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Biochemical Effects of Diabetes on the Eyes and Treatment Options

Senior Project

In partial fulfillment of the requirements for
The Esther G. Maynor Honors College
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By

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Biochemical Effects of Diabetes on the Eyes and Treatment Options

INTRODUCTION

Diabetes is a serious condition that has profound effects on the body. More specifically, diabetes can cause significant damage to the eye. Some of this damage can include retinopathy, macular edema, cataracts, glaucoma and even blindness. Although the effects of diabetes of the eye can be quite severe, if caught early enough, the disease can be managed and treated.

WHAT IS DIABETES?

According to the World Health Organization (WHO), diabetes mellitus is a disease that affects the production of insulin which results in the increase of glucose in the blood (hyperglycemia) (2010). Type one diabetes is what most people think of when they talk about diabetes. Type one most commonly occurs in children and is generally genetic in nature. It occurs when the pancreas fails to produce sufficient insulin levels and requires supplementation from an outside source such as an insulin pump or pen (WHO, 2010). Type two diabetes is by far the most common type of diabetes mellitus which accounts for 90% of all diabetes mellitus cases (WHO, 2010). This form of diabetes occurs when the body does not properly respond to the effects of insulin. Type two diabetes affects adults more frequently than children.

Typical symptoms involved with Type one diabetes are polyuria, increased thirst, excessive hunger, uncontrollable weight loss, mood swings, chronic fatigue and blurred vision. (Mayo Clinic, 2017). With Type one the only real risk factor would be genetic predisposition (American Diabetes Association, 2018). There are several risk factors for Type two diabetes most of which include diet and lifestyle. Some of them include

diagnostic tests such as a standard visual acuity test, dilated eye exam, and tonometry (measure of intraocular pressure) (NEI, 2015).

Diabetic cataracts are caused by an accumulation of sorbitol in the lens of the eye. This starts when the enzyme aldose reductase reduces glucose to sorbitol (Pollreisz & Schmidt-Erfurth, 2010). The real issue is when the enzyme sorbitol dehydrogenase fails to break down sorbitol to fructose at a rate that matches the reduction of glucose, and produces a buildup of sorbitol in the lens (Pollreisz & Schmidt-Erfurth, 2010). Due to the high levels of sorbitol in the lens, osmotic pressure causes a rapid influx of water into the cells of the lens. This causes a "collapse and liquefaction of lens fibers" (Pollreisz & Schmidt-Erfurth, 2010). Sorbitol is a polar molecule and cannot diffuse through the membrane of the lens (Pollreisz & Schmidt-Erfurth, 2010). As a result, the proteins in the lens begin to irregularly clump together and form the cataract.

TREATMENT

There are currently no drug therapies available for the treatment of diabetic cataracts. The only definitive cure is to surgically remove the cataracts and replace the lens with an intraocular lens (IOL). The IOL is a small, typically acrylic "biconvex optic" that will serve as the replacement lens (Fuller, 2013). The IOL has two arm-like structures called haptics that allow it to attach itself to the walls of the eye to maintain position

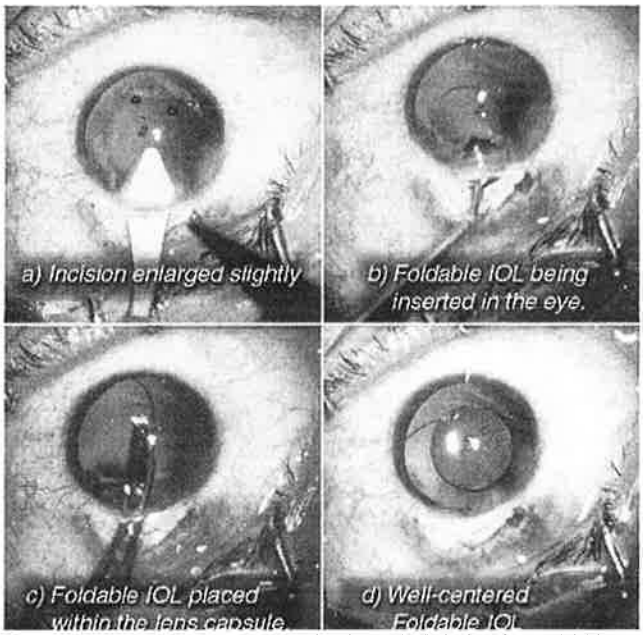

Figure 2: "Cataract Surgery," Charlotte Ophthalmology, 2018, https://eyesoncharlotte.com/procedures/cataract.php

(Fuller, 2013). The incision is not typically sutured closed but can be if any incisions had to be enlarged.

