

# Glucocorticoid-Induced Ocular Hypertension and Glaucoma

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**Abstract:** Glucocorticoid (GC) therapy is indicated in many diseases, including ocular diseases. An important side-effect of GC therapy is GC-induced ocular hypertension (GIOHT), which may cause irreversible blindness known as GC-induced glaucoma (GIG). Here, we reviewed the pathological changes that contribute to GIOHT including in the trabecular meshwork and Schlemm's canal at cellular and molecular levels. We also discussed the clinical aspects of GIOHT/GIG including disease prevalence, risk factors, the type of GCs, the route of GC administration, and management strategies.

**Keywords:** glucocorticoid, intraocular pressure, trabecular meshwork, aqueous humor outflow, mechanism, treatment

## Introduction

### Purpose and Method of Literature Search

Glaucoma is a leading cause of irreversible blindness worldwide.<sup>1</sup> One of the complications of glucocorticoid (GC) therapy is glucocorticoid-induced ocular hypertension (GIOHT). If GIOHT is left untreated, some patients may develop glaucomatous retinal ganglion cell loss, which is a subtype of glaucoma: glucocorticoid-induced glaucoma (GIG).

The initial reports of GIOHT/GIG were published in the 1950s.<sup>2-6</sup> Since then, there have been many studies attempting to understand the mechanism of GIOHT/GIG. This disease is important for scientists since GIOHT is frequently used as a disease model to study primary open-angle glaucoma. It is also important for clinicians since GC treatment is essential for many ocular and systemic diseases, and sometimes clinicians are in the dilemma of whether to continue GC treatment to control inflammation or to discontinue GC to preserve vision. We hope this article provides a quick overview of GIOHT/GIG with information from bench to bedside to both basic science researchers and clinicians.

The first part of this article reviews the basic-science aspects of the disease focusing on the potential molecular mechanisms. The second part of this article reviews the clinical aspects of the disease focusing on epidemiology as well as GC selection and administration.

Peer-reviewed literature was searched using the following terms in PubMed: ("glucocorticoid receptor"[tw] OR "steroid receptor"[tw] OR "corticosteroid receptor"[tw]) AND ("ocular hypertension"[tw] OR "glaucoma"); TM 11B-hydroxysteroid dehydrogenase glucocorticoid; 11B-hydroxysteroid dehydrogenase steroid responder; yap taz glucocorticoid receptor glaucoma; wnt signaling glucocorticoid receptor; tgfb2 glucocorticoid receptor; cross linked actin network glucocorticoid; trabecular meshwork extracellular matrix glucocorticoid; glucocorticoid glaucoma distal; POAG and steroid-induced glaucoma: rimexolone steroid glaucoma; loteprednol steroid glaucoma; fluocinolone acetonide implant iop; retrobulbar injection steroid IOP; intravenous steroid iop; cutaneous steroid glaucoma; glaucoma Cushing syndrome; steroid-induced glaucoma treatment. Searches were conducted until August 2023.

## Background

### Intraocular Pressure (IOP)

The eye is filled with aqueous humor, and this fluid generates IOP. Intraocular pressure is determined by aqueous humor production (inflow), aqueous humor outflow, and episcleral vein pressure. Aqueous humor outflow has two pathways: the major pathway is the trabecular meshwork (TM) outflow pathway, also called the conventional outflow pathway (the pressure-dependent pathway); the minor pathway is the uveoscleral outflow pathway (the pressure-independent pathway).<sup>7</sup> In GIG/GIOHT eyes, IOP elevation is primarily due to increased outflow resistance (or decreased outflow facility) in the TM outflow pathway.

In non-glaucomatous eyes, the normal IOP is approximately  $16 \pm 5$  mmHg. IOP higher than 21 mmHg is usually considered OHT. Ocular hypertension can lead to glaucomatous optic nerve damage (glaucoma), although some individuals may have OHT for years or even throughout their life span without developing glaucoma. However, OHT is still the most important risk factor for developing glaucomatous optic nerve damage. Besides, GIOHT is not as “natural” as those who have “spontaneous” OHT. Also, individuals who develop GIOHT are susceptible to developing primary open-angle glaucoma.<sup>8,9</sup> Therefore, people with GIOHT may be at higher risk of developing optic nerve damage.

### The Anatomy of the TM and Schlemm's Canal (SC)

As described previously, the majority of the aqueous humor drains through the TM outflow pathway. The tissue in this pathway includes the TM, Schlemm's canal (SC), collector channels, aqueous veins, and episcleral veins. The conventional outflow pathway tissue can be further divided into the proximal outflow tissue and the distal outflow tissue. The proximal outflow tissue refers to the TM and inner wall of SC. The distal outflow tissue refers to the outer wall of SC, collector channels, aqueous veins, and episcleral veins.

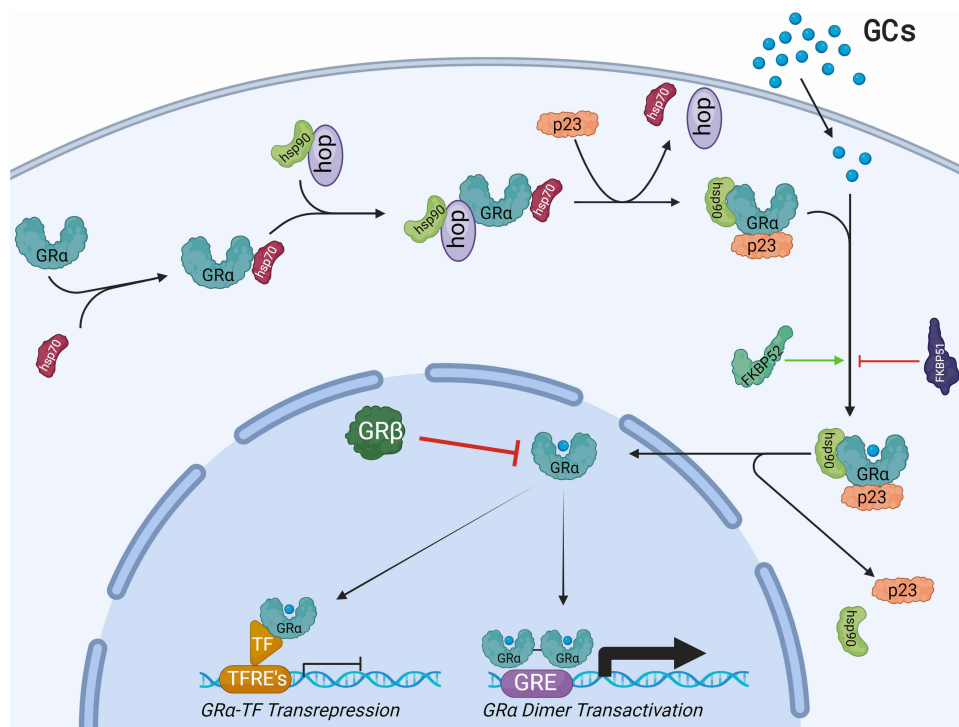
The TM and SC are the key tissues of the TM outflow pathway. The TM can be divided into 3 regions, depending on their location: the uveoscleral meshwork, the corneoscleral meshwork, and the juxtacanalicular region (JCT).<sup>7,10,11</sup> The uveoscleral meshwork is the most adjacent to the aqueous humor and is made of connective tissue trabeculae that create irregular openings through which aqueous humor passes.<sup>7</sup> Adjoining the uveal meshwork is the corneoscleral meshwork, which consists of trabecular beams with elliptical openings that get progressively smaller as the aqueous humor flows outward.<sup>7</sup> Next to the corneoscleral meshwork is the JCT, which consists of irregularly oriented fibrils and layers of TM cells that do not allow for aqueous to easily pass through.<sup>7</sup> The SC has an inner wall and an outer wall. The inner wall of SC is a single layer of endothelium-like cells attached to the basal lamina and/or the JCT ECM, and there are tight junctions between these cells.<sup>7,12</sup> The aqueous humor passes through this layer of cells via two types of pores: type I (transcellular) pores and type B (paracellular) pores.<sup>13</sup> The JCT and the inner wall of SC contribute to the majority of the aqueous humor outflow resistance.<sup>14,15</sup>

## Basic Science Review of GIG/GIOHT

### The Mechanism of GCs

Glucocorticoids function through glucocorticoid receptors (GRs). There are two GR isoforms: GR $\alpha$  and GR $\beta$ .<sup>16</sup> Glucocorticoid receptor  $\alpha$  is located primarily in the cytoplasm, bound to a large heterocomplex comprising several other chaperone proteins including heat shock proteins (HSP), the hop protein, p23, and immunophilins.<sup>17,18</sup> After binding to GCs, the GC-GR $\alpha$  complex translocates into the nucleus, binds to glucocorticoid response elements (GRE), and regulates gene expression. The entire process is finely controlled and involves several regulatory proteins (see Figure 1).

