



## Novel Drug Treatments for Diabetes Complications

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### ABSTRACT

Diabetes mellitus is a metabolic disease associated with elevated levels of blood glucose. It has become the most prevalent disease in the Saudi population according to the last report from the national prevention program. Diabetes cases can be divided into three types: type I, which requires insulin therapy; type II, which requires the use of hypoglycemic drugs, with or without insulin, and is the most common type in Saudi Arabia; and gestational diabetes, which occurs during pregnancy.

We must remember that diabetes can be very dangerous, causing complications in many parts of the body, like the nerves, heart, eyes, and kidneys. According to previous studies, these complications vary depending on the severity of diabetes. They may also affect the blood vessels of the retina, which can develop into diabetic retinopathy. Complications may also be fatal, in the cases of heart attacks, angina, and atherosclerosis. Additionally, they may cause poor circulation that leads to infection and gangrene, or cause neuropathy with numbness and a loss of pain sensations. Diabetic nephropathy is another harmful effect of diabetes that attacks the renal blood vessels.

In this article, my aim was to review newly discovered drugs that target and decrease the complications produced by diabetes. My focus here was on certain drugs, including those using nanotechnology, cell-based therapy, angiotensin-like 4, baricitinib, and hepatocyte growth factor (HGF) gene therapy.

### 1. Introduction

Diabetes mellitus, which is generally referred to as diabetes, is a disease associated with elevated levels of blood glucose, which is the main source of energy for the body. Normally, the body has a specific hormone called insulin, which is produced by the pancreas and enables cells to obtain blood glucose to produce energy [1].

There are several types of diabetes and the classifications are related to their causes. For instance, type 1 diabetes occurs if the body cannot synthesize insulin. Type 2 diabetes occurs if the body produces an inadequate amount of insulin, or cannot use insulin and is the most common type. There is also a state known as prediabetes in which there is an inadequate blood sugar level, which results in a high risk for type 2 diabetes (figure 1). Finally, gestational diabetes happens during pregnancy [2].

These types of diabetes require blood tests that include a fasting plasma glucose (FPG) test and a hemoglobin A1c (HbA1c) test to check blood glucose. Additionally, weight control, preparation of a carbohydrate controlled meal plan, exercise, and appropriate medication may be needed to regulate diabetes [3]. Over extended periods and without treatment, dangerous problems may arise and cause complications in several parts of the body, like the nerves, heart, eyes, and kidneys [4].

The World Health Organization (WHO) has reported that Saudi Arabia has the second highest incidence rate for diabetes in the Middle East and the seventh highest worldwide. In Saudi Arabia there are approximately 7 million diabetics and around 3 million prediabetics [6].

According to a cross-sectional study by the Department of Primary Care at King Fahad Armed Forces Hospital, the major clinical problem in Saudi Arabia is diabetes. They reported elevated levels in the Saudi population as being a public health problem, with a prevalence of 34.1% in males and 27.6% in females, both of which were associated with a high risk of obesity. A national prevention program has been promoted to prevent diabetes, treat risk factors in the community, and target high-risk groups [7].

Blood Sugar Levels Chart			
Normal & diagnostic ranges			
mg/dl	fasting		2 hrs post meal
	Min	Max	
Normal	70	99	<140
Prediabetes	100	125	140 - 199
T2 Diabetes	>126		>200
mmol/l	fasting		2 hrs post meal
	Min	Max	
Normal	4	6	<7.8
Prediabetes	6.1	6.9	7.8 - 11
T2 Diabetes	>7		>11.1

DIABETES MEAL PLANS | Get printable blood sugar charts & details on blood sugar goals at [DiabetesMealPlans.com/BS](https://DiabetesMealPlans.com/BS)

Figure 1: Blood glucose measurements. [5]

The main purpose of this literature review was to gain knowledge about several recent therapies used for diabetic complications.

### 2. Method:

This review was performed using reliable and popular medical databases, namely, PubMed, the Saudi Digital Library, Google Scholar, and the Web of Science (ISI). The terms used in the searches included diabetes mellitus, hyperglycemia, blood glucose, insulin, DM type I, DM type II, diabetes complication, and drug discovery. The studies were taken from 2006 to 2020.

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### 3. Overview of diabetes complications:

Diabetes can develop complications gradually and affect nearly every organ in the body over the long term, which may lead to disabling or even life-threatening complications [8]. Irregular blood sugar levels increase the incidence for the risk of complications (figure 2), including complications with the heart, blood vessels, eyes and kidneys.

