is a complex process that involves various inflammatory mediators, including chemokines and selectins, which are mediated by interactions with GAGs including CS, DS, and HS.[9-11]

Important events during inflammation include the recruitment of leukocytes from the circulation to the site of inflammation. Heparan sulfate plays a major role in the promotion of extravasation and migration of anti-inflammatory cells from the vasculature into tissues.[9-11] At the site of inflammation, HS establishes and provides cytokine gradients, which facilitate communication between bone marrow and progenitor inflammatory cells in the tissues (Figure 3).[9-11] Cells at the site of inflammation include macrophages

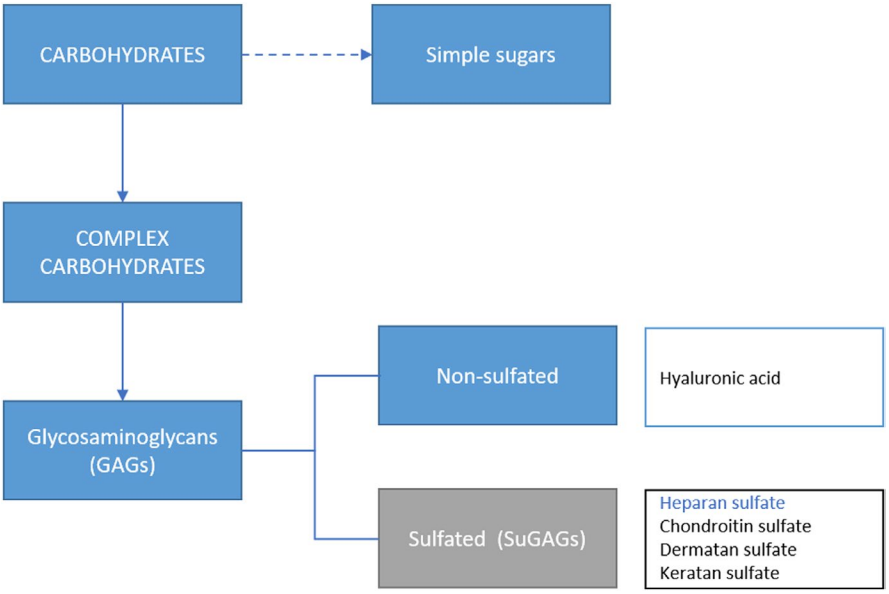

FIGURE 1 Carbohydrates can be divided into simple sugars and more complex glycans

TABLE 1 Differences between HA and HS

	Hyaluronic acid	Heparan sulfate
Sulfated	No	Yes
Covalently attached to proteins	No	Yes
Site of synthesis	Plasma membrane	Golgi apparatus
Major turnover regulators	*Synthesis:* HA synthase	*Synthesis:* HS synthase. N-deacetylase/ N-sulfotransferase. 2,3 and 6-0 sulfotransferases. C-5 epimerase
	Degradation: hyaluronidase	*Degradation:* heparanases
Tissue distribution	ECM of connective tissue	Cell surface, basement membranes and ECM

Note: Vega VL. Advanced skincare colloquiums. *Clinical insights*. 2017(1/2):1-4.[8]
Abbreviations: ECM, Extracellular matrix; HA, Hyaluronic acid; HS, Heparan sulfate.

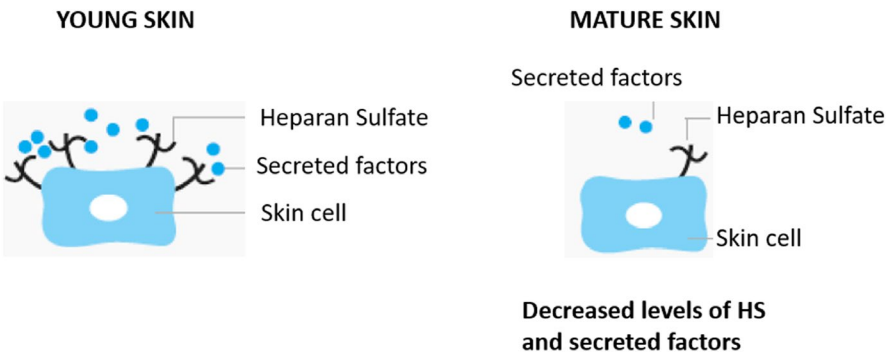

FIGURE 2 Endogenous heparan sulfate has a central role in preserving skin health. Endogenous heparan sulfate amplifies, binds, stores, and preserve secreted factors and is a natural hydrator.[9-11]

