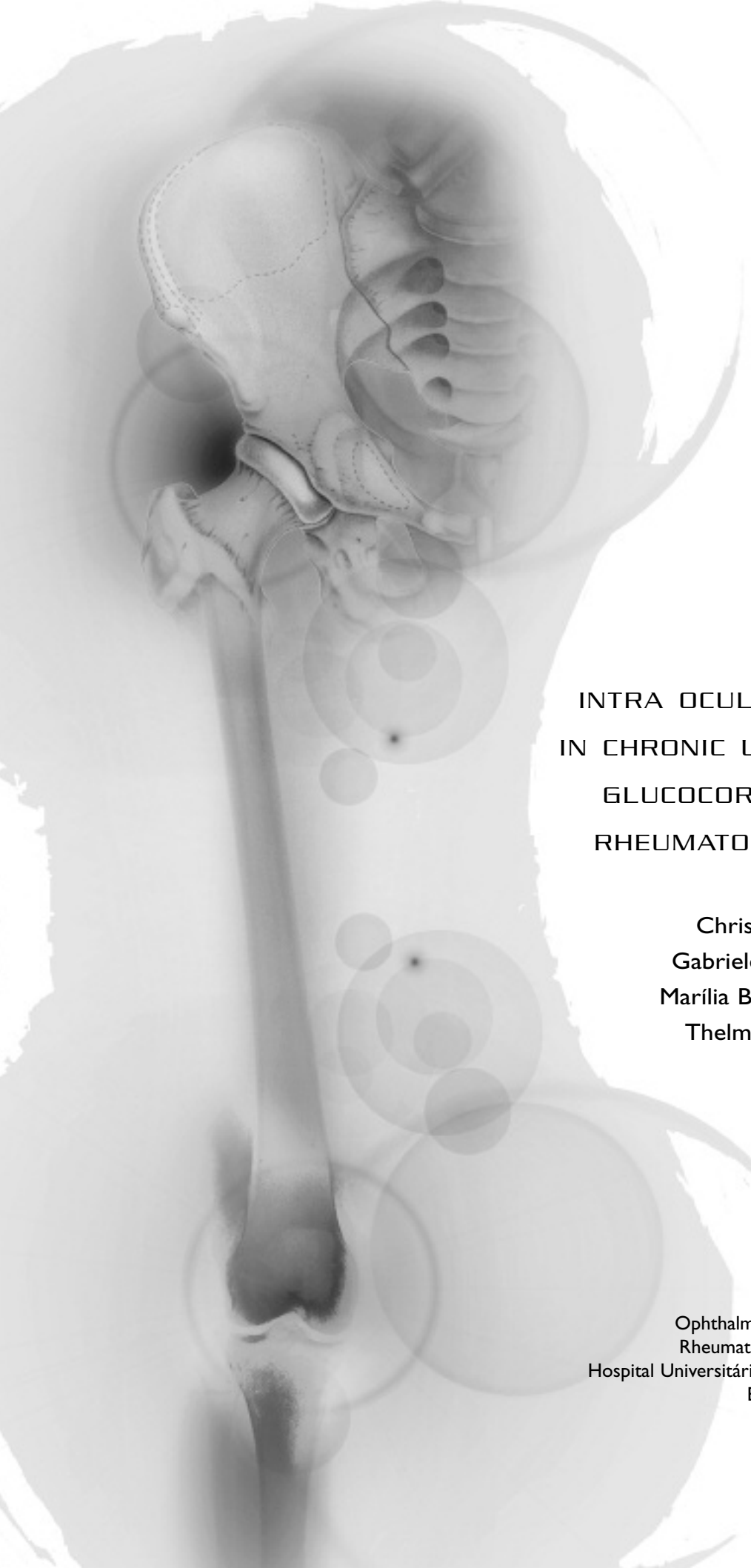

# INTRA OCULAR PRESSURE IN CHRONIC USERS OF ORAL GLUCOCORTICOIDS FOR RHEUMATOID ARTHRITIS

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## ABSTRACT

**Objective:** To evaluate intra ocular pressure (IOP) among rheumatoid arthritis (RA) patients who are chronic oral glucocorticoid users in low to moderate doses.
**Material and methods:** We have studied 125 subjects: 72 glucocorticoid users and 53 controls. The glucocorticoid users were RA patients treated with 5 to 40 mg/day of prednisone or equivalent. Controls were patients with osteoarthritis or with soft tissue rheumatic syndromes who had never used glucocorticoid orally or locally. The IOP was measured three times with Perkins tonometer in both eyes and the mean value was compared between groups. For statistical analysis we used the mean value between the IOP of both eyes.
**Results:** Among RA glucocorticoid users the mean dose was 9.7 mg of prednisone daily during a mean period of 71.1 months. The IOP of glucocorticoid users was 5.8% higher than controls. This difference did not reach statistical significance. The rise in IOP was not affected by the duration of glucocorticoid treatment or by the dose. No RA patient using oral glucocorticoids was found to have abnormal IOP in this study.
**Conclusions:** Low dose glucocorticoids causes a small (5.8%), non significant increase in intraocular pressure.

**Keywords**: Glucocorticoid; Glaucoma; Eye Diseases; Rheumatoid Arthritis.

## RESUMO

**Objetivo:** Estudar a pressão intra ocular (PIO) em portadores de artrite reumatóide (AR) em uso de doses moderadas e baixas de glicocorticóide por via oral.
**Casuística e métodos:** Foram estudados 125 indivíduos: 72 em uso de glicocorticóide e 53 controles. Os usuários de glicocorticóide eram pacientes com AR tratados com doses de 5 até 40 mg/prednisona/dia ou equivalente. Os controles eram pacientes com afecções reumáticas de partes moles e portadores de osteoartrite que nunca haviam feito uso de glicocorticóides orais ou tópicos. A PIO foi medida em ambos os olhos com tonômetro de Perkins por três vezes, sendo utilizada, para fins de estudo, uma média das três medidas. Para análise estatística considerou-se a média de PIO dos dois olhos.
**Resultados:** A dose média de glicocorticóide usada pelos pacientes com AR era de 9,7 mg/prednisona/dia por um tempo médio de 71,1 meses. A PIO dos usuários de glicocorticóide era 5,8% acima daquela dos controles. A diferença não atingiu significância estatística. Nenhum dos portadores de AR em uso de glicocorticóide tinha PIO anormal.
**Conclusões:** Doses baixas de glicocorticóides, usadas oralmente, causam um aumento pequeno (5,8%) e não significante da PIO.

**Palavras chave:** Glicocorticóides; Glaucoma; Doença Ocular; Artrite Reumatóide.

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## Introduction