Figure 3: "Cataract Surgery." Charlotte Ophthalmology, 2018. https://eyesoncharlotte.com/procedures/cataract.php

The prognosis for patients with diabetic cataract is good following surgery. Although the symptoms of a cataract can be eradicated with surgery, the management of consistent high blood sugar is the key to preventing diabetic cataract.

DIABETIC RETINOPATHY

Diabetic retinopathy is a condition of the eye that causes the retina to become damaged over time due to high levels of glucose in the eye (AOA, 2018). The retina is the portion of the eye that receives light stimuli and transfers them into nerve impulses to the brain which allows us to see (AOA, 2018). When chronic high levels of glucose persist in the eye, the capillaries and small vessels of the eyes begin to develop weak

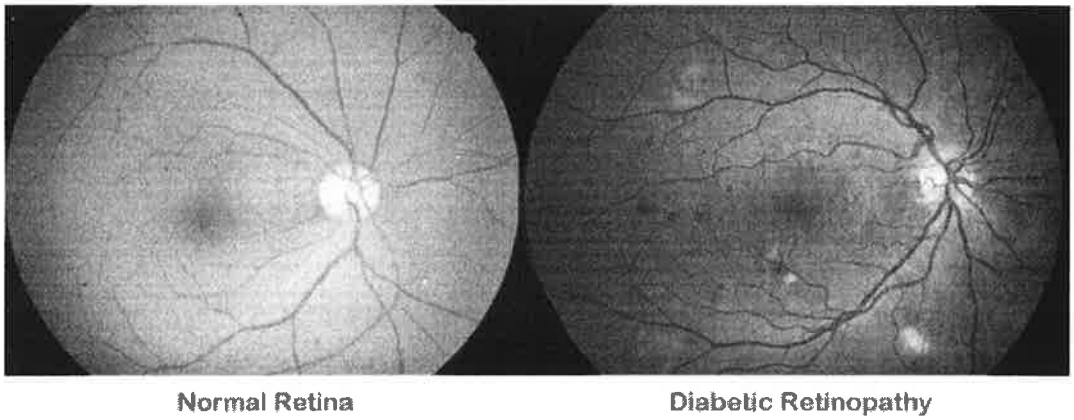

Figure 4: "Diabetic Retinopathy Compared to Normal Eye." BW Primary Care, 2018, bwprimarycare.com/services/retinal-eye-exam/.

The excess glucose in the vessels of the eyes causes a hypertonic solution around the blood vessel cells. As the glucose levels begin to increase, the hypertonicity of the solution increases. This causes the concentration of glucose to be much higher outside the cell. Due to the concentration gradient, the glucose from the outside of the cell will begin to move into the inside of the cell in an attempt to restore homeostatic levels. The excess glucose is then converted into sorbitol by aldose reductase (Pollreisz & Schmidt-Erfurth, 2010). As sorbitol builds up in the cells, it causes a hypertonic solution of sorbitol within the cells. Due to such a high concentration of sorbitol in the cell, water begins to flow into the cell in order to establish equilibrium. This causes the cell to swell and burst (lyse). The lysing of cells weakens the walls of the vessels causing the leakage at the root of diabetic retinopathy.

TREATMENT

There are several ways of treating diabetic retinopathy including medications, surgery and homeopathic treatments. The most common type of medication used to treat diabetic retinopathy is an anti-vascular endothelial growth factor (anti-VEGF) (Yorston, 2014). This type of medication prevents the abnormal growth of retinal vessels (Yorston, 2014). Since this type of drug can be used anywhere within the body to prevent vessel growth, it is extremely important to ensure that the medication is administered locally to the eye through the use of injection (Yorston, 2014). Lucentis®, Avastin®, and Eylea® are the three most common forms of the drug that are used today. Lucentis® and Avastin® are synthesized with the use of highly specialized monoclonal antibody that has been designed to only bind to any form of vascular endothelial growth factor (Yorston, 2014). Avastin® is the cheapest option for the patient but is not always as

Sutter, 2004). Photocoagulation (endolaser) can also be used to help "tack" or adhere a detaching portion of the retina (Helbig, Sutter, 2004). More often than not, surgery is not indicated for any sort of detachment that is not in jeopardy of threatening the fovea (Helbig, Sutter, 2004). This is due to the fact that the retina has the ability to seal the defect without surgical intervention. Once all the damaged vitreous is removed, the empty space must be filled in order to retain optimum ocular pressure. This restored normal pressure helps the retina heal. Restoration of pressure is often completed with the use of a gas bubble or silicone gel (Fuller, 2013). Often times, patients present with both diabetic retinopathy and cataract. In this case, a surgeon will opt to remove the cataract in order to gain better access to the posterior chamber (Helbig, Sutter, 2004).

