Section A-Research paper

"A Comprehensive Review of Treatment Strategies for Microvascular Complications in Diabetes"

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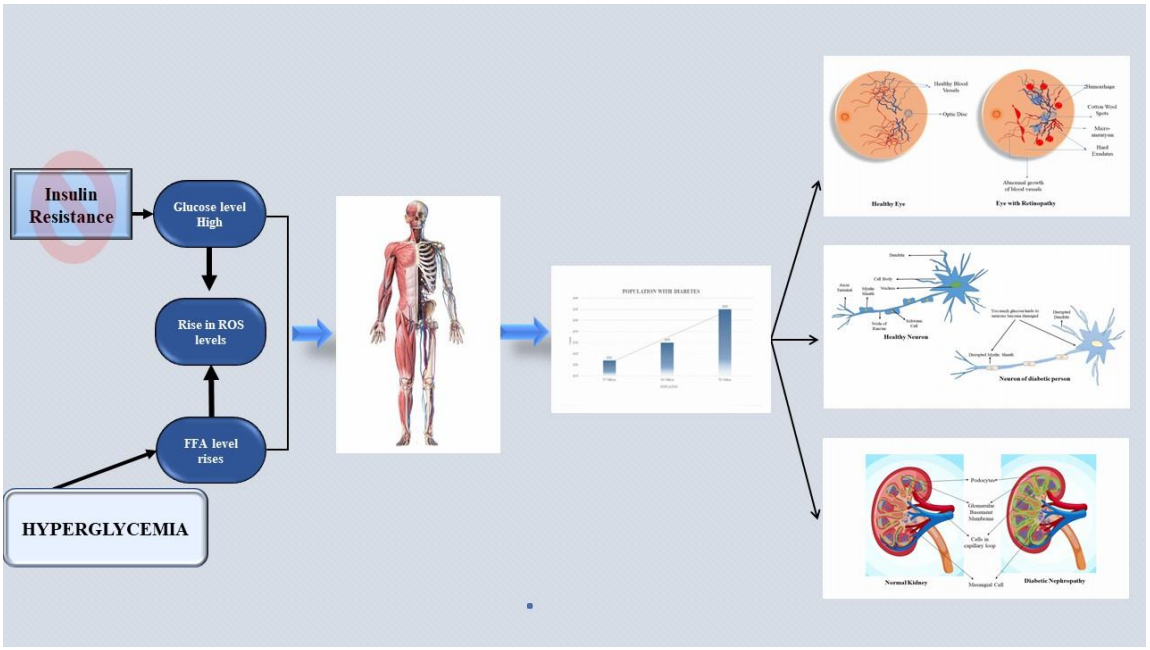
Highlights:

- The review discusses the global occurrence and pathophysiology of diabetes, providing a foundation for understanding microvascular complications.
- It explores the role of nanotechnology in managing microvascular complications, highlighting its potential for targeted therapies.
- Pharmacological and non-pharmacological treatment options for the management of microvascular complications are examined, offering insights into diverse approaches.
- The significance of biomarkers in diagnosing and monitoring diabetic complications is emphasized.

Graphical Abstract:



Section A-Research paper

Abstract:

Diabetes Mellitus is a persistent metabolic disorder marked by the presence of hyperglycemia arising from impairments in insulin secretion, insulin activity, or both. It is projected to pose a significant global health burden, with an estimated worldwide affected adult population of approximately 537 million by the end of year 2023. It is associated with several serious complications, including microvascular complications (retinopathy, nephropathy, and neuropathy) and macrovascular complications (cardiovascular disease, cerebrovascular disease, and peripheral vascular disease). This review provides an overview of the strategies for treatment in microvascular complications associated with Diabetes Mellitus. Neuropathy encompasses various manifestations such as sensory, motor, and autonomic dysfunction, leading to impairments in daily activities and reduced quality of life. Diabetic nephropathy, characterized by glomerular dysfunction and fibrosis, is a leading cause of end-stage renal disease. Retinopathy, involving damage to retinal blood vessels, is a leading cause of blindness in adults. Optimal management of glycemic control, blood pressure, and targeted therapies is crucial for preventing and managing diabetes-related complications. Implementing comprehensive strategies that include glycemic control, risk factor modification, and regular screening is essential in reducing the impact of these complications. Advancements in research and treatment modalities are necessary to enhance outcomes and improve the overall well-being of individuals with Diabetes Mellitus

Keywords: diabetic complications; nephropathy; neuropathy; retinopathy; Biomarker; pathophysiology; non-pharmacological treatments.

1.Introduction

Diabetes mellitus, a chronic metabolic disorder characterized by elevated blood glucose levels, represents a significant global health concern due to its widespread prevalence and the accompanying microvascular complications it entails (1). Insulin, produced by pancreatic beta cells, plays a crucial role in facilitating glucose uptake into cells for energy and exerting various other physiological functions. Insufficient insulin synthesis or reduced insulin sensitivity are the primary underlying causes of diabetes. The disease is categorized into several types, with type 1 and type 2 diabetes mellitus (DM) being the most common. Type 1 DM is characterized by an autoimmune-mediated destruction of pancreatic cells leading to insulin insufficiency, whereas type 2 diabetes is characterized by a progressive decline in insulin secretion and insulin resistance (2).While it is challenging to prevent type 1 diabetes, type 2 diabetes can be mitigated through adopting a healthy lifestyle, regular physical exercise, and maintaining a balanced diet. Early detection of diabetes is of paramount importance in providing effective care (Figure 1). Type 2 diabetes affects a significant portion of the population and gives rise to various complications affecting multiple organs such as the heart, nerves, eyes, kidneys etc. (2).

Diabetes will continue to be a significant contributor to global mortality and disability. By year 2023, it is projected that diabetes will directly cause 1.6 million deaths. The World Health Organization (WHO) predicts that the global adult population affected by diabetes will reach 537 million by end of 2023, with an anticipated increase to 700 million by year 2045 (Figure 2). Furthermore, diabetes will remain a leading cause of blindness, kidney failure, and amputations (3, 4).

Biomarkers represent a class of biological molecules typically detected in tissues, blood, and other bodily fluids. They serve as indicators for normal biological processes, pathological processes, or responses to exposures or interventions. Biomarkers encompass various types, including diagnostic, monitoring, response, predictive, prognostic, and safety markers. The fundamental diagnostic approach for biomarker identification involves extraction, separation, identification, and subsequent verification processes. (5)

In the context of diabetic retinopathy, age, furosine, vascular endothelial growth factor (VEGF) in serum and plasma, and antiplasmin emerge as prominent biomarkers. Elevated levels of these biomarkers suggest the presence of the disease. Conversely, myocardial infarction (MI), glycated hemoglobin (HbA1C), cholesterol levels, thyroid-stimulating hormone (TSH), and low-density lipoprotein (LDL) levels serve as primary biomarkers for diagnosing diabetic neuropathy, with any alterations in their levels utilized for diagnostic purposes (5).

