Summary Of Key Scientific Studies: Structure, Function and Microcirculatory Abnormalities in the Eye and Beneficial Effects of Structure of the Eye

The main function of the eye is to convert light that falls on it from the outside into electrical nerve impulses. These impulses then travel to the part of the brain responsible for vision, where they are interpreted as a visual scene. In the eye, light traverses through the tear film, cornea, anterior chamber, pupil, lens, and vitreous chamber to the retina, which sends the nerve impulses through the optic nerve to the brain. Vision is decreased if any one of these structures is abnormal, is irregularly sized, is not functioning adequately, or is not properly positioned in relation to the others.

The first thing light touches when entering the eye is a thin veil of tears that coats the front of the eye. Behind this lubricating moisture is the front of the eye, called the cornea. This clear covering helps to focus the light. To see clearly, the outermost layer, the tear film, must be intact and adequately lubricate the cornea. If the amount of tears produced is less than normal (dry eyes), the eyes will be uncomfortable and vision will be affected. The rounded shape of the cornea causes the light rays to bend as they pass through to the anterior chamber. If the cornea is misshapen or becomes cloudy and cannot allow enough light to pass through, then vision is severely hampered.

The conjunctiva is a thin, transparent membrane covering the cornea, and yet its function is vital – it protects the eye from airborne debris. This is actually only one of the protective features of the human eye. Others include the orbit (or eye socket), the eyelashes and, quite surprisingly, the eyebrows – their function being to stop sweat from running into the eye.

The anterior chamber is the space between the cornea and the iris (colored part of the eye). It contains fluid called the aqueous humor that bathes the structures in the front (anterior) part of the eye. The aqueous humor circulates throughout the front part of the eye and keeps a constant pressure within the eye. If the aqueous humor cannot enter and exit freely through the trabecular meshwork in the anterior chamber, pressure builds up in the eye and glaucoma develops.

After light passes through the aqueous humor, it passes through the iris. This is the colored part of the eye. In the center of the iris is the pupil, which is an opening that allows light through to the lens. The muscles of the iris

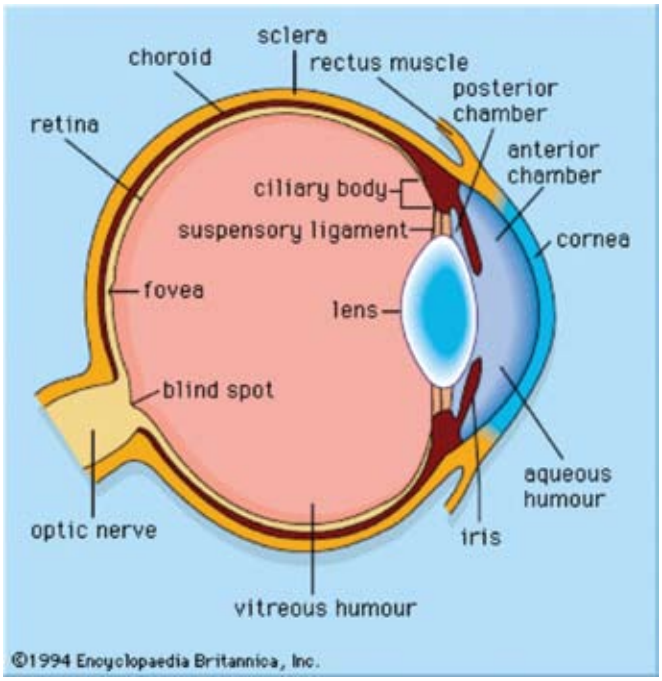

Figure 1: Structure of the Human Eye with the key anatomical features labelled

regulate the size of the pupil. In bright light the muscles constrict and the pupil becomes smaller; in the dark, the muscles dilate and open the pupil larger to let more light come through.

