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Thesis

Treatment Options for Diabetic Retinopathy

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Abstract

This literature review will compare and contrast different treatment options for patients with Diabetic Retinopathy. Diabetic Retinopathy is one of the most common causes of preventable blindness in America. I will examine ways to improve the quality of life for a Diabetic patient exploring treatments available to preserve their vision. Some surgical treatments include focal laser (photocoagulation), Pan Retinal Photocoagulation (PRP) also known as scatter laser and vitrectomy as well as newer treatments such as anti-VEGF (vascular endothelial growth factor) medicine or steroids that are injected into the eye. This research is on patients that have Diabetic Retinopathy and will help the reader determine which is the most favorable treatment for their patient.

Keywords: Diabetic Retinopathy (DR); Vascular Endothelial Growth Factor (VEGF); Neovascularization (NV); Diabetic Macular Edema (DME); Pan Retinal Photocoagulation (PRP)

Introduction

Diabetes is a chronic disease that occurs when the pancreas cannot produce insulin or the body cannot recognize insulin that is being produced. Cells provide our body's energy in the form of glucose and insulin transports glucose throughout the body's bloodstream. When insulin is not being produced or recognized then glucose is not being transported, which depletes the body's ability to produce energy. When glucose is not transported, it builds up to a high level and causes diabetes. There are two types of diabetes**:** Type 1 diabetes (previously known as insulin-dependent, juvenile or childhood-onset) is characterized by deficient insulin production and requires daily administration of insulin [1]. Type 2 diabetes mellitus was previously known as non-insulindependent diabetes mellitus (NIDDM) which are those diabetic patients that don't need insulin replacement for at least 6 months after diabetes has been diagnosed [2].

Diabetic retinopathy is caused by diabetes and affects the retina, the light sensitive tissue at the back of the eye. This affects the vision of up to 16 million Americans, contributing to 14% of new blindness cases each year.

Of the patients that are diabetic, 85% of this population does not know that they have diabetic retinopathy. Diabetic retinopathy occurs because of damage to the blood retinal barrier where pericytes are lost and damage to the retinal capillary basement membranes has taken place. For insulin dependent diabetes, Type I, duration of hyperglycemia is associated with retinopathy, neuropathy and nephropathy and is the most important risk factor. The complications of diabetes are usually present after at least 10 years duration of Type 1 diabetes. Diabetes mellitus can also damage blood vessels in the choriocapillaris, slowing the diffusion of oxygen and nutrients to the macula. Some signs of diabetic retinopathy near the macula include macular edema, macular ischemia and neovascularization [2,5,8].

Patients with diabetic retinopathy are often asymptomatic, yet some patients can experience blurry vision and/or metamorphopsia, which is distorted vision. Some other signs of diabetic retinopathy include vitreous hemorrhage, preretinal hemorrhage, tractional retinal detachment and neovascular glaucoma, all of which can cause vision loss. Another sign that is most common amongst young patients with uncontrolled diabetes is snowflake cataracts, which are bilateral posterior sub capsular opacities located in the lens.

The major vision threatening complication of diabetic retinopathy is diabetic macular edema. Patients that have diabetic retinopathy can still maintain good vision if they do not have macular edema. The macula is what provides fine, detailed vision in everyday life. Macular edema occurs when there is liquefaction necrosis of the retinal capillary or endothelial cells. This may involve pericytes degeneration and collection of fluid that occurs in a layer called Henle's layer of the retina. Management of Diabetes Mellitus is very important due to this factor which is vital to preventing vision loss in diabetic patients. Macular edema can be found using biomicrosopy and documenting the findings such as retinal thickening and/or hard exudates. Reducing the risk of developing diabetic macular edema by intensive blood glucose control is the first way to prevent vision loss. The second way to prevent vision loss is by laser photocoagulation. Patients that do not have macular edema can still maintain good vision even if they have advanced stages of the disease.

Therefore, management of diabetic macular edema has become crucial for ophthalmologists and optometrists in preventing vision loss to their diabetic patients.

