Effect of Glucose Intolerance on Refractive Error

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Abstract: Myopia is one of the leading causes of blindness and the incidence has steadily increased over the past few decades. There seems to be a trend of increasing incidence of myopia in kids and young adults. There were several associations and potential causes cited for this. The primary objective was to examine the mechanisms by which insulin affects ocular growth and development, investigate the relationship between insulin levels and the development and progression of myopia and hyperopia, and highlight the areas that require further research to better understand the role of insulin in refractive errors. Overall, this research aims to contribute to our understanding of the complex etiology of refractive errors and to identify potential targets for future interventions to prevent and manage these conditions. A literature search was done on PUBMED and Google scholar on the topic of insulin resistance, glucose intolerance associated with development of refractive errors. There was surprisingly limited research done on this topic despite the increasing burden of this problem on the healthcare system. Insulin triggers several mechanisms that determine the growth of the tissues of the eyeball. Changes in the growth of the eyeball from increased insulin levels causes an increase in the incidence of refractive errors. Animal research demonstrates mechanisms of the signaling pathways by which insulin affects the growth and development of the tissues in the eye. Further research to understand this modifiable cause should help decrease the burden of refractive errors as well as improve the quality-of-life.

1. Introduction

Myopia is one of the leading causes of blindness and the incidence has consistently increased over the past few decades. There seems to be a trend of increasing incidence of myopia in kids and young adults. There were several associations and possible causes cited for this occurrence. Ethnic origin with increased incidence in Asians followed by Hispanics and African Americans and least in Caucasians has been noted (Rudnicka et al., 2016). Increased exposure to blue light from gadgets and decreased time outdoors are among some of the proposed causes of this change (Wang et al., 2021; Chang et al., 2021). It was noted that there was a significant increase in incidence during the Covid times and most of the time spent was indoors (Chang et al., 2021).

Refractive errors, such as myopia and hyperopia, are the most common visual disorders worldwide. They are caused by a mismatch between the optical power of the eye and its axial length, resulting in blurred vision. While genetic and environmental factors have been implicated in the development of refractive errors, recent studies suggest that hormonal factors, such as insulin, may also play a role. Myopia, commonly known as nearsightedness, is a condition in which distant objects look blurry because the eyeball's axial length is greater than emmetropia. When the eyeball has a shorter axial length than emmetropia, a condition known as hyperopia, sometimes known as farsightedness, develops, blurring the image of nearby objects.

Insulin is a hormone that regulates glucose metabolism in the body, and it has also been shown to play a role in ocular growth and development. Insulin receptors have been found in various ocular tissues, including the cornea, iris, ciliary body, retina, and choroid, suggesting that insulin may have a direct effect on these tissues. Insulin promotes axial growth as well as stimulation of signaling pathways (Penha et al., 2012). Previous studies have found that insulin levels are positively correlated with the incidence and progression of myopia, with higher insulin levels associated with higher rates of myopia. Conversely, lower insulin levels have been associated with hyperopia.

2. Mechanisms by which insulin affects ocular growth and development

Insulin, a peptide hormone synthesized by the pancreas, plays a crucial role in regulating glucose metabolism and has been implicated in the development of various diseases. Insulin exerts its effects on the eye through various mechanisms, including insulin signaling pathways, the role of insulin-like growth factors (IGFs), and its effects on eye tissues.

2.1 Insulin Signaling Pathways (ISPs)

Insulin signaling pathways are a complex network of biochemical reactions that regulate cellular responses to insulin. The insulin receptor is expressed in various ocular tissues, including the retina, ciliary body, and lens. Activation of the insulin receptor by insulin results in the activation of downstream signaling pathways, including the phosphatidylinositol 3-kinase (PI3K)/Akt pathway, the mitogen-activated protein kinase (MAPK) pathway, and the mammalian target of rapamycin (mTOR) pathway. These pathways play important roles in regulating cell growth, proliferation, and differentiation in ocular tissues.

