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REVIEW PAPER

# The use of hyaluronic acid fillers in patients with autoimmune endocrinopathies; in particular, women with Hashimoto's disease – hints for aesthetic doctors

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## Abstract

The increase of the incidence of autoimmune diseases and, at the same time, a significant surge in the number of regenerative/anti-aging medicine treatments carried out, raises the need to systematise the current knowledge on the safety of the use of hyaluronic acid fillers in patients with autoimmune diseases and to frame management guidelines for aesthetic doctors. One of the most prevalent autoimmune diseases is chronic lymphocytic thyroiditis, so-called Hashimoto's disease, which affects one in every 5–10 women who visit a regenerative medicine doctor. Women in the perimenopausal and menopausal period, aged 40–54 years, were the single largest target group for aesthetic treatments. At the same time, Hashimoto's disease, similarly to other autoimmune disorders, constitutes a contraindication to most treatments with hyaluronic acid fillers and biostimulators. Due to the dysfunction of the immune system in this group of patients, there is a higher risk of adverse side effects, especially those of immunological nature. Based on the available literature, the incidence of adverse reactions after the use of hyaluronic acid-based fillers amounts to 0.01–1% and is undoubtedly underestimated. The most typical one is recurrent oedema and granulomas. The following paper reviews the existing literature on the safety of hyaluronic acid fillers in patients with autoimmune endocrinopathies.

**Key words:** autoimmune diseases, hyaluronic acid, Hashimoto's disease.

## Introduction

The worldwide prevalence of autoimmune diseases continues to rise, and according to epidemiological data these diseases affect 3–5% of the global adult population, with more than double the prevalence in women compared to men. The onset of these conditions peaks between the ages of 40 and 50 years [1]. One of the most prevalent is chronic lymphocytic thyroiditis, also known as Hashimoto's disease, in which the thyroid gland is gradually being damaged over the years, reducing hormone production and developing hypothyroidism. The prevalence of Hashimoto's disease with overt clinical hypothyroidism is estimated at 2–3%, while the subclinical form is found much more often and affects 4–10%. It occurs 5–10 times more frequently in women than in men, and the peak incidence is between the ages of 30 and 50 years [2–4]. Chronic lymphocytic thyroiditis is also more common in people with the history of other autoimmune diseases, such as vitiligo, Addison-Biermer anaemia, celiac disease, or type 1 diabetes mellitus [5]. Factors predisposing to its development are genetic (HLA polymorphism, CTLA 4, PTPN22, CD 40, ILR2) and environmental, such as tobacco smoking, bacterial and viral infections, exposure to chemical compounds: phthalates, bisphenol, iodine, or alterations in the composition of the microbiome, which lead to an impaired balance between the mechanisms of autotolerance sustained and regulated by T and B lymphocytes [5]. The autoimmune background of the disease was found in the 1960s and was associated with the presence of antibodies against thyroid peroxidase and against thyroglobulin, as well as lymphocytic infiltration in the thyroid gland. Antibodies against thyroperoxidase are found in 90% of patients, and against thyroglobulin in 80%, but they are also present in 15–20% of healthy individuals [6]. However, anti-TPO or anti-Tg antibodies may not be found in 25% of patients with Hashimoto's disease, as observed in the NHANES III study [7]. No correlation was noted between the levels of TPOAb antibodies and the severity of the disease. Nor has it been shown that damage to the thyroid gland is caused by direct involvement of antibodies. These destructive effects on the thyroid gland result from abnormal functioning of the immune system, with Th1 helper lymphocytes secreting cytokines that stimulate cytotoxic lymphocytes and NK (natural killers) cells to directly damage thyrocytes, and cytokines that stimulate thyroid cells to apoptosis [5]. The diagnosis of Hashimoto's disease is based on

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the finding of increased levels of anti-TPO antibodies in an individual with either goitre or atrophic thyroid and hypothyroidism. No effective causal treatment for chronic lymphocytic inflammation is available to inhibit the destruction of the thyroid gland; notably, it is not immunosuppressive therapy. The disease is managed by compensation of thyroid dysfunction [2].

