UNC PEMBROKE | MAYNOR HONORS COLLEGE

Biochemical Effects of Diabetes on the Eyes and Treatment Options

Senior Project

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Abstract

Diabetes is a serious metabolic disease that can cause a variety of damages all over the body if not treated and managed. Diabetes affects millions of people worldwide. If left untreated, diabetes can cause structural and functional damage to the eye. These damages include cataract, diabetic retinopathy, diabetic macular edema and glaucoma. Some of these diseases can be treated with medication and lifestyle changes. All of these diseases can be treated surgically. More recently there has been a big push for more natural treatment options to combat the multiple side effects of western medicine. This push has been shifted to studying the ways of traditional Chinese and Indian medicines. These natural treatment options use plants and other herbs to treat a wide variety of diseases such as diabetes.

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

obesity, lack of exercise, poor diet, smoking, etc (American Diabetes Association, 2018). Other risk factors include being male, race, age, and having a family history of Type two diabetes (American Diabetes Association, 2018). When the symptoms of diabetes are not properly treated, there could be significant damage to the tissue of the eyes.

DIABETIC EYE DISEASES AND TREATMENTS

CATARACT

A cataract is the gradual opaqueness of the lens. This typically occurs when the proteins of the eye begin to clump together which makes the lens lose its transparent nature (NEI, 2015) (Figure 1). This disease is generally characterized by aging but can often occur in diabetics who do not properly maintain healthy levels of glucose. Secondary cataracts are caused by the effects of another medical disease or trauma such as surgery (NEI, 2015). The most common symptoms of cataracts are blurry vision, fading of colors, excessive glare from light, diminished night vision, and double vision (NEI, 2015). Cataracts are often easy for the physician to diagnose, because they are characterized by the white, “cloudiness” of the lens (NEI, 2015). The physician can also perform other

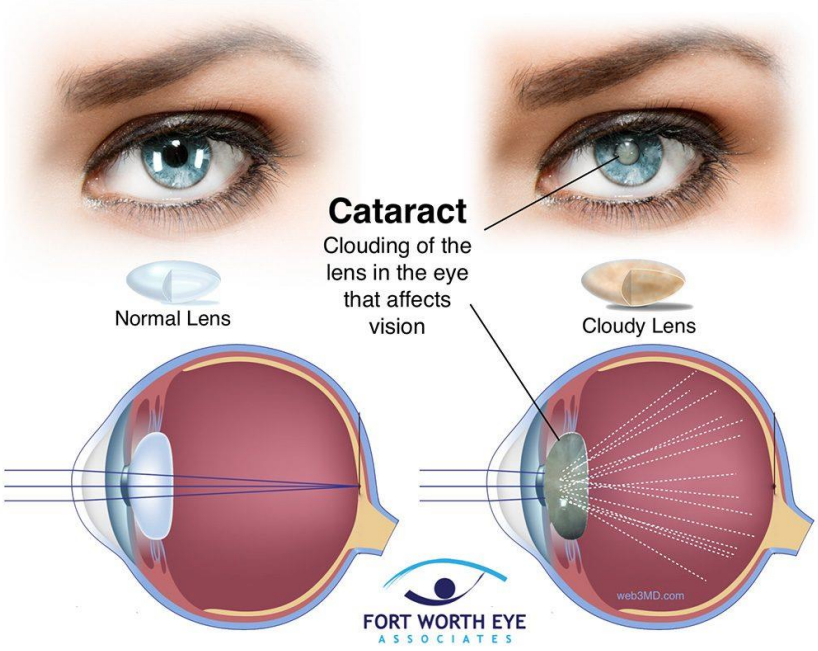

Figure 1:"Normal Lens Compared to Caratact Lens." Fort Worth Eye Associates, 2018, https://www.ranelle.com/cataract-surgery/