At the back of the pupil is the lens, a clear, pliable structure that changes the angle of the light rays as they enter the eye to focus them on the retina. Regulation of the shape of the lens allows the eye to focus on light reflecting from near or distant objects. It also has been shown that the lens helps to filter out ultraviolet light rays, which could damage the retina in the back of the eye.

Lying just behind the iris is the ciliary body which consists of the ciliary process and ciliary muscles. The ciliary body comprises two parts – the ciliary process and the ciliary muscle. It is the latter which regulates the shape of the crystalline lens. If the eye is focusing on a distant object the muscles relax, causing the ligaments to tighten and the lens to lengthen. If the eye is focusing on a nearby object the muscles tighten, the ligaments slacken, and the lens shortens. The lining of the ciliary body also secretes aqueous humor, the fluid which fills the front of the eye.

Behind the lens is another chamber called the vitreous chamber, which contains a clear jelly-like substance called the vitreous humor. Surrounding the vitreous chamber is the tough, fibrous, white part of the eye known as the sclera. Basically, this is the white of the eye. Attached to the sclera are six exterior muscles, which enable vision to the left, right, up and down. At the front of the eye, the sclera forms the cornea. The sclera helps protect the delicate structures inside the eye.

Behind the vitreous chamber is the retina, a paper-thin, delicate tissue that contains the photoreceptors that convert light into electrical signals, as well as other types of cells that process these electrical signals. The retina has many parts:

(i) **Blood vessels (Choroid):** Behind the retina is a layer of blood vessels called the choroid that brings nutrients to the retina. At the front of the eye, the choroid forms the ciliary body.

(ii) **The macula and the fovea:** This is at the center of the retina. The dead center of the macula is called the fovea. Because it's at the focal point of the eye, it has more specialized, light- sensitive nerve endings, called photoreceptors, than any other part of the retina.

(iii) **Photoreceptors:** There are two kinds of photoreceptors: rods and cones. These specialized nerve endings convert the light into electro-chemical signals.

(iv) **Retinal pigment epithelium:** Beneath the photoreceptors is a layer of dark tissue known as the retinal pigment epithelium, or RPE. These important cells absorb excess light so that the photoreceptors can give a clearer signal. They also move nutrients to (and waste from) the photoreceptors to the choroid. Bruch's membrane separates the choroid from the RPE.

Signals sent from the photoreceptors travel along nerve fibers to a nerve bundle at the back of the eye, called the optic nerve. It carries all the information collected from the eye to the brain (Snell and Lemp, 1998; Tortora and Grabowski, 1996; Vanderbilt Vision Research Center).

Functioning of the Eye and Role of Microcirculation

When a person's eye sees an object, the light travels from that object to the cornea, and then passes through the aqueous humor, pupil, lens and vitreous humor, to reach the retina. During this passage, the light becomes focused onto the macula. At the macula, the light causes chemical reactions in the photoreceptors that consequently send electrical messages from the eye to the brain. The brain recognises these messages and indicates to the person that this particular object has been seen.

As mentioned above, there are two types of photoreceptors (specialized nerve endings) - rods and cones, which synapse with bipolar cells. The rods and cones are two highly distinct networks of light-processing neurons. In the rods, visual nerve cells are very sensitive to dim light and motions, but unable to resolve colors and small contours. The other receptors, cones, are very proficient in deciphering colors and fine details, but unable to detect subtle movements in faint light. The Fovea centralis (which lies at the center of the macula) contains only cones while more peripheral parts of the retina contain cones and rods. Each cone in the fovea centralis synapses with one bipolar cell, which in turn synapses with one ganglion cell. On the other hand, several rods can synapse with one bipolar cell. As a result of 1:1 ratio of cones to bipolar cells, cones are responsible for visual acuity.

