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CASE REPORT

Clinical Observations of High Dose Oral 70 kDa Hyaluronan Fragments in Subcutaneous Fat Reduction, Inflammatory Erythema, and Facial Vitality: A Case Series of 11 Subjects

Ding Mingxing[1], Ma Wenhai[2], Jia Xiaoxiao[3], Jessica H Hui[3], Vera Gorbunova[4]*, Hui Mizhou[3]*

[1]*Changchun Jiahe Plastic Surgery Hospital, Changchun, China*

[2]*Changchun Jirun Jingyue Hospital (First Hospital of Jilin University, Jingyue Branch), Changchun, China*

[3]*Qingdao Hainuo Laboratory, Qingdao, China*

[4]*Departments of Biology and Medicine, University of Rochester, Rochester, New York, USA*

***Corresponding author:** *Vera Gorbunova, Departments of Biology and Medicine, University of Rochester, Rochester, New York, USA; Hui Mizhou, Qingdao Hainuo Laboratory, Qingdao, China*

Abstract

Background: The naked mole-rat exhibits exceptionally high tissue concentrations of hyaluronic acid and an almost complete absence of subcutaneous adipose tissue, suggesting a potential regulatory role of HA in adipogenesis and inflammatory homeostasis. This case series explored the clinical bioactivity of high-dose oral 70 kDa HA fragments in subcutaneous fat reduction, inflammatory facial erythema, and facial vitality.

Methods: Eleven Asian subjects received oral 70 kDa HA fragments (5 g/day) for 40 consecutive days. Changes in subcutaneous fat appearance, facial erythema, and facial vitality were evaluated using a modified 0-10 Numeric Rating Scale. Safety and gastrointestinal tolerance were monitored throughout the intervention.

Results: After 40 days, all participants demonstrated varying degrees of facial and/or body subcutaneous fat reduction, with noticeable improvement in facial erythema and vitality observed as early as day 7. No adverse events were reported. Incidental improvements in gastrointestinal discomfort and dry eye symptoms were observed in a small subset of participants.

Conclusions: High-dose oral 70 kDa HA fragments were safe and well tolerated and were associated with consistent improvements in subcutaneous fat appearance, inflammatory facial erythema, and facial vitality. Exploratory systemic effects were noted but require further confirmation in controlled studies.

Keywords

Hyaluronan fragments, Oral administration, Subcutaneous fat reduction, Anti-inflammation, Facial contour improvement

Introduction

The naked mole-rat (NMR) is a subterranean rodent characterized by extraordinary longevity, with a lifespan reaching up to 32 years, and a remarkably low incidence of age-related diseases, including cancer, chronic inflammatory disorders, and degenerative conditions [1-4]. A defining feature of NMR physiology is the exceptionally high concentration of hyaluronic acid (HA) in its tissues, accounting for nearly 6% of wet tissue weight-approximately ten times higher than that observed in other mammalian species. This unusually elevated HA content is widely recognized as a key contributor to the NMR's resistance to cancer, inflammation, oxidative stress, and tissue degeneration [1,3,4]. In addition, NMRs display a near-complete absence of subcutaneous adipose tissue, suggesting that abundant endogenous HA may exert inhibitory effects on adipocyte differentiation and lipid accumulation [5]. Mechanistically, high HA levels in NMRs are thought to stabilize the extracellular matrix (ECM) and modulate

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multiple signaling pathways, including those mediated by CD44, LYVE-1, and TRPV1, thereby maintaining anti-inflammatory balance and metabolic homeostasis [6-8].

