INTRODUCTION

Diabetes mellitus

Diabetes mellitus is a metabolic and chronic 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 small intestine into the patient’s lower abdomen.
- Then they will attach donor new sections of small intestine containing pancreas to patients small intestine or donor pancreas to patient urinary bladder and pancreas is connected to blood vessels.
- Do not disturb the patient’s pancreas to aid digestion.
- If the patient is also receiving a kidney transplant, the blood vessels of the new kidney will be attached to the lower part of a patient’s abdomen blood vessel.
- 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
Pancreatic islet transplantation and whole pancreas transplantation.

In type I diabetes, pancreatic β-cells does not produce insulin because
they are damaged or destroyed. These damaged β-cells cannot
convert glucose into energy.

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
food into energy.

Pancreatic islet transplantation involves the following steps:

1. Surgeon performs the pancreatic islet transplantation by using general
anesthesia. In this method, the surgeon removes the pancreas from
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.

2. The collected islets are purified and transferred into a patient. In
this method, which is performed along with the kidney transplantation.

The advantages of pancreatic islet transplantation are an
improvement in control of the blood glucose levels and reduce the need
for insulin injections and eliminate hypoglycemia. Whole pancreas transplantation benefits are less dependent on insulin
injection and eliminate hypoglycemia. 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.

Pancreatic islet allotransplantation

This 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 allotransplantation carried out only at hospitals which
have USFDA authorization for clinical research on pancreatic islet
transplantation. The radiologist performs these transplants frequently.
The radiologist uses ultrasound and X-rays to guide the catheter
through a small incision in the upper abdomen. Then, pancreatic islets are
then infused through the catheter slowly into the liver. Usually, a
patient receives a sedative and local anesthetic. In few cases, a
surgeon performs the pancreatic islet transplantation by using general
anesthesia. Patients regularly need two or more transplants to get a
sufficient amount of islets to reduce or stop their need for insulin.

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 allotransplantation 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

Immunosuppressants or antirejection drugs

These are medicines or drugs that lower the body's ability to reject
transplanted organs. These drugs are also called as anti-rejection
drugs.

Immunosuppressants are categorized into:

1. Induction Drugs: These are powerful anti-rejection drugs used at the
time of transplant.
2. 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.
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 regularize 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 rises 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 β-cells. The transferring of fibroblast-derived β-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 HIPSC (human induced pluripotent stem cells). For cell replacement therapy, transdifferentiation has become the tendency to produce β-cell resources. This method depends on cellular reprogramming and regeneration of β-cells. Regeneration of β-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. α-cells have the ability to convert into β-cells in zebrafish by utilizing β-cell ablation model. Glucagon and glucagon-like peptide-1 (GLP-1) have a strong effect on α-to-β cell transdifferentiation, and β-to-α cell transdifferentiation is also feasible in the case of opposition. Suppression of pancreatic duodenal home box 1, forkhead box 01, NK2 homebox 2 and transdifferentiated into α-cells and induced the dedifferentiation of β-cells. δ-cells of the pancreas are capable of transdifferentiate into insulin-producing cells [27-35] (Fig. 5).

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 β-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
will function for years in diabetic patients. 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].

**Treatment for type II diabetes mellitus**

\textbf{Antihypoglycemic agents}

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

**Insulin**

People who have IDDM cannot formulate insulin because of the damaged or ruined β-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.

**Insulin types**

There are different types of insulins. It 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.

**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.

**Insulin is administered by two routes (Fig. 6)**

1. Injection
2. Infusion

**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 ½ inch or more for adults and 3/16\textsuperscript{th} of an inch for infants. This syringe is injected into the layer of fat just below the skin.

**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.

**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 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, cabutamide 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 Ca^2+ 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

| First-generation sulfonylureas | Second-generation sulfonylureas | Third-generation sulfonylureas |
|-------------------------------|--------------------------------|--------------------------------|
| Acetohexamide                 | Glibenclamide                  | Glimepiride                    |
| Chlorpropamide                | Glipizide                      |                                |
| Tolazamide                    | Gliclazide                     |                                |
| Tolbutamide                   | Glyclopyramide                 |                                |

Table 2: Drugs used in meglitinide category

| Generic name | Brand name |
|--------------|------------|
| Repaglinide  | Prandin    |
| Nateglinide  | Starlix    |

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 [40-53].

