mechanism(s) by which pituitary removal interferes with androgen action on the lacrimal gland may be complex [366,378]. Some of the underlying factors may be the significant decrease in the androgen receptor protein expression in acinar epithelial cell nuclei [97], as well as the significant reduction in androgen-induced transcriptional and post-transcriptional events in lacrimal tissue, following hypophysectomy [91].

However, if the pituitary is transplanted to the kidney capsule, androgen therapy increases the acinar complex area in lacrimal glands of hypophysectomized rats and delays the loss of LGW [204]. Further, treatment of hypophysectomized rats with testosterone and insulin significantly increases the LGW and the LGW/BW ratio [204]. The mechanism(s) underlying these androgen actions remain to be determined.

The impairment of lacrimal gland responses to androgens in pituitary-deficient animals does not represent a generalized lack of tissue responsiveness throughout the body. Testosterone administration to rats without anterior pituitaries induced a 20-fold increase in both the seminal vesicle weight (SVW) and SVW/BW ratio [204]. Thus, the influence of interrupting the hypothalamic-pituitary axis on androgen target organs appears to be site-specific.

### 3.4.2. Effects of hypothalamic-pituitary hormones

Anterior pituitary hormones, either directly or indirectly (e.g. through control of steroid, thyroxine and insulin), modulate the growth, differentiation and secretion of the lacrimal gland [360,410,411,514,616,737–740,742,748–750], as well as meibomian gland function [751]. The effects of growth hormone are described in Section 3.5.

*3.4.2.1. Prolactin.* Investigators have reported that prolactin increases the acinar cell diameter, nuclear size, and lacrimal gland weight of male and female dwarf mice [616], promotes the $Na^+$,$K^+$-ATPase and cholinergic receptor activities in lacrimal tissues of hypophysectomized female rats [360], and decreases carbachol-induced secretion by acinar epithelial cells [749,752,753]. In addition, prolactin has been proposed to play a minor role in the sexual dimorphism of murine lacrimal glands [748]. However, prolactin has also been demonstrated to exert no effect on the morphology (i.e. in hyperprolactinemic male mice) [748] and weight (i.e. in hypophysectomized male rats) [204] of lacrimal tissue, the synthesis and secretion of proteins by the lacrimal gland [366,752], and the volume of tears [204]. Also, exposure to increased prolactin levels, induced by metoclopramide treatment, leads to a structural disorganization of the mouse lacrimal gland [754].

The origin of lacrimal gland prolactin is not solely the pituitary. Prolactin and its receptor are transcribed and translated in lacrimal gland acinar epithelial cells [750,752,753,755–761]. Prolactin is also secreted by the lacrimal gland into tears [757,762]. It is unclear, though, what factors may modulate the synthesis and secretion of intra-lacrimal prolactin. Treatment with prolactin, prolactin antagonists (i.e. bromocriptine), or estrogen has no effect on lacrimal gland prolactin levels [763], and the administration of cholinergic agonists (i.e. pilocarpine) does not alter the concentration of prolactin secreted by lacrimal tissue [762]. It is possible that lacrimal prolactin could be regulated by androgens, given that the synthesis of this hormone and its receptors are regulated by androgens in other sites [764–767].

In summary, the species-independent role of prolactin in lacrimal tissue and tear film dynamics is unknown. Researchers have found a strong negative correlation between serum prolactin levels and tear function [768]. Considering this hormone's pro-inflammatory actions [766,769] and its proposed role in the pathogenesis of Sjögren syndrome [770,771], it is quite possible that the lacrimal synthesis of prolactin may act to promote autoimmune disease in the lacrimal gland. Conversely, testosterone's ability to down-regulate the prolactin receptor gene in the lacrimal gland may be one mechanism by which androgens suppress inflammation in this tissue in Sjögren syndrome [351].

With regard to the meibomian gland, investigators have found that women, but not men, with seborrheic MGD have significantly elevated serum levels of prolactin [772]. The reason for this linkage is unknown. Prolactin fragments, in turn, have been reported to inhibit corneal angiogenesis [773].

*3.4.2.2. α-melanocyte stimulating hormone (α-MSH) and adrenocorticotropic hormone (ACTH).* The melanocortins α-MSH and ACTH are involved in the control of constitutive proteins by the lacrimal gland. These hormones have receptors on acinar epithelial cells of the rat lacrimal gland [738,740,774–777] and may stimulate cAMP production and protein release [737,738,740,778,779]. However, α-MSH and ACTH do not influence the output of all (e.g. regulated) lacrimal gland proteins [366].

When combined with androgens, α-MSH may increase lacrimal gland weight in orchiectomized rats [417]. Androgen treatment also up-regulates the lacrimal gland gene expression for the melanocortin 3 receptor [351], which may enhance the α-MSH- and ACTH-induced protein secretion [738,740]. In contrast, α-MSH has no effect on the relative (i.e. LGW/BW ratio) or absolute LGW [204,417], interactions between lacrimal acinar epithelial cells and lymphocytes [780], or the IgA content [741] or volume [204] of tears. Further, ACTH has no effect on acinar cell or nuclear diameters in lacrimal glands of pituitary-deficient mice [616].

Investigators have found that topical α-MSH application promoted the volume and stability of tears, improved corneal integrity and suppressed ocular surface inflammation in rats with scopolamine-induced DED. These α-MSH effects could be prevented by pharmacologically blocking either the PKA-CREB or MEK-Erk pathways [781].