and mast cells. Macrophages, following inflammatory stimulation, release chemokines and proteases, which are involved in ECM degradation.[9-11] Evidence indicates chemokines require HS to carry out their full range of functional activities during innate immunity, thus supporting the hypothesis suggesting molecules that interfere with the inflammatory activities, such as HS, may be of therapeutic interest.[9-11]

5 | LMW-HS CONTAINING CREAM FOR THE REDUCTION OF INFLAMMATION IMPROVES SIGNS OF FACIAL AGING

LMW-HS is a modified form of endogenous HS in which size (6-12 kDa), shape, and charge are optimized[12] for dermal penetration. This smaller version of HS (SENTÉ Inc.) was designed for

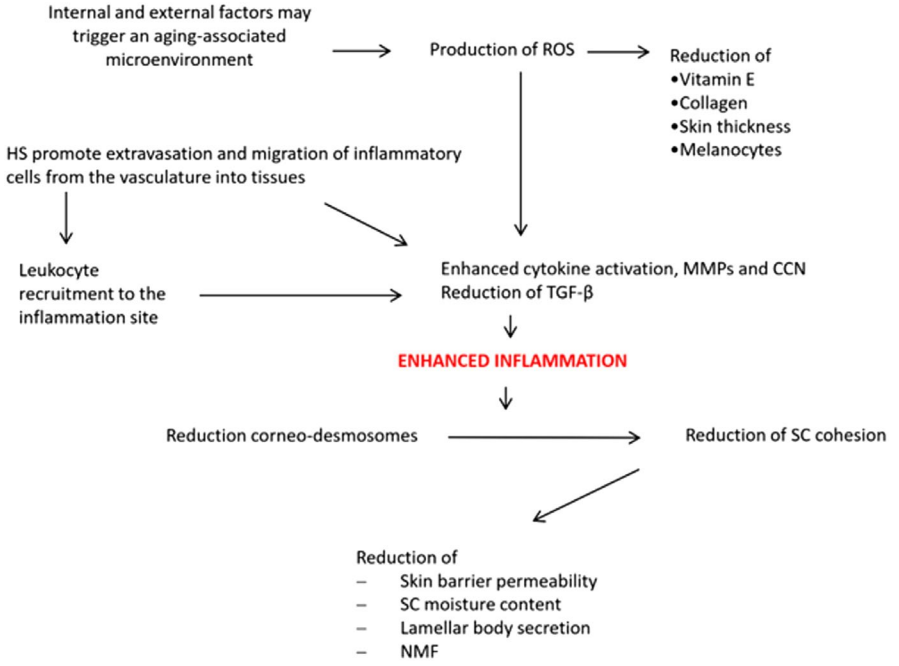

FIGURE 3 Inflammation and the role of heparan sulfate. The skin is a target of oxidative stress from both intrinsic (oxidative metabolism) and extrinsic (solar radiation) sources, enhancing inflammation. HS promotes extravasation and migration of inflammatory cells from the vasculature into tissues, where it establishes and provides cytokine gradients facilitating the communication between bone marrow and progenitor inflammatory cells in the tissues.[9-11]

