Diabetes: A overview on Metabolic Disorder of Carbohydrates Metabolism

Mr. Mahesh B. Kolpe[1], Miss. Kalyanee V. Gavande[2], Dr. Amol N. Khedkar[3], Miss. Vaishnavi K. Mokate [4]

[1,4]Student, Depatment of Pharmaceutical Science, Saikrupa Institute Of Pharmacy, Ghargaon, Ahmednagar, Maharashtra, India -413728
[2]Assistant Professor, Depatment of Pharmaceutical Science, Saikrupa Institute Of Pharmacy, Ghargaon, Ahmednagar, Maharashtra, India -413728
[3]Principal, Depatment of Pharmaceutical Science, Saikrupa Institute Of Pharmacy, Ghargaon, Ahmednagar, Maharashtra, India -413728

Abstract:
Diabetes mellitus (DM) is an increasing epidemic that is causing a significant socioeconomic burden on nations throughout the world. Due to the fact that current treatment approaches have serious side effects and have not addressed the disease's underlying causes, new treatment options for the management of diabetes mellitus are emerging quickly. In order to manage diabetes mellitus, this narrative review examines various treatment plans and the difficulties that come with them. Search engines like Web of Science, Pub med/Medline, and Scopus were used to find published articles on new developments in DM management. Keywords like DM, DM management, and gene therapy were also used to narrow down the results.
According to our research, promising advancements in the treatment of diabetes mellitus have been made through the use of various treatment modalities such as gene therapy, stem cells, nanotechnology, medical nutrition therapy, and lifestyle modification. Many obstacles have been faced when utilizing these techniques, though, such as optimizing them to guarantee the best possible blood pressure, cholesterol, and glucose regulation to reduce complications; enhancing patient adherence to pharmacological and lifestyle interventions; safety concerns; ethical dilemmas; and developing an efficient delivery system, among other things. In summary, pharmacological approaches in conjunction with lifestyle management and their optimization are essential for a clinical treatment plan that is both safe and effective.

Keywords: Diabetes Mellitus; Nanotechnology; Stem Cell; Nano-medicine; Hyperglycemia

1. Introduction
Diabetes mellitus (DM) is a long-standing, complex, and non-transmissible endocrine disease that is expanding quickly, posing clinical challenges worldwide and frequently associated with risks related to patients' complicated metabolic development. It is characterized by high blood levels of fats and glucose, as well as oxidative stress. These factors lead to long-term problems that affect many body organs, including the kidneys, eyes, nerves, and blood vessels. The World Health Organization (WHO)

states that diabetes is an epidemic that has a high risk of mortality and malaise. Approximately 387 million people worldwide suffer from this disorder, and by 2040, that number is expected to rise to over 640 million [1].

A 2017 report published by the International Diabetes Federation (IDF) stated that 425 million people worldwide have diabetes mellitus, of which over 90% are adults, and that 352 million of those people have impaired glucose tolerance (IGT) [2]. Hyperglycemia is not the only complication of type II diabetes mellitus (T2DM); kidney failure, blindness, heart attacks, strokes, and lower limb amputations are among the many complications that can arise [3]. Growing evidence from epidemiological studies has demonstrated that type 2 diabetes is a multifactorial disease influenced by multiple environmental and polygenic factors [1]. Therefore, because of genetic polymorphism and other multiple risk factors, T2DM is too complex to treat..

The annual prevalence of type 2 diabetes is increasing, although obesity-linked T2DM accounts for the majority of cases [5]. It has been estimated that ten percent or so of diabetics also have TIDM. Nonetheless, there is a risk of decreased blood glucose and a protracted risk of complications in the circulatory system associated with both types [6]. There is ample evidence to suggest that achieving normoglycemia will reduce the risk of complications associated with diabetes mellitus [7]. However, in individuals with TIDM, achieving near normoglycemia is limited by hypoglycemia episodes. Unaware of their hypoglycemic state, diabetics are susceptible to TIDM, which prevents them from achieving the necessary glycemic control Many people with TIDM who have recurrent low blood glucose are seen in DM health centers worldwide, and the concept of hypoglycemic unconsciousness presents significant clinical challenges. Fortunately, there are a lot of intriguing and beneficial advancements in the field for people with diabetes mellitus, including gene therapy, according to Bosch and colleagues [8].Currently, injecting insulin-like substances and taking hypoglycemic medications orally are the two main treatment approaches for type 2 diabetes. Though they have many negative effects, these medications are essential for treating type 2 diabetes [9, 10]. Since its discovery, insulin has been the mainstay for the treatment of uncontrolled insulin-deficient diabetes mellitus [11]. It must be acknowledged that the injection of exogenous insulin is essential for survival because of the extreme lack of beta cells. Despite the progress made in understanding the causes, consequences, and persistence of diabetes mellitus, as well as the development of insulin and its analogues, there are still major issues in ensuring precise glycaemic control without adverse side effects like low blood sugar and weight gain [7,12,13]. Thus, this emphasizes even more how crucial it is to use adjuncts or alternative methods in addition to insulin [14]. Thus, various alternative treatment regimens, such as those utilizing nanotechnology and stem cells, are utilized in this narrative review to manage two types of diabetes mellitus. gene therapy, medical nutrition therapy, changing one's lifestyle, and the difficulties posed by these methods.

