

## Diabetes and Nanotechnology –A recent advance in treatment of Diabetes

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**Abstract:** The combination of nanotechnology and medicine has created a new field “Nano medicine” to enhance human health care. Nanotechnology can provide sensing technologies for accurate and medical information, for diagnosis of diabetes. The aim of this review is to provide insights into the role of nanotechnology in diabetes diagnosis and treatment, shedding light on the potential of nanotechnology in this field and discussing the future prospects. Natural polymers are essential to daily life as our human forms are based on them. Natural products are considered as a major source of medicaments and, hence, they are extensively used by pharmaceutical industries.

**Keywords:** Nanotechnology, micro vascular, macro vascular, adipogenesis , keto acidosis, agranulocytosis, Non-insulin-dependent diabetes mellitus

## INTRODUCTION

The term “Diabetes Mellitus” is derived from two words - (a) the Greek word “diabetes” meaning “siphon”, referring to the increased urination seen in this disease; and (b) the Latin word “mellitus” meaning “honey or sweet”, referring to the sweet taste of the urine caused by spilling out of excess sugar in the urine[1]. Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. An imbalance in carbohydrate metabolism and its effects on other metabolic pathways cause diabetes mellitus.

According to the first World Health Organization (WHO) global report on diabetes an outstanding number of 422 million adults live with this Non-Communicable Diseases (NCD) worldwide[4] Just fewer than half a billion people are living with diabetes worldwide and the number is projected to increase by 25% in 2030 and 51% in 2045 [2].

In 2020, according to the International Diabetes Federation (IDF), 463 million people have diabetes in the world and 88 million people in the Southeast Asia region. Of this 88 million people, 77 million belong to India [3].

DM is classified into type 1 and type 2. However, DM can also occur during pregnancy- a type known as gestational DM. Clinically, type 1 DM presents as hyperglycemia as a result of acute or chronic insulin deficiency in plasma [5] In type 2 DM, the  $\beta$ -cells within the islets of Langerhans of the pancreas are hypersensitive to glucose in plasma, thereby eliciting the secretion of higher than normal insulin levels in the systemic circulation. The evidence of hyper insulinemia is an attempt to counter balance hyperglycemia, which further deteriorates and impairs  $\beta$ -cell function [6, 7]

Chronic hyperglycemia is accompanied by high mortality and morbidity due to its concomitant

micro vascular complications, such as nephropathy, neuropathy and retinopathy, as well as macro vascular complications which include cardiovascular diseases leading to myocardial infarction and stroke [8, 9]

#### Type 1 Diabetes Mellitus

Type 1 diabetes usually develops in childhood or adolescence. In type 1 diabetes mellitus, there is a lack of insulin product due to autoimmune pancreatic beta-cell destruction.. Type 1 diabetes mellitus Type 1 Diabetes is characterized by autoimmune destruction of insulin producing cells in the pancreas by CD4+ and CD8+ T cells and macrophages infiltrating the islets [19]

#### Type 2 Diabetes Mellitus

In type 2 diabetes these mechanisms break down, with the consequence that the two main pathological defects in type 2 diabetes are impaired insulin secretion through a dysfunction of the pancreatic  $\beta$ -cell, and impaired insulin action through insulin resistance [20]

Type 2 diabetes mellitus involves inadequate secretion of insulin. Early in the disease, insulin levels are often very high, and this situation may continue later in disease development. However, peripheral insulin resistance as well as increased production of glucose by the liver causes insulin levels to be inadequate to normalize levels of plasma glucose. Then, insulin production becomes reduced, and hyperglycemia worsens. Type 2 diabetes usually develops in adults, becoming more common with aging. Plasma glucose levels reach higher levels following meals in older than in younger adults. This is especially true following high-carbohydrate loads. The levels require more time to return to normal, partly due to increased accumulation of visceral and abdominal fat, along with decreased muscle mass

#### Complications of Diabetes Mellitus

Diabetes is associated with a number of complications. Acute metabolic complications associated with mortality include diabetic ketoacidosis from exceptionally high blood glucose concentrations (hyperglycemia) and coma as the result of low blood glucose (hypoglycemia) In diabetes, the resulting complications are grouped under “microvascular disease” (due to damage to small blood vessels) and “macrovascular disease” (due to damage to the arteries). Microvascular complications include eye disease or “retinopathy,” kidney disease termed “nephropathy,” and neural damage or “neuropathy” [16]

