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A Comprehensive Review on Diabetic Retinopathy and Mental Disorders

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ABSTRACT
Diabetes management should involve both systemic and ocular aspects. Regulation of hyperglycaemia, hypertension and dyslipidaemia plays a crucial role in the treatment of diabetic retinopathy. Ocular laser therapy is the core treatment for diabetic macular (focal/grid) oedema with severe non-proliferative and proliferative diabetes retinopathy. Combination therapy is strongly encouraged. Diabetic macular oedema management strategy is based on one or two intravitreal injections such as anti-VEGF and steroid therapy decreases the central macular thickness with focal laser or grid laser. Anti-VEGF therapy has been shown to be efficient as a medical treatment in proliferative patients with diabetic retinopathy. Specific pathophysiological manifestations of cognitive disorder in diabetes are not fully understood, but hyperglycaemia, vascular abnormalities, hypoglycaemia and insulin resistance are likely to play a key role. This study demonstrates the correlation between mental disorder and diabetic retinopathy. Patients of diabetes have also been shown to have cognitive dysfunction. The article describes therapies and details relevant to risk factors and signs of diabetic retinopathy. Herbal treatments such as sulfonylureas, metformin, Azadirachtaindica and their modes of action are part of this article.

KEYWORDS*: Diabetes mellitus, Diabetic retinopathy, Cognitive dysfunctions, Anti-VEGF, Laser Therapy, Metformin, Sulfonylureas*

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ABBREVIATIONS

DM	Diabetes mellitus
DR	Diabetic retinopathy
PDR	Proliferative diabetic retinopathy
NPDR	Non-proliferative diabetic retinopathy
VEGF	Vascular endothelial growth factors
BMI	Basal metabolic index
BMR	Basal metabolic rate
SBP	Systolic blood pressure
CSMO	Clinically significant macular oedema
GABA	Gamma amino butyric acid
PPAR	Peroxisome proliferative-activated receptor
GCL	Glutamate cysteine ligase
DMO	Diabetic macular oedema
CVD	Cardiovascular
LBM	Lean body mass
PRP	Panretinal photocoagulation
MALT	Mucosa-associated lymphoid tissue

I. Introduction

Diabetes is an inability of body to absorb food properly. Most of the food we eat has been converted to monosaccharides and disaccharides such as glucose or fructose[1]. Insulin (a hormone) is produced by the pancreas to take glucose into our body cells. As diabetes progresses, bodies cannot produce sufficient amount of insulin or use their own insulin as much as possible. The deposition of sugars is activated in your body. This is

also termed to be sugar in many countries[1,2]. Serious health problems including heart disorders, blindness, renal failure is associated with it (diabetes) and is the 7th principal cause of death in the United States[1]. In worldwide 19000 people from the developing countries are found to be affected by type 1 diabetes, but there is no good evidence of the prevalence of diseases in developing and sub-Saharan African countries in particular. The main cause of death in developing and emerging countries worldwide is non-commercial diseases, including diabetes, coronary conditions, stroke, cancer and chronic kidney failure[2]. The majority of people with diabetes are between 45 or 65 of age in emerging countries, while the remaining population is aged over 64 in developed countries. In the Middle East, Sub-Saharan Africa and Asia, the largest relative increase is also projected[2,3]. The proportion of premature deaths caused by high blood glucose in low- and medium-income countries is higher than in high-income countries and men than in women[4]. Asians are highly susceptible to racial and hereditary diabetes and are at higher environmental risk for younger-aged diabetes compared to the population of Western countries. The population of India and China is on the rise, increasing the incidence of diabetes in rural areas. Tobacco products continue to be developed by countries such as China and India and are therefore faced with a major public health issue (Table 1). Continuous use of alcohol often increases the risk of diabetes and other metabolic diseases in central and rural Asian countries[5].

Table 1: Country wise Prevalence of diabetic retinopathy[2]

Countries	**Age**	**Peoples**
United state	60 years	18.3% (8.6 million)
Africa	15 years	6299
Nigeria	45 years	2.0 %
Middle east crescent	64 years	82 million
Sub-saharan Africa	64 years	48 million
India	42.5 years	1 million

Types

Two major types of diabetes (Type 1 and 2) are reported. Type 1 diabetes, which may appear at all ages, is more prevalent in adolescents and young adults. Type 2 diabetes mainly affects adults but has recently begun to develop in children[6]. The depletion of B cells leads to the complete insulin deficiency that is usually correlated with immune systems which is classified as type 1 diabetes for individuals who undergo latent autoimmune disorder. Metabolic syndrome is associated with type 2 diabetes. Exocrine pancreatic disease (pancreatitis, cystic fibroid fibrosis), endoclinopathies (cushing syndromes), induced drugs (e.g. glucocorticoids, alpha interferons), beta-cell genetic defects (modal forms) and rare forms of autoimmune diabetes are additional specific types[7]. The last form of diabetes is a contraceptive glucose tolerance deficiency that occurs first or is diagnosed during pregnancy[8]. The prevalence of type 2 diabetes, coronary disorder, stroke, asthma and cancer is increased by obesity[2].

Symptoms

Diabetic retinopathy (DR) is a long-term diabetes condition that cannot be identified at an early stage because only a few signs are evident. Digital fundus photographs as well as optical coherence tomography (OCT) images are now standard criteria for DR diagnostics[9,10]. Symptoms of diabetic retinopathy include vision problems, too much thirst, excessive urination, poor recovery, severe dizziness, sudden weight loss (type 1 diabetes), infertility and weakness in the legs or hands (Diabetes Health Testing). Diabetic retinopathy occurs in diabetic patients when increased blood sugar (diabetic) damages the thin, light-sensitive tissue of the retina in the eye. Diabetic retinopathy may result in swelling of the macula area called the retina that leads to diabetic macular oedema[11,12].