When light strikes the rods, the protein rhodopsin present in the rods photo-dissociates into retinene and opsin. Rhodopsin in the rods has a maximum absorption spectrum of 507nm. This chemical dissociation produces electrical changes in the photoreceptors, which trigger a train of action potentials in the axons of the optic nerve. These events cannot be repeated in a given receptor until the rhodopsin is regenerated. This requires a series of chemical reactions in which one isomer of retinene is converted to another through the intermediate compound of vitamin A. In the dark, more rhodopsin can be produced and contained in the rods, so that the eyes become more sensitive to light adaptation after a short period of darkness. This is called scotopic vision or dark adaptation or night vision. Following exposure to high light intensity (glare or dazzle), the rods are bleached out. The time taken for the rhodopsin in the rods to be regenerated depends on various factors such as eye health, health of blood vessels supplying eye (blood bears the nutrients required for rhodopsin regeneration), nutritional status (dietary intake of nutrients required for rhodopsin regeneration), age, stress and genetic factors. Of these, healthy blood vessels are a major factor involved in ensuring optimum dark adaptation and recovery from

exposure to glare by maintaining the supply of nutrients essential for dark adaptation and recovery from exposure to glare of the eye.

The cones are responsible for color vision. There are three types of cones, each containing a distinct photopigment with maximum absorptions at 440 nm (blue), 535 nm (green), and 570 nm (red) respectively.

The retina is a very active tissue whose health depends on a continuous, adequate supply of nutrients and oxygen. All the retinal cells (rods and cones) are provided with oxygen and other nutrients from the retinal pigment cells (epithelium), which are supplied by the rich network of capillaries that constitute the microcirculatory network called the choroid. These capillaries are also efficient in the removal of waste products. Healthy vision and the human eye are related to the health of the individual parts of the eye. It is therefore essential that the blood vessels that constitute the microcirculation of the eye are maintained healthy, resulting in an optimum supply of nutrients to the various parts of the eye (Guyton and Hall, 2000; Tortora and Grabowski, 1996).

Circulatory Abnormalities (Microangiopathies) of the Eye

Definition and Causes of Microangiopathies of the Eye

Microangiopathies of the Eye are abnormalities affecting the blood vessels supplying the eye. These abnormalities usually arise with age or a consequence of systemic conditions such as diabetes, hypertension, infections, etc. Abnormalities that specifically affect the vasculature supplying the retina of the eye are collectively referred to as retinopathies. Abnormalities in blood vessels that surround the macula of the eye lead to a condition called Age-related Macular Degeneration. Retinopathies are classified based on their origin as follows (Reviewed in Dunbar, 2001; Muchnick, 1994; Sowka and Kabat, 1998):

Diabetic Retinopathy: The underlying causes of pathogenesis of diabetic retinopathy are hyperglycemia (increased plasma glucose levels) and the associated hypoxia (low tissue oxygen levels). As glucose levels build up in the plasma resulting from impaired uptake by the cells (due to insulin deficiency or cellular resistance to insulin), extensive glycation of proteins, lipids and DNA occurs leading to formation of advanced glycation end-products (AGEs). These AGEs affect the microcirculatory process in the retina of the eye in several ways. This includes damaging the structural integrity of the blood vessels which increases capillary permeability, increasing surface stickiness of blood cells thus impairing blood flow, and inducing oxidative stress and inflammatory reactions that damage the endothelial lining of the blood vessels causing vascular permeability. The decreased blood supply to the retina also results in local hypoxia which enhances the breakdown of the retinal capillaries. Pericytes, the cells that surround the capillaries and produce an inhibitor for angiogenesis, also degenerate. In the absence of this inhibitor, retinal neovascularization, or new vessel formation, is stimulated by vascular endothelial growth factor (VEGF) (Mandarino, 1992; Rosenblat and Benson, 2004).

Hypertensive retinopathy: High blood pressure can also affect the blood vessels and microcirculation in the eyes. High blood pressure alters the blood flow rate and enhances the shear force on the blood vessel walls. This can result in damage to the endothelial lining of the capillaries in the eye, weakening the capillary walls and increasing vascular permeability (Boudier, 1999; Plante, 2002).

