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Review Article

DIABETIC RETINOPATHY - CAN LEAD TO COMPLETE BLINDNESS

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ABSTRACT

Diabetes mellitus is a metabolic disorder. Chronic complications include cardiovascular disease, chronic renal failure and diabetic retinopathy.Diabetic retinopathy is one of the major complication of diabetes that affects the blood vessels by causing damage to the light-sensitive tissue at the back of the eye i.e., retina. At first, diabetic retinopathy may cause no symptoms or only mild vision problems. Eventually, diabetic retinopathy can result in blindness. The diabetic retinopathy can be broadly characterized into three stages: early non-proliferative, pre-proliferative and finally proliferative diabetic retinopathy. The chance of getting diabetic retinopathy is when the person has diabetes for a long time and it is poorly controlled. Other complications that may develop mainly include: cataracts, glaucoma, macular edema and retinal detachment. Surgeries are the main treatment for diabetic retinopathy. If it is neglected it may lead to complete blindness. Diabetic retinopathy can be prevented by monitoring blood glucose level periodically. The person with diabetes need to check and record their blood glucose level and make sure that the blood glucose level remains within the target range. Prevention is better than cure, it is better to prevent it than going for treatment once after facing the problem. So, the awareness of diabetic retinopathy is needed.

Keywords: Diabetic retinopathy, diabetes mellitus, retina, insulin.

INTRODUCTION

Diabetes mellitus[1] is a metabolic disorder in which a person has high blood glucose level because of two main reasons, either because the pancreas does not produce enough insulin or because cells do not respond to the insulin that is produced[2]. Diabetes without any proper treatment can cause many complications. Acute complications mainly include hyperglycemia, diabetic ketoacidosis, or non-ketotic hyperosmolar coma[3]. Chronic complications include cardiovascular disease, chronic renal failure and diabetic retinopathy. Adequate treatment of diabetes is thus important, as well as blood pressure control and life style factors such as cessation of smoking and maintaining a healthy body weight[4, 5].The total number of people with diabetes is projected to rise from 346 million in 2012 to 439 million by 2030.Diabetic retinopathy is responsible for 1.8 million of the 37 million cases of blindness throughout the world[6].

TYPES OF DIABETES MELLITUS

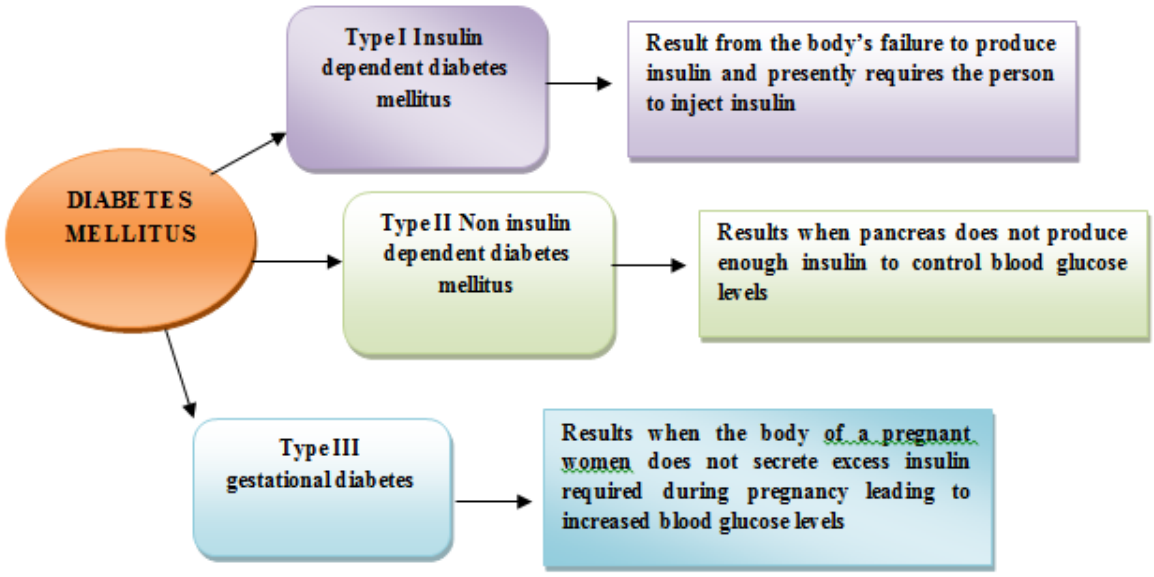

Figure 1: The three main types of Diabetes Mellitus

The figure 1 shows the three main types of diabetes mellitus (DM).