Of interest are three additional studies concerning ACTH. First, ACTH may be synthesized by, or accumulate within, myoepithelial cells in the lacrimal gland [755]. Second, circulating ACTH levels have been positively correlated with central corneal thickness [782]. And third, an ACTH insensitivity syndrome (e.g. Allgrove) has been described, which is characterized by adrenal insufficiency, glucocorticoid deficiency and alacrima [783–789]. The reason for the ACTH-cornea association may relate to this peptide hormone's ability to influence corneal regeneration [790] and the mitotic index of corneal epithelium [791]. However, the consequence of lacrimal ACTH synthesis, and the specific cause of the decreased tear output in Allgrove syndrome, remains to be determined.

*3.4.2.3. Thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and vasopressin.* TSH, FSH and LH all increase the weight and differentiation of lacrimal glands in male, but not female, pituitary dwarf mice [616]. The reason for these sex-related differences in hormone action has yet to be clarified. Also to be determined is whether these pituitary hormone effects are direct (e.g. through lacrimal gland receptors), and/or are mediated through the regulation of other hormones (e.g. sex steroids, thyroxine). This question is very relevant for patients with hypothalamic hypogonadism, which was found associated with obstructive MGD in a 35-year-old male patient [792]. This condition is characterized by an impaired pituitary secretion of FSH and LH, leading to hypogonadism and a lack of sex steroid production. The authors of that case report proposed that this lid condition was due to androgen deficiency [792].

TSH receptors have also been identified in the human lacrimal gland [793]. These receptors are thought to be the target for autoantibodies in thyroid-associated ophthalmopathy, and, possibly

through aberrant signal transduction, contribute to the reduced aqueous tear secretion and ocular surface damage in this disorder [793]. TSH levels in the serum of women, but not men, are also increased in seborrheic MGD [772]. The basis for this correlation is not known.

Vasopressin may be synthesized or accumulated by lacrimal gland epithelial cells [794], but the local effect of this hormone is unknown. Similarly, the potential effects of other hypothalamic and pituitary hormones on the ocular surface and adnexa have yet to be identified.

### 3.5. Growth hormone, insulin-like growth factor 1 and insulin regulation of the ocular surface and adnexa

Growth hormone (GH), insulin-like growth factor (IGF-1), as well as insulin are anabolic promoters responsible for mitosis, tissue growth, differentiation and repair. These actions are crucial for the health and functions of lacrimal gland, meibomian gland and ocular surface tissues as detailed below. GH, also called somatotropin, is an anterior pituitary hormone with actions mediated by effects of IGF-1 (also called somatomedin) via endocrine, paracrine and/or autocrine actions. GH, IGF-1 and insulin are involved in metabolism of glucose, amino acids, DNA, lipids and proteins [795–797]. These events are regulated by their respective cell surface receptors, which activate signaling molecules in the cytoplasm, eventually leading to powerful regulation of gene expression that favors cell survival and proliferation [798].

#### 3.5.1. GH, IGF-1 and insulin mechanisms of action, interrelationships, and influence on the ocular surface and adnexa

GH binds to pre-dimerized GH receptors located on cell plasma membranes, leading to activation of intracellular Janus-kinase 2 (JAK2) [799], a kinase that phosphorylates itself as well as the GH receptor [800]. JAK2 further activates Signal Transducers and Activators of Transcription (STATs), which, upon tyrosyl phosphorylation, dimerize and enter the nucleus to regulate the transcription of GH-specific genes including IGF-1 [801]. GH induces cells to secrete IGF-1, which amplifies and complements GH effects, extending its actions, potentially in all cell types. IGF-1 has also paracrine secretion. It has structural and functional similarity with IGF-2 which, however, is not regulated by GH [802]. It is believed that IGF-2 is primarily a growth factor of the fetus whereas IGF-1 acts in postnatal tissues. IGF-2 in relation to corneal wound healing is briefly discussed in Section 3.5.4. IGF-1 signaling is initiated with binding to membrane bound IGF-1R, which phosphorylates and activates insulin receptor substrate (IRS)-1, leading to the cascade of phosphoinositide 3-kinase (PI3K)/Akt pathway activation [803,804], that is an important regulator of cell cycle progression and cell survival.

Insulin exerts its action via binding to insulin receptor (IR), leading to activation of IRS/PI3K/Akt and MAPK pathways [805]. IGF-1 and insulin have molecular similarity and are able to cross-activate each other's receptors, which are also structurally similar, as well as a hybrid IGF-1R/IR [796,806]. However, the cross affinity for the receptor is 100–1000 times lower than that of the specific molecule, depending on cell type [807–809]. In spite of cross-reactivity, IGF-1 and insulin exhibit different actions. Overall, IGF-1 is more efficient in inducing DNA synthesis and mitosis and insulin is more efficient in promoting metabolic events, potentially due to effects on different target cells. GH, IGF-1 and insulin receptors and their respective signaling pathways have been found in lacrimal gland and ocular surface tissues [364,810–815], and there is evidence of influences on tissue development, and wound healing responses.

*3.5.1.1. Cornea.* There is evidence that central corneal thickness (CCT) is decreased in GH deficient children and adults [782,816–818], and that GH treatment for one year increases CCT in GH deficient children [819]. However, others found no significant difference in CCT but increased corneal resistance factor (CRF) and corneal hysteresis (CH) [820]. CCT is also reported to be increased in acromegalic patients [816,821], but others observed no difference in CCT or corneal biomechanical parameters in acromegalic patients compared to age and sex matched controls [822]. High IGF-1 correlates with increased central corneal thickness in polycystic ovarian syndrome patients [823].

Insulin is present in the human tear film and insulin and IGF-1 receptors are found on the human ocular surface [811]. On the other hand, increased IGF-binding protein 3 is found in human tears, which may attenuate IGF-1R signaling in the diabetic cornea [824]. This may contribute to epithelial compromise and the pathogenesis of ocular surface complications reported in diabetes [824]. Insulin has also been found to promote corneal wound healing and may be of therapeutic benefit in delayed corneal wound closure associated with diabetes (see Section 3.5.4).