How smoke cause diabetes?

The infection of the tissues is caused by smoke. When tobacco chemicals allow cells to be damaged, swelling and cell activity to be disrupted, inflammation occurs. Smoking lead towards oxidative stress, which occur when cigarette smoke compounds are mixed with body oxygen. This contributes to the damage at cellular level. Diabetes risk increases with inflammation and oxidative stress (General Health & Tobacco Survey, 1964-2014)[13].

How obesity cause diabetes?

Adipose tissue is now known as an endocrine brain and peripheral tissue organ that interacts through the secretion of hormones that control appetite and metabolism[14]. The position of the adipose tissue tends to modulate these roles by the size of the average adipocytes and the secretion of glucose and corticosteroids[15,16]. In fact, leptin levels increase in obesity[17], except in rare cases where the leptin gene is defective. This is due to the resistance of leptin to the cellular action. As explained below, this can be mechanically linked to insulin

resistance. Higher concentrations of free fatty acids derived from adipocytes have been found to be involved in insulin resistance in the liver and muscles[18,19]. Besides leptin, the tissue that modulates glucose metabolism and insulin activity often secretes a wide range of proteins[20]. The circulating rates of these proteins are increased for people with type 2 diabetes. Adiponectin is an exception that increases the action of insulin but circulates at lower levels of obesity[21].

II. Diabetic Retinopathy

Diabetic retinopathy (DR) is a retinal vascular disorder that affects diabetes mellitus and causes people to become blind. Type 2 diabetes can go unrecognized in subtly early stages for years. As a result, patients have diabetic retinopathy following early diagnosis of type 1 diabetes[22,23,24]. Diabetic retinopathy occurs in diabetic cases when small capillaries in the sensitive light retina are damaged and the ball goes out (microaneurysms are called)[25]. Over time, blood and fluid may continue to leak through these fragile vessels. Progression of the condition may impair vision (diabetic macular oedema) and excessive inflammation may result in the development of blood vessels, bleeding and fibrovascular scar tissue that loosens the retina (proliferative retinopathy) leading to untreated blindness[25,26]. This is much more common in people without diabetes and happens at an earlier age. Anterior ischaemic optic (optical nerve blood loss unexpectedly resulting in vision loss) neuropathy may occur as a result of glaucoma (optical nerve damage associated with increased intraocular pressure)[25]. Kerato-pathy and unexpected blockage of retinal arteries, contributing to serious visual problems[27,28].

Epidemiology

Worldwide, 30% diabetic retinopathy is found in individuals with diabetes mellitus. Common diabetic retinopathy is 34.6% and 6.96%, 6.81% respectively in cases of diabetic proliferative retinopathy and macular oedema[29]. In India, the incidence of diabetic retinopathy is 5.6 million. Populations with mild diabetic proliferative retinopathy and moderate NPDR are 2.9 and 2 million respectively. There are 111,258 and 296,688 individuals with severe NPDR and diabetic retinopathy[30].

Pathophysiology

Vascular diabetic retinopathy disorders are characterized by abnormal fluid movement, permeability dysfunction and capillary closure or non-perfusion. Two main mechanisms, microvascular leakage and microvascular occlusion, have contributed to changes in diabetes retinopathy. Diabetes allows the blood barrier to be broken first before DR progresses[31]. Aldose reductase affects the pericyte cell cycle, leading to pericyte loss. This interrupts self-regulation and causes disintegration of the blood retinal barrier and plasma leakage. Pericyte deficiency results in microaneurysm. Many causes, such as red blood cell shifts, contribute to poor oxygen transport and decreased stickiness and platelet aggregation due to damage and proliferation of capillary endothelial cells[12,31].

III. Mental Disorder

Multidimensional mental disorders are most common in diabetes and cognitive impairment, with six areas of working memory, auditory fluency, speech comprehension, emotional expression, visual form and perception[32]. Cognitive impairment shows the extent of cognitive disorder between normal aging and dementia, including specific categories of delirium, depression, amnesia, and other cognitive disorders[32,33]. Cognitive disorder is a symptom of diabetes that is less commonly understood and not well known. Cognitive defects have been observed in diabetic patients. Cognitive impairment and the patient's concern that hypoglycaemia may affect their memory over time[34]. Cognitive impairment mainly affects diabetic patients 2 years after diagnosis, with less positive effects than time in general intelligence, language, block size, method speed and comprehension. For people with type 1 diabetes, the slowdown in processing information and the loss of psychomotor capacity are the most serious cognitive deficiencies. Other deficiencies, such as vocabulary deficiency, general intelligence, vasoconstriction, perception deficits and attention, are often reported in type 1 diabetes[34,35].

Background of mental disorder

We're going to discuss the background and the brief history of mental illness. Mystical beliefs prevailed in prehistoric times at that point, people did not know why these diseases were occurring, so they did not know their territory, their health, their sorcery, and why. Every time the victims are treated with shamans, exorcisms and trepan[36]. The early procedure known as trepanning (8000 BCE-500 BCE) was used to expel evil forces from body to treat hysteria, insanity and pain. The theory of humour categorizes the origins of people (flegm, dark bile, yellow bile and blood). Aristotle defines the position of identity as a single unit of behaviour, feelings and thoughts. A psychiatrist from Persia (865-924 CE) reported signs and treatment of illness and