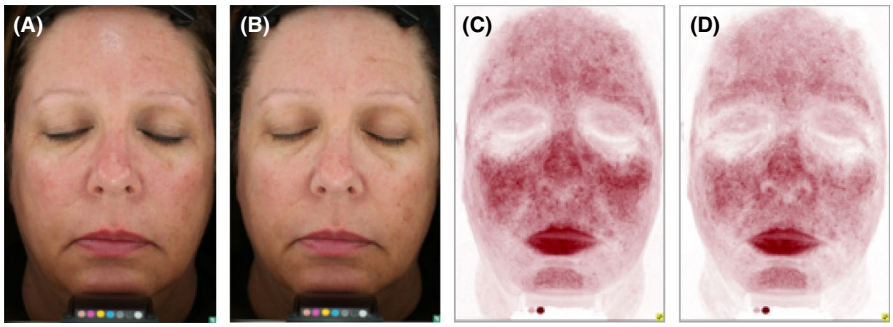

FIGURE 4 Case 1: LMW-HS containing regimen. Standard view. A, Before. B, After 12 wk. Cross-polarized view (Red channel). C, Before. D, After 12 wk. The forty-nine-year-old Caucasian female patient used the LMW-HS containing regimen (Dermal repair cream (am/pm) Moisturizer (am/pm), SPF 46 sunscreen (am), and a generic cleanser (am/pm) for 12 wk. The LMW-HS containing regimen demonstrated marked improvements and was well tolerated

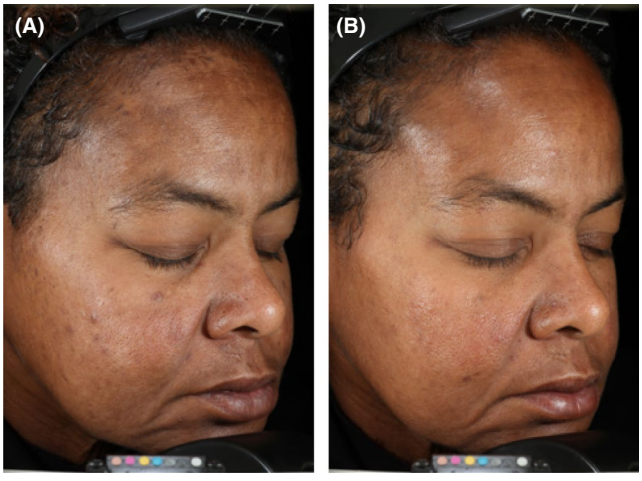

FIGURE 5 Case 2: LMW-HS containing repair cream. A, Before. B, After 8 wk. The forty-three-year-old African American male patient used the LMW-HS containing repair cream 1% (am/pm) for8 weeks. The LMW-HS containing cream demonstrated an improvement of his skin condition after eight weeks of use and was well tolerated

topical use in cream to enable skin penetration while preserving its activity.[8,12]

A study demonstrated effective penetration into human skin using skin explants of an LMW-HS containing cream compared to vehicle, as well as a significantly higher induction of collagen type 1 and elastin.[8]

An ex vivo study evaluated the penetration of LMW-HS into the skin. For this purpose, HS was covalently labeled with a fluorescent tag (fluorescein isothiocyanate [FITC]) and incorporated into a cream at a 0.5% concentration and applied to murine skin. The results show that the HS penetrated the skin within 48 hours of once-daily application.[12]

Application of the same mixture was repeated in a clinical study showing penetration to the epidermis and dermis at 24 hours following the application of the formulation at 12-hour intervals.[12]

A single-center, open-label study in 15 healthy subjects evaluated the use of an eye cream containing LMW-HS applied twice daily under the eye for 12 weeks. Results showed reported improvements in the appearance of periorbital hyperpigmentation