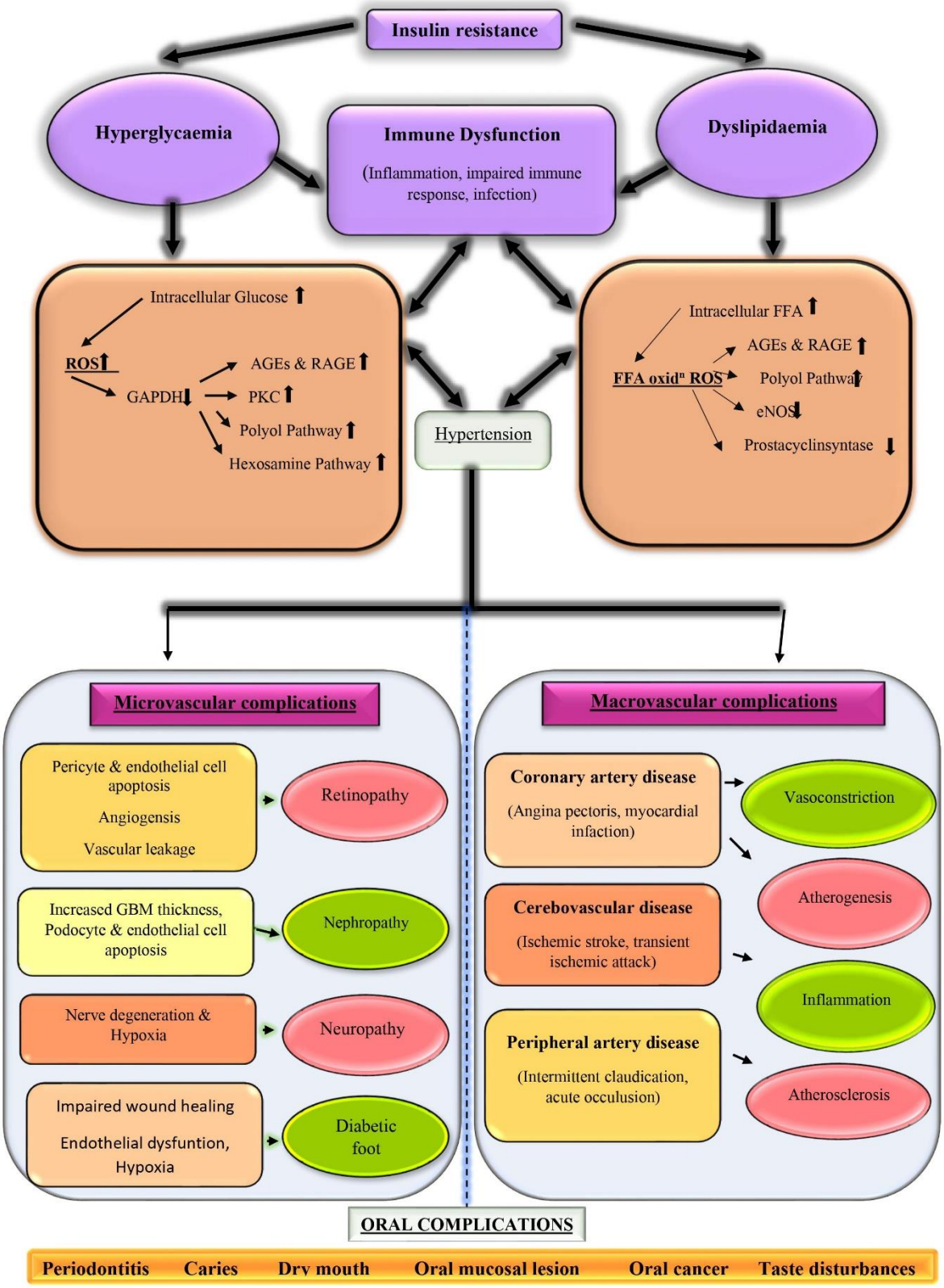


Figure 1: flowchart depicting the inter-relationship between the complications occurring due to diabetic condition.

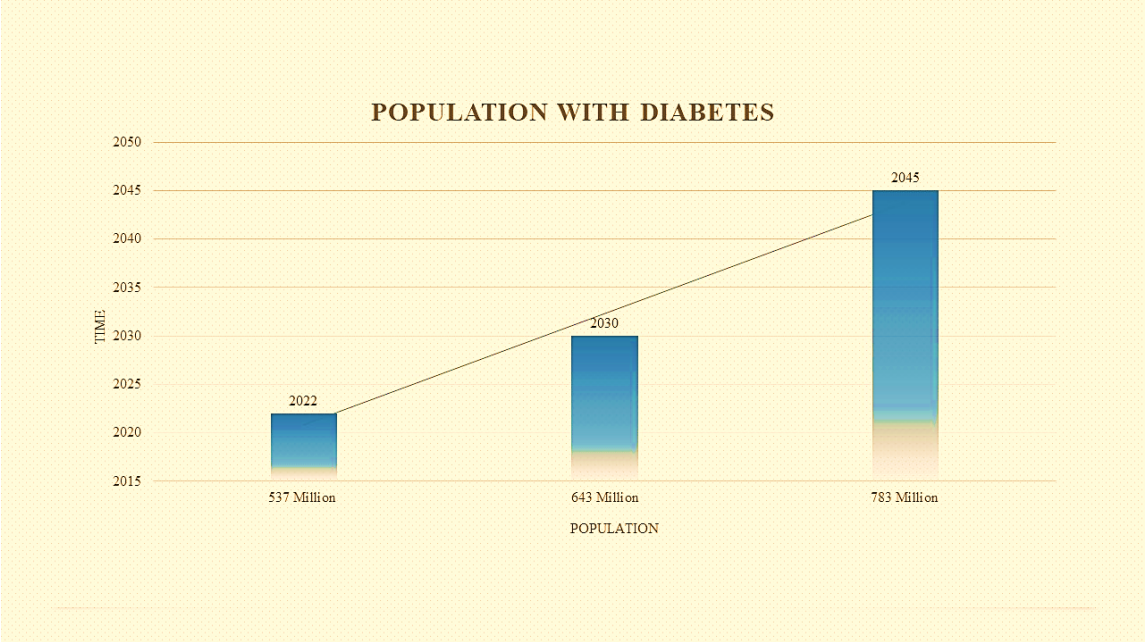


Figure 2: Graphs representing the increasing trend in diabetic population from year 2022-2045