When detected early, diabetic retinopathy can be treated and produce little to no significant damage to the eye. Proper diet and exercise can also help to prevent diabetes and limit damage to the eye. Long term, this disease is not curable but can be managed through treatments ranging from medications to surgery, depending on the severity of the damage to the retina.

DIABETIC MACULAR EDEMA (DME)

Diabetic Macular Edema (DME) is a disease affecting the retina. Specifically, in DME, it involves the macula, which is a portion of the retina that is located in the center

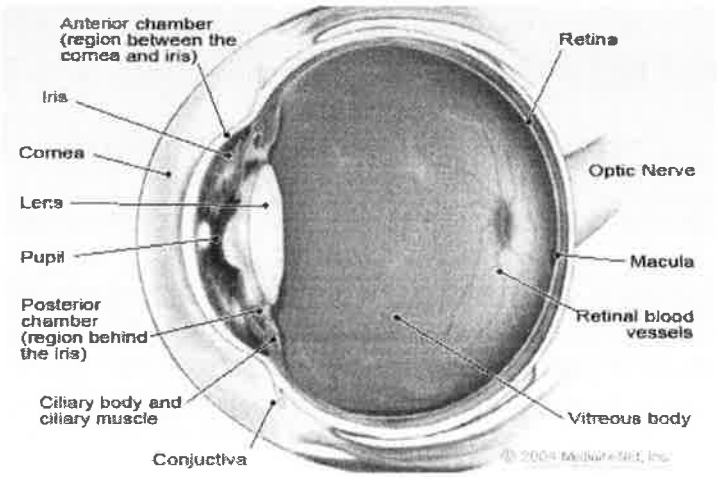

Figure 7: "Eye Anatomy." Medicine Net, 2018, https://www.medicinenet.com/image-collection/eye_anatomy_detail_picture/picture.htm

These drugs help to block the effects of VEGF in the tissues of the retina (Yorston, 2014).

However, with DME, physicians also may add a corticosteroid to the regiment. Corticosteroids aid in reduction of inflammation between injections and may reduce the need for frequent injections. Corticosteroids can be given to the patient in the form of a pill, eye drop or intramuscular injection (NEI, 2015). Examples of corticosteroids given for ocular edema (DME) include: betamethasone sodium phosphate (Celestone®), dexamethasone (decadron®), methylprednisolone acetate suspension (Depo-Medrol®) (Fuller, 2013). For more serious cases of DME, the physician may opt for an implantable release system for the steroid. Three implants are currently approved by the FDA for the treatment of DME, and they include Ozurdex®, Retisert®, and Iluvien® (NEI, 2015). Ozurdex® is an implantable device that releases dexamethasone (NEI, 2015). Retisert® and Iluvien® are both forms of the drug fluocinolone acetonide (NEI, 2015).

Surgical intervention is indicated for DME because vision is often being obstructed if the macula is inflamed. Surgery is performed as soon as possible to minimize the effects of the inflammation of the macula. As described earlier, a vitrectomy is performed to remove the damaged vitreous, and a laser may be inserted to cauterize any active bleeding vessels. Once all active bleeding and damaged vitreous are managed, the surgeon will evaluate the need of silicone or gas to replace the removed vitreous. Typical gases used to restore pressure are hexafluoride and perfluoropropane (Fuller, 2013).

new, weaker vessels growing onto the iris causing NVG (Figure 9) (AOA, 2018). As in acute narrow-angle glaucoma, the new vessels that grow on the iris causing obstruction of the aqueous humor (Rodrigues et al., 2016).

Just like in the other diabetic eye diseases discussed the main cause of damage is the high levels of glucose within the fluids of the eye. Excess glucose causes a hypertonic solution which moves water into the cell causing cell lysis. As glucose levels rise rapidly, it is converted into sorbitol by aldose reductase (Pollreisz & Schmidt-Erfurth, 2010). As sorbitol builds in the cells, it causes a hypertonic solution of sorbitol within the cells. Due to such a high concentration of sorbitol in the cell, water begins to flow into the cell in order to establish equilibrium, initiating cell lysis.

