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# Diabetes and Gene Therapy

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## ABSTRACT

As a risk factor for cardiovascular disease (CVD), diabetes mellitus, especially type 2, is an epidemic that requires global attention. Despite being in its early or pre-stages, diabetes causes significant amounts of CVD morbidity and death in addition to well-known microvascular consequences including retinopathy and nephropathy. Population-based screening is crucial for the early diagnosis of diabetes mellitus in order to prevent the emergence of vascular consequences, such as CVD, because the disease's origin and progression are asymptomatic. In order to effectively and simultaneously prevent CVDs in persons with established diabetes mellitus, numerous modifiable risk factors, such as hyperglycemia, hypertension, or dyslipidemia, must be addressed.

## INTRODUCTION

What is gene and gene therapy? Gene can be defining as the basic unit of heredity. Gene is actually a small sequence of nucleotides that can code a specific product by the process of transcription (RNA) or then by translation (proteins).Gene therapy is actually an experimental treatment of diseases. It is the medical strategy that addresses the underlying genetic issue in order to treat or prevent the disease.

## WHAT IS DIABETES?

Diabetes is a chronic health disorder that develops when the body does not produce enough insulin or the pancreas is unable to produce enough insulin for the body to properly break down glucose. Using two words as

1. Diabetes mellitus
2. Diabetes insipid

Diabetes insipid is actually a rare condition but it not associated with the insulin production. It is a condition with high urination as in case of Diabetes occurs. When a person has diabetes mellitus, their body doesn't create enough insulin or not produce insulin at all causing blood glucose level abnormally high. It is actually diabetes. Diabetes is an ancient Greek word means “to pass through, a large discharge of urine”. Here we are going to mainly concern with diabetes mellitus i.e. Diabetes. Its types and its gene therapy [1-10].

### Diabetes mellitus

It is a disease of carbohydrate metabolism that raises blood sugar levels because the body produces little or no insulin. Normal blood glucose level is less than 140 mg/dL (7.8 mol/L). If the glucose level exceeds to 200 mg/dL it means the person is diabetic. And if glucose level is in between 140 to 200 mg/dL it means it is a stage of prediabetes. Diabetes is actually a group of diseases. It depends how human body uses glucose. Glucose is a source of energy for Cells that make muscles and tissues. If there is no proper usage of glucose it may lead to many serious problem and can even affect vital organs like heart, kidney and brain [11-15].

Types of diabetes mellitus:

1. Prediabetese
2. Gestational diabetes
3. Diabetes mellitus type 1
4. Diabetes mellitus type 2

There is another type of diabetes as well, known as secondary diabetes or type 3. Type 1 and 2 are the chronic diabetes conditions while prediabetes and gestational diabetes are reversible types.

Prediabetes is not actually a diabetic stage rather it can be an indication of initiation of diabetes. In this circumstance glucose degree will increase but now no longer sufficient to

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be taken into consideration as kind 2 diabetes.

Gestational diabetes is a temporary condition associated with pregnancy. In this circumstance blood glucose stage will increase all through being pregnant however commonly go back to ordinary after delivery? However gestational diabetes is identified as a hazard element for the Type 2 diabetes later in life. Gestational diabetes may affect pregnancy and health of the baby. But it can be control by proper diet and medication if necessary [16-25].

**Two main types of diabetes are**

1. Diabetes mellitus type 1, which is also known as Insulin dependent diabetes and juvenile-onset diabetes, because it often begins in childhood.
2. Diabetes mellitus type 2, which is also known as insulin independent.

Type 1 diabetes mellitus Type 1 diabetes is an autoimmune disorder characterized by T cell mediated self-destruction of insulin secreting islets B cells. A condition called secondary diabetes also resembles type 1 in this case. The beta cells are being wiped out by disease or damage to the pancreas, not by the immune system. Both types differ from type 2 diabetes increase.

