Sexual Medicine, 2024, **12**, qfae067
https://doi.org/10.1093/sexmed/qfae067
Original Research

Hybrid high and low molecular weight chains of hyaluronan for clitoral injection is an effective modality treatment for increasing female sexual satisfaction: an interventional, randomized-controlled parallel study

Lina Mohammed Atef, MD[1], Ghada Farouk Mohammed, MD[1], Mohammed Saleh Al-Dhubaibi, MD[2], Mahmoud Soliman, MD[3], Saleh Salem Bahaj, PhD[4,*], Yasser S.N. Saleh, MD[1,2]

[1]Department of Dermatology, Venereology and Sexology, Faculty of Medicine, Suez Canal University, Ismailia, 41522, Egypt
[2]Dermatology, Department of Medicine, College of Medicine, Shaqra University, Dawadmi, 11961, Saudi Arabia
[3]Department of Neuropsychiatry, Ain-Shams University, Cairo, 11772, Egypt
[4]Department of Microbiology and Immunology, Faculty of Medicine and Health Sciences, Sana'a University, Sana'a, 72738, Yemen
*Corresponding author: Department of Microbiology and Immunology, Faculty of Medicine and Health Sciences, Sana'a University, Sana'a, 72738, Yemen. Email: salehbahaj2025@hotmail.com

Abstract

Introduction: Hormonal, behavioral, psychological, surgical, and pharmacopsychological treatment approaches contribute to female sexual dysfunction (FSD).
Aim: The study is conducted to assess the effectiveness of hyaluronan high and low molecular weight hybrid cooperative complexes (hybrid H-HA/L-HA) in treating females with SD and to compare the female sexual function index (FSFI), dermatological life quality index (DLQI), and female genital self-image scale (FGSIS) before and after therapy.
Methods: We divided the 60 female participants into two groups. Hybrid H-HA/L-HA was administered to form pili of 0.25 cc around the clitoris in the direction of clock positions of 12, 3, 6, and 9. In Skene's gland; 0.25 cc for each and 0.5 cc into the corpus/body of the clitoris. Two treatments were held 30 days apart.
The same procedure was repeated on the control group, but with saline as a placebo.
Outcomes: Women completed self-report questionnaires assessing sexual functioning using the FSFI, DLQI, and FGSIS before and after therapy.
Result: There was a significant ($P = 634.152$; $P < .05$) increase in the study group's weekly sexual interactions compared with the controls. The study group showed statistically significant amelioration in desire, arousal, lubrication, orgasm, satisfaction domains, overall score, and a decrease in pain following the first and second injection sessions ($P = .014$, .031, .003, .001, .011, .004, and .011, respectively). A comparison of the results between the two groups revealed significant improvement were found ($P = .025$).
There were significant improvements in the domains of the FGSIS compared with the controls ($P = .026$). The study group showed a substantial improvement in satisfaction with the way their genital area looked, comfort level when allowing a sexual partner to view their genital area, belief that their genitals smell perfectly fine without being self-conscious about them, and overall score ($P = .022$, .031, .003, .001, and .004, respectively) ($P < .05$).
The hybrid H-HA/L-HA sessions resulted in significantly greater positive perceptions and feelings, leisure activities, interpersonal interactions, and general assessments ($P = .021$, .021, and .020, respectively) ($P < .05$).
Clinical Implications: Female individuals with SD experience sexual improvements after hybrid H-HA/L-HA injection.
Strengths and Limitations: This is the first study focusing on female individuals with SD. We recommend conducting the study on a larger population and including their partners.
Conclusion: Hybrid H-HA/L-HA injection for rejuvenating the clitoral injection appears to be a reliable and safe method for enhancing female genital self-image, sexuality, and quality of life.

Keywords: female sexual function; FGSIS; FSFI; DLQI; hybrid H-HA/L-HA; O-shot.

Introduction

According to several studies, the prevalence of female sexual dysfunction (SD) among sexually active women is between 30% and 50%.[1-3] FSD is a diverse set of medical diseases with multiple causes and dimensions that have a negative impact on both physical and psychological health.[4] FSD is a prevalent condition in women of all ages, and it has a negative influence not only on their own female genital self-image but also on their quality of life.[5] FSD is classified into four primary classifications: sexual pain, low desire, low arousal, and orgasmic dysfunction. These criteria closely mirror the FSD criteria, which were revealed in 2013 by the fifth edition of the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM-5).[6] The separate

Received: June 4, 2024. **Revised:** September 4, 2024. **Accepted:** September 15, 2024

classifications of hypoactive female sexual desire disorder and female sexual arousal disorder were combined into a single diagnosis of female sexual interest/arousal disorder. Dyspareunia and vaginismus are also combined into one diagnosis, genito-pelvic pain/penetration disease.[7]

Many treatment modalities are followed for the management of FSD; such as local hormone therapy, counseling, pelvic physiotherapy, vaginal/rectal suppositories, topical lidocaine, capsaicin, vestibulectomy, bupropion, flibanserin, Phosphodiesterase-5 (PDE5) inhibitors (e.g., sildenafil), mindfulness, sex therapy, and yohimbine hydrochloride.[8]

Several complementary minimally invasive treatments have been used, and a few have been reported to have negative side effects, like hyaluronic acid (HA) fillers, calcium hydroxyapatite crystals, and platelet rich plasma (PRP).[9,10]

HA controls the tissue hydration and penetrability of small and large molecules.[11] Human fibroblasts were activated following intradermal administration of HA-containing combinations.[12]

Hybrid cooperative complexes of high and low molecular weight hyaluronan (hybrid H-HA/L-HA) regenerate and enhance wounded and undamaged connective tissue by inducing chemotaxis of stem cells at the point of the administration site, stimulating the production of growth factors.[13] Several investigations have demonstrated that hybrid H-HA/L-HA is safe, with no fibrotic development, infection, or other undesirable responses.[13] Hybrid H-HA/L-HA is non-expansive, nontoxic, and easily incorporated by tissue.

