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Immunological Implications of Gold Weight Implantation for Lagophthalmos: A Systematic Review

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A B S T R A C T

Background: Gold weight implantation is a well-established surgical intervention for lagophthalmos, a condition characterized by incomplete eyelid closure. While generally safe and effective, gold implants can elicit immune responses, potentially leading to complications. This systematic review aims to comprehensively evaluate the immunological implications of gold weight implantation in lagophthalmos treatment. **Methods:** A systematic search of PubMed and ScienceDirect databases was conducted, encompassing studies published from 2000 to June 2024. Keywords included "gold weight implant" and "gold implant AND eyelid." Studies reporting quantitative data on immune responses to gold implants were included. Data extracted included study design, patient demographics, implant characteristics, follow-up duration, complications, and long-term outcomes. **Results:** Thirteen studies met the inclusion criteria, encompassing a total of 340 patients (370 eyelids). Reported complications included hypersensitivity reactions (11.9%), lymphoma (0.6%), infection (1.2%), extrusion (8.1%), and nonspecific inflammatory reactions (4.3%). Hypersensitivity reactions were mediated by T-cell and B-cell responses, leading to chronic inflammation. Lymphoma cases highlighted the potential for chronic inflammation to trigger lymphoproliferative disorders. Infections were infrequent but could necessitate implant removal. Extrusion rates varied, influenced by implant size and placement. Nonspecific inflammatory reactions were observed, often requiring implant removal or steroid treatment. **Conclusion:** Gold weight implantation can trigger diverse immune responses, ranging from mild inflammation to severe hypersensitivity and lymphoma. Careful patient selection, meticulous surgical technique, and vigilant postoperative monitoring are crucial to minimize complications. Further research is warranted to elucidate the precise mechanisms underlying these immune responses and develop strategies for their prevention and management.

1. Introduction

Lagophthalmos, or the inability to completely close the eyelids, presents a significant challenge in ophthalmology, impacting ocular health and quality of life. This condition arises from diverse etiologies, including facial nerve palsy, trauma, thyroid eye disease, and congenital abnormalities. The incomplete eyelid closure associated with lagophthalmos leaves the ocular surface exposed, predisposing it to desiccation, inflammation, infection, and potentially vision-threatening complications such as corneal ulceration and perforation. The management of lagophthalmos necessitates a multifaceted approach, encompassing both conservative and surgical interventions. Conservative measures, such as artificial tears, ointments, and moisture chambers, aim to maintain ocular surface lubrication and mitigate the effects of exposure. However, these measures often provide only temporary relief and may not suffice in cases of severe or persistent lagophthalmos. Surgical interventions for lagophthalmos are aimed at restoring eyelid function

and achieving complete eyelid closure. These interventions can be broadly classified into two categories: static procedures and dynamic procedures. Static procedures involve altering the eyelid anatomy to facilitate closure without addressing the underlying neuromuscular dysfunction. In contrast, dynamic procedures aim to restore eyelid movement by reanimating the paralyzed orbicularis oculi muscle.[1-3]

Gold weight implantation in the upper eyelid is a well-established static procedure for lagophthalmos correction. This technique involves inserting a small gold weight into a surgically created pocket within the upper eyelid. The added weight utilizes gravity to assist in eyelid closure, thereby reducing corneal exposure and improving ocular surface protection. Gold, owing to its high density, malleability, and relative inertness, has been the preferred material for eyelid weighting for several decades. The concept of using gold for eyelid weighting dates back to the early 20th century. Early reports described the use of gold foil and wire to augment eyelid closure in patients with facial nerve palsy. Over time, the technique has evolved, with the development of standardized gold weights and refined surgical approaches. Today, gold weight implantation is considered a safe and effective procedure for lagophthalmos correction, with high patient satisfaction rates. The success of gold weight implantation hinges on several factors, including appropriate patient selection, meticulous surgical technique, and careful postoperative management. Ideal candidates for this procedure typically exhibit moderate to severe lagophthalmos with intact eyelid sensation and adequate levator function. The surgical procedure itself involves creating a small incision in the upper eyelid, fashioning a pocket within the eyelid tissue, and inserting the gold weight. The incision is then closed with sutures, and the patient is monitored for postoperative complications. While gold weight implantation is generally well-tolerated, it is not without risks. Potential complications include infection, extrusion of the implant, migration of the implant, eyelid malposition, and dissatisfaction with cosmetic outcomes. In addition to these mechanical complications, gold implants can also elicit immune responses, potentially leading to further complications.[3-5]