2. Pathophysiology:

Since DM has a complex pathogenesis and a wide range of presentations, any classification of the disorder is subjective but nonetheless helpful, and it is frequently impacted by the physiological conditions that exist at the time of diagnosis and evaluation. The current classification system is helpful in determining the necessary therapy and is based on both the pathogenesis and the etiology of the disease. Type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM), and diabetes caused or associated with specific conditions, pathologies, and/or disorders are the four main types or categories into which diabetes can be classified [Figure 1].

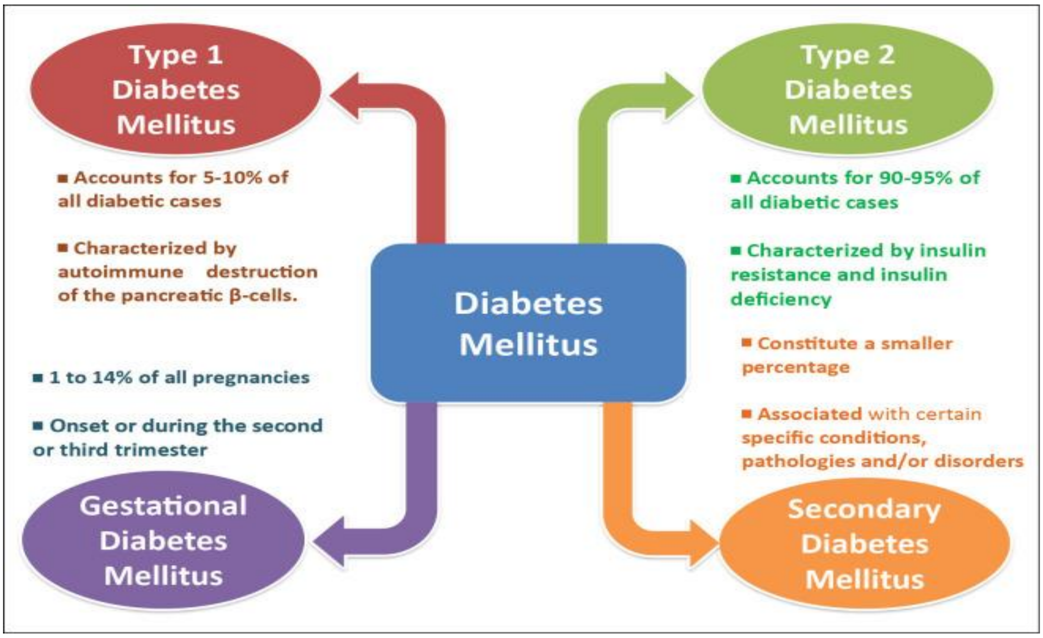


Figure 3[19] : Symptoms of Diabetes

2.1 Types of Diabetic Mellitus:

2.1.1 Type 1 diabetes (B-cell destruction, usually leading to absolute insulin deficiency)[15]

Type 1 diabetes is a chronic (life-long) autoimmune disease that prevents your pancreas from making insulin. Insulin is an important hormone that regulates the amount of glucose (sugar) in your blood. Under normal circumstances, insulin functions in the following steps:

- Your body uses glucose, or sugar, from the food you eat as its primary energy source.
- When glucose enters your bloodstream, your pancreas releases insulin in response.
- Insulin facilitates the uptake of blood glucose by muscle, fat, and liver cells, allowing the teither use it immediately for energy or store it for later. Insulin production by the pancreas is halted when glucose enters your cells and blood glucose levels drop.

Insufficient insulin causes hyperglycemia or elevated blood sugar, which impairs your body's ability to utilize the food you eat as fuel. If left untreated, this can result in major health issues or even death. Type 1 diabetes was previously known as juvenile diabetes and insulin-dependent diabetes.Type 1 diabetes (T1D) can strike anyone at any age, but it is most commonly diagnosed in early puberty (10 to 14 years old) and between the ages of 4 and 6. Type 1 diabetes affects people assigned female at birth almost equally to people assigned male at birth in the United States, where it is most common in non-Hispanic white people.

