Diabetes mellitus is a chronic and metabolic disorder which diminishes the activity of energy utilization from food by the human body for lifetime. It is a chronic metabolic disorder, which is characterized by chronic hyperglycemia, deficiency of insulin, and resistance to insulin. With diabetes mellitus, either your body loses the ability to produce insulin or there occurs improper use of the produced insulin. There are two major types of diabetes.

1. **Type I diabetes mellitus** (insulin-dependent diabetes mellitus [IDDM]).
2. **Type II diabetes mellitus** (non-insulin-dependent diabetes mellitus [NIDDM]).

### Type I diabetes mellitus
It is also called insulin-dependent diabetes or juvenile diabetes. It causes autoimmune and kidney disease, heart stroke, and nerve damage to the nerves which are present in feet. In this type, diabetes body's immune system attacks its own pancreas and stops the insulin secretion. One of the reasons for this type of diabetes is a genetic predisposition. It can be also the result of faulty pancreatic β-cells. Medical risks associated with this type diabetes are damage to the small blood vessels which are present in the eyes, kidneys, and nerves.

### Type II diabetes mellitus
It is also called as NIDDM and adult-onset diabetes. It is the most common and milder form of diabetes than type I diabetes mellitus. Nevertheless, it still can cause major health problems, especially the small blood vessels which are present in the eyes, nerves, and kidneys. It also increases the risk of heart diseases and heart dose. With this type II diabetes, the body's pancreas normally produces the insulin either the produced insulin is not enough or the body's cells are resistant to insulin [1-5].

**Pancreatic transplantation**
It is a surgical operation, and the normal pancreas is collected from an expired person and inserted into a person's body whose pancreas not works properly. Pancreatic transplantations are done to treat or control type I diabetes mellitus. The pancreas lies in the lower part of the stomach. The pancreas major function is to secrete a hormone called insulin, which regulates or controls the sugar absorption into body cells. Type I diabetes mellitus results when the pancreas does not produce sufficient insulin, causing sugar levels in the blood rise to dangerous levels.

The surgical team checks the heart rate, blood oxygen, and pressure throughout the procedure with a heart monitor leads attached to the chest and blood pressure cuff on arm of the patient.

After the patient is unconscious:
- A small cut is made the center of the patient abdomen.
- The surgeon keeps the new pancreas along with a small portion of the new kidneys.
- The new ureters by which urine passes from kidneys to bladder. Unless patient's own kidneys are causing major problems, such as infection or high blood pressure, they are not disturbed from their place.

Pancreas transplantation generally takes about 3 h. Along with that kidney-pancreas transplantation takes a few more hours.

### Complications of the procedure
Bleeding, blood clots, infection, urinary complications, hyperglycemia, donated organs failure, and donated organs rejection are the complications of the procedure.

### RESULTS
After pancreas transplantation, the new pancreas produces the insulin, so the patient does not require insulin therapy to treat type I diabetes. Even though there is compatibility between patient and the donor, patient’s immune system will try to reject the new pancreas. To avoid rejection of newly transplanted pancreas, patient needs medications to suppress the body's immune system the rest of life. Patients need to take anti-rejection drugs or immunosuppressants for the rest of life.
There are two types of pancreatic islet transplantations which are available:

Pancreatic islet transplantation
Diabetes should take insulin daily to live and to maintain the blood glucose into energy.

In type I diabetes, pancreatic β-cells does not produce insulin because the body’s immune system attacks its own pancreas and stops secreting insulin.

There are usually four classes of maintenance drugs:

- Induction drugs: These are powerful anti-rejection drugs used at the time of transplant.
- Maintenance Drugs: These drugs are used for long term.

There are usually four classes of maintenance drugs:

- Antiproliferative agents
  - Azathioprine, mycophenolate mofetil, and mycophenolate sodium.

- Calcineurin inhibitors
  - Cyclosporine and tacrolimus.

- Mammalian target of rapamycin inhibitor
  - Sirolimus.

- Steroids
  - Prednisone.

Transplanted pancreas and kidney survival rates are as follows:

Pancreas transplantation
In about 81% of people who undergoes pancreas transplantation, after 1 year, the transplanted pancreas is still working, and after 5 years, that rate of working is up to 53%.

Simultaneous pancreas and kidney transplantation
In about 90% of people who receive simultaneous pancreas-kidney transplantation, after 1 year, the transplanted kidney and pancreas are still working, and after 5 years, the rate of working is up to 78%.