Prior to the widespread recognition of NMR HA biology, our preclinical studies (Figure 1) demonstrated that daily subcutaneous injection of 100 mg HA fragments with an average molecular weight of approximately 35 kDa for 21 consecutive days resulted in significant reductions in subcutaneous fat, producing a noticeable "slimming" phenotype (US Patents 11839625B2, 11826380B2, and 11826381B2). Inspired by the HA-rich phenotype of NMRs, Zhang, et al. subsequently engineered laboratory mice with constitutively elevated HA expression, observing analogous phenotypic traits, including delayed aging, enhanced inflammatory resistance, and improved fur quality [1]. Earlier investigations had already suggested a link between HA metabolism and lipid homeostasis. In 2015, Park et al. reported that HA fragments inhibited adipocyte differentiation, reduced fat deposition, and modulated intestinal barrier function in murine models [5,9]. Subsequently, Mariko et al. confirmed the safety of high-dose oral HA administration in rats, identifying no-observed-adverse-effect levels of 3462 mg/kg/day in males and 3563 mg/kg/day in females [10]. Our own animal studies further demonstrated that HA fragments with molecular weights of 35 kDa and 70 kDa exhibit comparable tissue permeability and biological activity, and can be rapidly absorbed into systemic circulation via the intestinal lymphatic system [11]. Collectively, these findings highlight the potential role of HA fragments in regulating lipid metabolism and inflammatory balance. In addition, Bellar, et al. validated the safety and tolerability of high-concentration oral HA fragments in human subjects [12].

Based on these preclinical and early clinical observations, the present case series aimed to evaluate the clinical efficacy of high-dose oral 70 kDa HA fragments (5 g/day; Product Standard No. Q/0285HND042) in modulating subcutaneous fat metabolism and improving cutaneous conditions in humans. The primary study endpoints included: (i) changes in facial and body subcutaneous fat mass and overall body weight; (ii) improvement in inflammatory facial erythema and enhancement of facial vitality; and (iii) gastrointestinal safety and tolerance. This study seeks to translate the unique anti-aging and metabolic regulatory mechanisms observed in NMRs into a clinically applicable intervention, providing both theoretical rationale and preliminary clinical evidence for the potential use of HA fragments in lipid metabolism modulation and anti-inflammatory cutaneous therapy.

Cases and Methods

Patient information

This case series included 11 Asian participants (7 females and 4 males) who presented to the Department of Aesthetic Medicine at Changchun Jiahe Plastic Surgery Hospital, China. All participants sought non-invasive improvement of facial contour and skin condition, primarily due to concerns related to subcutaneous fat accumulation or facial laxity, most commonly manifested as facial fullness and double chin.

Participants ranged in age from 28 to 69 years. Facial fat accumulation was attributed to multiple factors, including postpartum hormonal changes, natural aging, collagen loss, and sedentary lifestyle. The mean participant height was 168.4 ± 7.2 cm, and the mean baseline body weight was 72.3 ± 9.8 kg. Except for Case 11, none of the participants had a history of chronic systemic disease. Case 11 had a 20-year history of hypertension and a 15-year history of type 2 diabetes mellitus, both managed with stable oral medications.

Cases 1 and 11 reported persistent dry eye symptoms, while Cases 10 and 11 presented with chronic bowel dysfunction characterized by approximately four bowel movements per day. Given the potential association between these symptoms and the mucosal regulatory effects of HA, they were included as secondary observational endpoints. All participants refrained from fat-reduction procedures, cosmetic injections, or facial rejuvenation treatments for at least two weeks prior to study initiation.

Treatment protocol

All participants received a standardized intervention consisting of oral administration of 5 g of food-grade 70 kDa HA fragments (Product Code: Q/0285HND042; sodium hyaluronate concentrate) once daily in the morning on an empty stomach for 40 consecutive days. No dietary restrictions or exercise regimens were imposed, and participants maintained their habitual lifestyle throughout the study period to minimize confounding factors.

Evaluation methods

Participants independently assessed and reported clinical outcomes using a modified 0-10 Numeric Rating Scale (NRS) [13,14] at baseline and after 40 days of treatment. Evaluations covered four domains: subcutaneous fat reduction, improvement in inflammatory erythema and skin tone, enhancement of facial vitality, and gastrointestinal tolerance.