2. Diabetic Retinopathy

Diabetes retinopathy is an eye condition that results in blindness and loss of vision in diabetic patients. DR affects the blood vessel in the retina region (the light-sensitive layer of tissue in the back of the eye) (Figure 3&4). According to the experiment that was conducted in 2019, 25.48% of patients were diagnosed with DR in which 19.08% were having NPDR (non-proliferative diabetic retinopathy), 1.18% PDR (proliferative diabetic retinopathy), 4.94% DME (diabetic macular edema) and 0.35% were having both PDR (proliferative diabetic retinopathy) and DME (diabetic macular edema). In type1 DM patients, DR was diagnosed in 32.47% patient, including NPDR in 24.65%, PDR in 1.6%, DME in 5.40%, and PDR with DME in 0.98% of patients whereas in type 2 DM patients, DR was found in 23 % of cases, including NPDR in 17.22%, PDR in 1.05%, DME in 4.81%, and PDR with DME in 0.15% of cases. NPDR and DME were found significantly more often in type 1 DM patients than in type 2 DM patients. (6,7)

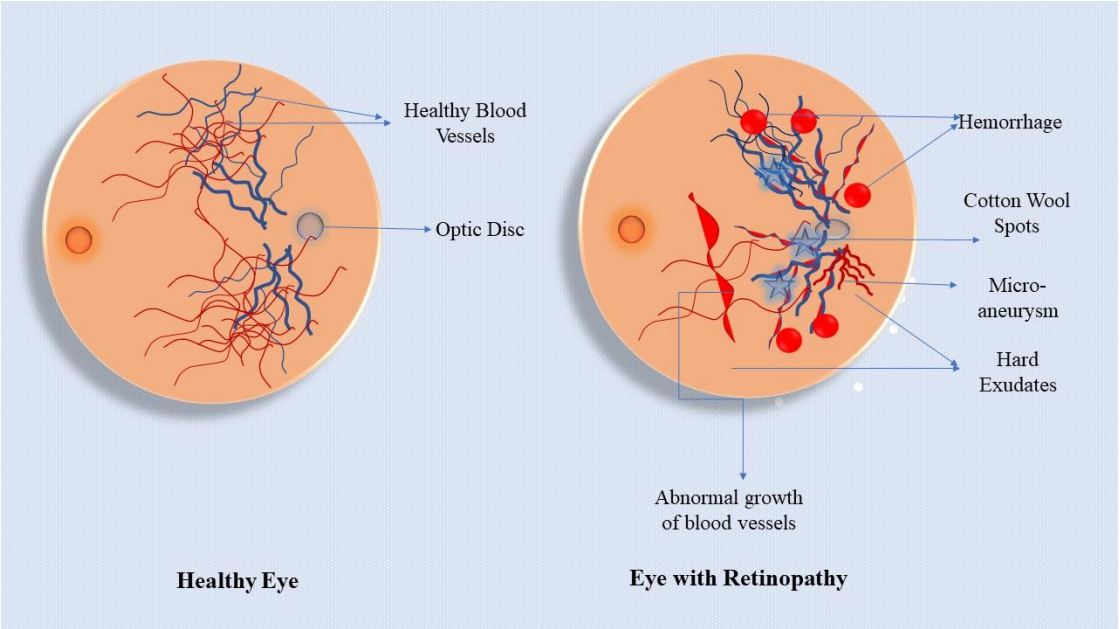


Figure 3: Diagrammatic representation of Healthy eye and eye with diabetic retinopathy

Combination of ranibizumab (Lucentis) and aflibercept (Eylea), anti VEGF therapy and laser therapy are the common conventional therapy for the treatment of diabetic retinopathy. Patient discomfort, continuous exposure to laser and retinal scarring are the drawbacks of these therapies. (8)

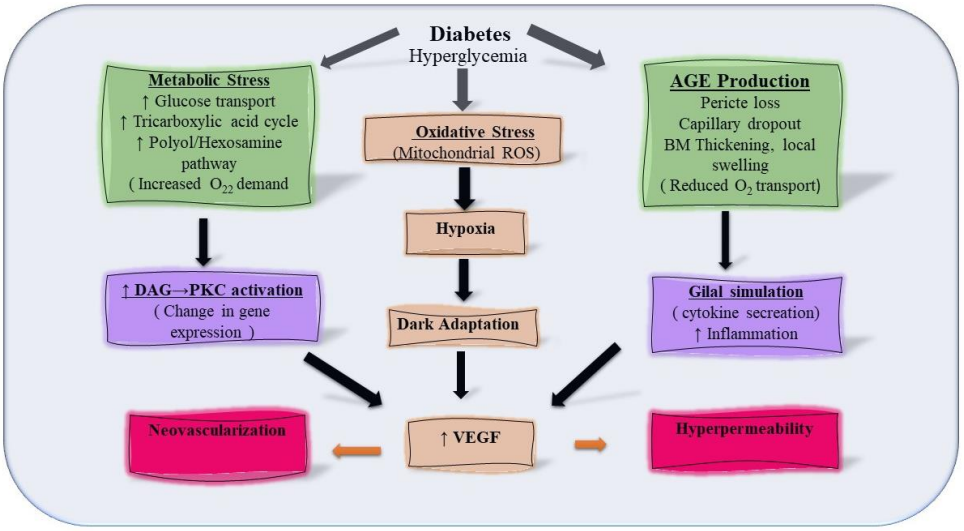


Figure 4: Physiological pathway of diabetic retinopathy

2.1 Non-Pharmacological treatments of Diabetic Retinopathy

2.1.1. Laser therapy (LT)

Laser therapy, also known as Light Amplification by Stimulated Emission of Radiation, is widely utilized across various medical fields, including ophthalmology, for the treatment of retinal vascular diseases such as proliferative diabetic retinopathy (PDR), diabetic macular edema (DME), retinal vein occlusions, central serous chorioretinopathy, choroidal neovascularization, and vascular tumors. Recent advancements in laser technology have significantly improved treatment outcomes by minimizing collateral tissue damage, reducing patient discomfort, and mitigating complications.

In the context of poorly perfused retinal areas, laser photocoagulation is employed to selectively destroy retinal cells. By reducing the retinal oxygen demand (ROD), this approach promotes increased oxygen perfusion. Moreover, it downregulates the production of angiogenic factors and vascular endothelial growth factor (VEGF). Photoreceptor cells in the retina are highly metabolically active and abundant. Targeting a fraction of these photoreceptors through photocoagulation during panretinal photocoagulation (PRP) treatment helps lower VEGF production by the retina, consequently reducing vascular permeability and retinal edema (14,15).

Focal laser is an additional technology employed to target the confined area of macular edema located at the posterior pole of the eye. The development of methodologies for this technology is an ongoing process, and the precise mechanisms are not fully elucidated. It is hypothesized that focal laser treatment may involve the removal of leaking microaneurysms in the retina. This process can potentially lead to improved patient outcomes by stimulating cytokine production, which aids in the reabsorption of fluid in the macular region (16-18).