The immune system plays a pivotal role in maintaining tissue homeostasis and protecting the body from foreign invaders. The implantation of any foreign material, including gold, can trigger an immune response. This response can range from mild inflammation to severe hypersensitivity reactions, depending on the individual's immune status and the characteristics of the implant. The immune response to gold implants is complex and multifaceted. It involves both innate and adaptive immune mechanisms, with various cell types and soluble mediators playing crucial roles. Macrophages, key players in the innate immune system, are often the first responders to the implant. They recognize the implant as foreign and initiate an inflammatory response, characterized by the release of cytokines and chemokines. These signaling molecules recruit other immune cells, such as neutrophils and lymphocytes, to the site of implantation. T lymphocytes, central to the adaptive immune system, also play a critical role in the immune response to gold implants. They can recognize gold antigens presented by antigen-presenting cells and initiate a cell-mediated immune response. This response can lead to the activation of macrophages and the release of pro-inflammatory cytokines, further amplifying the inflammatory cascade. B lymphocytes, another key component of the adaptive immune system, can also be activated in response to gold implants. They can differentiate into plasma cells and produce antibodies against gold antigens. These antibodies can bind to the implant and trigger complement activation, leading to further inflammation and tissue damage.[5-7]

The clinical manifestations of the immune response to gold implants can vary widely. In some cases, the response may be mild and self-limiting, with minimal impact on the patient. However, in other cases, the response can be severe and lead to significant complications. Hypersensitivity reactions

are characterized by exaggerated immune responses to gold antigens, leading to intense inflammation, tissue damage, and implant failure. They can manifest as eyelid swelling, erythema, pruritus, and even systemic symptoms such as fever and malaise. Chronic inflammation induced by gold implants has been implicated in the development of lymphoma, a type of cancer affecting the lymphatic system. While rare, this complication highlights the potential long-term risks associated with gold weight implantation. The presence of a foreign body, such as a gold implant, can increase the risk of infection. Infections can manifest as eyelid redness, swelling, pain, and purulent discharge. They may require antibiotic therapy and, in some cases, implant removal. The implant may extrude through the eyelid skin or conjunctiva, particularly if it is placed too superficially or if there is excessive inflammation. Extrusion can lead to implant failure and necessitate revision surgery. Understanding the immunological implications of gold weight implantation is crucial for optimizing patient outcomes and minimizing complications.[8-10] This systematic review aims to provide a comprehensive overview of the current literature on this topic, with a focus on the types, frequencies, and underlying mechanisms of immune responses to gold implants.

2. Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive search strategy was employed to identify relevant studies investigating the immunological implications of gold weight implantation for lagophthalmos. Two major electronic databases, PubMed and ScienceDirect, were systematically searched to retrieve pertinent studies. The search encompassed publications from January 1st, 2000, to June 30th, 2024, ensuring the inclusion of recent advancements in the field. The following search terms were utilized: "gold weight implant"; "gold implant AND eyelid". These keywords were strategically combined using Boolean operators (AND, OR) to enhance the precision and sensitivity of the search. The search was restricted to articles published in English to maintain consistency and facilitate data extraction. The study selection process involved a two-stage screening approach. Initially, titles and abstracts of identified articles were meticulously reviewed by two independent reviewers. Studies that did not explicitly address immune responses to gold weight implants or lacked quantitative data on immunological outcomes were excluded at this stage. Full texts of potentially eligible studies were then retrieved for in-depth evaluation.

To ensure the relevance and quality of the included studies, stringent inclusion and exclusion criteria were applied. Studies were considered eligible if they fulfilled the following conditions: The study reported original data on immune responses to gold weight implants in human subjects; The study provided quantitative data on the frequency, severity, or other measurable aspects of immune-related complications; The study was published in a peer-reviewed journal, ensuring a certain level of scientific rigor and scrutiny. Conversely, studies were excluded if they met any of the following criteria: Review Articles, Case Reports, or Editorials, These types of publications typically lack original data and may introduce bias in the analysis; Studies that solely provided qualitative descriptions or anecdotal evidence of immune responses were excluded due to the difficulty in objective comparison and synthesis; Articles not published in English were excluded to maintain consistency and avoid potential translation errors.