The regulation of eye growth is initiated by insulin, which binds to insulin receptors (INSR), phosphorylates INSR substrate protein, causes PI3K to activate AKT, activates mTOR, starts cell growth regulation, and releases MMP-2/TGF-2 and other cytokines in the process. (Li et al., 2021). In one study, activation of the PI3K/Akt pathway was found to promote the proliferation of retinal pigment epithelial cells (RPE), while inhibition of this pathway led to decreased proliferation and increased apoptosis of these cells (Cai et al., 2012). RPE cells are one of the most important cells and are closely related to the occurrence of eyeball growth and

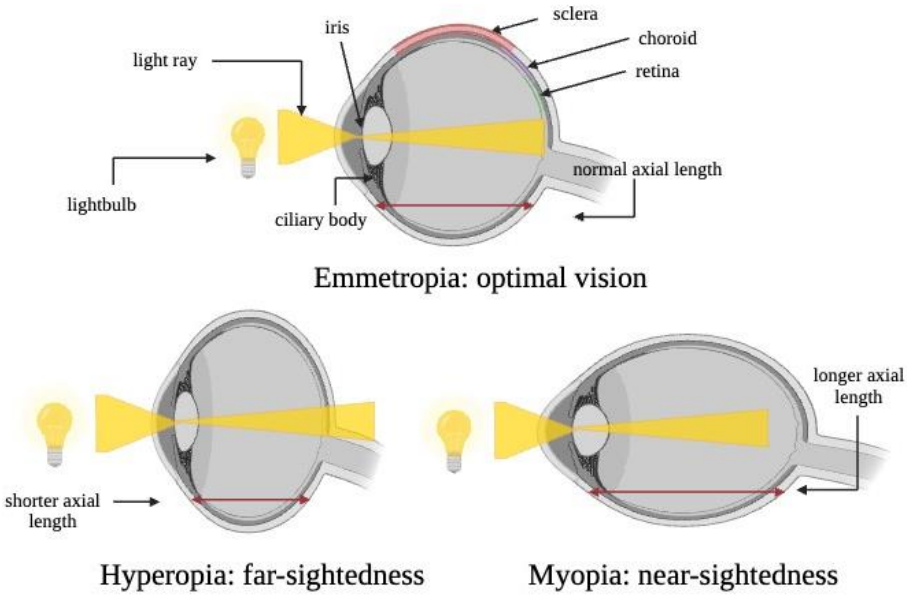


Figure 1. (shown above) Refractory error visuals. This figure shows the three types of refractive error. Copyrighted by: Prisha Yelamanchili (2023)

myopia. Insulin regulated the secretion of PM-related factors via the PI3K/AKT/mTOR signaling pathway in retinal pigment epithelial cells, and thus probably promoted the development of pathological myopia (PM). (Li et al., 2021). The MAPK pathway has been shown to regulate the differentiation of retinal ganglion cells, with activation of this pathway promoting the development of these cells into functional neurons (Moustardas et al., 2023; Zhang et al., 2023). The mTOR pathway has also been implicated in the regulation of cell growth and proliferation in ocular tissues. mTOR activation promotes the growth and proliferation of retinal pigment epithelial cells, while inhibition of this pathway leads to decreased proliferation and increased apoptosis of these cells (Wang et al., 2022; Casciano et al., 2022).

2.2 Role of insulin-like growth factors (IGFs)

Insulin also interacts with IGFs to regulate ocular growth and development. IGFs are a family of growth factors that share structural and functional similarities with insulin. IGFs are synthesized by various ocular tissues, including the retina, ciliary body, and choroid in the eye. Insulin and IGFs bind to similar receptors, but IGFs have a higher affinity for their receptors than insulin does. The interaction between insulin and IGFs regulates various cellular processes, which include cell growth, differentiation, and survival. One study investigated whether the combination of insulin-like growth factor 1 (IGF1) and fibroblast growth factor 2 (FGF2) influence ocular growth in eyes with unrestricted vision. They found that myopia, with a refractive defect of more than 15 diopters, occurred in treated eyes. Intraocular pressure (IOP) in the eyes rose quickly after treatment and increased in a dose-dependent way. IGF1 and FGF2 therapy decreased changes in anterior chamber depth, lens thickness, and high IOP seven days after treatment, although elevations in the vitreous chamber persisted. It was concluded that the combination of IGF1 and IGF2 increased the rate of ocular growth, contributing to extreme myopia (Ritchey et al., 2012).