Pancreas transplantation after kidney transplantation
In about 87% of people who receive pancreas transplantation after kidney transplantation, after 1 year, the transplanted pancreas is still working, and after 5 years, the rate of working is up to 70%.

Diet
No dietary restrictions are required after pancreatic transplantation.

Pancreatic islets
It is also called as islets of Langerhans; these are the minute clusters of cells which are dispersed throughout the pancreas.

It consists of numerous types of cells including β-cells, pancreatic β-cells which produces the insulin hormone, and enzymes which help the body to digest food.

When the blood glucose or blood sugar levels increase after a meal, the pancreas will release insulin into the bloodstream. Insulin is required for absorption of glucose from the bloodstream and for conversion of glucose into energy.

In type I diabetes, pancreatic β-cells does not produce insulin because the body’s immune system attacks its own pancreas and stops secreting the insulin. Due to this situation, blood glucose levels will increase instead of being absorbed by the body cells. People who have type I diabetes should take insulin daily to live and to maintain the blood sugar levels normal.

Pancreatic islet transplantation
There are two types of pancreatic islet transplantations which are available:

- Allotransplantation
- Autotransplantation.

Pancreatic islet allotransplantation
It is a procedure in which islets from a deceased donor pancreas are purified and transferred into a patient. In pancreatic islet allotransplantation to remove islets from a diseased donor, they use specialized enzymes. Then, the collected islets are purified and counted in the laboratory. A patient receives two transplantations with an average of 500,000–600,000 islets per each transplantation. After implantation, the β-cells in the islets start to release insulin. This type of transplantation is performed in patients whose type I diabetes levels are high and difficult to control. The main aim of this transplantation is to help the patients achieve normal glucose levels without daily insulin injections and eliminate hypoglycemia.

Pancreatic islet autotransplantation
In patients with chronic, long-lasting, and severe pancreatitis, which can be accomplished only by pancreatic islet autotransplantation, the procedure of pancreatectomy is carried out. Pancreatic islet autotransplantation cannot be carried out in the patients with type I diabetes. It is carried out in the hospital and the surgeon will administer general anesthesia to the patient. First and foremost, surgeon will remove the pancreas, followed by pancreatic islets extraction and purification. Using catheter, the islets are infused into the liver of the patient. Then, the infused islets will secrete the insulin which maintains the blood glucose levels.

The advantages of pancreatic islet autotransplantation are an improvement in control of the blood glucose levels and reduce the need for insulin injections to control the blood glucose levels and hindrance of hypoglycemia. Whole pancreas transplantation is the alternative for this method, which is performed along with the kidney transplantation.

Whole pancreas transplantation benefits are less dependent on insulin and longer duration of pancreas function. The main drawbacks with the whole pancreas transplantation are major surgery, which involves major risk of complications.

Immunosuppressive or anti-rejection medications are needed to avoid the rejection, and it is a common problem associated with transplantation.

Immunosuppressive or anti-rejection medications are tacrolimus, sirolimus, and daclizumab. For example, immunosuppressive drugs used in islet transplantation contain alemtuzumab, anti-thymocyte globulin, basiliximab, belatacept, etanercept, everolimus, and mycophenolate mofetil.

Anti-rejection medications have immediate side effects which may include gastrointestinal problems, mouth sores, and stomach upset and risk of developing certain tumors and cancers (Fig. 1).

Diet and nutrition
The person who undergoes pancreatic transplantation should follow a particular diet suggested by the dietician or a health-care provider [6-20].

Stem cells
It is an alternative for transplantable β-cells. These stem cells have a remarkable capacity to develop into different cell types in the body. It...
acts as an internal repair system in many tissues. When the division of stem cells occurs, each divided new cell has the capacity to remain as a stem cell or become different types of cell with a more specific function such as brain cells, muscle cells, and red blood cells (Fig. 2).

Stem cells are available in two potential sources:
1. Embryonic stem cells (ES)
2. Induced pluripotent stem cells.

**ES cells**
ES cells, induced pluripotent stem cells, and pancreas-derived stem cells are able to distinguish into beta-cells. Hepatic stem cell expressing pancreatic and duodenal homeobox-1 (PDX-1) distinguished into beta-cells and improves excessive glucose levels in the blood of diabetic mice. ES cells are separated from blastocysts, and it can be distinguished into ectoderm, endoderm, and mesoderm cells. They can also distinguish into insulin-producing cells, and these cells are able to secrete insulin in response to glucose stimuli and to regulate the glucose levels in the blood of diabetic mice when it transferred into diabetic mice (Fig. 3).