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 increase 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 3: Drugs used in thiazolidinedione category

| Generic name     | Brand name |
|------------------|------------|
| Rosiglitazone    | Avandia    |
| Pioglitazone     | Actos      |

Insulin sensitizers
Biguanides
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The only drug used in biguanides is metformin

Table 4: Drugs used in AGI category

| Generic name | Brand name |
|--------------|------------|
| Acarbose     | Precose    |
| Miglitol     | Glyset     |

AGI: α-glucosidase inhibitor

Table 5: Drugs used in DPP-4 inhibitor category

| Generic name | Brand name |
|--------------|------------|
| Sitagliptin  | Januvia    |
| Vildagliptin | Galvus     |
| Saxagliptin  | Onglyza    |
| Linagliptin  | Tradjenta  |

DPP-4: Dipeptidyl peptidase-4

Table 6: Drugs used in SGLT2 inhibitors

| Generic name     | Brand name |
|------------------|------------|
| Canagliflozin    | Invokana   |
| Dapagliflozin    | Farxiga    |
| Empagliflozin    | Jardiance  |

SGLT2: Sodium-glucose cotransporter-2

Fig. 8: Mechanism of the action of metformin

Fig. 9: Mechanism of action of thiazolidinedione
**Fig. 10: Mechanism of the action of dipeptidyl peptidase-4 inhibitors**

**Table 7: List of patents in the treatment of diabetes**

| Title                                                                 | Patent No.                  | Inventors       | Year             | References                                                                                   |
|-----------------------------------------------------------------------|-----------------------------|-----------------|------------------|---------------------------------------------------------------------------------------------|
| Substituted aromatic compounds and pharmaceutical compositions for   | WO2016054726 A1            | Gagnon et al.   | April 14, 2016   | Substituted aromatic compounds and pharmaceutical compositions for the prevention and treatment of diabetes, WO2016054726 A1, April 14, 2016 |
| the prevention and treatment of diabetes                              |                             |                 |                  |                                                                                             |
| DPP-4 inhibitor combined with a further antidiabetic agent, tablets   | US9155705 B2                | Friedl et al.   | October 13, 2015 | Friedl et al. DPP-4 inhibitor combined with a further antidiabetic agent, tablets compromising such formulations, ther Brad, and process for their preparation, US9155705 B2, 2015 |
| compromising such formulations, their use, and process for their     |                             |                 |                  |                                                                                             |
| preparation                                                            |                             |                 |                  |                                                                                             |
| Diabetes therapy                                                      | US9149478 B2                | Klein et al.    | October 06, 2015 | Klein et al. Diabetes Therapy, US9149478 B2, 6th Oct 2015                                     |
| Vasoprotective and cardioprotective antidiabetic therapy              | US9034883 B2                | Klein et al.    | May, 19 2015     | Vasoprotective and cardioprotective antidiabetic therapy, US9034883 B2, 19, May 2015.        |
| Combination therapy for the treatment of diabetes and related        | US8513264 B2                | Mark et al.     | August 20, 2013  | Combination therapy for the treatment of diabetes and related conditions, US8513264 B2, August 20, 2013 |
| conditions                                                            |                             |                 |                  |                                                                                             |
| Heterocyclic receptor agonist for the treatment of diabetes and       | US8288384 B2                | Chen et al.     | October 16, 2012 | Heterocyclic receptor agonist for the treatment of diabetes and related conditions, US8288384 B2, October 16, 2012 |
| related conditions                                                    |                             |                 |                  |                                                                                             |
| Uses of DPP-4 inhibitors                                              | US8232281 B2                | Klaus et al.    | July 31, 2012    | Uses of DPP-4 inhibitors, US8232281 B2, July 31, 2012                                     |
| N-linked heterocyclic receptor agonists for the treatment of diabetes | US8183381 B2                | Ma and Rabbat   | May 22, 2012     | N-linked heterocyclic receptor agonists for the treatment of diabetes and metabolic disorders, US8183381 B2, May 22, 2012 |
| and metabolic disorders System and method for distinguishing among    | US8180441 B2                | Gill et al.     | May 15, 2012     | System and method for distinguishing among cardiac ischemia, hypoglycemia, and hyperglycemia using an implantable medical device, US8180441 B2, May 15, 2012 |
| cardiac ischemia, hypoglycemia, and hyperglycemia using an implantable|                             |                 |                  |                                                                                             |
| medical device                                                        |                             |                 |                  |                                                                                             |
| Neural stimulation for treatment of metabolic syndrome and type II    | US7689277 B2                | Dobak III       | March 30, 2010   | Neural stimulation for the treatment of metabolic syndrome and type II diabetes, US7689277 B2, March 30, 2010 |
| diabetes                                                             |                             |                 |                  |                                                                                             |
| Combination therapy for the treatment of diabetes and related        | WO2010029089 A2             | Mark et al.     | March 18, 2010   | Combination therapy for the treatment of diabetes and related conditions, WO2010029089 A2, March 18, 2010 |
| conditions                                                            |                             |                 |                  |                                                                                             |

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

**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).

**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 drug 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 AGIs 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 gluconeogenesis, 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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