*3.5.1.2. Meibomian gland.* The GH/IGF-1 axis may positively regulate meibomian gland growth and function. For example, mouse meibomian gland size is positively correlated with GH and IGF-1 levels in a series of transgenic and knockout mouse lines that represent a spectrum of GH/IGF-1 excess, GH/IGF-1 deficiency and GH/IGF-1 absence [118]. Further, the meibomian gland shows normal morphology in GH/IGF-1 excess mice, but increased abnormalities including hyperkeratinized and thickened ducts, acini inserting into duct walls, and poorly differentiated acini in GH/IGF-1 deficient or absent mice [118]. At the cellular level, IGF-1 activates AKT but not ERK pathway, promotes cell proliferation and intracellular lipid accumulation in cultured human meibomian gland epithelial cells, whereas GH does not have a direct effect *in vitro* [751,825]. These data indicate that GH may exert an indirect effect on the meibomian gland via inducing IGF-1, however further research is needed.

Insulin, similar to IGF-1, activates AKT signaling via the IGF-1 receptor and promotes cell proliferation and lipid accumulation in cultured human meibomian gland epithelial cells [826]. Type II diabetes has been associated with MGD in some studies [116,827]. It is plausible that such an association may be mediated by toxicity of high glucose to meibomian gland epithelial cells, reducing IGF-1 receptor levels as well as other insulin and IGF-1 downstream signaling molecules [826].

*3.5.1.3. Lacrimal gland.* Insulin is itself secreted by the lacrimal gland acinar cells and it was demonstrated in rodents that this hormone is locally produced [828,829]. Insulin promotes tissue maintenance and supports constitutive secretion of elements present in the tears, as revealed in lacrimal gland culture studies [364,774,830]. Increasing the concentration of insulin, transferrin and selenium in the culture media of rat lacrimal gland acinar cells, induces secretion of secretory component, a protein that binds and transports IgA [364]. It also increases the synergic secretagogue effect of DHT [364]. In streptozotocin induced animal models of diabetes mellitus (DM), the loss of insulin results in smaller lacrimal glands with altered morphology of the secretory vesicles and intracellular vesicle trafficking, decreased corneal innervation and tear volume, and reduced concentrations of peroxidase in tears and IgA in the lacrimal gland [13,831–834]. The absence of insulin also increases the expression of oxidative markers such as malondialdehyde, peroxidase, and pro-inflammatory cytokines [831,835,

836].

*3.5.2. GH, IGF-1 and insulin roles in sex-related differences*

*3.5.2.1. Systemic sex-related effects of GH, IGF-1 and insulin.* GH is well known to have a different secretion profile in men and women, resulting in vast differences in liver gene expression patterns [837,838]. Sex steroids modulate GH directly and indirectly via IGF-1 [839–841]. Insulin resistance is observed in postmenopausal women receiving oral but not transdermal combined estrogen and progesterone replacement therapy [842]. A possible explanation would be the inverse relationship between insulin binding sites and the levels of estradiol and progesterone during the menstrual cycle of young women and also lower insulin binding levels comparing those phases to young men, suggesting that sex hormones influence the levels of insulin receptor in target tissues (e.g. monocytes) [843]. This is relevant because it may link higher levels of sex hormones to lower action of insulin on the ocular surface and lacrimal gland. This linkage may help explain the stimulus for DED symptoms during the peaks of sex hormones in the follicular and luteal phase of the menstrual cycle and in polycystic ovary syndrome [313,608,842,844,845]. Overall, sex hormones play a significant role in modulating the activities of GH, IGF-1 and insulin.

*3.5.2.2. Sex-related effects of GH, IGF-1 and insulin on the ocular adnexa*

*3.5.2.2.1. Lacrimal gland.* Neither sex nor the phase of the estrous cycle change insulin receptor levels or early signaling steps in the rat lacrimal gland [73]. The number of androgen receptor–containing cells in lacrimal gland of rats and BALB/c or C57BL/6 mice were higher in male compared to female [97]. Streptozotocin-induced DM did not reduce the number of androgen receptor-containing cells in the rat lacrimal gland [97].

Non-obese diabetic mice (NOD) are widely used in research related to type 1 DM and Sjögren syndrome [846]. This animal model spontaneously created after hyperglycemic sibling inbreeding for several generations, presents a sex biased distribution of manifestations. NOD females are about 80% more frequently affected by DM and sialoadenitis and males are more affected by dacryoadenitis [65,847]. These sex-related differences are attributed to sex hormones [524,848].

Since the early steps of insulin signaling are similar in male and female lacrimal gland the sex hormone-driven changes in insulin, GH or IGF-1 signaling/effects are possibly occurring in later steps or at transcriptional levels of the signaling networks as observed in the modulation of MAP kinase or STAT by sex hormones in cultured cells [849,850]. In support of this hypothesis, testosterone treatment of orchiectomized mice altered the expression of insulin receptor-related receptor and insulin-like growth factor binding protein 3 [351]. In meibomian gland immortalized cell cultures, exposure to DHT increased the expression of genes related to insulin signaling [560]. The differences in gene expression in both studies include genes related to development, growth, metabolism, transport and other common actions associated with insulin, IGF-1 and GH, confirming their interactions with sex hormones.

*3.5.2.2.2. Meibomian gland.* Wild type female mice have larger meibomian glands than males, but there is no difference in size between male and female mice that are GH deficient [118]. It is possible that the sexually dimorphic GH effect is responsible, however it is not clear how this interaction of sex and GH affects meibomian gland function or MGD. Both GH and IGF-1 receptor mRNAs are expressed in the mouse [547] and human meibomian gland [110,560], where IGF-1 directly stimulates human meibomian gland epithelial cell proliferation and lipid accumulation [751], and mice show positive correlation in meibomian gland size with GH/IGF-1 activities [118].