## Epidemiology of aesthetic medicine procedures

At the same time, the number of people undergoing anti-aging medicine treatments is growing year on year, with 35.5 million aesthetic medicine and plastic surgery procedures performed in the United States in 2022, up more than 11% from 2021, almost 6 times more frequently in women than in men [8]. The most common were treatments with botulinum toxin type A and dermal fillers such as hyaluronic acid and calcium hydroxyapatite. In 2022, the number of filler treatments in the United States reached 4.5 million, of which more than 80% were performed with hyaluronic acid (HA) products, compared to about 600,000 such treatments in 2016 [8]. Women in the perimenopausal and menopausal period, aged 40–54 years, were the single largest target group for aesthetic treatments [8]. Based on epidemiological data, an average of one in five carry anti-TPO antibodies, while one of the established contraindications for the use of tissue fillers is autoimmune diseases, including Hashimoto's disease.

Dermal fillers have been available for more than 40 years, but over time the manufacturing technology, and consequently the quality and safety of the products, have significantly improved. Dermal fillers made their debut in the 1970s, and initially consisted of animal-derived collagen, which was used as dermal implants. Among others, bovine collagen or collagen derived from cows was used. The products were known as Zyderm and Zyplast. The animal collagen was treated by the human organism as a foreign body, so an allergy test was performed before the procedure to rule out type 1 hypersensitivity. It often caused oedema and did not yield long-lasting satisfactory results. Bovine collagen, as well as some human collagen fillers, were used until the early 2000s, when the United States Food and Drug Administration (FDA) approved the use of hyaluronic acid fillers. Hyaluronic acid is a polysaccharide belonging to the glycosaminoglycan group, found in all organisms. It is one of the compounds with an identical chemical structure in bacteria and mammals. It is a natural substance that can be found in almost every cell of our body [9]. The gel matrix of hyaluronic acid acts as a scaffold to bind structural proteins such as collagen and elastin. As a non-organ-specific molecule, it presents a minimal risk of immunogenicity, and therefore, due to its stability at the site of implantation, it is the molecule of first choice for use as a dermal filler in anti-aging medicine treatments [9]. Its size and shape correspond with healthy or inflamed tissue, and the interaction of hyaluronic acid (HA) with immune cells can influence their response. Specifically, higher molecular weight HA tends to predominate in healthy tissues, while when tissue is damaged and/or infected, HA is degraded, resulting in an inflammatory response. After the inflammation subsides, the extracellular matrix is restored, and tissues are again dominated by HA in the form of a large glycosaminoglycan [9].

Regarding patient safety, HA fillers offer several advantages over other fillers, such as superior lifting capacity (less volume of the product is required to achieve a mid-face lift), better longevity, no requirement for dermal allergy test, as well as the fact that the effects of HA fillers can be reversed with hyaluronidase. An additional advantage of HA related to safety is that it undergoes natural degradation over time [10]. Although it would seem that treatments with this compound are perfectly safe [10, 11], nothing could be further from the truth. Adverse events associated with its use are difficult to estimate because official statistics of complications are not collected. The onset of delayed complications for various HA fillers and their durability may be longer than previously thought, which has a huge impact on the development of treatment plans [12].

The of note are serious complications such as the following:

- anaphylactic reaction,
- bacterial infections, biofilm – a collection of microorganisms resistant to antimicrobials, most often resulting from contamination of the hyaluronic acid of questionable quality or failure to observe aseptic techniques during the treatment,
- skin necrosis,
- granulomatous inflammation,
- blindness [10–16].

## Complications associated with the use of hyaluronic acid

As mentioned above, the epidemiology of adverse events after the use of hyaluronic acid is hard to determine. Hyaluronic acid treatments are performed not only in medical practices, proper medical records are not always kept, and complications are not reported and centrally recorded. Based on the available literature, the incidence of adverse reactions after the use of hyaluronic acid-based fillers amounts to 0.01–1% and is undoubtedly underestimated [16, 17]. As previously mentioned, contraindications to the use of most hyaluronic acid fillers include autoimmune diseases, including Hashimoto's disease. Due to the abnormal functioning of the immune system, patients with autoimmune diseases face a higher risk of adverse reac-

tions, and in particular delayed type IV immune-mediated reactions. The most typical is recurrent oedema lasting up to 11 months, with an average requirement of 8 weeks of treatment with glucocorticoids, antihistamines, and hyaluronidase [13–16].