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

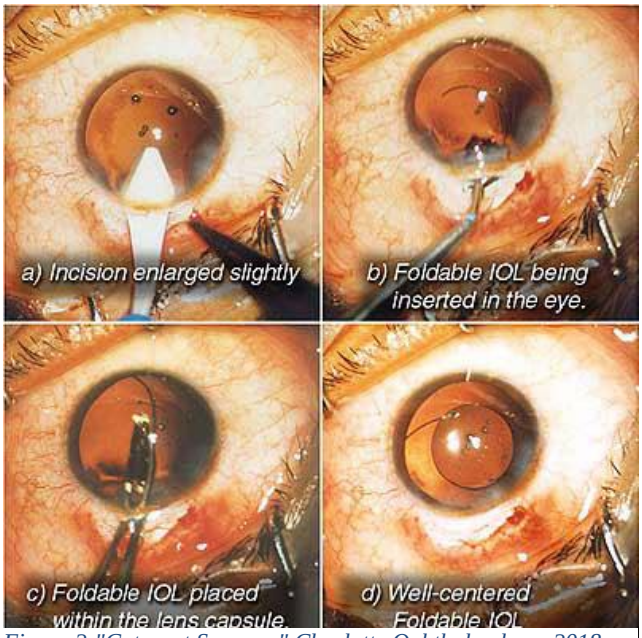

Figure 2:"Cataract Surgery." Charlotte Ophthalmology, 2018, https://eyesoncharlotte.com/procedures/cataract.php

(Fuller, 2013). The procedure begins with the conscious sedation of the patient. The surgeon will make a small stab incision with a diamond blade into the cornea at a structure where the cornea meets the sclera called the limbus (Figure 2 and 3) (Fuller, 2013). A second incision is made into the anterior chamber to access the lens. The capsule is inflated with the use of a thick, jelly like substance called viscoelastic that is used to hold the capsule open once the cataract is removed. Once proper inflation of the capsule is obtained, the surgeon will make an incision into the capsule with the use of a cystotome (Fuller, 2013). The membrane of the capsule will be peeled away in a circular fashion with the use of capsulorrhexis forceps (Fuller, 2013). A syringe with balanced salt solution (BSS) is inserted into the incision and injected to hydro-dissect the lens from the back of the capsule (Fuller, 2013). A phacoemulsification tool is then inserted to break up and remove the pieces of the lens in quadrant sections (Fuller, 2013). Once all large pieces of the capsule are removed, an irrigation and aspiration (I&A) handpiece is inserted to remove any smaller pieces or any residual pieces of the anterior capsule (Fuller, 2013). This step ensures that there are no extra pieces left that may cause obstruction of vision. Once the I&A step is completed, the capsule is re-inflated with a viscoelastic and the lens can be inserted (Fuller, 2013). The addition of viscoelastic at this step ensures proper lubrication for the new lens to be positioned (Figure 2 and 3). After the position of the lens is checked by the physician, the viscoelastic will be removed and replaced with BSS solution (Fuller, 2013). The incisions will be closed with the use of BSS and weck-cel sponges as the tissues of the eye can seal and heal themselves rapidly

(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

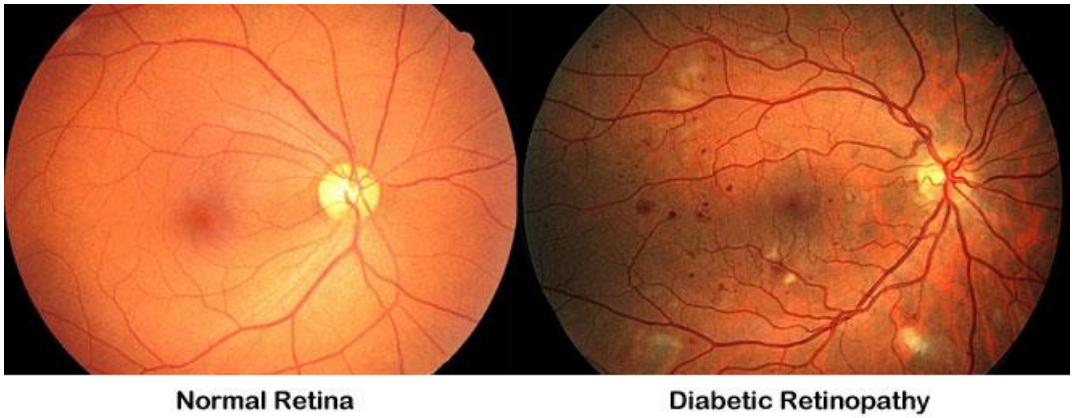

Figure 4: "Diabetic Retinopathy Compared to Normal Eye." BW Primary Care, 2018, bwprimarycare.com/services/retinal-eye-exam/.

spots and or holes (Figure 4). This causes the fluid in the eye to spill into the posterior cavity of the eye. The spillage of this fluid is what causes the retina to become inflamed which leads to diminished vision (AOA, 2018).