Arteriosclerotic retinopathy: Arteriosclerotic retinopathy is the ocular manifestation of arteriosclerosis, a systemic condition in which the arterial walls thicken and harden. The risk factors for arteriosclerotic retinopathy include heart disease and elevated serum cholesterol. Arteriosclerotic retinopathy can also be involved in hypertensive retinopathy. Arterial occlusion can occur as a result of arteriosclerotic retinopathy.

Sickle cell retinopathy: Sickle cell anemia occurs mostly in people from Africa, South and Central America, the Middle East and South-East Asia. It is a serious hereditary condition in which the red blood cells can become sickle-shaped (that is, shaped like a "C"). Sickle-shaped cells don't move easily through blood. They're stiff and sticky and tend to form clumps and get stuck in blood vessels. The clumps of sickle cells block blood flow in the blood vessels that lead to the limbs and organs. Blocked blood vessels can cause pain, serious infections, and organ damage. Visual symptoms are absent early in the disease. However, as the disease progresses, the retina doesn't get enough blood and can weaken, leading to serious problems, including blindness. Patients also need to be

followed closely to check if the reduced blood flow to the retinal induces neovascularisation (Yedgar et al, 2002).

Retinal vein and artery occlusion: Retinal vein occlusion generally occurs in the elderly. There is usually a history of other systemic disease, such as diabetes or high blood pressure. The central retinal vein (CRV), or the retinal veins branching off of the CRV, can become compressed, thus stopping the drainage of blood from the retina. This may occur if the central retinal artery hardens. Symptoms of retinal vein occlusion include a sudden, painless loss of vision or field of vision in one eye. There may be a sudden onset of floating spots (floaters) or flashing lights. Vision may be unchanged or decrease dramatically. Retinal artery occlusion generally is the result of an embolism that dislodges from somewhere else in the body and travels to the eye. Transient loss of vision may precede an occlusion. Symptoms of a central retinal artery or branch occlusion include a sudden, painless loss of vision or decrease in visual field. Ten percent of the cases of a retinal artery occlusion occur because of giant cell arteritis (a chronic vascular disease) (Aetna IntelliHealth).

Age-related Macular Degeneration (AMD or ARMD): AMD is a disease associated with aging that affects the macula of the eye. There are two forms of AMD, Dry and Wet AMD, of which the latter involves abnormal vascular function. Wet AMD occurs when abnormal blood vessels behind the retina start to grow under the macula. These new blood vessels tend to be very fragile and often leak blood and fluid. The blood and fluid raise the macula from its normal place at the back of the eye. Damage to the macula occurs rapidly. Factors that affect systemic circulation such as hypertension, arteriosclerosis, obesity and smoking increase risk of Wet AMD (Jager et al, 2008).

Risk factors for Microangiopathies of the Eye

It is evident from the description of the pathogenesis of the disease described above that there are several risk factors that affect blood vessels in the eye and promote development of ocular microangiopathies. The key risk factors are:

- Damage to endothelial lining of blood vessels
- Capillary fragility (weakening of blood vessel wall)
- Capillary permeability
- Local oxidative stress in blood vessels
- Local inflammation in blood vessels
- Increased blood viscosity
- Decreased blood flow rate
- Local vascular hypoxia

Disease Complications of Microangiopathies of the Eye

Microangiopathies of the eye, irrespective of the underlying cause, are associated with fragile and permeable blood vessels. In early stages, this leads to bulging of the vessel walls, bleeding into the eye (hemorrhages), leakage of fluid and proteins (exudates), formation of small clumps of dead retinal cells called cotton wool exudates, and occlusion (closure) of the vessels. In more advanced stages, there can be decreased blood flow (ischemia) and a lack of oxygen to surrounding tissues (hypoxia). This can trigger the release of angiogenic factors that cause new blood vessels to grow (neovascularization). The newly-grown blood vessels are highly leaky, causing further haemorrhaging and leakage of fluid. The retina can become edematous (swollen), or the retina can break away from the mesh of blood vessels that nourish it (retinal detachment). These can severely affect vision or even result in blindness (Huether and McKane, 2004; Reilly, 2002; Rosenblat and Benson, 2004).