Following are the symptoms of type 1 diabetes

- Extreme thirst
- Dry mouth
- Frequent urination
- Fatigue
- Blurry vision
- Fruity smell to your breath

Types 1 diabetes can lead to following complications especially if it is not well controlled. These include: Cardiovascular disease

- Skin problem
- Gum disease
- Pregnancy problems

**Treatment of diabetes**

- Treatment for type 1 diabetes includes taking insulin.
- Carbohydrate fat and protein counting.
- Frequent blood sugar monitoring.

Treatment of type 1 diabetes is difficult and complex, especially with conventional pharmacotherapy. Gene therapy has emerged as one of the potential therapeutic modalities for treating T1MD. T1DM gene therapy has been conducted in animal models and preclinical studies. Several interventions at the gene level are currently being investigated. In particular, overexpression of genes and proteins required for T1DM transplantation of gene-expressing cells for T1DM stem cell-mediated gene therapy Gene vaccination Immunological progenitor cell-mediated gene therapy and vectors.

Researchers at the University of Wisconsin School of medicine and public health are one step closer to developing a gene therapy for type 1 diabetes mellitus a development that one day could eliminate the need for daily insulin. The study describe a small sequence of DNA that when injected into veins of diabetic rats create insulin producing cells that help normalize blood sugar level and perfect regulation of glucose metabolism. It is the 1st known study to demonstrate how a DNA base gene therapy has the potential to treat type 1 diabetes. After receiving the therapy the diabetic rats had insulin and glucose levels that exactly resembled what you would find in healthy animals. This therapy works by sensing increase level of glucose concentration after meal. After that meal DNA is injected to produce insulin similar to the way pancreatic cells do [26-30].

But instead of targeting pancreatic cells, the therapy only targets the liver. We chose liver as the ideal target for this therapy because of its regenerative capacity. For therapy, DNA must enter and attach to millions of cells, so the liver's ability to replace dead cells is a clear advantage. The treatment essentially makes the liver work like a small pancreas.

**Stem Cell Gene Therapy**

Stem cells are of great benefit to cell based gene therapy. They are self-renewing and thus might reduce or eliminate the necessity for repeated administrations of therapeutic cells. From several decades now type 1 diabetes patient are treated with exogenous insulin therapy or by islets transplantation into portal vein. However stem cell therapy help in repair of lesion of pancreatic tissue which further secrete insulin and manage blood glucose level [31-35].

**Benefit of stem cell mediated gene therapy**

These therapies solve the problem of lowering the ratio of donor the need for toxic lifelong immunosuppressive drugs and graft failure. A study carried out showed that novel cellular replacement therapies that are based on stem cells into pancreatic cells can be used for type 1 diabetes treatment because in it only single cell type is affected. This study shows that it also have some disadvantages.

There are many ethical issues regarding to this treatment.

Transgenic strategies epigenetic failure is the disadvantages that limit their use to in vitro assays or preclinical models. However another study conducted by Wu that showed that one of the disadvantage of this therapy is hypoglycemia that involves the inconvenience of multiple daily injections or lifelong subcutaneous infusions of insulin which can be

solved. In order to become functioning B cells these both types of stem cells have to be transformed in a multiple differentiation process such as the progresses through endoderm pancreatic endoderm and endocrine phase [36-40].

**Diabetes mellitus type 2**

Condition in which not enough insulin (hormone) is produced by the body or insulin is not properly working which means insulin resistance. This condition may lead to hyperglycemia (high blood glucose level). It is common type of diabetes among people worldwide. It mostly associated with age factor i.e. people with age group 40 may have high risk of having diabetes type 2 and obesity. But it is also affecting children and teens. High level of glucose can be damaging so body try to remove it out thus excessive urination occur and it is the basic symptom of diabetes some other common symptoms are as follow:

- Increased thirst (polydipsia)
- Increased hunger (polyphagia)
- Extreme fatigue.

These symptoms can also be seen in type 1 but in type 2 these are more gradually developed and patient with type 2 diabetes don't even know for long time of having diabetes before its diagnosis [41-45].