2.1.2 Symptoms of Type -1diabetes

If a diagnosis is delayed, untreated Type 1 diabetes can be life-threatening due to a complication called diabetes-related ketoacidosis (DKA). Seek emergency medical care if you or your child is experiencing any combination of the following symptoms:

- Fruity-smelling breath.
- Nausea and vomiting.
- Abdominal (stomach) pain.
- Rapid breathing.

- Confusion.
- Drowsiness.
- Loss of consciousness.

2.1.3 Causes of Type-1 Diabetes:

When the insulin-producing cells in your pancreas are unintentionally attacked and destroyed by your immune system, type 1 diabetes results. This breakdown can take place over the course of months or years, leading to an absolute lack of insulin (deficiency).

Even though the precise cause of Type 1 diabetes is still unknown, scientists are certain that heredity plays a significant role. If there is no family history of the illness, there is a 0.4% chance of developing it. You run a 1% to 4% risk if your mother was born into a family with Type 1 diabetes, and a 3% to 8% risk if your father did. Your chance of having Type 1 diabetes can reach 30% if both of your biological parents have the disease.

Scientists believe that if you have a genetic predisposition to developing Type 1 diabetes, then certain things, like a virus or environmental toxins, can set off your immune system to attack cells in your pancreas.

2.1.4 Diagnosis:

Type 1 diabetes is relatively simple to diagnose. If you or your child has symptoms of Type 1 diabetes, your healthcare provider will order the following tests:

2.1.4.1 Blood glucose test:

A blood glucose test is used by your healthcare provider to measure the amount of sugar in your blood. They might ask you to complete a fasting test, which requires you to abstain from food and liquids for at least eight hours prior to the test, and a random test. If the test results indicate that your blood sugar is significantly elevated, you probably have Type 1 diabetes.

2.1.4.2 Glycosylated hemoglobin test (A1C):

Your doctor may perform an A1C test if the results of your blood glucose test show that you have diabetes. Your blood sugar levels are averaged over a period of three months.

2.1.4.3 Antibody test:

This blood test determines whether you have Type 1 or Type 2 diabetes by looking for auto-antibodies. Proteins called auto-antibodies accidentally target the tissue in your body. Type 1 diabetes is indicated by the presence of specific auto antibodies. Most individuals with Type 2 diabetes do not have auto-antibodies.

The following tests are also likely to be ordered by your doctor in order to evaluate your general health and determine whether you have diabetes-related ketoacidosis, a dangerous acute complication of untreated or undetected Type 1 diabetes:

2.1.4.4 The basic metabolic panel

Is a blood test that counts eight different chemicals in your blood. The panel offers useful details about the metabolism and chemical balance of your body.

2.1.4.5 Urinalysis:

An examination of the visual, chemical, and microscopic components of your urine, or pee, is called a urinalysis. It allows providers to measure a variety of aspects of your urine. If you are diagnosed with Type 1, your doctor will probably order a test to look for ketenes, a chemical released by your body when it needs to burn fat for energy instead of glucose. It can be fatal for your blood to become acidic due to an excess of ketenes.

2.1.4.6 Blood gas in the arteries:

To measure the levels of oxygen and carbon dioxide in your blood, an arterial blood gas (ABG) test requires a sample taken from an artery in your body.

2.2 Idiopathic diabetes.

The etiology of certain types of type 1 diabetes is unknown. While some of these patients are predisposed to ketoacidemia and have persistent insulinopenia, they do not exhibit any signs of autoimmunity. Nevertheless, this group of patients with type 1 diabetes is very small. The majority of those who do have Asian or African ancestry. This type of diabetes causes episodes of episodic ketoacidosis and varying degrees of insulin insufficiency in between episodes. This type of diabetes is not HLA related, is strongly inherited, and does not show immunological evidence of B-cell autoimmunity. For affected patients, insulin re-placement therapy may or may not be absolutely necessary.

2.3 Type 2 diabetes (ranging from predominantly insulin resistance with relative insulin deficiency to predominantly an insulin secretary defect with insulin resistance][15]

Diabetes type 2 is a condition in which the body is unable to properly utilize food as fuel. To assist your cells in utilizing glucose (sugar), your pancreas produces the hormone insulin. However, as time passes, your pancreas produces less insulin, and your cells begin to reject it. As a result, your blood sugar levels rise too high. Type 2 diabetes's elevated blood sugar levels can cause major health issues like heart disease, stroke, or even death.

