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AN OVERVIEW ON RELATION BETWEEN RETINOPATHY AND MICROALBUMINURIA IN TYPE TWO DIABETES MELLITUS WITH THEIR TREATMENT & PREVENTION

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ABSTRACT

The development of new drug delivery system gained more importance in the field of research in which nanotechnology is the most considered approach. The nanotechnology-based systems such as nanoparticles, nanoliposomes, niosomes, nanomicelles, nanoemulsions, nanogels, cyclodextrins, dendrimers, and quantum dots are developed as a new formulation for drug delivery. The rationale behind the nanoparticle systems is its ability to formulate a sustained, controlled release dosage form, painless, safe, non-invasive system to overcome the major barriers in the treatment of DR. Based on the nanoparticles, some approaches are exploited for more effective conveyance of drug toward the posterior segment. Thus, these advanced delivery systems progress the therapeutic efficacy of the drug and patient's obedience and life quality. In this review, the new therapeutic treatments and their managements were discussed and methods of drug delivery to reach the posterior segment of eye. Understanding the impact of a condition from thepatient's perspective is important, and different types of patient-reported outcomes or instruments are available to help with this. This review article summarises the current evidence on the impact of diabetic retinopathy (DR) and its associated vision impairment on patient-reported outcomes. We have included research that has used a range of outcome measures to assess the impact of DR on generic health-related quality of life, utility, vision-functioning and vision-specific quality of life. This review also offers clarification on frequently misused psychometric terminologies to help clinicians and researchers better understand the literature associated with patient-reported outcome research. Overall, the evidence suggests that DR, particularly in its vision-threatening stages, has a substantial, negative impact on the patient.

Keywords: Retina, Diabetic retinopathy, Diabetes, Microalbuminuria, Conventional Drugs

INTRODUCTION

Diabetic retinopathy (DR) is one of the most common complications of diabetes mellitus and is characterized by degeneration of retinal neurons and neoangiogenesis, causing a severe threat to vision. Nowadays, the principal treatment options for DR are laser photocoagulation, vitreoretinal surgery, or intravitreal injection of drugs targeting vascular endothelial growth factor. However, these treatments only act at advanced stages of DR, have short term efficacy, and cause side effects.

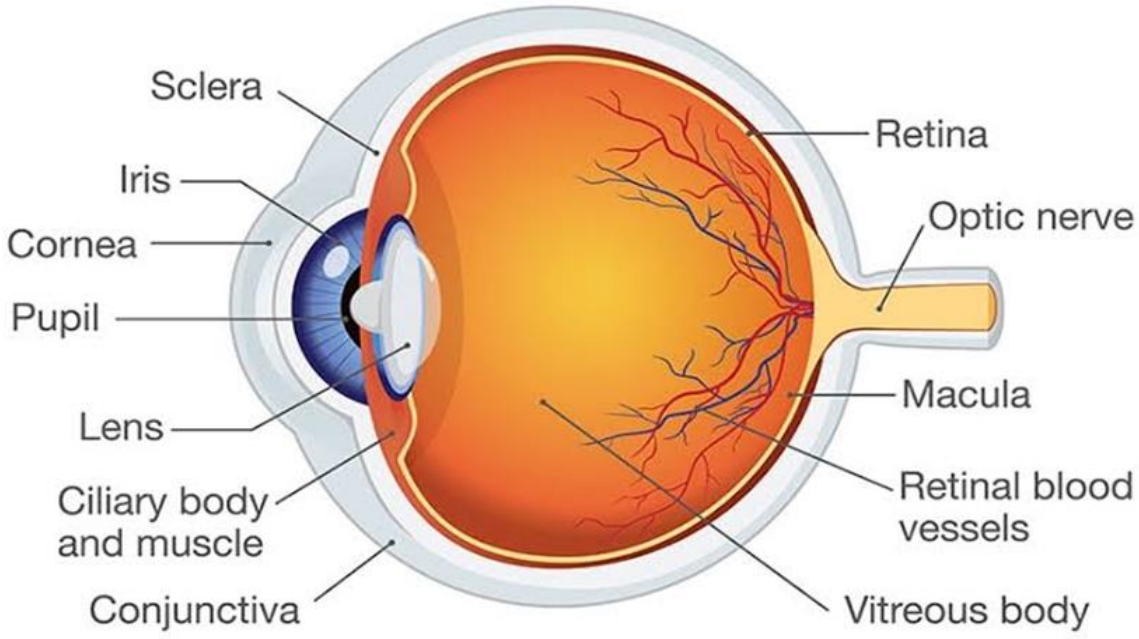
Diabetic retinopathy (DR) is a multifactorial microvascular complication of diabetes mellitus caused by damage to the blood vessels of the retina, the light-sensitive tissue located at the back of the eye. DR has been included by the World Health Organization in the priority list of eye diseases which can be partly prevented, but not cured yet. In its early stages, DR may cause only mild vision problems but, over time, persistent high blood sugar levels can lead to the obstruction of the tiny blood vessels that nourish the retina, cutting off its blood supply. As a result, the eye reacts by triggering an abnormal growth of new retinal vessels, causing micro-hemorrhages and edemas in the macular region, thus leading to severe visual impairment and eventually blindness. These intra-retinal microvascular changes are used to classify DR into non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). NPDR is characterized by a complex array of vasodegenerative lesions within the retinal microvascular bed, such as thickening of capillary basement membranes (BMs), loss of pericytes and vascular smooth muscle cells, capillary occlusion and microaneurysms. PDR is caused by an abnormal growth of new blood vessels (retinal neovascularization) in response to inflammation and/or ischemic damage and hypoxia, eventually giving rise to vitreous hemorrhages and tractional retinal detachment. A direct consequence of inner blood–retinal barrier (iBRB) breakdown is the development of macular edema. Retinal neovascularization and macular edema are the result of increasing secretion of pro-inflammatory cytokines, and pro-angiogenic growth factors, among which predominates the vascular endothelial growth factor (VEGF) . The retina is a highly metabolic active tissue, and high-glucose concentrations are particularly detrimental to its functioning.

Radiation retinopathy (RR) is a chronic and progressive condition that may result from the exposure to any source of radiation including: external beam radiation, plaque brachytherapy, proton beam radiation, helium ion radiotherapy, and gamma knife radiotherapy. RR may be secondary to the treatment of intraocular tumors such as choroidal melanomas, retinoblastomas, and choroidal metastasis or from unavoidable exposure to excessive radiation from the treatment of cephalic, nasopharyngeal, orbital, and paranasal tumors among other

malignancies. Following the Collaborative Ocular Melanoma Study (COMS) therapeutic options for choroidal melanomas, the most common primary malignancy of the eye, have shifted from enucleation of the eye to plaque brachytherapy for medium-size melanomas since the survival rate has been found to be similar. This shift towards globe salvaging strategies has increased the use of radiation and consequently increased its complications with the incidence of RR ranging from 3 to over 20%. A recent retrospective study reported an incidence of RR with associated retinal neovascularization (proliferative RR) of 5.8% at fi ve years and 7% at ten and 15 years in 3 841 eyes treated with plaque radiotherapy for uveal melanoma.