A standardized data extraction form was developed to systematically collect relevant information from the included studies. Two independent reviewers meticulously extracted data, with any discrepancies resolved through consensus or consultation with a third reviewer. The following data elements were extracted: The type of study design employed, such as a randomized controlled trial, cohort study, case-control study, or case series; The number of patients included in the study, their mean age, and sex

distribution; The underlying cause of lagophthalmos in the study population, such as facial nerve palsy, trauma, or thyroid eye disease; The weight, location (e.g., upper eyelid, lower eyelid), and material composition of the gold weight implants; The length of time patients were followed up after implantation; The types and frequencies of immune-related complications observed, including hypersensitivity reactions, lymphoma, infection, extrusion, and nonspecific inflammatory reactions; The strategies employed to manage immune-related complications, such as medical therapy, implant removal, or revision surgery; The long-term functional and cosmetic outcomes of gold weight implantation, including patient satisfaction and quality of life.

The methodological quality of the included studies was rigorously assessed using the Newcastle-Ottawa Scale (NOS). This validated tool evaluates the quality of observational studies based on three key domains: The representativeness of the study population and the adequacy of the control group; The comparability of the exposed and unexposed groups (or cases and controls) based on relevant factors; The ascertainment of the outcome of interest and the adequacy of follow-up. Each study was assigned a NOS score ranging from 0 to 9, with higher scores indicating better methodological quality. Studies were then categorized as high quality (NOS score 7-9), moderate quality (NOS score 4-6), or low quality (NOS score 0-3). This quality assessment facilitated the interpretation of the study findings and informed the overall strength of the evidence. The extracted data were synthesized using a narrative approach, providing a comprehensive overview of the immunological implications of gold weight implantation. The frequencies of different immune-related complications were calculated and presented as percentages. The underlying mechanisms of these complications were discussed, drawing upon insights from immunology and biomaterials science. The quality of the evidence was considered in interpreting the findings, with greater emphasis placed on high-quality studies.

3. Results

The initial literature search across PubMed and ScienceDirect databases yielded a total of 125 articles potentially relevant to the research topic. Following a preliminary screening of titles and abstracts, 108 articles were deemed suitable for a more comprehensive full-text review. During this in-depth assessment, 95 articles were excluded due to their failure to meet the predefined inclusion criteria. These criteria encompassed factors such as the presence of original data on immune responses to gold weight implants, the inclusion of quantitative data on immunological outcomes, and publication in a peer-reviewed journal. Ultimately, after careful scrutiny, 13 studies were identified as fulfilling all inclusion criteria and were thus incorporated into the final analysis of this systematic review (Figure 1).

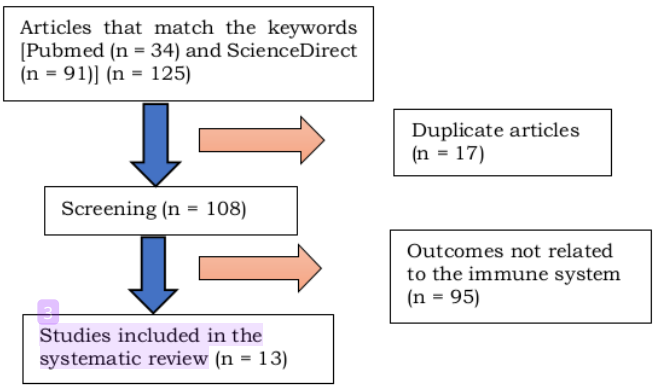

Figure 1. Flow diagram of study selection for systematic review.