2.3.1

2.3.2 Symptoms:

Symptoms of Type 2 diabetes tend to develop slowly over time. They can include:

- Blurred vision.
- Fatigue.
- Feeling very hungry or thirsty.
- Increased need to urinate (usually at night).
- Slow healing of cuts or sores.
- Tingling or numbness in your hands or feet.
- Unexplained weight loss.

2.3.2 Causes:

- When the body stops responding to insulin and the pancreas produces less insulin than necessary, type 2 diabetes develops. They do not consume sugar in the proper amounts. Your blood sugar level rises. Insulin resistance is the state in which cells don't react to insulin. Usually, it results from:

- Factors related to lifestyle, such as inactivity and obesity.
- Genes that aren't functioning properly in cells, or genetics.

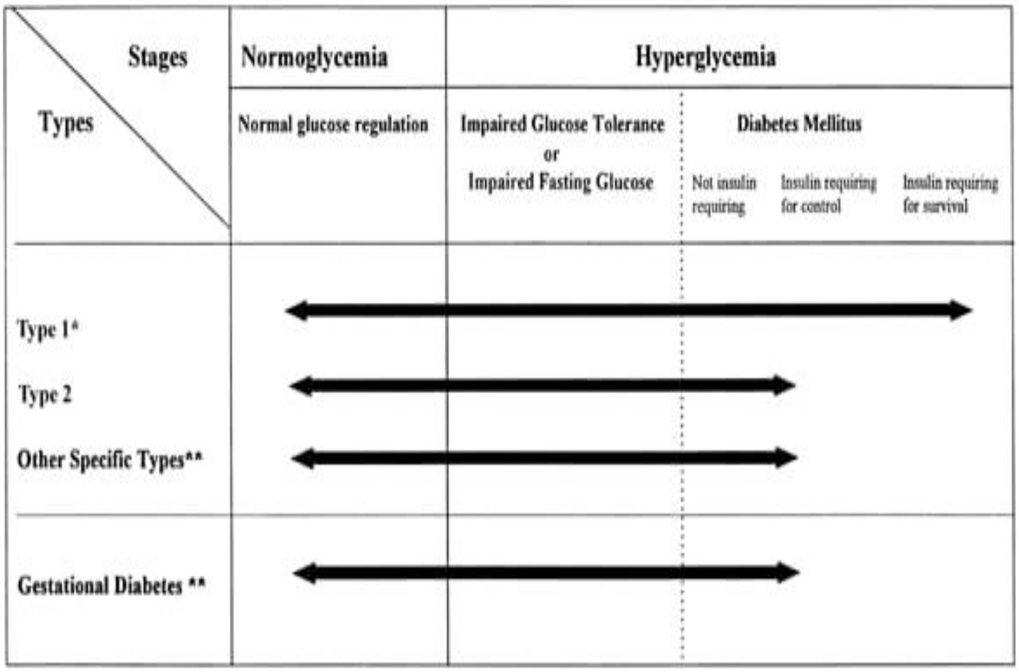


Figure 2 [18] :Disorder of glyacemia: etiology types and stages.

2.4 Gestational Diabetes:

When a woman's blood sugar levels rise too high during pregnancy, she can develop gestational diabetes (GD). Between weeks 24 and 28, midway through a pregnancy, GD typically first manifests.

It is not a guarantee that you had diabetes prior to becoming pregnant if you develop GD. Pregnancy is the cause of the condition's appearance. When it comes to pregnancy, people with Type 1 and Type 2 diabetes face different challenges.

2.5 Type 3C Diabetes:

When your pancreas sustains damage that impairs its capacity to produce insulin, type 3c diabetes develops. Diabetes is caused by damage to the pancreas, which can result from diseases like cystic fibrosis and chronic pancreatitis. Type 3c diabetes is also brought on by a pancreatectomy, which removes the pancreas.

A blood sugar (glucose) level that is too high results in diabetes. It arises when your body isn't reacting to insulin's effects appropriately or when your pancreas isn't producing enough or any of the hormone insulin.

There are two primary roles for your pancreas:

Produces digestive enzymes as part of its exocrine function.

Endocrine function: secretes hormones that regulate blood sugar levels, primarily glucagon and insulin.

Your pancreas's capacity to produce the digestive enzymes is frequently impacted by the pancreatic damage that results in Type 3c diabetes. The term exocrine pancreatic insufficiency (EPI) describes this condition.