The WHO recommends that screening should be done for any condition that is an important health problem, has an effective treatment that can be delivered early, usually before symptoms of the condition are apparent, when facilities for diagnosis and treatment are available, when screening is feasible and cost-effective, and when subjects can be followed up longitudinally. Diabetic retinopathy fulfils most of these criteria and some studies have shown that screening can reduce the rate of blindness due to DR.

ANATOMY AND PHYSIOLOGY OF THE RETINA



Structure of retina

The retina is the innermost of the three coats of the eye and is responsible for converting the image of the external environment into neural impulses that can be transmitted to the brain. The retina is underlined by the retinal pigment epithelium (RPE), which is a simple epithelial layer that acts as a selective semipermeable barrier. The retina is highly metabolically active with the highest oxygen consumption, relative to weight, of

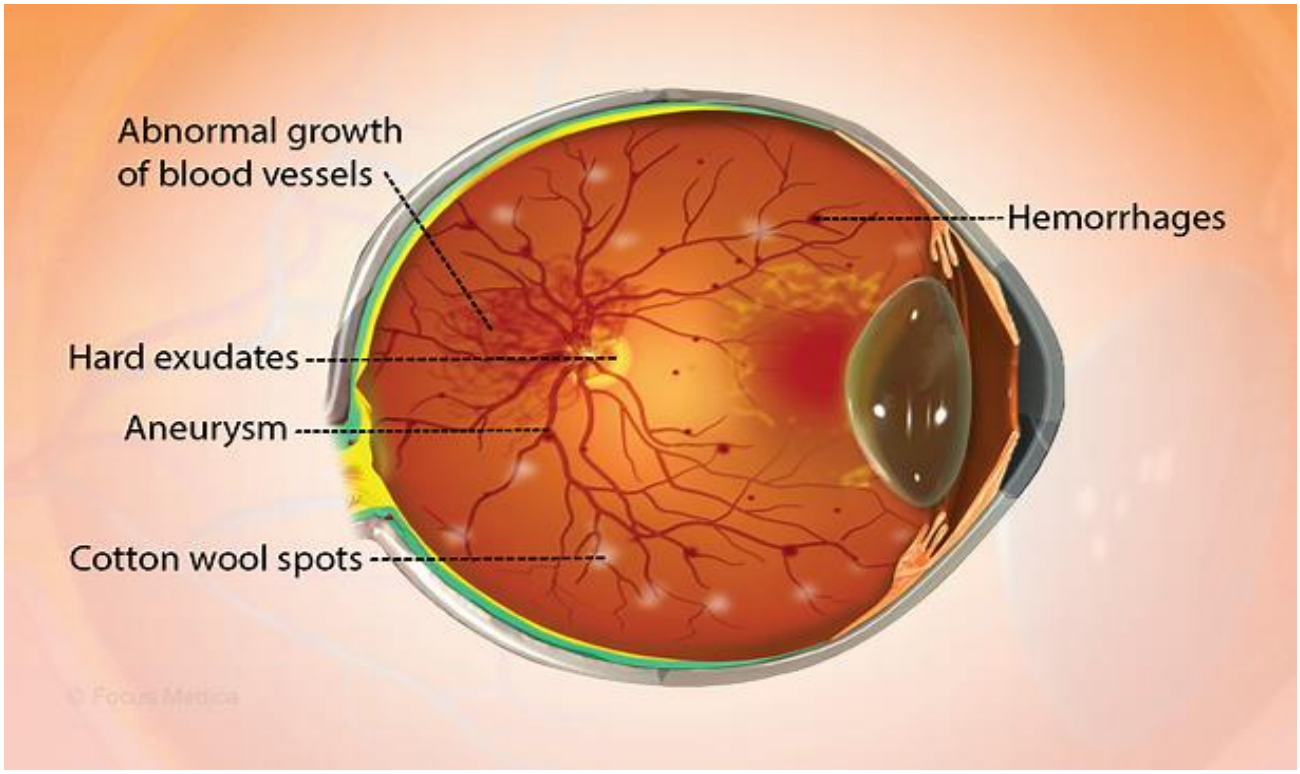
any human tissue.

The RPE is composed of a continuous monolayer of simple cuboidal cells located between the capillaries of the choroid and the neurosensory retina. In a normal eye, RPE cells are hexagonally shaped and packed together like cobblestones with a mottled brown colour due to the presence of melanin. RPE cells have developed a complex structural and functional polarity that allows them to perform their highly specialised roles, with the RPE cell membrane having distinct apical, basal and lateral surfaces. The apical surface of the cells is covered with microvilli.

The basal surface is convoluted into numerous basal infoldings, resulting in a high surface area suitable for transport properties. The lateral surfaces of adjacent RPE cells are joined by four types of junction: tight junctions, adherent junctions, desmosomes and gap junctions.This highly selective BRB provided by the RPE serves to maintain a regulated homeostatic environment for this highly specialized tissue. Systemic drug administration does not guarantee high intraocular drug levels, at least in part because of the integrity of this barrier. As light travels through the pupil it is focused onto the macula – the part of the retina responsible for central sharp vision and colour discrimination. The macula is also the area affected by age-related macular degeneration and central swelling in diabetic disease. There are multiple layers within the neurosensory retina itself and the inner surface is made up of ganglion cells that transmit impulses from the deeper retinal layers to the brain by way of the optic nerve. Light must travel through the ganglion cell layer and pass through the middle layers to reach the photoreceptor cells that ultimately transform light into recognizable signals for the brain. Light must, therefore, travel through the thickness of the retina before striking and activating the rods and cones (photoreceptor cells). Any disruption of the intervening layers would thus compromise vision. The critical factors are the acid/base status and the lipophilicity of the molecule. It appears that drug-related toxic effects on the retina described in humans and animals are unrelated to melanin binding: melanin binding and retinal toxicity are two separate entities, the latter being related to the intrinsic toxicity of the compound rather than its ability to bind. Melanin binding has also been found to be protective against the ocular toxicity of some drugs. However, photosensitising agents such as the phenothiazines may become bound to melanin within the retina, absorb visible and ultraviolet radiation and, as a result, generate damaging free radicals.

Retinal Cell	Characteristics
Rods (Photoreceptors)	More light-sensitive than cones. Particularly important for night vision. Can detect a single photon of light of suitable wavelength. Have poor point resolution and are not present in the fovea. Rods respond only to one narrow band of light frequency, and rod-only retinas are entirely colour blind. Rods contain one pigment type and are not responsible for colour vision.
Cones (Photoreceptors)	Operate at higher light intensities and are the main receptor of 'daylight' vision, since rods saturate at very low light levels and essentially cease to function. Responsible for colour, based on the existence of three subtypes of cones sensitive to three distinct light wavelengths. Cones have a much shorter outer segment than rods.
Bipolar Cell	Have a dendritic process, a cell body and an axon. The cells are not myelinated, and their excitation produces an inhibitory generator potential. Synaptic input to bipolar cells is from receptor cells (the rods and cones) and also from another type of interneuron, the horizontal cells.
Ganglion Cells	The ganglion cell layer is the innermost layer of the retina. They have relatively large cell bodies, and from these arise long myelinated axons that exit the eye and make up the optic nerve/tract synapsing in the lateral geniculate or optic tectum of the midbrain. Ganglion cells are inhibited by bipolar cells, which are themselves inhibited by rods/cones, which in turn are inhibited by light.
Horizontal Cells	Horizontal cells synapse with rods/cones and the bipolar cells. They have axons, but apparently do not develop action potentials. Generally, the horizontals receive synaptic input from the light receptor cells.
Amacrine cells	Amacrine cells lack an axon. The cells receive their synaptic input from bipolar cells. Their many cell processes ramify throughout the layer between bipolar and ganglion cells, and these processes synapse onto other bipolar cells. They are apparently inhibitory and may act as a regulator of bipolar action.