mental illness[37]. In the Medieval period (500-1500 CE), people thought that only physical or intellectual health had been restored by God. This was believed, in the 17th century, that if an insane man behaves like an ape, he would be handled as such. In the 17th century, Robert Burton developed a therapeutic practice music, food program and stressed the importance of addressing problems with close friends or physicians. People with mental health problems were frequently treated in secretly during the 17th century[38]. They've made a madhouse for patients to check out. Houses for patients, separate from other houses built in the 18th century. Mental illness was considered to be an amoral weakness in that period. Hospitalization began in the 18th century, while social regulation was carried out in the 19th century. The community plays a crucial role in the treatment of mental illness. The challenge lies in the unchained treatment of patients, phenology and animal magnetism[38]. Patients engaged in life-related activities and assisted in social activities. Therapeutic procedures in the 1930s included the replacement of teeth, large intestines, fatigue inducement, sleep deprivation and lobotomy. The diagnosis of mental disorders[36] was initiated in 1954 with thorazine. Throughout 1986, the number of US patients in mental institutions declined to 100,000. The most serious cases currently rely on care such as hospitalization, persistent institutionalization, cognitive and behavioural intervention, rehabilitation exercises, and positive psychology are commonly used[37,38].

IV. Complications and Consequences

Diabetes mellitus is a complicated condition with several dietary and metabolic consequences. Vitamin D, vitamin B12, B1, magnesium and chromium food disorders are harmful to patients with diabetes. Nutrition flaws in type 1 diabetes can be properly detected and addressed[39]. DMT patients are typically obese, but their LBM compared to non-diabetes is relatively low compared to their elevated BMR propensity for intercurrent starvation. Optimum management of hyperglycaemia for all diabetics, as well as the expected weight reduction for obese patients, are needed both to prevent further problems and to facilitate increased glycaemic surveillance in certain situations with regard to nutritional deficiencies and care as soon as possible[40]. There are many recurrent and severe symptoms of diabetes. Acute risks include diabetic ketoacidosis and hyperglycaemic syndrome, hyperglycaemia; nephropathy, retinopathy, neuropathy, macrovascular disease, peripheral vascular disease, and stroke associated with MALT and metformin complications[41,42]. Diabetic retinopathy (eye disease) impaired vision and blindness in some cases. Renal disorders (diabetic nephropathy) do not work or may stop working. Feet problems include wounds and sores. Mouth disorders, for example, gum disease or tooth defect in some situations. Inflammation of the cardiovascular system, such as heart attack, stroke, and systemic inflammation of the heart and blood arteries (low blood flow in the legs and legs). Nerve damage (diabetes neuropathy) in the head, neck, legs and legs, stupor, tingling or discomfort (ADA, heart disease)[43].

RELATIONSHIP BETWEEN DIABETIC RETINOPATHY AND COGNITIVE IMPAIRMENT

It indicates a significant cognitive disability for people with minimal diabetic retinopathy. If diabetic retinopathy is missing and people with poorer retinopathy, vocabulary and concentration deficits than more severe diabetes retinopathy[33], the executive function of the individual is two to three times higher cognitive loss and the focus and naming of patients without retinopathy has been two to three times higher. Retinopathic diabetic patients are at higher risk of cognitive impairment than diabetic patients with no retinopathy. Patients with retinopathy in both eyes had severe impairment compared to those with retinopathy in the single eye. People with behavioural problems must also be changed in the sensory rehabilitation of diabetic retinopathy. Cognitive impairment has been shown to be serious in non-proliferative retinopathy cases[44].

PREVENTIONS

Without action, diabetes-are more than 50% higher in the next 10 years without a reduction in diabetes. In order to avoid type 2 diabetes, people should gain and maintain their healthy body weight. In most days, be physically active for at least 30 minutes with moderate intensity of regular exercise. Diabetes treatment requires a decrease in blood glucose and an accumulation of identified risk factors for blood vessels. To prevent complications, tobacco must also be stopped[45]. The best way to prevent the complications of diabetes is to avoid diabetes, including diabetic retinopathy. By exercising 30 minutes each day or five days a week, we simply prevent diabetes by reducing the number of people living with type 2 diabetes[46]. However, people work together to inform and inspire our health care providers and policy makers and to implement all possible measures to change the current pattern of diabetes, and the risk of serious eye problems can be minimized by as much as 95% for those who have already diagnosed diabetes[25].

V. Treatments

Insulin is required for people with type 1 diabetes, and people with type 2 diabetes may require oral medication, but insulin may also be required. Control of blood pressure and foot-care is also needed[45]. Other savings include cost control (which leads to blindness) and retinopathy (which leads to blood lipid control).

Early signs of kidney disease and diabetes diagnosis have been tested. Such interventions should include a healthy diet, physical activity, body weight and nicotine abstinence[45,46]. Giving bitter gourd fresh juices may treat some symptoms of diabetes, including polyuria, polydipsia, and polyphagia[47]. Glycaemic control is consistently lower in insulin-treated patients than in other therapies. Insulin is the most effective glucose regulation agent for hypoglycaemia, relative to other oral drugs, being the only major dose limiting factor. As the dose increases, insulin has more and more adverse effects[46,47]. Retinopathy can be reversed in people with severe glucose control in diabetic type 1 conditions, and existing diabetic retinopathy can be prevented. The prospective UK study found that intensive glucose control in patients with type 2 diabetes such as retinopathy would reduce the rate of microvascular disease[48].

Laser therapy

In fact, laser treatments use a compact light-intensity laser to treat diabetic retinopathy against aggressive microaneurysms. Laser photocoagulation is an important visual therapy for retinopathy with diabetes and has been classified as pane retinal, concentration or grid[49]. The likelihood of extreme vision loss was effectively reduced by pane retinal photocoagulation, Focal and grid lasers. By these therapies diabetic retinopathy is minimized from clinically significant macular oedema to mild vision loss (CSMO). In the case of CSMO, both are equipped to reduce vascular leakage in areas of dispersed retinal blood disintegration by focusing the laser on microaneurysms or grid laser burns[50]. Both will contribute to an acute loss of central vision. Choroidal neovascularization can rarely cause subretinal fibrosis. On the other hand, the side effects of comprehensive PRP have peripheral visual field limitations and low dark tolerances. Vitreous haemorrhage may occur in the presence of neovascularization during therapy[49].