Specific to diabetic retinopathy, there can occur a temporary blurring because the sugar in the blood can diffuse into the lens of the eye and cause it to swell, thus changing the focal point of the eye. Over time, this swelling is thought to damage the lens and cause it to become cloudy, resulting in a cataract. The high blood sugar levels may also eventually damage the cells lining the trabecular meshwork toward the front of the eye, where the fluid (called aqueous humor) flows out from within the eye. If the trabecular meshwork does not function correctly, the fluid cannot flow out of the eye properly and the pressure inside the eye can increase. This high pressure inside the eye can damage the optic nerve and cause permanent vision loss. This process is called glaucoma. In fact, diabetic retinopathy is the leading cause of blindness in people ages 20 to 74. In the United States, new cases of blindness most often are caused by diabetic retinopathy (Huether and McKane, 2004; Reilly, 2002; Rosenblat and Benson, 2004).

In the case of AMD, the fluid from the leaking blood vessels gathers and lifts the macula, distorting central vision. Central vision is needed for seeing objects clearly and for common daily tasks such as reading and driving.

With time, a small blind spot may develop in wet AMD, and gradually lead to the loss of central vision.

Biological and Analytical Indicators for assessing Microangiopathies of the Eye

Risk factors for Microangiopathies in the eye are mainly assessed using fluorescien angiography. The ophthalmologist or optometrist uses fluorescein angiography to determine the extent of vessel leakage and perfusion that are a risk factor for microangiopathies. The fluorescein dye is injected into the body through a vein in the hand. The fluorescein molecule binds to proteins in the blood and it excited by light of 490 nm (blue light). A retinal camera filters the light, such that only blue light enters the eye. Photos taken in rapid succession reveal the extent of perfusion and leakage in the eye and also specifically in the retina. Other analytical examinations used to assess risk of developing microangiopathies in the eye are analysis of capillary fragility by Parrot's angiosterrometer or Lavollay's suction cup method, examination of the ocular fundus, examination of visual acuity in low light, examination of visual acuity at short and long distance, test of peripheral vision, analysis of erythrocyte deformability and filterability and retinographic examination. Abnormalities in any of these parameters are an indicator of abnormalities in microcirculation in the eye, and an increased risk for developing microangiopathies in the eye.

MASQUELIER'S® OPCs Reduces Risk of Microangiopathies of the Eye

What is MASQUELIER's OPCs?

Oligomeric proanthocyanidin complexes (OPCs) or procyanidolic oligomers (PCOs) are common components of a variety of plants, and found in economically feasible quantities in sources such as grape (*Vitis vinifera*) seeds and French pine (*Pinus maritima*) bark. OPCs gained prominence in food supplement form during the 1990's in the fields of nutrition and disease risk reduction due to their numerous health-promoting effects. OPCs consist of multiples of the basic unit chemically refered to as flavan-3-ol. OPCs mainly consist of 2 to 5 multiples of the flavan-3-ol unit. Single flavan-3-ols are called catechins. When catechins are present in the plant material from which OPCs are extracted, catechins are always co-extracted. This is how commercially available OPCs products always contain a certain percentage of catechins.