The GR binding proteins play an important role in the activation of the GR. Wang et al reported the structure of the GR loading complex using high-resolution cryo-electron microscopy and the role of these proteins.<sup>18</sup> They described 4 stages of activation of the GR beginning with an association with hsp70 in an inactivated state. The Hop protein then loads the hsp70-GR receptor, with hsp90 creating the inactivated hsp70-GR-hop-hsp90 complex. After hsp90 ATP hydrolysis, hop and hsp70 dissociate and p23 associates, creating the activated, “client-maturation” GR-hsp90-p23 complex.<sup>18</sup> This complex is further regulated by the association with immunophilins FKBP52 and FKBP51.<sup>19</sup> The presence of FKBP52 leads to a higher affinity for GR-ligand binding and the presence of FKBP51 antagonizes FKBP52.<sup>19</sup> It has been reported that higher levels of FKBP51 contribute to GC resistance.<sup>20</sup> After the complex binds to the GC, the GR undergoes conformational change and nuclear



**Figure 1** The glucocorticoid receptor signaling pathway. The cytosolic glucocorticoid receptor alpha (GR $\alpha$ ) is associated with several chaperone proteins including heat-shock protein (HSP) 70, HOP, and HSP 90. After the recruitment of p23 and displacement of HSP 70 and HOP into the complex, the GR $\alpha$  achieves “client-maturation” and is able to bind to glucocorticoids (GCs). Immunophilins influence the affinity of GC binding with FKBP51 decreasing GC-GR $\alpha$  affinity and FKBP52 increasing GC-GR $\alpha$  affinity. These chaperone proteins facilitate the translocation of GC-GR $\alpha$  to the nucleus. The nuclear GC-GR $\alpha$  complex monomer, together with other transcription factors (TFs), functions as a transrepressor to inhibit gene expression. The GC-GR complex may also dimerize and function as a transactivator to increase gene expression. The GR beta (GR $\beta$ ) is an alternatively spliced, dominant negative form of GR $\alpha$ . Created with Biorender.com.

translocation.<sup>21,22</sup> Once in the nucleus, the GR $\alpha$  acts as a transcription factor through either transactivation or transrepression.<sup>23</sup> In the transactivation mode, the GR $\alpha$  dimerizes and binds to the glucocorticoid response elements (GRE) at the promoter region of the target genes.<sup>24,25</sup> In the transrepression mode, the GR $\alpha$  remains as a monomer and interacts with other transcription factors (AP-1, NF- $\kappa$ B) resulting in the inhibition of target gene expression.<sup>24,26</sup> The anti-inflammatory mechanism of GCs is complicated. Traditionally, it is believed that the inhibition of proinflammatory factors by GR transrepression plays a key role.<sup>27</sup> However, studies have shown that the upregulation of anti-inflammatory factors by GR transactivation is also important.<sup>28</sup>

There have not been many reports on the role of GR-mediated transactivation/transrepression in GC-related ocular side effects, especially GIOHT/GIG. Recently, Patel and colleagues tried to dissect the GR transactivation and transrepression sub-pathways in GIOHT using the GR<sup>dim</sup> mice that have impaired GR transactivation but normal GR transrepression.<sup>23</sup> They found that these GR<sup>dim</sup> mice did not develop GIOHT or GC-inducible changes in the TM after periocular DEX injections, which suggests that GIOHT is mediated through GR-transactivation.

Glucocorticoid receptor  $\beta$  is produced through alternative splicing of the GR gene *NR3C1*.<sup>29</sup> In contrast to GR $\alpha$  that has a fully functioning ligand-binding domain (LBD) at the c-terminus, the GR $\beta$  lacks this LBD domain. Although GR $\beta$  is unable to bind to GC, it is still able to dimerize with GR $\alpha$ , resulting in an inhibition of GR signaling by acting as a dominant negative transcription factor.<sup>29</sup> Some studies showed that GR $\beta$  is decreased in the glaucomatous TM cells.<sup>30–32</sup> Patel and colleagues overexpressed GR $\beta$  in the TM of DEX-induced OHT mice using the Ad5 adenovirus.<sup>33</sup> They found that GR $\beta$  overexpression inhibited DEX-induced fibronectin, myocilin, and collagen 1 expression in the mouse TM, decreased DEX-induced OHT, and improved outflow facility. Therefore, it is hypothesized that GR $\alpha$ /GR $\beta$  ratio may determine an individual's GC responsiveness.<sup>29</sup>

There are different mechanisms to regulate GR $\alpha$ /GR $\beta$  ratio in the cell, including GR alternative splicing, GR translocation, and GR polymorphisms.<sup>21,22,34–41</sup>

### (a) Glucocorticoid receptor alternative splicing

As described previously, GR $\alpha$  and GR $\beta$  originate from alternative splicing, and therefore the regulation of alternative splicing contributes to different GR $\alpha$ /GR $\beta$  ratios. Spliceosomes are protein complexes consisting of ribonucleoproteins and serine-arginine proteins (SRp).<sup>41</sup> Jain and colleagues investigated the role of different SRps in GR splicing.<sup>38</sup> They found that SRp30c and SRp40 overexpression decrease GR $\alpha$ /GR $\beta$  ratios and DEX-induced GR signaling activity in human TM cells. They also found that Bombesin, a peptide that decreases SRp20 while increasing SRp30c and SRp40 levels, decreases GR $\alpha$ /GR $\beta$  ratio, and suppresses DEX responses in human TM cells.<sup>38</sup> In another study conducted by the same group, the authors found that a microbial-derived compound, thailanstatin, which regulates alternative splicing, increases GR $\beta$  (decreases GR $\alpha$ /GR $\beta$  ratio) and effectively attenuates the effect of DEX on human TM cells.<sup>39</sup>

### (b) Glucocorticoid receptor translocation

To activate the GR signaling pathway, GR $\alpha$  needs to translocate from the cytoplasm to the nucleus. Zhang et al reported that the hsp90 inhibitor, 17-AAG, decreases GR $\beta$  nuclear translocation and increases its degradation in the cytoplasm, and therefore increases GR $\alpha$ /GR $\beta$  ratio.<sup>21</sup> Since GR $\beta$  nuclear translocation requires FKBP51, they studied the effect of FK506 (an FKBP51 inhibitor) on GC-induced GR translocation in two transformed human TM cell lines (NTM5 and GTM3). In non-glaucomatous NTM5 cells, FK506 increased DEX-induced GR $\beta$  nuclear translocation. In contrast, such an increase of nuclear GR $\beta$  was not observed in glaucomatous GTM3 cells.<sup>22</sup> These studies suggest that GR $\beta$  nuclear translocation may affect GR signaling activity in different TM cells and may contribute to differential GC responsiveness.<sup>21,22</sup>

### (c) Glucocorticoid receptor polymorphisms

Fingert et al studied 48 single nucleotide polymorphisms (SNPs) in three groups of subjects: POAG patients, GC responders, and normal (non-glaucomatous, non GC-responder) patients.<sup>35</sup> These SNPs are associated with GR genes, FKBP genes, and SRp genes. They found that there was no significant difference in any of the SNPs among the three groups, suggesting that none of these SNPs are of high heritable risk in developing GIG or POAG.

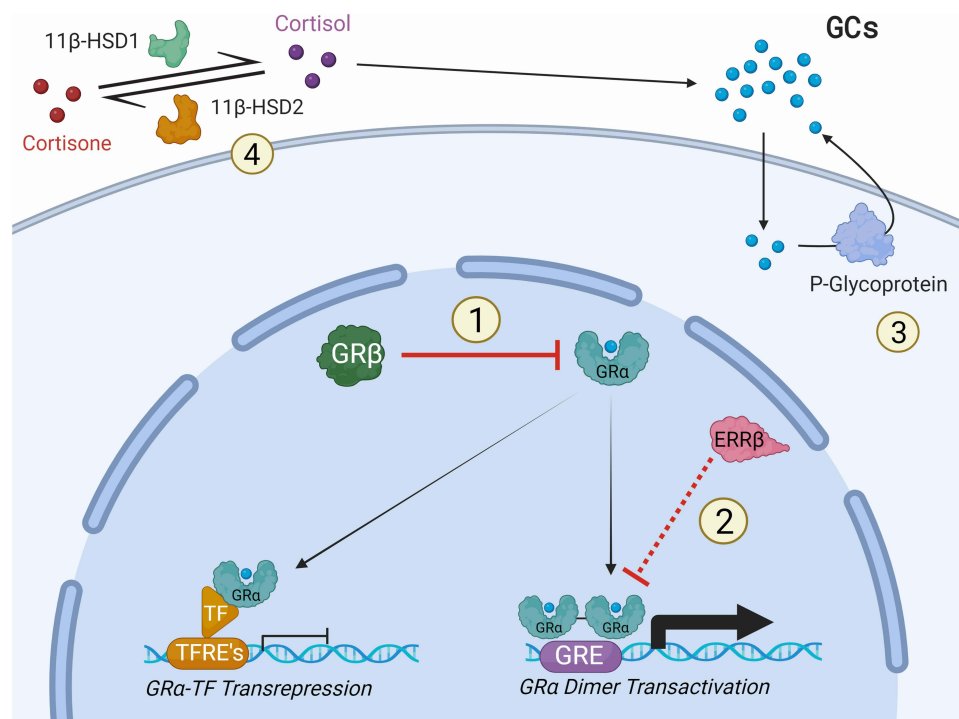
In non-eye related studies, a biallelic polymorphism (*Bcl1*) in the GR gene *NR3C1* was reported to be associated with GC responders compared to non-responders (in that study, responders/non-responders refer to disease treatment outcome, not IOP) in patients with inflammatory bowel disease.<sup>37</sup> This polymorphism is associated with GC responsiveness in lymphocytes.<sup>34</sup> However, Wang et al and Gerzenstein et al both found that there is no significant association between the *Bcl1* polymorphism or other polymorphisms and the development of GIOHT, suggesting that they are unlikely to play a role in ocular GC responsiveness.<sup>36,40</sup>

## Other Potential Regulatory Proteins of GR Signaling

Several other proteins may play a role in regulating GR signaling (Figure 2). The estrogen-related receptor  $\beta$  (ERR $\beta$ ; also known as estrogen receptor-related 2) belongs to the orphan nuclear receptor family, a subgroup of the nuclear receptor superfamily. Trapp et al found that ERR $\beta$  inhibited the transcriptional activity of GRs in non-ocular cells.<sup>42</sup> However, there is a lack of reports of such regulation in the TM.

LEM1 is a transporter protein found in the yeast, and it actively transports several molecules, including GCs, out of the cell.<sup>43,44</sup> Kralli et al reported that the human gene *Mrd1*, also known as *ABCB1*, is functionally similar to LEM1 and produces a protein, P-glycoprotein, which actively transports GCs from the cell.<sup>43</sup> Liu et al studied the effect of polymorphisms in the *ABCB1* gene on the susceptibility of developing POAG.<sup>44</sup> They found that two polymorphisms in the *ABCB1* gene, 2677 G> T/A and 3435 C> T, are associated with susceptibility to POAG. Since POAG is closely related to GIOHT/GIG (over 90% POAG patients are GC-responders),<sup>45,46</sup> *ABCB1* may play a role in GIOHT/GIG.