Anti-vascular endothelial growth factor agents

Vascular endothelial growth factor is developed in response to capillary depletion and hypoxia formation of micro-aneurysms. It is the central mediator for the degradation of ischemia retina from angiogenesis and blood-retina[51,52]. Three anti-VEGF drugs are currently under investigation: Pegaptanib Sodium, Ranibizumab and Bevacizumab. Pegaptanib is a shortened 28-base RNA aptamer bound to VEGF165 and to long VEGF isoforms[53]. The effect of pegaptanib was improved VA performance, decreased centrally-densified retinal thickness and reduced photocoagulation therapy usage for 36 weeks in DMO-patients. Ranibizumab is a humanized fragment of monoclonal antibody specifically designed for all human VEFG isoforms[53]. This drug therapy may maintain or enhance AV and reduce the thickness of the retinal tubes[54]. Bevacizumab is a comprehensive humanized VEGF-specific monoclonal antibody that binds all human VEGF isoforms with their biological active ingredients[53]. VEGF therapy also reduces diabetic retinopathy. This method uses intravitreal injections of anti-VEGF drugs under topical anaesthesia as an eye procedure[55]. Anti-VEGF agents in macular diabetic oedema are reported as centre-implicated macular diabetic oedema while the laser treatment classification is limited to non-centric diabetic oedema[48]. Diabetic retinopathy can be controlled by lipid control because we are positive for higher levels of serum lipid in diabetes with retinal hard exudate (liquid)[49]. Physicians use different medicines to manage mental disorders. In order to treat stress, the use of chromium, cranial electrical stimulation, inositol, omega-3 polyunsaturated fatty acid (fish oil) and meditation are beneficial.

VI. Herbal Treatments of Mental Disorders And Diabetic Retinopathy With Their Mode Of Action

Herbs are of high quality and are often used by people as medicines. Herbs are used for the treatment of mental disorders including loss of memory, anxiety, insomnia and sleeplessness. Smooth primrose is used as anxiolytic and minimizes child hyperactivity (e.g. kings-cure-all, EPO, flu, wild herbs and primeval rhythm). A stinky rose, a member of the Lilly genus, is antioxidant and is used to prevent memory loss and prevent strokes (Allium sativum, AIL, Camphor of misery, da-souan, Nectar of gods, poor human treacle, smelly rose). Gotu Kola (India water navel term, marshy penny, centellaasiatic, and brahman) is used to reduce exhaustion, anxiety, depression, memory and improve intelligence and intellectual skills. Kava comes from the nodulous root and is a member of the black pepper family. It is used for normal sleep and relaxation. Kava works on the same GABA-growing CNS receptor and region, working to moderate anxiety. Lavender has been shown to contain essential oils and to demonstrate the results of CNS depressants, anticonvulsant function and chloral hydrate sedation in rats. Herbs are used for pain, restlessness, anxiety and nervous exhaustion. Lemon Balm is a popular remedy used to relieve fear and sleeplessness. Rosemary shows seizure activity and may lead to an increase in GABA. Skullcap is used to relax the body. Several Chinese medicines have often dealt with psychological problems. Bai Zi Yang Xine WAN used herbal medicine for sleeplessness and mental restlessness. Ayurvedic medicines such as corporeal and herbal enema are used in India, with lower blood-free radicals, improved vitality, increased immunity and reduced signs of disease. As agitation and sedatives, Ahiphenam Papaver

Somniferum was used as a neurological energetically improved tonic and as a nerve tonic Jatamansi used to diagnose fear, nervousness and insomnia[56]. Herbal plants have remained the most valuable medicinal source since early cultivation. Various herbs are used to treat diabetes retinopathy.

Pinus pinaster

It is a member of the family of pinaceae and is an evergreen herb. The extract of pycnogenol was produced from the outer bark of this herb. Pycnogenol-reducing compounds contribute to a reduction in the quantity of advanced glycation finishing products responsible for DR in diabetic patients[57]. It improves blood leakage and blood fluid resistance to retinal cells in the bloodstream[58]. It inhibits the development of oedema[59]. Due to its free radical scavenging activity, its potent antioxidant, it leads to a decrease in the body's reactive oxygen species, which are responsible for the aggregation of the glycolytic metabolite in advanced glycation materials. Pycnogenol radicular scavenging properties often suppress progressive Glycation products that are responsible for the development of diabetic retinopathy in diabetic patients[57].

Azadirachtaindica

Azadirachtaindicais a fast-growing family member of the Meliaccae family. Ait is generally referred to as Neem in India and other Asian countries such as Pakistan, Bangladesh, Sri Lanka, Nepal and in particular parts of Africa. As a beta adrenergic, Azadirachtaindica promotes insulin release and increases hyperglycaemia and decreases diabetic retinopathy[60].

Mechanism of action

Azadirachta Indica (Quercetine-3-O-beta-D-glucoside, Myricetine-3-O-rutinoside, Kaempferol-3-O-beta-D-glucose and Quercetine-3-O-alpha-L-rhamnoside) is said to be active in anti-hyperglycaemic activity vice versa and to serve as beta-adrenergic agents and to induce insulin release. These may include beta-adrenergic receptor agonists in beta pancreatic cells, activating the adenyl cyclase system, improved cyclic output of 3'5' AMP, and activation of protein kinase A, and the exocytotic cycle of calcium reactions to insulin release, decreased hyperglycaemia, and decreased diabetes retinopathy[60].

