Is hyaluronic acid filler still a potential risk factor for an autoimmune reaction?

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ABSTRACT

Background: Rejuvenation of the skin with hyaluronic acid (HA) filler is considered to be one of the most favourable procedures in the field of aesthetics. Nevertheless, some adverse effects still occur though infrequently, and are associated with its use. Previous research has suggested that HA filler may stimulate antibodies. Consequently, an investigation of the immune interactions associated with use of HA filler is an important area for investigation.

Objectives: The aim of this research is to investigate whether HA filler influences the initiation of an autoimmune reaction in healthy women who had received HA filler by screening for autoantibodies in the blood. Results will be compared with age-matched apparently healthy control women who did not receive the filler.

Methods: Serum samples were obtained from 44 females who had received HA filler and 44 females who had not as a control group. The enzyme-linked immunosorbent assay (ELISA) technique was utilised to measure serum concentrations of anti-Thyroglobulin (Tg), anti -thyroid peroxidase (TPO), rheumatoid factor (RF), anti-nuclear antibody (ANA) and anti-centromeres.

Results: The number of women who tested positive for the measured autoantibodies was not statistically significant (p=0.803) between those who had received HA filler (n=10/44, 25%) and the control group (n=11/44, 22.7%).

Conclusion: Based on our result HA filler procedures do not induce an autoimmune reaction in women who received HA filler compared to controls. And consequently, HA filler procedures are relatively safe, and these results contradict the findings of other non-controlled works.

KEY WORDS:
Hyaluronic acid (HA); filler; autoantibodies; autoimmune diseases; skin

INTRODUCTION

Filler injections, in general, are popular cosmetic intervention for individuals seeking non-invasive rejuvenation.[1] The main use of filler is the correction of soft tissue loss, arising due to injury, ageing or disease. However, with the rising popularity and awareness, dermal fillers are increasingly being used for volume enhancement and replacement practices.[2]

Hyaluronic acid (HA) fillers are considered of highest standard among dermal fillers.[3] HA fillers were originally obtained from animals such as rooster combs. However, currently most HA filler products are obtained through bacterial fermentation, with equine streptococci.[4]

HA is a glycosaminoglycan consisting of regularly-repeating non-sulphated disaccharide units of glucuronic acid and N-acetylglucosamine.[5] HA is found in most connective tissues, and in the vitreous humour of the eye, and it is responsible for maintaining the structural integrity of other tissues.[6]

Recently, Sharquie et al. showed that HA can be used in the treatment of autoimmune diseases such as morphea (scleroderma) and systemic sclerosis. For several years thereafter, although there was no activation or induction of any autoimmune diseases, HA injections were shown to induce new collagen formation.[7]

Several adverse effects have been found to be associated with the use of HA filler.[8] These adverse effects can be categorised as: those that occur in the period immediately following treatment; those that occur up to several days post-therapy; and delayed events, that can occur weeks to years after treatment.[9] Early-onset adverse events include redness, swelling, bruising, itching and pain or tenderness at the site of the injections, following treatment. This may also result due to subsequent infection.[10]

Transient swelling at the site of injection is normal for all dermal fillers and usually dissipates within seven days of the treatment. However, some individuals who are injected with HA filler may develop an immunological response such as angioedema (antibody-mediated oedema). This is due to the IgE-antibody mediated immune response; such a response is known as a Type I hypersensitivity reaction.[8,11] Type I hypersensitivity occurs within minutes or hours of exposure to HA filler. Oedema may be limited to the site of injection, or the reaction may be severe. Anaphylactic shock has also been reported.[12]

Recipients may also develop non-antibody-mediated (delayed) oedema, in which T-lymphocytes, rather than antibodies, mediate oedema; known as type IV delayed hypersensitivity reactions.[13] These delayed reactions are characterised by erythema, induration, and oedema, and are known to occur between 48-72 hours after the injection of the filler.[14] The foreign-body granuloma is another type of immunological reaction and may occur when the immune

system responds to a foreign body that cannot be contained by the usual mechanisms. This reaction can develop several months or even years after the injection and presents as red, firm papules or nodules.[12] Biofilms can also be associated with HA filler injections.[15]

Autoimmune diseases are complex conditions in which the immune system attacks healthy tissue. This can lead to a loss of self-tolerance and an assault on endogenous cells. A reduced tolerance towards self-antigens or modified self-antigens can trigger autoantibody production.[16] The generation of autoantibodies plays a crucial role in the pathogenesis of many diseases, as these autoantibodies can mediate both systemic inflammation and tissue injury.[17]

There are some reports in the literature that HA fillers might induce immune reactions in the form of autoantibodies and cytokine release and hence, patients with an autoimmune disease, such as systemic lupus erythematosus (SLE) are not advised to have HA fillers.[12,18,19] Unfortunately, there is insufficient evidence and knowledge about adverse effects with HA fillers, despite their use globally. Consequently, this study intends to explore this gap in clinical knowledge. Should a correlation exist between HA use and autoimmune adverse effects, then this question whether autoantibody testing should be mandatory for all individuals who choose HA filler injections.