The stem cell production from a pluripotent resource is called as induced pluripotency. For the production of pluripotent stem cells, somatic stem cells are reprogrammed under specific conditions; such type of cells is called as induced pluripotent stem cells. These cells exhibit rise in the activity which is similar to ES cells. These are preferred as the best choice for the cell-based treatment for diabetes mellitus. For the production of induced pluripotent stem cells (iPSC), fibroblast cells are induced and later these cells are converted into pancreatic beta-cells. The transferring of fibroblast-derived beta-cells into diabetic mouse controlled the blood glucose levels [21–26] (Fig. 4).

**Transdifferentiation**
Patients fibroblasts transdifferentiation into pancreatic like cells might render most straightforward clinical application of reprogrammed cells based therapy without the concerns of HESC (human embryonic stem cells) or with HIPS (human induced pluripotent stem cells). For cell replacement therapy, transdifferentiation has become the tendency to produce beta-cell resources. This method depends on cellular reprogramming and regeneration of beta-cells. Regeneration of beta-cells will occur from different pancreatic progenitor cells in the grown person pancreas. Acinar ductal transdifferentiation is a mechanism by which acinar cells are distinguished into duct cells. In addition to this, acinar cells have the capability to distinguish into adipocytes and hepatocyte-like cells, controlled by the microenvironment. 

**Gene therapy**
A foreign gene is introduced into any cell type in the body, permitting it to produce insulin which is called as gene therapy. The introduced gene would be either insulin gene itself or a gene encoding factor which activates the insulin gene, thereby allowing the ectopic production of insulin. Differentiation of stem cell into beta-cells in the patient by means of molecular intervention would be included in this gene therapy.

**Cell replacement therapy**
One of the most potent therapies for diabetes mellitus is cell replacement therapy of insulin-producing cells. This therapy includes the islet cell transplantation contributed by the pancreas of the donor; these cells

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**Fig. 1: Pancreatic islet transplantation**

**Fig. 2: Stem cell transplantation**

**Fig. 3: Embryonic stem cells**

**Fig. 4: Induced pluripotent stem cells**
Cell replacement therapy encompasses all techniques that involve the expansion or creation of \textit{in vitro} insulin-producing cells followed by their implantation in the patient. The cells can be from beta origin, may be immortalized to permit absolute expansion in culture, or manipulate the non-beta-cells to produce insulin. On the other hand, they can be originated from stem cells [29,35-40].

Treatments for type II diabetes mellitus

\textbf{Antihyperglycemic agents}

- Insulin
- Insulin secretagogues
  - Sulfonylureas
  - Meglitinides
- Insulin sensitizers
  - Metformin HCl
  - Thiazolidinedione
- \(\alpha\)-glucosidase inhibitors (AGIs)
- Dipeptidyl peptidase-4 (DPP-4) inhibitors
- Sodium-glucose cotransporter-2 (SGLT2) inhibitors.

\textbf{Insulin}

People who have IDDM cannot formulate insulin because of the damaged or ruined \(\beta\)-cells in their pancreas. For that reason, patients who have type I diabetes will need insulin injections to allow their body to process glucose and to avoid complications from hyperglycemia.

\textbf{Insulin types}

There are different types of insulins. It is categorized from rapid acting to long-acting insulins, from analog insulin through to human insulins. Insulin can be categorized based on how the insulin is derived and how quickly it works.

\textbf{Forms of insulin}

There are three forms of insulin which are available.

1. Analog insulin: Analog insulin is a laboratory-grown human insulin.
2. Animal insulin: Animal insulin comes from animals.
3. Human insulin: Human insulin is laboratory-made insulin.

\textbf{Insulin is administered by two routes (Fig. 6)}

1. Injection
2. Infusion

\textbf{Injection}

\textbf{Insulin syringe}

This is a regular method for insulin delivery. In this method, insulin syringe is an injection device. The disposable, plastic syringes currently are available in three sizes as 30, 50, and 100 units of insulin. The needles are fine with the length ranging from \(\frac{1}{2}\) inch or more for adults and \(\frac{3}{16}\) of an inch for infants. This syringe is injected into the layer of fat just below the skin.