OPCs were first extracted and studied in detail by the French investigator, Dr. Jack Masquelier of the University of Bordeaux, France. He patented the method of extracting OPCs (single and oligomeric flavan-3-ols) from pine bark in 1951 and from the seeds of grapes (*Vitis vinifera*) in 1970. Professor Masquelier confirmed the composition, health effects, and lack of toxicity of these products. Dr. Masquelier identified two important biological activities of the OPCs products during the course of his years of research, namely their protective effect on collagen (a key constituent of human blood vessels) and their string antioxidant activity. This formed the basis for the subsequent identification of the numerous beneficial health effects of these products related to blood vessel health and antioxidant activity throughout the human body. Although phyto-nutrients by nature, OPCs, in fact, originally rose to fame in France as vascular herbal medicines for preventing and treating vascular ailments such as varicose veins and diabetic retinopathy. The dietary supplement MASQUELIER's Original OPCs consists of single and oligomeric (2-5 units) forms of flavan-3-ols extracted from grape (*Vitis vinifera*) seeds. MASQUELIER's Original OPCs consists of about 85% flavan-3-ols of which 50-60% are single and dimeric (two units) flavan-3-ols and void of polymeric proanthocyanidins. The manufacturing process is designed to primarily select the single and oligomeric (2-5 units) flavan-3-ols because these have the maximum desirable biological activity.

The ability of the MASQUELIER's Original OPCs to exert many health-promoting effects (strengthening blood vessels, supporting efficient vein function, decreasing microangiopathies in the eye, promoting healthy circulation, protecting cells against oxidative damage, reducing inflammation, etc.) have been established through several scientific studies conducted by various universities in humans, experimental animals and *ex vivo* (studies performed on cells grown in the laboratory or in test tubes). The specific studies that confirm that

MASQUELIER'S Original OPCs strengthens blood vessels and reduces risk of microangiopathies of the eye are described below.

Scientific Evidence from Animal and Laboratory studies of beneficial effects

In initial research studies, Dr. Masquelier and his co-workers observed mice that had orally ingested the active ingredient of MASQUELIER's Original OPCs that had been radioactively- labelled to trace its absorption, its distribution and excretion in the body. The radioactive label was found to be maximally retained in collagen-rich tissues, particularly blood vessels (LaParra et al, 1977; LaParra et al, 1978), indicating that the OPCs compound had possible biological activity on blood vessel walls. In subsequent experimental studies Dr.Masquelier's research laboratory and other research laboratories demonstrated that MASQUELIER's Original OPCs could bind directly to collagen and elastin, proteins essential to the structure and functioning of the blood vessel. These labs also elucidated the ability of MASQUELIER's Original OPCs to promote the synthesis of collagen, elastin and other glycoproteins present in the blood vessels wall such as fibronectin, and to protect collagen and elastin from excessive degradation by the enzymes collagenase and elastase respectively (Gavignet-Jennin et al, 1988; Masquelier et al, 1981; Tixier et al, 1984). The levels of collagen and elastin proteins in the walls of blood vessels play an important role in maintaining their normal structure and function. The level of collagen and elastin in walls of blood vessels is maintained through a balance between synthesis and destruction by the enzymes collagenase and elastase respectively. However, if when amounts or activity of collagenase or elastase are excessive, levels of collagen and elastin in blood vessel wall decrease, and can lead to weakening the blood vessel wall making it more permeable. This brings about the leakage of blood and fluid into the surrounding tissue, which can have pathological consequences such as the development of microangiopathies in the eye.

Further scientific studies performed by various research investigators in experimental animals with MASQUELIER's Original OPCs provided validation of their ability to reinforce blood vessels and promote their healthy function by binding to collagen and elastin proteins, enhancing their synthesis and protecting them from degradation.

The ability of MASQUELIER's Original OPCs to decrease the permeability of blood vessels in rats by blocking the destructive effect of the enzyme collagenase on collagen was researched by Gavignet-Jenin and his co-workers (1988). The authors observed that MASQUELIER's Original OPCs significantly decreased blood vessel permeability induced by collagenase and concluded that the product strengthened blood vessels. A similar ability of MASQUELIER's Original OPCs to protect elastin protein (another important structural constituent of human blood vessel walls) from the destructive effect of the enzyme elastase was observed by scientists in experimental rabbits (Tixier, 1984). Further evidence for the ability of the MASQUELIER's Original OPCs to protect and strengthen the blood vessel wall was provided by a study conducted in guinea pigs by Pfister (1982). The study demonstrated that OPCs bind collagen and elastin, promote collagen synthesis and polymerization and inhibits degradation of collagen and elastin.