To extend the longevity of hyaluronic acid in tissues, it undergoes chemical modification, or so-called cross-linking. Chemical cross-linking of hyaluronic acid leads to the formation of a viscoelastic polymer. Cross-linking is a process in which individual chains of hyaluronic acid are joined together by chemical bonds into larger conglomerates, so that the liquid substance is transformed into a gel – a soft solid (a specific type of 3-dimensional matrix is formed). This process makes it possible to obtain a structure of acid that the body clears much more slowly – not within a few days, but many months. Cross-linking, on the one hand, protects hyaluronic acid molecules from degradation, and on the other - gives it specific physicochemical properties: viscosity, density, malleability, or lifting capacity for tissue. Importantly, the antigenicity of the hyaluronic acid subjected to processing remains unchanged, and its biocompatibility is preserved. The most common compound used to cross-link hyaluronic acid is called BDDE (1,4-butanediol-diglycidyl-ether). Among other compounds used for cross-linking are PEG (polyethylene glycol) or divinyl sulfone (DVS), formaldehyde, and ethyl sulfone.

When injected into soft tissues, fillers containing hyaluronic acid or other substances induce an influx of phagocytic neutrophils and mononuclear cells, stimulating macrophage recruitment and fibroblast activation. This reaction occurs because the immune system is unable to enzymatically degrade or phagocytise the injected substances. The inflammatory reaction to hyaluronic acid fillers, despite their simple composition, is multifaceted. These dermal fillers are essentially composed of hyaluronic acid, water, and a cross-linking agent. Each of these components can induce and promote the development of an inflammatory response. Hyaluronic acid itself, despite being a natural and common constituent of the human body, can have a pro-inflammatory effect; particularly it applies to the short chains of HA [16].

Furthermore, hyaluronic acid does not bind directly to proteins, so it does not form typical proteoglycans, but it can serve as an attachment site for other proteoglycans. These structures can trigger inflammatory reactions. High local concentrations of water can also trigger the inflammatory process by causing a local alteration in osmotic pressure. The last of the 3 main components of hyaluronic acid fillers, the cross-linking agent, may play a key role in the immunogenic potential of the entire product [16].

Hyaluronic acid plays a crucial role in the inflammatory process; thus, the use of HA fillers in patients with autoimmune diseases is still controversial. In fact, HA in inflamed tissues helps to promote the inflammatory response, and when injected as a dermal filler, it can potentially promote reactivation of the primary disease [17]. Consequently, a product approval for a significant proportion of commercially available hyaluronic acid fillers and biostimulants contains a contraindication of autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, mixed connective tissue disease, and chronic lymphocytic thyroiditis.

This is also because there are few scientific reports available on the use of cross-linked hyaluronic acid in autoimmune diseases. There are isolated case reports and low-quality clinical studies that require verification on a large cohort of patients [18, 19]. One of them evaluated the effects of hyaluronic acid (but non-cross-linked) and platelet-rich plasma in patients with scleroderma. Ten female patients aged 18–70 years with systemic scleroderma (SSc) and unresponsive to commonly used treatments were included in the study. They underwent 3 injections of HA filler and platelet-rich plasma at an interval of 15–20 days, and were followed up at 1, 3, and 24 months after treatment. Already after the first injection, the patients noticed a significant improvement in their skin lesions, showing greater mouth opening and increased thickness of the upper lip. The treatment significantly improved patients' quality of life, indicating that non-cross-linked hyaluronic acid combined with platelet-rich plasma may be a viable therapeutic alternative [18, 19]. Asian researchers, meanwhile, used BDDE-crosslinked hyaluronic acid to treat eyelid retraction in 13 patients with thyroid orbitopathy and, after a one-year follow-up period, found this treatment to be safe and effective with long-lasting results, which is, however, highly controversial and questionable [20].