This study aims to investigate the immunological effect of HA filler on Iraqi women, by investigating whether it has a role in the formation of autoantibodies.

SUBJECTS AND METHODS

This study was approved by the scientific ethics committee of the College of Medicine, University of Baghdad. The immunological tests were done in the Teaching Laboratories, Medical City, and in the College of Medicine. This study was conducted from December 2018 to December 2019 and involved 88 females aged between 22–65 years. After the full history of the participants was obtained and a complete medical examination was done by a specialist to exclude any individuals who had any clinical suspicion of autoimmune disease. Subject with family histories of autoimmune disease were excluded. In addition, subjects who have been injected with botulinum toxin were excluded. All subjects had histories of receiving recurrent HA injections for the previous few years and at the time of examination were included, while those who had received all their recurrent injections for one year and less were excluded.

Blood samples were collected from subjects who attended a private dermatology and cosmetology clinic. Information regarding the objectives and procedures was given to all participants of both study groups and formal consent was obtained before the onset of the study.

All the 88 women were divided into two groups. First, 44 women received an HA filler (WRHA) at least twice, with the most recent injection having occurred within the previous four-to-six months. A second group was made up of 44 who had not received HA filler (WNRHA) controls.

Blood samples were collected in gel tubes and the serum was removed by centrifugation at 1000-3000 rpm for 10 minutes. It was then frozen at -20°C. Each serum sample was analysed for anti-Tg, anti-TPO, RF and anti-centromeres by enzyme-linked immunosorbent assay (ELISA) (euroimmune Company, Germany). The serum ANA level was determined using ANA-8S (detection of IgG antibodies against 8 different cellular and nuclear antigens: U1-snRNP 70 kDa, SS-B, SS-A 60/52 kDa, Scl-70, Cenp-B, Jo-1, snRNP complex (snRNP/Sm), Sm) ELISA kits (Aesku.group, Germany), according to the manufacturer's instructions. The absorbance was measured at 450 nm using a plate reader.

Statistical analysis

Statistical analysis was conducted using the SPSS statistical package (Version 20; SPSS, IBM), and Microsoft Office Excel (2010) was used to create the graphics. A chi-squared (χ^2) test was employed to compare the qualitative variables (demographic parameters and assays as positive or negative results), and a student's T-test, an analysis of variance (ANOVA) test, and a least significant difference (LSD) test were used to compare the quantitative variables. The statistically significant difference (P-value) was set at $p < 0.05$.

RESULTS

The age range of the WRHA group was 22-62 years, with a mean of 37.57±1.512 years. That of the 44 apparently WNRHA control group was 24-65 years with a mean of 38.32 ±1.625 years. The results indicate that there were no statistically significant differences (p=0.736) between the ages of the two groups, but Table I shows a not significant difference (p=0.792) between the age distribution between the two groups.

± The results of the Anti-Tg assay show a not significant difference (*p*=1.000) between the control and WRHA groups (Negative (38, 86.4%) and Positive (6, 13.6%)) Table I, Whereas, mean of anti-Tg assays revealed that highly significant difference (p<0.001) with sharply increased mean level of positive anti-Tg in sera of control group (376.468± 86.623) more than Negative anti-Tg (22.997±2.898), and positive anti-Tg in sera of WRHA group (356.793±171.4) more than negative anti-Tg (20.764±3.698). A not significant difference (p=0.824) was found between mean of positive anti-Tg in the sera of the control group (376.468±186.623) and the WRHA group (356.793±171.4). There was also a not significant difference (p=0.949) between mean of Negative anti-Tg (22.997±2.898) in the sera of the control group and the in the WRHA group (20.764±3.638). This data is shown in Table II.