**Risk Factors**

Diabetes type 2 is mainly because of unhealthy lifestyle. Mainly unhealthy diet is the reason because it is a metabolic disease. Obesity, unhealthy diet, low physical activity, high blood pressure, smoking and family history are the risk factors for diabetes mellitus 2 type. As diabetes is a group of diseases thus it is not only associated with high blood glucose level rather it affects different body organs like kidney, heart, brain or muscles. But in extreme cases this may lead to organ failure [46-50].

**Treatments, cure or preventions**

There is no cure for type 2 diabetes but, Because the major problem is unhealthy life style so the major solution is changing life style like by using healthy food, balance diet and regular exercise. If it is not enough then anti diabetic medication is prescribed. In some cases insulin injections are also prescribed. All the complications can be prevented by maintaining a healthy blood glucose level and blood pressure.

**Diabetes mellitus type 2 and gene therapy**

As we already know that diabetes mellitus type 2 is a chronic metabolic disease that is characterized by hyperglycemia resulting from less or insufficient production of insulin as well as insulin resistance. In diabetes mellitus 2 type (T2DM) patients there is not only high glucose level in their blood but also have many serious complications like heart attack, blindness, kidney failure, stroke and lower limb amputation. There are many factors that cause T2DM, as it's miles a multifactorial sickness related to each genetic and environmental elements consequently it's miles complex to cure [51-55].

Most commonly used method to treat type 2 diabetes is oral management of hypoglycemic dealers and injections of insulin. Although these agents are playing important role in type 2 diabetes therapies but still there are many adverse effects. So, new strategies are being introduced in the place of these treatments of T2DM which include gene therapy.

**Type 2 diabetes potential targets for gene therapy:**

Gene therapy is not a new idea for the treatment of diabetes, rather it was considered several years ago. Diabetes gene therapy focuses mainly on type 1 diabetes, but many genes are likely to cause type 2 diabetes. About at least 75 independent genetic loci have been identified for type 2 diabetes. For example, three novel mutations in the KCNJ11 gene are directly associated with the development of early-onset autosomal dominant T2D disease [56-60].

Many genes have polymorphic effects and can cause type 2 diabetes, but their applicability in type 2 diabetes gene therapy is very low because of the different polymorphic effects among different populations together but there are some genes that have the potential to treat type 2 diabetes. One of the examples is the region of nucleotide-linked oligomerization like protein receptor 3 (NLRP3). Any inhibition of the NLRP3 gene reduced inflammation, protected pancreatic beta cells from apoptosis, and thus prevented the development of T2D disease in mice. We can say that all genes involved in the onset, development and decline of T2D disease can be used as targets for T2D gene therapy. Here are some of the goals associated with gene therapy for type 2 diabetes.

**GENES THAT REGULATE GLUCOSE HOMEOSTASIS**

**Glucose transporters (GLUTs) and sodium-glucose co-transporters (SGLTs)**

GLUT2 and GLUT4 are targets of type 2 diabetes gene therapy by restoring their liver and muscle expression. SGLT is involved in the absorption of filtered glucose from the kidneys into the bloodstream. There is an effective strategy to reduce hyperglycemia in patients with type 2 diabetes by inhibiting SGLT1 or increasing SGLT2.

**Fibroblast growth factor (FGF)**

FGF1 knockout mice exhibit a diabetic phenotype that increases blood glucose levels and insulin resistance. FGF19 also has central nervous system-related antidiabetic effects. FGF21 is involved in the control of glucose and lipid homeostasis.

**Sirutin 6 (SIRT6)**

It has critical role in metabolic diseases like type 2 diabetes. It promotes pancreatic insulin secretion, inhibit hepatic gluconeogenesis and triglyceride synthesis and suppress adiposity.