For fat reduction, participants evaluated six anatomical regions: cheek fullness, double chin prominence, upper eyelid thickness, posterior upper arm fat thickness, posterior thigh fat thickness, and abdominal subcutaneous fat thickness assessed via pinch test. Scores ranged from 0 ("no perceptible reduction") to 10 ("reduction achieving the participant's ideal aesthetic outcome"). Body weight was measured at baseline and post-treatment using a calibrated digital scale. For erythema and skin tone, scores ranged from 0 ("no improvement") to 10 ("complete resolution and

ideal skin tone"). Facial vitality was rated from 0 ("no improvement") to 10 ("marked enhancement in vitality and expressiveness"). Gastrointestinal tolerance was evaluated based on discomfort and bowel frequency, with scores ranging from 0 ("no discomfort") to 10 ("severe, intolerable discomfort").

Additional observations, including changes in dry eye symptoms or appetite, were recorded daily by participants and verified by attending physicians during follow-up visits.

Result

General observations

All 11 participants completed the full 40-day oral intervention. Following daily administration of 5 g of 70 kDa HA fragments, all participants reported varying degrees of facial and body subcutaneous fat reduction accompanied by subjective improvement in overall appearance. No participant discontinued treatment or withdrew, indicating excellent compliance and tolerability.

Reduction of facial and body fat

After 40 days of treatment, most participants reported improved facial contour and visibly reduced double chin. Nine participants achieved scores ≥ 7 for both cheek fullness and double chin reduction. Participant 2 rated both parameters as 10, indicating achievement of their ideal aesthetic outcome (Figure 2). Mean reduction scores were 7.2 for cheek fullness, 7.5 for double chin, 7.2 for upper eyelid thickness, 5.8 for upper arm thickness, 5.8 for thigh thickness, and 6.4 for abdominal thickness, demonstrating consistent fat reduction across multiple anatomical regions (Table 1).

All participants experienced body weight reduction, with a mean decrease of 4.2 kg (range: 2-8 kg) (Table 2). Notably, weight loss occurred without dietary restriction or exercise intervention, suggesting a potential direct regulatory effect of oral 70 kDa HA on lipid metabolism.

Improvement in skin condition and facial vitality

Most participants reported noticeable improvements in facial complexion and vitality as early as day 7 (Figure 2). The mean score for reduction in inflammatory erythema was 5.5 ± 0.8, indicating mild-to-moderate improvement. Facial vitality scores were similarly elevated (5.5 ± 0.8), with participants describing brighter skin tone, reduced flushing, and enhanced expressiveness (Table 3).

Gastrointestinal tolerance and additional observations

All participants demonstrated excellent gastrointestinal tolerance to high-dose oral administration, with no reports of gastric pain, bloating, or clinically significant gastrointestinal discomfort during the intervention period. Among participants with pre-existing gastrointestinal symptoms (Cases 10 and 11), rapid symptomatic improvement was observed. Specifically, gastrointestinal comfort scores decreased from a baseline average of 4-5 to 0-1 by day 2 of treatment. In parallel, bowel irregularities associated with gastrointestinal discomfort improved, with