Given the barriers that females with SD face from diagnosis to treatment, as well as the disease's impact on female genital self-image, sexual performance, and quality of life, do women who receive hybrid H-HA/L-HA injections in the clitoris improve the preceding parameters when compared with women of the same age who receive saline?

The objective of this study was to assess the effectiveness of hyaluronan high and low molecular weight hybrid cooperative complexes hybrid H-HA/L-HA in treating females with SD and to compare the female sexual function index (FSFI), dermatological life quality index (DLQI), and female genital self-image scale (FGSIS) before and after therapy. The results also provided insights into the safety and tolerability of the procedure.

Methods

This is an interventional, randomized-controlled parallel trial of females with SD. After receiving a permit from the institutional ethical committee (CMD/DMD/SU/2022/01/076), the investigation was selected to take place in the Dermatological Outpatient Department for 12 months, and in accordance with the provisions of the Helsinki Declaration, each contestant signed a written agreement after being completely informed. Cases requiring medical treatment were assigned to the outpatient unit. Controls included relatives and friends who attended with individuals and provided otherwise healthy escort services to participants visiting the dermatological outpatient department. The Consolidated Standards of Reporting Trials strengthening guidelines were followed (Figure 1).

This study was selected to evaluate the consequences of administering a new nanohybrid complex of hyaluronic acid technology (NAHYCOT)-based filler devised and constructed (WO/2012/032151) for the injection, currently accessible on shelves as (Profhilo®)[14] in treating females with different levels of SD. To assess the Dermatology Life Quality Index (DLQI), Female Sexual Function Index (FSFI), and Female Genital Self-Image Scale (FGSIS) in female with SD before and after of injection of clitoris.

Participants inclusion criteria

Females were sexually active, but they had different levels of sexual impairment [dyspareunia, female orgasmic disorder, hypoactive sexual arousal disorders, or anorgasmia]. Female individuals aged 18 to 60 are capable of consenting.

Participants exclusion criteria

Those with previous episodes of urinary tract disorders, who are pregnant, on a current COVID-19 therapy program, have a body mass index (BMI) greater than 35, have a history of a pelvic floor prolapse, have used hormonal contraceptives or intrauterine devices, have used birth control implants, are taking medication for depression, or have a long-term illness that affects sexual function. In addition, we established that skin collagen integrity can affect sexuality. Our goal with Profhilo® is to boost collagen synthesis and stem cell activation during clitoral injection, thereby improving sexuality.

Participants with inflammatory responses, keloidal variations, immunodeficient conditions, allergy (hypersensitivity), blood diseases such as sickle cell anemia, photointerventions, filler modalities, or treatment within the previous 6 months to 1 year, and infectious diseases such as herpes genitalis were also excluded from the study. In addition, those who declined to provide consent. Following a computer-based random assignment, we selected 98 participants who agreed to participate in the study; however, only 60 females completed the study. They include participants who exhibit numerous symptoms of sex difficulties but have not responded to previous interventions. Prior to beginning therapy, participants provided an extensive health history of presenting illness, sexual history, gynecological history, birth control and hormone therapy history, medications, psych history, and a standardized screener (FSFI, FGSIS, and DLQI).

Physical exam included: general appearance, abdominal examination, presence of dermatological lesions (±biopsy), Q tip testing for vulvodynia, vaginal pH for atrophic vaginitis, microscopy/KOH testing for clue cells, or parabasal cells.

Investigations: thyroid stimulating hormone, prolactin, sex hormone-binding globulin, estradiol, total testosterone, and calculated free testosterone.

Participants were advised not to employ any therapeutic techniques during the trial.

The use of hybrid H-HA/L-HA was a novel approach, yet it has many similarities to PRP administration. Therefore, the selection was based on research employing PRP in female SD management.[15]

Sample size

The sample size was determined using the formula below[16]:

Where:

n is the sample size.

$\mathbf{Z}_{\alpha/2} = 1.96$ (The critical value that divides the central 95% of the Z distribution from the 5% in the tail).

$\mathbf{Z}_{\beta} = 0.84$ (The lower 20% of the Z distribution was separated from the upper 80% by this critical value.)

σ = FSFI estimated standard deviation = 7.21[15]