Another protein that may play a role in the susceptibility of developing GIOHT/GIG is 11 $\beta$ -hydroxysteroid dehydrogenase (11 $\beta$ -HSD), which has two isozyme forms: 11 $\beta$ -hydroxysteroid dehydrogenase 1 (11 $\beta$ -HSD1) and 11 $\beta$ -hydroxysteroid dehydrogenase 2 (11 $\beta$ -HSD2). 11 $\beta$ -HSD1 converts cortisone to cortisol, and 11 $\beta$ -HSD2 converts cortisol



**Figure 2** The regulation of glucocorticoid receptor signaling. Several proteins participate in the regulation of glucocorticoid receptor (GR) signaling. 1) The presence of GR $\beta$ , an alternatively spliced, dominant negative form GR $\alpha$ , inhibits GR signaling. 2) The estrogen-related receptor  $\beta$  (ERR $\beta$ ) may inhibit GR transcriptional activity (in non-ocular cells). 3) P-glycoprotein actively transports glucocorticoids (GCs) out of the cell. 4) 11 $\beta$ -hydroxysteroid dehydrogenase 1/2 (11 $\beta$ -HSD 1/2) regulates the conversion of cortisol from cortisone and may contribute to increased GR signaling.

to cortisone.<sup>47</sup> It is known that high cortisol levels are a known risk factor for OHT and POAG.<sup>48–52</sup> Carbenoxolone (CBX) is an inhibitor of 11 $\beta$ -HSD1 and was reported to lower IOP.<sup>47,53,54</sup> Rauz et al showed that 11 $\beta$ -HSD1 is expressed in corneal endothelium and ciliary non-pigmented epithelium, but not in TM cells.<sup>47</sup> However, they found that oral delivery of CBX lowered baseline IOP in healthy individuals. The authors hypothesized that 11 $\beta$ -HSD1 may contribute to GIOHT/GIG through several mechanisms including increasing cortisol in the aqueous humor.

## Cross-Talk Between the GR Signaling Pathway and Other Signaling Pathways

### The YAP/TAZ Pathway

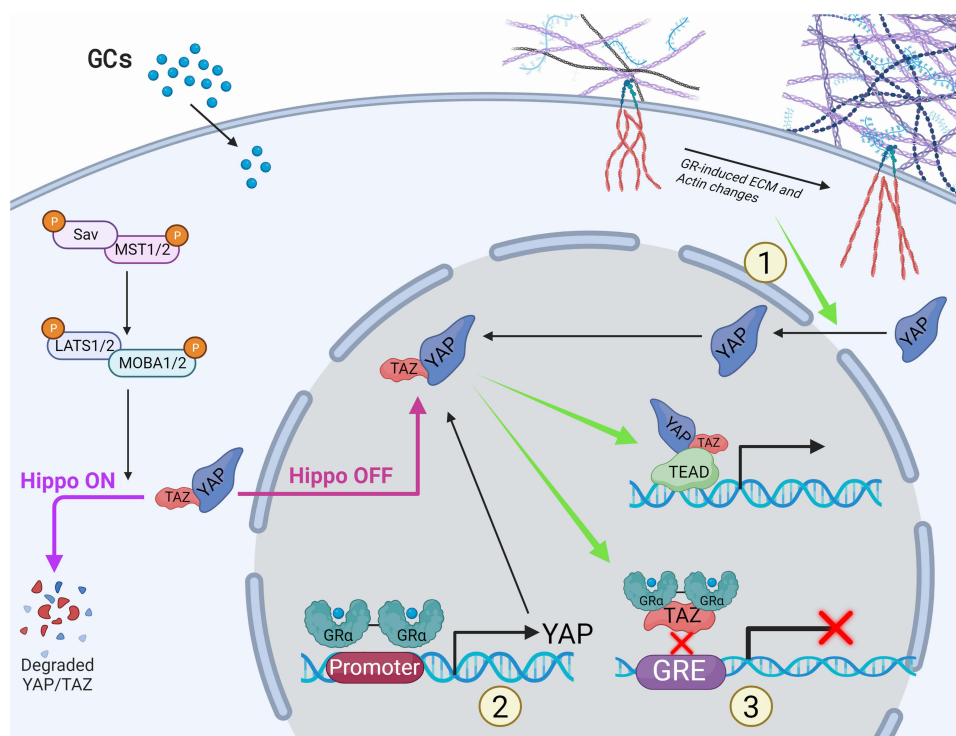
The Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ) are two proteins that play important roles in many biological processes, including adequate organ growth, through cellular signaling and regulation of gene expression.<sup>55</sup> YAP/TAZ is commonly associated with the Hippo pathway, but there are other regulators of YAP/TAZ signaling, including mechanotransduction through cell structure, shape, and polarity, as well as intercellular communications.<sup>55,56</sup> The YAP/TAZ pathway is also implicated in the development of several types of tumors.<sup>57,58</sup>

The Hippo pathway was originally discovered in *Drosophila*.<sup>59–63</sup> In mammalian cells, when the Hippo pathway is on, MST1/2 forms a complex with the protein SAV1 and both proteins are phosphorylated and activated.<sup>55</sup> Phospho-MST1/2 subsequently phosphorylates LATS 1/2 and MOB1A/B. Phospho-LATS 1/2-MOB1A/B complex phosphorylates YAP/TAZ leading to YAP/TAZ degradation. Without nuclear YAP/TAZ, gene expression is turned off. When the Hippo pathway is off, unphosphorylated MST1/2, SAV1, Mob1, and LATS1/2 lead to YAP/TAZ nuclear translocation where it binds to TEAD transcription factors and turns on gene expression.

Mechanotransduction is an important regulator of YAP/TAZ signaling, and part of this regulation is triggered by the changes in tension and conformation of F-actin.<sup>56</sup> In brief, high-tension focal adhesions activate YAP/TAZ signaling, and low-tension focal adhesions inhibit YAP/TAZ signaling.<sup>64</sup>

There is an important cross-talk between GR signaling and YAP/TAZ (see Figure 3). Sorrentino and colleagues found that in breast cancer cells, the GR binds directly to the YAP promoter region and increases its expression.<sup>58</sup> In addition,





**Figure 3** The cross-talk between glucocorticoid receptor and YAP/TAZ signaling pathways. The glucocorticoid receptor (GR) signaling pathway and the YAP/TAZ pathway cross-talk via 1) glucocorticoid (GC)-induced changes in ECM and actin cytoskeleton may lead to increased nuclear translocation of YAP; 2) the GR $\alpha$ -GC complex binds directly to the YAP gene promoter and increases its expression; 3) YAP/TAZ signaling inhibits GR signaling as TAZ prevents the binding of GR $\alpha$  to glucocorticoid response elements (GRE's) which inhibits target gene transcription.

GC-induced fibronectin expression and actin reorganization increase YAP nuclear translocation in those cells.<sup>58</sup> These effects are inhibited when the cells are co-treated with the GR antagonist RU486.<sup>57,58</sup> Nakamura and colleagues found that GC-induced YAP activity may contribute to vocal folds fibrosis.<sup>65</sup>

Although GR signaling activates YAP/TAZ signaling, in contrast, YAP/TAZ signaling inhibits GR signaling. For example, Xu et al found that in hepatocytes, TAZ acts as an inhibitor of GR signaling by preventing its binding to the GRE of gluconeogenic genes since TAZ-knockout mice exhibit higher levels of glucose production and concentration in the blood.<sup>66</sup>

Recent studies have shown that YAP/TAZ signaling plays an important role in glaucoma-related ocular tissues including the lamina cribrosa,<sup>67</sup> retinal capillary endothelial cells,<sup>68</sup> and TM.<sup>69–71</sup> The cross-talk between YAP/TAZ and GR signaling in the TM may contribute to GIOHT/GIG. Recently, Yoo and colleagues investigated the effect of statins, which are YAP/TAZ signaling inhibitors, on GC-treated TM cells.<sup>71</sup> They found that Simvastatin significantly decreases nuclear YAP/TAZ and attenuates high extracellular matrix (ECM) stiffness induced by DEX. Their data suggested that Simvastatin may have therapeutic applications for GIOHT/GIG.<sup>71</sup>

## The Wnt Pathway

The Wnt signaling pathway is evolutionarily conserved with a wide range of biological functions including the regulation of cell proliferation, cell fate determination, cell polarity during development, cell migration, apoptosis, and stem cell maintenance.<sup>72</sup> Dysregulation of the Wnt signaling pathway has been reported in the pathogenesis of a variety of human diseases including developmental diseases, degenerative diseases, cancers,<sup>73</sup> and glaucoma.<sup>74,75</sup> The first member of the Wnt signaling pathway was identified in 1982,<sup>76</sup> and since then, studies on Wnt signaling have been steadily increasing. The Wnt gene was originally derived from integrase-1 in mouse breast cancer and the wingless gene of *Drosophila*.<sup>76,77</sup> Because the two genes and functional proteins are similar, researchers combined the terms as the Wnt gene.<sup>78</sup>