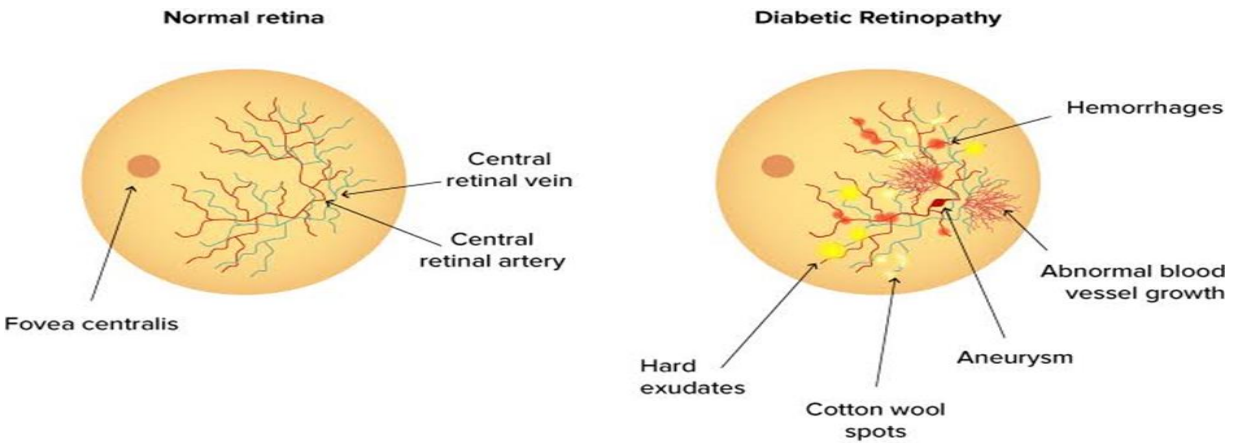
The key retinal cell populations.



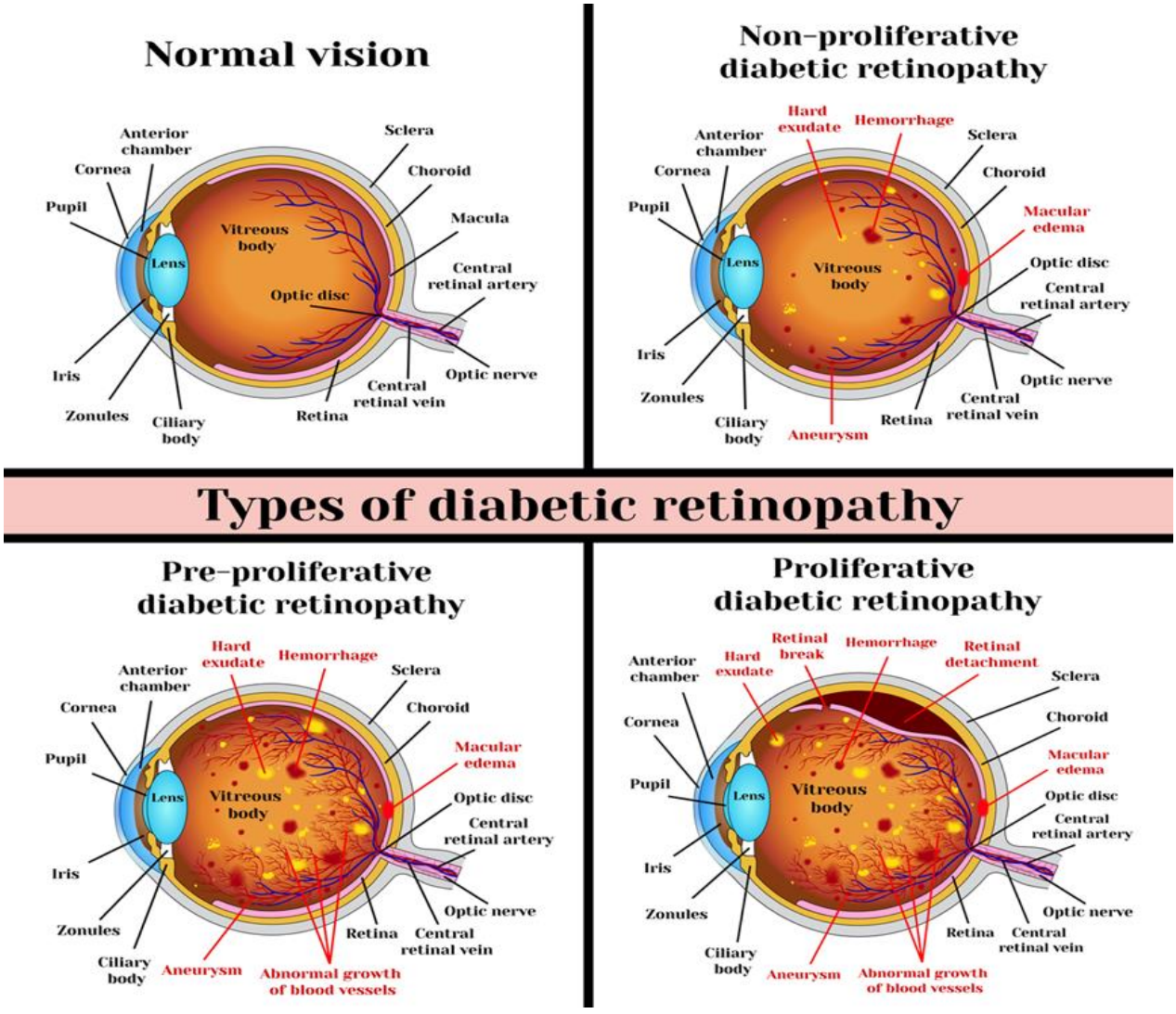
Diabetic retinopathy

Retinopathy is a general term referring to any damage or disease that affects the retina, which is the light-sensitive tissue located at the back of the eye. The retina plays a critical role in vision, as it converts light rays into electrical signals that are sent to the brain through the optic nerve. When the retina is damaged or diseased, it can lead to vision problems or even blindness.

Retinopathy means that disease has damaged the retina. The retina is the part inside the eye that senses light. Different diseases can cause retinopathy. There can be partial or complete loss of vision. Retinopathy can develop slowly or suddenly, can get better on its own or lead to permanent damage. The retina contains many blood vessels. Abnormalities in these vessels are a major cause of retinopathy.