There are two main types of diabetic retinopathy: proliferative and non-proliferative (Figure 5). Proliferative diabetic retinopathy is the most severe form of the two types. It is characterized by deprivation of oxygen to the retina, which eventually leads to tissue necrosis and blindness (AOA, 2018). As the tissues of the retina struggle to remain functional, they rapidly try to regrow new vessels that are much more fragile than their predecessors (AOA, 2018). Since these new vessels are much weaker, they continue to leak blood and other fluids into the posterior cavity of the eye, which will continue to cause blurred vision (AOA, 2018). A common complication of proliferative diabetic retinopathy is retinal detachment due to excessive scarring that often requires surgical intervention to correct (AOA, 2018). Non-proliferative diabetic retinopathy is a less severe form of the two. It is often described as the form of the disease in its earliest stage (AOA, 2018). The excess of glucose in the eye causes the vessels to weaken and form microaneurysms (AOA, 2018).

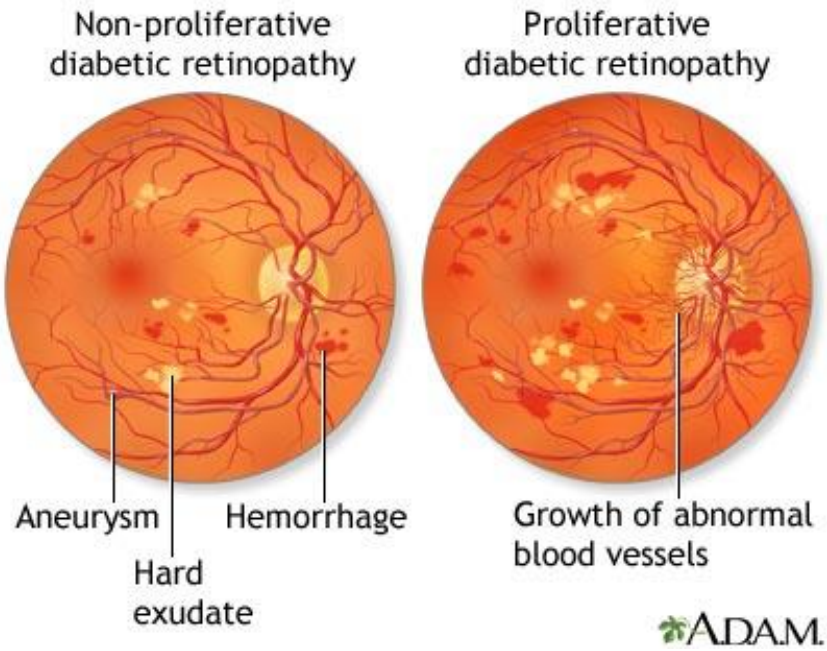

Figure 5: "Non-Proliferative Compared to Proliferative." Eye Ris Vision, 2018, http://www.eyerisvision.com/diabetic-retinopathy.html

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

effective as Lucentis® or Eylea® (Yorston, 2014). Eylea® is not made from monoclonal antibodies, but is an artificial protein that was synthesized to have receptors for the VEGF molecule (Yorston, 2014). The presence of these receptors allows the VEGF to bind to the synthetic protein and hinders the VEGF from damaging the eye (Yorston, 2014). These medications are not a cure for diabetic retinopathy, but they can help to greatly reduce the symptoms.