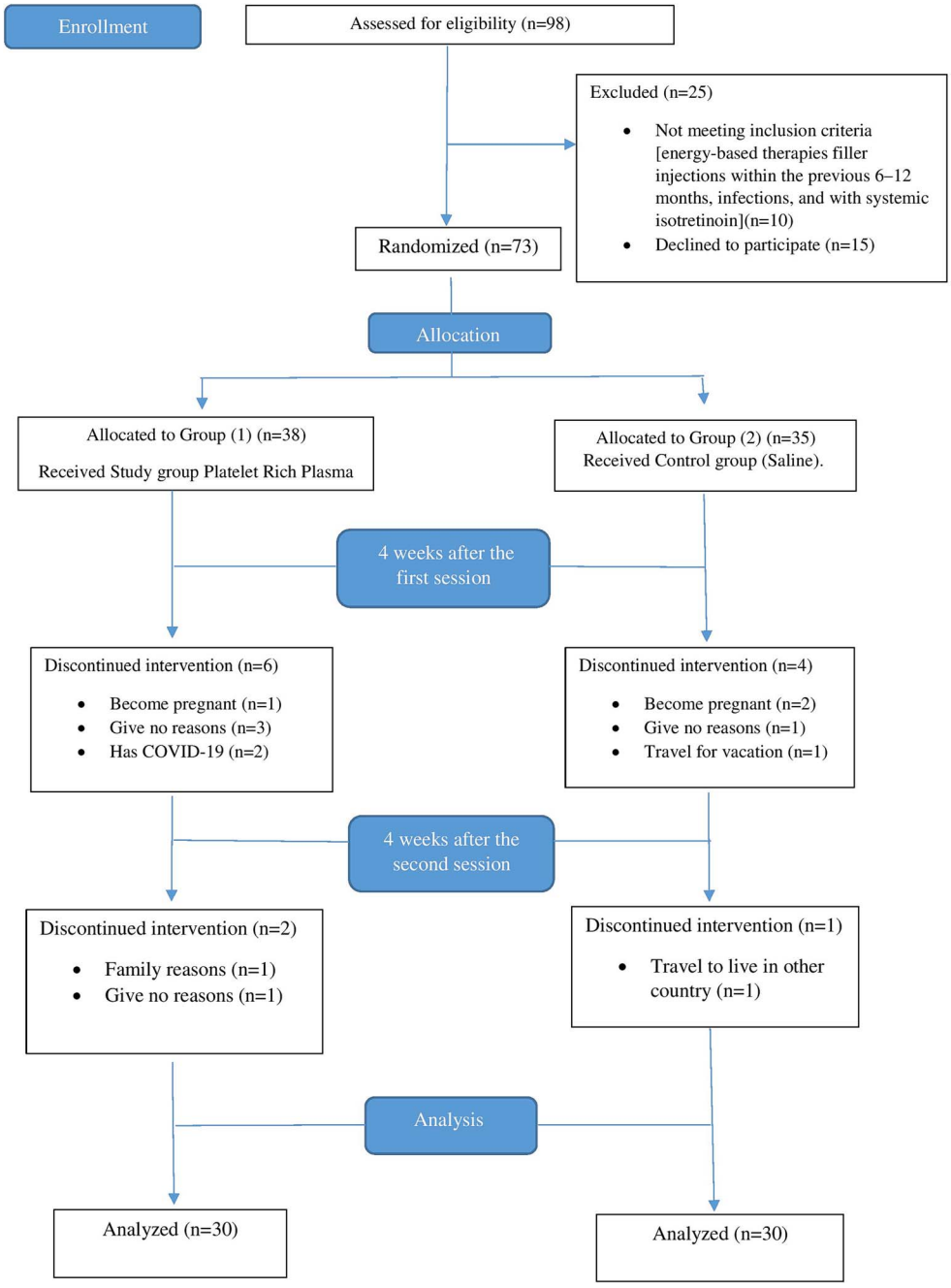

Figure 1. Consolidated standards of reporting trials (CONSORT) flow Diagram,Hybrid H-HA/L-HA = hybrid cooperative complexes of high and low molecular weight hyaluronan.

μ_1 = mean in the study group = FSFI before PRP = 24.31[15]
μ_2 = mean in the control group = FSFI after PRP = 29.63[15]
Therefore, after accounting for a 10% drop rate, the sample size was determined to be 30 individuals.

Participants preparation

The stages were carried out under identical conditions, with equivalent tools, by similar healthcare practitioners, and using an identical approach.

Anesthesia

With occlusion, topical anesthetic cream lidocaine 2.5% was applied for 60 minutes while stimulating diffusion through the mucosal membrane.

Preparation before injection

The surgical region was washed with saline before applying povidone iodine to maintain healthy and non-inflamed skin. The hybrid H-HA/L-HA was sterilely drawn into a syringe.

Position of the participant

After draining the bladder, the patients were placed on the operating board in the dorsal lithotomy position, which accentuated the genital area.

Study group hybrid H-HA/L-HA

Before to obtaining consent, the respondents were sufficiently warned about the innovative therapy. The product under

examination, hybrid H-HA/L-HA is a healthcare tool made and distributed by IBSA Farmaceutici Italia Srl (Lodi, Italy) that includes hybrid H-HA/L-HA with preloaded hypodermic glass syringes for local injections. This study focused on recently built secure hybrid cooperative HA complexes (NAHYCO).[11] The HA content in 2 mL of neutralized sodium chloride physiological solution was 3.2%, with 32 mg of low molecular weight HA and 32 mg of high molecular weight hyaluronic acid. The creation of both high and low molecular HA weights in the single syringe allows for the incorporation of intrinsic HA to be tiered in an approach that incorporates stabilized HA hybrid complexes.[11] The material being researched is in widespread use hybrid H-HA/L-HA and is supported by the study's authors. Hybrid H-HA/L-HA was administered to form pili of 0.25 cc around the clitoris in the direction of clock positions of 12, 3, 6, and 9. The pili were 0.25 cc in Skene's gland each and 0.5 cc in the clitoral area. Hybrid H-HA/L-HA applications were performed using 31-G needles. Two sessions were held 30 days apart.

The control group (saline)

The exact procedure was used with the control group while standardizing the procedure but with saline as a placebo.

Post-treatment protocol

Following the procedure, fusidic acid cream was applied twice daily for a couple of days. Participants who received hybrid H-HA/L-HA received permission to return home and engage in sexual activity within 48 hours of the procedure. Participants were free to continue their normal sexual activities at their usual hours and in their usual fashion.

Assessments

The first assessment was performed at the first visit after patient consent, and the second assessment was performed 1 month later. The study collected sociodemographic clinical data using evaluation methods such as the FGSIS-4,[17] FSFI,[18] and DLQI.[19]

Data on biometrics and socio-demographics

The biodata and sociodemographic personal forms were created using a succinct collection of questions designed to collect information about the individual. Name, level of education, age, and Fitzpatrick skin type classification—type I has the fairest skin and type VI has the darkest—were among the factors discovered.

Female fenital self-image scale

The four-item FGSIS on a four-point likert scale (strongly disagree, disagree, agree, and agree strongly) was used to measure what women think about their sexual organs and their feelings about them.[17]

Female sexual function index

The FSFI examined sexual achievement. The FSFI is a 19-item questionnaire that examines desire, arousal, lubrication, vaginal penetration pain, satisfaction, and orgasm. The total score was calculated, with higher scores indicating better sexual satisfaction.[18]

Dermatological life quality index

The DLQI was designed to measure quality of life. The questionnaire included 10 questions on the participants' current feelings and features of the disease. It addressed signs and symptoms such as itching, pain, and irritation; emotions such as embarrassment, distress, and anger; daily activities such as shopping and housework; clothing, social and recreational activities, physical activity, educational opportunities, sexual behavior, and interpersonal relationships such as those with one's spouse, acquaintances, and family. It has also addressed possible therapies.[19]

Dermatological life quality index-IV

Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, is a widely used manual for diagnosing mental illnesses and is published by the American Psychiatric Association. This was done eliminate out any other potential psychological issues.[6]

Statistical analysis

Data analysis was carried out using IBM SPSS applications (version 25). Demographic data were presented using descriptive statistics, such as percentages, frequency ranges, averages, and standard errors. The outcomes of the chi-square test were the presence of statistically significant differences between category variables. When the chi-square test assumptions were violated, Fisher's considered test was applied. *P*-value less than .05 was considered statistically significant. The analyses were performed using SAS 9.2 software (SAS Institute).