\textbf{Insulin pen}

There are two types of insulin pens which are available.

1. Reusable pens
2. Disposable pens

\textbf{Reusable pens}

The reusable pen is loaded with a cartridge of insulin before its use. 150–300 units of insulin can be held in one cartridge. A cartridge may provide sufficient insulin based on the size of your dose which may last for many days. A new cartridge can be loaded after the usage of the previous one reusable pen can be used generally for many years.

\textbf{Disposable pens}

Disposable pens are filled with insulin and discarded after its use. 300 units of insulin can be held in most of the disposable insulin pens which are more convenient than the reusable pens because no need of filling any cartridges. These are most costlier compared to reusable pens.

\textbf{Infusion}

In a hospital under the medical supervision, insulin may be injected directly into the vein. It is added to intravenous fluids, blood sugar, and insulin doses which are strictly monitored by the specialists. It is only given during the surgery or stay in the intensive care unit.

\textbf{Insulin pump}

It is also known as continuous subcutaneous insulin infusion device. These are the most sophisticated form of insulin delivery. Insulin pumps are computerized devices, small in size that is programmed to transport insulin under the skin. These are durable and last for many years, but certain components of the insulin pump and the insulin supply are changed every few days.
Insulin secretagogues
These are one type of medicine used for type II diabetes treatment. A person with type II diabetes does not make sufficient insulin or body cells have insulin resistance. In that condition, insulin secretagogues help the pancreas to secrete or release insulin. Insulin helps to maintain blood glucose levels normal.

Sulfonylureas
These are the first oral medicine available for the treatment of type II diabetes mellitus. For diabetes treatment, carbutamide is the first clinically useful sulfonylurea [36,41-43].

Types of sulfonylureas
• First-generation sulfonylureas.
• Second-generation sulfonylureas. Drugs comes under sulfonylureas are given in Table 1
• Third-generation sulfonylureas.

Mechanism of action
By stimulating the pancreas to more insulin release, these are effective only when the β-cell activity is still present. It blocks the adenosine triphosphate (ATP)-sensitive K+ channels in β-cells and decreases the K permeability of β-cells. This action causes the Ca2+ entry into the cell and depolarization of the cells, which causes improvement in the secretion of the insulin. The released insulin will reduce the blood glucose levels [41,42,44-47] (Fig. 7).

Table 1: Drugs used in sulfonylureas

<table>
<thead>
<tr>
<th>First‑generation sulfonylureas</th>
<th>Second‑generation sulfonylureas</th>
<th>Third‑generation sulfonylureas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetohexamide</td>
<td>Glibenclamide</td>
<td>Glimepiride</td>
</tr>
<tr>
<td>Chlorpropamide</td>
<td>Gliclazide</td>
<td></td>
</tr>
<tr>
<td>Tolazamide</td>
<td>Glyclopyramide</td>
<td>Gliquidone</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>Glipizide</td>
<td></td>
</tr>
</tbody>
</table>

Meglitinides
These are oral medicines utilized for the treatment of type II diabetes mellitus. Meglitinides work similarly as sulfonylureas. It reduces the blood glucose levels by increasing the secretion of insulin by the pancreas. These are fast acting and disperse quickly, so they frequently must be taken many times a day.

Currently, two forms of meglitinides are available in the market (Table 2).

Mechanism of action
It stimulates the pancreatic insulin secretion and, after meals, reduces the glucose levels rise in the blood [49-53].

Insulin sensitizers
Biguanides
This is one of the classes of medications used for the treatment of type II diabetes mellitus. It starts to lower the blood glucose by two ways. Primarily, it starts to decrease the amount of glucose produced by the liver. It increases the glucose absorption by muscle cell and reduces the insulin resistance.

The only drug used in biguanides is metformin

Table 2: Drugs used in meglitinide category

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Brand name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repaglinide</td>
<td>Prandin</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>Starlix</td>
</tr>
</tbody>
</table>

Table 3: Drugs used in thiazolidinedione category

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Brand name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosiglitazone</td>
<td>Avandia</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Actos</td>
</tr>
</tbody>
</table>

Insulin sensitizers
Biguanides
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The only drug used in biguanides is metformin

Table 4: Drugs used in AGI category

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Brand name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acarbose</td>
<td>Precose</td>
</tr>
<tr>
<td>Miglitol</td>
<td>Glyset</td>
</tr>
</tbody>
</table>