Type 1 Diabetes Mellitus: Insulin-dependent diabetes mellitus (IDDM) or juvenile diabetes. Body fails to produce insulin; this type of diabetes is further classified as immune-mediated or idiopathic, results from destruction of β-cells of the islets of Langerhans in the pancreas usually leading to absolute insulin deficiency [7]. There is no preventive measure against type 1 diabetes and the person requires injecting insulin or wearing an insulin pump.

Type 2 Diabetes Mellitus: Non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes. The

cells fail to use insulin properly; sometimes there may be absolute insulin deficiency [8].

Type 3 Diabetes Mellitus: Gestational diabetes, the pregnant women develop a high blood glucose level when the body does not secrete excess insulin required during pregnancy. It may precede development of type 2 DM.

SYMPTOMS OF DIABETES:

Increased production of urine, unusual thirst, tiredness as glucose goes waste as it is not converted to energy, loss of weight, feeling sick, increased appetite, blurred vision[9] etc.

DIABETES MONITORING:

Optimal management of diabetes involves measuring and recording their own blood glucose levels and noting the effect of food and exercise[10]. Glucose meter is mainly used to measure blood glucose levels.The result is measured either in mg/dL (milligrams per deciliter) or mmol/L (mill moles per liter) of blood[11, 12]. Patients have to modify their lifestyle to better control their diabetes. Especially patient dependant on insulin, the patient involvement is most important in achieving effective dosing and timing[13, 14].

Modern approaches to treat diabetes primarily rely upon dietary, lifestyle management and often combined with regular ongoing blood glucose level monitoring[15, 16]. Diet management allows us to control and provide awareness on the types of nutrients entering the digestive system and hence it indirectly controls blood glucose levels[17, 18].

ROLE OF INSULIN:

Insulin the principal hormone - produced by beta cells of the islets of Langerhans in the pancreas.The islets of Langerhansthe regions of pancreas that contain its endocrine hormone producing cells[19, 20]. It approximately constitutes 1 to 2% of the mass of the pancreas.Hormones produced by the islets of Langerhans are secreted directly into the blood flow. Insulin mainly regulates the uptake of glucose from the blood into most cells i.e., primarily muscle and fat cells, but not central nervous system cells.

SYNTHESIS OF INSULIN:

Insulin consists of two polypeptide chains, the A- and B- chains which are linked together by two disulfide bonds. It is first synthesized as a single polypeptide called preproinsulin in pancreatic β-cells. Preproinsulin consists of 24- signal peptide residue which directs the polypeptide chain to the rough endoplasmic reticulum. The signal peptide is than cleaved in to polypeptide which is trans located into lumen of the rough endoplasmic reticulum forming proinsulin[21]. In the rough endoplasmic reticulum the proinsulin is folded into the correct conformation with three disulfide bonds are formation[22]. The proinsulinis

transported to the Trans- Golgi Network (TGN) where the immature granules are formed[23, 24]. Transport to the TGN may take about 30 min. The Proinsulin undergoes maturation into active Insulin by the action of cellular endopeptidases also known as Prohormoneconvertases (PC1 and PC2)[25]. The endopeptidases cleave at 2 positions, releasing a fragment called the C-peptide and leaving 2 peptide chains.The A- and B- chains which are than linked by 2 disulfide bonds. The resulting active insulin is than packed inside mature granules and are released by the beta cells of the islets of Langerhans in the pancreas into the circulation after getting the metabolic signals for glucose[26].

The deficiency of insulin or the insensitivity of its receptors plays a crucial role in all forms of diabetes mellitus. Humans are capable of digesting many carbohydrates in food e.g : starch and some disaccharides such as sucrose can be converted to simple monosaccharides within a few hours[27]. Insulin is released into the blood by β-cells of pancreas, in response to rising levels of blood glucose typically after eating. Insulin is used by about two-thirds of the body's cells to absorb glucose from the blood for use as fuel and for conversion to other needs or for storage[28].