Results

The biographical and anthropometric details of the research population are presented in Table 1. Age, BMI, smoking status, length of marriage ($P = 301.113$, 601.131, 351.130, and 356.201, respectively) and other characteristics did not significantly differ across the groups. Interestingly, after the first and second injection sessions, there was a significant ($P = 634.152$, $P < .05$) increase in the study group's weekly sexual interactions compared with the controls (Table 2). The study group showed a substantial improvement in all categories, including desire, arousal, lubrication, orgasm, satisfaction domains, overall score, and a decrease in pain following the first and second injection sessions ($P = .014$, .031, .003, .001, .11, .004, and .011, respectively) (Table 3). Furthermore, a comparison of the study group results to the controls showed significant improvement ($P = .025$) (Table 3).

In addition, we observed significant improvements in every domain of the FGSIS following the first and second injection sessions of hybrid H-HA/L-HA compared with the controls ($P = .026$). The study group showed a substantial improvement in all categories, including satisfaction with the way their genital area looked, comfort level when allowing a sexual partner to view their genital area, a belief that their genitals smell perfectly fine without being self-conscious about them, and overall score ($P = .022$, .031, .003, .001, and .004, respectively) ($P < .05$) (Table 4).

The initial and subsequent administration of the hybrid H-HA/L-HA sessions resulted in significantly greater positive perceptions and feelings, leisure activities, interpersonal interactions, and general assessments ($P = .021$, .021, and .020, respectively) ($P < .05$; Table 5).

Table 1. Distribution of female's demographic characteristics.

		Study group Frequency (n)	Control group Frequency (n)	Significance test
Age		30.2 ± 3.1	28.4 ± 1.1	301.113
BMI	**Underweight < 18.5**	0	0	601.131
	Normal 18.5-24.9	25	23	
	Over weight 25-29.9	5	7	
	Obese 30-34.9	0	0	
	Extremely obese 35<	0	0	
Smoking	**Yes**	0	0	351.130
	No	30	30	
Residence	**Rural**	0	0	511.125
	Urban	30	30	
Religion	**Muslim**	30	30	202.211
	Non-muslim	0	0	
Sexual orientation	**Heterosexual**	27	27	231.126
	Lesbian	1	1	
	Bisexual	2	2	
	Other	0	0	
Living together (before and after hospitalization for study group)	**Yes**	30	30	149.233
	No	0	0	
Duration of marriage (years)	**< 15**	14	17	356.201
	≥ 15	16	13	
Education	**Middle school**	7	9	311.232
	High school	6	9	
	Associate degree	8	7	
	University	9	5	
Profession	**Civil servant**	6	5	656.211
	Worker	10	12	
	Housewife	9	6	
	Other	5	7	
Chronic illness	**No**	30	30	232.312
	Other	0	0	
Obstetric history	**Duration of marriage (years)**	14.54 ± 6.21	12.23 ± 4.13	154.254
	Duration of complaint	5.32 ± 1.45	2.56 ± 2.48	254.368
	Number of vaginal deliveries	2.45 ± 1.14	2.11 ± 1.94	124.147
	Number of cesarean deliveries	1.25 ± 1.05	1.42 ± 1.41	125.364

n = number *Statistically significant at $P < .05$

Table 2. Comparison of weekly sexual intercourse frequency between control and study groups.

	Study group		Control group		Test Statistics (ANOVA)	*P*
	Average ± SD	Median (min-max)	Average ± SD	Median (min-max)		
Before injection session	**2.2 ± 1.2**	**2 (1-4)**	**2.2 ± 1.2**	**2 (1-3)**	**634.152**	**0.04** *
After first injection session	**3.2 ± 3.2**	**2.2 (1-5)**	**2.1 ± 1.1**	**2 (1-3)**		
After second injection session	**3.6 ± 2.7**	**2.1 (1-6)**	**2.4 ± 1.3**	**2 (1-4)**		

SD = standard deviation Min = minimum Max = maximum p: p value for comparing between the studied group *: Statistically significant at $P \leq 0.05$

Table 3. Female sexual function index of the participants.

	Study group			Control group			ANOVA test *P* value
	Before injection session Mean ± SD	After first injection session Mean ± SD	After second injection session Mean ± SD	Before injection session Mean ± SD	After first injection session Mean ± SD	After second injection session Mean ± SD	
Desire	2.01 ± 1.21	3.5 ± 1.43	4.6 ± 2.31	3.12 ± 1.26	3.23 ± 1.32	3.67 ± 1.44	.014*
Arousal	3.01 ± 1.21	4.13 ± 1.21	5.01 ± 2.21	2.65 ± 1.21	2.10 ± 1.12	2.42 ± 2.21	.031*
Lubrication	2.02 ± 1.21	4.33 ± 1.21	5.23 ± 2.11	2.21 ± 1.23	2.31 ± 2.41	2.12 ± 1.21	.003*
Orgasm	1.34 ± 1.15	3.11 ± 2.21	5.65 ± 2.02	1.12 ± 1.35	2.21 ± 1.21	2.11 ± 2.31	.001*
Satisfaction	2.24 ± 1.32	3.13 ± 1.31	5.23 ± 2.42	2.68 ± 1.12	3.21 ± 1.02	3.14 ± 1.21	.011*
Pain	4.42 ± 1.24	4.76 ± 3.12	5.31 ± 1.22	4.22 ± 2.08	3.32 ± 1.52	4.25 ± 1.21	.011*
Total	19.32 ± 7.72	30.64 ± 4.32	36.58 ± 5.03	21.23 ± 5.22	22.24 ± 4.21	24.31 ± 4.13	.004*
P value	.004*			.07			.025*

SD = standard deviation p: p value for comparing between the studied group *: Statistically significant at $P \leq 0.05$

Table 4. Female genital self-image scale of the participants.