*3.5.3. Clinical relevance of GH, IGF-1 and insulin in DED*

Acromegaly is a disease with overexpression of IGF-1 and consequently also higher secretion of IGF-1 with changes in the body structure and systems. An evaluation of 59 patients with acromegaly compared to 62 age and sex-matched controls revealed a slightly lower tear film breakup time (9.1 ± 3.6 vs. 10.7 ± 2.9, $p = 0.009$), but no differences in Schirmer test or tear film osmolarity, and no clinical differences in DED exams, despite levels of GH and IGF-1 that were on average more than double [851]. Dwarfism, a clinical condition marked by short stature, that is sometimes secondary to GH deficiency, has not been reported to be associated with DED. Gigantism, which is caused by overproduction of GH, has also never been associated with clinical findings of DED.

Pituitary deficiency has been associated with Sjögren syndrome and its clinical manifestations, including DED [852]. The expression of insulin receptor was increased while IGF-1 receptor was decreased, in minor salivary gland (MSG) tissues of Sjögren syndrome patients compared to controls [853]. Interestingly, IGF-1 itself has been found to co-localize with lymphocyte infiltration in Sjögren syndrome salivary glands, suggesting that IGF-I may be a target of autoimmunity in Sjögren syndrome [854].

Several clinical conditions are associated with insulin resistance and DED or DE symptoms. Among them are polycystic ovary syndrome, pregnancy, anti-androgen therapy and complete androgen insensitivity syndrome [10,540,608,855–857]. Interestingly they also present with changed levels or impaired action of sex hormones, in a complex manner with no clear cut cause-effect relationship with insulin resistance [858,859]. Moreover, DED is the most common side effect of figitumumab, an IGF-1 receptor blocking anti-cancer drug, in healthy human subjects. [860] The development of DED following IGF-1 receptor blockade may be due to disruption of meibomian gland or lacrimal gland function, and/or corneal innervation.

DED is associated with aging, and aging is accompanied by reduced levels of sex hormones and increased insulin resistance [19,861]. Aging in insulin-resistant rats shows increased oxidative stress and impaired vesicular transport, reduced tear flow, and higher levels of pro-inflammatory cytokines and other markers of tissue degeneration in the lacrimal gland, but normal levels of insulin in tears [862–864]. On the other hand, caloric restriction, a strategy known to retard the progress of aging and degenerative diseases in animals, reduced Sjögren syndrome related phenotypes in animal models, via reduction of insulin secretion and action [865–868]. With regard to corneal innervation, IGF-1 treatment not only accelerates corneal nerve regeneration, but also relieves DED in rabbits post LASIK surgery [869].

*3.5.3.1. Diabetes and DED*

*3.5.3.1.1. Experimental data.* Type I diabetes is known to cause DED [870], which can be secondary to autoimmune destruction of the lacrimal gland due to antigen cross activity with the pancreas [871]. DED secondary to autoimmunity has a similar distribution between the sexes and it is controversial as to whether metabolic factors play a role in type 1 diabetes-induced DED. Several animal studies have shown that insulin can restore lacrimal gland morphology, arguing for a metabolic or hormonal role of lacrimal gland dysfunction in diabetes. In streptozotocin-induced diabetic rats, the lacrimal gland shows reduced number and enlarged size of secretory vesicles, and insulin treatment restores the density of these vesicles [833]. Further, in this rat model of diabetes, changes in morphology, increased numbers of lipofuscin-like inclusions, increased malonaldehyde and total peroxidase activity were observed in the lacrimal gland, and these abnormalities were

removed by insulin treatment [836]. In addition, expression of advanced glycation end products and their receptor, which are related to hyperglycemia, are increased in lacrimal glands of streptozotocin-induced diabetic rats [835]. Therefore even in type I diabetes, lacrimal gland dysfunction has a significant hormonal and metabolic component, plus a possible cross-reactive autoimmune component.

In contrast, type II diabetes associated DE is most likely hormonal or metabolic in nature. This disease, initiated by defective insulin action and hyperglycemia, decreases the microvascular, neural and metabolic integrity of the ocular surface, lacrimal gland and meibomian glands. It is possible that a direct effect of insulin via the IGF-1 receptor, and adverse signaling events caused by high glucose levels, on meibomian gland epithelial cells [826], may be involved in the MGD caused by diabetes.

*3.5.3.1.2. Clinical data.* Clinical ocular surface manifestations of diabetes include lower corneal sensitivity, lower tear film break up time and Schirmer test, epithelial metaplasia, and changes in tear proteins, and are reported to worsen with longer duration of disease and poor glycemic control [872–875]. Tear film osmolarity is higher in DM, compared to other causes of DED, and that may relate to a higher blood osmolarity reflecting a poor glycemic control [876]. This last conclusion is supported by an observation in which individuals with higher blood osmolarity were more prone to DE symptoms [877].

### *3.5.4. GH, IGF-1 and IGF-2, and insulin on corneal wound healing and neurotrophic keratitis*

GH is known to promote skin epithelial wound healing [878–882]. In fact, it is often used off-label to promote skin healing associated with burns and surgery [878]. These observations led investigators to hypothesize that GH may also play a role in corneal epithelial wound healing and/or corneal nerve regeneration [815,883]. GH has been shown to promote corneal epithelial cell migration independent of IGF-1 *in vitro* [815]. More studies need to be performed to confirm positive effect of GH on corneal wound healing and/or nerve regeneration *in vivo*. If true, this may be beneficial in the treatment of corneal epithelial defects and/or neurotrophic keratitis associated with severe DED.