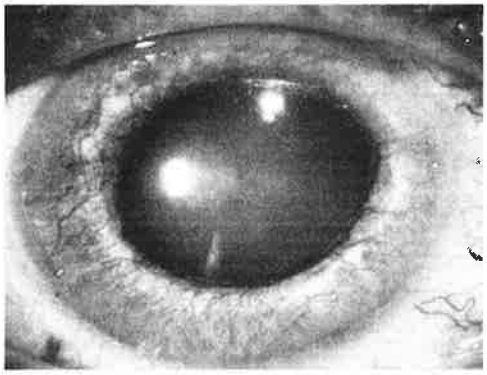

Figure 9:"Abnormal Vessel Growth on the Iris." 2018, http://www.mrcophth.com/glaucoma/rubeosisiridis.html

TREATMENT

There are several ways to treat neovascular glaucoma. Olmos and Lee say that there are two components to treating NVG (2012). One being the medicinal and surgical treatment of NVG, and the second being the long-term prevention of new vasculature on the iris (Olmos & Lee, 2012). NVG intraocular pressure can be controlled with a wide variety of drugs such as beta-blockers, carbonic anhydrase inhibitors and several others (Olmos & Lee, 2012). Carbonic anhydrase inhibitors, typically prescribed with oral medications do not provide adequate control of intraocular pressure alone (Rodrigues et al., 2016). These drugs work by "suppressing aqueous production and possibly increasing uveoscleral outflow" (Rodrigues et al., 2016). Just like in diabetic retinopathy,

This is the goal of the surgery because removal of the meshwork allows the aqueous humor to flow freely to the Canal of Schlemm (Fuller, 2013). When indicated, a shunt will be placed to further assist in drainage (Fuller, 2013).

If left untreated, severe glaucoma can cause blindness in just 2-5 days (Mosby's, 2013). It is critical to begin treatment as soon as possible. Surgical intervention is the best line of treatment when glaucoma is suspected. Anti-VEGF medications should be started as soon as possible when neovascular glaucoma is diagnosed. With these interventions, vision may be saved. Above all, the maintenance of steady glycemic activity is the key in preventing glaucoma.

FUTURE TREATMENTS

According to Gardner and Chew (2016), the future of treatment for diabetic retinopathy lies with research in "vitreous proteomics to reveal molecular targets for therapy." This type of treatment would provide personalized care for each patient with diabetic retinopathy.

Dr. Lloyd Paul Aiello says that the key to advancing the treatment of diabetic macular edema is through the use of target specific anti-VEGF medications (2014). This type of medication is not currently approved by the FDA for use in the United States, but it is being used in the United Kingdom. The only significant issue with anti-VEGF drugs is that they are not target specific in that they can transfer to other locations in the body and inhibit the growth of new vessels there. He also states that improvement in retinal imaging and noninvasive visualization will be key in the diagnosis and treatment of diabetic macular edema (Aiello, 2014).

medicine along with phytotherapy, the use of plants as medicines, can also treat and prevent diabetes mellitus.

There have been many studies that suggest the use of plant based materials to treat Type two diabetes. In January of 2018, Governa et al. published an article in the journal *Molecules* that describes the use of plants and herbs to treat Type 2 diabetes. Among all of the plant species described, Governa et al. claimed that the tested materials all had a few mechanisms of action in common such as: "inhibition of α-glucosidase and of AGE formation, the increase of GLUT-4 and PPARs expression and antioxidant activity" (2018). The enzyme α-glucosidase is responsible for the breakdown of the alpha form of glucose chains. By inhibiting α-glucosidase in the gut, the amount of glucose in the blood can be greatly reduced. In the case of diabetes it is beneficial to prevent the reuptake of glucose since the body is unable to effectively process glucose, therefore, making it advantageous to decrease the amount of glucose in the blood by secreting it as waste. This will greatly decrease the osmotic stress created on the body by the absence of abundant glucose. There are several plant compounds that can serve as a natural alternative to the current medicinal forms of α-glucosidase inhibitors on the market. Furthermore, advanced glycation end products (AGE) cause a wide variety of issues for diabetic patients. AGEs are typically lipids or amino acids that become glycosylated (addition of a sugar) (Singh et al. 2014). This glycosylation is problematic, because it interferes with the regular function of these molecules. In the case of enzymes, the glycosylation can cause a change in conformation which can result in the loss of that enzyme's ability to perform its action (Singh et al. 2014). In the case of the breakdown of glucose, there are 10 enzymes involved in glycolysis. If any one of those enzymes

"inhibiting α-glucosidase, increasing GLUT-4 translocation, glucose uptake, and insulin activity" (Governa et al. 2018).