2.1.2 Vitrectomy

Vitreous gel removal, known as vitrectomy, is a surgical procedure that involves the extraction of the gel-like fluid occupying two-thirds of the eye. This procedure aims to eliminate dysfunctional blood vessels responsible for bleeding, thereby preventing vitreous hemorrhage. Despite the potential risks of serious complications such as cancer, hemorrhage, and retinal detachment, vitrectomy exhibits a high success rate compared to other methods (19).Vitrectomy is particularly beneficial for patients with advanced diabetic retinopathy (DR) as it helps prevent visual field defects and vision loss. The technique involves extracting blood from the

vitreous and resolving retinal detachment caused by internal injuries. Initially, a 20-gauge (20G) vitrectomy technique was employed, but it has been upgraded to the minimally invasive 23-gauge (23G) vitrectomy. This newer approach utilizes smaller surgical incisions, leading to enhanced incising efficiency over a period of 12 months (19,20).

2.2 Pharmacological Treatment of Diabetic Retinopathy

Nanotechnology based treatments

Nanotechnology operates at the atomic and molecular levels, offering significant advancements in the fields of science, technology, treatment, diagnosis, and biomedical applications (Table 1&2) (20). In pharmaceuticals, nanotechnology has gained substantial importance, enabling drug delivery through various routes such as ocular, inhalation, oral, parenteral, rectal, and topical administration. Nanomedicines utilize nanoparticles to enhance therapeutic or diagnostic agent efficacy, while minimizing toxicity through improved drug targeting (21). Pharmacological treatment of diabetic retinopathy Table 1.

2.2.1. Polymeric nanomicelles

Polymeric nanomicelles, self-assembled structures formed by amphiphilic polymers, have emerged as innovative tools for addressing challenges in drug delivery, particularly for the treatment of diabetic retinopathy through ocular drug delivery. By incorporating biocompatible and biodegradable polymers at the nanoscale, polymeric nanomicelles overcome limitations associated with poorly permeable tablets and biological barriers (22). Various materials, including synthetic polymers (micelles, dendrimers, hydrogels), lipids, proteins (albumin nanoparticles), and inorganic compounds (cerium oxide nanoparticles), are commonly used for nanoparticle synthesis (23).

Nanoparticles (NPs) offer advantages in bypassing barriers in the body, particularly the blood-neural barriers (BNB) and blood-brain barrier (BBB), as depicted in Figure 3. The therapeutic effects exerted by NPs depend on their physicochemical properties, such as surface charge, size, and shape (24). Size plays a critical role, as NPs smaller than 5 nm are typically eliminated from tissues through renal secretion. Cellular uptake and biodistribution are influenced by surface charge, with positively charged NPs exhibiting greater mobility compared to neutral and negatively charged NPs. The shape of NPs affects biodistribution and adhesion patterns (24,25).

2.2.2. Nanoliposomes

Nanoliposomes are small vesicles characterized by a lipid bilayer external membrane and a hydrophilic core. The properties of liposomes such as fluidity of the bilayers, lipid composition, size, surface charge, and preparation process, significantly influence their behavior and functionality (26). One unique characteristic of liposomes is their ability to encapsulate drugs of both hydrophilic and lipophilic nature, making them suitable for dual-delivery therapeutics. To achieve ionic drug loading, cationic or anionic lipids are utilized. However, the application of liposomes for posterior eye delivery is limited due to challenges such as drug loading restrictions, short shelf life, and difficulties in sterilization (27).Liposomes have shown promise in the treatment of eye diseases, including diabetic retinopathy (DR). For instance, a liposome-based nanosystem was evaluated for the delivery of a functional gene in the form of an artificial virus. This liposome-protamine-DNA complex demonstrated efficient and cell-specific delivery, holding potential for DR treatment (27,28).

Over ten liposomal formulations have been approved for use, while several others in clinical and preclinical development. Specifically for retinal diseases, two products have already entered the market: (1) Visudyne® (Novartis Pharmaceuticals, USA), approved by the FDA in 2019 for the treatment of predominantly subfoveal choroidal neovascularization in patients with age-related macular degeneration (AMD); (2) Photrex® (Miravant Medical Technologies, USA), currently in Phase III clinical studies for the treatment of AMD and awaiting FDA approval (29).

2.2.3. Niosomes

Bilayer structures resembling liposomes consist of non-ionic surfactant molecules that enclose an aqueous compartment. These structures are preferred over other vesicular structures for ocular transport due to their chemical stability, ready availability of raw materials, and cost-effectiveness. Unlike phospholipids, the handling of surfactants does not require special precautions and conditions, making them more convenient for use (30,31).

2.2.4. Nano micelles

Nanomicelles consist of amphiphilic molecules that spontaneously assemble in aqueous media, forming organized systems where the polar head groups interact with the surrounding solvent while

the hydrophobic tails orient toward the core of the nanomicelle. In many aspects, nanomicelles resemble liposomes, with the former composed of a monolayer and the latter consisting of a lipid bilayer. Due to their nanoscale size and enhanced permeation, nanomicelles are preferred for ocular delivery (32).The formation of nanomicelles involves the use of surfactants and polymeric systems. Negatively charged surfactants (e.g., sodium dodecyl sulfate; SDS), positively charged surfactants (e.g., dodecyl trimethylammonium bromide; DTAB), and nonionic surfactants (e.g., n-dodecyl tetraethylene monoether; C12E4) are employed in nanomicelle formation (33). While these systems efficiently distribute into and across the sclera, their effectiveness in other environments is limited, possibly due to the absence of lymphatic clearance and blood vasculature (34).Polymeric nanomicelles are considered one of the most promising delivery systems in nanomedicine. They exhibit a unique core-shell structure, where the internal core (hydrophobic) is encapsulated by a hydrophilic shell. The hydrophobic portion can be composed of polyesters (e.g., polycaprolactone and poly(D, L-lactide)), polyethers (e.g., polypropylene oxide), or polyamino acids (e.g., poly(β-benzyl-L-aspartate)). The hydrophilic nature is achieved by using poly(ethylene glycol) (PEG) and its derivatives (35,36).

2.2.5. Nano-emulsions

Nanoemulsions are oil-in-water (o/w) emulsions composed of a liquid lipid core surrounded by a lipid monolayer, forming a complete structure. The use of surfactants provides stability to these structures and their small size enhances membrane permeability, allowing for deeper penetration into ocular tissues and improved drug uptake. Consequently, nanoemulsions offer faster therapeutic action with smaller doses, resulting in fewer ocular side effects and reduced application frequency, thereby enhancing patient compliance (37,38).In studies conducted on rabbits, this system demonstrated non-irritant properties and successful control over the release rate of loteprednol etabonate into the rabbit aqueous humor. Moreover, it was able to enhance the bioavailability of the ocular drug compared to similar formulations available in the market (38,39).