Other names for Type 3c diabetes include:
1.Pancreatogenic or pancreatogenous diabetes mellitus.
2.Pancreatic diabetes.
3.Pancreoprivic diabetes.

2.5.1 Symptoms:
It's high blood sugar. There are some people who may not exhibit any symptoms at all, particularly those with type 2 diabetes, gestational diabetes, or prediabetes. The signs and symptoms of type 1 diabetes usually appear more rapidly and intensely.

Symptoms of both type 1 and type 2 diabetes include the following:

- Experiencing an increase in thirst.
- Often urinating.
- Reducing weight naturally.
- Ketoses being present in the pee. A byproduct of the breakdown of fat and muscle that occurs when there is insufficient insulin available is ketenes.
- Feeling worn out and feeble.
- Experiencing mood swings or being agitated.
- Seeing things fuzzy.
- Experiencing slow-healing lesions.
- Recurring infections, including skin, gum, and vaginal infection

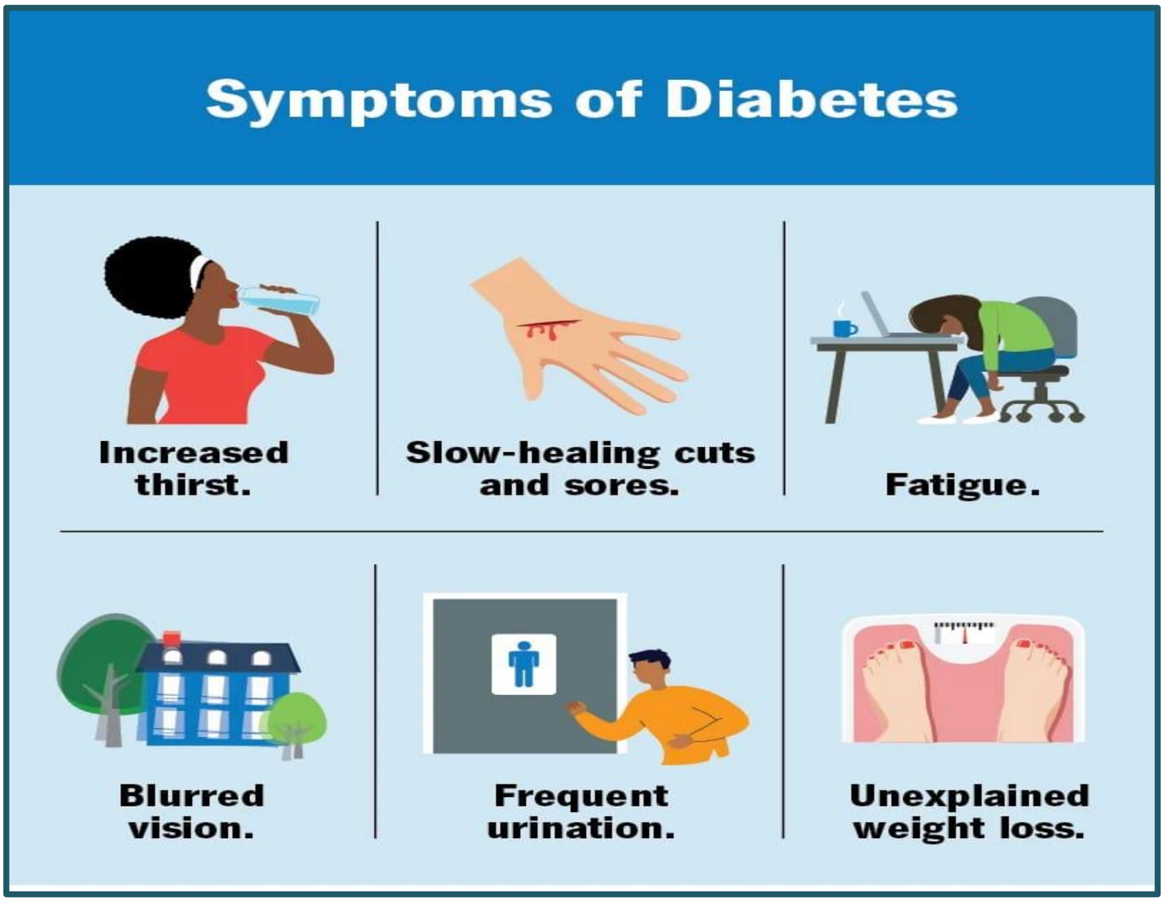


Figure 3 [19] : Symptoms of Diabetes

2.6 Causes of diabetes include:

1.Insulin resistance:

Insulin resistance is primarily responsible for type 2 diabetes. Insulin resistance is the result of your muscles, fat, and liver cells not responding to insulin as they should. Insulin resistance can be caused by a number of conditions and factors, ranging from genetics to obesity, inactivity, poor diet, hormone imbalances, and certain medications.