	Study group			Control group			ANOVA test *P* value
	Before injection session Mean ± SD	After first injection session Mean ± SD	After second injection session Mean ± SD	Before injection session Mean ± SD	After first injection session Mean ± SD	After second injection session Mean ± SD	
I am satisfied with the appearance of my genitals	2.1 ± 0.23	3.0 ± 0.10	4.0 ± 0.70	2.3 ± 0.12	2.1 ± 0.13	2.9 ± 0.29	.022*
I would feel comfortable letting a sexual partner look at my genitals	2.5 ± 0.41	2.5 ± 0.50	3.5 ± 0.50	3.1 ± 0.40	3.1 ± 0.31	3.4 ± 0.51	.031*
I think my genitals smell fine	2.4 ± 0.42	2.5 ± 0.55	3.5 ± 0.60	2.6 ± 0.51	2.35 ± 0.11	2.3 ± 0.52	.003*
I am not embarrassed about my genitals	2.5 ± 0.50	3.0 ± 0.23	4.0 ± 0.10	2.4 ± 0.71	2.4 ± 0.22	2.6 ± 0.62	.001*
Total	5.9 ± 0.3	10.1 ± 1.7	13.1 ± 2.7	7.1 ± 0.5	7.1 ± 1.5	6.9 ± 1.5	.004*
P value	0.003*			0.08			.026*

SD = standard deviation p: p value for comparing between the studied group *: Statistically significant at $P \leq .05$

Table 5. Dermatology life quality index characteristics of the studied population between groups.

	Study group			Control group			Test statistics (ANOVA)	*P*
	Before injection session Average ± SD	After first injection session Average ± SD	After second injection session Average ± SD	Before injection session Average ± SD	After first injection session Average ± SD	After second injection session Average ± SD		
Symptoms and feelings	1.57 ± 0.811	1.03 ± 0.11	0.16 ± 0.22	1.12 ± 1.11	1.12 ± 1.12	1.31 ± 2.11	1.121	.021*
Daily activities	0.02 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.151	.520
Leisure	0.31 ± 1.112	1.11 ± 1.12	2.56 ± 0.10	0.32 ± 1.32	0.12 ± 1.12	0.12 ± 1.22	3.112	.021*
Work and school	0.64 ± 0.07	0.32 ± 1.10	0.13 ± 0.12	1.12 ± 0.41	1.02 ± 0.12	1.12 ± 0.22	1.321	0.521
Personal relationships	3.35 ± 0.623	2.10 ± 0.11	0.03 ± 0.12	2.11 ± 0.11	2.11 ± 1.31	2.15 ± 1.21	1.151	.020*
Treatment	3.03 ± 0.325	2.13 ± 0.210	1.04 ± 0.30	3.43 ± 1.23	3.14 ± 1.21	3.52 ± 1.32	3.136	.613
Total	11.01 ± 1.23	13.21 ± 1.20	15.13 ± 1.20	13.32 ± 1.01	13.67 ± 1.12	13.65 ± 2.31	1.135	.313
Test statistics	1.175			3.525			3.124	
P	0.024*			0.714			.017*	

SD = standard deviation p: p value for comparing between the studied group *: Statistically significant at $P \leq .05$

Safety and tolerability

Throughout the course of the investigation, neither the study nor the control groups encountered any unfavorable results or side effects. Furthermore, because it does not enter the body into the renal system, liver, heart, nerves, or other organs, no toxicity has been documented in prior investigations.[20,21]

Discussion

The purpose of this study was to investigate the effects of hybrid H-HA/L-HA injections into the clitoral region on sexual functioning and the participants' impressions of their genitals.

According to the information we have, no investigations have examined the effects of clitoral injection with hybrid H-HA/L-HA on sexual function, although numerous studies have assessed the effects of biological stimulation administration in the intravaginal and intraclitoral areas and their influence on sexual activity.[15,22,23]

About significant changes in the results of the survey, we found that a favorable influence started with the first treatment of hybrid H-HA/L-HA. Following the treatment, we found that patient satisfaction had increased. Hybrid H-HA/L-HA has been applied in several fields, such as wound healing and cosmetic and esthetic procedures.[11,24] It's a widely used, minimally invasive technique with a range of uses.

Many cellular membrane receptors are involved in the response to biostimulants and anti-inflammatory agents.[25]

In the tissue injected with hybrid H-HA/L-HA, transforming, vascular endothelial, epidermal, insulin-like, and fibroblast growth factors (GFs) are among the most important GF generated by activated keratinocytes, fibroblasts, and stem cell adibocytes.[11] GF-1 promotes angiogenesis, connecting tissue renewal, and the migration of immune cells while inhibiting the breakdown of collagen.[26]

Vascular endothelial growth factor (VEGF) stimulates angiogenesis, which improves blood circulation and enables the delivery of nutrients to tissue.[26,27] Fibroblast growth factor is necessary to stimulate angiogenesis in conjunction with VEGF. Platelet GF, tissue GF (TGF), and epidermal GF (EGF) have been shown to considerably boost VEGF secretion in previous research.[26,27] EGF and insulin-like growth factor-1 promote angiogenesis, mesenchymal cell division, and endothelial cell chemotaxis. Hybrid H-HA/L-HA minimizes the healing process and promotes epithelialization. [26,27]