2.2.6. Nanoparticles

Various materials are utilized in the formation of nanoparticles (NPs), including natural and synthetic polymers, metal oxides, silica, and noble metals. Polymeric NPs can encapsulate a variety of bioactive or drug molecules, such as chemotherapeutic agents, proteins, and nucleic acids. Natural polymers like albumin, gelatin, sodium alginate, and chitosan, as well as synthetic polymers like poly(lactic acid) (PLA),

polyvinyl alcohol (PVA), poly(ethylene-covinyl acetate) (PEVA), and poly(methyl methacrylate) (PMMA), have been engineered to develop polymeric NPs (40-42).To avoid the need for repeated intraocular surgical procedures, slowly degrading polyesters like PLA are preferred, as they enhance bioavailability and prolong drug release. Stimuli-responsive polymeric NPs, which can change their physicochemical properties in response to external stimuli, pose new challenges in nanomedicine (43). Light-responsive NPs have been developed using a far ultraviolet (UV) light-sensitive polymer to encapsulate the small molecule angiogenesis inhibitor, nintedanib (BIBF 1120). These light-responsive NPs can maintain drug levels and inhibit angiogenesis after implantation (44).

2.2.7. Nanogels

Nanogels are nanoscale hydrogel particles that exhibit unique properties due to their small size and cross-linked structure. The kinetics of nanogels can be influenced by the degradation of the cross-links as well as external stimuli, such as pH and temperature (45). These nanogels have demonstrated the ability to traverse ocular biological barriers, making them potential candidates for intraocular drug delivery and as delivery carriers to the retina. Nanogels possess the essential properties required for efficient ocular drug delivery and offer an alternative to conventional eye drops for the treatment of ocular diseases (41, 42). Biomarkers for diagnosis of diabetic retinopathy are given in Table 2.

Table 1: Nano formulations used for treatment of diabetic retinopathy

Nano-Base Formulations	Drug	Method Of Formulation	References
Fenofibrate-loaded biodegradable nanoparticles	Fenofibrate, poly (lactic-co-glycolic acid), Tween 80, dichloromethane	Emulsification	(46)
A non-invasive nanoparticle-mediated delivery of triamcinolone acetonide ameliorates	Triamcinolone acetonide, Polycaprolactone, Pluronic® F-68, Poly (d, l-lactide-co-glycolide)	Nanoprecipitation	(47)
Celecoxib-loaded nanoparticles	Celecoxib, chitosan, sodium alginate, poly-ε-caprolactone (PCL), poly-L-lactide, and poly-D, L-lactide-co-glycolide	Emulsification solvent diffusion	(48)
α-Lipoic acid in soluplus® polymeric nanomicelles	α-Lipoic acid (ALA), sodium dioctylsulfosuccinate, Soluplus	Freeze drying	(49)
Chitosan-sodium alginate-fatty acid nanocarrier	Lutein, chitosan, oleic acid	Ionotropic gelation	(50)
PPAR-gamma agonist as	Pioglitazone,	Single emulsion solvent	(51)

surface-modified polylactic acid-co-glycolic acid (PLGA) nanoparticles	dichloromethane, polysorbate 80, Polyvinyl alcohol and mannitol	evaporation	
Enhancement of scutellarin oral delivery efficacy by vitamin B12-modified amphiphilic chitosan derivatives	Scutellarin, Chitosan, Deoxycholic acid, Vitamin B12	Self-assembly in aqueous medium	(52)
Intravitreal injection of bevacizumab-chitosan nanoparticles	Bevacizumab, chitosan	Emulsification evaporation	(53)
Liposomes	Inulin	Nanoprecipitation	(54)
Solid lipid nanoparticle	Ibuprofen	Nanoprecipitation	(55)
Nano emulsion	Ciclosporin	Emulsification evaporation	(56)
Micelles	Dexamethasone	Nanoprecipitation	(57)
Solid lipid nanoparticle	Ciclosporin	Nanoprecipitation	(55)
Liposomes	Diclofenac sodium	Nanoprecipitation	(54)
Nano emulsion	Dexamethasone	Emulsification evaporation	(56)
Nanosuspension	Flurbinprofen	Emulsification evaporation	(58)
Discosomes	Timolol maleate	Nanoprecipitation	(59)
Liposomes	Acetazolamide	Nanoprecipitation	(54)
Solid lipid nanoparticle	Diclofenac sodium	Nanoprecipitation	(55)
Nano emulsion	Pilocarpine	Emulsification evaporation	(56)
Dendrimers	Tropicamide	Nanoprecipitation	(60)
Niosomes	Cyclopentolate	Emulsification evaporation	(54)
Dendrimers	Pilocarpine nitrate	Nanoprecipitation	(60)
PLGA Nanoparticle	Tacrolimus	Emulsification/diffusion method	(54)
Chitosan coated liposomes	Flurbiprofen	Modified ethanol injection method	(54)

Table 2: Biomarkers for Diabetic Retinopathy

Biomarkers	Function	Observation	References
AGEs, Srage and pentoside (serum)	AGEs affect the biochemical and physical properties of proteins and the extracellular matrix (ECM)	Levels of these biomarkers were high in patient with DR	(61)
Furosine (glycated collaged) and CMIL (skin biopsy)	Function as reliable marker and indicator of the nutritional value of heat-treated food,	Progession in the level of Furosine+ CML	(62)
VEGF (serum)	To create new blood vessels during embryonic	Levels were increased significantly	(63)

	development, new blood vessels after injury.		
VEGF (plasma)	To create new blood vessels during embryonic development.	Levels were constant	(64)
α 2 anti-plasmin	plasmin proteolysis, inhibition of plasminogen binding to fibrin, and cross-linking fibrin	Significant elevation in level of α 2 anti-plasmin	(65)
ICAM-1(intercellular adhesion molecule1)	plays a role in inflammatory processes and in the T-cell mediated host defence system	Significant changes in level	(66)
Apelin13	reduced brain infarct size in a dose-dependent manner	Significant increase in levels in serum	(67)
BDNF (serum)	facilitates synaptic transmission and regulates gene expression by increasing levels of synapsis	Significant decreased in level in serum	(68)
Chemerin(serum)	regulate adipocyte differentiation and stimulate chemotaxis of dendritic cells and macrophages	Significant increase in levels in serum	(69)
Lipoprotein	play a key role in the absorption and transport of dietary lipids by the small intestine, in the transport of lipids from the liver to peripheral tissues, and the transport of lipids from peripheral tissues to the liver and intestine	Levels were elevated	(69)
Folate (plasma red cell folate)	important in red blood cell formation and for healthy cell growth and function.	Levels were low in DR patient	(70)
Homocysteine(serum)	break down homocysteine to create other chemicals your body needs	Higher plasma levels	(71)
PEDF (plasma)	function as a tumour suppression protein and to downregulate in many	DR patients have significantly elevated levels of PEDF.	(72)

	types of solid tumours		

3. Diabetic Neuropathy

Diabetic nephropathy (DN**)** is majorly associated with chronic kidney diseases and cardiovascular complications (**Figure 5)**. According to the European Diabetes (EURODIAB) Prospective Complications Study Group and whereas in patients with type 2 diabetes, the incidence of DN was 2.2% per year and the prevalence 10 years after diagnosis 25% in the U.K. Prospective Diabetes Study (UKPDS) (9). Conventionally a combination of ACE inhibitor and Angiotensin2 receptor blockers were used for example combination of aliskiren and irbesartan, but pulmonary oedema and hyperglycemia restricted their use (10).