Normal vs diabetic retina



Types of diabetic retinopathy

- **Diabetic retinopathy**

Diabetic retinopathy develops in people with type 1 or type 2 diabetes. It takes years to develop. Two kinds of diabetic retinopathy have the potential to diminish vision:

- In nonproliferative retinopathy, blood vessels in the retina deteriorate. Deteriorating blood vessels can become blocked or deformed. Fluids, fats and proteins leak out of the abnormal blood vessels. Fluid can collect in the retina. This swelling impairs sharp vision.
- In proliferative retinopathy, new, structurally unstable blood vessels grow on the surface of the retina. These unstable blood vessels cause frequent minor bleeding. The bleeding causes local irritation and scarring.
- Proliferative retinopathy can cause retinal detachment. This is a separation of the layers of the retina. It is one of the most serious consequences of proliferative retinopathy.

- **Hypertensive retinopathy**

Hypertensive retinopathy occurs in people who have high blood pressure. High blood pressure causes blood vessel abnormalities. Abnormalities may include thickening of the small arteries, blockages of retinal blood vessels and bleeding from them. Sudden, severe high blood pressure may cause swelling of the optic nerve People with this disease frequently have no symptoms in the early stages.

Central serous retinopathy begins for reasons that are not well understood. In this condition, fluid accumulates in the membrane behind the retina. The fluid seeps in between layers of the retina and causes them to separate. This results in blurred vision or poor night vision.

MAJOR RISK FACTOR FOR DIABETIC RETINOPATHY:

The risk factors of DR can be broadly divided into modifiable and non-modifiable factors. The modifiable risk factors include hyperglycaemia, hypertension, hyperlipidemia and obesity. In contrast, duration of diabetes, puberty and pregnancy are the non-modifiable risk factors for DR development and progression.

- **Hyperglycaemia**

The Diabetes Control and Complications Trial (DCCT) and UKPDS were the two landmark clinical trials that showed tight glycaemic control [HbA1c value of 7% or less] could reduce the risk of DR development and progression in T1DM and T2DM patients, respectively. In DCCT for T1DM, intensive treatment (median HbA1c of 7.2%) reduced the DR incidence (2+ETDRS steps) and progression (3+ ETDRS steps) by 76%

(95%CI 62–85%) and 54% (95%CI 39–66%), respectively, as compared with conventional treatment(median HbA1c of 9.1%). It is suggested that early glycaemia normalization can halt hyperglycaemia-induced pathological processes associated with enhanced oxidative stress and glycation of cellular proteins and lipids. In the Action to Control Cardiovascular Risk in Diabetes Eye study, intensive control of HbA1c (median of 6.4%) decreased the progression of DR from 10.4% to 7.3% over 4 years. However, the results may carry limited clinical relevance as the author defined progression of DR as 3+ ETDRS steps on a 17-point scale, and this finding was only applicable to those with mild retinopathy.

- **Hypertension**

In spite of several epidemiologic studies not finding blood pressure to be a consistent risk factor for DR incidence and progression, multiple randomized controlled trials (RCTs) have demonstrated the bene-fits of tight blood pressure (BP) control as a major modifiable factor for DR incidence and progression. The UKPDS was the first RCT that showed the importance of tight BP control in reducing retinopathy. A total of 1048 hypertensive T2DM patients were randomized into intensive BP control (target systolic/diastolic BP: <150/85 mmHg) versus conventional control group (target BP: <180/<105 mmHg). After 9 years of follow-up, patients with tight BP control had a reduction of risk in DR progression by 34% (99%CI 11–50) and visual acuity deterioration by 47% (99%CI 7–70). It has been shown that every 10 mmHg increase in systolic blood pressure was associated with 10% increased risk of early DR and 15% risk of PDR or DME. On the other hand, anti-hypertensive medications that target the renin–angiotensin system, including angiotensin II receptor antagonists (Candesartan and Losartan) and angiotensin-converting-enzyme inhibitor (Enalapril), may have additional benefit in slowing DR progression, independent of their hypotensive properties.

- **Hyperlipidemia**

Various studies have reported inconsistent results on the effect of lipid on the development and progression of DR and DME. DCCT showed that the severity of DR correlated positively with increasing triglycerides and inversely with high-density lipoprotein (HDL) in T1DM. However, there was no association between total cholesterol and DR shown in the Multi-Ethnic Study of Atherosclerosis (MESA) and the Chennai Urban Rural Epidemiology Study (CURES) Eye Study. Of the subset in the lipid panel, triglycerides were shown to be related to the presence of DR and the low-density lipoprotein was related to DME. In Sankara Nethralaya-Diabetic Retinopathy Epidemiology and Molecular Genetic Study (SN-DREAMS), high serum low-density lipoprotein, high non-high density lipoprotein cholesterol and high cholesterol ratio were related to DME..

Prevention of retinopathy

Prevention of retinopathy involves managing risk factors, maintaining a healthy lifestyle, and adhering to regular eye examinations. While it may not be possible to prevent retinopathy completely, especially in cases where there's a strong genetic predisposition, taking steps to minimize risk factors can help slow down the progression of the disease and reduce the severity of its consequences. Here are some strategies for preventing or delaying the onset of retinopathy:

1. Control underlying conditions: Managing underlying health conditions, such as diabetes and hypertension, is crucial in preventing retinopathy. This involves maintaining blood sugar, blood pressure, and cholesterol levels within the recommended target range.

2. Regular eye examinations: Regular eye exams, particularly for those at a higher risk of developing retinopathy, can lead to early detection and timely intervention, preventing or delaying the progression of the disease. The recommended frequency of eye exams may vary depending on individual risk factors and the advice of your eye care professional.

3. Maintain a healthy diet: Consuming a balanced diet rich in fruits, vegetables, whole grains, lean proteins, and healthy fats can help manage blood sugar and blood pressure levels, reducing the risk of retinopathy. Foods rich in antioxidants, vitamins A, C, and E, and omega-3 fatty acids can also promote eye health.

4. Exercise regularly: Engaging in regular physical activity can help control blood sugar, blood pressure, and cholesterol levels, thereby reducing the risk of retinopathy. Aim for at least 150 minutes of moderate-intensity aerobic exercise or 75 minutes of vigorous-intensity aerobic exercise per week, combined with muscle-strengthening activities on two or more days per week.

5. Maintain a healthy weight: Achieving and maintaining a healthy weight can help prevent or manage conditions like diabetes and hypertension, which are risk factors for retinopathy.

6. Quit smoking: Smoking can increase the risk of retinopathy and other eye diseases, as well as exacerbate underlying conditions like diabetes. Quitting smoking can significantly reduce the risk of developing retinopathy.

7. Limit alcohol consumption: Excessive alcohol consumption can contribute to high blood pressure and poor blood sugar control, both of which are risk factors for retinopathy. Limiting alcohol intake can help maintain

overall health and reduce the risk of retinopathy.

8. Manage stress: Chronic stress can negatively impact blood pressure and blood sugar levels, increasing the risk of retinopathy. Employing stress management techniques such as deep breathing, meditation, yoga, or engaging in hobbies can help maintain overall well-being and reduce the risk of retinopathy.
9. Monitor blood sugar during pregnancy: Pregnant women with diabetes or gestational diabetes should closely monitor and manage their blood sugar levels to reduce the risk of developing retinopathy or worsening existing retinopathy.

By following these preventive measures, you can significantly reduce the risk of developing retinopathy or delay its progression. Remember to consult with your healthcare provider or eye care professional for personalized recommendations based on your individual risk factors and health status.