Low molecular weight HA stimulates keratinocyte and fibroblast growth while regenerating and moisturizing the aged skin. D'Agostino et al.[11] explored the technology, rheological advantages, and biological aspects of these materials. high molecular weight HA acts as a dermal scaffolding

agent due to its stronger adhesion to water molecules and interaction with collagen and proteoglycans. Hybrid H-HA/L-HA can stimulate cell growth in face adipose tissue, which includes noncommittal staminal cells that develop into dermal fibroblasts.[28]

The administration of a high-osmolality complex such as a hybrid H-HA/L-HA into a lymphatic vessel-rich area enhances absorption until an osmotic equilibrium is achieved. Water molecules are drawn into the lymphatic partially permeable wall microvascular endothelium, allowing them to move across the interstitium and achieve overall rebalancing, which results in optimal dermal cell proliferation.[29] In tight association with growth factors, hybrid H-HA/L-HA promotes collagen synthesis and angiogenesis, improving the sensory experience, perception, and sexual health. This approach aligns with other less-invasive techniques such as PRP in treating multiple disorders by boosting and remodeling collagen formation, such as stress urine incontinence, perineal scars, and lubrication issues.[16,22]

To the best of our information, no research into the usage of hybrid H-HA/L-HA in the corpus/body of the clitoris has been released. A new age of less-invasive and low-risk intervention strategies has arisen to improve sexual function by boosting female sexual pleasure.[30,31]

At the end of, after the trial, we discovered a significant difference across all FSFI disciplines following two hybrid H-HA/L-HA sessions spaced for four weeks. Following the initial administration, the FSFI characteristics began to improve. The favorable effect became more pronounced as the number of repetitions rose. As a result, the total number of hybrid H-HA/L-HA sessions that must be repeated can be calculated depending on the participant's requirements and the condition's complexity. These outcomes match with earlier ones.[32,33]

Enhancement and remodeling of collagen, elastin, and connective tissue cells improved sexuality and FSFI score,[16] which was consistent with our findings.

Our findings demonstrated a relationship between improved hybrid H-HA/L-HA outcomes and increased satisfaction levels. Furthermore, there was a link between better hybrid H-HA/L-HA administration and age, duration of marriage, and number of vaginal or cesarean birth times. There have been no reports of harmful consequences after vaginal applications yet. There were no negative effects from management in our investigation.

Hybrid H-HA/L-HA injection outcomes varied statistically considerably across all FSFI disciplines and total scores. Furthermore, throughout the total study population, FSFI aspects were substantially linked with hybrid H-HA/L-HA injection. Hybrid H-HA/L-HA administration linked strongly with all FSFI categories and total scores, particularly if they had a long-term claim, a high number of vaginal births, or cesarean deliveries. The study found that hybrid H-HA/L-HA sessions significantly enhanced genital self-image ($P < .05$). Similarly, our study's findings show that genital improvements produced by enhanced collagen synthesis influence female genital self-image. This was the first study to demonstrate a link between collagen development and female genital self-image.

The hybrid H-HA/L-HA injection group had significantly higher sexual activity ($P < .05$). After the intervention, the FSFI scores in the hybrid H-HA/L-HA study groups improved significantly ($P < .05$). This has been backed up by increased nerve-ending sensitivity, hydration, lubrication, and reduced lack of moisture. Other research discovered that genital disorders have an adverse impact on a woman's esthetic and psychosexual life. As a consequence, there was vaginal drying during sexual activity, diminished sexual readiness, reduced pleasure, little or no erotic activity, difficulty producing an orgasm, and dyspareunia.[34] Maaty and associates discussed the same thing in terms of psoriasis, a chronic dermatological disease that produces skin deformity.[35]

Many experts believe that a favorable genital self-image has a direct relationship with sexuality. Our findings indicated that females' sexual motivation and well-being were strongly affected by their perceptions of genital appearance. This was also validated by improved hydration, lubrication, reduced dryness, and increased skin firmness. According to the study findings, participants who underwent both cosmetic operations and vulvoplasty had significantly improved sexual performance. Our research found that positive genital self-image was linked to sexuality, desire, and quality of life. This is consistent with (Andersen 1999),[36] who described women who have robust sexual self-schemas as "humans" who "are emotionally warm and enthusiastically effectively obtainable to intimate relationships and sexual interactions, liberal in their own behaviors to sex, and typically free of awareness, disappointment, or sexual stress." [36] Andersen explored how prior sexual frequency, the severity of the disease, and menopausal state influenced gynecological cancer participants' sexual responsiveness to the impacts of sexual identity. [36] Females with negative sexual orientation were found to be the only significant predictors of sexual attention; those with negative sexual identity reported higher sexual comorbidities following malignancy. [36] Andersen hypothesizes that in the presence of a sexually stressful event, such as cancer, a sexually abusive self-schema results in sexual issues, but positive self-schemas guard against disturbance. [36]

Perceptions and emotions, entertainment, interpersonal interactions, leisure, and sexual activity were substantially related to the positive self-image of genitalia and sexual engagement in lightened genital areas, and our outcomes coincided with those of Berman and associates.[37] Individuals who had poor genital self-image reported less sexual pleasure and more sexual problems.[38-40]

Participants with aged genital skin and mucosae are extremely embarrassed and avoid sex.[40]

In the present investigation, the DLQI was used to determine the nature and severity of the women's sociopsychological difficulties. The findings indicate that participants with low DLQI scores had significantly worse sexual experiences and a negative genital self-image. These findings were consistent with those of other investigations.[41-43] This was the initially conducted study to look at how genital restoration using hybrid H-HA/L-HA affected genital self-image and sexual response in contrast to other rejuvenation methods. To accommodate all scenarios and avoid sex variances, we intended to pursue only one gender. As a result, the scope of this investigation was somewhat limited. Furthermore, only females were researched because sexual disorders in women were not well understood in our own nation.

Strengths and limitations

One of the study's strengths is the use of trustworthy and valid measures for participant assessment, such as FGSIS, FSFI, and DLQI. Some similar study flaws were found in

all self-reported research techniques and research information, including prejudices based on retroactive memories and broader cultural preferences. Moreover, the characteristics of the sample limited how broadly the findings could be applied.