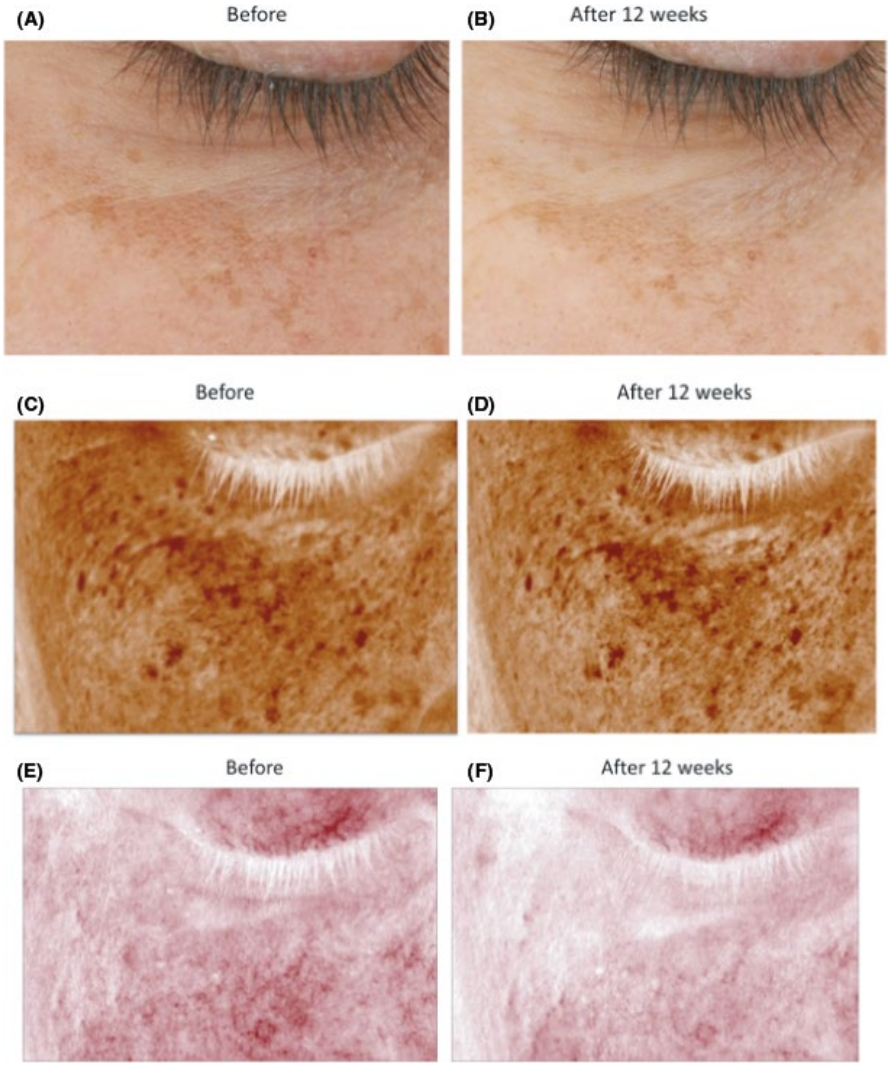

FIGURE 6 Case 3: LMW-HS containing eye cream. Standard view. A, before. B, at 12 wk. Cross-polarized view (Brown channel). C, before. D, at 12 wk. Cross-polarized view (Red channel). E, before. F, at 12 wk. The fifty-year-old Caucasian female used the LMW-HS containing eye cream (am/pm) for 12 wk. The LMW-HS containing eye cream demonstrated an improvements in the appearance of periorbital hyperpigmentation after 12 wk of use and was well tolerated

and wrinkles as early as Week 2, with continuous improvement up to Week 12.[13] The investigators discussed the fact that inflammation promotes the deposit of hemosiderin contributing to the blue-gray color of under-eye circles and theorized that topically applied LMW-HS containing cream decreases inflammation.[13] Hemosiderin is an iron-containing, golden-brown, granular pigment derived from ferritin, the initial iron-storage protein. As iron accumulates within the cell, aggregates of ferritin molecules form hemosiderin. Most hemosiderin in macrophages located in tissues throughout the body is derived from the breakdown of erythrocytes.[13]

Heparan sulfate plays a central role in modulating skin repair and is a key participant in the down-regulation of inflammation associated with tissue repair.[9-11] Based on this concept, an LMW-HS containing cream may reduce inflammation in those patients with signs of facial skin aging.[8,12,13] A dermal repair cream containing LMW-HS demonstrated an improvement in the appearance of mature or photo-damaged skin. Studies confirmed improved skin hydration, barrier function, firmness, and elasticity.[12]

Three typical cases illustrate the results obtained with LMWS-HS application (Figure 4A-D; Figure 5A and B; Figure 6A-F).