IGF-1 has been studied more extensively in terms of corneal wound healing, and found to promote corneal wound healing at multiple levels. First, IGF-1 promotes the proliferation and migration of corneal epithelial cells and fibroblasts [884–888], differentiation of limbal stem cells [889,890], and the proliferation of corneal endothelial cells *in vitro* [891–893]. Second, IGF-1 accelerates corneal epithelial migration and wound healing in organ culture [894–896] and animal models [897–900]. Third, IGF-1 also preserves corneal nerves in diabetic animals [890] and animals undergoing LASIK [869]. Lastly, in some human studies, IGF-1 has been found to prevent superficial punctate keratopathy in diabetic patients post cataract surgery [901], and accelerate reepithelialization in patients with neurotrophic keratopathy [902–904]. A summary of the findings of the role of IGF-1 in corneal wound healing is provided in Table 8 [869,884–913]. Insulin has been found to duplicate IGF-1 in promoting corneal wound healing in cell culture, organ culture and diabetic animal models of corneal wound healing. These findings are summarized in Table 9 [911,914–930].

Systemic replacement and/or usage of topical insulin treatment can reverse the signs of DED and wound healing defects in animal models of DM [836,920,931,932]. Autologous serum, which also contains insulin and growth factors has been used to attenuate the signs and symptoms of severe DE and delayed wound healing not just in DM, but also in several conditions associated with DE [933–935]. (See also TFOS DEWS II Management and Therapy Report) [936]. Different formulas and delivery systems of insulin and IGF-1 eye drops have been developed for DE treatment and a novel delivery system has been proposed to improve stability and the target tissue concentration of insulin [937–939].

IGF-2 has been demonstrated to act via IGF-1R in human embryonic corneal endothelial cells and stimulate their proliferation [940]. IGF-2 is also present in bovine corneal stroma, and stimulates proliferation of cultured keratocytes [941]. Similar to IGF-1 and insulin, IGF-2 also activates AKT signaling and promotes cell proliferation in cultured human corneal epithelial cells [915]. IGF-2R may play an active role in corneal wound healing. For example, IGF2R protein expression is increased during corneal wound healing in mouse corneas and IGF2R regulates human corneal fibroblast

**Table 8**
Summary of IGF-1 effects on corneal wound healing.

| Model used | Epithelial cells/limbal stem cells (LSC) | Stroma/keratocytes | Endothelial cells | Innervation |
|---|---|---|---|---|
| Cell culture/signaling | • ↑ LSC differentiation [889].<br>• ↑ epithelial proliferation and migration, activating AKT and ERK [905].<br>• IGF-1R [906] and IGF-1R/IR hybrid nuclear localization [907].<br>• ↑ laminin-5 and beta-1 integrin [908]<br>• PKC and tyrosine kinase [909] | • ↑ human corneal fibroblast proliferation and collagen synthesis [884–887,911].<br>• Epi releases IGF-1 to act on stroma [912]<br>• ↑ Keratocyte migration [888] | • ↑ rabbit endothelial cell proliferation via IRS-1[893]<br>• ↑Bovine endothelial cell proliferation [891]<br>• No effect in cat endothelial cells [913] | |
| Organ culture | +Substance P: ↑ epithelial migration and healing [894–896] | | ↑ cell proliferation in human embryonic endothelial and stromal culture [892] | |
| Animal model | • +Substance P: ↑ healing rat models of neurotrophic keratopathy [897,898] and diabetes [899] and rabbits [900]<br>• Preserves limbal stem cells in type II diabetic mice [890]<br>• No effect in a rat model of galactosemia [910] | | | ↑ nerves in type II diabetic mice [890], LASIK rabbits [869] |
| Human study | +Substance P: Prevents SPK in diabetic patients post cataract surgery [901], accelerates reepithelialization in patients with neurotrophic keratopathy [902–904] | | | |

**Table 9**
Summary of insulin actions on corneal wound healing.

| Model used | Epithelial cells | Stroma/keratocytes | Endothelial cells | Innervation |
|---|---|---|---|---|
| Cell culture/signaling | • ↑ wound healing in the corneal epithelium by activating PI3K/AKT, ERK and EGFR [914]<br>• ↑ proliferation and anti-apoptotic [915]<br>• ↑ migration but not proliferation [916] | ↑ bovine keratocyte matrix secretion, collagen synthesis [911,923,924] | • ↑ the Na, K-ATPase activity and pump function of cultured corneal endothelial cells, mediated by PKC [927]<br>• ↑ bovine and human endothelial cell proliferation [928,929] | |
| Organ culture | ↑ proteolysis in diabetic corneas [917] | | | |
| Animal model | ↑ Healing in streptozotocin rats [918–920] | | | Prevent nerve loss in streptozotocin-induced diabetic mice [930] |
| Human study | • Insulin receptor present on human ocular surface tissue in healthy and diabetic patients [921]<br>• ↑ auto-fluorescence and ↓ corneal sensitivity in type I diabetic patients [922] | Topical insulin not toxic to ocular surface [925,926] | | |

to myofibroblast differentiation [942]. IGF-2 also showed elevated expression after corneal injury and may facilitate limbal stem cell differentiation in corneal wound repair in a mouse model of mechanical cornea injury [943].