Diabetic retinopathy can often be treated through surgical vitrectomy, which is often more effective than other treatments. A vitrectomy is the surgical removal of the jelly-like material in the back of the eye (Fuller, 2013). This is because it eliminates the need for frequent intraocular injections, therefore, decreasing the likelihood of obtaining an infection due to poor sterile technique. Posterior vitrectomy is often indicated for patients who have active bleeding into the vitreous humor (Figure 6), and those who have the potential for traction on the retinal tissues due to scarring (Helbig, Sutter, 2004). During a vitrectomy, microsurgical ports are inserted into the eye in order to gain access into the posterior chamber of the eye (Fuller, 2013). A small instrument called a vitrector is inserted through the port; this allows the surgeon to gently remove the damaged portions of the vitreous (Fuller, 2013). If any active bleeding is still occurring, an endolaser may be inserted in order to control the bleeding (Helbig,

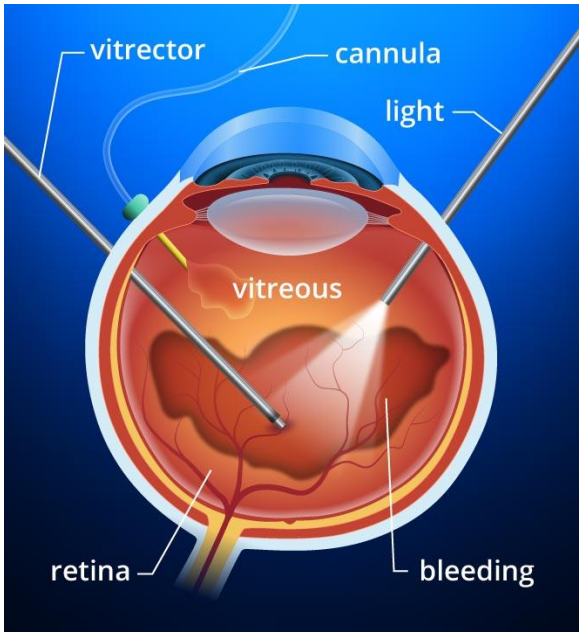

Figure 6: "Surgical Treatment of Diabetic Retinopathy." All About Vision, 2018, https://www.allaboutvision.com/conditions/diabetic-treatment.htm

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

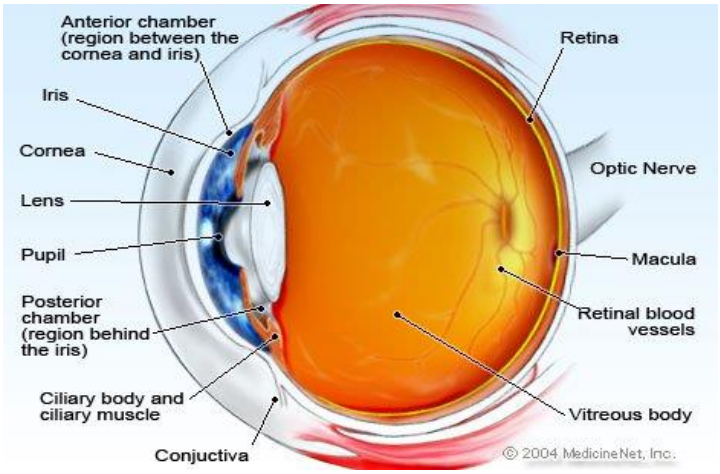

Figure 7: "Eye Anatomy." Medicine Net, 2018, https://www.medicinenet.com/image-collection/eye_anatomy_detail_picture/picture.htm

of the back of the eye. The macula (Figure 7) is “a distinct area of acute vision that lies near the optic nerve” (Fuller, 2013). It is responsible for the focusing of vision. Similar to diabetic retinopathy, when the vessels of the eye become inflamed and leak fluids into the vitreal space, it causes the macula to swell which causes macular edema. The easiest way for the physician to diagnose DME is to perform a fluorescein angiogram and an Amsler Grid Test (NEI, 2015). The fluorescein angiogram is a procedure involving a dye that is injected intravenously, and once it migrates to the eye a camera is used to photograph the back of the eye (NEI, 2015). The damaged portions are visualized because the fluorescein dye glows yellow, therefore, any leakage will be indicated by the flow of yellow dye (Fuller, 2013). The Amsler Grid Test can be used to determine whether a patient's center of vision has shifted or if any blind spots have occurred (NEI, 2015).

The eye is affected in the same way that it is in diabetic retinopathy, but the tissues of the macula are affected in particular. The excessive levels of glucose in the blood cause the cells to absorb the excess glucose. Once glucose is converted, sorbitol accumulates in the cells causing the rapid influx of water causing the cell to rupture. The spillage of these fluids causes the macula to swell and most often diminishes or completely blocks vision.