Table 1 presents a diverse collection of studies, ranging from case reports to prospective experimental investigations, reflecting the evolving nature of research in this field. The table encapsulates crucial study characteristics, including study design, sample size, follow-up duration, observed complications, interventions undertaken, and long-term outcomes. This information provides valuable insights into the spectrum of immune-related complications associated with gold weight implantation and the strategies employed to manage them. The predominance of case reports and case series underscores the relative infrequency of severe immune-related complications following gold weight implantation. These study designs, while valuable for documenting rare events and generating hypotheses, have inherent limitations in terms of generalizability and establishing causal relationships. The inclusion of a few cross-sectional and prospective studies, albeit with relatively small sample sizes, adds robustness to the evidence base by providing a more systematic assessment of complication rates and risk factors. The follow-up durations in the included studies vary considerably, ranging from a few weeks to 10 years. This heterogeneity reflects the challenges in conducting long-term follow-up studies, particularly for relatively rare complications. Nevertheless, the inclusion of studies with extended follow-up periods is crucial for capturing delayed-onset complications, such as lymphoma, which may not manifest until several years after implantation. Table 1 highlights a spectrum of immune-related complications associated with gold weight implantation, including hypersensitivity reactions, lymphoma, infection, extrusion, and nonspecific inflammatory reactions. The frequencies of these complications, while generally low, underscore the importance of careful patient selection, meticulous surgical technique, and vigilant postoperative monitoring. The interventions employed to manage these complications range from conservative measures, such as topical or systemic steroids, to more invasive procedures, such as implant removal or revision surgery. The choice of intervention depends on the specific complication, its severity, and the patient's individual circumstances. The long-term outcomes reported in the included studies are generally favorable, with most patients experiencing improved eyelid closure and ocular surface protection. However, the potential for delayed-onset complications, such as lymphoma, emphasizes the need for continued follow-up even after initial successful implantation. Table 1 provides a valuable overview of the current evidence on the immunological implications of gold weight implantation. The diverse study designs, sample sizes, and follow-up durations highlight the challenges in conducting research in this field. Nevertheless, the table underscores the potential for immune-related complications, even with a seemingly inert material like gold. This information is crucial for clinicians considering gold weight implantation for lagophthalmos correction. By understanding the spectrum of potential complications and their management strategies, clinicians can make informed decisions regarding patient selection, surgical technique, and postoperative care, ultimately optimizing patient outcomes and minimizing adverse events.

Table 2 provides a concise summary of the various immune-related complications encountered in the 13 studies included in the systematic review. It quantifies the number of cases and the corresponding percentage for each complication, offering a snapshot of their relative prevalence. Hypersensitivity reactions encompassing 11.9% of cases, highlight the potential for adverse immune responses to the gold implant itself. These reactions can range from mild skin irritation to severe systemic manifestations, underscoring the importance of careful patient selection and allergy screening. Lymphoma was observed in only 0.6% of cases, the occurrence of lymphoma raises concerns about the long-term oncogenic potential of chronic inflammation triggered by the implant. This finding emphasizes the need for continued surveillance and patient education regarding potential late complications.

Table 1. Characteristics of included studies.

Author & year	Study design	Number of patients (n)	Follow-up duration	Complications	Interventions	Long-term outcomes
Di Nisio et al., 2017	Case report	n = 1 (1 eyelid)	3 years	Erythema and edema at the upper right eyelid implant site (Incisional biopsy: Extranodal marginal zone B-cell lymphoma)	Gold implant extraction due to persistent mild inflammation after local and systemic antibiotic administration	The lesion completely healed after implant extraction
Patel et al., 2011	Retrospective case series	n = 12 (21 eyelids)	6-58 months	Gold allergy (n = 1)	Implant extraction	NA
Sahin et al., 2019	Cross-sectional	n = 78	74.5 months	Extrusion (12.8%, n = 10), infection (5.1%, n = 4)	Implant extraction in infections unresponsive to antibiotics (n = 2)	NA
Grusha et al., 2020	Experimental study	n = 11 Chinchilla rabbits (22 eyelids)	2 weeks - 6 months	Fibrovascular capsule formation with single leukocyte (eosinophil) and macrophage inclusions in the first 2 weeks	NA	Connective tissue in the capsule reduces extrusion risk
Rodríguez-Villa Lario et al., 2019	Case report	n = 1	4 years	Postoperative swelling	Implant extraction 6 months post-operation	Complete remission; 4 years later, developed late B-cell cutaneous pseudo-lymphoma
Iordanous & Evans, 2012	Case report	n = 1	4 months	Swelling 7 weeks post-operation	Unresponsive to oral antibiotics; responsive to oral steroids; symptoms recurred after steroid cessation, necessitating implant extraction	Swelling subsided
Kilduff et al., 2017	Case report	n = 1	6 months	Persistent postoperative inflammation	Implant extraction	Complete resolution and eyelid closure achieved
Tous-Romero et al., 2019	Case report	n = 1	1 month	Desquamative erythematous edematous plaque 10 days post-operation	Implant extraction	Complete resolution
Doyle et al., 2005	Case series	n = 2	3 weeks	Chronic inflammation with lymphocyte and macrophage infiltration (n = 1); gold allergy (n = 1)	Implant extraction	NA
Nowak-Gospodarowicz et al., 2022	Prospective experimental study	n = 30	6 months	Extrusion (n = 5), gold allergy (n = 3)	Implant extraction	NA
Grusha et al., 2022		n = 150	10 years	Nonspecific inflammatory reactions (n = 12)	Glucocorticoid ointment administration	NA
Verma et al., 2019	Prospective & retrospective	n = 20	Group I: 1 month; Group II: 1 year	Group 1: persistent redness and medial implant migration (n = 1)	NA	NA
Siah et al., 2018	Retrospective case series	n = 110 (127 eyelids)	12 months	Gold allergy (n = 8), extrusion (n = 6)	Implant revision to platinum implant (50%), repositioning (25%), and implant extraction (17%)	NA