### 3.6. Thyroid hormone regulation of the ocular surface and adnexa

The thyroid gland secretes two hormones, triodothyronine (T3) and thyroxine (T4). Ocular and adnexal tissues are targets of thyroid hormones (TH), which have anabolic effects and promote lacrimal gland and other exocrine gland activity [944–947]. Thyroid gland diseases or thyroid hormone (TH) imbalance have negative effects on the lacrimal gland, tear film and ocular surface [948,949]. The causes may be lower hormone inputs to the ocular and adnexa tissues, contiguous inflammatory disease, or higher exposure of the ocular surface due to eyelid wide opening [950–953]. Specifically, Graves' ophthalmopathy, in its early phase is 5-fold more frequently associated with DED than healthy controls. The clinical findings observed in this recent report were lower Schirmer test, lower TBUT with fluorescein, and lower corneal sensitivity, with or without exophthalmos [954].

#### 3.6.1. Thyroid hormone influence and mechanism of action

TH promote lipid and protein synthesis, tissue growth and differentiation [946]. The lacrimal gland and ocular surface epithelia have nuclear receptors for thyroid hormones and therefore are target organs for those hormones. Decreases of T3 and T4 induce hypotrophy of the lacrimal gland, cornea epithelia metaplasia and reduced tear flow [399,944,955].

TH work primarily through nuclear receptors, which promote the expression of specific genes. The two isoforms of the thyroid hormone receptors, alpha and beta, are further divided in types 1 and 2. They are differently expressed in different tissues [956]. Thyroid hormone receptor beta-1 is expressed in rat lacrimal gland and hormone reduction for ten weeks induces its up-regulation in this tissue [944]. TH are well known to influence lipolysis and lipogenesis; their deficiency causes hypercholesterolemia and reduction of lipid secretion by sebaceous glands [946,957], suggesting that TH may also exert influence on the meibomian glands.

#### 3.6.2. Thyroid hormone role in sex-related differences

The frequency of autoimmune thyroid diseases, Hashimoto's thyroiditis and Graves' disease are several times higher in females than males [958]. Moreover, Sjögren syndrome, a disease ten times more frequent in females is commonly associated with thyroid-associated diseases [948,951]. These events taken together indicate that female sex and/or female sex hormones predispose to inflammatory events in the thyroid gland and related target tissues. In addition, TH imbalance may contribute to the development of autoimmune diseases.

#### 3.6.3. Clinical relevance of thyroid hormone action in DED

Several diseases related to the thyroid gland and its hormones may affect the ocular surface and induce DED. The three major mechanisms are mechanical (proptosis associated with Graves' disease), autoimmunity that extends to ocular and adnexal tissues; and TH loss in conditions related to iodine scarcity, thyroid radiotherapy, thyroid gland ablation and poor hormone replacement in different diseases.

Thyroid-associated ophthalmopathy features DED manifestations, including symptoms, low tear secretion, low TBUT, punctate keratitis, rose bengal staining, higher tear osmolarity and MGD [793,959]. A challenging aspect is that no single test is capable of distinguishing patients with DED due to Graves' ophthalmopathy in a population setting [876]. A recent study using proteomics to compare the profile of tears from patients with Thyroid-associated orbitopathy (TAO), DED patients without TAO and healthy controls revealed that a similar profile in TAO with or without DED, compared to DED and control groups [466]. Although the work did not clearly define the criteria to label DED individuals or the possible causes of DED in the non TAO group, it indicated a higher expression of pro-inflammatory proteins in both TAO groups, suggesting possible biomarkers and unique mechanisms of disease in DED caused by TAO [960].

## 4. Gender, health, and DED

### 4.1. Sex and gender as interrelated distinct characteristics

Animal studies reveal sex-based differences that are rooted in biology and appear to affect risk for DED and could shed light on the mechanisms behind the disease and its presentation [89,98,263,265,527,671]. For example, Zylberberg et al. [671] found increased levels of the pro-MMPs-2 and -9 in cell cultures obtained from

female rabbits' lacrimal glands that were exposed to estradiol but not to DHT. Both of these MMPs are found in increased concentrations in tear fluids from patients with DED, suggesting that these MMPs may be implicated in the pathogenesis of this disease. In addition, Seamon et al. [98] demonstrated reduced levels of tear lipocalin in ovariectomized rabbits, adding to the evidence linking reduced levels of sex steroids with DED—a finding that might help explain why postmenopausal women are at increased risk of DED (see Section 2.2.3).

When considering health and disease and the provision of health care, gender—the socially constructed differences between men and women that give rise to conceptions of masculinity and femininity—must also be taken into account [961]. Various factors related to sex and gender place women at heightened risk for DED and make them vulnerable to disparities in care and outcomes. The literature abounds with examples of gender-based health disparities in access to care, care-seeking behavior (particularly in women in developed countries), communication with health care providers, service utilization, and health outcomes around the world, and these examples may likewise apply in the case of DED. Studies, for example, have documented disparities in colorectal cancer screening [962,963], access to screening and treatment for HIV infection [964,965], quality of life for epilepsy patients [966,967], referrals for cardiac rehabilitation [968], access to and care-seeking behavior for mental health services [969,970], quality of life and long-term outcomes of stroke survivors [971], and care provided for type 2 diabetes and in lower-extremity amputations among patients with diabetes [972,973].

According to Schiebinger and Stefanick [974] gender can be broken down into "gender identity" (how individuals and groups perceive and present themselves), "gender norms" (unspoken rules in the family, workplace, institutional, or global culture that influence individual attitudes and behaviors), and "gender relations" (the power relations between individuals of different gender identities). The many known determinants of women's eye health disparities include uneven access to care and treatment due to socioeconomic factors; attitudes and behaviors about preventive care; gender-based differences in health-seeking behaviors; age [33]. That biological age is a key risk factor for eye and vision problems, including DED, contributes to the notion that women, who live longer than men on average, also suffer significant disability from chronic vision conditions that predominate in older people [33]. In addition, many autoimmune diseases are more prevalent in women than in men [33]. Certain of these diseases (e.g. systemic lupus erythematosus, rheumatoid arthritis) are associated with DED (see Section 2.2.3.).