Additionally, hyperinsulinemia suppresses hepatic synthesis of insulin-like growth factor binding protein-1 which increases free-insulin-like growth factor-1 which in turn decreases growth hormone secretion by negative feedback. This decreases the levels of insulin-like growth factor binding protein–3 which reduces the effectiveness of the body's natural retinoids in activating genes that would limit scleral cell proliferation (Mori et al., 2001; Fisher et al., 1999).

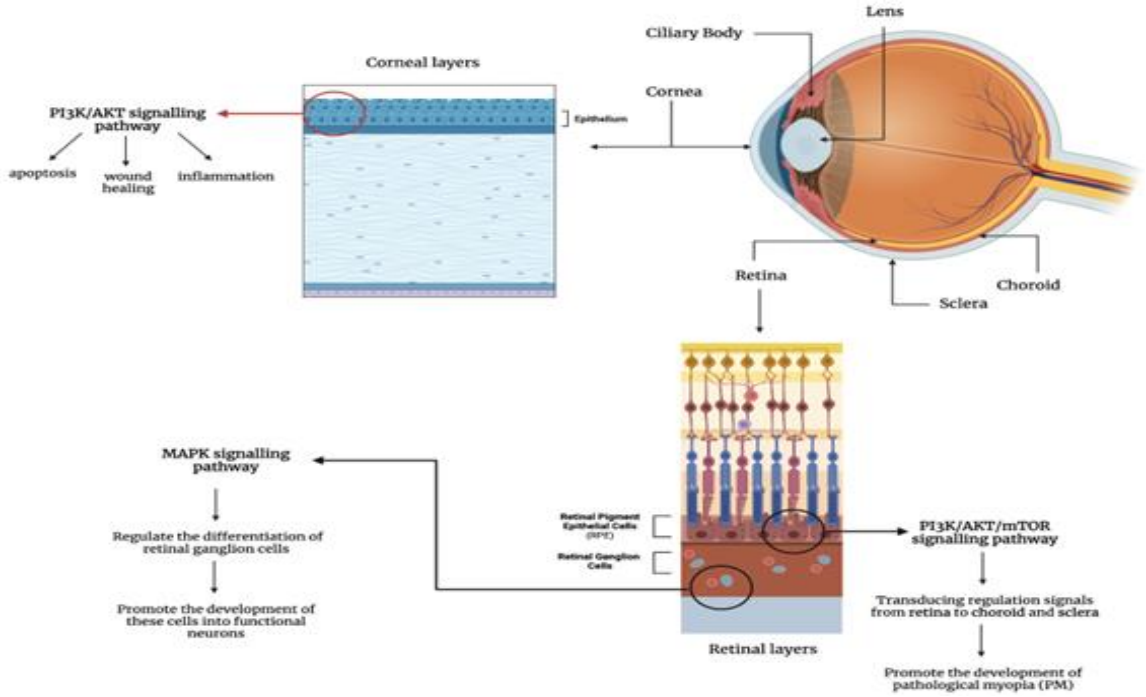


Figure 2. *(shown Left) Insulin Signaling Pathways Location and Function in the Eye. This figure shows the locations of different ISPs in the eye as well as their functions. Copyrighted by: Prisha Yelamanchili (2023)*