TREATMENT

Diabetic Macular Edema (DME) is treated in much the same way as diabetic retinopathy. There are drugs and surgical interventions that can be applied to slow the progression of the disease. Anti-VEGF injections are among the best medications for the treatment of DME. These include Avastin®, Eylea®, and Lucentis® (Yorston, 2014).

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).

With anti-inflammatory medications, surgical intervention, and proper diet and exercise, management of DME can be achieved. This disease is not curable, but proper management can help patients achieve normal vision. Importantly, immediate surgical intervention when blind spots first occur can help prevent permanent blindness.

GLAUCOMA

Glaucoma is characterized as the "abnormal condition of elevated pressure within an eye" (Mosby's, 2013). There are several ways in which the pressure of the eye becomes elevated. One being open-angle glaucoma (Figure 8), where the space at which the aqueous humor flows from the anterior chamber to recirculate remains open, but the flow is too slow and causes a buildup of the aqueous humor in the eye (Mosby's & NEI, 2013 & 2015). There is also a form of glaucoma called acute narrow-angle glaucoma. This form involves the same path of flow. In this case, the path is slightly obstructed by the iris which causes too little of an angle for the aqueous humor to flow (Mosby's, 2013). Most specifically related to diabetes is a form of glaucoma called neovascular glaucoma (NVG). NVG is characterized as a form of secondary glaucoma because it stems from diabetic retinopathy. As stated earlier, diabetic retinopathy is the spillage of this fluid that causes the retina to become inflamed leading to the growth of

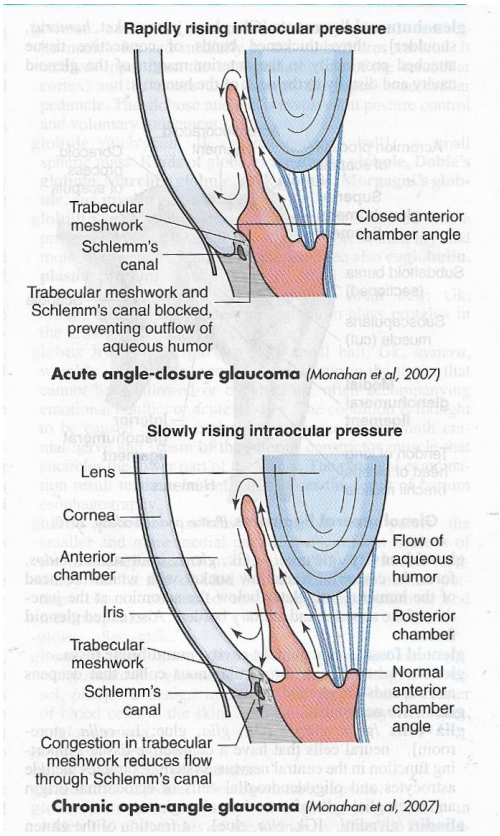

Figure 8: "Types of Glaucoma." Mosby's Medical Dictionary, 2013

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.

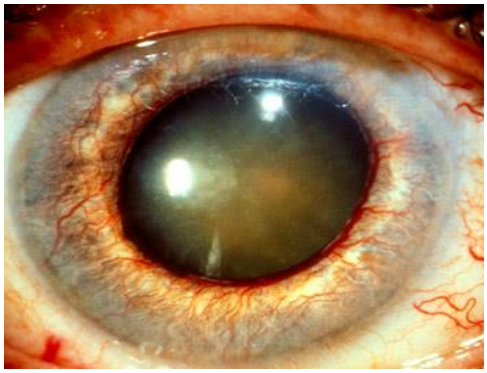

Figure 9:"Abnormal Vessel Growth on the Iris." 2018, http://www.mrcophth.com/glaucoma/rubeosisiridis.html

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,

corticosteroids can be administered via eye drops or oral medication to control any damaging inflammation. The implication of anti-VEGF medication is also important when there is a suspicion of the early stages of NVG to prevent worsening new vascular growth on the iris (Olmos & Lee, 2012).