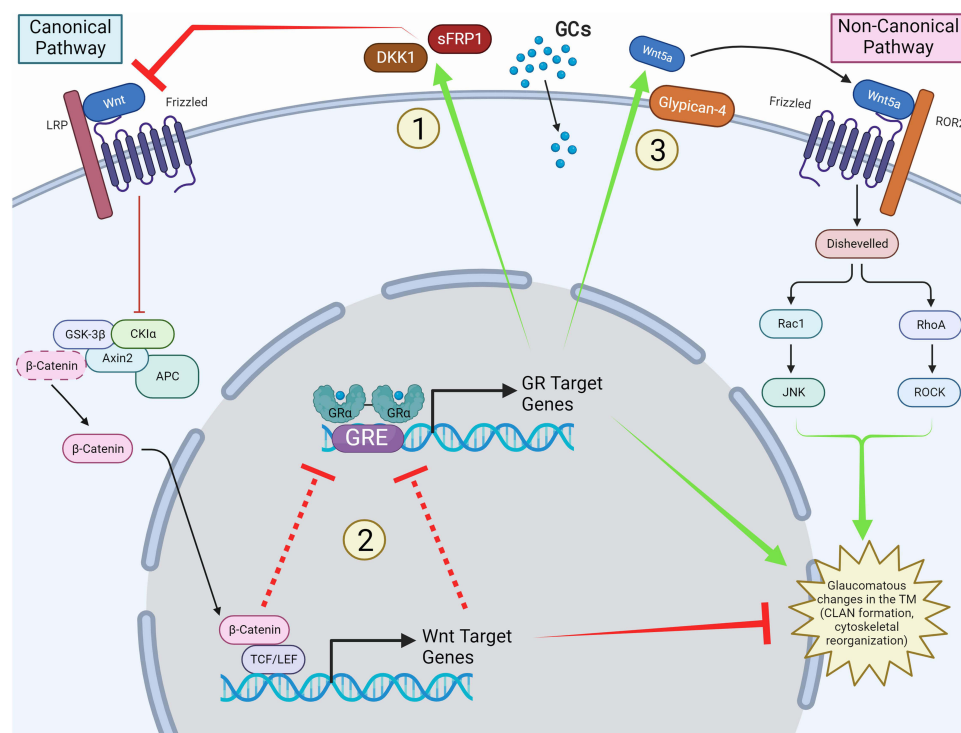
The Wnt signaling pathway includes the canonical and noncanonical pathways.<sup>72</sup> The noncanonical Wnt pathways are independent of  $\beta$ -catenin-Tcell factor/lymphoid enhancer-binding factor (TCF/LEF). They include the Wnt/Ca<sup>2+</sup>

pathway, PCP pathway, and Rho/Rock pathway. The canonical Wnt pathway, also known as the Wnt/ $\beta$ -catenin pathway, involves the nuclear translocation of  $\beta$ -catenin and transcriptional regulation via TCF/LEF transcription factors.<sup>79</sup> In the canonical Wnt pathway, in the absence of Wnt ligands,  $\beta$ -catenin undergoes degradation by the degradation complex formed by Axin2, adenomatous polyposis coli (APC), glycogen synthase kinase-3 $\beta$  (GSK3 $\beta$ ), and casein kinase-1 $\alpha$  (CK1 $\alpha$ ).<sup>80</sup> When Wnt ligands bind to their transmembrane receptor Frizzled and co-receptor lipoprotein receptor-related protein 5/6 (LRP 5/6), the degradation complex disassembles, which allows cytosolic  $\beta$ -catenin to accumulate and translocate into the nucleus. Nuclear  $\beta$ -catenin associates with T-cell factors 1/3/4 (TCF1/3/4) or lymphoid enhancer binding factor 1 (LEF-1). They bind to the TCF/LEF binding element and regulate gene expression.<sup>81</sup>

The Wnt pathway cross-talks with the GR pathway in several ways (Figure 4). The antagonists of the Wnt pathway such as dickkopf1 (DKK1)<sup>74</sup> and sFRP1<sup>82</sup> are elevated in the glaucomatous TM. Overexpression of the two Wnt inhibitors induces OHT in human and/or mouse eyes.<sup>74,82</sup> Mao and colleagues showed that there is a functional canonical Wnt signaling pathway in the TM and plays an important role in the regulation of IOP in the mouse eye.<sup>83</sup>

Bermudez and colleagues showed that the canonical Wnt pathway inhibitor DKK1 is elevated in the bovine TM after DEX treatment.<sup>46</sup> More importantly, they found that DKK1 is more elevated in bovine responder TM cells compared to non-responder TM cells. In a recent study, Sugali and colleagues showed that the activation of canonical Wnt signaling attenuates DEX-induced GR signaling activity and pathological changes in the TM as well as prevents DEX-induced OHT in a mouse model.<sup>74</sup> In contrast, inhibition of the canonical Wnt signaling enhances GR signaling. Ragunathan's group also showed that DEX induces the expression of DKK1, DKK2, and SFRP1 in TM cells.<sup>84</sup>

Non-canonical Wnt signaling, in contrast, may contribute to glaucomatous changes. Yuan and colleagues reported the induction of Wnt5a by DEX, which contributes to cytoskeletal reorganization and CLAN formation via ROR2/RhoA/Rock signaling.<sup>85</sup> Also, Rao's group recently reported that glypican-4 mediates DEX and Wnt5a-induced changes in TM cell cultures.<sup>86</sup>



**Figure 4** The cross-talk between glucocorticoid receptor and Wnt signaling pathways. The glucocorticoid receptor (GR) signaling pathway and the Wnt signaling pathway cross-talk via 1) glucocorticoid (GC)-induced expression of DKK1 and SFRP1 inhibits the canonical Wnt signaling pathway in the TM; 2) canonical Wnt signaling inhibits GR signaling via unknown mechanisms; 3) GC-induced Wnt5a activates non-canonical Wnt signaling which is mediated by glypican-4.

## The TGF $\beta$ Pathway

TGF $\beta$  is a cytokine, which plays a key role in various biological processes including growth, differentiation, cell death, and migration.<sup>87–91</sup> Three different isoforms have been identified in mammals: TGF- $\beta$ 1, TGF- $\beta$ 2, and TGF- $\beta$ 3.<sup>92</sup> They bind to their transmembrane receptors TGF $\beta$ RI and TGF $\beta$ RII, which are serine/threonine kinases. Binding of TGF $\beta$  to its receptors activates TGF $\beta$  signaling via the phosphorylation of Smad2/3. Phospho-Smad2/3 and the co-Smad (Smad4; not phosphorylated) form a complex, and the complex translocates to the nucleus where it binds to the Smad binding element (SBE) to regulate gene transcription.<sup>93</sup>

Among different TGF $\beta$  proteins, TGF $\beta$ 2 is one of the most well studied in glaucoma pathogenesis and plays an important role in the cross-talk to GR signaling (Figure 5). TGF $\beta$ 2 levels are elevated in the aqueous humor and TM tissue of POAG patients.<sup>94,95</sup> Experimentally, excessive TGF $\beta$ 2 induces pathological changes including formation of CLANs, excessive synthesis and deposition of ECM proteins including fibronectin, Collagen I, IV, etc, in the TM as well as elevates IOP in perfusion cultured human eyes as well as in vivo rat and mouse eyes.<sup>95–99</sup>

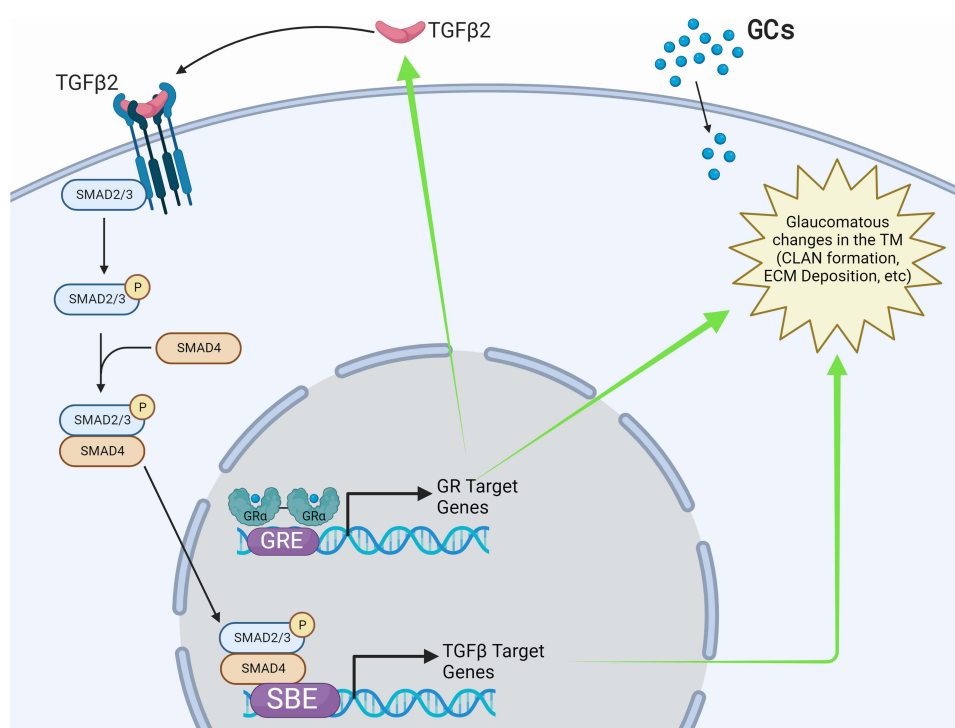
Kasetti and colleagues showed that DEX elevates TGF $\beta$  signaling by inducing TGF $\beta$ 2 expression in the TM.<sup>100</sup> They also showed that Smad3 knock-out mice (with impaired TGF $\beta$  signaling) fail to develop ER stress or DEX-induced OHT. Their data suggested that DEX-mediated effects require/are via TGF $\beta$  signaling.

## Glucocorticoid-Induced Pathological Changes in the TM, ECM, SC, and Distal Outflow Tissue

### Glucocorticoid-Induced Changes in TM Cells

#### Cross-Linked Actin Networks (CLANs) in the TM

One of the unique features of TM cells (not seen in the inner wall of SC cells) is the formation of cross-linked actin networks (CLANs).<sup>101</sup> Cross-linked actin networks are formed by F-actin and many actin-binding proteins.<sup>102–104</sup> They consist of many small triangles and these triangles further form dome-shaped, three-dimensional structures frequently observed in the perinuclear region.<sup>101,105</sup> CLANs are GC and TGF $\beta$ 2-inducible in TM cells, and more importantly,



**Figure 5** The TGF $\beta$  signaling pathway mediates the effect of the GR signaling pathway in the TM. Glucocorticoids (GCs) induce the expression of TGF $\beta$ 2 which activates the TGF $\beta$  signaling in the TM, and this process seems to be SMAD3 dependent.



glaucomatous TM cells and tissues form more CLANs.<sup>95,101,106–108</sup> Other nonhuman TM cells, such as bovine<sup>83,109</sup> and mouse<sup>110</sup> TM cells, also form CLANs.