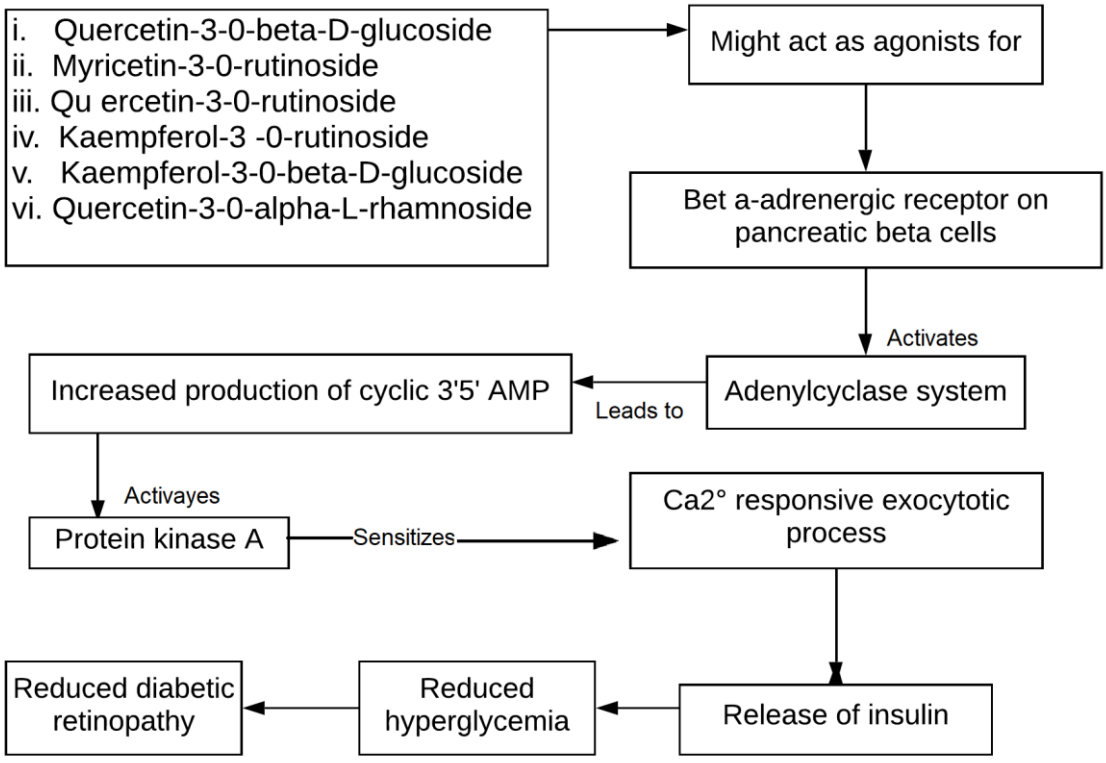

Figure 1: Mode of action of Azadirachtaindica

Ginkgo biloba

A large tree in the Ginkgoaccae family, and now a surviving family member, believed to be the oldest tree in the world. The chemical components present in this plant are terpenes such as ginkgolides, bilobaids and

flavonoids. It is anti-inflammatory due to its inhibitory activation of the platelet. Inflammatory response, which is a key factor in diabetes retinopathy pathogenesis, can therefore be prevented[61].

Mode of action

Gingko biloba is known to be a thinner of blood. Because of this function, it improves the blood flow in the body, decreases the probability of leukocytes adhesion and prevents some inflammatory behaviour[62]. It behaves as an anti-inflammatory substance due to its inhibitive stimulation of platelets. Because of this, an inflammatory reaction that plays a key role in DR pathogenesis can be effectively stopped. The anti-oxidant properties of flavonoids are responsible for this plant. They help to squeeze out ROS in the body and thus reduce oxidative stress in the body[61]. Inhibiting the activities of endothelial NO synthase among ginkgolides is caused by Ginkliode A and prevents the degradation of NO levels in the body. As a result of these vasorelaxant activities, hypertension in capillaries is reduced and diabetic retinopathy is prevented[63].

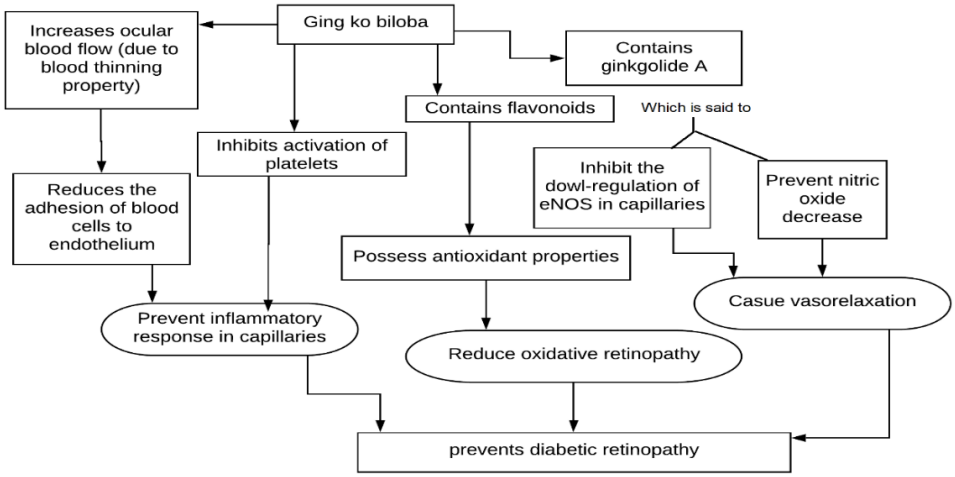

Figure 2: Mode of action of Gingko biloba

Sulfonylureas (mode of action)

Sulfonylureas cause hypoglycaemia through pancreatic β-cells that stimulate insulin release. They communicate with ATP-sensitive potassium channels on the β-cell plasma membrane causing cell membrane depolarization. It activates the voltage-gated channels that allow the circulation of Ca^{+2} ions and the release of insulin granules[64]. Acute administration of sulfonylurea in type 2 DM-patients increases the release of pancreatic insulin and may increase insulin eves further by reducing the clearance of hepatic hormones. Initial studies have shown that the hypoglycaemic effects of sulfonylurea involve functioning pancreas[65].