2.Autoimmune disease:

Your immune system attacking the cells in your pancreas that produce insulin causes type 1 diabetes and LADA.

3.Hormonal imbalances:

Insulin resistance is brought on by hormones released by the placenta during pregnancy. If your pancreas is unable to produce enough insulin to overcome insulin resistance, you may develop gestational diabetes. Type 2 diabetes is also a possible side effect of acromegaly and Cushing syndrome, two other hormone-related disorders.

4.Pancreatic damage:

Your pancreas's capacity to produce insulin may be impacted by a disease, surgery, or injury, which could lead to Type 3c diabetes.

5.Mutations in genes:

MODY and neonatal diabetes can be brought on by specific genetic mutant

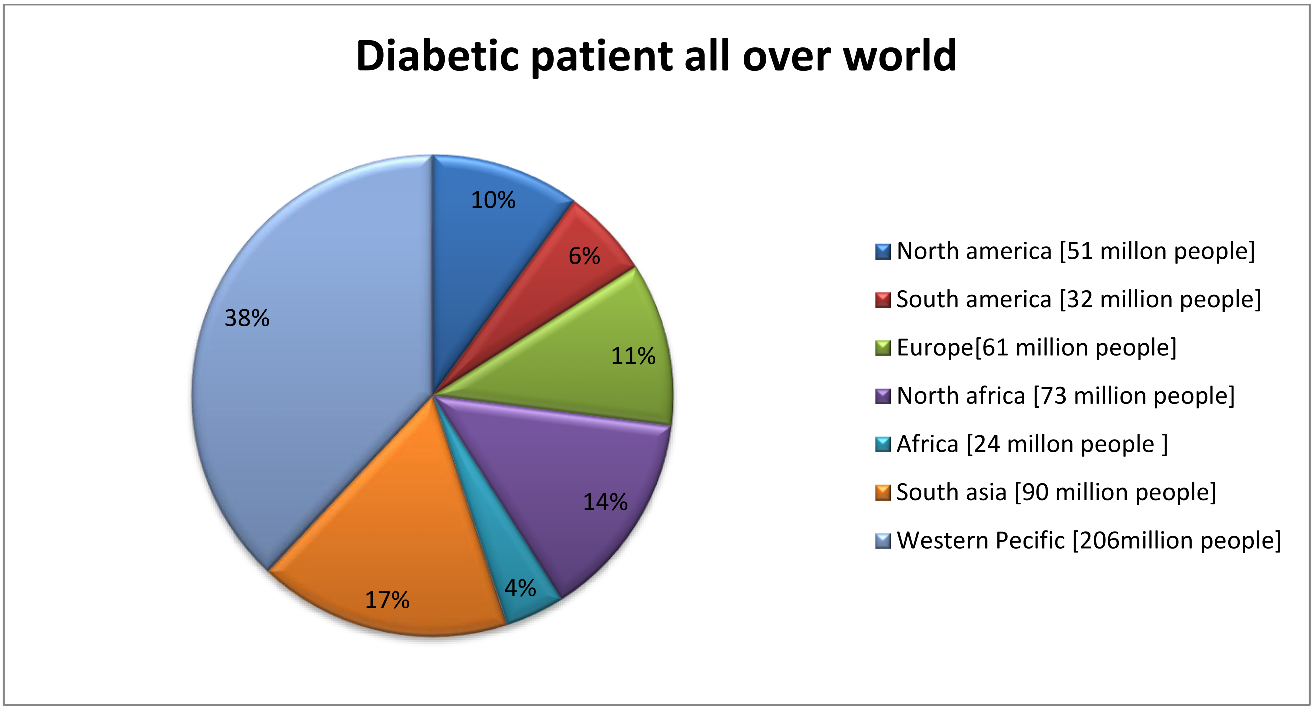


Figure 4: Diabetic patient in all over world 2021

(**Source** :IDF Atlas 10th Edition)

3. Management of Diabetes:

Diabetes is managed using a variety of contemporary strategies. Nonetheless, meeting all goals for DM management depends on early diagnosis [20]. The goal of each patient's treatment is to accomplish a specific result. In order to guarantee a personalized approach to diabetes management, these goals are established from the very first day of the clinic visit.