Although the detailed mechanisms by which CLANs form are still unclear, studies have shown that several signaling pathways participate in/affect CLAN formation. Besides GR and TGF $\beta$  signaling as described previously, Peters' group showed that the activation of the integrin signaling pathway contributes to CLAN formation.<sup>104,111,112</sup> Also, Yuan et al reported that DEX-induced noncanonical Wnt signaling increases CLAN formation.<sup>85</sup>

Multiple studies have investigated the potential intervention to prevent or reverse CLAN formation. Clark et al found that tetrahydrocortisol (THF), a cortisol metabolite, inhibits CLAN formation in GC-treated TM cells without blocking GR activity.<sup>107</sup> Montecchi-Palmer and colleagues reported that the Rho-associated protein kinase (ROCK) inhibitor can completely or partially prevent CLAN formation and/or dissolve formed CLANs.<sup>105</sup>

However, the contribution of CLANs to OHT is still not clear. Recently, Peng and colleagues developed a stably transformed GTM cell line, which expresses the LifeAct-GFP fusion protein.<sup>113</sup> This cell line enables live imaging of the actin cytoskeleton. Using this TM cell line, the authors showed that CLANs increase TM cell stiffness, inhibit TM cell phagocytosis, and decrease cells' responsiveness to the actin depolymerization agent latrunculin B. The first two effects are also observed in primary human TM cells. The authors speculated that increased TM cell stiffness and decreased phagocytosis may contribute to increased outflow resistance and IOP.<sup>113</sup> However, more research is needed to test this hypothesis.

### Increased TM Cell Stiffness

Raghunathan and colleagues reported that after DEX treatment for 3 days, there is about 2-fold increase in primary human TM cell stiffness.<sup>84</sup> It is still not entirely clear how DEX treatment elevates TM cell stiffness. Yuan et al and Fujimoto et al showed that DEX induces actin stress fibers<sup>85</sup> and activates the ROCK pathway.<sup>114</sup> Both events contribute to actin cytoskeletal contraction and reorganization, which could increase cell stiffness.<sup>115</sup> Recently, Peng and colleagues used a vital actin dye SiR-actin to stain primary human TM cells for live imaging and atomic force microscopy.<sup>113</sup> They showed that the TM cells with DEX-induced CLANs are stiffer than those treated with DEX but without CLANs, and the cells without CLANs are as soft as non-DEX treated control cells. As described previously, DEX-induced CLAN formation could be one of the contributors of elevated cell stiffness besides actin cytoskeleton contraction and other changes. How stiffer TM cells contribute to OHT is still not entirely clear, but many studies have shown that stiffer TM cells produce stiffer ECM and have compromised mechanosensory functions, which could increase outflow resistance and IOP.<sup>115–118</sup>

### Decreased TM Cell Phagocytosis

Trabecular meshwork cells have the unique capability of phagocytosis, which enables them to clean up tissue/cell debris (eg, pigment, red blood cells, etc) and to maintain a clear pathway for aqueous humor drainage. Zhang and colleagues showed that DEX decreased TM cell phagocytosis and this decrease may contribute to OHT.<sup>32,119</sup>

### Elevated Endoplasmic Reticulum (ER) Stress

Zode and colleagues showed that in DEX-induced OHT mouse eyes, ER stress markers such as GRP78, ATF4/6, and CHOP are elevated in the mouse anterior segment.<sup>120</sup> Cotreatment with the ER stress inhibitor, 4-PBA, reduces DEX-induced ER stress markers and OHT. This study suggested that ER stress plays an important role in GIOHT/GIG.<sup>120</sup>

### Cell Adhesion

Integrins are important cell-matrix adhesion proteins. Peters' group has conducted extensive investigations on GC-induced integrin changes in the TM. They found that DEX activates  $\alpha\beta3$  integrins through conformational changes, which is likely via an inside-out process (ie, cytosolic changes activate  $\alpha\beta3$  from within), as well as increases  $\alpha\beta3$  integrin expression and affinity via the calcineurin/NFAT pathway.<sup>112,121,122</sup> Besides, the integrin signaling pathway affects phagocytosis and CLAN formation in the TM.<sup>103,112,123,124</sup>

### Glucocorticoid-Induced Changes in the TM ECM

The ECM is a key component of the TM outflow pathway. Glucocorticoids induce the accumulation of ECM proteins such as glycosaminoglycans, fibronectin, and collagens<sup>19,125,126</sup> by increasing their production and/or decreasing

metalloproteinases (MMPs, which degrade ECM).<sup>127–129</sup> There are fingerprint-like materials at the JCT ECM underneath the inner wall of SC in GIOHT/GIG eyes.<sup>130</sup> Overby's group also reported an increase in the basement membrane of the inner wall endothelium of SC in GIG eyes.<sup>131</sup>

Besides changes in the amount of ECM, GCs make TM ECM stiffer, which may contribute to increased outflow resistance and GIOHT. Raghunathan and colleagues studied the effect of DEX on TM ECM.<sup>84</sup> The authors treated TM cells with or without DEX and then removed the cells using a mild detergent. Using atomic force microscopy, they found that DEX increases the stiffness of the ECM around the treated cells. The short-term stiffness change induced by DEX can trigger changes in gene expression and lead to altered ECM deposition/composition in the long term, thus creating a feedforward loop perpetuating the glaucomatous changes.<sup>84</sup> GCs may also inhibit MMP activation/activity by the induction of PAI-1, an inhibitor of tissue plasminogen activator (tPA), although there are limited reports.<sup>132</sup> However, treatment with tPA was shown to lower IOP in GIOHT animal models. In a sheep GIOHT model, Gerometta and colleagues showed that intravitreal injection of tPA decreases IOP.<sup>133</sup> Kumar and colleagues showed that the administration of tPA lowers IOP in a mouse GIOHT model.<sup>134</sup> Gindina and colleagues observed that tPA does not exert its effect on MMP expression through enzymatic activity, but rather through a cytokine-mediated fashion as both enzymatically active and inactive tPA had similar effects on MMP expression after GC administration.<sup>135</sup>

### Glucocorticoid-Induced Changes in the SC

Underwood and colleagues reported that DEX increases fluid flow resistance, tight junction formation and the associated protein ZO-1, as well as a reduction in interendothelial spaces.<sup>136</sup> Glucocorticoids also induce actin cytoskeletal changes in SC inner wall cells, causing elevated cortical stiffness.<sup>137</sup> Importantly, increased SC inner wall cell stiffness is also observed in POAG eyes.<sup>138</sup> Therefore, high SC inner wall stiffness is likely to compromise pore formation and therefore to increase outflow resistance.<sup>137</sup> Overby and colleagues found that in human donor eyes with long-term GC use, the SC basement membrane is more continuous and shows the morphology of a thick band.<sup>131</sup>

### Glucocorticoid-Induced Pathological Changes in the Distal Outflow Tissue

Most of the GIOHT/GIG research focuses on the proximal outflow tissues (TM and SC). Recently, the distal outflow tissue has drawn increasing attention in glaucoma research. Rosenquist et al showed that the distal outflow tissue may contribute to about 25%–50% of the total outflow resistance.<sup>139</sup> Gonzalez Jr. et al showed that the distal outflow tissue expresses contractile tissue markers using 2-photon imaging.<sup>140</sup> McDonnell and colleagues reported that endothelin-1 significantly elevates outflow resistance in perfusion cultured human donor eyes with the TM removed (thus these eyes only had distal outflow tissues), and this elevation could be reversed by co-treatment with a nitroxide donor compound.<sup>141</sup> Chowdhury and colleague developed an approach to culture vascular distal outflow cells and showed that these cells are biologically different from TM cells.<sup>142</sup> More importantly, a recent clinical study reported that one-eighth of the minimally invasive glaucoma surgery (surgical procedures that partially/completely remove the TM or open the TM from inside the eye) patients may still develop GIOHT,<sup>143</sup> suggesting that the distal outflow tissue may also contribute to GIOHT/GIG.

## Clinical Science Review of GIG/GIOHT

### Clinical Features of GIG/GIOHT

The clinical features of GIOHT/GIG are very similar to those of POAG. Unlike some POAG patients who do not show OHT (normal tension glaucoma), all GIOHT/GIG patients have elevated IOP. Depending on the responsiveness of these patients, their IOP may be significantly higher than that of POAG patients, which may lead to rapid disease progression.

### Glucocorticoid Responsiveness and the Type of GCs

The type of GCs affects GC responsiveness (Table 1).<sup>31</sup> Bojikian et al found that the incidence of GIOHT (defined as >50% increase in baseline IOP) following topical prednisolone post-cataract treatment to be 2.1% in non-glaucomatous eyes and 8.4% in glaucoma eyes.<sup>144</sup> Rajendrababu et al analyzed GC response after the same treatment (topical prednisolone post-cataract treatment) and found that 3.2% (2.8% moderate and 0.4% high responders) non-glaucomatous patients had GIOHT (>6 mmHg increase in IOP).<sup>145</sup> Badrinarayanan et al found that 28% of non-glaucomatous eyes developed OHT  $\geq 21$  mmHg after

**Table I** A Comparison of the Incidence of Glucocorticoid-Induced Ocular Hypertension (GIOHT) of Different Glucocorticoids