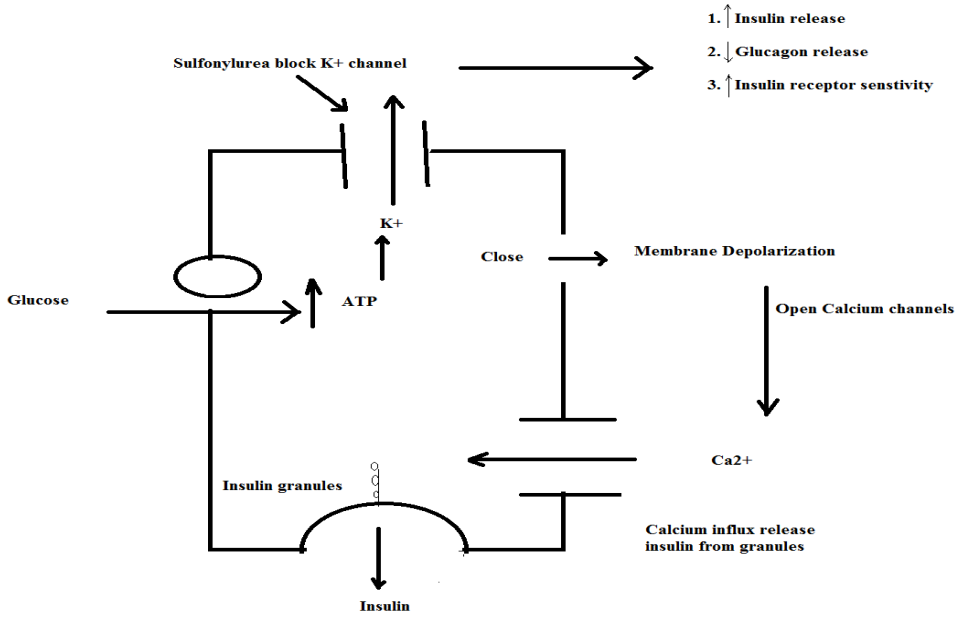

Figure 3: Mode of action of Sulfonylureas

Metformin (mode of action)

Metformin modes of action are not completely known. It is not hypoglycaemic nor anti hyperglycaemic[66]. It causes no release of pancreatic insulin and even in high doses does not cause hypoglycaemia[67]. The exposure of metformin does not cause a major effect on glucagon, adrenaline, growth hormone or somatostatin. Peripheral glucose consumption was improved by around 20-30% and hepatic glucose production decreased when administered orally but not intravenously[68,69]. Metformin also indicates that the concentration of serum triglycerides and fatty acids decreases and the lipid oxidation rate that implicitly prevents gluconeogenesis decreases[69]. In obese patients with Type 2 diabetes, statistically and clinically meaningful reductions in body weight have been correlated with metformin therapy and independent of their effect on glycaemic function[70].

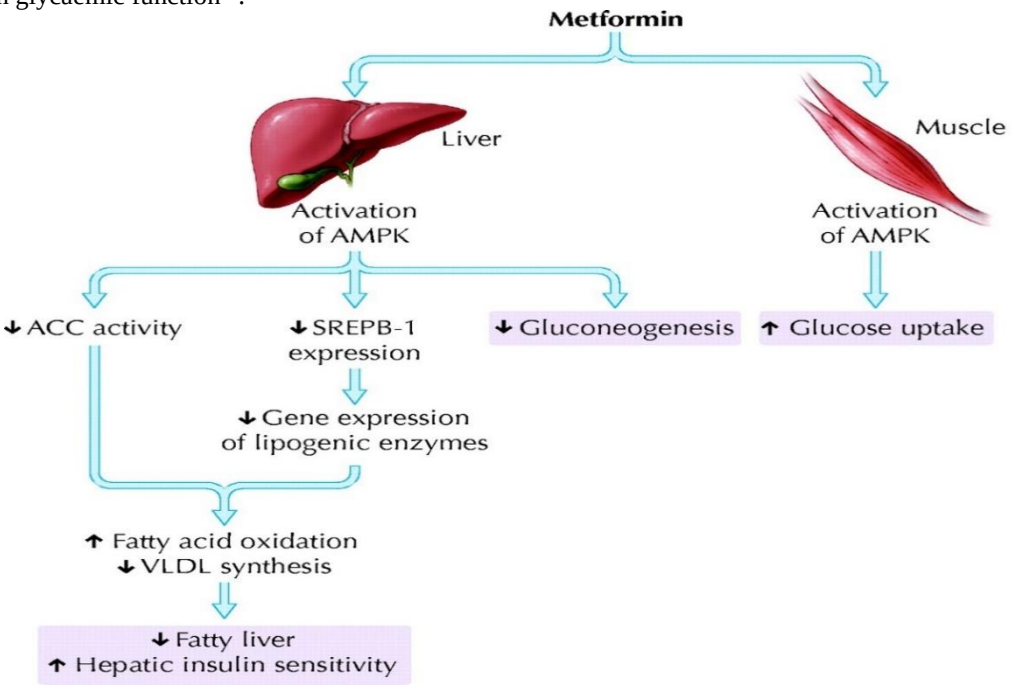

Figure 4: Mode of action of Metformin

Thiazolidinedione (mode of action)