There are two types of surgical intervention that will help alleviate the symptoms of glaucoma. If the iris angle is not severely occluded, the surgeon may opt to do a procedure called an iridotomy. In this procedure, the surgeon will use a laser to cut a small hole in the iris to help the aqueous humor flow without obstruction (Fuller, 2013). If obstruction is much more severe, the surgeon may suggest a trabeculectomy with the insertion of a shunt (Figure 11). In this procedure, the surgeon will make a small incision in the limbus to create a scleral flap (Fuller, 2013). A diamond knife is used to create a stab wound in the cornea to drain the aqueous humor from the anterior chamber (Fuller, 2013). The surgeon will dissect down to the trabecular meshwork and use tiny scissors to excise it (Fuller, 2013). If indicated, the surgeon will asses whether or not a shunt will be needed and insert the cannula of the shunt into the anterior chamber. The body of the shunt will be sutured to the sclera to ensure that the shunt will not fall out of place.

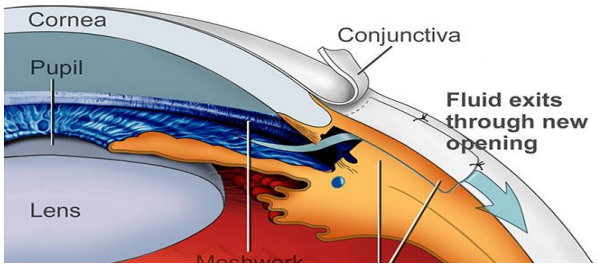

Figure 10:"Trabeculectomy." All About Vision, 2018, https://www.allaboutvision.com/conditions/glaucoma-surgery.htm

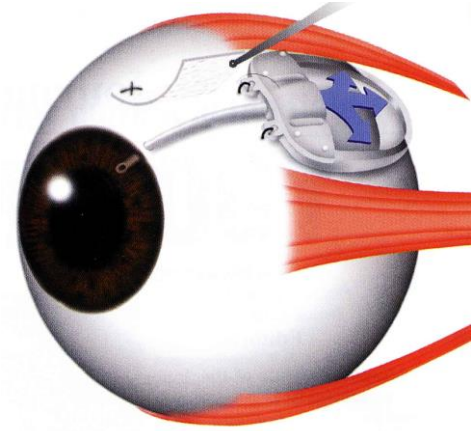

Figure 11:"Tube Shunt for Treatment of Glaucoma." San Antonio Eye Institute, 2018, http://sanantonioeyeinstitute.com/glaucoma-tube-shunts/

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).

There is a possible treatment option for cataracts that does not involve surgery. Dr. Peter F. Kador is conducting clinical trials using a drug that reduces cataract formation (2017). He is currently testing this eye drop on dogs and has found that eighty-five percent of the dogs had diminished cataracts (Kador, 2016).

Current research is being done to reduce the effects of neovascular glaucoma. Researchers in Taiwan have been studying the effects of anti-VEGF medications for the treatment of neovascular glaucoma. They found that after surgery if intraocular pressure remained at normal pressure, vessels regressed off of the iris (Sun et al. 2018). On the other hand if intraocular pressure remained unchecked and rose again after surgery, new vessels began to grow on the iris (Sun et al. 2018). They propose that the key is possibly the control of other factors associated with VEGF such as transforming growth factor beta-1&2 (Sun et al. 2018).

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.

HOMEOPATHIC TREATMENT

Over the years there have been many studies written on the benefit of herbal supplements and plants to treat Type 2 diabetes mellitus. More specifically, there are several research studies that suggest that traditional Chinese and Indian

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

becomes modified, it can change the native state and render it unfunctional. For example if hexokinase at the beginning of glycolysis gets damaged, glucose will never begin the process of glycolysis. As a result, glucose could be actively taken up into the bloodstream without regulation which can cause increase osmotic stress. The increase of the activity of GLUT-4, a glucose transporter protein, allows for more active uptake of glucose to muscle and fat cells (Huang and Czech 2007). If more glucose molecules are taken back into the fat and muscle cells, there are less in the blood causing osmotic stress. The increase in peroxisome proliferator-activated receptor (PPARs) expression is important because this molecule is also involved in the reuptake of glucose into lipid tissues (Jay and Jun 2007). Among the plants and herbs described are *Allium cepa L., Azadriachta indica A. Juss, Momordica Charantia L., Ocimum Tenuiflorum L., Panax Ginseng, Panax quinquefolius, Rehmannia glutinosa, and Trigonella foenum-graecum* are all worth noting.