Treatment Options for Retinopathy	Description
Laser treatment	Laser treatment, such as focal laser photocoagulation or panretinal photocoagulation, is commonly used to treat diabetic retinopathy. It involves using laser beams to seal leaking blood vessels or shrink abnormal blood vessels in the retina.
Anti-VEGF injections	Intravitreal injections of anti-VEGF (vascular endothelial growth factor) medications, such as ranibizumab, aflibercept, or bevacizumab, can be administered to reduce abnormal blood vessel growth and leakage in the retina. These injections are typically given in a series of treatments.
Vitrectomy	Vitrectomy is a surgical procedure that involves removing the gel-like substance (vitreous) from the middle of the eye to treat severe cases of diabetic retinopathy or complications like vitreous hemorrhage or retinal detachment. It may also involve removing scar tissue or performing additional repairs to the retina.

Steroid injections	Intravitreal injections of steroids, such as triamcinolone acetonide, may be used to reduce inflammation and swelling in the retina associated with diabetic macular edema (DME). These injections may be performed as a standalone treatment or in combination with other therapies.
Oral medications	In certain cases, oral medications like corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs) may be prescribed to manage inflammation and edema in the retina. These medications are typically used for diabetic macular edema (DME) treatment.
Blood sugar control	Maintaining good blood sugar control is essential in managing diabetic retinopathy. Consistently managing blood glucose levels through medication, diet, and lifestyle modifications can slow the progression of retinopathy and reduce the risk of complications.
Blood pressure control	Keeping blood pressure within a healthy range is crucial for managing retinopathy. Controlling high blood pressure helps preserve the health of blood vessels in the eyes and reduces the risk of worsening retinal damage.
Regular eye exams	Regular eye exams, including dilated retinal examinations, are important for detecting and monitoring retinopathy. Early detection allows for timely intervention and treatment, which can help prevent further vision loss.
Healthy lifestyle habits	Adopting a healthy lifestyle, including maintaining a balanced diet, engaging in regular physical activity, avoiding smoking, and managing other health conditions (such as cholesterol and kidney problems), can support overall eye health and slow the progression of retinopathy.
Retinal implants	For individuals with advanced retinopathy and severe vision loss, retinal implants may be an option. These devices are surgically implanted in the eye to bypass damaged photoreceptor cells and directly stimulate the remaining healthy retinal cells, allowing for some degree of vision restoration.
Corticosteroid	Intravitreal implants that slowly release corticosteroids, such as dexamethasone,

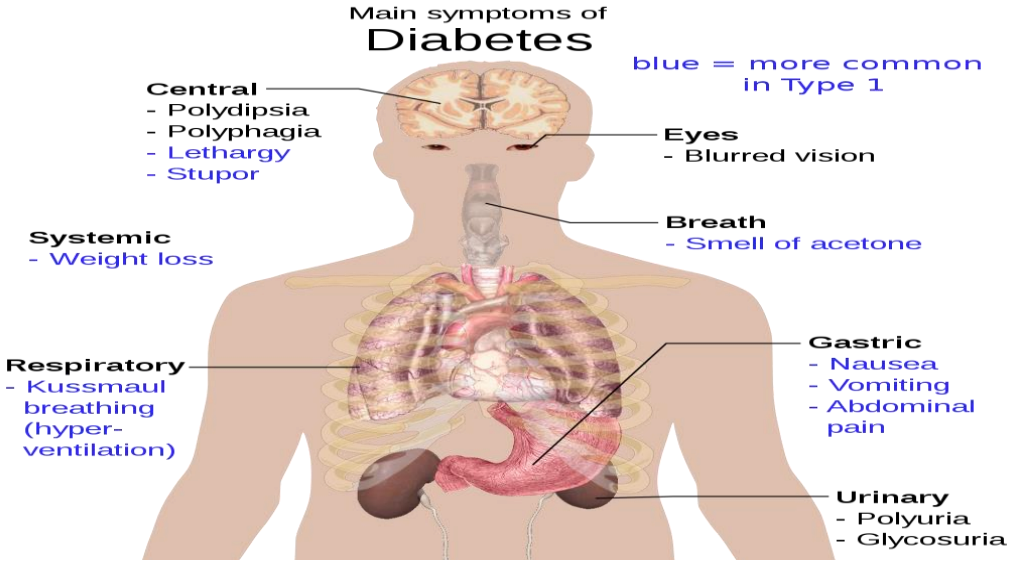
implants	can be used to treat diabetic macular edema (DME) by reducing inflammation and fluid buildup in the retina. These implants provide sustained drug delivery over an extended period.
Low vision aids	Low vision aids, such as magnifiers, telescopic lenses, or electronic visual aids, can help individuals with advanced retinopathy make the most of their remaining vision. These aids can enhance visual function and improve daily activities and quality of life.
Supportive therapies	Additional supportive therapies, such as nutritional supplements (e.g., omega-3 fatty acids, antioxidants), may be recommended to support retinal health and potentially slow the progression of retinopathy. These should be used under the guidance of a healthcare professional.
Patient education and self-care	Education about diabetes management, regular eye care, and self-care measures, such as maintaining healthy blood sugar levels, blood pressure control, and lifestyle modifications, is vital. Empowering patients with knowledge and encouraging adherence to self-care practices can help manage retinopathy effectively.
Management of comorbidities	Managing other comorbid conditions, such as hypertension, dyslipidemia, and kidney disease, is essential for overall health and the management of retinopathy. Collaborative care between different healthcare providers may be necessary to optimize treatment outcomes.
Ongoing monitoring and follow-up	Regular monitoring and follow-up appointments with an eye care specialist are crucial to track the progression of retinopathy, assess treatment efficacy, and make any necessary adjustments to the treatment plan. This ensures that the condition is effectively managed over time.

Treatment Options for Retinopathy

DIABETES

Diabetes mellitus refers to a group of diseases which affect the body blood by sugar i.e., glucose. Glucose plays a vital role for health because it is an important source of energy for the cells that make up the muscles and tissues. Glucose is the main source of fuel for brain.

Diabetes mellitus is a group of metabolic diseases having high blood sugar levels for prolonged periods. This high blood sugar level produces the symptoms of frequent urination, increased thirst and hunger. This may lead to many complications if not treated timely. Acute complications include diabetic ketoacidosis and nonketotic hyperosmolar coma. Severe long-term complications include heart disease, stroke, kidney failure, foot ulcers and damage to the eyes. Diabetes is due to either the pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced.



Symptoms of diabetes

Types of Diabetes

There are two types of Diabetes.

1. Type 1 Diabetes.
2. Type 2 Diabetes

Diabetes is a group of metabolic disorders characterized by high blood sugar levels over a prolonged period. It occurs when the body cannot effectively produce or use insulin, a hormone that regulates blood sugar. There

are two main types of diabetes:

1. Type 1 diabetes: Also known as juvenile diabetes or insulin-dependent diabetes, it is an autoimmune disease where the body's immune system attacks and destroys the insulin-producing beta cells in the pancreas. As a result, the pancreas produces little or no insulin. Type 1 diabetes typically develops in children and young adults, but it can occur at any age. People with this type of diabetes need to take insulin injections or use an insulin pump to manage their blood sugar levels.