Glucocorticoids have been extensively used in rheumatology because of their immunomodulatory and anti-inflammatory effects. Joint inflammation in rheumatoid arthritis (RA) patients is particularly sensible to this type of drug and many RA patients use these medications in low doses for a long period of time[1]. Higher doses are required for extraarticular involvement[1].

Despite the positive effects of glucocorticoids in RA, patients who use them are at risk of side effects. Among such side effects is glaucoma[2].

Glaucoma is a complication when patients use glucocorticoids as eye drops or sprays, but very few studies addressed this question when glucocorticoids are used orally.

The present study examines the effects of chronic oral glucocorticoid use on the intra ocular pressure (IOP) of RA patients.

## Methodology

This study was approved by the local Ethics Committee and all patients gave informed consent. We studied 125 subjects: 72 RA patients on glucocorticoids and 53 as controls. The controls were patients with osteoarthritis and soft tissue rheumatic syndromes without any glucocorticoid use (oral or local). This sample corresponds to the patients who attended the Hospital Universitário Evangélico de Curitiba during a recruitment period of 6 months and that were willing to participate in the study.

We considered chronic users patients that used oral glucocorticoids continuously for at least 6 months.

Both groups were submitted to three sequential measurements of IOP of each eye in the same day and the mean of these three measurements was the value considered for analysis. Patients were also questioned about relatives with glaucoma.

The measurement of IOP was taken by a single ophthalmologist using a Perkins tonometer. Patients with inflammatory ophthalmologic disease were excluded.

The data was analyzed using the mean pressure of both eyes. As the IOP obtained values followed Gaussian distribution, we used Student's t test to study the difference between pressure means. Pearson's correlation test was used for evaluation of IOP in RA glucocorticoid users according to dose and therapy duration with the help of the software Graph Pad Prism, version 4.0. The significance adopted was 5%.The sample size showed 73% power to reject a type 2 error.