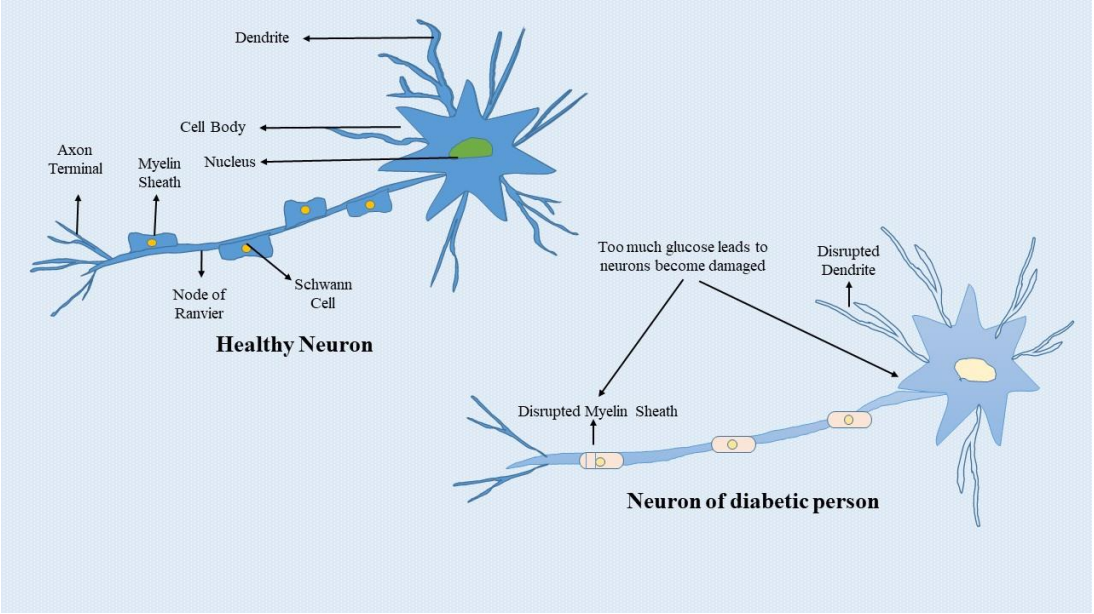


Figure 5: Diagrammatic representation of healthy neuron and neuron in diabetic neuropathy

3.1 Non-Pharmacological treatments of Diabetic Neuropathy

3.1.1 Spinal Cord Stimulation (SCS)

Spinal cord stimulation (SCS) is a pain neuromodulation technique employed for the management of various conditions. A fully implanted SCS system comprises two main components: the lead, which functions as an electrode, and the implantable pulse generator (IPG). By targeting the dorsal horn region of the spinal cord, this system induces neurochemical changes and suppresses the hyperexcitability of neurons, thereby providing pain relief (73).

In the context of painful diabetic peripheral neuropathy (PN), SCS has been investigated in studies and has demonstrated significant reductions in pain intensity (Figure 8). However, it is important to note that certain serious adverse effects are associated with the implementation of SCS. Inflammation following SCS implantation and dural puncture are among the potential complications, with subdural hematoma and, in rare cases, fatal outcomes reported in isolated instances (73, 74).

3.1.2.Transcutaneous Electrical and Electromagnetic Stimulation

Transcranial magnetic stimulation (TMS) is a neuromodulation and neurostimulation technique that operates based on the principle of electromagnetic radiation inducing an electric field within the brain. The effects of TMS can vary depending on the stimulation parameters and modulation duration, leading to either suppression or amplification of neural activity (77). Low-frequency TMS is known to induce inhibition of motor cortex excitability, while applying frequencies above a certain threshold can result in long-lasting inhibitory effects. In the case of patients suffering from diabetic polyneuropathy, the application of TMS has demonstrated a reduction in pain intensity (78).

3.1.3. Repetitive Magnetic Stimulation

Repetitive Magnetic Stimulation (rMS) is being investigated as a non-pharmacologic treatment option for diabetic neuropathy. By applying repetitive magnetic pulses to specific brain regions associated with neuropathic symptoms, rMS aims to modulate neural activity and potentially alleviate pain and other symptoms. This non-invasive technique shows promise in improving nerve function and reducing neuropathic pain in individuals with diabetic neuropathy. Ongoing research is focused on optimizing the stimulation parameters and evaluating the long-term efficacy of rMS in this context. If successful, rMS could provide a valuable adjunct therapy for diabetic neuropathy management. (78-80)

3.1.4. Photon Stimulation

Photon stimulation, specifically photo biomodulation or low-level laser therapy (LLLT), holds potential as a treatment modality for diabetic neuropathy. By utilizing pulsed infrared light therapy and image biomodulation with varying wavelengths, it can enhance cell metabolism and accelerate tissue and cellular repair processes at the cellular level. LLLT operates through photochemical modulation, triggering specific changes using targeted wavelengths and energy densities. This noninvasive technique employs monochromatic light within the far-infrared to near-infrared range (630 to 1000 nm), making it a promising therapeutic approach for managing diabetic neuropathy

and potentially alleviating associated symptoms (79).

3.1.5. Acupuncture

Acupuncture, an invasive procedure rooted in Chinese medicine, utilizes the concept of meridians and acupoints to target specific areas, even though meridians are not recognized as anatomical structures. These meridians serve as a theoretical framework for understanding the distribution of acupoints. Acupuncture is primarily based on empirical experience and has been investigated in the context of diabetic neuropathy (81). In a 10-week single-blind sham-controlled randomized controlled trial (RCT) conducted by Garrow et al., patients with intractable peripheral pain in the lower limbs due to diabetes were enrolled. The study found that adjuvant acupuncture led to an improvement in pain intensity, although the difference was not statistically significant when compared to the sham intervention. However, a statistically significant improvement was observed in the acupuncture group. This suggests that acupuncture may hold potential as a therapeutic intervention for managing diabetic neuropathy-related pain, although further research is needed to establish its efficacy (82).

3.1.6. Repetitive Vibration Stimulation

Repetitive Vibratory stimulation (RVS) refers to the application of repetitive pulses using a device, which can be targeted either to the entire body or a specific painful area. Repetitive Vibration Stimulation is being explored as a non-pharmacological treatment for diabetic neuropathy. It involves the application of rhythmic vibrations to the affected areas to stimulate sensory nerve fibres and improve nerve function (83). RVS has shown promise in reducing neuropathic pain, enhancing blood flow, and promoting nerve regeneration in individuals with diabetic neuropathy. Ongoing research aims to optimize vibration parameters, determine treatment protocols, and assess the long-term effectiveness of RVS as a therapeutic option for diabetic neuropathy management. Further studies are needed to establish its efficacy and provide more comprehensive evidence (84).