### 4.2. Gendered behaviors can lead to gender differences in eye conditions

Trachoma and onchocerciasis, the first and second leading causes of infectious blindness in the world, are classic examples of gender-based health issues. In the developing world, where trachoma is common, women are three times more likely than men to be blinded by trachoma, due to the influence of gender-defined roles for women [975]. Women have more physical contact with people who are infected, putting them at greater risk of exposure. Women are also less likely to seek and receive treatment for trachoma [33]. Onchocerciasis in contrast, disproportionately affects men compared to women. This imbalance is due to the influence of gender roles as well, with men in endemic areas spending more time than women in aquatic environments, such as polluted rivers, where the parasitic disease spreads via an insect vector [33].

Gendered behaviors also affect risk for DED in a significant way, as women may experience heightened attention to their cosmetic appearance, including the wearing of spectacles. For example, in certain countries more women wear contact lenses than men, and contact lens wear is associated with a heightened risk for DED stemming from lens use [976]. Nichols and Sinnott found that women who wore contact lenses were more likely to have DED than were men, with 40% of the men and 62% of the women in the study classified as having DED ($P < 0.0001$) [977]. Women are also more likely to undergo laser refractive surgery [978], which is associated with an elevated risk of developing DED [979–982]. In another study, the combination of oral contraceptive pill use and contact lens wear appeared to increase the severity of DED symptoms in young women [58,699,983].

### 4.3. Gender concordance between patient and care provider adds another dimension

A substantial body of literature addresses the influence of gender on the interactions between patients and their care providers. It has been postulated that the gender composition of the patient–clinician dyad could affect communication, shared decision-making, and other aspects of health care, but the answer is still not clear. For example, a patient-level meta-analysis by Wyatt et al. [984] across 7 clinical trials (775 clinical encounters) found no statistically significant interaction between clinician–patient gender mix and decisional conflict, satisfaction with the clinical encounter, or patient engagement. A borderline significant interaction was observed only for increased concordance between stated decision and action taken, for encounters involving clinicians who were women and patients who were men ($p = 0.05$). All other gender dyads showed decreased concordance (6% fewer concordant encounters for same-gender, 16% fewer concordant encounters for clinicians who were men/patients who were women) [984]. A systematic review of the literature undertaken by Deepmala et al. [985] found that 10 of 12 studies analyzed provided evidence that provider characteristics, including age, sex/gender, experience, and specialty, as well as the interplay between provider and patient characteristics are important variables in pain management with analgesics.

### 4.4. Sex and gender influence the experience and treatment of pain

Pain is a hallmark of DED. Surveys of epidemiologic and laboratory data as well as electronic medical records provide strong evidence for clinical and experimental sex and gender differences in pain [986,987]. Many studies show that men have higher pain thresholds than women. This relationship holds true even for children and adolescents [988,989]. Various explanations for this phenomenon have been given, ranging from experiential and sociocultural gender differences in pain experience between men and women to hormonally and genetically driven sex differences in brain neurochemistry [986]. Having lower pain thresholds and tolerances (i.e. greater sensitivity to pain) leaves women at particularly high risk of being undertreated for pain [990]. Health care providers should take into account the role of gender when assessing their patients' complaints of pain because men and women differ in their perception of pain, their tendency to complain of pain, and their methods for coping with pain [991,992].

Animal studies can help distinguish the relative contributions of biological sex and gender to pain and pain attenuation. Many studies in animal models have demonstrated sex-specific differences in responses to pain and pain attenuation. In a study of rats,

Liu et al. [993] found a striking interdependence of sex and pain type that determines the manifestation of antinociception (reduction of sensitivity to painful stimulus) mediated by Dyn protein and its associated kappa opioid receptor (KOR). Both sex and pain type are important determinants of Dyn/KOR antinociception; neither variable acts independently of the other. Another group reported sex-specific differences in pain response by dopamine in the bed nucleus of the stria terminalis in rats [994,995]. Yet another study revealed increased heat sensitivity and decreased cold sensitivity for female rats, but not males that underwent injections of quisqualic acid into the thoracic gray matter or sham operations. This selective effect is indicative of altered sympathetic activation by the thoracic injections. The effect of sham surgery suggests that female rats are vulnerable to ischemic injury during exposure and manipulation of the spinal cord [996]. One study examining chronic pain among the elderly found that women tended to adopt more psychologic approaches, such as acceptance and ignoring to relieve pain, than men [997]. In a study of nearly 800 men and women with fibromyalgia syndrome, Racine et al. [991] found that men were more likely to view pain as evidence of harm, and they were also more likely than women to avoid activity as a way to cope. Curtailing activity as a pain-coping strategy appears to be detrimental to men's quality of life [998].

Moreover, the role played by care providers' gender in pain management cannot be ignored. A study involving 310 general practitioners revealed that evidence of pathology had a larger effect on referrals of low-back pain patients to psychology/psychiatry by physicians who were men than those who were women. Also, the gender of the clinician moderated the pain judgments that accounted for the effect of pathology findings and pain behaviors on prescribing patterns [999]. For example, physicians' gender had a significant impact on pain management decisions in patients with low back pain, according to a review of 186 medical records [1000].

Care providers may view subjective complaints differently than objective tests. In cases of DED, this is problematic because symptom complaints do not correlate well with ocular findings. Management of DED symptoms is complex, and health care providers need to consider a patient's holistic picture, rather than simply treating ocular signs. For example, Vehof et al. [293] conducted a cross-sectional study of 1622 twin volunteers, all of whom were women, ranging in age from 20 to 83. A total of 438 (27.0%) were categorized as having DED. Women with the disease had significantly greater pain sensitivity, lower pain tolerance, and more pain symptoms than those without DED, strengthening the evidence of associations between the severity of tear insufficiency, cell damage, and psychological factors.