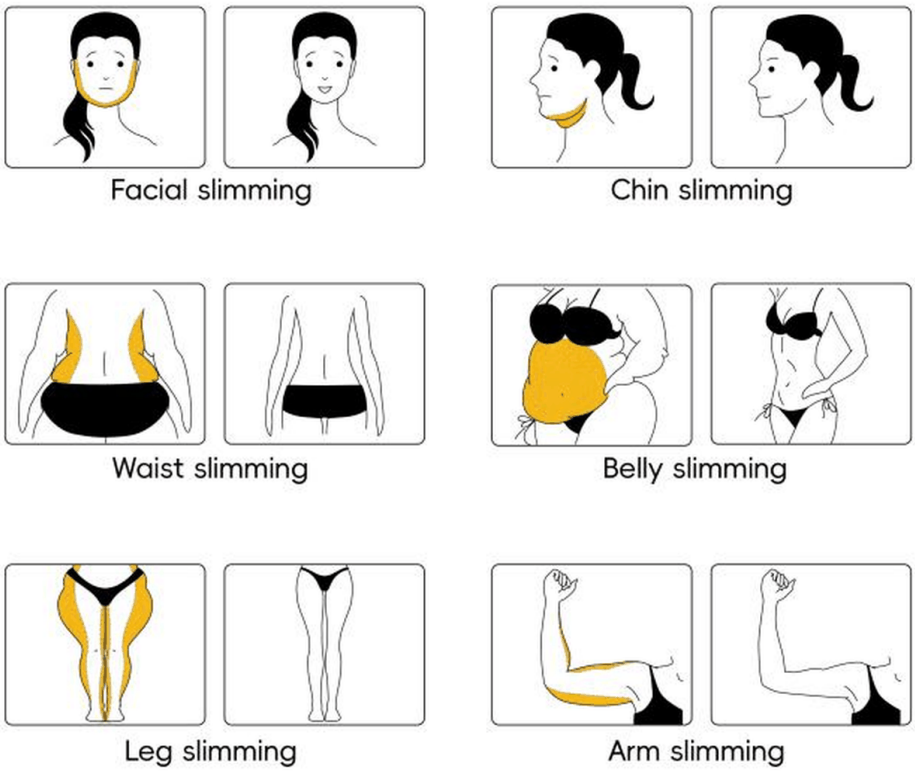

Figure 1: Schematic illustration of the pattern of body fat elimination after injection.

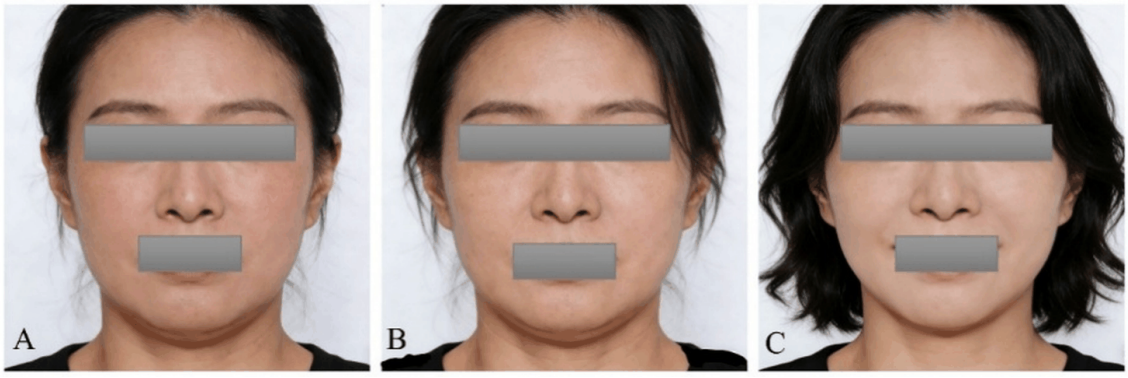

Figure 2: Post-treatment comparison images provided by Participant 2.
A: Before treatment; B: After 7 days of treatment; C: After 40 days of treatment.

Table 1: Subcutaneous fat reduction scores after 40 days of oral treatment (0-10 scale).

Parameter	1	2	3	4	5	6	7	8	9	10	11	Mean ± SD
Reduction in cheek fullness	8	10	8	7	7	7	7	8	7	4	6	7.2 ± 1.4
Reduction in double chin	9	10	8	7	7	8	7	9	8	4	6	7.5 ± 2.4
Reduction in eyelid thickness	8	9	8	7	7	7	7	7	8	4	7	7.2 ± 1.2
Reduction in upper arm thickness	7	8	7	6	6	5	5	6	6	3	5	5.8 ± 1.2
Reduction in thigh thickness	7	8	7	6	5	5	5	6	7	3	5	5.8 ± 1.3
Reduction in abdominal thickness	8	9	7	7	6	6	5	7	7	3	6	6.4 ± 1.4

Table 2: Changes in body weight after 40 days of treatment (kg).