There are two types of diabetic retinopathy: non-proliferative diabetic retinopathy and proliferative diabetic retinopathy. The lesions in the retina at the stage of non-proliferative diabetic retinopathy are within the retina and include micro-aneurysms, small 'dot and blot' hemorrhages, 'splinter' hemorrhages, intraretinal microvascular abnormalities (IRMA) and 'cottonwool' spots. Proliferative diabetic retinopathy has micro vascular pathology with capillary closure in the retina which leads to hypoxia of tissue. The hypoxia leads to release of vaso-proliferative factors which stimulate new blood vessel formation to provide better oxygenation of retinal tissue. Ischemia of the retina can lead to neovascularization which is growth of new vessels, neovascularization of the disc (ND), neovascularization of the retina (NE), neovascularization of the iris (NI) and neovascularization the angle (NA). Neovascularization of the angle can lead to complications such as neovascular glaucoma which can be due to secondary open-angle or angle-closure glaucoma. Pan-retinal photocoagulation can cause regression of the abnormal growth of new vessels on the iris and angle which is helpful in this situation. A patient with non-proliferative diabetic retinopathy is at risk for developing proliferative diabetic retinopathy.

Diabetic retinopathy

Diabetic retinopathy (DR) is one of the leading causes of blindness worldwide among adults aged 20-74 years old and is the most common microvascular complication of diabetes. One of the early processes of DR is retinal neuro-degeneration, which participates in the microcirculatory abnormalities that occur in DR. Retinal neurodegeneration includes apoptosis and glial activation which have been found in patients with diabetes without any ocular complications. In early stages of the disease, no treatment has been implemented although it may be beneficial to start treatment that would prevent the disease from advancing. During advanced stages of diabetic retinopathy, there are treatments that are used to preserve vision. These treatments include laser photocoagulation, intravitreal corticosteroids, intravitreal anti-vascular endothelial growth factor (VEGF) agents and vitreoretinal surgery [3].

Neuro-retina and optic nerve

Neuronal apoptosis occurs in the retinal ganglion cell layer which results in a decrease of the retinal nerve fiber layer thickness. Glial cells show reactive changes which occur mostly in Muller cells. Muller cells normally do not express glial fibrillary acidic protein (GFAP) but an aberrant expression of GFAP is shown in diabetes. Muller cells are the principal glial cells of the retina and they contain glycogen, mitochondria, intermediate filaments and glial fibrillary acidic protein (GFAP). Muller cells provide structural support for the retina and span across the thickness of the retina. They play an important role in retinal microangiopathy in a diabetic patient's eye [4].

Diabetic retinopathy results from long-standing diabetes or poorly controlled diabetes which remains as the world's leading vascularassociated cause of blindness today. The Diabetes Control

and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS) states 5 factors that would benefit the patient by improving the control of blood glucose such as:

- Reducing the risk of diabetic eye disease by one-quarter
- Decreasing serious deterioration of vision by nearly one-half
- Preventing early kidney damage by one-third
- Preventing strokes by one-third
- Preventing death from diabetes-related causes by one-third.

Systemic blood sugar control is the primary goal of treatment with either of the following: laser photocoagulation, anti-VEGF therapy, intra-vitreal corticosteroids and vitreoretinal surgery [5].

Laser photocoagulation uses a laser beam that destroys and then seals abnormal, leaky blood vessels in the retina. This treatment is associated with significant side effects by destroying a large area of peripheral retina. There are 2 types: Focal photocoagulation and scatter (pan-retinal) photocoagulation.

The Early Treatment Diabetic Retinopathy Study group suggests that pan-retinal photocoagulation may be most beneficial to patients with severe non-proliferative retinopathy, and that clinically significant diabetic macular edema can be treated using argon laser photocoagulation decreased the rate of vision loss [3,6].