2. Type 2 diabetes: This is the most common form of diabetes, accounting for around 90-95% of all cases. Type 2 diabetes occurs when the body develops insulin resistance, meaning that the cells do not respond effectively to insulin, or the pancreas does not produce enough insulin. This type of diabetes is often associated with obesity, physical inactivity, and genetic factors. It usually develops in adults, but it can also occur in children and adolescents due to increasing rates of childhood obesity.

Other forms of diabetes include gestational diabetes, which occurs during pregnancy and usually resolves after childbirth, and several rarer types caused by genetic mutations, diseases of the pancreas, or drug-induced conditions.

Common symptoms of diabetes include increased thirst, frequent urination, uned weight loss, fatigue, blurred vision, and slow-healing wounds. If left untreated, diabetes can lead to serious complications, such as heart disease, stroke, kidney failure, blindness, and nerve damage. Management of diabetes generally involves monitoring blood sugar levels, adopting a healthy diet, engaging in regular physical activity, and taking medications or insulin as needed.

Prevention Strategies for Diabetes	Description
Maintain a healthy weight	Achieve and sustain a healthy weight to reduce the risk of diabetes.
Follow a healthy diet	Consume a balanced diet low in saturated and trans fats, sugar, and refined carbohydrates.
Engage in regular physical activity	Aim for at least 150 minutes of moderate-intensity aerobic activity or 75 minutes of vigorous activity per week, along with strength training exercises twice a week.
Avoid sedentary behavior	Limit prolonged sitting and incorporate physical activity throughout the day.
Maintain a healthy blood pressure	Adopt a low-sodium diet, engage in regular exercise, practice stress management techniques, and, if necessary, take medication to control blood pressure.
Limit alcohol consumption	If you choose to drink alcohol, do so in moderation. Women: up to one drink per day; Men: up to two drinks per day.
Avoid smoking	Quit smoking, as it is strongly linked to an increased risk of diabetes and other health problems.
Get regular check-ups	Regular medical check-ups help with early detection of prediabetes or diabetes. Follow your healthcare provider's advice on screening tests and management.
Manage stress	High levels of stress can contribute to unhealthy lifestyle habits. Practice stress management techniques such as exercise, relaxation techniques, hobbies, and seeking support from loved ones.
Get enough sleep	Aim for 7-8 hours of quality sleep each night. Poor sleep patterns and inadequate sleep have been associated with an increased risk of diabetes.

Stay hydrated	Drink an adequate amount of water throughout the day to maintain hydration and support overall health. Limit the consumption of sugary beverages.
Limit processed and sugary foods	Processed foods and those high in added sugars contribute to weight gain and an increased risk of diabetes. Opt for whole, unprocessed foods whenever possible.
Monitor your blood sugar levels	If you have prediabetes or a family history of diabetes, monitor your blood sugar levels regularly. This can help identify any changes and allow for early intervention.
Educate yourself and stay informed	Stay updated on the latest research, guidelines, and recommendations for diabetes prevention. Education empowers you to make informed decisions about your health.
Encourage a supportive environment	Surround yourself with a supportive network of friends and family who can help you maintain a healthy lifestyle and provide encouragement along the way.
Stay consistent with healthy habits	Consistency is key. Make healthy eating, regular exercise, and other preventive measures a lifelong commitment rather than a temporary fix.
Get support from healthcare professionals	Consult with healthcare professionals, such as doctors, dietitians, and diabetes educators, who can provide personalized guidance, monitoring, and support in your diabetes prevention journey.
Set realistic goals and track progress	Establish realistic goals for your lifestyle changes and track your progress. This can help keep you motivated and provide a sense of accomplishment as you work towards preventing diabetes.
Involve family and friends	Engage your family and friends in your diabetes prevention efforts. Encourage them to adopt healthy habits with you, as it can create a supportive environment and make lifestyle changes easier.
Be mindful of portion	Practice portion control and mindful eating. Pay attention to portion sizes and

sizes	listen to your body's hunger and fullness cues. This can help maintain a healthy weight and prevent overeating.
Limit processed meat consumption	Reduce your intake of processed meats such as sausages, hot dogs, and deli meats. These foods have been linked to an increased risk of diabetes.
Consider diabetes prevention programs	Explore diabetes prevention programs available in your community or online. These programs often provide education, support, and resources to help individuals make sustainable lifestyle changes.
Monitor blood pressure and cholesterol	Regularly check your blood pressure and cholesterol levels. High blood pressure and abnormal cholesterol levels can increase the risk of diabetes.
Stay motivated and stay positive	Maintaining a positive mindset and staying motivated is crucial for long-term success. Celebrate your achievements, focus on the benefits of a healthy lifestyle, and seek support during challenging times.

Prevention Strategies for Diabetes

Treatment of Diabetes Mellitus

The treatment is to overcome the precipitating cause and to give high doses of regular insulin. The insulin requirement comes back to normal once the condition has been controlled [65] the aims of management of diabetes mellitus can be achieved by:

1. To restore the disturbed metabolism of the diabetic as nearly to normal as is consistent with comfort and safety.
2. To prevent or delay progression of the short and long term hazards of the disease.
3. To provide the patient with knowledge, motivation and means to undertake this own enlightened care..

Noval drug in delivery

Management strategies for treatment of diabetes mellitus

1. Type 1 diabetes is undeviatingly treated with insulin and some diet control is required.
2. Type 2 diabetes is often linked with obesity. It is basically a disease of insulin resistance. which is commonly treated with oral hypoglycemic agents. Though insulin is not required initially, but administration of insulin may be needed sometimes because of a decrease in the insulin secretion.

Insulin Therapy

More than 60,000 insulin injections are taken by the patients throughout their life[9]. In type 1 diabetes, good glycemic control usually requires at least two or more often three or more daily insulin injections. Such invasive and rigorous technique urges the search for alternative more pleasant methods for administering insulin [10]. The conventional and most anticipated method for the insulin administration is by subcutaneous injections.

The various problems associated with the subcutaneous method of insulin delivery:

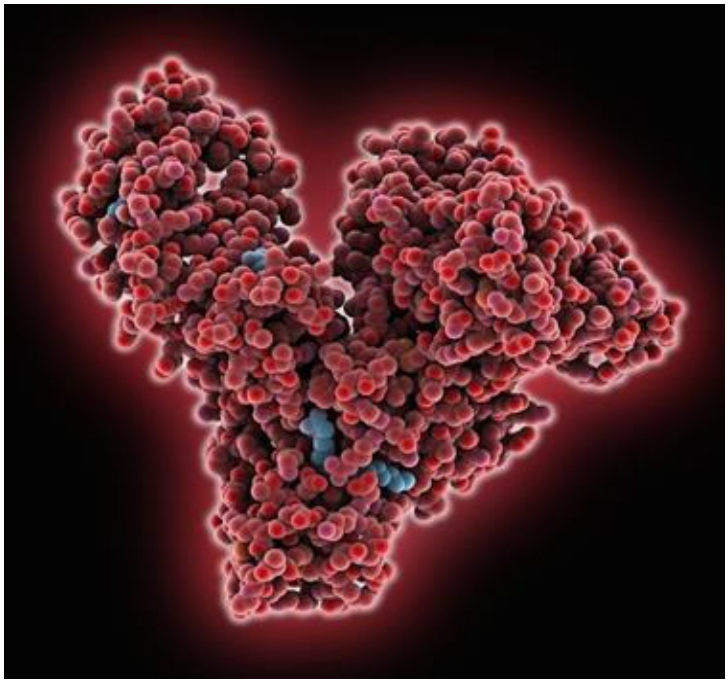
- Local pain
- Inconvenience of multiple injections, especially for those requiring multiple dose injections of four times a day.
- Occasional hypoglycemia as a consequence of an overdose, itching, allergy, hyperinsulinemia and insulin lipodystrophy around the injection site.