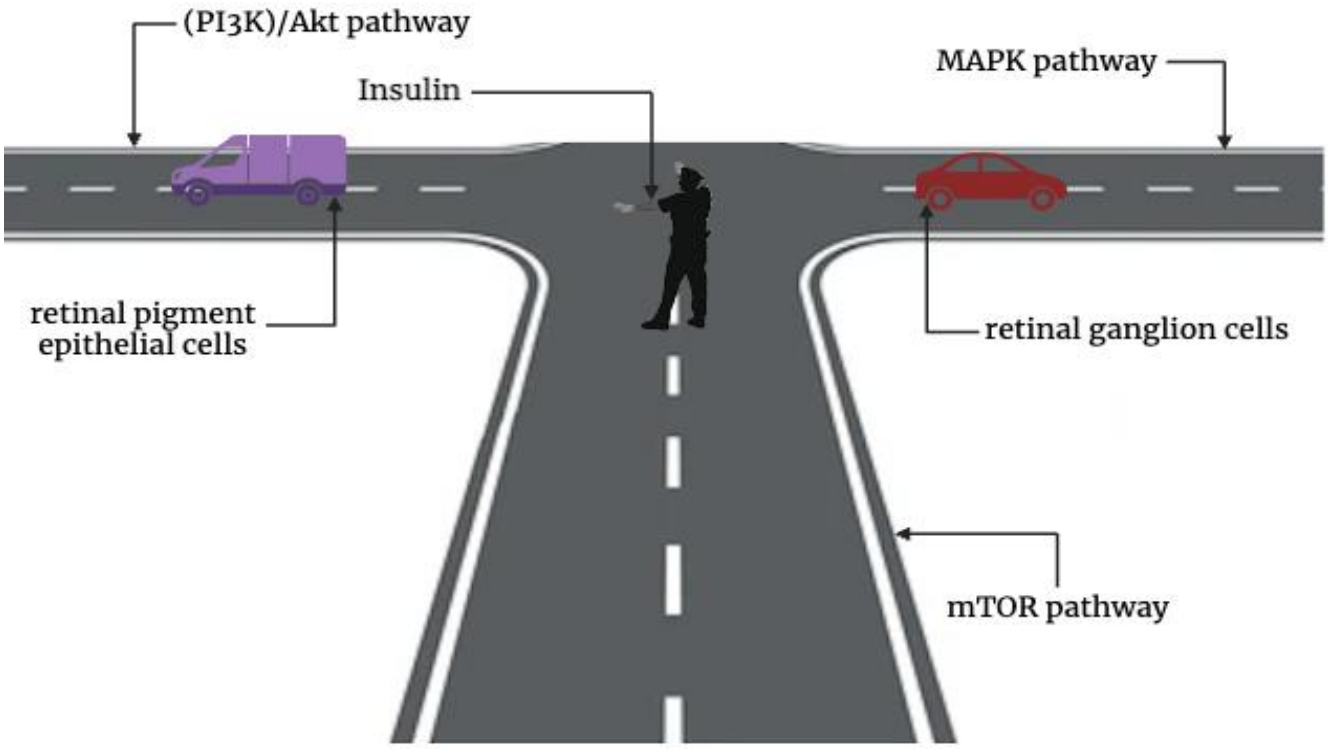


Figure 3. (shown above) Insulin-Traffic analogy. This figure displays a simplified analogy of how ISPs work. Copyrighted by: Prisha Yelamanchili (2023)

3. The Effect

3.1 Effect of Insulin on Eye Tissues

Insulin has direct effects on ocular tissues, including the retina, ciliary body, and lens. Insulin receptors are expressed in these tissues, and insulin has been shown to regulate cellular processes such as glucose transport, protein synthesis, and DNA synthesis (Naeser et al., 1997). Insulin has also been shown to modulate the expression of various genes involved in ocular growth and development. Insulin is one of the major hormones that promote tissue growth. Because of its function in stimulating development and preventing protein breakdown, it is the only protein hormone in the body that also reduces blood sugar levels. Ocular development by insulin has been studied in animal models. According to animal studies, injecting insulin into the eye can cause the expansion of the eye axis and the thinning of choroidal tissue , which have shown that insulin plays a major part in the development of animal ocular myopia. A greater quantity of insulin may also affect an animal's eyes, increasing myopia and the axial length of the eye, according to further investigations (Li et al., 2021).