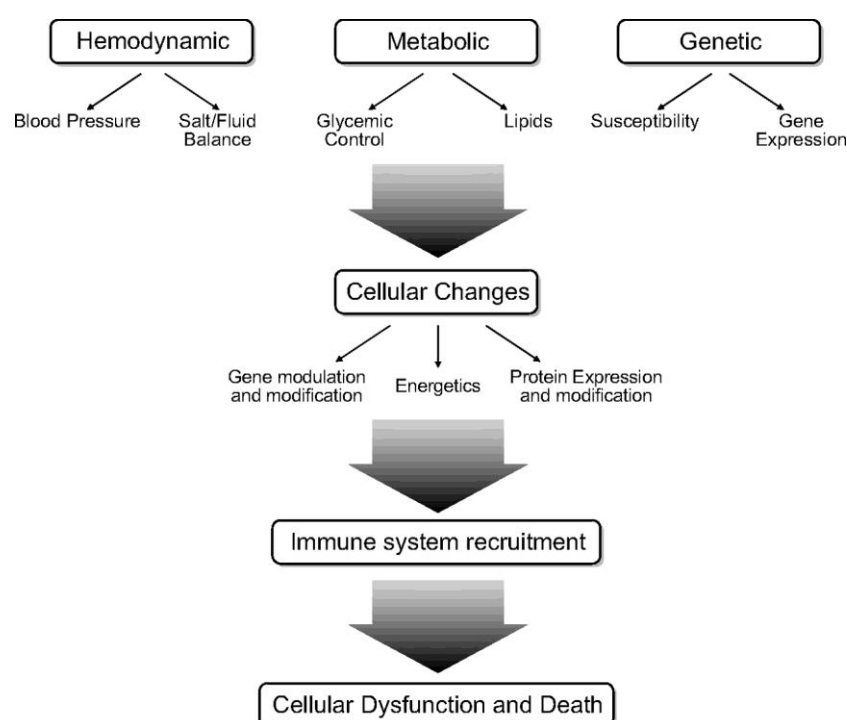


Fig: Schematic overview of the major areas contributing to diabetic complications.

## **Pathophysiology of type 2 diabetes (NIDDM)**

On the basis of oral glucose tolerance testing the essential elements of NIDDM can be divided into four distinct groups

- i) Those with normal glucose tolerance.
- ii) Chemical diabetes (called impaired glucose tolerance).
- iii) Diabetes with minimal fasting hyperglycemia (fasting plasma glucose less than 140 mg/dl).
- iv) Diabetes mellitus in association with overt fasting hyperglycemia (fasting plasma glucose greater than 140 mg/dl)

The individuals with impaired glucose tolerance have hyperglycemia in spite of having highest levels of plasma insulin, indicating that they are resistant to the action of insulin. In the progression from impaired glucose tolerance to diabetes mellitus, the level of insulin declines indicating that patients with NIDDM have decreased insulin secretion. Insulin resistance and insulin deficiency are common in the average NIDDM patients [10].

Most patients with the common form of NIDDM have both defects. Recent evidence has demonstrated a role for a member of the nuclear hormone receptor super family of proteins in the etiology of type 2 diabetes [11]. Relatively new classes of drugs used to increase the sensitivity of the body to insulin are the thiazolidinedione drugs. These compounds bind to and alter the function of the peroxisome proliferators-activated receptor  $\gamma$  (PPAR $\gamma$ ). PPAR $\gamma$  is also a transcription factor and when activated, binds to another transcription factor known as the retinoid  $x$  receptor (RXR). When these two proteins are complexed a specific set of genes becomes activated. PPAR $\gamma$  is a key regulator of adipocyte differentiation; it can induce the differentiation of fibroblasts or other undifferentiated cells into mature fat cells. PPAR $\gamma$  is also involved in the synthesis of biologically active compounds from vascular endothelial cells and immune cells [11]

### **Mechanism**

The blood delivers glucose to provide the body with energy to perform all of a person's daily activities. The liver converts the food a person eats into glucose. The glucose is then released into the bloodstream. In a healthy person, the blood glucose level is regulated by several hormones, primarily insulin. Insulin is produced by the pancreas, a small organ between the stomach and liver. The pancreas also makes other important enzymes released directly into the gut that helps digest food. Insulin allows glucose to move out of the blood into cells throughout the body where it is used for fuel. People suffered diabetes either do not produce enough insulin (type 1 diabetes) or cannot use insulin properly (type 2 diabetes), or both (which occurs with several forms of diabetes). In diabetes, glucose in the blood cannot move efficiently into cells, so blood glucose levels remain high. This not only starves all the cells that need the glucose for fuel, but also harms certain organs and tissues exposed to the high glucose levels. [22]

## **Diabetes Signaling Pathways**

The pathogenesis of diabetes is related to various signaling pathways, like insulin signaling pathway, AMPK pathway, and PPAR regulation and chromatin modification pathways. These signaling pathways have become the major source of the promising novel drug targets to treat metabolic diseases and diabetes.