Anti vitreoretinal endothelial growth factor (antiVEGF)

VEGF is found in the retinal pigment epithelium and capillaries, specifically the endothelial cells and is expressed by retinal endothelial cells and retinal pigment epithelial cells. VEGF has a functional role in playing the key regulator in physiological and pathological angiogenesis which stimulates the development of new vessels. VEGF initiates angiogenesis which is up regulated by hypoxia and works by restoring oxygen to these oxygen-deficient areas. In diseases such as diabetes the cells begin starving for nutrients and oxygen which eventually lead to over expression of VEGF contributing to the development of diabetic retinopathy. The breakdown of the blood retinal barrier in the eye is VEGF dependent, which is why ANTI-VEGF is a preferred form of treatment to use with laser photocoagulation [7].

In cases of macular edema, triamcinolone acetinide is used which reduces inflammation, decreases the breakdown of the blood ocular barrier and improves visual acuity. Intravitreal Triamcinolone has been shown to decrease the thickness of the macula and can improve visual acuity by two lines of improvement [5].

Vitrectomy is removal of the vitreous gel in diabetic retinopathy which may improve vision. Vitrectomy is beneficial for patients with DME because it creates a physical release of tractional forces that the vitreous gel applies on the macula, therefore increases the amount of oxygen available to the macula. This will decrease its vascular permeability and further resolvement of DME. The amount of oxygen increase would signal decrease in VEGF which would decrease vascular permeability leading to reduced macular thickness [5].

Discussion

To differentiate a non-proliferative diabetic retinopathy from proliferative diabetic retinopathy there is a 4-2-1 rule. A non-proliferative diabetic retinopathy includes severe retinal hemorrhages in 4 quadrants, venous beading in 2 quadrants, and intra-retinal microaneurysms in 1 quadrant. The patient is labeled in severe non-proliferative diabetic retinopathy if they meet 1 of 3 criteria within 4-2-1 rule. Once patients developed proliferative diabetic retinopathy, treatment for neovascularization is delayed until patient has high risk characteristics which are: neovascularization of the disc greater than ¼ disc diameter or any neovascularization of the disc or neovascularization elsewhere with a vitreous hemorrhage or pre-retinal hemorrhage [5].

Clinically significant macular edema requires treatment and includes any one of the following criteria:

- Retinal thickening at or within 500 um (1/3 disc diameter) of the foveal center
- Hard exudates at or within 500 um of the foveal center, if associated with thickening of the adjacent retina
- Retinal thickening greater than one disc area in size within 1 disc diameter of the center of the fovea [5] (see figure 2).

Laser photocoagulation treatment

Focal photocoagulation is used on a specific spot that is located near the macula to seal specific leaky blood vessels in the retina. This laser treatment is effective in the treatment of Diabetic

maculopathy in preventing visual loss. Scatter (pan-retinal) photocoagulation is used to stop the blood vessels from growing by making a minimum of 1200 burns on the retina. This treatment may require 2 or more treatment sessions. These burns spare the central retina around the fovea and the optic disc, but are applied within the blood vessel arcades and in peripheral regions. These laser burns are each 500 microns, 0.05-0.2 second's duration, and placed one spot size interval apart. After treatment, the patient may experience blurry vision up to 10 days and especially longer in patients with Diabetes Type 2. The blurry vision is thought to be due to temporary macular edema caused by disruption of the blood brain barrier during treatment [2]. After 2-4 weeks of treatment, approximately 50% of disc new vessels will have completely regressed. If new vessels persist on the disk, then an additional treatment of 1000-1500 laser burns is given in between the previous laser scars [2,5,9,10].

In a patient with proliferative diabetic retinopathy, pan retinal laser photocoagulation is the treatment used if any one of the high-risk characteristics is seen in the retina. Photocoagulation for diffuse leakage around the macula may be applied in a "grid" fashion to prevent leakage – grid macular photocoagulation. Diffuse or focal leakage can be identified by fundus fluorescein angiography, which is done with black and white retinal photography using the contrast dye, sodium fluorescein, injected into the blood. Fundus fluorescein angiography is done on diabetics to determine if macular thickening is resulting from hypoxia or an accumulation of fluid. When a patient has clinically significant macular edema, focal laser treatment should be considered. If a patient has enlarged foveal avascular zones on intra-vitreal fluorescein angiography, the laser does not enter that area to preserve the patients vision. Patients with extensive macular edema may benefit from combining laser treatment with intravitreal injection of triamcinolone acetinide. Poor laser candidates would be patients with extensive foveal ischemia. Some complications of laser photocoagulation would be extensive tissue damage in the retina [3,4].

