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ORAL CORTICOSTEROIDS AND THE LONG-TERM RISK OF CATARACT: A COMPREHENSIVE SYSTEMATIC REVIEW

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ABSTRACT

Background: *A cataract can lead to visual deterioration, resulting in reduced vision capacity and partial or complete reversible vision loss. The most commonly associated risk factors for cataract include aging, diabetic retinopathy, glaucoma, and some medications such as glucocorticoids. Glucocorticoids are utilized in a variety of disorders, as long- and short-term, treatment such as topical ocular steroid usage, allergic rhinitis and inflammatory bowel disease as a result, the chance of cataract may increase and put a significant burden in countries.*

The aim: *This study aims to show about oral corticosteroids and the long-term risk of cataract.*

Methods: *By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2014 and 2024 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.*

Result: *In the PubMed database, the results of our search brought up 79 articles, whereas the results of our search on SagePub brought up 208 articles, on Google Scholar brought up 26.000 articles. The results of the search conducted for the last year of 2014 yielded a total 25 articles for PubMed, 73 articles for SagePub, and 18.000 articles for Google Scholar. The result based on title screening, a total 2 articles for PubMed, 36 articles for SagePub, and 397 for Google Scholar. In the end, we get a total of 10 papers. We included five research that suitable the criteria.*

Conclusion: *Using glucocorticoids either as inhaler and/or orally will increase the risk and prevalence of posterior subcapsular cataract and other ocular complications such as glaucoma.*

Keyword: *Corticosteroid, cataract, oral corticosteroid, glucocorticoids.*

INTRODUCTION

Cataract is a prevalent eye condition characterized by an increasingly opaque lens over time leading to blurred vision. Cataract is the most common treatable cause of acquired blindness worldwide. Eye examination showing the presence of cataract and surgery is the treatment of choice when loss of vision affects daily activities. It has for decades been reported that long-term use of systemic corticosteroids may be associated with the development of cataract. The first study was published almost six decades ago. The type of cataract usually associated with long-term systemic corticosteroid treatment is posterior subcapsular cataract (PSC).[1,2]

Cataract and glaucoma were first described as side effects of systemic glucocorticoid (GC) therapy as early as 1953. In particular, posterior subcapsular cataracts (PSCs) are a subtype of cataracts that occur more frequently in GC-exposed patients. Similarly, GC exposure can lead to steroid-induced glaucoma, a type of open angle glaucoma. These conditions can lead to visual impairment, resulting in significant disability and cost to the healthcare system. As GCs remain widely prescribed in rheumatoid arthritis (RA) and many other inflammatory diseases, any increased risk might lead to a significant public health burden.[3]

EULAR guidelines advocate that clinicians inform their patients of the risk of side effects associated with GCs before commencing treatment. However, for cataract and glaucoma, the magnitude of risk is rarely reported and current literature has not been reviewed to determine if the risk can be accurately quantified. Specific questions, such as how this is influenced by dose and duration of therapy, also have not yet been addressed.[3]

Glucocorticoids a class of drug known to cause posterior subcapsular cataract, particularly in people above the age of 40 are prescribed for a variety of diseases including ocular conditions (e.g., macula edema), asthma, arthritis and inflammatory bowel disease. The data here showed an average of ~9 M annual steroid prescriptions in Australian over the 5 years from 2014 to 2019. Over that period, the annual number of steroid prescriptions increased 7.7% to 9,725,044 in 2018/19, and the associated costs increased by 42.9% to $203M. A UK trial found, on average, patients require 6.5 glucocorticoid prescriptions, and approximately 50% of these patients were 45 years and above. Using this as a guide, this equates to ~1.5 M Australians using prescription steroids in 2018/19 with approximately 750,000 patients 45 years or older. In Australia, the increased risk of PSC due to glucocorticoids is OR 2.5 for inhaled and OR 4.1 for oral corticosteroids. Glucocorticoids were also associated with an increase in nuclear cataracts, with an OR of 2.0 for inhaled and 3.5 for oral corticosteroids (mean age 63 years).[4]