Insulin also involves in conversion of glucose to glycogen for internal storage in liver and muscle cells. Decreased glucose levels cause the reverse conversion of glycogen to glucose. This is mainly controlled by the glucagon hormone, which acts exactly in the opposite manner to insulin. Glucose which is produced from internal liver cell stores as glycogen re-enters to the bloodstream; muscle cells lack the necessary export mechanism. When insulin levels increase anabolic processes, such as cell growth and duplication, protein synthesis, and fat storage takes place[29]. When the amount of insulin available is insufficient, cells respond poorly to the effects of insulin or if the insulin itself is defective.The glucose will not be absorbed properly by the body cells nor will it be stored properly in the liver and muscles. The net effect is persistent high levels of blood glucose. This high blood sugar produces the symptoms such as polyuria i.e., frequent urination, polydipsia i.e., increased thirst and polyphagia i.e., increased hunger[30].

DIABETIC RETINOPATHY:

Diabetic retinopathy is one of the major common complications of diabetes that affects the blood vessels by causing damage to retina[31]. The retina is the light-sensitive layer of cells at the back of the eye. It converts light into electrical signals. These signals are sent to the brain through the optic nerve and the brain interprets them to produce the images. So, retina needs a constant supply of blood, which it receives through a network of tiny blood vessels. Over time, a continuously high blood glucose level can cause these blood vessels to become blocked or to leak. This damages the retina and stops it from working. It is an ocular manifestation of systemic disease which affects up to 80-85% of all patients who have had diabetes for 10 years or more[32].

The research indicates that it could be reduced if there was proper treatment and monitoring of the eyes[33]. The longer a person suffers with diabetes, the higher his or her chances of developing diabetic

retinopathy. There are mainly three stages of diabetic retinopathy. First stage is called Non-proliferative stage and the Pre-proliferative diabetic retinopathy is second stage and the third stage Proliferative diabetic retinopathy, which is more advanced and even more severe. The various stages of diabetic retinopathy shown in figure: 2. Other complications that may develop mainly include: Cataracts- indicated by the cloudiness of the eye lens, Glaucoma- mainly due to increased pressure in the eye that can lead to blindness, Macular edema- blurry vision mainly due to fluid leaking into the area of the retina that provides sharp central vision and retinal detachment- scarring that may cause part of the retina to pull away from the back of eyeball position[34, 35].

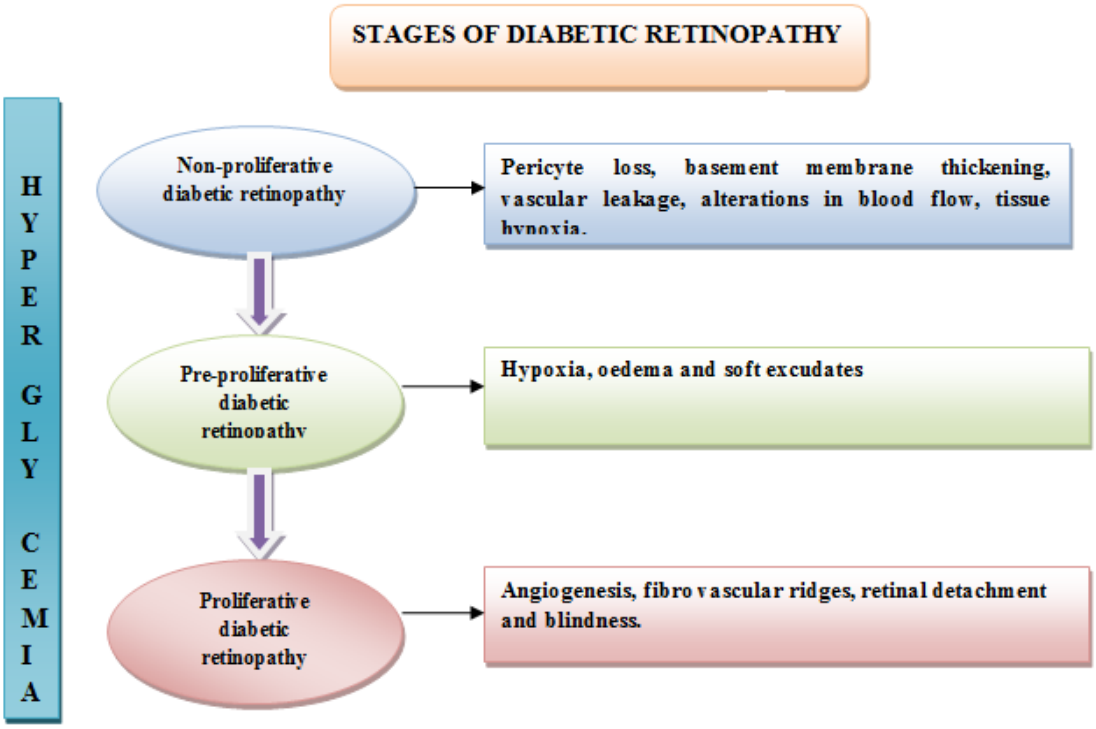

Figure 2: Various stages of Diabetic Retinopathy

SIGNS AND SYMPTOMS:

Diabetic retinopathy does not usually cause any noticeable symptoms until it has reached an advanced stage. If it is not identified and treated, it can lead to sudden blindness. Symptoms of diabetic retinopathy mainly include: sudden changes in vision, blurred vision, slow vision loss over time, pain in the eye, double vision, floaters in vision and difficult to see at night times[36]. Many people with early diabetic

retinopathy have no symptoms before major bleeding occurs in the eye as shown in figure 3. In the early stage of diabetic retinopathy i.e., non-proliferative the blood vessels in the eye are larger in certain spots, sometimes blood vessels that are blocked, small amounts of bleeding i.e., retinal hemorrhages and fluid may leak into the retina. In more advanced retinopathy i.e., proliferative we can see new blood vessels starting to grow in the eye that are fragile that can bleed, small scars develop on the retina and in other parts of the eye[37].

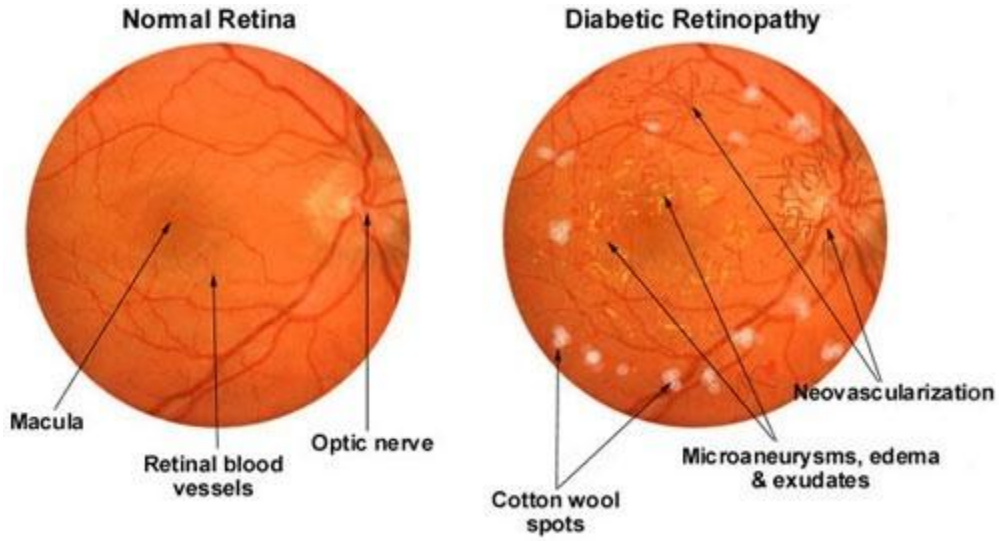

Figure 3: Difference between Normal Retina and Diabetic Retinopathy

TESTS:

Everyone with diabetes should have regular eye exams by an ophthalmologist who is skilled in the treatment of diabetic retinopathy. It can be diagnosed by dilating eye pupils with eye drops and then carefully examining the retina[38, 39]. During which your eyes are not dilated, is not an adequate substitute for a full exam done by an ophthalmologist. Other eye exams for people with diabetes can include:

Visual acuity testing: This test measures the eye's ability to focus and to see details at near and far distances. It can help mainly to detect vision loss and other eye problems.

Ophthalmoscopy and slit lamp exam:These tests allow the doctor to examine the back and other structures within the eye. It is used to detect clouding of the lens and changes in the retina.

Gonioscopy: It is used to find out whether the drainage angle is open or closed. This test is done to detect glaucoma, a group of eye diseases that can cause blindness by damaging the optic nerve.

Tonometry: It measures the pressure inside the eye, which is called intraocular pressure. It is used to detect glaucoma as diabetes mainly increases the risk of glaucoma.

The doctor may also suggest test called an optical coherence tomography (OCT) to check for fluid in

retina. Sometimes a fluorescein angiogram is done in order to check for and locate leaking of blood vessels in the retina, especially if symptoms such as blurred or distorted vision are reported. This is mainly due to damage or swelling of the retina.