## The immunomodulatory impact of PEG in fillers

Based on the available literature, the use of polyethylene glycol as a crosslinking agent appears to have a significant immunomodulatory effect, compensating for the pro-inflammatory effects of the other filler components and even causing the complete product to exhibit a local anti-inflammatory effect. This is highly desirable from the point of view of the safety of treatments for patients, particularly those with Hashimoto's disease [21–23]. Jeong *et al.* showed that PEGylated hyaluronic acid (PEG-HA) fillers *in vitro* have high biosafety and reduce immune cell recruitment, reactive oxygen species (ROS) production, and expression of pro-inflammatory cytokines (mRNA) such as tumour necrosis factor (TNF) αand interleukin (IL) 8, both at rest and under stimulation. These findings suggest that PEGylated hyaluronic acid fillers carry a very low risk of immune-mediated adverse events, especially

granulomatous reactions, and even induce an anti-inflammatory phenotype in immune cells, which may contribute to the beneficial effects of PEG- HA [21–23]. The results of a prospective study evaluating the efficacy and safety of Neauvia Stimulate and Neauvia Hydro Deluxe injectables in patients with autoimmune thyroid diseases were published in May 2023. The study included 15 women aged 26–62 years, 14 with Hashimoto's disease and one with Graves's disease, who received 2 ml of Neauvia Stimulate by subcutaneous injection technique in the mid-face area. Neauvia Stimulate is a soft tissue filler combining PEG-crosslinked hyaluronic acid (26 mg/ml) with 1% calcium hydroxyapatite (size 8–12 µm) and the addition of glycine and l-proline [24]. Histology was performed on complete surgical specimens of skin and subcutaneous tissue from the treated areas. In addition, peripheral blood levels of anti-TPO and anti-TG antibodies were assessed before and 150 days after Neauvia Stimulate injection. In all patients, a perioperative risk analysis was performed in the form of post-treatment course monitoring; data were collected 5, 21, and 150 days after the treatment [24]. None of the 15 patients developed oedema during the first few days post injection. The hyaluronic acid product was palpable in 3 patients (20%) after 3 days and in one patient after 5 days. None of the patients experienced injection site tenderness, redness, or nodule formation in the treatment area 4 days after the injection. No adverse reactions were recorded during the 150-day follow-up [24]. No significant changes in the concentration of anti-TPO and anti-TG antibodies were observed. The average concentration of anti-TPO antibodies before hyaluronic acid injection was 257.21 UI/ml, and after 150 days 254.14 UI/ml, respectively, anti-Tg antibodies 266.33 UI/ml and 267.24 UI/ml. Histology specimens from 5 study participants were assessed for immune response at the tissue level at 7, 21, and 150 days after Neauvia Stimulate injection. All patients showed a significant reduction in the severity of the inflammatory infiltrate manifested by a drop in the expression of CD 4+ T lymphocytes, CD 8+ T lymphocytes, B lymphocytes, as well as monocytes and macrophages indicated by a significant reduction in the expression of CD 68+ antigen [23]. Based on the results, a reduction in the number of antigen-recognising T lymphocytes (CD4+), cytotoxic T lymphocytes (CD8+), and CD68+ innate immune cells caused by injection of Neauvia Stimulate suggests that PEGylated hyaluronic acid gel fillers are not identified as a foreign body. Cross-linking substances in PEGylated hyaluronic acid gel fillers may have contributed to the high biocompatibility of the injected product, which lowers the risk of immune response-related adverse events, such as granuloma formation [23]. Hyaluronic acid-based filler cross-linked with polyethylene glycol should be considered as a reasonable and apparently safe choice for Hashimoto's disease patients. However, further studies involving a larger cohort of patients with autoimmune diseases are needed [24].

## Hints for qualifying patients with thyroid autoimmune diseases for aesthetic treatments

As mentioned in the introduction, due to the ever-increasing prevalence of autoimmune diseases, the ever-increasing number of aesthetic medicine treatments, and the lack of clear guidelines for the management of patients with autoimmune endocrinopathies in the aesthetic doctor's practice, we have attempted to formulate them. The most common disease of the endocrine system is chronic lymphocytic thyroiditis, which was briefly noted in the introduction. The diagnosis of Hashimoto's disease is based on clinical signs and symptoms of hypothyroidism and the presence of anti-TPO antibodies; however, it should be remembered that 25% of cases of Hashimoto's disease are seronegative [25].