AGI: α-glucosidase inhibitor

Table 5: Drugs used in DPP-4 inhibitor category

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Brand name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin</td>
<td>Januvia</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>Galvus</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>Onglyza</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>Tradjenta</td>
</tr>
</tbody>
</table>

DPP-4: Dipeptidyl peptidase-4

Table 6: Drugs used in SGLT2 inhibitors

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Brand name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>Invokana</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>Farxiga</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>Jardiance</td>
</tr>
</tbody>
</table>

SGLT2: Sodium-glucose cotransporter-2

Fig. 8: Mechanism of the action of metformin

Fig. 9: Mechanism of action of thiazolidinedione
Table 7: List of patents in the treatment of diabetes

<table>
<thead>
<tr>
<th>Title</th>
<th>Patent No.</th>
<th>Inventors</th>
<th>Year</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-4 inhibitor combined with a further antidiabetic agent, tablets compromising such formulations, their use, and process for their preparation</td>
<td>US9155705 B2</td>
<td>Friedl et al.</td>
<td>October 13, 2015</td>
<td>Friedl et al. DPP-4 inhibitor combined with a further antidiabetic agent, tablets compromising such formulations, their use, and process for their preparation, US9155705 B2, 2015</td>
</tr>
</tbody>
</table>

**Metformin**

*Mechanism of action*

Metformin starts its action in two ways. Primarily, it helps to stop the production of new glucose from the liver. It also helps to control the insulin sensitivity by transporting the glucose into cells effectively (Fig. 8).

**Thiazolidinediones**

These are new form of drugs for type II diabetes treatment (Table 3).

**DPP-4: Dipeptidyl peptidase-4**

**Mechanism of action**

It reduces the blood sugar levels by increasing the fat, liver, and muscle sensitivity to insulin. These are referred as insulin sensitizers or euglycemic. It will take the time to show their therapeutic action. The main side effects of this drugs are fluid retention, weight gain, and anemia [54-58] (Fig. 9).

**AGI**

These are widely used in type II diabetes treatment. It delays the carbohydrate absorption from the small intestine and reduces the
postprandial blood glucose levels and insulin levels.

Drugs come under AGIs which are given in Table 4.

AGIs reversibly hinder a number of α-glucosidase enzymes, consequently delaying the absorption of glucose from the gut. The therapeutic effects of AGI are not only based on a delayed complex carbohydrate digestion but also on the metabolic effects of colonic starch fermentation. Acarbose is the most widely prescribed AGI. The other AGIs are voglibose and miglitol [59-63].

**Novel antidiabetic agents**

**DPP-4 inhibitors**

DPP4 inhibitors are a class of oral hypoglycemic agents which block DPP4 enzyme secreted by brush border of the intestine. These are used for type II diabetes treatment (Table 4).

**Mechanism of action**

GLP-1 and incretin secreted by the small intestine. DPP4 enzyme stops the GLP-1and incretin release. DPP4 inhibitors inhibit the DPP4 enzyme production, and because of this action, GLP-1 and incretin production increase in the body. GLP-1 increases the insulin production by inhibiting the glucagon release and reduces the blood sugar levels [64-69] (Fig. 10).

**SGLT2 inhibitors**

**Mechanism of action**

SGLT2 inhibitors are the latest class of oral hypoglycemic agents for type II diabetes mellitus treatment (Table 6).

SGLT2 inhibitor blocks the SGLT2 protein involved in the reabsorption of glucose up to 90% in the proximal renal tubule. It results in increased excretion of the glucose from renal tube and lowers glucose level in the blood. These also increase the insulin sensitivity, decrease glucogenesis, and improve insulin release from pancreatic β-cells [70-75] currently available patents are presented in (Table 7).

**CONCLUSION**

Diabetes mellitus is a slow killer with no curable treatments. On the other hand, its complications can be cut down through proper understanding and appropriate treatment. Three major complications are related to heart attack, kidney damage, and blindness. It is necessary to keep that the blood sugar levels of a patient should be normal to avoid any complications. One of the disadvantages by keeping the blood glucose level will lead to hyperglycemia that creates many severe complications. The objective of this article is to provide an idea about the current status of diabetes mellitus research and innovative therapies for the cure.

**AUTHORS’ CONTRIBUTIONS**

All the authors have contributed equally.

**CONFLICTS OF INTEREST**

There are no conflicts of interest between authors.

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