Clinical trials data reveal that many patients cannot achieve long lasting glycemic control because of non-compliance . Also, there have been reports of hypoglycemic episodes following multi dose injections of insulin

To overcome the disadvantages of traditional method numerous new approaches have been developed to decrease the suffering of the diabetic patients, which includes the use of supersonic injector, infusion pump, sharp needles and pens. Some of these techniques reduced the pain encountered by the diabetic patients, but they offer incomplete convenience. New concepts are presently investigated to deliver insulin using oral, pulmonary, nasal, ocular and rectal routes, but the eventual goal would be to eradicate the need to deliver insulin exogenously and regaining the ability of patients to produce and use own insulin. The success of the route of administration is judged on the basis of its ability to elicit effective and predictable lowering of blood glucose level and therefore minimizing the risk of diabetic complications. It is clear that several difficulties have to overcome with the use of formulation and application device's technology. The various explored routes and other techniques of insulin delivery are discussed as under.

ALBUMINURIA

Albumin is a **family of globular proteins** that are commonly found in **blood plasma** and differ from other blood proteins in that they are not glycosylated. Albumin is the **most common protein** found in blood plasma and it helps to ensure blood stays in arteries and veins, and helps carry hormones, vitamins, and enzymes throughout the body. Albumin is made in the **liver** and quickly carried to the bloodstream. Albumin levels in the blood can be measured by a blood test and can indicate various health conditions.



Albumin

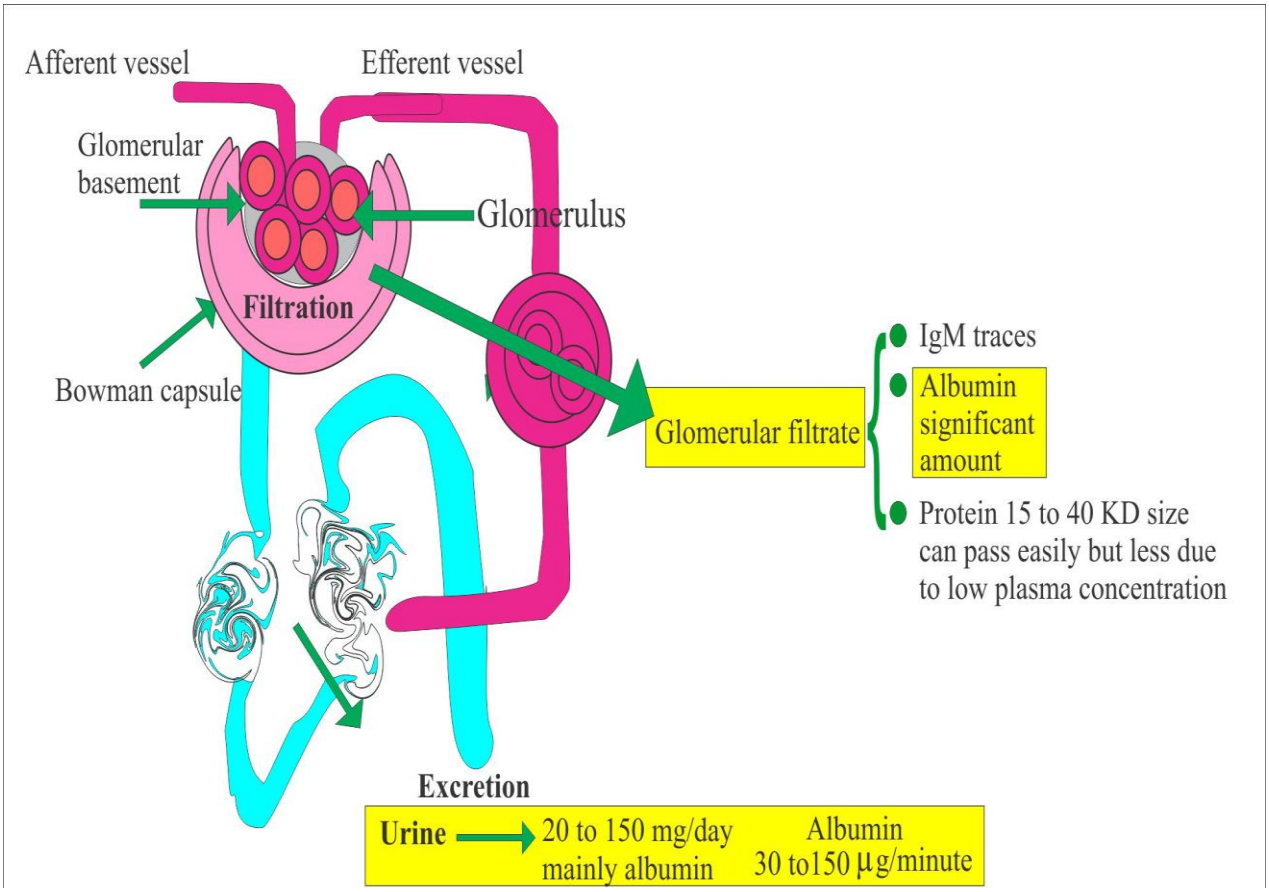
- Albumin is used to **treat blood volume loss** resulting from trauma such as a severe burns or an injury that causes blood loss. It works by replacing the body fluids lost due to excessive trauma, bleeding, surgery, or kidney dialysis.
- Albumin is used to **treat low albumin levels** caused by surgery, dialysis, abdominal infections, liver failure, pancreatitis, respiratory distress, bypass surgery, ovarian problems caused by fertility drugs, and other many other conditions.
- Albumin is used as a **drug delivery** agent that carries certain drugs through the bloodstream. These include methadone, propranolol, thiopental, furosemide, warfarin, methotrexate, and many others.

MICROALBUMINURIA

Microalbuminuria is a condition where a small amount of a protein called albumin is present in the urine. It can be a sign of kidney damage, especially in people with diabetes or high blood pressure.

Some of the symptoms of microalbuminuria are :

- Foamy urine
- Swelling of the skin, ankles, hands, tummy or face



Albumin excretion

Causes :

Microalbuminuria is caused by kidney damage. Some of the medical conditions that can lead to kidney damage and microalbuminuria are:

- Diabetes
- High blood pressure
- Obesity
- Metabolic syndrome
- Polycystic kidney disease
- Chronic kidney disease

These conditions can affect the glomerular filtration system of the nephron, which is responsible for filtering out proteins like albumin from the urine. When the glomerular filtration barrier is damaged, albumin can leak into the urine and cause microalbuminuria.