In daily medical practice, we may encounter several clinical situations:

1. A patient with established diagnosis of hypothyroidism in the course of Hashimoto's disease treated with a fixed dose of L-thyroxine – before proceeding with aesthetic treatment, assess the TSH concentration (the assay should be performed within the last month preceding the treatment) - if the concentration of thyroid stimulating hormone is within the reference values, proceed with the treatment – if not, refrain from the treatment and refer the patient to an endocrinologist.

2. A patient with newly diagnosed hypothyroidism (within the last 2 months) or with diagnosed and treated hypothyroidism, but after modification of L-thyroxine dose within the 2 months preceding the treatment – assess TSH concentration. If the TSH concentration is within the reference values, perform the treatment. If the TSH concentration is outside the normal range, refrain from the treatment and refer the patient to an endocrinologist.

When choosing a hyaluronic acid filler based on evidence-based medicine, the selection of a product cross-linked with polyethylene glycol (PEG) seems appropriate.

3. A patient with suspected Hashimoto's disease based on:

A. Clinical symptoms: weight gain, weakness, fatigue and decreased exercise tolerance, lethargy, general psychomotor retardation, slowing of the speech, feeling cold, easy freezing, dry, cold, pale, yellowish skin, decreased perspiration, excessive keratosis of the epidermis, e.g. on the elbows, subcutaneous oedema, i.e. myxoedema, causing thickening of facial features, dis-

tinctive swelling of the eyelids and hands, dry, brittle, thinning hair, and loss of eyebrows.

B. Comorbidities: type 1 diabetes mellitus, Addison-Biermer anaemia, adrenal insufficiency, celiac disease, psoriasis, vitiligo, rheumatoid arthritis, polycystic ovary syndrome, and recurrent miscarriage in women with or without infertility [25].

C. Positive family history of autoimmune diseases, including thyroid disease.

If, after the patient's examination and identifying 3A and/or 3B and/or 3C, you suspect Hashimoto's disease, refrain from treatment and refer the patient to an endocrinologist.

Aesthetic doctors are less likely to meet a patient with Graves' disease, an autoimmune thyroid disease in which the body produces antibodies against the TSH receptor (TSHR), found in the cells of the thyroid gland. Antibodies against the TSH receptor (so-called TSH receptor antibody – TRAb) stimulate the secretory function of the thyroid gland, which leads to the development of symptoms of hyperthyroidism (among other things, weight loss, despite usually good appetite), weakness, heat intolerance, anxiety, irritability, psychomotor agitation, difficulty concentrating, insomnia, hand tremors, palpitations, paroxysmal atrial fibrillation, diarrhoea, or menstrual disorders in women) [26, 27]. The activation of cellular response against the same antigen found in fibroblasts can lead to increased secretion of pro-inflammatory cytokines, autoimmune inflammation, and the development of extra-thyroidal manifestations of the disease, including thyroid orbitopathy, an ocular manifestation caused by inflammation of the soft tissues of the orbit, leading to temporary or permanent damage to the organ of vision.

Graves' disease is much less prevalent than Hashimoto's disease, affects about 1% of the world's adult population, is 10 times more prevalent in women, and has a peak incidence between the ages of 30 and 50 years [26, 27]. It usually progresses with overt clinical hyperthyroidism confirmed biochemically by decreased serum TSH levels and increased (less often normal) free thyroid hormone levels (usually FT4 determination is sufficient; if normal, determine FT3). In overt hyperthyroidism, a significant predominance of FT3 increase over FT4 increase is an unfavourable prognostic signal - the response to antithyroid therapy (which inhibits the production of thyroid hormones) is inferior. In the remission phase, the results of hormonal tests are normal. In addition, increased levels of TRAb are found in the serum, which confirms the diagnosis (antibodies should be determined before starting or within the first 3 months of antithyroid treatment), and their normalisation indicates immune remission of the disease [26, 27]. It should be remembered that an isolated increase in TRAb is not sufficient for the diagnosis of Graves' disease (it can be found in relatives of Graves' patients who do not develop symptoms of the disease) and that the disease has a seronegative form [26, 27]. The primary method of treatment is pharmacological therapy with thyrostatic thiamazole, and only if allergic to thiamazole, with propylthiouracil. The optimal duration of first-line pharmacological treatment is 12–18 months, and according to the most recent guidelines from the American Society of Endocrinology of 2016, longer if the goal is to achieve sustained immune remission [28].