6 | LIMITATION

LMW-HS containing cream is supported by proof-of-concept clinical studies demonstrating its efficacy and subject satisfaction. Studies with a larger number of subjects would be appropriate to confirm these findings.

7 | CONCLUSIONS

In aging skin, elevated oxidative stress stimulates inflammation involved in extracellular-matrix degradation. In the skin, HS has a range of functional activities during innate immunity. The LMW-HS containing topical formulation applied for reducing signs of facial skin aging penetrates the skin and, when applied in the periorbital

area, reduced the appearance of hyperpigmentation and wrinkles. The LMW-HS containing formulation applied to photo-damaged skin demonstrated its therapeutic potential.

ACKNOWLEDGMENTS

The authors disclosed receipt of the following financial support for the research and authorship of this paper: This work was supported by an unrestricted educational grant from SENTÉ® Laboratories, USA.

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REFERENCES

1. Krutmann J, Bouloc A, Sore G, Bernard BA, Passeron T. The skin aging exposome. *J Derm Science*. 2017;85(3):152-161.
2. Addor FAS. Beyond photoaging: additional factors involved in the process of skin aging. *Clin Cosmetic Investigational Dermatol*. 2018;11:437-443.
3. Tu Y, Quan T. Oxidative stress and human skin connective tissue aging. *Cosmetics*. 2016;3(3):1-12.
4. Gkogkolou P, Bohm M. Advanced glycation end products: key players in skin aging? *Dermatoendocrinol*. 2012;4(3):259-270.
5. Owen CM, Pal L, Mumford SL, et al. Effects of hormones on skin wrinkles and rigidity vary by race/ethnicity: four-year follow-up from the ancillary skin study of the Kronos Early Estrogen Prevention Study. *Fertil Steril*. 2016;106(5):1170-5.e3.
6. Mekic S, Jacobs LC, Hamer MA, et al. A healthy diet in women is associated with less facial wrinkles in a large Dutch population-based cohort. *J Am Acad Dermatol*. 2019;80(5):1358-63.e2.
7. Katta R, Kramer MJ. Skin and diet: an update on the role of dietary change as a treatment strategy for skin disease. *Skin Therapy Lett*. 2018;23(1):1-5.
8. Vega VL. Advanced skin care colloquiums. *Clin Insights*. 2017;1/2:1-4.
9. Farrugia BL, Lord MS, Melrose LJ, Whitelock JM. The role of heparan sulfate in inflammation and the development of biometrics as anti-inflammatory strategies. *J Histochem Cytochem*. 2018;66(4):321-336.
10. Kumar AV, Katakam SK, Urbanowitz AK, Gotte M. Heparan sulphate as a regulator of leukocyte recruitment in inflammation. *Curr Protein Pept Sci*. 2015;16(1):77-86.
11. Dyer DP, Salanga CL, Volkman BF, Kawamura T, Handel TM. The dependence of chemokine-glycosaminoglycan interactions on chemokine oligomerization. *Glycobiology*. 2016;26(3):312-326.
12. Gallo RL, Bucay VW, Shamban AT, et al. The potential role of topically applied heparan sulfate in the treatment of photodamage. *J Drugs Dermatol*. 2015;14(7):669-674.
13. Colvan L, Fleck T, Vega VL. Global periorbital skin rejuvenation by a topical eye cream containing low molecular weight heparan sulfate (LMW-HS) and a blend of naturally derived extracts. *J Cosmet Dermatol*. 2019;18(2):530-538.

How to cite this article: Bucay V, Gold MH, Andriessen A. Low molecular weight heparan sulfate containing facial skin care for reducing inflammation and restoring aged-skin homeostasis. *J Cosmet Dermatol*. 2020;00:1–6. https://doi.org/10.1111/jocd.13528