Insulin plays a critical role in regulating ocular growth and development through various mechanisms. Insulin-like growth factor (IGF2) mediates insulin actions by affecting the axial length in animal models. A translator factor, ZENK secreted by glucagon amacrine cells, mediates insulin effect on the axial growth and myopia development. Insulin directly causes eye elongation and synthesis of scleral glycosaminoglycan (GAG). Insulin injection enhanced axial myopia and inhibited hyperopia renovating a negative lens (M.P.Feldkaemper et al 2009). Glucagon was the opposite of insulin, causing thickening of the choroid and slowed down eye elongation (Jing Yang et al., 2022).

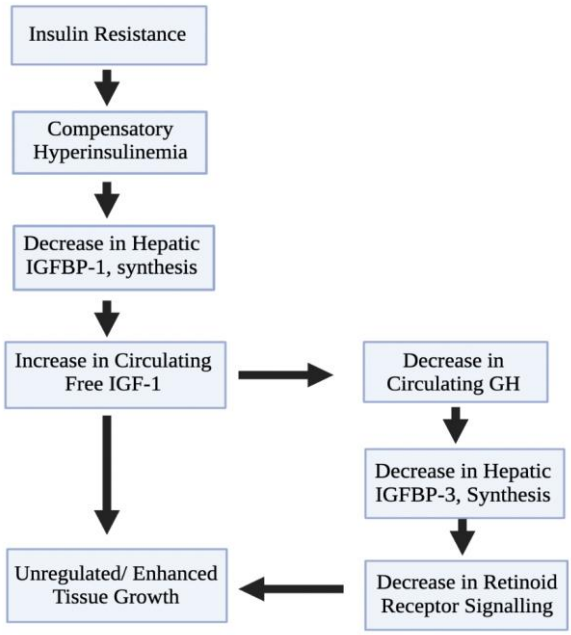
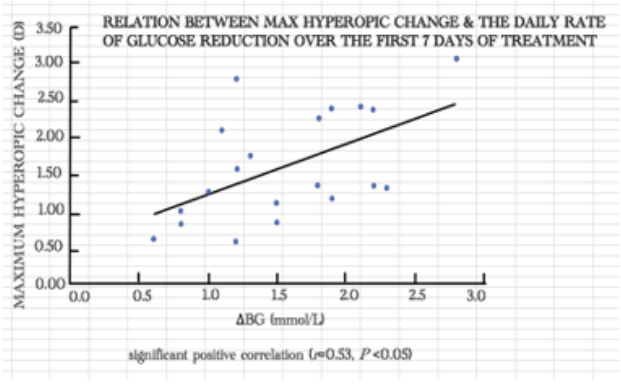


Figure 4. (shown above) Reproduced from Cordain et al., 2002. This figure shows the effect of IGFs.

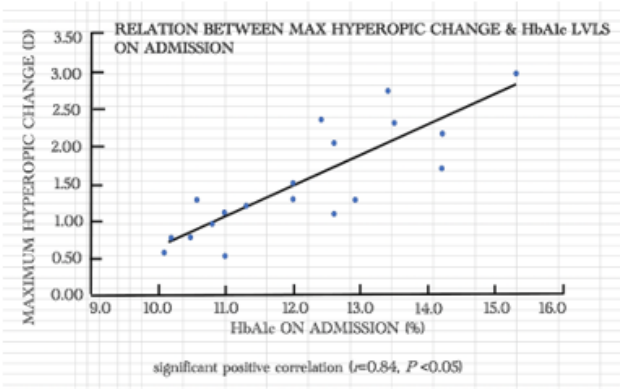
3.2 Effect of hyperglycemia on refraction

The effect of blood glucose levels on refraction has been symptomatically known for a long time. For example, there is blurred vision in patients with hypoglycemia which

improves with treatment. Hyperopic changes were noted over several weeks of treatment for hyperglycemia and improvement of hemoglobin A1c. There was a positive correlation between hyperopic change and plasma glucose reduction, correction of hyperglycemia. In the study there is no correlation with random blood glucose, blood pressure, fasting C-peptide or age or a body mass index or cholesterol levels. There were also no changes in the intraocular pressure or the radius of the anterior corneal curvature or the depth of the anterior chamber, lens thickness, vitreous length on the axial length. The physiology behind this hyperopic change is not very well understood (Li et al., 2010).