Management of a patient with Graves' disease in an aesthetic medical practice:

1. A patient diagnosed with Graves' disease treated with low doses of thyrostatic medications (i.e. thiamazole up to 10 mg per day, propylthiouracil up to 50–100 mg per day), euthyroid, i.e. TSH, fT4, and fT3 concentrations in the month preceding the treatment as well as TRAb concentration are within the reference values – proceed with the treatment.

When choosing a hyaluronic acid filler on the basis of evidence-based medicine, the selection of a product cross-linked with polyethylene glycol (PEG) seems appropriate.

2. A patient diagnosed with Graves' disease, receiving pharmacotherapy and not euthyroid, i.e. TSH concentration below the lower limit of normal, and fT4 and fT3 above the upper limit of reference values, or when TSH concentration is below the lower limit of normal, while free thyroid hormones remain within reference values – refrain from the treatment until the concentration of TSH and free thyroid hormones normalise.

3. A patient with a history of thyroid orbitopathy after successful systemic treatment with glucocorticoids or other immunosuppressive medications, TRAb levels within normal limits – before proceeding, current ophthalmologic evaluation and/or contrast-enhanced orbital magnetic resonance imaging to evaluate the activity of the inflammatory process is necessary – if ophthalmologic evaluation indicates inactive disease ≤ 3/7 in the CAS (Clinical Activity Score) and/or absent inflammatory infiltration in the soft tissues of the orbits, proceed with the treatment.

4. A patient with a history of thyroid orbitopathy after successful systemic treatment with glucocorticoids or other immunosuppressive medications, TRAb levels above normal, despite CAS clinical activity score ≤ 3/7 (inactive disease) – refrain from treatment.

## Addison's disease in the context of aesthetic medicine

Primary adrenal insufficiency, also known as Addison's disease, is a very rare endocrine disease that we may see in aesthetic practice. It is a syndrome of clinical signs and symptoms caused by long-term deficiency of adrenal hormones, mainly cortisol, due to direct injury of the adrenal glands. The prevalence of Addison's dis-

ease in the Caucasian population is 40–110 per million. The onset of the disease is usually in the third or fourth decade of life. Its prevalence in women is much higher than in men. Currently, the most common (70–90% of cases) cause of Addison's disease is autoimmunity, which is the body's production of antibodies that damage the adrenal glands [29, 30]. Enzymes involved in steroidogenesis (the production of hormones of the adrenal cortex) are autoantigens: most often 21-hydroxylase, less often 17-hydroxylase and 20–22-lyase [29, 30]. Autoimmune inflammation of the adrenal cortex leads to slow and painless degradation of the organ. In over 50% of cases, adrenal insufficiency is accompanied by autoimmune diseases of other endocrine organs (thyroiditis, premature ovarian failure, type 1 diabetes) and other autoimmune diseases (vitiligo, $B_{12}$ deficiency anaemia, celiac disease). These disorders combine to form autoimmune polyglandular syndromes (APS). Treatment of Addison's disease involves chronic, lifelong substitution of glucocorticoids, mineralocorticoids, and occasionally androgens [30].

If a patient with Addison's disease treated with hydrocortisone substitution comes to the aesthetic clinic, an additional 20 mg of hydrocortisone orally one hour prior to the treatment should be ordered together with a twofold increase in the following dose taken on the same day. If an Addison's disease patient has another concomitant endocrinopathy, such as hypothyroidism, follow the recommendations for Hashimoto's disease.

## Conclusions

Aesthetic medicine is a very young medical discipline with few clinical studies of high quality and sufficient credibility to formulate management recommendations. We hope that the above treatment guidelines will be helpful to clinicians practicing anti-aging medicine. Let the guiding principle be the one preached by the father of medicine, Hippocrates – "primum non nocere" – first, do no harm. Patient safety takes priority. May we use the best available medical knowledge when qualifying a patient for the treatment and choose the right product, especially when treating patients with autoimmune diseases.

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