The cataracts caused by glucocorticoid steroids are centrally-located, posterior subscapular cataracts with vacuoles suggesting they relate to aberrant migration of lens epithelial cells (LECs) along the posterior capsule. At present, there is little data describing the molecular mechanisms of steroid-induced cataracts in human lenses. While steroids can bind to lens proteins, this is generally discounted as a mechanism for cataract formation as they do so with lower affinity than other proteins that do not induce cataract.[4]

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we compare and contrast the oral corticosteroids and the long-term risk of cataract. It is possible to accomplish this by researching or investigating the oral corticosteroids and the long-term risk of cataract. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine about oral corticosteroids and the long-term risk of cataract.

In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2014, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used " oral corticosteroids and the long-term risk of cataract." as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: *(("*Corticosteroids*"[MeSH Subheading] OR "*Oral corticosteroids*"[All Fields] OR "*Cataract*" [All Fields]) AND ("*Risk of cataract*"[All Fields] OR "* Oral corticosteroids are risk of cataract *"[All Fields]) AND ("*Long-term impact of

corticosteroids"*[All Fields]) OR ("*Complications of lonf-term oral corticosteroid" *[All Fields]))* used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and cannot have been seen anywhere else.

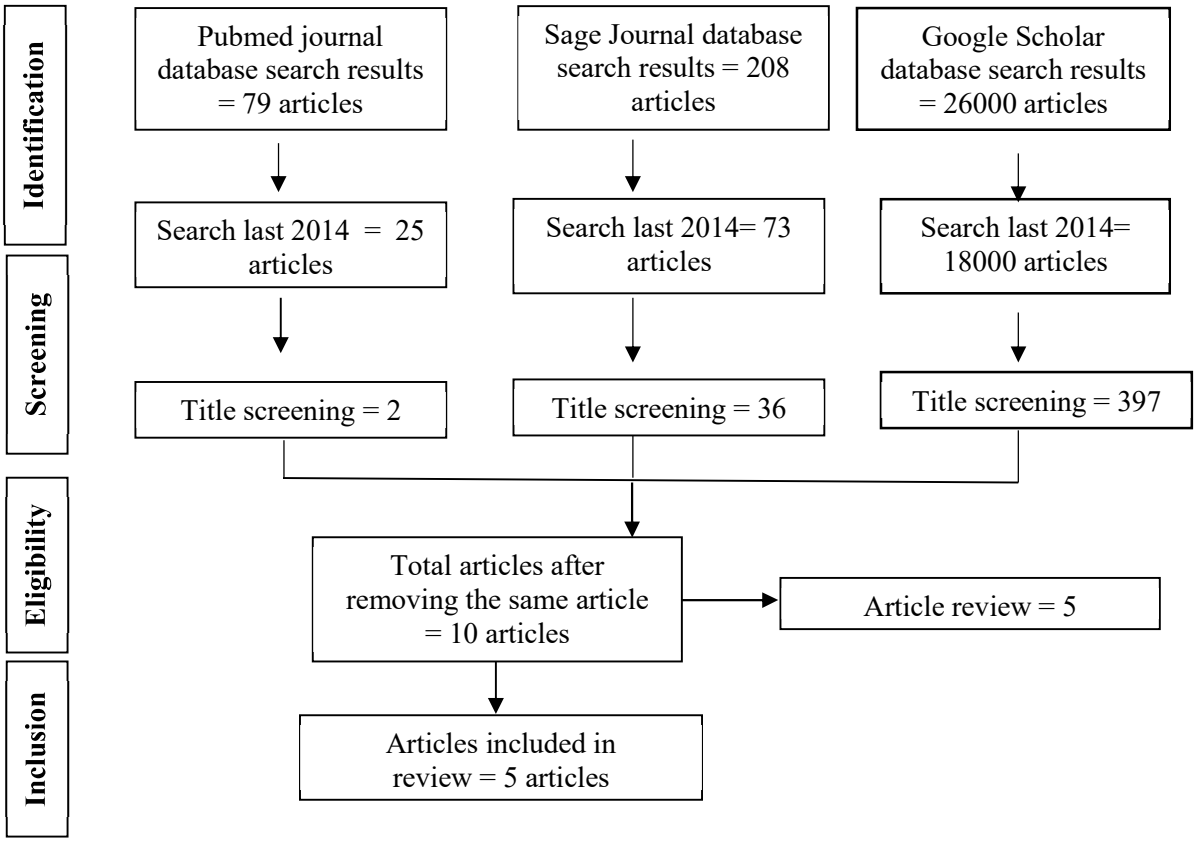

Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

From the PubMed database, the results of our search get 79 articles, whereas the results of our search on SagePub get 208 articles, on Google Scholar 26.000 articles. The results of the search conducted for the last year of 2014 yielded a total 25 articles from PubMed, 73 articles from SagePub, and 18.000 articles from Google Scholar. The result from title screening,

a total 2 articles for PubMed, 36 articles for SagePub, and 397 for Google Scholar. In the end, we compiled a total of 10 papers. We included five research that met the criteria.

Alsomali, AI *et al* (2024)[5] showed) the varying levels of awareness regarding the risks associated with chronic steroid use and cataract development in Al Ahsa City, Saudi Arabia. The findings emphasize the crucial role of education and knowledge in influencing health-related behaviors. Tailored educational interventions are imperative to enhance awareness, particularly among populations at risk, ultimately facilitating informed decision-making and improving overall health outcomes.