Another plant used was *Azadriachta indica A. Juss* or neem, but in this plant it was found that only the leaves of the species provided any significant data (Governa et al. 2018). Governa et al. described an in vivo rat study that showed a slight decrease in the rise of blood glucose. The study also showed a return to baseline levels for "serum insulin, lipid profile and insulin signaling molecules as well as GLUT-4 proteins" in rats who had been on a high-fat diet (Governa et al. 2018). A 400 mg/kg dose of neem was given to both the rats on the high-fat diet and to the normal rats within this study (Governa et al. 2018). As with the other species the main mechanism of action was α-glucosidase inhibition.

The next species described was a climbing vine known as *Momordica charantia L.* It was thought that only the melon of this plant could be used to produce the anti-diabetic effect, but it was found later that using the whole plant provides the greatest effect. In the first study, no significant results were obtained in the normalization of fasting blood glucose or reduction in A1c compared to the placebo, but using the whole plant lowered blood glucose and even increased the amount of insulin found in plasma (Governa et al. 2018).

The next plant is one native to India called *Ocimum tenuiflorum* or tulsi and mainly fresh or dried leaves are used from this plant. The most recent study showed great promise in that the researchers gave 30 obese to overweight young subjects 250 milligrams of tulsi twice a day over a period of 8 weeks, and what was discovered was a 28.49% decrease in plasma insulin and a 24.79% decrease in insulin resistance (Governa

to traditional treatment options when supplemented at 5-100 grams per day (Governa et al. 2018). Fenugreek assists traditional medication by lowering blood glucose due to the added stimulation of peripheral tissues taking in glucose (Governa et al. 2018).

Governa et al. explains that the most challenging part of using herbal alternatives is the lack of a structurally sound clinical trial. Most trials had the issue of small sample size, and not significant enough data to make it to clinical trial.

Wang et al. wrote an article in the Journal of Evidence-Based Complementary and Alternative Medicine in April of 2013 also describing the anti-diabetic effects of, more specifically, the medicinal properties of traditional chinese and indian herbs. In the article, Wang et al. discuss some of the same anti-diabetic herbs as Governa et al. (2018) such as *Momordica charantia* and *Trigonella foenum-graecum* and ginseng (2013). Since these three herbs and plants are mentioned in both articles for their hypoglycemic effects, it is worth further study and possible clinical trials for human subjects. Some other herbs and plants are also mentioned such as *Morus alba L., Pueraria lobata, Tinospora cordifolia, and Ocimum basilicum.*

Morus alba L. is more commonly known as the mulberry tree and grows throughout most Asian countries (Wang et a. 2013). An in vitro study showed increased uptake of glucose by fat cells which shows a translocation of the GLUT-4 protein when the tissue was exposed to mulberry leaf extract (Wang et a. 2013). The extract also successfully reduced insulin resistance in diabetic rats over an eight week treatment period, and during this trial, the rats also showed signs of lower fasting blood glucose and urinary glucose (Wang et a. 2013).

glucose is produced by the body when fasting, therefore, reducing fasting blood glucose levels.

Ocimum basillicum is more commonly known as basil and originated in India (Wang et a. 2013). Although the studies suggest that basil itself could not stand alone as a treatment for Type 2 diabetes mellitus, it did show significant results as being a supplemental part of diet (Wang et a. 2013). Basil is an easy plant to grow, and could potentially be easily incorporated into the diets of patients. In a clinical trial completed in India, patients with diabetes mellitus were given basil leaf extract and experienced a dramatic decrease in fasting blood glucose (21.0 mg/dL) and postprandial blood glucose (15.8 mg/dL) (Wang et a. 2013).

There are four main diabetic eye diseases worth noting: retinopathy, macular edema, cataracts, and glaucoma. Although these diseases can manifest in different locations of the eye. Their main causal factor is high levels of glucose in the blood due to diabetes. On the molecular level, most of these diseases are caused by the same metabolic pathway. The difference is the tissues that they affect. Overall, the key to preventing these diseases is the proper management of diabetes on a daily basis. There are several treatment options avalible for the treatment and management of theses diseases. In leu of Western medications, there are is big push to the more natural and herbal treatment and management of these diseases. Although there are no diffinitive studies that show the benefit of these treatment options, more research is being done to prove their effectiveness. Most studies seem to show that it is more on an individual basis for treatment.

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