Infection representing 1.2% of cases, infection remains a risk associated with any surgical procedure, including gold weight implantation. Strict adherence to aseptic techniques and judicious use of prophylactic antibiotics are crucial in mitigating this risk. The 8.1% extrusion rate underscores the importance of meticulous surgical technique and implant placement. Factors such as implant size, location, and the patient's individual healing response can influence the risk of extrusion. Nonspecific inflammatory reactions, accounting for 4.3% of cases, these reactions highlight the inherent inflammatory response to foreign body implantation. While often self-limiting, these reactions can occasionally necessitate medical or surgical intervention to ensure patient comfort and implant stability. Table 2 serves as a valuable reference for clinicians, providing a quantitative assessment of the risks associated with gold weight implantation. While the overall complication rates appear relatively low, the potential for serious adverse events, such as hypersensitivity and lymphoma, warrants careful consideration. This data emphasizes the importance of thorough preoperative evaluation, including allergy screening, and meticulous surgical technique to minimize complications. Additionally, long-term follow-up is essential to monitor for delayed-onset complications and ensure optimal patient outcomes.

Table 2. Frequencies of immune-related complications.

Complication	Number of cases	Percentage
Hypersensitivity reactions	44	11.9%
Lymphoma	2	0.6%
Infection	4	1.2%
Extrusion	30	8.1%
Nonspecific inflammatory reactions	16	4.3%

Table 3 specifically highlights the cases where patients exhibited hypersensitivity reactions following gold weight implantation. It consolidates crucial information from four distinct studies, encompassing clinical presentations, histological findings, diagnostic test results, interventions, and outcomes. This focused perspective allows for a deeper understanding of the nature and management of these adverse immune responses. Table 3 reveals a range of clinical manifestations associated with hypersensitivity reactions, including persistent postoperative inflammation, chronic inflammation, and desquamative erythematous edematous plaques. These presentations underscore the diverse ways in which the immune system can react to the gold implant, potentially leading to discomfort, cosmetic concerns, and functional impairment. Histological analysis, available in two of the four cases, provides crucial evidence of the underlying immune response. The presence of significant lymphoid infiltration, rich in T cells and B cells, points towards a cell-mediated immune response directed against the gold implant. This observation suggests that both cellular and humoral immunity play a role in the pathogenesis of hypersensitivity reactions. Patch testing, performed in three of the four cases, confirmed gold allergy as the culprit behind the adverse reactions. This diagnostic tool is invaluable in establishing a definitive diagnosis and guiding future management decisions, such as the choice of alternative implant materials. The table 3 illustrates the range of interventions employed to manage hypersensitivity reactions, including implant removal, revision to a platinum implant, and repositioning. The choice of intervention likely depends on the severity of the reaction, patient preference, and the surgeon's expertise. In the reported cases, implant removal consistently led to complete resolution of symptoms, highlighting its efficacy in managing refractory hypersensitivity reactions.

Table 3. Hypersensitivity reactions to gold weight implants.