Minkus, CL *et al* (2021)[6] showed that the absolute risk of cataract formation in intermediate uveitis cases receiving tertiary uveitis care is moderate, contributing to (usually) temporary visual loss in this population, and permanent loss of accommodation in younger patients. There was an increased incidence of cataract in patients with concurrent anterior uveitis causing posterior synechiae, and in cases with epiretinal membrane. The time-updated degree or duration of intraocular inflammation in intermediate uveitis cases seemed to have less impact than was captured by inflammatory complications; the latter may represent the cumulative degree of inflammatory severity. Patients treated with higher time-updated doses of topical and periocular corticosteroids were at higher risk of cataract than those treated with lower doses, whereas low corticosteroid doses (such as prednisolone acetate 1% less than two drops per day, use of a single periocular injection or oral corticosteroids (especially at 7.5 mg/day or less)) did not, on average, appear to increase the risk of cataract substantially. Therefore, cataract risk might be reduced by minimizing use of local corticosteroid therapy, within the constraints of other potential adverse effects of treatment in a particular patient's context.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Alsomali, AI *et al*., 2024[5]	Saudi arabia	A cross-sectional study	417	Our study results show that 69.8% (n=291) of participants were female, and 30.2% (n=126) were male, with the majority (62.6%, n=261) having a university education. Notably, 91.1% (n=380) reported no steroid use, while 8.9% (n=37) reported long-term use, and 10.1% (n=42) used steroids topically. There are moderate awareness levels regarding cataract and steroid associations, with 68.1% (n=284) recognizing topical steroids as the common culprits. Logistic regression highlighted the positive correlation between knowledge of cataract risks due to steroid use and actual steroid use, corroborated by a notable 73.0% (n=27) steroid usage among high-awareness individuals.
Minkus, CL *et al*., 2021[6]	USA	Retrospective cohort study	1302	Among 2,190 eyes of 1,302 patients with intermediate uveitis the cumulative incidence of cataract formation was 7.6% by one year (95% CI=6.2–9.1%), increasing to 36.6% by ten years (95% CI=31.2–41.6%). Increased cataract risk was observed in eyes with concurrent anterior uveitis causing posterior synechiae (HR=2.68, 95% CI=2.00–3.59, p<0.001), and in eyes with epiretinal membrane formation (HR=1.54, 95% CI=1.15–2.07,