Conclusion

Female genital rejuvenation with the hybrid H-HA/L-HA therapy modality seems to be an easy and effective technique for renewing the genital area. Because of their pro-adipogenic and pro-collagenogenic qualities, hybrid H-HA/L-HA is beneficial. One minimally invasive option for improving female genital self-image, sexuality, and quality of life is hybrid H-HA/L-HA injection.

Author contributions

LA. G.M. MS. YS. and M.A. conceived and performed experiments, wrote the manuscript, and secured funding. G.M. SB. YS and M.A. Performed experiments. G.M. and M.A. provided reagents. LA. G.M., SB YS. and M.A. provided expertise and feedback.

Funding

There are no sponsors or fund for the research; the author supported it.

Conflicts of interest

There are no conflicts of interest.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical approval

Institutional review board and Research Ethical Committee in accordance with the Helsinki Declaration guidelines.

References

1. McCabe MP, Sharlip ID, Lewis R, *et al.* Incidence and prevalence of sexual dysfunction in women and men: a consensus statement from the fourth international consultation on sexual medicine 2015. *J Sex Med*. 2016;**13**(2):144–152. https://doi.org/10.1016/j.jsxm.2015.12.034
2. Nicolosi A, Laumann EO, Glasser DB, Moreira ED Jr, Paik A, Gingell C. Global study of sexual attitudes and behaviors investigators' group. Sexual behavior and sexual dysfunctions after age 40: the global study of sexual attitudes and behaviors. *Urology*. 2004;**64**(5):991–997. https://doi.org/10.1016/j.urology.2004.06.055
3. Starc A, Jukić T, Poljšak B, Dahmane R. Female sexual function and dysfunction: a cross-National Prevalence Study in Slovenia. *Acta Clin Croat*. 2018;**57**(1):52–60. https://doi.org/10.20471/acc.2018.57.01.06
4. Rosen R, Brown C, Heiman J, *et al.* The female sexual function index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther*. 2000;**26**(2):191–208. https://doi.org/10.1080/009262300278597
5. Khajehei M, Doherty M, Tilley PJ. An update on sexual function and dysfunction in women. *Arch Womens Ment Health*. 2015;**18**(3):423–433. https://doi.org/10.1007/s00737-015-0535-y
6. American Psychiatric Association ed. In: Bell CC, ed. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC, USA: American Psychiatric Association; 2013: 429–440.
7. Clayton AH, Valladares Juarez EM. Female sexual dysfunction. *Med Clin North Am*. 2019;**103**(4):681–698. https://doi.org/10.1016/j.mcna.2019.02.008
8. Krakowsky Y, Grober ED. A practical guide to female sexual dysfunction: an evidence-based review for physicians in Canada. *Can Urol Assoc J*. 2018;**12**(6):211–216. https://doi.org/10.5489/cuaj.4907 Epub 2018 Feb 23. PMID: 29485038; PMCID: PMC5994984
9. Kon E, Mandelbaum B, Buda R, *et al.* Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: from early degeneration to osteoarthritis. *Arthroscopy*. 2011;**27**(11):1490–1501. https://doi.org/10.1016/j.arthro.2011.05.011
10. Sclafani AP. Safety, efficacy, and utility of platelet-rich fibrin matrix in facial plastic surgery. *Arch Facial Plast Surg*. 2011;**13**(4):247–251. https://doi.org/10.1001/archfacial.2011.3
11. D'Agostino A, Stellavato A, Busico T, *et al.* In vitro analysis of the effects on wound healing of high- and low-molecular weight chains of hyaluronan and their hybrid H-HA/L-HA complexes. *BMC Cell Biol*. 2015;**16**(1):19. https://doi.org/10.1186/s12860-015-0064-6
12. Avantaggiato A, Girardi A, Palmieri A, Pascali M, Carinci F. Comparison of bio-revitalizing injective products: a study on skin fibroblast cultures. *Rejuvenation Res*. 2015;**18**(3):270–276. https://doi.org/10.1089/rej.2014.1654
13. Mohammed GF, Al-Dhubaibi MS. Triple steps acne scar revision technique: a new combination therapeutic modality for atrophic acne scars. *J Cosmet Dermatol*. 2022;**21**(10):4659–4668. https://doi.org/10.1111/jocd.14944 Epub 2022 Apr 9. PMID: 35348282
14. Cassuto D, *et al.* Safety assessment of highand low-molecular-weight hyaluronans (Profhilo®) as derived from worldwide post-marketing data. *Biomed Res Int*. 2020;8159047.
15. Long C-Y, *et al.* A pilot study: effectiveness of local injection of autologous platelet-rich plasma in treating women with stress urinary incontinence. *Scientific Reports*. 2021;**11**:1584.
16. Dardeer HHM, Mohamed ML, Elshahat AM, Mohammed GF, Gadallah AM. Platelet-rich plasma: an effective modality to improve sexuality in FGM/C. *Sexologies*. 2022;**31**(4):394–402.
17. Mohammed GFAE, kaream, Hassan H. Validity and reliability of the Arabic version of the female genital self-image scale. *J Sex Med*. 2014;**11**(5):1193–1200. https://doi.org/10.1111/jsm.12494
18. Anis TH, Gheit SA, Saied HS, Al kherbash SA. Arabic translation of female sexual function index and validation in an Egyptian population. *J Sex Med*. 2011;**8**(12):3370–3378. https://doi.org/10.1111/j.1743-6109.2011.02471.x
19. Finlay AY, Khan GK. Dermatology life quality index (DLQI)–a simple practical measure for routine clinical use. *Clin Exp Dermatol*. 1994;**19**(3):210–216. https://doi.org/10.1111/j.1365-2230.1994.tb01167.x
20. David-Raoudi M, Tranchepain F, Deschrevel B, *et al.* Differential effects of hyaluronan and its fragments on fibroblasts: relation to wound healing. *Wound Repair Regen*. 2008;**16**(2):274–287. https://doi.org/10.1111/j.1524-475X.2007.00342.x
21. Agolli E, Diffidenti B, Zitti N, *et al.* Hybrid cooperative complexes of high and low molecular weight hyaluronans (Profhilo®): review of the literature and presentation of the VisionHA project. *Esperienze Dermatologiche*. 2018;**20**(1):5–14. https://doi.org/10.23736/S1128-9155.18.00470-3
22. Jb N. O-shot: platelets rich plasma in intimate female treatment. *J Women's Health Care*. 2017;**06**(05):5–14.
23. Goldstein AT, King M, Runels C, Gloth M, Pfau R. Intradermal injection of autologous platelet-rich plasma for the treatment of vulvar lichen sclerosus. *J Am Acad Dermatol*. 2017;**76**(1):158–160. https://doi.org/10.1016/j.jaad.2016.07.037