## Insulin

In diabetes, the insulin resistance is partly mediated by lowering insulin receptor (IR) expression level. This is followed by impaired tyrosine phosphorylation of IR and subsequent tyrosine phosphorylation of IRS-1 and the attenuated association the regulatory subunit (P85) of phosphoinositide-3 kinase (PI3K) with IRS-1. This results in subsequent deactivation of its catalytic subunit (P110). Therefore, when the reduction of PI3K signaling pathway occurs, the protein kinase AKT will be activated and the reduction of glucose transport will occur. PI3K subsequently activates glycogen synthase kinase (GSK)  $3\beta$  pathway to regulate glycogen and lipid synthesis and stimulate glucose uptake. PI3K also regulates cell proliferation through Ras/Mek/ERK pathway.[23]

## AMPK

AMP-activated protein kinase (AMPK) acts as a central energy sensor. Activated AMPK deactivates gluconeogenic enzymes PEPCK and G6Pase thereby decreasing hepatic glucose production. It increases glucose uptake by inducing glucose transporters (GLUT). AMPK also stimulates lipid metabolism by decreasing malonyl-CoA levels through inhibiting acetyl-CoA carboxylase (ACC) and activation of malonyl-CoA decarboxylase (MCD). The natural product berberine (BBR) was discovered to reduce body weight, improve glucose tolerance, and ameliorate insulin action by activation of AMPK in peripheral tissue.[23]

## PPAR

Peroxisome proliferators-activated receptors (PPARs) are ligand-activated transcription factors, which have been used as promising therapeutic targets for drug discovery against metabolic syndrome. There are three isoforms for PPARs. PPAR $\alpha$  is expressed in liver, heart, muscle and kidney and regulates fatty acid metabolism and transport. PPAR $\gamma$  is expressed in adipose, muscle and macrophage, and regulates adipogenesis and lipid storage. PPAR $\delta$  is ubiquitously expressed and is involved in fat oxidation, energy expenditure and lipid storage. [23]

## Antidiabetic Drugs Classification

Class	Drugs	Mechanism of action	Adverse effects	Contraindications
<b>Insulins</b>	Short-acting insulin (regular insulin) ► Rapid-acting insulins (insulin aspart, insulin glulisine, insulin	Inject insulins	► Weight gain ► Blood sugar that drops too low, or hypoglycemia	► Hypersensitivity to drug/class/compon

	glulisine) ▶Intermediate-acting insulin (insulin isophane) ▶Long-acting insulins (insulin degludec, insulin detemir, insulin glargine, ) ▶Combination insulins (insulin aspart protamine-insulin aspart, insulin lispro protamine-insulin lispro, etc)		▶ Rashes, bumps, or swelling at an injection site	ent. ▶ Dosage may need to be reduced in severe renal impairment
<b>GLP-1 agonists</b>	albiglutide ▶dulaglutide ▶exenatide ▶liraglutide ▶semaglutide (Oral <u>semaglutide</u> <u>Rybelsus</u> is the first oral GLP-1 receptor)	Direct stimulation of the GLP-1 receptor	▶Nausea ▶ Increased risk of pancreatitis and possibly pancreatic cancer	Preexisting, symptomatic gastrointestinal motility disorders
<b>Amylin analogs</b>	▶ pramlintide	Reduce glucagon release ▶ Reduce gastric emptying ▶ Increase satiety	Risk of hypoglycemia ▶ Nausea	Gastroparesis
<b>Biguanide</b>	▶ Metformin	Acts on the liver to reduce gluconeogene	Lactic acidosis ▶ Weight loss ▶Gastrointesti	Chronic kidney disease ▶ Liver failure ▶ Metformin must

		sis and causes a decrease in insulin resistance via increasing AMPK signalling.	nal complaints are common (e.g. diarrhea, abdominal cramps) ►Reduced vitamin B12 absorption	be paused before administration of iodinated contrast medium and major surgery
<b>Sulfonylureas</b>	►gliclazide ►glyburide ►chlorpropamide  glimepiride ►tolazamide ► tolbutamide	► Increase insulin secretion from pancreatic $\beta$ -cells	Risk of hypoglycemia ► Weight gain ►Hematologic changes: agranulocytosis, hemolysis	Severe cardiovascular comorbidity ►Obesity ►Sulfonamide allergy particularly long-acting substances)
<b>Meglitinides</b>	nateglinide ► repaglinide	Increase insulin secretion from pancreatic $\beta$ -cells	Risk of hypoglycemia ► Weight gain	Severe renal or liver failure
<b>DPP-4 inhibitors</b>	alogliptin ►linagliptin ►saxagliptin ► sitagliptin	hibit GLP-1 degradation → promotes glucose-dependent insulin secretion	Gastrointestinal complaints ►Pancreatitis ►Headache, dizziness ► Arthralgia	Liver failure ► Moderate to severe renal failure
<b>SGLT-2 inhibitors</b>	dapagliflozin ►canagliflozin ►empagliflozin ► ertugliflozin	Increased glucosuria through the inhibition of SGLT-2 in the kidney	Genital yeast infections and urinary tract infections ► Polyuria and dehydration ►Diabetic ketoacidosis	Chronic kidney disease ► Recurrent urinary tract infections
		Reduce intestinal		Any preexisting intestinal