These scientific studies therefore demonstrated the ability of the MASQUELIER's Original OPCs to promote synthesis of collagen and elastin proteins in blood vessel walls, protect them from excess degradation. The studies therefore established the efficacy of MASQUELIER's Original OPCs in strengthening blood vessels such as those that are essential to microcirculation in the eye, and potentially reducing blood vessel abnormalities such as micrsoangipathies in the eye.

Scientific evidence from Human studies of the beneficial effects

Based on the early observations made in *ex vivo* and animal studies of the beneficial effects of MASQUELIER's Original OPCs on blood vessels, scientists began to investigate if MASQUELIER's Original OPCs could strengthen blood vessel structure and function in humans and reduce the risk of diseases caused by weakening of blood vessel wall such as micrangiopathies in the eye. The results from a series of such trials conducted in human subjects are described below.

In a double-blind, placebo-controlled trial conducted by Arne (1982), the author studied the effect of supplementation with MASQUELIER's Original OPCs on 30 subjects with increased risk for developing retinopathy associated with diabetes. The criteria that were examined to assess the risk for developing retinopathy were

increased capillary fragility, micro-aneurysms, increased capillary permeability and exudates using procedures such as angiographic and retinographic examinations, visual acuity at short and long distance, muscular tone in the eye, bio-microscopic examination of the anterior chamber of the eye and examination of the ocular fundus. The results of the study demonstrated that 80% of the subjects taking MASQUELIER's Original OPCs demonstrated an improvement in the risk factors, compared to only 47% of the subjects taking placebo that demonstrated an improvement based on angiographic and retinographic examination. The study demonstrated that MASQUELIER's Original OPCs is an excellent product for subjects with increased risk of developing retinopathy associated with diabetes, both due its high efficacy and tolerance.

In an open study by Fromantin, the effects of supplementation with MASQUELIER's Original OPCs were examined in subjects manifesting risk factors for retinopathy including capillary fragility, micro-aneurysms, exudates and hemorrhages. The results demonstrated that MASQUELIER's Original OPCs induced an improvement in capillary structure in 12 out of 26 subjects, an improvement in capillary fragility using Parrot's angiosterrometer in 11 out of 26 subjects, and an improvement in the condition of the ocular fundus in 15 out of 26 subjects. Overall, supplementation with MASQUELIER's Original OPCs induced amelioration and gave favourable results in 80% of the subjects in the study. The author therefore concluded that subjects with risk factors for retinopathy enrolled in the trial greatly benefited from MASQUELIER's Original OPCs intake, with tolerance for MASQUELIER's Original OPCs being excellent.

In an open study, Biard (1980) studied if MASQUELIER's Original OPCs could decrease capillary fragility in subjects, a key risk factor for developing microangiopathies of the eye. The results demonstrated that MASQUELIER's Original OPCs caused a decrease in capillary fragility (measured by Lavollay suction cup method) in 41 out of 48 subjects enrolled in the study (85% of the subjects), while capillary fragility was unchanged in the remaining 7 subjects. The results of the study supported the role of MASQUELIER's Original OPCs in reducing capillary fragility and supporting vascular health in the eye, and thereby confirmed its positive role in reducing risk of developing microangiopathies of the eye and retinopathy.

In a randomized, double-blind, placebo-controlled, cross-over study by Verin et al, the authors evaluated the effect of MASQUELIER's Original OPCs in improving risk factors for microangiopathies of the eye. The primary analytical parameter used to assess risk of developing microangiopathies of the eye was dynamic visual acuity or visual acuity in low light performed at start of study and at the end of the first 30-day study period. Secondary analytical parameters used to assess risk were overall condition of the eye as assessed by the physician, and based on assessment of visual acuity from near and far, color vision (Fransworth test), electroretinogram, ophthalmoscopic examination. The results demonstrated that MASQUELIER's Original OPCs supplementation significantly improved analytical parameters used to assess risk of developing microangiopathies in 26 out of 30 subjects enrolled in the study, while placebo intake induced positive results in only 4 out of 30 subjects enrolled in the study. The authors observed that supplementation with MASQUELIER's Original OPCs therefore yielded a statistically greater positive effect on risk of developing microangiopathies of the eye compared to supplementation with placebo (E=4.016), confirming the efficacy of MASQUELIER's Original OPCs.