3.2. Pharmacological Treatment of for Diabetic Neuropathy

Pharmacologic treatment plays a crucial role in managing diabetic neuropathy by alleviating symptoms and slowing down disease progression (**Table 3)**. Medications such as anticonvulsants, antidepressants, and analgesics are commonly used to control neuropathic pain and improve quality of life for individuals with diabetic neuropathy. Biomarkers for diagnosis of diabetic neuropathy are given in Table 4.

Table 3: Pharmacological treatment for diabetic neuropathy

Drug	Dose	Mechanism	Side Effect
Pregabalin	150-600 mg	Inhibits the voltage gated.calcium channel and A T gated potassium channel	Dizziness, blurred vision,drowsiness.
Gabapentin	300-3600 mg	Inhibition of voltage gatedcalcium channel	Confusion, dizziness gastrointestinal issues, abnormal thinking
Duloxetine	60-120 mg	SNRI	Gastrointestinal issues,somnolence, hyperhidrosis
Venlafaxine	37.5-225 mg	SNRI or SSRI at low doses	somnolence, hyperhidrosis,prolonged QT
Amitriptyline	10-150 mg	Inhibition of voltage gated,sodium channels,NDMA receptors, andreuptake of serotonin andnorepinephrine	Gastrointestinal issues,orthostatic hypotension, drmouth, urinary retention,and QTc prolongation.
Tapentadol	100-250 mg	μ-opioid receptor agonist and norepinephrine reuptake inhibitor	Addiction, paradoxicalhyperalgesia, respiratory,depression, gastrointestinal issues.
Topical Capsaicin	0.075-8%	Vanilloid receptor agonist	Burning sensation and dermal Irritation
Topical Lidocaine	5%	Inhibition of voltage gated,sodium channels.	Dermal irritation
α-Lipoic acid	100-1800 mg	Antioxidant	Nausea, gastrointestinal issues
Actovegin	600- 2000 mg	Anti-hypoxic agent	Nausea

Table 4: Biomarkers for Diabetic Neuropathy

Biomarkers	Functions	Observations	References
Age	-	Chances of neuropathy increases significantly with increase in age	(85)
Bmi(kg/m2)	-	BMI slightly decreases in patient	(86)
Hba1c(%)	Measures the amount of blood sugar (glucose) attached to haemoglobin.	Slight increase in level as compared to normal person	(87)
Ast(u/l)	Determines the liver functioning by measuring levels of aspartate aminotransferase (ast) in the blood	Slight decrease in level	(88)

Alt(u/l)	Help your liver break down proteins to make them easier for your body to absorb.	Slight decrease in level	(89)
Ggt(u/l)	The first liver enzyme to increase in your blood when any of your liver bile ducts become blocked or constricted	Slight decrease in level	(90)
Total cholesterol(mg/dl)	To determine whether your cholesterol is high and to estimate your risk of heart attacks and other forms of heart disease and diseases of the blood vessels	Slight increase in level	(91)
Hdl-c(mg/dl)	Helps remove other forms of cholesterol from your bloodstream.	Slight increase in level	(92)
Ldl-c(mg/dl)	Carried cholesterol to cells that need it. Elevated ldl levels are associated with an increased risk of cardiovascular disease.	Slight increase in level	(92)
Tg(mg/dl)	-	Slight increase in level	(93)
Tsh(pmol/l)	Regulate the production of hormones by the thyroid gland.	Slight decrease in level	(94)
Ft3(pmol/l)	-	Slight decrease in level	(94)
Ft4(pmol/l)	-	Level of ft4 remains constant	(94)
Ua(pmol/l)	-	Slight increase in level	(94)
C-peptide	Plays a key role in the correct folding of insulin and the formation of disulphide bridges.	Slight increase in level	(95)
Vitamin b12	Vitamin b12 is needed to form red blood cells and dna.	Slight decrease in level	(96)
Crp	It's sent into your bloodstream in response to inflammation.	Slight decrease in level	(96)
Esr	Reveal inflammatory activity in your body	Slight increase in level	(97)
Fibrinogen	The formation of fibrin that binds together platelets and some plasma proteins in a haemostatic plug	Slight increase in level	(97)

4. Diabetics Nephropathy

Diabetic neuropathy (DNP) is another common and significant complication of diabetes and is damage to the nerve due to high blood sugar levels. The condition usually develops slowly and sometimes over the period of several decades **(Figure 6)**. According to a journal in 2019 DNP occurs in about 11% of patients with type 2 diabetes. Older adults are mostly affected, and those with recently diagnosed or well-controlled diabetes (11). Antidepressants such as Amitriptyline, desipramine and imipramine were used initially but hypoglycaemia, UTI and sexual dysfunction limits the use of these drugs (12).

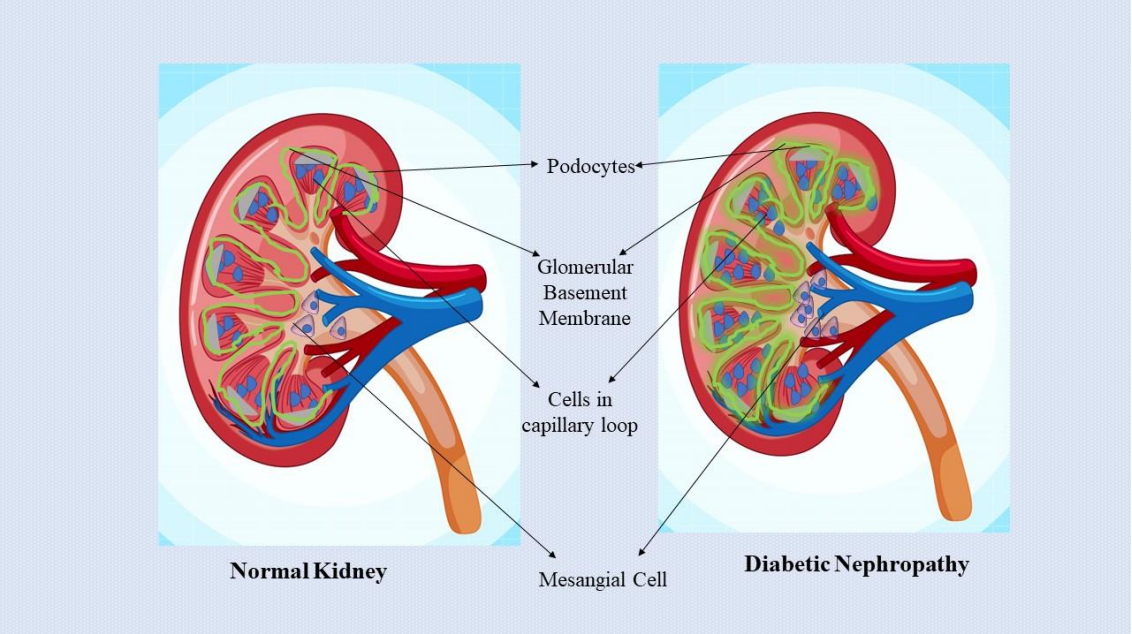


Figure 6: Diagrammatic representation of the differences between healthy kidney and diabetic nephropathic condition.