VEGF treatment

Laser photocoagulation still remains the gold standard treatment for proliferative diabetic retinopathy and diabetic macular edema but it is not effective in many patients. Retina specialists favor the use of anti-VEGF agents for the management of diabetic macular edema, Although only some of these drugs are FDA approved for intraocular use ranibizumab and pegaptanib, many are currently being used off label in clinical practices like bevacizumab. Ranibizumab (Lucentis) is a humanized monoclonal antibody fragment retrieved from the parent molecule of bevacizumab (Avastin) against VEGF. Bevacizumab (Avastin) is a full length humanized monoclonal antibody against all isoforms of VEGF and binds to the VEGF molecule to prevent receptor binding. It has the USFDA approval for intravenous treatment for metastatic colon cancer. Although bevacizumab does not have USFDA approval for intravitreal use for ocular diseases, it has been used off label and is very effective in inhibiting neovascularization associated with various retinal proliferative vascular diseases such as choroidal neovascularization, proliferative diabetic retinopathy, neovascular glaucoma, diabetic macular edema, and macular edema secondary to retinal vein occlusions. It has been shown that 1 week after using bevacizumab, there is regression of iris neovascularization. Anti-VEGF treatment is still an invasive procedure which may lead to some adverse effects such as endophthalmitis, retinal detachment and systemic complications due to its availability in entering the systemic circulation. Anti-VEGF agents are used with caution in diabetics and patients with impaired wound healing, heart disease, kidney failure, proteinuria and hypertension. These anti-VEGF drugs are used as adjunct therapies to laser treatment, but there is an increasing trend towards using them as primary treatment for diabetic macular edema.

Anti-VEGF agents are proving to be far superior to the laser treatments which are associated with extensive resultant tissue damage [10-14].

Intravitreal corticosteroids treatment

When using intravitreal Triamcinolone Acetonide as continued treatment, repeated for 2 years, this effect can remain advantageous. Intravitreal triamcinolone acetonide is used to treat diffuse macular edema. Triamcinolone has a relatively shorter length of action which shows good results in reducing diabetic macular edema for about 3 month intervals. Multiple intervals may be needed to maintain its effects as the diabetic macular edema may reoccur. Triamcinolone is very useful because it can reduce inflammation post-surgery which would decrease macular edema in a case of a vitrectomy. There are some complications such as glaucoma and cataract encountered with the intravitreal injections of corticosteroids. These steroid induced complications can be

avoided with the use of anti-VEGF and for this reason; anti- VEGF they are becoming the preferred choice of treatment in cases of diabetic macular edema with coexisting glaucoma and in cases unmanageable to lasers and intravitreal steroids. New advances in medicine have led to the development of Retisert, which is an intravitreal corticosteroid implant that releases Fluocinolone Acetonide slowly over 3 years. However, this is still under study [5,15].

Vitreoretinal surgery treatment

Indications for vitrectomy done in diabetic eyes would be a nonclearing vitreous hemorrhage, nonclearing vitreous hemorrhage with a tractional retinal detachment, severe diffuse DME refractory to laser photocoagulation, and severe diffuse DME with rapid loss of central vision. The suggestions for vitrectomy may be indicated for any one of the following conditions:

- Dense vitreous hemorrhage resulting from leaky blood vessels causing decreased vision, especially when present for several months.
- Traction retinal detachment involving and progressing within the macula, new vessels indicate a risk of a vitreous hemorrhage which grow and set down fibro vascular tissue, which is prone to contract causing along the retinal surface and posterior vitreous face and traction on the retina.
- Macular epiretinal membranes recent-onset with displacement of the macula
- Severe retinal neovascularization and fibrous proliferation that is unresponsive to laser photocoagulation
- Dense pre-macular hemorrhage [5].