## Results

The control group age range was 18 to 84 years with a mean of 48.9 ±16.8 years. In the glucocorticoid group patients' age varied from 14 to 79 years with a mean of 45.8±17.02 years. One patient from the control group and two from the glucocorticoid group had first degree relatives with glaucoma. None of them had previous history of high IOP.

In the RA glucocorticoid group, the dose of this drug was between 5 and 40 mg of prednisone/day (mean of 9. 7±6.6 mg/day; median of 10 mg/day). Sixty RA patients were using up to 10mg of prednisone/day, 9 up to 20mg and 3 more than 30mg. The patients who used more than 30mg/day were doing so for extra articular manifestations of RA (none of them ocular). Demographic data is summarized in Table I.

The IOP in the control and glucocorticoid users

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**Table I. Demographic Data in Controls and Glucocorticoid Users**

| | Controls | Corticoid Users |
|---|---|---|
| Number of patients | 52 | 73 |
| Mean age (years) | 48.9±16.8 | 45.8±17.0 |
| Number of patients with relatives with glaucoma | 1 | 2 |
| Gender (female:male) | 42:11 | 60:12 |

groups is present in Table II.

The mean intraocular pressure was 12.8 mm in the control group and 13.4 mm in the glucocorticoid group corresponding this difference to a t value of -1.28 (p=0.20). The difference between means was of 0.58 (confident interval of 95% = -0.31 to 1.48). (Figure 1). RA glucocorticoid users showed an increase of 5.8 % in IOP (p=0.137).

No patients (RA glucocorticoid users and controls) had an IOP higher than 20 mm Hg, which is considered the upper limit of normal.

Analyzing the rise in intraocular pressure of RA patients and the duration of glucocorticoid use we found no correlation (r=0.027 and p= 0.824) between these two variables. (Figure 2).

A weak relationship (r= 0.1725 and p=0.0553) was found between IOP and the daily dose of glucocorticoid in RA glucocorticoid treated patients. This data is depicted in Figure 3.

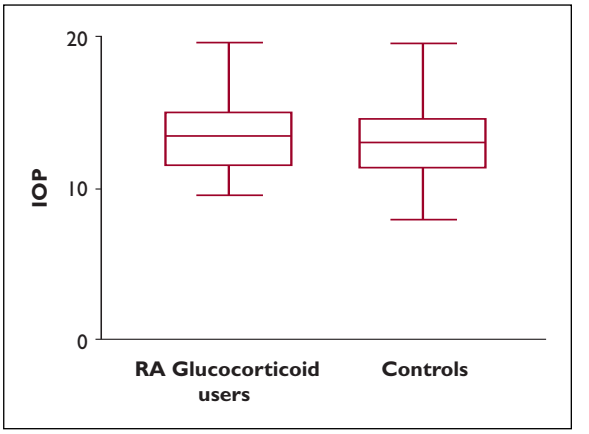


**Figure 1.** Intra ocular pressure in RA glucocorticoid users and controls.

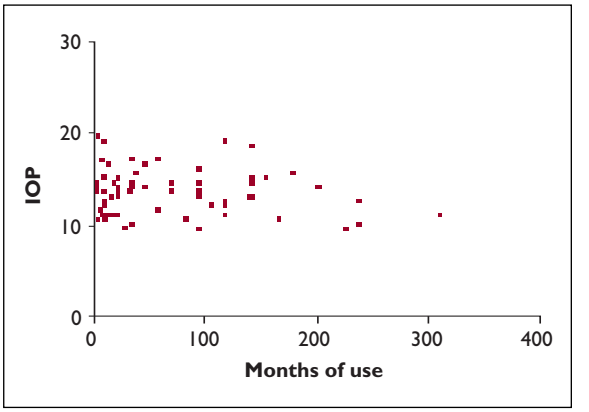


**Figure 2.** Intra ocular pressure in RA glucocorticoid users according to use time.

## Discussion

The mechanisms of glucocorticoid action have been divided by Buttgereit et al in three main groups[3]:

1) mechanisms that causes genomic modifications;
2) mechanisms that do not cause genomic alterations but are mediated by receptors;
3) physico-chemical mechanisms.