Thiazolidinedions are proliferative-activated selective gamma receptor agonists for nuclear peroxysomes. The PPAR receptors are used in major tissues such as adipose, skeletal and liver. It is clear that

these receptors can be essential regulators for differentiation in adipose, lipid homeostasis, insulin resistance and vascular endothelial function[71,72]. Thiazolidinedione works mainly by lowering insulin resistance through peripheral tissue, but also by reducing the blood glucose output of the liver[73]. Thiazolidinedions increase the transport of glucose to the muscle tissue and to the adipose tissue by improving the synthesis and translocation of glucose transporting proteins in particular[72]. Thiazolidinedions may also be able to activate a gene that regulates the metabolism of free fatty acids in peripheral tissue, thereby reducing triglycerides and non-starch fatty acids and leading to adipocyte differentiation[74].

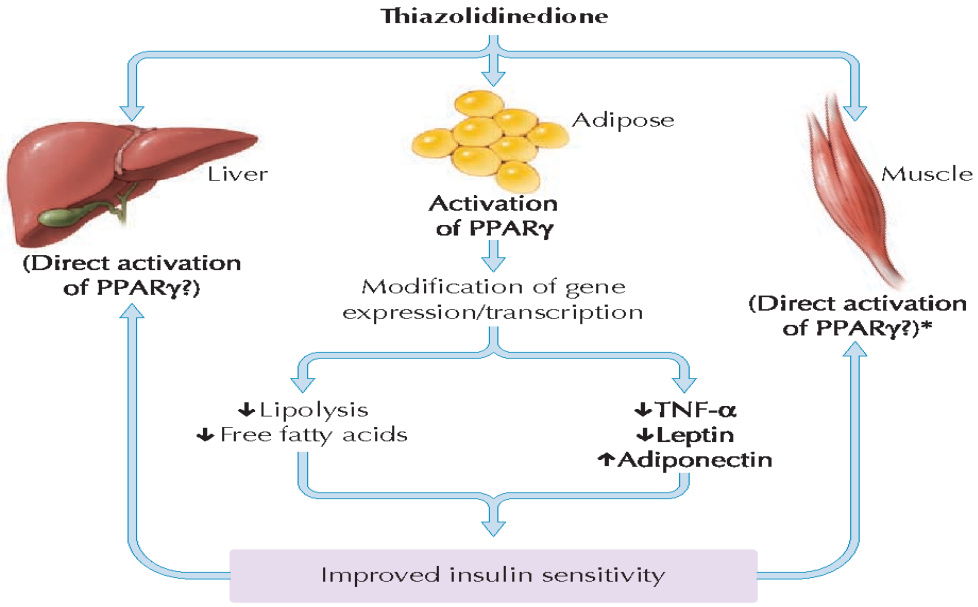

Figure 5: Mode of action of Thiazolidinedione

FACTS ABOUT DIABETIC RETINOPATHY

Roughly 371 million people worldwide have diabetes, 4.8 million of whom are dead and 552 million or one in 10 of whom will suffer from diabetes if trends continue by 2030.

Table 2: Country wise prevalence rate of diabetes.

Sr.no	Country	Patients	Year	Reference
1.	U.S.	26 million 6761.7(1000s)	2013 2013	75
2.	North America and Caribbean	38 million	2013	76
3.	Europe	55 million	2013	77
4.	South-East Asia	70 million	2013	78
5.	Middle-East and North Africa	34 million	2013	79
6.	Africa	15 million	2013	79
7.	China	92.3 million 53238.4(1000s)	2013 2013	 80
8.	India	50.8 million 31920.0(1000s)	2010 2012	81
9.	Brazil	13.4 million	2013	79
10.	Russian Federation	12.7 million	2013	78
11.	Mexico	10.6 million	2013	78
12.	Indonesia	7.6 million	2013	79
13.	Egypt	7.5 million 3755.3(1000s)	2013 2013	80
14.	Japan	7.1 million 3558.7(1000s)	2013 2013	79
15.	Pakistan	6.6 million 3356.3(1000s)	2013 2013	81