PATHOGENESIS:

Diabetic retinopathy results in microvascular retinal changes. Hyperglycemia-induced intramural pericyte death and the thickening of the basement membrane lead to incompetence of the vascular walls. These damage the blood-retinal barrier and also make the retinal blood vessels become more permeable. The pericyte death is mainly caused when hyperglycemia persistently activates protein kinase C-δ (PKC-δ, encoded by Prkcd) and p38 mitogen-activated protein kinase (MAPK) to increase the expression of a previously of PKC-δ signaling, Src homology-2 domain–containing phosphatase-1 (SHP-1) and a protein tyrosine phosphatase. This signaling cascade leads to PDGF receptor- dephosphorylation and a reduction in downstream signaling from this receptor, resulting in pericyte apoptosis. Small blood vessels in the eye – are especially vulnerable, the over accumulation of glucose and/or fructose damages the tiny blood vessels in the retina[40]. During the initial stage, i.e., Non-proliferative diabetic retinopathy, most people do not notice any change in their vision. Early changes that are reversible are sometimes termed as simplex retinopathy. Some people develop a condition called macular edema. In which the blood vessels get damaged resulting in leakage of fluid and lipids onto the macula, the part of the retina. This fluid makes the macula swell, which blurs vision[41].

TREATMENT OF DIABETIC RETINOPATHY:

The patient with proliferative diabetic retinopathy will need prompt surgical treatment. But people with the non-proliferative diabetic retinopathy may not need surgical treatment. However, they should be closely followed by an eye doctor who is trained to treat diabetic eye diseases. Once the doctor notices new blood vessels growing in retina (neovascularization) or develop macular edema, treatment is usually needed[42]. Sometimes surgery is also recommended for severe non-proliferative diabetic retinopathy depending on specific problem of retina various options include:

Focal laser treatment: It is also known as photocoagulation[43], it stops or slows the leakage of blood and fluid from the eye. In laser treatment, leaks from abnormal blood vessels are treated with laser burns. Focal laser treatment is usually done in single session. The vision will be blurred for about a day after the procedure. It is usually done in single session. Sometimes small spots can be seen in visual field that is usually related to the laser treatment. The spots will usually disappear within week days[44].

Scatter laser treatment: This laser treatment, also known as pan retinal photocoagulation. The abnormal blood vessels are shirked the area of retina away from the macula are treated with scattered by laser burns.

The burns cause the abnormal new blood vessels to shrink. It is done in doctor's clinic. It is usually done in two or more sessions. There may be some loss of peripheral vision or night vision after the procedure[45].

Vitrectomy: Surgeries are the main treatment for diabetic retinopathy. It is done in surgery center or hospitals by using local or general anesthesia. It involves removal of blood from the middle of the eye i.e., vitreous as well as scar tissue that tugging on the retina by using delicate instruments and replace with salt solution, which helps to maintain eye's in normal shape. And sometimes a gas bubble must be placed in the eye cavity to help reattach the retina. Vitrectomy may be accompanied by laser treatment. It often stops the progression of diabetic retinopathy, but it is not a permanent cure. As diabetes is a lifelong condition, so future retinal damage and loss of vision are possible. Even after treatment the patient need regular eye exam. Sometimes, additional treatment may also be needed[46].

New treatment for diabetic retinopathy, include medication that may help to prevent abnormal blood vessels forming in the eye. These medications are directly injected into the eye. These appear promising, but still long trials yet to be done[47].

CONCLUSION

All people with diabetes mellitus are at high risk of getting diabetic retinopathy. The longer a person has diabetes, the higher the risk of developing diabetic retinopathy. After 20 years of diabetes, nearly all patients with Type I diabetes and >60% of patients with Type II diabetes have some degree of retinopathy. During pregnancy, diabetic retinopathy may also be a problem for women with diabetes. So it is recommended that all pregnant women with diabetes have dilated eye examinations each trimester in order to protect their vision.

The best measure for prevention of loss of vision from diabetic retinopathy is strict glycemiccontrol. The person with diabetes need to check and record their blood sugar level and make sure that the blood sugar level remains within the target range. Blood pressure and high cholesterol levels increases risk of diabetic retinopathy. So, better to keep blood pressure and cholesterol under control[48, 49]. Eating healthy foods, exercising regularly and losing of excess weight can help[50]. Smoking can also increase the risk of various diabetes complications, including diabetic retinopathy. Talk to the doctor about various ways to stop smoking or to stop using other types of tobacco.

Diabetic retinopathy is preventable through strict glycemic control and annual dilated eye exams by an ophthalmologist. Prevention is better than cure. So, the awareness of diabetic retinopathy is needed.

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