				p=0.004). Higher dose corticosteroid therapy was associated with significantly higher incidence of cataract, especially time-updated use of topical corticosteroids ≥2 times/day or ≥4 periocular corticosteroid injections. Low dose corticosteroid medications (oral prednisone 7.5mg daily or less, or topical corticosteroid drops <2 times/day) were not associated with increased cataract risk.
Bamahfouz, A *et al*., 2024[7]	Saudi Arabia	A cross-sectional study	866	Overall, 866 respondents (males = 42.5%, females = 57.5%) were enrolled in this survey (mean age = 28.08, SD = 13). The participants' correct responses to questions about steroid-induced cataracts showed inadequate representation (below 50%). Additionally, most of the participants (94.23%) had a poor understanding of steroid-induced cataracts.
Guclu, OA & Ismayilov, AS., 2023[8]	Turkey	Cross-sectional clinical study	101	Patients had a mean age of 66.4 ± 11.9 years, and 46.5% (n = 47) were female. A unit increase in the length of inhaled corticosteroids (ICS) and long-acting β-agonists (LABA) combination use was associated with a 1.02-fold increase in cataract risk (OR: 1.02, CI: 1.01–1.04, p = 0.016), and current smokers had 10.8 times as many cataracts (OR: 10.79, CI: 1.70–68.30, p = 0.011). Patients who used a nebulized corticosteroid had a 9.15 times higher risk of developing dry eyes than those who did not (OR: 9.15, CI: 2.34–35.75, p = 0.001). In patients using ICS-LABA, in comparison to formoterol beclomethasone, salmeterol fluticasone was found to increase the risk 7.49-fold for DED (OR: 7.49, CI: 1.48–35.75, p = 0.015).
Price, DB *et al*., 2018[9]	USA	Cohort study	48234	We matched 24,117 pairs of patients with median record availability before SCS initiation of 9.9 and 8.7 years and median follow-up 7.4 and 6.4 years in SCS and non-SCS arms, respectively. Compared with patients in the non-SCS arm, patients prescribed SCS had significantly increased risk of osteoporosis/osteoporotic

				fracture (adjusted hazard ratio 3.11; 95% CI 1.87–5.19), pneumonia (2.68; 2.30–3.11), cardio-/cerebrovascular diseases (1.53; 1.36–1.72), cataract (1.50; 1.31–1.73), sleep apnea (1.40; 1.04–1.86), renal impairment (1.36; 1.26–1.47), depression/anxiety (1.31; 1.21–1.41), type 2 diabetes (1.26; 1.15–1.37), and weight gain (1.14; 1.10–1.18). A dose-response relationship for cumulative SCS exposure with most adverse outcomes began at cumulative exposures of 1.0–<2.5 g and for some outcomes at cumulative exposures of only 0.5–<1 g (vs >0–<0.5 g reference), equivalent to four lifetime SCS courses.

Bamahfouz, A *et al* (2024)[7] showed the risk factors of chronic usage of steroid therapy and its effects on cataracts was inadequate among most of the participants, although the majority are highly educated. Educational campaigns should be conducted to increase public knowledge about cataracts, which would thus decrease the prevalence of the condition and its associated complications. Awareness about cataracts should be further encouraged among Saudi subjects to improve the outcomes and enhance early screening of the disease and the measures for preventing it.

Guclu, OA & Ismayilov, AS (2023)[8] showed that administering bronchodilators or corticosteroids via nebulizer but not inhaler is related to greater rates of dry eye. Smoking, aging, and long-term inhaler steroid use were all linked to an increased risk of cataracts. Longitudinal and larger sample size studies are needed to evaluate the cause-effect relationship.