Table 3: Historical overview of diabetic retinopathy

Sr. No.	Observations	Conclusion	References
1.	Moderate to severe compared to no retinopathy. Significant retinal arteriolar narrowing is 40 percent more likely in male diabetic patients.	Diabetic retinopathy has a strong relationship with cognitive impairment and increase the risk near three folds.	33,82
2.	The incidence of all micro-and macro-vascular diabetes complications caused by hospitalization and increased cholesterol and was diagnosed with Fluorescein Angiography in patients with proliferative retinopathic diabetics.	Diabetic retinopathy is a high risks factor of neuropsychiatric morbidity and mortality.	83,84
3.	The frequency of cardiovascular events with type 2 diabetes is widely read in high fluctuations in plasma glucose levels. The results are based on patients with retinopathy and the lack of insulin retinopathy was twice as frequent in patients without retinopathy.	The extent of hyperglycaemia but not fasting plasma glucose variation in elderly type 2 diabetic patients highly correlates diabetic retinopathy, irrespective of other known risk factors.	85
4.	The objective is to investigate the time-to-effect interactions between systolic blood pressure (SBP) and the symptoms of nephropathy and retinopathy in patients with type 2 diabetes. 90 patients had nephropathy and 113 had retinopathy.	Nephropathy and retinopathy development correlated with time-to-effect association with SBP. Short term effect was stronger for both while nephropathy was evident and retinopathy at borderline for long term effect.	86,87
5.	In the treatment of diabetic retinopathy, regulation of hyperglycaemia, high blood pressure and dyslipidaemia is of great importance.	Anti-VEGF medication in the proliferative diabetic retinopathy patient was found to be effective as an alternative.	88
6.	We found that group 2 with age, gender and BMI did not differ in the first group, but in the second group with duration of diabetes. It has been found that 7 percent of HbA1c has significant variables affecting diabetic retinopathy.	BMI, HbA1c percentage and time span of diabetes are major contributors of diabetic retinopathy in type 2 DM patients.	7,89
7.	Diabetic retinopathy as a dependent variable indicates an increased risk of anaemia compared to those that do not experience anaemia.	Each 10th person in a diabetes mellitus population might be anaemic. Anaemia diagnosis and treatment would have a significant impact on the management of microvascular problems, such as diabetic retinopathy.	90
8.	When the incidence of retinopathy tests is very small, even for those who are not tested after treatment, the incidence of eye disease is very low compared to previous cases.	Throughout Scotland, most newly diagnosed diabetic type 2 patients screened within an optimal time period and found a decrease in disease prevalence even in delayed screening.	91
9.	The primary focus on the senses of contrast and perception of luminance was the measurement of value in the development of diabetes retinopathy. Retinopathy eyes reported a higher loss than retinopathy-free eyes. The contrast-sensitive method has a number of benefits for separating retinopathy patients from non-retinopathy patients.	These strategies can help to track diabetic patients ' visual function, and to identify early retinal damage signs.	92,93
10.	The main objective is to define the risk factors for retinopathy and microalbuminuria and their association with diabetic patients of type 2. In diabetic patients of type 2, Microalbuminuria has retinopathy with diabetes and a strong predictor of retinopathy.	Microalbuminuria is a valid marker of retinopathy and is associated with diabetic retinopathy in T2DM patient.	94
11.	Our research supports the extension of the diagnosis period beyond the currently recommended 12 months in patients with type 2 diabetes mellitus. The focus is primarily on the assessment of diabetic retinopathy.	Annual screening for retinopathy is mandatory for patients with diabetes mellitus.	11
12.	The main focus of the research is on the incidence of retinopathy and risk factors correlation in patients with type 2 diabetes. Results show that the incidence of retinopathy is steadily increasing with the increase in the duration of diabetes.	For patients with T2DM, diabetic retinopathy is a primary health problem. It can manifest for disability, impairment and high healthcare costs.	95
13.	The main focus is to investigate the potential role of diabetic retinopathy23-kd prolactin variation. We have two patient classes with retinopathy, and without retinopathy we see variations between two groups in diabetic duration and systolic hypertension, but no variations in prolactin level were observed.	Prolactin has no protective role in diabetic retinopathy.	96
14.	After a correlation test, we analyse how 334 out of 500 patients with mean diabetic retinopathy are diagnosed with a total of 1000 eyes and 573 patients with diabetic retinopathy are classified as non-proliferative retinopathy.	Retinopathy and systemic complications are correlated with long term diabetes and hyperlipidaemia is a key marker for retinopathy.	97

15.	The study found a noticeable increase in the flow rate in the eye in moderate diabetic retinopathy and reduces the flow rate in severe diabetic retinopathy. Decreased cervical arteries leads to reduced blood flow.	Diabetic retinopathy decreases the velocity of ocular blood flow.	98
16.	The main focus is on the interaction between diabetic retinopathy and pulse wave rates. Patients with diabetes retinopathy have a higher pulse velocity (PWV) than patients with non-diabetic retinopathy.	Diabetic retinopathy increases pulse wave velocity and it should be taken as marker for retinopathy.	99
17.	miR-15a is the main regulator in both pro-inflammatory and pro-angiogenic processes. miR-15a was recognized as a regulator of pro-inflammatory and proangiogenic pathways by binding and inhibiting the central enzyme to the metabolism of sphingolipids. miRNA and RNAi, Quantitative Real-Time PCR, Western Blotting and Mass Spectrometry are all used for retinal Ischemia-Reperfusion.	miR-15a directs pro-angiogenic pathways and sphingolipid metabolism by regulating ASM and VEGF-A formation in diabetic retina and bone marrow	100

VII. Conclusion

Diabetes implies that the body does not directly process food intakes into the sugar or glucose used in the body as energy. Insulin has been used to regulate diabetes because of the build-up of blood sugar in the body. Diabetes is a major issue that is growing around the world today. Diabetes is a condition that results in a variety of complications including heart problems, retinopathy (blindness) and kidney failure. It is America's seventh largest cause of death. It is spread mainly in Crescent, Sub-Saharan Africa, and India. Retinopathy and cognitive impairment association is high in diabetes. Retinopathy patients were at higher risk than diabetic patients without retinopathy for cognitive impairment. Diabetic retinopathy leads to diabetic impairment and mental illness. Further effective and efficient studies are needed to fully address the association between cognitive impairment and retinopathy. The connection between diabetic retinopathy and cognitive dysfunction has been studied in the future, with further research exploring the function of other variables including CVD frequency, gender and ethnicity. Retinopathy can be a major cause of cognitive impairment and likelihood of dementia in the case of diabetes, and other inflammatory and metabolic conditions may lead to cognitive compromised disease. Both options require more study to include new health management tools and early cognitive impairment treatments and to understand the relationship of diabetes to retinopathy and cognitive impairment.

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Asim Hussain, et. al. "A Comprehensive Review on Diabetic Retinopathy and Mental Disorders." *IOSR Journal of Biotechnology and Biochemistry (IOSR-JBB), 6(3*), (2020): pp. 38-51.