In an open study by Sarraco and Estachy (1981), the authors assessed the effect of MASQUELIER's Original OPCs in decreasing risk of retinopathy. The results of the study demonstrated that MASQUELIER's Original OPCs induced a decrease in capillary fragility in conjuctiva of the eye (measured using the Lavollay suction cup method), an important risk factor for developing retinopathy, in 15 out of 20 subjects (ie. in 75% of subjects)studied. The study results therefore indicated that MASQUELIER's Original OPCs was very effective in reducing risk of retinopathy through its ability to decrease vascular fragility, a risk factor for retinopathy.

Verin et al (1978) conducted an open study to assess the efficacy of MASQUELIER's Original OPCs in decreasing microaneurysms and hemorrhages in the eyes of subjects with diabetes. Microaneurysms and hemorrhages in the eye in diabetic subjects are a major risk factor for developing retinopathy. Subjects received 100mgday of MASQUELIER's Original OPCs for 1 year. Primary outcomes assessed were change in number of microaneurysms and hemorrhages, as determined by fluorescence angiography, during the course of the study. Secondary outcomes

assessed were change in visual acuity and peripheral vision. The number of microaneurysms decreased in 18 eyes, remained unchanged in 51 eyes, and increased in 3 eyes during the course of the study. Retinal haemorrhages decreased in 38 eyes, remained unchanged in 25 eyes and increased in 9 eyes. The authors concluded that the MASQUELIER's Original OPCs is of great value in improving condition of eye and decreasing risk of developing retinopathy in subjects with diabetes. The positive results observed in this study which was conducted over a period of 1 year and during which the subjects were examined at frequent intervals strengthened this conclusion.

Soyeux et al (1987) undertook a study to assess the effect of MASQUELIER's Original OPCs on blood flow rate and blood viscosity assessed by measuring erythrocyte filterability and deformability in diabetic subjects. In diabetes, the persistent hyperglycemia induces alterations of the proteins that constitute the erythrocyte membrane and its cytoplasm, and also an increase in glycosylated haemoglobin levels, leading to alteration in erythrocyte structure and its deformability. Erythrocyte deformability and filterability decrease with time and complicate the flow of these cells in microvessels. This may result in increased blood viscosity, decreased rate of blood flow, blood stasis and local vascular hypoxia that are key risk factors contributing to the development of retinopathies in the eyes of diabetic subjects (McMillan, 1997; Yedgar et al, 2002). Soyeux et al studied 15 subjects with diabetes taking 400mg/day MASQUELIER's Original OPCs for 15 days. Primary outcomes assessed were erythrocyte deformability index and blood viscosity at start of study, at day 14 (end of study) and 6 weeks after termination of study. The average erythrocyte deformability index decreased marginally by day 14 compared to the start of the study. However, at the end of week 6 following termination of the study, the average erythrocyte deformability index markedly increased relative to the start of the study. The viscosity of the blood samples remained unchanged during the course of the study and during the follow-up period. This suggested that intake of MASQUELIER's Original OPCs induced an increase in erythrocyte deformability, and thereby could increase RBC filterability and reduce risk of diabetic retinopathy. The authors observed that the dual effect of MASQUELIER's Original OPCs – the vasculo-protective effect observed in previous studies and the possible effect in increasing erythrocyte deformability and filterability and thereby improving blood flow rate – indicate a beneficial role for MASQUELIER's Original OPCs in decreasing risk of retinopathy associated with diabetes.

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