24. Dicker KT, Gurski LA, Pradhan-Bhatt S, Witt RL, Farach-Carson MC, Jia X. Hyaluronan: a simple polysaccharide with diverse biological functions. *Acta Biomater*. 2014;**10**(4):1558–1570. https://doi.org/10.1016/j.actbio.2013.12.019
25. Vigetti D, Karousou E, Viola M, Deleonibus S, De Luca G, Passi A. Hyaluronan: biosynthesis and signaling. *Biochim Biophys Acta*. 2014;**1840**(8):2452–2459. https://doi.org/10.1016/j.bbagen.2014.02.001
26. Gurtner GC, Werner S, Barrandon Y, Longaker MT. Wound repair and regeneration. *Nature*. 2008;**453**(7193):314–321. https://doi.org/10.1038/nature07039
27. Barrientos S, Stojadinovic O, Golinko MS, Brem H, Tomic-Canic M. Growth factors and cytokines in wound healing. *Wound Repair Regen*. 2008;**16**(5):585–601. https://doi.org/10.1111/j.1524-475X.2008.00410.x
28. Pessa JE, Nguyen H, John GB, Scherer PE. The anatomical basis for wrinkles. *Aesthet Surg J*. 2014;**34**(2):227–234. https://doi.org/10.1177/1090820X13517896
29. Redbord KP, Busso M, Hanke CW. Soft-tissue augmentation with hyaluronic acid and calcium hydroxyl apatite fillers. *Dermatol Ther*. 2011;**24**(1):71–81. https://doi.org/10.1111/j.1529-8019.2010.01380.x
30. Emhardt E, Siegel J, Hoffman L. Anatomic variation and orgasm: could variations in anatomy explain differences in orgasmic success? *Clin Anat*. 2016;**29**(5):665–672. https://doi.org/10.1002/ca.22703
31. Puppo V, Gruenwald I. Does the G-spot exist? A review of the current literature. *Int Urogynecol J*. 2012;**23**(12):1665–1669. https://doi.org/10.1007/s00192-012-1831-y
32. Runels C, Melnick H,Debourbon E, Roy L. A pilot study of the effect of localized injections of autologous platelet rich plasma (PRP) for the treatment of female sexual dysfunction. *J Women's Health Care*. 2014;**3**(4):169. https://doi.org/10.4172/2167-0420.1000169
33. Sukgen G, Ellibeş Kaya A, Karagün E, Çalışkan E. Platelet-rich plasma administration to the lower anterior vaginal wall to improve female sexuality satisfaction. *Turk J Obstet Gynecol*. 2019;**16**(4):228–234. https://doi.org/10.4274/tjod.galenos.2019.23356
34. Hassanin IMA, Helmy YA, Fathalla MMF, Shahin AY. Prevalence and characteristics of female sexual dysfunction in a sample of women from upper Egypt. *Int J Gynaecol Obstet*. 2010;**108**(3):219–223. https://doi.org/10.1016/j.ijgo.2009.09.031
35. Maaty ASHA, Gomaa AHA, Mohammed GFA, Youssef IM, Eyada MMK. Assessment of female sexual function in patients with psoriasis. *J Sex Med*. 2013;**10**(6):1545–1548. https://doi.org/10.1111/jsm.12119
36. Andersen BL. Surviving cancer: the importance of sexual self-concept. *Med Pediatr Oncol*. 1999;**33**(1):15–23. https://doi.org/10.1002/(SICI)1096-911X(199907)33:1<15::AID-MPO4>3.0.CO;2-L
37. Berman L, Berman J, Miles M, Pollets D, Powell JA. Genital self-image as a component of sexual health: relationship between genital self-image, female sexual function, and quality of life measures. *J Sex Marital Ther*. 2003;**29**(sup1):11–21. https://doi.org/10.1080/713847124
38. Benabe E, Fuentes Y, Roldan G, Ramos M, Pastrana M, Romaguera J. The perceptions of female genital self-image and its associations with female sexual distress. *Int J Gynaecol Obstet*. 2021;**157**(1):90–95. https://doi.org/10.1002/ijgo.13827
39. Dewitte M, Reisman Y. Clinical use and implications of sexual devices and sexually explicit media. *Nat Rev Urol*. 2021;**18**(6):359–377. https://doi.org/10.1038/s41585-021-00456-2
40. Fudge MC, Byers ES. An exploration of psychosocial factors associated with female genital self-image. *Gend Issues*. 2020;**37**(2):153–172. https://doi.org/10.1007/s12147-019-09242-2
41. Nappi RE, Cucinella L, Martella S, Rossi M, Tiranini L, Martini E. Female sexual dysfunction (FSD): prevalence and impact on quality of life (QoL). *Maturitas*. 2016;**94**:87–91. https://doi.org/10.1016/j.maturitas.2016.09.013
42. Papadopoulos L, Bor R, Legg C. Coping with the disfiguring effects of vitiligo: a preliminary investigation into the effects of cognitive-behavioural therapy. *Br J Med Psychol*. 1999;**72**(3):385–396. https://doi.org/10.1348/000711299160077
43. Parsad D, Dogra S, Kanwar AJ. Quality of life in patients with vitiligo. *Health Qual Life Outcomes*. 2003;**1**(1):58. https://doi.org/10.1186/1477-7525-1-58