**Complications**

Many complications are associated with type 2 diabetes mellitus. These have direct effect on the life style and health of the patient. Some of the complications are as follow

1. Diabetic kidney disease.
2. Diabetic cardiomyopathy
3. Diabetic peripheral neuropathy
4. Diabetic naphropathy

Targets that involve in these complications are as, DKD common in T2DM patients cause by increased level of alpha transforming growth factor. DCM is associate with NLRP3. Hsp70 modulation is helpful in both T1DM and and T2DM to correct DPN [61-65].

**How genes deliver for gene therapy**

Like identification of targeted gene the determination of suitable method or system of gene transfer is also very important. Genes transfer to the patient's body by means of vector. Methods are classified on the basis of vectors use in gene delivery.

1. Viral gene delivery.
2. Non-viral gene delivery.

**Viral gene delivery**

Viral genes that can be injected or administered orally exploit the natural ability of viruses to enter cells and transfer their genetic material into the nucleus and express proteins [66-70].

**Non-viral gene delivery**

Direct delivery of naked DNA into cells using different materials to transport genetic material into target cells. Like the use of liposomes and cationic polymers.

In recent years, bacteria have been used as vectors for disease transmission. This delivery system was quickly developed and adopted orally. It is believed to be the most efficient alternative to a non-viral gene delivery system.

Improved insulin secretion and sensitivity.

Many genes are involved in insulin production and insulin resistance. Glucagon-like peptide 1 (GLP1) is involved in the stimulation of glucose-dependent insulin secretion, increasing the expression of insulin genes. Many genes are involved in insulin resistance and beta cell dysfunction.

Etiological diabetes (type 3c) (secondary diabetes)

Diabetes can also develop as a direct result of other diseases, including diseases of the exocrine pancreas. Type 3c diabetes is diabetes secondary to pancreatic diseases, involving the exocrine and digestive functions of the pancreas. Causes:

- Chronic pancreatitis
- Lacking genes in the E2F group
- Pancreatic diseases
- Pancreatic resection.

Pancreatic inflammation leads to the destruction of the islet cells in case of chronic pancreatitis which is basic cause of type 3c diabetes mellitus. Any damage to pancreas or removal of pancreas by some reason leads to this type of diabetes [71-75].

**How to diagnose T3c diabetes mellitus**

Diagnoses of type 3c diabetes mellitus is not easy, it is one of the most complex type of diabetes as compare to type 1 and 2. It involves many factors and many different diseases associated with pancreas.

**Treatment**

Although there may be no right remedy for kind three however a few elements are used as remedy like fitness care, insulin availability and right digestion. In sufferers with kind 3c diabetes mellitus treating exocrine pancreatic insufficiency, stopping or treating a loss of fats-soluble vitamins (particularly nutrition D) and restoring impaired fats hydrolysis and incretion secretion are key-capabilities of scientific therapy [76-80].

Type three Diabetes Some research has proposed that Alzheimer sickness have to additionally be labeled as a sort of diabetes referred to as kind three diabetes. This arise whilst neurons in our mind not able to reply to insulin.

**Symptoms of type 3 diabetes**

- Memory loss
- Difficulty in completing many tasks
- Misplace often things
- Sudden change in personality.

**Causes of type 3 diabetes**

- A diet high in calories sugar and fat
- Genetics
- Low socioeconomic status
- Family history

- Additionally having the APOE4 gene can increase person risk of the condition.

**Cure of diabetes 3**

There is no cure of type 3 diabetes. Doctor prescribes drugs that slows down its progression or treat its symptoms. Increase physical activities. Monitoring blood pressure [81].

## CONCLUSION

Currently, several interventions at the gene level are being investigated, including overexpression of genes and proteins required to fight T1D. Inoculation of cells expressing genes against T1D stem cells Gene-mediated gene therapy Vaccination with immune precursors Cell and vector-mediated gene therapy. Researchers at the University of Wisconsin School of Medicine and Public Health are on the verge of developing a gene therapy for type 1 diabetes, a developmental approach that could eliminate the need for daily insulin. The study describes a small sequence of DNA that, when injected into the veins of diabetic rats, induces insulin-producing cells that normalize blood sugar levels and perfectly regulate glucose metabolism.

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