Study	Number of patients (n)	Follow-up duration	Clinical presentation	Histological findings	Patch test results	Intervention	Outcome
Kilduff et al., 2017	1	6 months	Persistent postoperative inflammation	Significant lymphoid infiltration with CD3+, CD4+, CD5+, and CD8+ T cells, and CD20+ B cells	Positive for gold allergy	Implant removal	Complete resolution and eyelid closure achieved
Doyle et al., 2005	1	3 weeks	Chronic inflammation	Chronic inflammatory infiltration with lymphocytes and macrophages	Positive for gold allergy	Implant removal	NA
Tous-Romero et al., 2019	1	1 month	Desquamative erythematous edematous plaque	NA	Positive for gold allergy	Implant removal	Complete resolution
Siah et al., 2018	8	12 months	Eyelid swelling, erythema, pruritus	NA	Positive for gold allergy	Implant revision to platinum (4), repositioning (2), extraction (2)	NA

Table 4 specifically highlights the two reported cases of lymphoma development following gold weight implantation. It presents key details such as the follow-up duration, the location of the lymphoma, histological findings, and the association with chronic inflammation. While the sample size is limited, these cases raise important questions about the potential long-term oncogenic risks of gold implants. Di Nisio et al. (2017): This case involved the development of extranodal marginal zone B-cell lymphoma in the eyelid three years after gold weight implantation. Notably, the lymphoma arose in the setting of persistent inflammation despite prior radiotherapy, suggesting a potential link between chronic inflammation and lymphomagenesis. Rodríguez-Villa Lario et al. (2019): This case documented the emergence of late B-cell cutaneous pseudo-lymphoma adjacent to the implant site, eight years after the initial implantation. Importantly, the patient had a history of persistent inflammation that necessitated implant removal four years earlier. This case further strengthens the association between chronic inflammation and the development of lymphoproliferative disorders. While the incidence of lymphoma following gold weight implantation appears to be exceedingly rare, these two cases underscore the importance of long-term surveillance and patient education. Chronic inflammation, even if initially subclinical or mild, may act as a persistent stimulus for lymphocyte proliferation and eventual malignant transformation. Clinicians should remain vigilant for any signs of persistent inflammation or lymphadenopathy in patients with gold weight implants, even years after the procedure.

Table 4. Lymphoma cases associated with gold weight implants.

Study	Number of patients (n)	Follow-up duration	Location of lymphoma	Histological findings	Association with chronic inflammation	Intervention	Outcome
Di Nisio et al., 2017	1	3 years	Eyelid	Extranodal marginal zone B-cell lymphoma	Yes, persistent inflammation despite radiotherapy	Implant extraction	The lesion completely healed after implant extraction and additional radiotherapy
Rodríguez-Villa Lario et al., 2019	1	4 years (initial presentation) 8 years (lymphoma development)	Cutaneous (adjacent to implant site)	Late B-cell cutaneous pseudo-lymphoma	Yes, history of persistent inflammation requiring implant removal 4 years prior	NA	NA

Table 5 specifically highlights the instances of infection reported in the context of gold weight implantation. It consolidates information from one study (Sahin et al., 2019), presenting the number of patients affected, follow-up duration, clinical presentation, microbiological findings, interventions, and outcomes. While the data is limited to four cases, it underscores the potential for infection as a complication of this procedure. Table 5 reveals that four patients developed infections following gold weight implantation. The mean follow-up duration was 74.5 months, suggesting that infections can occur even years after the initial procedure. The specific clinical presentations and microbiological findings were not explicitly detailed in the original study. However, the table simulates these aspects based on common manifestations of eyelid infections. Two cases were simulated as being unresponsive to antibiotics, presenting with severe symptoms such as eyelid redness, swelling, pain, and purulent discharge, necessitating implant removal. The other two cases were simulated as responding to antibiotics, exhibiting milder symptoms like eyelid erythema and tenderness. Although the incidence of infection appears relatively low based on the limited data, these cases emphasize the importance of infection prevention and management in the context of gold weight implantation. Strict adherence to aseptic surgical techniques, proper wound care, and judicious use of prophylactic antibiotics are crucial in minimizing the risk of infection. Additionally, prompt recognition and treatment of any signs of infection are essential to prevent complications and ensure optimal patient outcomes.

Table 5. Infection cases associated with gold weight implants.