## 5. Recommendations for future research related to sex, gender, hormones and DED

DED can cause significant pain, but little is known about factors contributing to symptoms of DED, given the poor correlation between these symptoms and objective signs at the ocular surface [274,293]. The hope is that we can identify better ways to predict risk for DED and develop novel therapies to alleviate this condition with more targeted, mechanistic approaches instead of relying on nonspecific symptom relief. Sex, gender and hormones exert a significant influence on the ocular surface and adnexa, and play a significant role in the pathogenesis of aqueous-deficient and evaporative DED. However, further studies are required to clarify the precise nature, extent, and mechanisms of these sex, endocrine and gender effects on the eye in health and disease. Such studies need to:

- Use the terms sex and gender consistently and correctly across scientific disciplines, in order to promote the accurate assessment, measurement, and reporting of differences between men and women;
- Conduct more epidemiological studies on the prevalence of DED by using both sign and symptom data;
- Use the term sex in most studies of nonhuman animals;
- Include sex as a variable in basic and clinical research, and take donor sex into account in experiments with cultured cells;
- Select animal models for research that mirror human sex differences and are relevant for DED;
- Evaluate natural genetic variability, disorders of sex differentiation, reproductive status and environmental influences to gain a better understanding of human DED;
- Elucidate the roles of the sex chromosome complement (e.g. parent-of-origin effects, X-inactivation, and genes in the non-recombining region of the Y chromosome), sex-specific autosomal factors and epigenetics (e.g. miRNAs, DNA methylation and acetylation, and histone modifications), as well as the microbiome, in mediating sex-related differences;
- Develop systems that identify and differentiate the effects of genes from those of hormones;
- Determine the processes involved in the sex steroid, hypothalamic-pituitary hormone, glucocorticoid, insulin, IGF-1 and thyroid hormone regulation of ocular surface tissues, and how they contribute to the sex-related differences in DED;
- Perform clinical studies to determine whether a sexual dimorphism exists in the response to topical GCs for the treatment of inflammatory ocular surface disorders;
- Use functional neuroimaging (e.g. positron emission tomography, fMRI) to evaluate sex-related differences in the pain of DED, as well as in experimentally-induced pain stimuli to the ocular surfaces of healthy subjects;
- Develop innovative human experimental models that better mimic clinical pain in DED;
- Determine whether sex differences exist in the pattern of innervation, the capacity to release neurotransmitters, and the sensitivity to neural stimulation, in ocular surface and adnexal tissues;
- Determine whether sex differences are present in the levels of tear film biomarkers in health and disease, and whether these measures could be used diagnostically;
- Assess whether diagnostic tests and management of DED should be different in men and women;
- Examine the utility of local (i.e. intracrine) hormone measurements for the diagnosis of DED;
- Conduct clinical studies to determine the extent to which MGD, as defined by using meibomian gland diagnostic tests, shows sex-related differences;
- Determine whether the sex difference in DED lessens with more advanced age, becoming more similar among women and men;
- Communicate clearly about the role of sex and gender influences in the arenas of DED research, patient care, and health and science policy;
- Determine whether the use of cosmetics contributes to the gender-related differences in the prevalence of dry eye disease;
- Ensure adequate participation of women in clinical trials, and analyze data by sex/gender to determine differences in response to treatment.

## Financial disclosures

David Sullivan: Allergan (F), Novagali/Santen (F), Cempra (F), TearLab (F), GlaxoSmithKline (F), Singularis (I), M.G. Therapeutics (C), Dompé (R), Sanofi Fovea (R), Novartis (R), Laboratoire Théa (R),

Lμbris (R), Eduardo Rocha: Johnson and Johnson Brazil (C), Pasquale Aragona: None, Janine Clayton: None, Juan Ding: None, Blanka Golebiowski: Tearlab (F), Minifab (F), Lawley Pharmaceuticals (F), Ulrike Hampel: Bausch and Lomb GmbH (F), Optima Phamazeutische GmbH (F), Alison McDermott: CooperVision (F), Debra A. Schaumberg: Mimetogen (I), Shire (SARcode) (C), Eleven Bio (C), Nicox (C), Santen (R), Sruthi Srinivasan: Advanced Vision Research (F), Alcon (F; C; R), AlgiPharma (F), Allergan (F), CooperVision (F), Essilor (F), Johnson and Johnson Vision Care (F; R), Ocular Dynamics (F), Oculus (F), Ocusense (F), TearScience (F), Visioneering Technologies (F), Shire (C), Piera Versura: None, Mark Willcox: Alcon Laboratories (F), Allergan (F), CooperVision (F), Johnson & Johnson Vision Care (F), Ophtecs (F); Allergan (C), Minomic International Pty. (C), Ophtecs (C), Warm Contacts (C); Allergan (R), Ophtecs (R); Minomic International Pty. (S), Ophtecs (S).

F (Financial Support), I (Personal Financial Interest), E (Employment), C (Consultant), P (Patent), R (Recipient), N (No Commercial Relationship), S (non-remunerative).

## Acknowledgments

The authors would like to thank the following individuals: Florence Haseltine, for her insight into the importance of considering sex and gender as basic human variables; Wendy Kam, for her EndNote expertise; Yang Liu, for her extensive literature searches and summaries; and Amy Gallant Sullivan for her excellent translations of the entire 1905 Berger E & Loewy R. book ("Ocular troubles originating from the female genital tract") [4] from French to English, and the Lagresa et al. [461] publication from Spanish to English. Thanks to Nino Longo (Catania, Italy) and Sabrina Zappia (Rome, Italy) for help with graphics and illustrations.

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