Graph 1. (shown above) Reproduced from Li et al., 2010. This graph demonstrates the relationship between the maximum hyperopic change and the daily rate of glucose reduction over the first week of treatment.



Graph 2. (shown above) Reproduced from Li et al., 2010. This graph demonstrates the relationship between the maximum hyperopic change and HBA1C levels on admission.

4. Methods

A PUBMED and Google Scholar search was conducted with the terms, “incidence of refractive errors,” “causes,” “mechanisms,” “research on increased incidence of myopia,” “effect of insulin on the eye,” “Effect of glucose intolerance on refractive errors.” When the search was broad, about 587 articles were pulled with filters for age and articles in English between 1946 and 2023. When the search was narrowed to the various keywords, there were four articles addressing the topic. All the articles were reviewed to understand the concepts and available research. It was noted that the articles on this topic were focused on finding various etiologies for the refractive errors, genetic versus environmental. There was a suggestion for understanding the incidence of this problem based on geographic locations. Articles involving treatment of refractive errors and diabetic retinopathy were reviewed to understand the concepts but were not the areas of review for this paper. Then the mechanisms postulated for development of refractive errors from elevated levels of insulin and glucose intolerance were summarized.

5. Results

Based on existing research, insulin is known to influence ocular growth and development. Insulin is a hormone that regulates blood sugar levels and plays a role in various physiological processes including cell growth, proliferation, and differentiation. Insulin receptors have been found in various ocular tissues such as the cornea, iris, ciliary body, retina, and choroid, indicating that insulin can directly affect ocular tissues. Studies have shown that insulin levels are positively correlated with the incidence and progression of myopia, with higher insulin levels associated with higher rates of myopia (Li et al., 2010). This may be because insulin promotes the growth of ocular tissues and increased axial length, which could contribute to the development of myopia. On the other hand, lower insulin levels have been associated with hyperopia, due to a lack of insulin-induced growth. Therefore, it can be hypothesized that insulin has a significant effect on refractive errors such as myopia and hyperopia, with higher insulin levels associated with an increased risk of myopia and lower insulin levels associated with an increased risk of hyperopia. Disturbances in insulin signaling may lead to abnormal eye growth and the development of myopia (Li et al., 2021). It has also been shown that acute hyperglycemia is associated with myopic refraction, but refraction becomes less myopic with lowering the levels of hyperglycemia (Li et al., 2010). Further research is needed to fully understand the underlying mechanisms and to determine the optimal insulin levels for maintaining normal ocular growth and development.There also needs to be more understanding on the effect of changes in blood glucose levels on refraction.

5. Limitations

While previous studies have shown that insulin levels are correlated with the development and progression of refractive errors such as myopia and hyperopia, there is still a lack of good understanding about the underlying mechanisms by which insulin affects ocular growth and development. There is limited research that helps with targets for intervention to decrease the incidence of refractive errors. There is a need for further research in this area as it can have a major impact on the healthcare system.

Conclusions

We understand the various pathways by which insulin plays a role in the development of the eye and how hyperinsulinemia pathologically affects this process causing refractive errors. There seems to be an association between incidence of hyperinsulinemia and increased prevalence of myopia in kids and young adults. When examining the intricacies of ocular biology, it becomes obvious that insulin is crucial in determining how we see. Because insulin levels and eye axis length are positively

correlated, it is possible for myopia to develop and excessive eye growth to result from problems with insulin signaling.

These discoveries reveal a fascinating link between our metabolic functions and the complex neural circuits that control our vision system. This study discussed the intriguing possibility of managing refractive error with drugs that target insulin levels. These findings open up a new world of possibilities and imply that glycemic management and steady insulin levels might have a beneficial effect on refractive error. This information might fundamentally alter how these refractive errors are managed and treated by realizing the pivotal function of insulin in ocular development and function.

Additionally, we highlight the areas that require further research. Changing our approach to this general medical condition would affect the quality-of-life in several ways, including significant positive effects on reading and education. The implications are extensive, opening up new opportunities to improve ocular health outcomes and drastically impact the lives of countless people.

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