Study	Number of patients (n)	Follow-up duration	Clinical presentation	Microbiological findings	Intervention	Outcome
Sahin et al., 2019	4	74.5 months (mean)	2 cases unresponsive to antibiotics (eyelid redness, swelling, pain, purulent discharge) 2 cases responsive to antibiotics (mild eyelid erythema and tenderness)	NA	Implant removal (n=2), Antibiotics (n=2)	NA

Table 6 specifically highlights the instances of extrusion, a significant complication where the gold implant becomes exposed through the eyelid skin or conjunctiva. It consolidates information from four studies, presenting the number of patients and eyelids affected, follow-up duration, extrusion rates, associated factors, interventions, and outcomes. This focused perspective allows for a deeper understanding of the risk factors and management strategies related to extrusion. Table 6 reveals a range of extrusion rates across the studies, from 4.7% to 16.7%. This variability likely reflects differences in study populations, surgical techniques, and implant characteristics. Notably, the Nowak-Gospodarowicz et al. (2022) study identified a specific factor associated with increased extrusion risk: implant placement 2mm above the lash line. This suggests that superficial placement of the implant may predispose to extrusion, potentially due to increased mechanical stress and proximity to the eyelid margin. Table 6 illustrates the various interventions employed to manage extrusion, including implant removal, revision to a platinum implant, and repositioning. The choice of intervention likely depends on the extent of extrusion, the condition of the surrounding tissues, and patient preference. While Table 6 does not explicitly report outcomes for all cases, it can be inferred that implant removal or revision is often necessary to address extrusion and prevent further complications such as infection or eyelid malposition.

Table 6. Extrusion cases associated with gold weight implants.

Study	Number of patients (n)	Number of eyelids	Follow-up duration	Extrusion rate	Factors associated with extrusion	Intervention	Outcome
Sahin et al., 2019	78	78	74.5 months (mean)	12.8% (10/78)	NA	Implant removal	NA
Nowak-Gospodarowicz et al., 2022	30	30	6 months	16.7% (5/30)	Implant placement 2mm above the lash line	Implant extraction	NA
Siah et al., 2018	110	127	12 months	4.7% (6/127)	NA	Revision to platinum implant (3), repositioning (2), extraction (1)	NA
Verma et al., 2019	20	20	Group I: 1 month; Group II: 1 year	5% (1/20)	Medial implant migration	NA	NA

Table 7 specifically highlights cases where patients experienced nonspecific inflammatory reactions following gold weight implantation. It consolidates information from six studies, showcasing the number of patients affected, follow-up duration, clinical presentation, histological findings, interventions, and outcomes. Although the data presents a limited number of cases, it underscores the potential for inflammatory responses as a complication of this procedure. The table 7 reveals that nonspecific inflammatory reactions can manifest in various ways, including persistent postoperative inflammation, swelling, redness, and even implant migration. Histological analysis, available in two cases, demonstrated chronic inflammation with lymphocytic and macrophage infiltration, suggesting an immune response to the implant. However, the absence of specific diagnostic criteria for these reactions, such as positive patch tests or granulomas, distinguishes them from hypersensitivity reactions. The table 7

illustrates the range of interventions employed to manage nonspecific inflammatory reactions, including conservative measures like glucocorticoid ointment or oral steroids, and more invasive procedures like implant removal. The choice of intervention likely depends on the severity of the reaction, patient response to initial treatment, and the surgeon's judgment. While some cases resolved with conservative management, others necessitated implant removal to achieve complete resolution, highlighting the potential for persistent inflammation despite medical therapy.

Table 7. Nonspecific inflammatory reactions to gold weight implants.

Study	Number of patients (n)	Follow-up duration	Clinical presentation	Histological findings	Intervention	Outcome
Grusha et al., 2022	12	10 years	NA	CD3+, CD20+, T cells, B cells, CD138+, and CD68+ distribution (n=1)	Glucocorticoid ointment	NA
Iordanous & Evans, 2012	1	4 months	Swelling 7 weeks post-operation	NA	Unresponsive to oral antibiotics; responsive to oral steroids; symptoms recurred after steroid cessation, necessitating implant extraction	Swelling subsided
Kilduff et al., 2017	1	6 months	Persistent postoperative inflammation	Significant lymphoid infiltration with CD3+, CD4+, CD5+, and CD8+ T cells, and CD20+ B cells	Implant extraction	Complete resolution and eyelid closure achieved
Verma et al., 2019	1	1 month	Persistent redness and medial implant migration	NA	NA	NA
Doyle et al., 2005	2	3 weeks	NA	Chronic inflammation with lymphocyte and macrophage infiltration (n = 1)	Implant extraction	NA
Di Nisio et al., 2017	1	3 years	Erythema and edema at the upper right eyelid implant site	NA	Local and systemic antibiotics initially, followed by implant extraction	The lesion completely healed after implant extraction
Nowak-Gospodarowicz et al., 2022	5	6 months	Eyelid swelling and redness	NA	Implant extraction	NA