Glucocorticoid Medication	Incidence of GIOHT	Study
Dexamethasone Implant (0.35–0.7 mg) Implant (Unspecified Dose) Intracameral Injection (0.4 mg) Intracameral Injection (0.4 mg) Intravenous (6–12 mg/m <sup>2</sup> /day) Intravitreal Injection (0.4 mg) Intravitreal Injection (0.8 mg)	11–15% Combined Eyes* 17% Non-Glaucoma Eyes 0% Pediatric Eyes 0% Combined Eyes* 100% Pediatric Eyes 0% Non-Glaucoma Eyes 16.7% Non-Glaucoma Eyes	Kiddee et al (2013) <sup>148</sup> Badrinarayanan et al (2022) <sup>146</sup> Mataftsi et al (2012) <sup>149</sup> Chang et al (2009) <sup>150</sup> Yamashita et al (2010) <sup>151</sup> Chan et al (2010) <sup>152</sup> Chan et al (2010) <sup>152</sup>
Fluocinolone Implant (0.59–2.1 mg) Implant (0.19 mg)	66–79% Combined Eyes* 24.4% Combined Eyes*	Kiddee et al (2013) <sup>148</sup> Lebrize et al (2022) <sup>153</sup>
Fluticasone Inhaled (250 µg/day)	0% Pediatric Eyes	Alsaadi et al (2012) <sup>154</sup>
Methylprednisolone Intravenous (1 g/day)	0% Non-Glaucoma Eyes	Acar et al (2012) <sup>155</sup>
Prednisolone Acetate 1% Topical (4 drops/day) Topical (4 drops/day) Topical (6 drops/day/4-week taper)	2.1% Non-Glaucoma Eyes 8.4% Glaucoma Eyes 3.2% Non-Glaucoma Eyes	Bojikian et al (2021) <sup>144</sup> Bojikian et al (2021) <sup>144</sup> Rajendrababu et al (2021) <sup>145</sup>
Prednisone Oral (40 mg/day)	22.2% Pediatric Eyes	Tripathi et al (1992) <sup>156</sup>
Triamcinolone-Acetonide Intravitreal Injection (4 mg) Intravitreal Injection (4 mg) Intravitreal Injection (4 mg) Intravitreal Injection (2–4 mg) Intravitreal Injection (Unspecified Dose) Intravitreal Injection (Unspecified Dose) Peribulbar Injection (20–40 mg) Retrobulbar Injection (20 mg) Retrobulbar Injection (20 mg) Subconjunctival Injection (Unspecified Dose) Subtenon Injection (20 mg) Subtenon Injection (20 mg) Subtenon Injection (40 mg) Suprachoroidal Injection (4 mg) Suprachoroidal Injection (4 mg) Suprachoroidal Injection (4 mg)	32.1% Combined Eyes* 37.5% Non-Glaucoma Eyes 36.5% Non-Glaucoma Eyes 50% Non-Glaucoma Eyes 28% Non-Glaucoma Eyes 0.72% Combined Eyes* 24% Non-Glaucoma Eyes 22.5% Combined Eyes* 8% Non-Glaucoma Eyes 20.6% Non-Glaucoma Eyes 34.1% Non-Glaucoma Eyes 48% Pediatric Eyes 36% Combined Eyes* 0% Non-Glaucoma Eyes 0% Non-Glaucoma Eyes 11.5% Combined Eyes*	Kiddee et al (2013) <sup>148</sup> Ding et al (2011) <sup>157</sup> Chang and Wu. (2008) <sup>158</sup> Chuang et al (2010) <sup>159</sup> Badrinarayanan et al (2022) <sup>146</sup> Jain et al (2014) <sup>160</sup> Chew et al (2011) <sup>161</sup> Hirooka et al (2006) <sup>162</sup> Kawaji et al (2007) <sup>163</sup> Spiers (1965) <sup>164</sup> Yamamoto et al (2008) <sup>165</sup> Laffranco Dafflon et al (1999) <sup>166</sup> Yalcinsoy et al (2022) <sup>167</sup> Ateeq et al (2023) <sup>168</sup> Marashi and Zazo (2022) <sup>169</sup> Yeh et al (2020) <sup>170</sup>

**Note:** \*Both non-glaucomatous and glaucomatous eyes were included in the study.

triamcinolone-acetonide injection, and 17% of non-glaucomatous eyes that received a DEX implant were GC responders (IOP  $\geq 21$  mmHg).<sup>146</sup> In a pediatric study, Krag et al found that 56% of children receiving systemic GCs had OHT (net increase in IOP  $\geq 6$  mmHg from baseline or a peak IOP  $\geq 21$  mmHg).<sup>147</sup>

In 1975, Cantrill et al found that highly potent GCs are associated with a higher risk of GIOHT.<sup>171</sup> In general, older GCs such as DEX, betamethasone, and prednisolone are more likely to induce OHT compared to newer GCs such as loteprednol etabonate, rimexolone, or difluprednate.<sup>172,173</sup> Some studies showed that loteprednol etabonate is less likely

to induce OHT ( $\geq 10$  mm Hg from baseline) after short- or long-term use.<sup>174,175</sup> Several characteristics of loteprednol etabonate make it an attractive alternative to older GCs: it is more rapidly metabolized after GR activation due to the replacement of a ketone group with an ester group at the carbon 20 position, and it is highly lipophilic with high affinity for the GR which allows for excellent penetration in the ocular tissue.<sup>175</sup> In a study that compared loteprednol etabonate to prednisolone, Price et al found that loteprednol etabonate was not inferior to prednisolone in the prevention of DMEK graft rejection and with less chance to induce GIOHT.<sup>176</sup>

Raj et al compared the effect of prednisolone to rimexolone after corneal transplantation, and they found a significant decrease in the mean IOP elevation postoperatively after switching from prednisolone to rimexolone.<sup>177</sup> Likewise, Chen et al reported a decrease in IOP over a 12 month follow-up for pediatric uveitis patients who were switched from DEX, prednisolone, or difluprednate to rimexolone.<sup>178</sup> They also reported that rimexolone provided adequate treatment for pediatric anterior uveitis patients.<sup>178</sup>

In 2022, Kao et al studied the effects of difluprednate vs prednisolone after Ahmed glaucoma valve surgery.<sup>172</sup> They observed that treatment success rates of the two GCs were comparable for 1-year post-operation. They also observed that the effort of the two GCs on IOP was similar. However, the patients receiving difluprednate required less additional glaucoma medications compared to those who received prednisolone.

These studies suggest that newer GCs may decrease the risk of GIOHT/GIG and have similar efficacy to older GCs.

## Risk Factors of GIOHT/GIG

### POAG and GC Responsiveness

Armaly and Becker first reported that POAG patients are at higher risk of developing GIOHT/GIG in the 1960s,<sup>5,6,179</sup> suggesting that POAG patients are more likely to be GC responders. Their studies showed that about 40% of the general population are responders: among them, approximately 32% showed a moderate response (6–15 mmHg increase in IOP or IOP between 25–31 mmHg) and approximately 4% showed a dramatic response ( $>15$  mmHg increase in IOP or IOP  $>31$  mmHg).<sup>180,181</sup> In POAG-suspects and POAG patients, more than 90% are GC responders.<sup>5,179</sup>

Although new GCs have been developed to minimize GIOHT/GIG, POAG patients are still susceptible to GIOHT/GIG.<sup>182</sup> A retrospective analysis reported a high risk of developing OHT in patients who received one or more intravitreal DEX implants.<sup>31,183</sup> They also found that glaucoma patients who required dual or triple therapy have higher risk of developing GIOHT. Maier et al studied the incidence of IOP elevation in the patients who received Descemet's membrane endothelial keratoplasty (DMEK) at 12 and 36 months post operation.<sup>184</sup> Postoperative treatment for these patients included one GC eye drop 5 times daily that was weaned to 1 to 2 times daily over the course of 3 to 4 months, which was then continued for a full year postoperatively, unless an increase in IOP was identified.<sup>184</sup> They found that the main risk factor for developing GIOHT was preexisting POAG.<sup>184</sup> In addition, the mean IOP for preexisting glaucoma patients was significantly higher than that for non-glaucoma patients for the entire follow-up period.<sup>184</sup>

It is important to note that the family history of POAG also increases the risk of GIOHT/GIG, which was first reported by Armaly who found that 62% of offspring of glaucoma patients had an increase  $>6$  mmHg in response to GC treatment.<sup>185</sup> In another study, Bartlett et al found that after topical administration of GCs in healthy, first-degree offspring of POAG patients, 69% of them had an IOP increase of no less than 5 mmHg.<sup>186</sup> Mitchell et al found a significant association between the use of inhaled GC and developing OHT/GIG in patients with a family history of glaucoma.<sup>187</sup> Although family history is involved, just like POAG, which is a multifactorial disease, GC responsiveness is also complex involving multiple genetic and environmental factors.<sup>188</sup>

The relationship between POAG and GIOHT/GIG was further demonstrated from a reversed perspective: patients who have a significant IOP elevation in response to GC treatment are more likely to develop POAG.<sup>8</sup> Lewis et al studied patients with no previous glaucoma diagnosis, and found that 13% of high responders developed POAG over a period of 5 or more years.<sup>9</sup> However, the same study showed that low responders had zero diagnoses of POAG during the same follow-up period.

All these studies show that GIOHT/GIG and POAG are closely related, and that is why GIOHT/GIG animal models are frequently used as POAG research models.

## Age

Older age was considered a risk factor of GIOHT/GIG.<sup>6,179,188,189</sup> Interestingly, recent studies have suggested that younger age is a risk, not older age.<sup>145</sup> Choi et al performed a retrospective observational study involving 570 eyes of 455 adult patients who received intravitreal DEX injection and compared the rate of GIOHT based on approximate decade of life.<sup>182</sup> They found that the greatest rate of GIOHT was in the youngest group (16–30 years) with 42.9% of patients developing an IOP elevation  $\geq 10$  mmHg. The rate of IOP steadily decreased with each increasing decade of life, with the lowest rate of IOP elevation  $\geq 10$  mmHg seen in patients 81–90 years at 9.1%.<sup>182</sup> Malclès et al reported a similar finding in that patients with age  $\leq 60$  years were at increased risk.<sup>183</sup> In addition, it was reported by Friedman et al that in eyes with uveitis, age  $< 50$  years increased the risk of IOP elevation following GC treatment.<sup>190</sup>

Pediatric studies have demonstrated that the risk of GIOHT/GIG is increased in young children.<sup>191,192</sup> Lam et al studied the effect of GC eye drops in pediatric patients who received strabismus surgery.<sup>193</sup> In that study, the patients were divided into two groups and received GC eye drops either 4 times daily or 2 times daily. The authors found that IOP elevation after GC treatment is age dependent: young children ( $< 6$  years old) showed greater net increase in IOP and less time to reach peak IOP. These studies suggest that caution should be taken with GC treatment in children and young adults and alternative options should be sought when appropriate.