3.1 Internal Intervention for Lifestyle Modification in Diabetes

Changing one's lifestyle is essential to managing diabetes. Patients with pre-diabetes and diabetes, respectively, should consider it. A healthier diet, more exercise, and a decrease in sedentary behavior are some suggested lifestyle changes. The patient's condition may determine the appropriate exercise. The exercise contributes to a decrease in plasma glucose levels. It is advised that diabetic subjects consume a diet high in fruits, vegetables, and whole grains, steer clear of fattening dairy products and lean meats, and minimize sugar and fattening foods. Reducing alcohol consumption and quitting smoking are two more lifestyle adjustments [21, 22]. Usually, the lifestyle adjustments are customized.

Though the aforementioned tactics aid in the efficient management of diabetes, it may be difficult to communicate with or continually remind the subjects to complete them. Web- or internet-based programs have been implemented to increase adherence to the lifestyle modifications. It is possible to support diabetes self-management with the help of these web-based tactics [23].

3.2 Nanotechnology and Diabetes

Nanoparticles (less than 100 nanometers) are used in nanotechnology. These nanoparticles are created by adjusting certain molecules or atoms within a material. Nanomedicine is the term used to describe the use of nanotechnology in medicine. Combining the understanding of nanotechnology with the application of medications or diagnostic compounds to enhance their ability to target particular cells or tissues is known as nanomedicine. Through the application of cutting-edge nanotechnology-based glucose measurement and insulin delivery techniques, diabetes research has utilized nanotechnology in a number of ways to improve the outcomes of diabetic management in diabetics [24, 25]. Non-invasive methods of delivering insulin and creating a more effective vaccine, such as gene- and cell-based treatments for type I diabetes, are made possible by nanotechnology [24]

The mass of the beta cell provides information about how well it functions in secreting insulin. TIDM is brought on by the gradual loss of beta cells [27]. Using nanotechnology to quickly identify the stage of beta cell loss can enable the rapid application of therapeutic interventions to stop it. For magnetic resonance imaging (MRI), magnetic nanoparticles (MNPs) are an excellent contrast agent due to their unique physical characteristics. This may make it possible to identify the stages of beta-cell loss early on. The aforementioned challenges in CGM can be addressed by nanomedicine. The three main parts of the glucose-sensing apparatus are the transducer, the reporter, and the detector.

.The transducer transforms the measurement into an output signal while the detector measures the glucose level. At last, the reporter transforms the signal into a form that can be understood. In nanotechnology, glucose sensors are typically made of nanoparticles, which are primarily composed of three molecules: glucose oxides', glucose-binding proteins, and glucose-binding small molecules [24, 28]. This allows for an accurate measurement of the glucose level. The accurate and quick detection of glucose is made possible by the coupling of these nanoparticles as transducers [28].

3.3 Medical Nutrition Therapy in Diabetes

A registered dietitian nutritionist offers treatment based on nutrition, which is known as medical nutrition therapy (MNT). In order to help with the management of diabetes mellitus, it includes nutrition diagnosis along with therapeutic and expert counseling services. MNT is essential to the management and education of diabetes. International collaborative groups for diabetes management have made recommendations on MNT in an effort to reform and offer courses for adverse nutritional transition [29, 30]. Because MNT affects glycaemia, for example, it has been used to treat GDM, where carbohydrate (CHO) is the primary causative agent. The Institute of Medicine states that low-CHO diets, which have long been used to treat GDM, are safe and that expectant mothers need at least 175 g of CHO per day. Furthermore, MNT has reportedly had a major impact on patients, particularly women and newborns, and has been shown to be essential in the treatment of other forms of DM [37]. MNT primarily maintains euglycemia by preventing ketogenesis and metabolic acidosis while allowing for adequate weight gain during pregnancy and fetal growth. However, MNT has not yet determined the ideal diet for DM in terms of energy content and the distribution, quality, and quantity of macronutrients [37]. Studies have indicated that, when carbohydrate intake is specifically considered, the nutritional needs of GDM patients are the same for all pregnancy cases. Though the evidence is still preliminary, a low-glycemic index diet has been found to be more beneficial than the traditional intervention of restricting carbohydrates in the management of GDM. Restrictions on calories are essential for managing obesity or overweight.

According to reports, MNT has been tasked with creating signature diet plans that are both patient- and medically-focused. Through this, it is hoped that registered dieticians (RDs) and practicing dialectologists will collaborate to provide nutritional guidelines based on evidence for use by MNT in the management and prevention of DM and related co morbidities. According to indications, MNT may be a highly effective, affordable, and widely available therapeutic approach that is crucial for managing and preventing diabetes [30].