Complications for vitrectomy would be either of the following: vitreous hemorrhage, which usually clears in a few weeks, retinal tears associated with vitrectomy sites and retinal holes. Vitrectomy has been shown to accelerate the progression of cataracts. Vitrectomy has 3 incisions made through pars plana to remove opacified gel. Results of vitrectomy are a high success when it is combined with laser to remove the opacity and control the neovascularization process. Visual results vary due to the state of the macula [2,5].

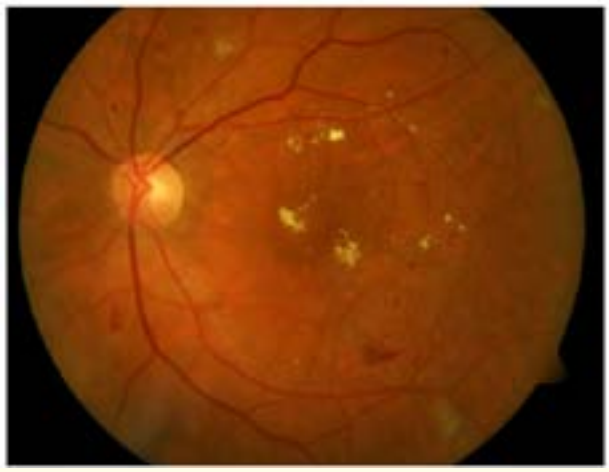

Figure 1: Diabetic Retinopathy http://www2.it.lut.fi/project/imageret/diaretdb1/.

Kauppi, T., et al. DIARETDB1 diabetic retinopathy database and evaluation protocol, In Proc of the 11th Conf. on Medical Image Understanding and Analysis (Aberystwyth, Wales, 2007).

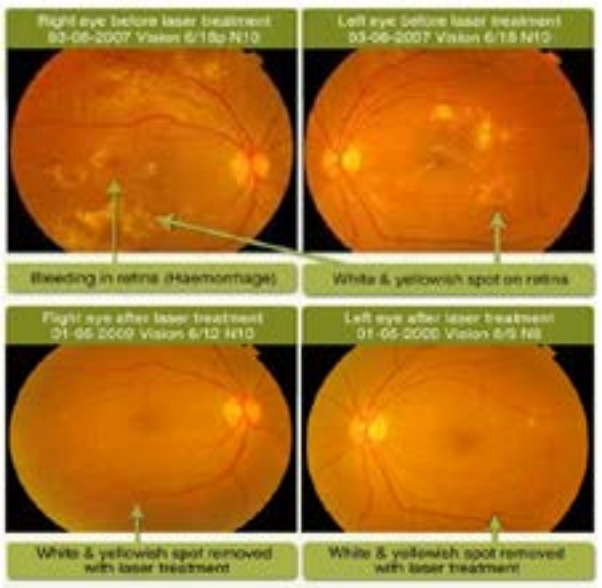

Figure 2: Diabetic Retinopathy treated with laser treatment/ Anti-VEGF. (Clinically Significant Macular Edema) http://www.drushti.com/interesting_cases/4/ diabetic_retinopathy_treated_with_laser_treatment.html

Conclusion

Diabetic retinopathy is primarily treated by glucose control and a healthy regime of diet with exercise. The most favorable treatment, in the next step, would be anti- VEGF treatments as primary treatment or as combined therapy with laser. These include ranibizumab, pegaptanib and off-label bevacizumab. Although the standard of therapy for neovascularization in diabetic retinopathy and diabetic macular edema is laser photocoagulation, with an injection of Bevacizumab as an adjunct treatment of proliferative diabetic retinopathy, neovascularization can be reduced immensely. Even in cases with iris neovascularization, this injection of Bevacizumab is an effective way to treat it. In conjunction of anti-VEGF with Triamcinolone, intravitreal corticosteroids are the preferred treatment of choice in cases of diabetic macular edema.

People with diabetes should have a complete eye exam through dilated pupils at least once a year. With timely treatment; adequate control of blood sugar, blood pressure and cholesterol levels, most of all cases of blindness from diabetes can be prevented.

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