Parameter	1	2	3	4	5	6	7	8	9	10	11	Mean ± SD
Body weight reduction (kg)	3	6	8	4	2	4	5	5	3	2	4	4.2 ± 1.7

Table 3: Scores for reduction in facial erythema and improvement in facial vitality after 7 days.

Parameter	1	2	3	4	5	6	7	8	9	10	11	Mean ± SD
Reduction in inflammatory erythema	5	7	7	5	5	5	5	5	6	5	6	5.5 ± 0.8
Improvement in facial vitality and expressiveness	5	7	6	6	6	6	6	6	6	5	6	5.5 ± 0.8

defecation frequency normalizing from approximately four times per day to once daily. During long-term follow-up, Case 11 reported a persistent subjective sensation of enhanced satiety or reduced gastric capacity at 6 months post-treatment, suggesting a possible mild appetite-suppressing effect.

In addition, two participants with long-standing refractory dry eye symptoms reported complete symptom resolution after 40 days of treatment, with no recurrence during 4-6 months of follow-up.

Discussion

This case series demonstrates that high-dose oral administration of 70 kDa HA fragments (5 g/day for 40 consecutive days) produced consistent clinical benefits across all participants, including reduction of facial and body subcutaneous fat, alleviation of inflammatory erythema, enhancement of facial vitality, and improvement in gastrointestinal comfort. All participants tolerated the intervention well, with no adverse events observed.

The significant reductions in cheek fullness and double chin scores suggest that 70 kDa HA fragments may modulate subcutaneous fat metabolism. This observation is supported by preclinical evidence indicating that low-molecular-weight HA fragments (35-70 kDa) are absorbed via LYVE-1-mediated lymphatic transport [11] and can inhibit adipocyte differentiation while promoting lipid catabolism [5]. The relatively modest overall body weight reduction compared with localized fat reduction may reflect the hydrophilic nature of HA and its capacity for tissue water retention. As body composition was not directly assessed, net weight changes likely represent a balance between fat loss and increased tissue hydration.

The rapid improvement in facial erythema and skin quality aligns with the established anti-inflammatory, antioxidant, and lymphatic circulation-enhancing properties of HA fragments [15,16]. These effects parallel the natural anti-inflammatory phenotype of NMRs, in which high endogenous HA levels confer resistance to chronic inflammation and tissue degeneration. Although NMRs rely on endogenous HA expression whereas this study utilized exogenous supplementation, both approaches may converge on shared signaling pathways, including CD44 and TRPV1.

Improvements in gastrointestinal function observed in several participants are consistent with preclinical

findings showing that oral HA fragments enhance intestinal barrier integrity, upregulate tight junction proteins, and reduce inflammatory injury [17]. Absorption through the mesenteric lymphatic system, as demonstrated by Khandmaa, et al. [11], may enhance systemic bioavailability while minimizing first-pass metabolism.

The resolution of chronic dry eye symptoms in two participants further suggests that oral HA fragments exert systemic mucosal-protective and anti-inflammatory effects beyond the gastrointestinal tract. This cross-tissue efficacy reinforces the concept that HA fragments can modulate conserved biological pathways across multiple organ systems.

Limitations of this study include the small sample size, absence of a control group, and reliance on subjective self-assessment measures. Objective assessments such as imaging-based fat quantification or inflammatory biomarker analysis would strengthen future investigations. Nonetheless, this study represents the first clinical observation suggesting that high-dose oral 70 kDa HA fragments may influence subcutaneous fat metabolism, inflammation, and mucosal protection in humans.

Conclusion

This case series suggests that high-dose oral administration of 70 kDa HA fragments (5 g/day for 40 days) can significantly reduce facial and body subcutaneous fat, producing a discernible facial slimming effect. Improvements in facial erythema, complexion, and vitality were observed within 7 days of treatment initiation. Additionally, gastrointestinal discomfort and refractory dry eye symptoms improved in affected participants. These findings provide preliminary clinical evidence supporting the potential application of oral HA fragments in lipid metabolism modulation and systemic anti-inflammatory interventions.

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Competing Interests

Author have declared that no competing interests exist.

Consent and Ethics Statement

Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

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