Allium cepa L. is more commonly known as onion. In all of the studies, onion was able to exhibit antidiabetic effects in any form of the plant including powder, oil, juice and extracts (Governa et al. 2018). In the article that was reviewed primarily, 100 grams of onion was administered to Type 1 and Type 2 patients. The administered 100 grams of onion had significant effects by reducing fasting blood glucose by 89 mg/dL in Type 1 patients and by 40 mg/dL in Type 2 patients (Governa et al. 2018). It also affected induced hyperglycemia by reducing hyperglycemia by 120 mg/dL in Type 1 patients and by 159 mg/dL in Type 2 patients. Also in a study done in 2009, using freeze dried powder into a controlled diet demonstrated lower “serum cholesterol, triacylglycerol and LDL- cholesterol” (Governa et al. 2018). Onion products are able to do this by

"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

et al. 2018). There was also a reduction of lipid profile, body weight and body mass index all relative to the control group (Governa et al. 2018).

The Chinese believe that ginseng has many medicinal and restorative properties. There are two species of ginseng that are described in the article, *Panax ginseng* and *Panax quinquefolius* (Governa et al. 2018). In a study completed through a series of sixteen trials, researchers noted a significant result in the decrease of fasting blood glucose in patients with and without diabetes who were given 0.1-20 grams of ginseng over the course of 4-24 weeks (Governa et al. 2018). In 2016, there was a study that administered 0.96-13.6 grams of ginseng per day for 4-20 weeks that also received significant results (Governa et al. 2018). During this study some patients were given ginseng alone and some were given ginseng as a supplemental treatment along with traditional treatments (i.e. insulin, metformin, etc.) (Governa et al. 2018). What was found was that both groups did not experience reduction in A1c levels, but fasting glucose and postprandial insulin levels improved in the patients who were given ginseng without traditional treatments (Governa et al. 2018).

Dried roots and rhizomas of the *Rehmannia glutinosa* plant was studied in the form of an aqueous solution. This aqueous solution was administered in doses of 200 milligrams per kilogram per day to normal and diabetic rats and resulted in a significant decrease in blood sugars for the rats (Governa et al. 2018). In a similar study, it was shown to reduce “AGE-induced inflammatory responses” (Governa et al. 2018).

The aromatic herb fenugreek or *Trigonella feonum-graecum L.* is used in the form of the dried ripe seeds of the plant. Although this herb has not been demonstrated as a stand alone treatment option for diabetes, it has been shown to provide a significant boost

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).

Pueraria lobata is a viney plant that grows throughout Southeast Asia (Wang et a. 2013). It is more commonly known as kudzu which is an invasive species in North America (Wang et a. 2013). The root of the plant is the most common usage for its medicinal properties. This plant was also in vitro tested with fat cells and what was found was similar to the results of the *Morus alba* plant due to the active uptake of glucose into the fat cell (adipocyte) (Wang et a. 2013). A clinical trial in China also showed that diabetes mellitus patients who were taking the kudzu root showed a decrease in the hemoglobin A1c levels (Wang et a. 2013). It is thought that the kudzu root does this by "inhibiting α-glucosidase, increasing PPAR activity, and an increase in the amount of GLUT-4 proteins" (Wang et a. 2013).

Tinospora cordifolia is a succulent plant found mostly in the tropical regions of India (Wang et a. 2013). It is has been used throughout traditional Indian medicine for a wide variety of ailments, but most recently its effects at reducing or putting an end to diabetes mellitus has been in the spotlight. Rats with diabetes mellitus were given a seventy percent ethanol solution of *T. cordifolia* and experienced a significant decrease in blood glucose levels after receiving a 100 or 200 mg/kg dose of the solution over a two week period (Wang et a. 2013). This is astounding due to such a short period of turn around in terms of results. When these diabetic rats were given a dose of 250 mg/kg, it was shown to prevent the development of diabetic retinopathy (Wang et a. 2013). The question remains here: how much in advance should this be given to patients in order to prevent diabetic retinopathy? *T. cordifolia* was also shown to reduce the amount of gluconeogenesis within the rats (Wang et a. 2013). Reducing the rate of natural gluconeogenesis could prove helpful, because it will decrease the rate in which more

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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