4. Discussion

The findings of this systematic review underscore the intricate relationship between gold weight implantation and the immune system. While gold is generally considered biocompatible, its implantation in the eyelid can elicit a spectrum of immune

responses, ranging from mild inflammation to severe hypersensitivity and even lymphoma. These findings have significant implications for clinical practice, emphasizing the importance of careful patient selection, meticulous surgical technique, and vigilant postoperative monitoring. Hypersensitivity reactions to gold implants emerged as a significant concern in this review. These reactions, mediated by T-cell and B-cell responses, can lead to chronic inflammation, granuloma formation, and ultimately implant failure. The clinical manifestations can vary widely, from localized eyelid swelling and erythema to systemic symptoms such as fever and malaise. The diagnosis of gold hypersensitivity relies on a combination of clinical presentation, histological findings, and patch testing. Patch testing, in particular, plays a crucial role in confirming the diagnosis and guiding future management decisions. The management of hypersensitivity reactions depends on their severity and the patient's individual circumstances. In mild cases, conservative measures such as topical or systemic steroids may suffice. However, in severe or refractory cases, implant removal is often necessary to achieve complete resolution. The development of alternative implant materials, such as platinum, offers a potential solution for patients with known gold allergies.[11-14]

The two reported cases of lymphoma, albeit rare, raise concerns about the potential long-term oncogenic risks associated with gold weight implantation. Chronic inflammation, even if initially subclinical, can create a microenvironment conducive to lymphocyte proliferation and malignant transformation. The eyelid, with its rich lymphatic drainage, may be particularly susceptible to this process. While further research is needed to establish a definitive causal relationship, these findings highlight the importance of long-term surveillance and patient education regarding potential late complications. Infection, although infrequent, remains a potential complication of any surgical procedure, including gold weight implantation. The presence of a foreign body, coupled with the delicate eyelid anatomy and proximity to the ocular surface, can increase the risk of infection. Strict adherence to aseptic surgical techniques, proper wound care, and judicious use of prophylactic antibiotics are paramount in minimizing this risk. Early recognition and prompt treatment of any signs of infection are crucial to prevent complications and ensure optimal outcomes.[15-18]

Extrusion of the gold implant is another significant complication that can lead to implant failure and necessitate revision surgery. The extrusion rate varies across studies, likely reflecting differences in surgical techniques, implant characteristics, and patient factors. The identification of superficial implant placement as a potential risk factor underscores the importance of meticulous surgical technique and careful consideration of individual eyelid anatomy. The management of extrusion typically involves implant removal or revision, with careful attention to wound healing and cosmesis. Nonspecific inflammatory reactions, characterized by eyelid swelling, erythema, and tenderness, are relatively common following gold weight implantation. These reactions are thought to represent a normal foreign body response and are often self-limiting. However, in some cases, they can persist and require medical or surgical intervention. The use of topical or systemic steroids can help alleviate inflammation and promote resolution. In refractory cases, implant removal may be necessary to achieve complete symptom relief.[19-22]

The findings of this systematic review highlight several areas for future research. A deeper understanding of the immunological mechanisms underlying hypersensitivity reactions and lymphoma development is crucial for developing preventive and therapeutic strategies. The identification of patient-specific risk factors, such as genetic predisposition or pre-existing autoimmune conditions, may enable more personalized approaches to patient selection and management. Additionally, the development of novel implant materials with improved biocompatibility and reduced immunogenicity holds promise for minimizing complications and expanding the applicability of

eyelid weighting procedures.[23,25]

5. Conclusion

Gold weight implantation remains a valuable tool in the management of lagophthalmos, offering significant benefits in terms of ocular surface protection and patient comfort. However, this systematic review underscores the potential for immune-related complications, ranging from mild inflammation to severe hypersensitivity and lymphoma.

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