The results show a not significant difference (p=0.367) of anti-TPO assay between the two groups and an increase in the frequency and percentage of negative anti-TPO in the sera of the WRHA group (36, 81.8%) and of the control group (39, 88.6%) compared to the positive results of women in the WRHA group (8, 18.2%) and women in the control group (5, 11.4%). See Table I

An examination of the mean study of anti-TPO assays shows a highly significant difference (p<0.001), with hardly elevation in mean level, between the positive anti-TPO in the sera of the

Table I: Distribution of parameters among studied groups

Parameters		Studied groups		Pearson Chi-Square (p -value)
		WNRHA filler (Control)	WRHA filler	
Total (N)		44	44	
Age groups /years	20-30	14 (31.8%)	13 (29.5%)	p=0.792
	31-40	12 (27.3%)	16 (36.4%)	
	41-50	12 (27.3%)	9 (20.5%)	
	51-60	6 (13.6%)	6 (13.6%)	
Anti-thyroglobulin (Tg)	Positive	6 (13.6%)	6 (13.6%)	p=1.000
	Negative	38 (86.4%)	38 (86.4%)	
Anti-TPO	Positive	5 (11.4%)	8 (18.2%)	p=0.367
	Negative	39 (88.6%)	36 (81.8%)	
Rheumatoid factor (RF)	Positive	1 (2.3%)	1 (2.3%)	p=1.000
	Negative	43 (97.7%)	43 (97.7%)	
ANA-8S	Positive	2 (4.5%)	1 (2.3%)	p=0.557
	Negative	42 (95.5%)	43 (97.7%)	
Total assays results	Positive	10 (22.7%)	11 (25%)	p=0.803
	Negative	34 (77.3%)	33 (75%)	

Table II: Mean distribution of serum anti-Thyroglobulin, anti-TPO according to studied groups

Assays		Studied groups		ANOVA test (p -value)	LSD test (p -value)
		WNRHA filler (Control)	WRHA filler		
		Mean ± Std. Error	Mean ±Std. Error		
Anti-Tg	Positive	376.468±186.623	356.793±171.4	p<0.001	P1=0.00 HS
					P2=0.824 NS
	Negative	22.997±2.898	20.764 ±3.698		P3=0.949 NS
					P4=0.00 HS
Anti-TPO	Positive	273.378±118.072	345.069±108.697	p<0.001	P1=0.00 HS
					P2=0.240 NS
	Negative	13.625±1.913	10.265±1.116		P3=0.891 NS
					P4=0.00 HS

*P1= WRHA filler – Positive Vs WRHA filler – Negative,
P2= WRHA filler – Positive Vs WNRHA filler (Control) – Positive,
P3= WRHA filler – Negative Vs WNRHA filler (Control) – Negative &
P4= WNRHA filler (Control) – Positive Vs WNRHA filler (Control) – Negative.
* NS= Not significant (p >0.05) & HS= Highly significant (p<0.01).

Table III: Mean distribution of age, serum rheumatoid factor (RF), ANA-8S, anti-centromere according to studied groups

Parameters	Studied groups		T-test (p -value)
	WNRHA filler (Control)	WRHA filler	
	Mean ± Std. Error	Mean ± Std. Error	
Total (n)	44	44	
Age	38.32±1.625	37.57±1.512	p=0.736
Rheumatoid Factor (RF)	6.738±0.6548	5.669±0.7904	p=0.301
Anti-Centromeres	2.802±0.0159	2.758±0.0172	p=0.061
ANA-8S	0.389±0.0301	0.369±0.0239	p=0.612

control group (273.378±118.072) and the Negative anti-TPO (13.625±1.913), and the positive anti-TPO in the sera of the WRHA group (345.069±108.697) with the Negative anti-TPO (10.265±1.116).

Moreover, a not significant difference (p=0.24) exists between mean of Positive anti-TPO in sera of the control group (273.378±118.072) and the Positive anti-TPO in sera of WRHA group (345.069±108.697). There was also a not significant difference (p=0.891) once more between mean of Negative anti-TPO (13.625±1.913) in the sera of the control group and the Negative anti-TPO (10.265±1.116) in sera of WRHA group. This data is shown in Table II.

A not significant difference (p=1.0005) was noted alongside a similar trend in frequency in serum RF between the negative results of the control and WRHA groups (43, 97.7%). Similar results were shown in terms of Positive RF values (1, 2.3%) (see Table I). There appeared to be a statistically not significant difference (p=0.301), with a slight increase between the RF mean values of the control group (6.738±0.6548) and the WRHA group (5.669±0.7904) (see Table III).

The mean serum anti-centromere assay results in the control group (2.802±0.0159) were comparable to those of the WRHA group (2.758±0.0172). However, this difference was not statistically significant (p=0.061). All of the results of the anti-centromeres test for apparently healthy women in both studied groups were negative. (see Table III).

The data shows that the percentage of negative serum ANA-8S in the control group (42, 95.5%) was higher than the positive results (2, 4.5%). The WRHA group presented with a similar finding of serum ANA-8S assays results negative (43, 97.7%) and positive (1, 2.3%)). This was a not significant difference (p=0.557). A statistically not significant difference (p=0.612) was found between the mean outcome of serum ANA-8S assays results in sera of the control group (0.389±0.0301) and of the WRHA group (0.369±0.0239) (see Table III).