The first mechanism is the most studied one. It happens when the glucocorticoid molecule binds to intra cytoplasmatic receptors. After this the complex is transferred to the cell nucleus where it

**Table II. Distribution of Intraocular Pressure in the Studied Population**

| IOP | 8-10mm Hg | 11-12mm Hg | 13-14mm Hg | 15-16mm Hg | 16-20mm Hg |
|---|---|---|---|---|---|
| With glucocorticoid n (%) | 3 (4.17%) | 17 (23.61%) | 21 (29.17%) | 19 (26.39%) | 12 (16.67%) |
| Without glucocorticoid n (%) | 6 (11.54%) | 14 (26.92%) | 13 (25.0%) | 14 (26.96%) | 5 (9.62%) |

n = number of studied patients; IOP = intra ocular pressure; mmHg = millimeters of mercury

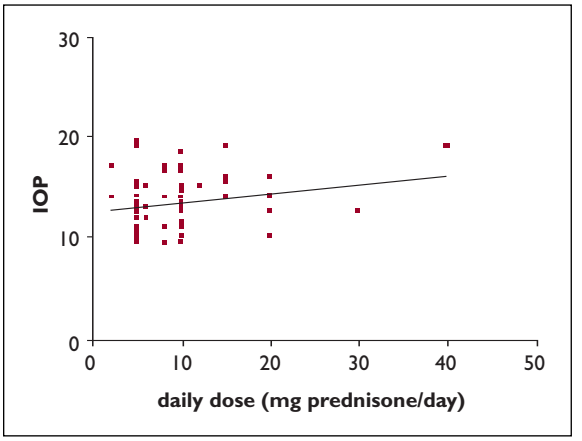


**Figure 3.** Intraocular pressure in RA glucocorticoid users according to daily use.

binds to DNA and acts by increasing or decreasing the RNA messenger transcription (RNAm). The therapeutic actions, as well as the side effects of glucocorticoids, are caused by the increased or decreased synthesis of chemical mediators-controlled by DNA transcription into RNAm[3,4].

The other mechanisms are less studied, but it is known that they require higher doses of glucocorticoid in order to appear. The physico-chemical mechanisms are seen only in cases of glucocorticoid pulse therapy[2]. This mechanism is mediated by changes in the passage of ions through the cytoplasmatic membrane[2].

The time required to act through each of the mechanisms follows the reverse order of the needed dose[2].

There are doubts on which of the mechanisms might be involved in glaucoma appearance. According to Underwood et al glucocorticoids raise the production of ZO-1- a protein present in the intercellular gaps of Schlemm Canal, causing increased resistance to transendotelial flow of aqueous humor[5]. This results from genomic action by glucocorticoid which requires low doses to occur. There is a very interesting observation by Mc Carthy et al. referring that people with open angle glaucoma have higher levels of endogenous corticoids[6].

Our findings showed that no RA patient using glucocorticoid had abnormal IOP. Corticosteroid in doses below 40mg/day given orally caused just a small rise in the intraocular pressure (5.8% above baseline) without statistical significance. One must be careful in the interpretation of these data as they can be due to chance or statistical underpower as the sample size gave only a 73% chance to rejected a type 2 error.

The literature has many observations stating that locally used corticosteroid increases the intra ocular pressure with considerable morbidity[7, 8, 9]. This may be explained by the fact that local use can cause higher concentrations, firing some type of mechanism other than the genomic action. As far as we know, no study has addressed the question of IOP during the oral use of this drug.

We could not find any influence of daily glucocorticoid use in the value of IOP. However, one should note that, in this study, the median used dose was low (10mg/day of prednisone). Studies with a higher number of patients and a higher dose may be able to demonstrate this.

Another question to be taken into account is that glucocorticoid glaucoma as well as juvenile glaucoma and open angle glaucoma suffer genetic influence, such as allelic variations of myociclin gene (MYOC)[10]. In the studied population the positive history for familial glaucoma was very low, so we cannot exclude the risk of greater increase in IOP with oral corticosteroids in these families.

## Conclusion

In this study all RA patients under glucocorticoid treatment had normal IOP. Low dose oral glucocorticoid use in RA patients causes a small, non significant increase in the IOP.

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