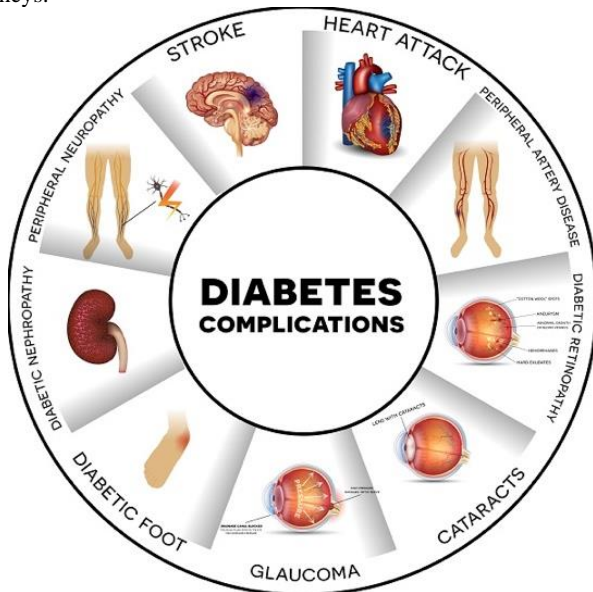


Figure 2: Types of diabetes complication [9].

The main complications involved with diabetes include cardiovascular disease, which is a common problem. Diabetes may enhance several cardiovascular problems and can be fatal in instances including heart attacks, coronary artery disease (angina), strokes, and narrowing of the arteries (atherosclerosis) [10]. Risk factors, like high cholesterol, hypertension, 55 years of age or older, obesity, low physical activity levels, or smoking, contribute to increases in heart disease. The chances of stroke in diabetic patients are 1.5 times higher than in the normal population [11].

Diabetic patients may also suffer from poor circulation due to a narrowing and hardening of the blood vessels, especially in the feet and legs. This may lead to infections, delays in the healing process, and the development of gangrene, which could require an amputation. These outcomes are 25 times more prevalent in diabetics compared to healthy people [10]. Another aspect of the foot problems originates from neuropathy. In this instance, the walls of the capillaries that nourish nerves become damaged resulting in numbness, tingling, or the loss of all sensation or pain. This sensory loss may cause the patient to be unaware of a cut or heat on their feet; thus, an injury can easily occur. The feet need protection in the form of washing followed by fully drying the feet, especially between the toes. Use of a moisturizer is also recommended, but not between the toes, and suitable shoes should be worn [12].

Nerve damage, called neuropathy, is proportional to the degree and duration of hyperglycemia (figure 3). The injury to the peripheral nerves is related to mechanisms such as oxidative stress and sorbitol accumulation. The most common form of neuropathy is chronic sensorimotor polyneuropathy, which produces a burning sensation, "electrical" pain, and tingling of the feet.

Nerve damage can also generate problems related to digestion, including vomiting, nausea, constipation or diarrhea, and bladder dysfunction. Moreover, men may experience erectile dysfunction [13].

Kidney disease or diabetic nephropathy results in damage to the small blood vessels and filtering units in the kidneys. Early damage may go unnoticed, but the first sign is an elevated protein or microalbumin level in the urine. If diabetic nephropathy is left untreated, it may increase the blood pressure and increase protein release into the urine. The advanced stages are characterized with an impaired kidney function and increases in serum creatinine. Finally, the patient may require dialysis or a kidney transplant in end-stage kidney failure [15].

Most diabetic patients will develop diabetic retinopathy through damage to the retinal blood vessels. This increases the risk of reduced vision, cataracts, glaucoma, and can lead to blindness [16].

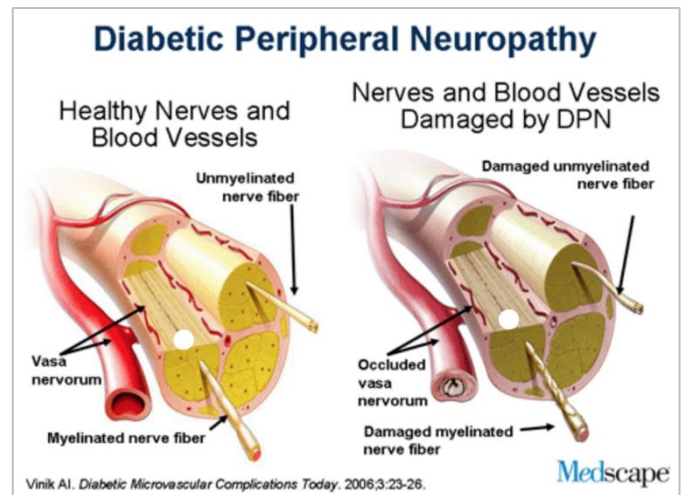


Figure 3: Diabetic neuropathy complication [14]

### 4. Newly Discovered Drugs:

The main purposes for the treatment of diabetic patients are to control blood glucose levels, maintain an appropriate body weight, and decrease plasma free fatty acids (FFA), triglycerides, and the LDL/HDL ratio. Treatment is also aimed at regenerating or protecting active pancreatic  $\beta$ -cells, which helps lower the cardiovascular risk associated with diabetes and limit the progression of other complications. The classical drugs for diabetes are limited to achieving a target of efficacy, even when used in combination therapy. Therefore, scientists have examined new techniques to improve health and decrease the complications of diabetic patients [17].