4.1. Non-Pharmacological treatment Diabetics Nephropathy

Acupuncture, ultrasound-guided local injections (UGLI), other spinal operations, physical agent modalities, traction, therapeutic exercise, orthosis application, and patient education are some of the non-pharmacological treatments for nephropathy that are available (98).

4.2. Pharmacological treatment Diabetics Nephropathy

The optimal therapeutic approach for diabetic patients with early or advanced diabetic neuropathy (DN) involves aggressive management of hypertension, with a focus on renin-angiotensin system (RAS) blockers, along with addressing dyslipidemia, hyperglycemia, and albuminuria. This comprehensive treatment strategy includes dietary modifications, exercise, and smoking cessation. It encompasses glycemic and blood pressure control, ACE inhibition, statin therapy, aspirin use, reduced fat intake, moderate exercise, and smoking cessation. Patients with DN often require multiple antihypertensive medications, including RAS blockers, to achieve target blood pressure levels. Type 1 diabetes patients may require intensive insulin therapy, while type 2 diabetes patients may need two or more medications for glucose control, along with lipid-lowering medication and antiplatelet therapy for cardiovascular protection (99). Biomarkers for diagnosis of diabetic nephropathy are given in Table 5.

Table 5: Biomarkers for diabetic nephropathy.

Biomarker	Method Of Detection	Status In Diabetic Nephropathy	References
Transferrin	Urine	Elevated	(100)
Type 4 collagen	Urine	Elevated	(101)
Ceruloplasmin	Urine	Elevated	(102)
Fibronectin	Plasmin/ urine	Both elevated	(103)
Ngal	Urine	Elevated	(104)
Kim1	Urine	Elevated	(100,102)
Nag	Urine	Elevated	(101)
L-fabp	Urine	Constant	(100)
A1m	Urine	Elevated	(103)
Rbp	Urine	Elevated	(105)
Flcs	Urine	Elevated	(105)
8-ohdg	Urine	Elevated	(106)
Pentosidine	Urine/ serum	Both elevated	(107)
Aga	Urine	Elevated	(100)
Tnfα	Urine/ serum	Both elevated	(108)
Tnfr1/2	Serum	Elevated	(101)
Il-6	Urine/ serum	Both elevated	(105)
Vegf	Urine/serum	Both elevated	(104)
Ace2	Urine/serum	Elevated	(100)

5. Future perspectives

According to reports, diabetes affects approximately 5-10% of the global population, and this prevalence continues to rise. However, significant financial resources are allocated within the

healthcare system to address the needs of individuals with diabetes and its associated consequences.

Despite these efforts, the scientific community is actively engaged in research endeavors to discover more effective treatments for diabetes with minimal side effects.

The future prospects of diabetic treatment appear promising, the integration of AI holds great potential to revolutionize the management of diabetes by improving diagnostic accuracy, optimizing treatment plans, and enabling personalized healthcare approaches. AI-driven algorithms and advanced data analysis techniques will empower healthcare professionals to make more informed decisions and provide tailored interventions for individuals with diabetes. Furthermore, the continuous growth in research and technology will play a pivotal role in shaping the future of diabetes care. Ongoing scientific investigations will deepen our understanding of the underlying mechanisms of diabetes, paving the way for innovative therapeutic strategies and preventive measures. With each passing day, advancements in technology will lead to the development of novel interventions, improved glucose monitoring devices, and more efficient delivery methods for diabetes management

The convergence of healthcare and technology holds immense potential to enhance patient outcomes, improve quality of life, and mitigate the burden of diabetes on healthcare systems. By harnessing the power of AI and embracing cutting-edge research findings, the healthcare community can confidently navigate the future of diabetic treatment, ensuring that individuals with diabetes receive the best possible care.

6.Conclusion

In conclusion, the escalating prevalence of diabetes has heightened its significance as a contributing factor to cardiovascular and neuronal disorders. Embracing a healthy lifestyle assumes a critical role in effectively managing diabetes, yielding favorable outcomes. Complementing lifestyle modifications, appropriate medication and regular check-ups have demonstrated efficacy in mitigating major diabetes-related complications. Current research endeavors are focused on the development of innovative technologies and methods that offer shorter treatment durations and minimized adverse effects. Notably, nanotechnology has emerged as a prominent area of interest in diabetes treatment, leveraging its nanoscale properties to enable early detection and overcome significant barriers.

The future of diabetes treatment holds promise, with advancements underway and expectations rising through continuous innovation and development. Scientists are actively exploring the extensive integration of nanotechnology into diabetes treatment. As healthcare systems increasingly prioritize improvement, the global impact of diabetes is anticipated to gradually decline. In summary, the evolving epidemic nature of diabetes necessitates appropriate treatment to avert dire consequences. While the management of diabetes presents challenges associated with financial and personal burdens, comprehensive treatment approaches can significantly enhance quality of life, mitigate medical costs, and decelerate the progression of complications. Despite the absence of a definitive cure for diabetes, the biotech industry is actively pursuing curative solutions, and research outcomes signal promising prospects for the future of diabetes treatment.

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Abbreviations:

Abbreviations	Full Form
DNP	Diabetic neuropathy
DN	Diabetic nephropathy
UGLI	Ultrasound-guided local injections
DM	Diabetes mellitus
DR	Diabetic retinopathy
NPDR	Non-proliferative diabetic retinopathy
DME	Diabetic macular edema
LT	Laser therapy
ROD	Retinal oxygen demand
BBB	Blood brain barrier
SCS	Spinal cord stimulation
TMS	Transcranial magnetic stimulation

MI	Myocardial infraction
TSH	Thyroid stimulating harmone
LDL	Low density lipid
EURODIAB	Epidemiology and Prevention of Diabetes study.
UKPDS	U.K. Prospective Diabetes Study.
UTI	Urinary tract infection
BBB	Blood brain barrier
BRB	Blood retinal barrier
SDS	Sodium dodecyl sulfate
DTAB	dodecyl trimethylammonium bromide
PEG	Poly ethylene glycol
NPs	Nanoparticle
PLA	Polylactic acid
PVA	Polyvinyl alcohol
PEVA	polyethylene-covinyl acetate
ALA	α-Lipoic acid
ECM	Extracellular matrix
STDC	Strength time duration constant
IPG	implantable pulse generator
LDLR	Low-depth laser remedy