Price, DB *et al* (2018)[9] showed in a broad asthma population initiating SCS, including both acute and maintenance SCS, and followed over a median exposure period of over 7 years indicate that increasing cumulative exposure and increasing mean daily exposure to SCS places patients at a high risk of potentially life-changing SCS-related adverse outcomes. The onset of some outcomes was associated with cumulative SCS exposure of only 0.5–<1 g, equivalent to four lifetime courses of SCS. These findings underscore the importance of improving the awareness of SCS-related adverse effects in patients with asthma and support the need for continuing development and identification of alternative treatments for treating asthma exacerbations and for patients with severe asthma to reduce exposure to SCS. In conclusion, our findings suggest urgent need for reappraisal of when patients need specialist care and consideration of effective steroid-sparing medications.

DISCUSSION

Corticosteroids are hormone mediators produced by the cortex of adrenal glands that are further categorized into glucocorticoids (major glucocorticoid produced by the body is cortisol), mineralocorticoids (major mineralocorticoid produced in the body is aldosterone), and androgenic sex hormones. Endogenous cortisone was first isolated in 1935 and synthesized in 1944. In 1948, Dr. Philip S Hench published administered cortisone (called Compound E at that time) to a 29-year-old woman who was bed-ridden secondary to active rheumatoid arthritis. The patient was able to walk after three days of treatment. This case was published in 1949, and in 1950, Philip S. Hench, Edward C. Kendall, and Tadeusz Reichstein were awarded the Nobel Prize in Physiology or Medicine "for their discoveries relating to the hormones of the adrenal cortex, their structure, and biological effects.[10,11]

Corticosteroids are used widely for their immunosuppressant and anti-inflammatory properties. They may be used individually or in combination with other drugs and are prescribed in both short and long courses depending on the condition being treated and the response of the patient. The adverse effects from short-course use have been described recently and include changes in mood and behaviour, vomiting and sleep disturbance. Long-course use of corticosteroids may lead to additional side effects. Many of the side effects are reversible if the medication is stopped, while others may be permanent.[12,13]

A cataract is an opacification of the eye's crystalline lens that prevents the light rays from reaching the retina, leading to a visual impairment that significantly affects the patient's quality of life. A complicated cataract refers to the opacification of the crystalline lens secondary to intraocular diseases, mainly intraocular inflammatory conditions that include anterior, intermediate, or posterior uveitis. However, other intraocular conditions have also been identified that lead to the

development of complicated cataracts. It is especially disabling in the younger age group because of the visual impairment and need for cataract surgery with its own complications.[14]

Cataract formation in uveitis occurs due to uncontrolled inflammation and also because of the use of steroids. Managing the case of a complicated cataract is a challenging task for an ophthalmologist, as it also requires meticulous control of the inflammation and management of the primary intraocular disease. Hence, a multidisciplinary approach is required.[14]

A case-control study by Garbe et al quantified the association between CS use and the ocular hypertension-open angle glaucoma spectrum (OR 1.41; 95% CI 1.22 to 1.63). Similar to other steroid-associated complications, the odds of ocular hypertension or open-angle glaucoma also increased with steroid dosage (OR 1.26 for <10 mg/day prednisone equivalent; OR 1.37 for 10-20 mg/day; OR 1.88 for >20 mg/day).(Koshi)

In addition, a literature review by Prokofyeva et al revealed that CS-induced cataracts are usually posterior and subscapular: a rare presentation in patients not taking CS. The review also revealed that various forms of CS (i.e., inhaled, topical, parental, and oral) were associated with an increased risk of cataracts. Oral, parental, and inhalational CS led to cataracts more frequently than CS applied topically. The group at highest risk of CS-induced cataracts was oral CS use for >5 years (OR 3.25; 95% CI 1.39 to 7.58).[15]

CONCLUSION

Using glucocorticoids either as inhaler and/or orally will increase the risk and prevalence of posterior subcapsular cataract and other ocular complications such as glaucoma.

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