**Nanotechnology:** Initially, nanoparticles were used as imaging contrast agents to diagnose type 1 diabetes early. Then, new techniques involved incorporating implantable devices with glucose nanosensors that check blood glucose levels accurately and help supply the physiological requirements for insulin by glucose responsive nanoparticles. Thus, complications can decrease and there may be a delay in their appearance due to stable glucose levels [18].

**Cell-based Therapies:** These are novel methods that depend on the use of stem cells to enhance healing for chronic wounds of a diabetic's feet. One study found that injected CD34+ cells in diabetic mice with wounds improved the healing rate and increased revascularization. The authors suggested that stem cells were attracted to endothelial progenitor cells that have critical functions and play a role in wound healing [19].

**Angiopoietin-like 4:** In a new study by the National Eye Institute, the researchers observed diabetic retinopathy cases and found the specific protein concerned with the advanced stage. They found vascular endothelial growth factors (VEGFs) already present in samples of eye fluid with another protein called angiopoietin-like 4 (ANGPTL4). This explained why certain people who have diabetic retinopathy are non-responsive to anti-VEGF drugs and opened a new field of drug discovery.

The results further suggest that an increased effectiveness of treatment or prevention of diabetic retinopathy can occur through enhanced targeting of both ANGPTL4 and VEGF. In addition, ANGPTL4 can be used as a biomarker to support therapy for individual diabetic retinopathy patients. One of the anti-VEGF drugs was Aflibercept (EYLEA) that was approved as an injection with two different doses, 2 mg every 4 or 8 weeks, to treat diabetic retinopathy [20].

**Connexin43 hemichannel blockers:** Odunayo.O et al, described in their research a novel therapy for Diabetic retinopathy (DR) called Cx43 blockers. The connexin43 hemichannels play pathogenesis roles in chronic inflammatory diseases like DR. Especially, the high level of glucose leads to downregulation of Cx43 that causes further mitochondrial transport pores damage. Also, it promotes the release of cytochrome c from mitochondria and leading to accelerated apoptosis of retinal endothelial cells. So, Cx43 blockers can prevent the degeneration sequence by targeting upstream disease mechanisms and help to prevent the onset of DR [21].

**Baricitinib:** This drug started as an arthritis treatment but now has a new use in the treatment of damage due to diabetic nephropathy. Researchers at the University of Michigan Medical School reported

favorable results through a clinical trial that suggests decreased kidney damage, which was associated with an increased efficacy, decreased side effects, and a sustained impact, although with higher doses.

The study showed Janus kinase/signal transducers and activators of transcription (JAK STAT) play a role in immune diseases, such as rheumatoid arthritis, and have activity in kidney cells damaged by diabetes. Scientists studies the actions of baricitinib through an international clinical trial over a period of 14 months including 129 adults. The results suggested that the drug reduced the urinary albumin/creatinine ratio (UACR) and produced lower levels of a small protein called IP-10 and soluble tumor necrosis factor receptor 2 (sTNFR2), which aids in the detection of kidney inflammation [22].

**HGF gene therapy (HGF) gene therapy (VM202):** This approach uses HGF and non-viral gene therapy to treat painful diabetic neuropathy complications. One study found that, in 104 patients, there was improved activity and a reduction of the mean pain score after 3 months. The results reported that 48.4% of patients decreased their pain  $\geq 50\%$  with no serious side effects associated with treatment [23].

**Levodopa with Carbidopa:** These are the famous combination of medications used to treat symptoms of Parkinson's disease or to treat neuro injury caused by carbon monoxide. Levodopa is converted to dopamine, while carbidopa inhibits the break down of levodopa.

The American Diabetes Association, in February 2020, published research by Cara T et al, 2020, about this combination and its novel use to detect and restore Diabetic Retinopathy. The diabetic patients, without clinically detectable retinopathy, were randomly divided into 2 groups. They were treated for a period of two weeks with one group with high dose and the other with low dose Sinemet (levodopa with carbidopa). Both groups were then compared with nondiabetic persons. The researchers assessed oscillatory potential (OP) implicit-time after 2 weeks, in which the results showed significant restoration changes similar to the control values, in the diabetic patients. Finally, the delay of OP by Sinemet could be used for the early detection of retinopathy and may reverse DR dysfunction [24].

## 5. Conclusion:

Unfortunately, over long periods, diabetes generates many complications that can attack several organs. Although improvements in medical technology, like nano- or gene therapy, produce many drugs, few are approved after long clinical trials. However, patients can avoid or decrease the severity of complications through various steps. For instance, patients can take medications carefully, monitor their blood sugar and cholesterol levels frequently, make healthier meal plans, exercise regularly, and check for foot wounds daily. In addition, eye (retina) screening tests and urinary microalbumin measurements are recommended annually. Going forward, there should be greater cooperation between researchers to improve the status of diabetic patients and suggest accurate therapy methods to avoid complications.

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