There was a not significant difference (p=0.803) between the number of subjects have a positive result in total autoantibodies test between both study groups, where the number of positive results in the WRHA groups was 25% (n=11/44) and in the control group was 22.7% (n=10/44) (see Table I).

DISCUSSION

Many research have reported about the presence of immune reactions to HA fillers.[14] It has been observed that the use of dermal fillers may lead to autoimmune disease or accelerate its progress, and thus, autoimmune patients are warned against using dermal fillers.[12,20] We examined to whether a statistically significant difference existed in the levels of circulating antibodies – namely anti-Tg, anti-TPO, RF, serum anti-centromeres and ANA-8S – between apparently healthy women (*n*=44) who had received at least two HA filler injections and an age-matched healthy control female subjects women (*n*=44) who had not.

In our study, the anti-Tg results showed no statistically significant difference between the two study groups. In each group, there was a positive result (*n*=6/44, 13.6%). As many studies have shown that anti-Tg circulating antibodies can be detected in about 10-15% of healthy young subjects of the general population.[21,22] We can conclude that the positivity of anti-Tg has no significant relationship with injections of HA fillers.

The anti-TPO antibodies showed a statistically not significant difference between the study filler group with a positive result (n=8/44, 18.2%) with those apparently healthy women (n=5/44, 11.4%). Many studies had shown that 10–15% of normal individuals can have an elevated anti-TPO titre.[23,24] So HA filler had no effect on raising anti-TPO antibodies levels in our study. The low positivity of anti-Tg and anti-TPO in this study had no pathological effect on individuals using HA fillers.

Our study showed that HA filler had no effect on the level of RF because statistically not significant differences were observed between women who received the HA filler and the control. The level of RF was positive for one woman only (n=1/44, 2.3%) in each study group. A number of studies have noted that 5–10% of healthy adults are RF seropositive.[25,26] This could explain the single positive result in each group.

The positivity for ANA in the group of women who had received HA filler was *n*=1/44 (2.3%) which had no statistically significant difference from the control group which showed two women (*n*=2/44, 4.5%) positive for ANA, These values can be attributed to the percentage of the ANA in healthy individuals which is up to 20%.[27] Accordingly, ANA could be assessed as normal rather than pathological. However, none of the subjects in the two groups developed any positivity to anti-centromeres. Therefore, we can say that HA filler plays no role in the increase of anti-centromere antibodies.

HA filler has been shown by some previous studies to be safe in certain patients with autoimmune disease. Most recently, Sharquie et al.,[7] showed that HA is a useful therapeutic agent in the treatment of sclerosis in patients with scleroderma (morphea) but did not exacerbate the disease in any patient. Hence, the use of HA is justified in patients with autoimmune disease, especially morphea. Ponzo et al.,[28] assessed the safety of a range of corrective cosmetic treatments, including HA, for facial defects in a retrospective study of patients with autoimmune connective tissue disease. They found no exacerbation of the severity of the disease or worsening of their symptoms, suggesting that HA fillers can be safely used for this disease group.

The findings of our study demonstrated that there was no statistically significant increase in the autoimmune response that could be induced by HA fillers in women when compared with an age-matched female control group. Although some retrospective studies have shown induction of autoantibodies by HA injection, these studies were limited to only seven cases with no healthy control.[29]

Our study suggest that HA fillers are not unsafe in otherwise healthy patients with regards to an antibody response. However, they have the potential to cause an immediate and delayed allergic reaction which resolves spontaneously over time and has no apparent connection with autoimmune diseases. Fillers can also have additional side effects like migration and biofilm formation hence consent should be taken from individuals.

CONCLUSION

This is the first study to challenge the findings of the previous literature showing that HA filler can induce autoantibodies and autoimmune diseases, leading to many doctors advising against these fillers for patients with autoimmune diseases. As the findings of this study demonstrates, there is no significant difference in the number of individuals showing an antibody response for anti-Tg, anti-TPO, RF, serum anti-centromere and ANA-8S when compared to a control group. These antibodies are important markers of an autoimmune response in a range of autoimmune diseases including scleroderma and thyroid autoimmunity. The lack of a significant difference in positive tests for these antibodies in serum samples suggests that HA fillers are unlikely to be a risk factor for the development of the autoimmune disease. Accordingly, physicians may advice the use of HA injections to healthy patients or patients with an autoimmune disease without significant risk.

LIMITATION

The limitations of this study include lack of randomisation of the subjects, lack of baseline result of the immunological markers in the subjects and no placebo have been administrated to the control group. So further studies are strongly recommended with a larger sample size as a random placebo study to have more conclusive and confirmatory findings.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest regarding the publication of this article.

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