## Other Risk Factors

Connective tissue disorders,<sup>194</sup> increased axial length,<sup>144,145,195</sup> and type I Diabetes Mellitus<sup>196</sup> have also been reported to increase the risk of developing GIOHT/GIG.

## Methods of GC Administration

All methods of GC administration are associated with GIOHT/GIG, but the incident rate of each method is different (see Table 1). Common methods of GC administration include ocular, extraocular, and systemic administrations.<sup>31,189,197</sup>

Ocular administration includes topical, intraocular, and periocular routes. Extraocular administration includes inhaled and intranasal GC delivery. Systemic administration includes oral, intravenous, percutaneous, and excessive endogenous production. Studies show that GIOHT/GIG tends to occur more quickly with ocular administration, usually within weeks to months compared to systemic administration, which may occur after months or years of GC use.<sup>189,198</sup>

It is also important to understand that drug formulation may affect the risk of developing GIOHT/GIG as well. Hydrophilic compounds, such as GC phosphates, do not penetrate the cornea as well as lipophilic compounds, such as GC acetates. This may account for some of the differences in GC potency and the risk of IOP elevation.<sup>199,200</sup>

## Topical Application

Topical GC use is more likely to lead to GIOHT/GIG than systemic use.<sup>188,189,201</sup> Sihota et al found that 73.5% of GIG cases were caused by topical GC administration.<sup>202</sup> Topical GC treatment is often used for various ocular diseases and as a post-operative/post-procedural regimen for ophthalmologic surgeries and laser treatments. Chronic GC users, most of whom have ocular inflammation such as uveitis and allergic conjunctivitis, are at high risk of developing GIOHT.<sup>197</sup> Cessation of GC eye drops usually leads to pressure normalization within a few weeks,<sup>173,201</sup> but some could last up to 18 months.<sup>31</sup> As previously discussed, newer GCs may provide a better option in treating inflammation with decreased risk of IOP elevation compared to older GCs.

However, in very few cases, GIOHT persists even after GC cessation.<sup>203</sup> We hypothesize that these patients may be at the preclinical stage of POAG (no IOP elevation), and there have already been pathological changes in their TM. The use of GCs accelerates these irreversible damages in the TM and brings these patients from preclinical POAG to clinical POAG with OHT.

## Intraocular Injection

Intraocular administration most commonly refers to intravitreal injection but also includes intracameral injection and suprachoroidal injection. The use of intravitreal GCs has been continually increasing for retinal and choroidal diseases due to the proximity of GCs to the target tissue.<sup>204,205</sup>



Intravitreal injection may be a single injection of GCs or an implantation of a sustained-release device. Similar to topical administrations, drug solubility plays an important role. Hydrophilic GCs, such as DEX sodium phosphate, have a shorter half-life in the vitreous compared to hydrophobic GCs, such as triamcinolone acetonide.<sup>206,207</sup> In addition, the status of the vitreous can influence drug bioavailability in the eye. Beer et al found that the elimination half-life of triamcinolone acetonide was decreased by approximately 83% in eyes with vitrectomy compared to that in non-vitrectomized eyes.<sup>208</sup> Chin et al reported similar results, with a reduction of approximately 50% in triamcinolone acetonide half-life in vitrectomized eyes vs non-vitrectomized eyes.<sup>209</sup>

The most commonly used GCs for intravitreal injection are triamcinolone acetonide and DEX.<sup>31</sup> Many studies have shown that on average, about 32.1% of the eyes developed GIOHT after 4mg triamcinolone acetonide injection.<sup>148</sup> However, several other studies have reported the incidence of GIOHT after triamcinolone acetonide injection to be higher, with one study reporting up to 50%.<sup>157–159,210</sup> In a United Kingdom national survey, the mean time between triamcinolone acetonide injection and reaching maximum IOP was 16 weeks although it could range from 1.5 weeks to 71 weeks.<sup>160</sup> For DEX, one study found that 16.7% of the eyes developed GIOHT after 0.8mg DEX injection and that 0% of eyes developed GIOHT following 0.4mg DEX injection over a 4-week period.<sup>152</sup>

Implantable devices decrease the risk associated with repeated intravitreal injections and provide a sustained, low-dose GC treatment. This leads to less exposure of the TM to GCs and may decrease systemic side effects.<sup>211</sup> Two GCs are currently available for implantable devices: fluocinolone acetonide (administered as a non-degradable implant) and DEX (administered as a degradable implant).

In a review of several studies, the incidence of significant IOP elevation after 3.5 mg DEX implant was 11%.<sup>148</sup> This rate is less than that resulting from 0.59 mg fluocinolone acetonide implant (66%).<sup>148</sup> Recently, a large study assessed the safety of DEX implants, and it reported that 26.5% of the subjects experienced a significant increase in IOP.<sup>212</sup> Over 90% of these patients were managed with IOP-lowering eye drops and 0.5% required surgical treatment to lower their IOP.<sup>212</sup> Similarly, in another study with patient data obtained from 4 European countries, it showed that in 1 year follow-up of patients who received fluocinolone acetonide implant, 24.4% of them developed significant IOP elevation.<sup>153</sup>

Intracameral injection (delivery to the anterior chamber) and suprachoroidal injection (delivery to the suprachoroidal space) are also used for GC administration.<sup>211</sup> Mataftsi et al concluded that intracameral injection of preservative-free DEX did not increase the risk of GIOHT/GIG in pediatric patients after cataract surgery.<sup>149</sup> Another study performed by Chang et al found that intracameral DEX injection at the end of cataract surgery significantly decreased the anterior chamber inflammation but did not increase the risk of GIOHT compared to the eyes that did not receive a DEX injection.<sup>150</sup> Intracameral injections may avoid compliance issues, but also involve other risks that are not associated with topical treatment. Further studies should be conducted to understand the risk of developing GIOHT/GIG after intracameral GC treatment in the long term.

Suprachoroidal injection is primarily used to treat retina and choroid diseases, and triamcinolone acetonide is clinically available. Muya et al compared the pharmacokinetics and distribution of suprachoroidally injected triamcinolone acetonide to those of intravitreally injected triamcinolone acetonide using rabbit eyes.<sup>213</sup> They found that there was a significantly higher exposure of retinal pigmented epithelium, choroid, and sclera tissues to triamcinolone acetonide in suprachoroidally injected eyes compared to intravitreally injected eyes. However, the exposure was similar in the retina between the two methods.<sup>213</sup> Furthermore, the exposure of the lens, iris, and vitreous humor to triamcinolone acetonide was significantly decreased with minimal exposure in the aqueous humor in the suprachoroidal injection group.<sup>213</sup> Recently, several other studies evaluated the efficacy of suprachoroidal injection of GCs in several retinal diseases including diabetic macular edema,<sup>168,169</sup> uveitic macular edema,<sup>170,214,215</sup> and retinal detachment secondary to Vogt-Koyanagi Harada disease.<sup>216</sup> The results showed good efficacy with no significant increase in IOP. Therefore, suprachoroidal GC injection may be an alternative to intravitreal injection for treating retinal disease when GIOHT/GIG is a concern.

## Periocular Injection

Periocular administration includes subconjunctival, subtenon, peribulbar, and retrobulbar injections. The concentration of GCs is higher in the anterior chamber using subconjunctival and subtenon injections. Peribulbar and retrobulbar injections lead to greater GC localization close to the retina and vitreous.<sup>197</sup> The GCs injected subconjunctivally enter

the eye through passive diffusion through the sclera.<sup>211</sup> Subconjunctival injection is more efficient for ocular GC delivery compared to oral administration.<sup>217</sup> However, some studies have shown that subconjunctival injection is less efficient since significant amounts of GCs leak through the injection site.<sup>218</sup>

Periocular injection of GCs also induces OHT. Some studies showed that 20.6% of scleritis patients developed OHT after subconjunctival injection of triamcinolone acetonide.<sup>164</sup> Subtenon injection of GCs seems to cause high GIOHT incidence.<sup>219</sup> Yamamoto et al reported GIOHT in 34.1% of the patients<sup>165</sup> while Lafranco Dafflon et al reported GIOHT in 36% of the patients after subtenon GC injection.<sup>166</sup> In a study of pediatric uveitis patients, Yalcinsoy et al observed GIOHT in 48% of the patients after subtenon GC injection.<sup>167</sup> Chew et al evaluated the effect of peribulbar injection of triamcinolone acetonide, and the authors reported that 24% of the patients developed significant IOP elevation.<sup>161</sup> For the retrobulbar GC injection, Hirooka et al retrospectively evaluated the incidence of GIOHT and found that the rate was 22.5%.<sup>162</sup> However, Kawaji et al found that retrobulbar injection of triamcinolone acetonide caused GIOHT in only 8% of the patients.<sup>163</sup>

## Inhalation and Intranasal Administration

In 1997, Garbe et al conducted a large case–control study showing that prolonged use (3 months or more) of inhaled GCs at high doses increased the risk of OHT and glaucoma.<sup>220</sup> However, the authors did not have proper controls for POAG family history or high myopia, and there were concerns with the conclusions of that study and the true effect of inhaled GCs and the development of GIOHT/GIG.<sup>221</sup> In 1999, Mitchell et al found a significant association between high doses of inhaled GCs and elevated IOP/glaucoma, but only in patients that had first-degree relatives with POAG.<sup>187</sup>

Since the publication of those studies, there have been conflicting reports. In 2017, Nath et al conducted a prospective observational study to investigate the prevalence of glaucoma in elderly patients receiving inhaled GCs.<sup>222</sup> They found that the prevalence of glaucoma was 3.92% and the prevalence of OHT 16%. They also observed a dose-dependent relationship showing that 42.8% of the patients receiving high doses (501–1000 µg) of inhaled GCs daily developed OHT. Thus, the authors concluded that higher doses and longer usage of inhaled GCs are associated with GIOHT/GIG.<sup>222</sup> In contrast, several studies have found no association between inhaled glucocorticoids and GIOHT/GIG.<sup>223–226</sup> One such study was conducted by Gonzalez et al who conducted a case–control study for elderly patients who were taking inhaled GC and started on glaucoma treatment.<sup>227</sup> They found that there was no dose-related association nor long-term use relationship between inhaled GC and GIOHT/GIG. Similarly, in a pediatric study conducted by Alsaadi et al, it was observed in children between 5 and 15 years of age there was no association between normal dose GC and the development of elevated IOP.<sup>154</sup> In 2021, a comprehensive meta-analysis that included 18 studies and 31,665 subjects was conducted by Ishii et al to determine the association between inhaled GC and GIOHT/GIG.<sup>228</sup> The results of their analysis showed no evidence that linked inhaled GC with ocular hypertension, glaucoma prevalence, or glaucoma incidence. Interestingly, they found there may be a reduced risk of glaucoma in patients who receive inhaled GC.