Treatment Of Microalbuminuria With Nutraceuticals

Nutraceuticals are food-based substances that are used for the prevention and treatment of diseases. They may have beneficial effects on health and wellness by providing nutrients, antioxidants, anti-inflammatory agents, or other bioactive compounds. Nutraceuticals are not regulated by the FDA, but by the FTC, which means they do not need to prove their safety and efficacy before marketing.

There is limited evidence on how nutraceuticals can help in the treatment of microalbuminuria, which is a condition where there is a small amount of albumin (a type of protein) in the urine, indicating early kidney damage. It is a common complication of diabetes, especially type 2 diabetes, and can lead to diabetic nephropathy (kidney disease) if left untreated.

Some studies have suggested that certain nutraceuticals may have a protective effect on the kidneys and reduce albumin excretion in people with diabetes and microalbuminuria. These include:

- **Omega-3 fatty acids:** These are polyunsaturated fats that are found in fish oil, flaxseed oil, walnuts, and some other foods. They may have anti-inflammatory and anti-oxidant properties that can improve blood flow to the kidneys and prevent kidney damage.
- **Curcumin:** This is a yellow pigment that is derived from turmeric, a spice used in Asian cuisine. It may have anti-inflammatory, anti-oxidant, and anti-fibrotic effects that can modulate the expression of genes involved in kidney injury and inflammation.

- **Resveratrol**: This is a polyphenol that is found in red wine, grapes, berries, peanuts, and some other foods. It may have anti-inflammatory, anti-oxidant, and anti-diabetic effects that can improve insulin sensitivity, glucose metabolism, and endothelial function.
- **Vitamin D:** This is a fat-soluble vitamin that is synthesized by the skin when exposed to sunlight or obtained from food or supplements. It may have anti-inflammatory and immunomodulatory effects that can regulate the renin-angiotensin system, which is involved in blood pressure regulation and kidney function.

When albuminuria occurs, it can indicate a problem with the kidneys' filtering system or damage to the glomeruli, the tiny filtering units in the kidneys. It can be classified into three categories based on the amount of albumin present in the urine:

1. Microalbuminuria: This is a mild increase in albumin levels in the urine, typically ranging between 30 to 300 mg per 24 hours.
2. Macroalbuminuria: A more significant increase in albumin levels in the urine, usually above 300 mg per 24 hours.
3. Persistent albuminuria: When albuminuria is consistently present over an extended period, usually three or more months.

Medications for albuminuria:

(a.) Angiotensin-converting enzyme (ACE) inhibitors: These medications help to lower blood pressure and reduce the pressure inside the glomeruli, thereby reducing proteinuria and protecting kidney function.

(b.) Angiotensin II receptor blockers (ARBs): Similar to ACE inhibitors, ARBs lower blood pressure and reduce pressure within the glomeruli, helping to decrease proteinuria and preserve kidney function.

(c.) Diuretics: These medications help to remove excess fluid from the body, reducing swelling (edema) and lowering blood pressure.

1. Lifestyle modifications:

(a.) Diet: Adopting a healthy diet that is low in sodium, saturated fats, and refined sugars can help manage blood pressure, blood sugar levels, and cholesterol. In some cases, a healthcare provider may recommend a low-protein diet to reduce the workload on the kidneys.

(b.) Exercise: Engaging in regular physical activity can help manage blood pressure, blood sugar levels, and body weight, all of which can impact kidney health.

(c.) Smoking cessation: Smoking can exacerbate kidney damage and increase the risk of cardiovascular disease. Quitting smoking is an important step in preserving kidney function and overall health.

(d.) Weight management: Maintaining a healthy body weight can help reduce the risk of diabetes, hypertension, and other conditions that can contribute to albuminuria.

2. Monitoring and follow-up: Regular follow-up visits with a healthcare provider are important for patients with albuminuria to monitor kidney function, assess the effectiveness of treatment, and adjust medications or interventions as needed. This may involve periodic urine and blood tests, blood pressure monitoring, and imaging studies.

3. Advanced treatments: In severe cases of kidney damage or when kidney function is significantly compromised, more advanced treatments may be necessary, such as:

(a.) Dialysis: This treatment involves using a machine to filter waste and excess fluid from the blood when the kidneys are no longer able to do so effectively.

(b.) Kidney transplantation: In cases of end-stage renal disease, a kidney transplant may be considered. This involves replacing the damaged kidney with a healthy donor kidney.

SUMMARY

The retina, a delicate and intricate neural tissue located at the back of the eye, is responsible for converting light into electrical signals that are transmitted to the brain, enabling vision. However, the retina is susceptible to damage and dysfunction, particularly in individuals with diabetes. This thesis explores the anatomy and physiology of the retina, focusing on the development of retinopathy in association with diabetes, and examines the potential role of albuminuria and microalbuminuria as indicators or predictors of retinopathy.

The retina is composed of several layers, each serving a distinct function in visual processing. Photoreceptor cells, namely rods and cones, capture light and initiate the visual signal cascade. Bipolar cells transmit these signals to ganglion cells, whose axons form the optic nerve, connecting the retina to the brain. Specialized cells, such as the retinal pigment epithelium (RPE), provide vital support and nourishment to the retinal layers. Understanding the structure and function of these components is crucial to comprehending retinopathy development.

Diabetes, a chronic metabolic disorder characterized by hyperglycemia, poses a significant risk to retinal health. Prolonged exposure to elevated blood glucose levels damages the blood vessels supplying the retina, leading to retinopathy. The disease progresses through various stages, including mild non-proliferative retinopathy, moderate to severe non-proliferative retinopathy, and advanced proliferative retinopathy. The mechanisms underlying retinopathy involve microvascular alterations, increased vascular permeability, inflammation, and oxidative stress, ultimately leading to retinal cell death and impaired vision.

Albuminuria, the presence of excess albumin in urine, is an established marker of kidney damage in diabetes. Recent research has suggested a potential association between albuminuria and retinopathy, indicating that the pathophysiological processes leading to microvascular damage in the kidneys and the retina may share common underlying mechanisms. Microalbuminuria, characterized by a slight elevation in urine albumin levels, may serve as an early indicator of renal and retinal dysfunction, providing an opportunity for early intervention to prevent or delay the onset of retinopathy.

Understanding the intricate relationship between the retina, diabetes, albuminuria, and microalbuminuria has significant clinical implications. Healthcare professionals can utilize this knowledge to enhance screening strategies for retinopathy in diabetic patients, particularly those with albuminuria or microalbuminuria. Additionally, the identification of common pathways and risk factors can aid in the development of targeted interventions and therapies to prevent or manage retinopathy and associated complications effectively.

This thesis delves into the anatomy and physiology of the retina, exploring its vulnerability to damage in the presence of diabetes. By investigating the association between retinopathy, diabetes, albuminuria, and microalbuminuria, this research sheds light on the intricate interplay among these factors. The findings have important implications for healthcare professionals, enabling them to optimize patient care, enhance disease management strategies, and minimize the visual impairment burden faced by individuals with diabetes. Continued research in this area is essential to further elucidate the mechanisms of retinopathy development and identify novel therapeutic approaches to combat this vision-threatening complication.

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