<b>Alpha-glucosidase inhibitors</b>	acarbose ►miglitol ► voglibose	glucose absorption	Gastrointestinal complaints (flatulence, diarrhea, feeling of satiety)	conditions (e.g.,inflammatory bowel disease) ►Severe renal failure
<b>Thiazolidinediones</b>	Pioglitazone Rosiglitazone	Reduce insulin resistance through the stimulation of PPARs (peroxisome proliferator-activated receptors) ►Increase transcription of adipokines	Weight gain ►Edema ►Cardiac failure ►Increased risk of bone fractures (osteoporosis)	Congestive heart failure ► Liver failure

### Nanotechnology and diabetes

Nanotechnology is a new and important technology in the 21st century. With the rapid development of nanotechnology, it has been widely used in medicine, materials science, electronic industry, energy industry, and other disciplines and fields [12, 13]

The term “Nanotechnology” is used to describe the manipulation of matter on an atomic, molecular and supramolecular scale where unique quantum mechanical effects take place. Thus, the reduction of at least one dimension at the nanoscopic scale (1–100 nm) involves the design, production, characterization and application of various nanoscale materials in different potential areas providing novel technological advances [15]

Over the past few years nanotechnology has found fertile ground in the development of novel delivery modalities that can potentially enhance anti-diabetic regimes efficacy. All efforts have been targeted towards two main vital steps: (a) to protect the drug by encapsulating it into a Nano-carrier system and (b) efficiently release the drug in a gradual as well as controllable manner [14] The challenge of using natural polymers or developing new biomaterials is not only to understand their mode of action in nature but also to coordinate the complex. The challenges of nanotechnology in medical application are mainly manifested in an unstable preparation process and lack of bio safety evaluation system [21]

Natural polymers can be derived from a wide variety of sources, from plants, animals, and microorganisms. Due to their similarity with the extracellular matrix, high biocompatibility, and high water holding capacity, natural polymers–based scaffolds are appealing for skin repair and regeneration purposes. Nanotechnology has been applied to a wide range of medical pathological conditions, such as cancer, Parkinson's disease, Alzheimer's disease, tuberculosis and diabetes mellitus [17]

Breakthroughs in Nanotechnology have strongly affected the scientific world mainly in the field of medicine since the size of NPs is similar to that of most biological molecules. Nanotechnology promised a total absence of lag time between glucose detection and insulin delivery, avoiding dangerous situations, such as hypoglycemia. [24]



## Conclusion

The global burden of diabetes is increasing worldwide as it is a costly disease for developing economies of the world. As a new technology, nanotechnology is the most promising scientific field of this century. With the development of nanotechnology, more and more new nano materials will be developed and applied in medical treatment, which will promote the development of modern medicine, bring forward new ideas, and make new contributions to the prevention and treatment of diseases. Nanotechnology has proven beneficial in treating diabetes mellitus by not only improving the catalytic properties of electrodes but also by increasing the available surface area of the sensor-receptor complex. This can revolutionize insulin delivery through enhanced oral formulations and islet encapsulation. Natural polymers have received much more attention in the last decades due to their potential applications in the fields related to environmental protection and the maintenance of physical health so we can say that biopolymers can be good substitute for the synthetic polymers and many of the side effects of the synthetic polymers can be overcome. Research efforts are required to isolate, identify and interpret or authenticate the effectiveness of bioactive compounds. Further, some detailed investigations should be aimed at understanding the effectiveness of isolated compounds in treating other human illnesses. Earlier intervention and continued treatment are the keys to achieving the treatment goals.

## Abbreviations

Diabetes Mellitus (DM)  
World Health Organization (WHO)  
Non-Communicable Diseases (NCD)  
International Diabetes Federation (IDF)  
Non-insulin-dependent diabetes mellitus (NIDDM)  
Peroxisome proliferators-activated receptor  $\gamma$  (PPAR $\gamma$ )  
Retinoid x receptor (RXR)



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