The result of the studies investigating the association between intranasal GC use and GIOHT/GIG is also inconsistent.<sup>220,225,229</sup> Most of the studies conclude that there is no association between intranasal GC use and OHT. In 2019, Valenzuela et al conducted a meta-analysis including 10 randomized controlled trials and 2226 patients.<sup>230</sup> They found there was no absolute risk of developing OHT when taking intranasal GCs. They also found there were zero cases of glaucoma reported within a year of follow-up. On the contrary, Bielory et al concluded that with increased availability of over-the-counter intranasal GCs, some individuals may develop elevated IOP, especially those with risk factors, and therefore should be monitored.<sup>231</sup>

The results of these studies suggest that there is a low risk of GIOHT/GIG with inhaled and intranasal GC treatment. However, IOP monitoring may be important for individuals taking high-dose or long-term inhaled or intranasal GCs, especially for those with risk factors such as disease and/or family history of POAG. A baseline IOP and IOPs at 1 and 3 months from the initiation of GC treatment are recommended for monitoring potential GIOHT/GIG.<sup>31</sup>

## Oral Administration

In 1962, Bernstein and Schwartz reported that long-term use of oral GCs induced significant OHT.<sup>232</sup> Other studies also showed an association between oral GC use and GIOHT/GIG.<sup>197,220,233</sup> Tripathi et al reported that for every 10 mg of prednisone taken orally daily, there was a reciprocal increase of 1.4 mmHg in the mean IOP.<sup>156</sup> Generally, oral use of GCs is less likely to develop GIOHT/GIG compared to topical use. However, one study showed that elderly patients who

took 80 mg or more of hydrocortisone orally daily might have a similar risk of developing GIOHT/GIG as those receiving topical GCs.<sup>234</sup>

### Intravenous Injection

Intravenous GCs are first-line treatment for several diseases including multiple sclerosis.<sup>235</sup> Acar et al studied the effect of high dose intravenous methylprednisolone on IOP in multiple sclerosis patients with acute relapse.<sup>155</sup> They found an initial significant increase in IOP during treatment and within 1-month post treatment. However, at two and three months after, IOP returned to normal levels and the patients showed no glaucomatous optic nerve damage.<sup>155</sup> Another study by Yamashita et al investigated the effects of systemic DEX, including intravenous administration, on IOP in pediatric patients with acute lymphoblastic leukemia.<sup>151</sup> They found that there was a significant rise in IOP in all patients with max IOP between treatment cycle 5 and 11. Thus, patients receiving intravenous GCs, especially those receiving long-term treatments, should be monitored for GIOHT/GIG.

### Percutaneous GC Absorption

Cutaneous application of GCs may induce GIOHT/GIG.<sup>236–238</sup> Most of these cases consisted of cutaneous application of GCs to the periorbital region. The skin of the eyelids/periorbital region is relatively thinner than other parts of the body, which facilitates GC penetration and absorption resulting in high concentrations of GCs in the eye. Takakuwa et al described a new clinical entity as “atopic glaucoma” which is glaucoma associated with atopic dermatitis.<sup>239</sup> They found that 48 out of 62 eyes with atopic glaucoma had used GC ointments.<sup>239</sup>

However, Haeck et al conducted a retrospective study to determine the effect of cutaneous GC application on the risk of IOP elevation and glaucoma.<sup>240</sup> They included 88 patients in their analysis, and found that 37 patients regularly applied GCs to the eyelids and periorbital regions. Among the 88 patients, only one developed transient OHT. Therefore, the authors concluded that there was no association between cutaneous topical GC and risk of GIOHT/GIG.<sup>240</sup>

Although the result of these studies is not consistent, the risk of GIOHT/GIG induced by cutaneous GC treatment seems to be lower than the other GC administration methods. However, for patients who use topical GC treatments regularly on the eyelid and periorbital region, IOP monitoring may be necessary.

### Elevation of Endogenous GCs

Elevated IOP has been documented in diseases with high levels of endogenous GCs such as Cushing's syndrome.<sup>241–244</sup> In a recent case report, Habib et al described a male patient with OHT who was initially managed with close monitoring.<sup>244</sup> Three months later, he was diagnosed with Cushing's syndrome due to a microadenoma in the pituitary gland. After surgical removal of the microadenoma, his IOP returned to normal level. Therefore, the patient was diagnosed with GIOHT. For GIOHT patients resulting from elevated endogenous GCs, treatment of the underlying disease that leads to GC elevation should be initiated promptly to normalize IOP and prevent irreversible optic nerve damage.<sup>245</sup>

More importantly, as described previously, it is known that high cortisol levels are a known risk factor of POAG, while POAG is a risk factor of GIOHT/GIG. Therefore, high endogenous cortisol levels (which do not have to be as high as in diseases such as Cushing's syndrome) are likely a risk factor of GIOHT/GIG.

## Management of GIOHT/GIG

GIOHT may cause irreversible optic nerve damage and loss of vision (GIG). Thus, early diagnosis and intervention are necessary. General management of GIOHT/GIG includes the following: discontinuation of GC therapy if possible or switch to an alternative GC with less risk of inducing OHT, removing deposited GCs, as well as IOP-lowering eye drops and/or surgeries if required.<sup>246</sup> For most patients, IOP will drop quickly as long as GCs are discontinued swiftly.<sup>246</sup> For patients with chronic GIOHT/GIG, IOP may normalize after 1 to 4 weeks after GC discontinuation.<sup>247</sup> One study showed that after GIOHT/GIG diagnosis, some patients required anti-glaucoma treatment for up to 18 months after discontinuation of GC use.<sup>202</sup> For patients who experience OHT after intravitreal GC injection or GC-sustained release device implantation, removal of GCs or GC-sustained release devices may be needed to control their IOP.<sup>248</sup> Also, Rezkallah et al showed that the XEN gel stent (Allergan Inc., CA), which is a drainage device between the anterior chamber and the subconjunctival space, successfully lowered IOP in 5 GIOHT patients caused by DEX implants.<sup>249</sup> Furthermore, they found that it was safe to resume GC treatment with the implanted GC device and the concurrent use of the XEN gel

stent.<sup>249</sup> Medications and surgical treatments for GIOHT/GIG are practically identical to those for POAG, including IOP-lowering eye medicines, laser trabeculoplasty, drainage implant surgery, and filtering surgery.<sup>250</sup> Several recent studies have shown that selective laser trabeculoplasty (SLT) is a safe and effective treatment for GIOHT/GIG.<sup>251–254</sup> Davidson et al evaluated the efficacy and safety of SLT in patients who developed GIOHT due to the requirement of GC treatment after endothelial keratoplasty.<sup>252</sup> They found that SLT may be a safe option to control IOP, which allows the continuation of GC treatment in patients at high risk of graft rejection.<sup>252</sup>

Patients with GIOHT/GIG should be monitored regularly and closely to determine their responses to treatment and to prevent further optic nerve damage. Goñi et al proposed the following method for IOP monitoring:<sup>255</sup> 1) a baseline IOP measurement and determination of glaucomatous damage; 2) risk factor assessment including IOP  $\geq 15$  mmHg, family history, previous episodes of GC-induced IOP elevation, glucocorticoid dosage, etc; 3) if IOP is  $>21$  mmHg, then visual field testing as well as imaging of the optic nerve and retinal nerve fiber layer should be collected; treatment initiation can be delayed and a follow-up within 6 weeks is warranted; 4) if IOP is  $>25$  mmHg, then visual field testing and imaging studies should be performed with initiation of first treatment using medical treatment or laser intervention. Follow-up should be conducted within 6 weeks, if IOP is  $>25$  mmHg and the patient has received  $\geq 2$  medical therapies, then referral to a glaucoma specialist is warranted.

Potential novel therapies are under research, which target various aspects of the complex mechanism of GR signaling and/or GIOHT/GIG. For example, tPA lowered IOP in sheep and mouse GIOHT models by increasing the activity MMP's and prevented, at least partially, GC-induced pathological changes in the TM.<sup>133–135,256,257</sup> Using the same sheep model, Gerometta and colleagues showed a reduction in IOP after introducing a GC-inducible MMP1 gene expression vector into GIOHT sheep eyes.<sup>258</sup> Patel and colleagues showed that the viral mediated expression of GR $\beta$  attenuated GC-induced OHT in mouse eyes.<sup>33</sup> Sugali and colleagues also showed that viral mediated expression of Wnt3a to activate the Wnt pathway prevented GIOHT in the same mouse model.<sup>74</sup> Further research should be conducted to better understand the complexities of the disease process and potential therapies that can be translated into clinical use.

## Conclusion

Glucocorticoid-induced glaucoma is a complex secondary glaucoma that can lead to severe vision loss and even blindness. Glucocorticoids induce POAG-like changes the TM and SC. The GR signaling pathway is complicated with multiple regulators and it cross-talks with many other signaling pathways. Regardless of the method of GC administration and GC types, there is a risk for general population, especially those with POAG or family history of POAG, to develop GIOHT/GIG. The risk level also depends on many other factors. Early diagnosis and treatment of GIOHT/GIG are important to prevent optic nerve damage and to preserve visual function.

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## Disclosure

The authors report no conflicts of interest in this work.

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