3.4 Gene Therapy and Diabetes Mellitus:

Gene therapy is a technique in which the exogenous normal gene is incorporated to treat the symptoms of a disease caused by a defective gene. Its benefit is that any disease can be cured with a single treatment, and gene therapy is currently creating new treatment options across various medical specialties [31]. These days, gene manipulation includes gene editing and modulation in addition to gene addition [32,11]. Another way to conceptualize gene therapy is as a way to introduce a gene or modify an existing gene within a cell to treat an illness [33]. This strategy aims to correct aberrant genes that have been identified as the causing factor in any disease and to successfully stop the disease from starting or from progressing further. Three main intervention techniques are used in the gene therapy approach: (i) introducing a new gene into the body, (ii) replacing the malfunctioning gene with a functional gene, and (iii) suppressing the malfunctioning genes that cause the illness [34, 35]. Somatic gene therapy and germ line gene therapy are two more subcategories of gene therapy. Germ line gene therapy targets the reproductive cells, whereas somatic gene therapy primarily targets the somatic cells, also known as the diseased cells. The disease is prevented from spreading to future generations by gremlin therapy [35]. The potential of gene therapies to treat a variety of conditions that are challenging to treat with traditional therapies, such as diabetes mellitus, autoimmune disorders, heart diseases, and cancers, has led to their application as a trend in evolving therapeutics [36].

3.5 Stem Cell Therapy in Diabetes:

The traditional methods of treating DM have many negative side effects and fail to address the root causes of the condition. Thus, the search is on for a better alternative treatment plan. Currently, the management of diabetes mellitus (DM) employs a cellular-based therapeutic approach that involves transplanting islets or the pancreas to stimulate the production of insulin-secreting beta cells. Because there aren't enough organ donors, this strategy is limited. These issues prompt research into the viability of creating beta cells from stem cells. One significant tool that may be utilized in the treatment of diabetes mellitus is the unique ability of stem cells to rebuild.. The recent supply/demand issues with islet transplantation may be avoided if a replenish able islets source is developed using stem cells, providing DM patients with a sustained supply of beta cells for insulin secretion. Therefore, research on stem cells has emerged as a viable strategy for the treatment of diabetes mellitus. The goal of stem cell DM therapy is to use pluripotent or multipotent stem cells to replace damaged or malfunctioning pancreatic cells. This method has made use of the potential of different types of stem cells, such as adult stem cells, ESCs, and induced pluripotent stem cells (iPSCs), to create surrogate beta cells or restore the physiological function of beta cells through a variety of techniques.

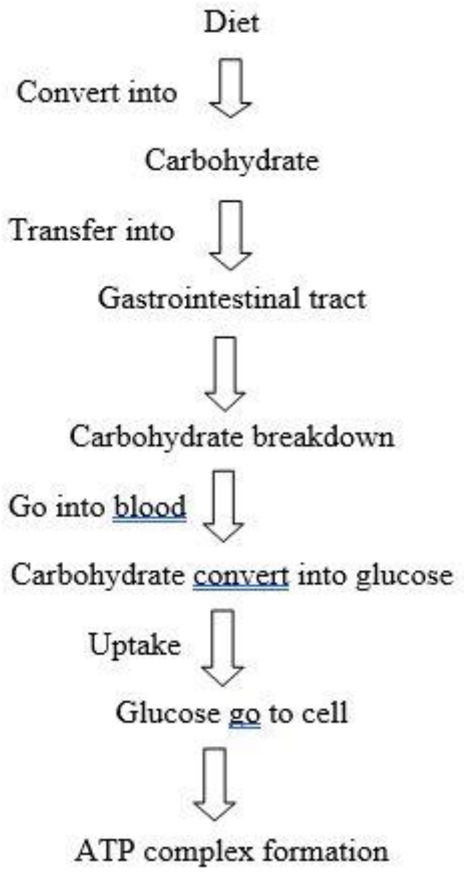
The creation of stem cells from a variety of tissue sources, including adipose tissue, skin, bone marrow, umbilical cord blood, periosteum, and dental pulp, has been made easier by technological advancements. The pancreas is typically the first organ of choice when looking for promising stem cells. Research utilizing animal models has suggested that the optimal pancreatic beta-cell mass could be restored by making a small amount of pancreatic tissue available [38]. This occurs as a result of the pancreatic duct's differentiated beta cells replicating and dedifferentiating, which creates pluripotent cells that produce more beta cells. Further research revealed that it may be possible to create these ducal cell populations in vitro and instruct them to form clusters that synthesize insulin [39, 40]

4. MEDICATION USE IN DM

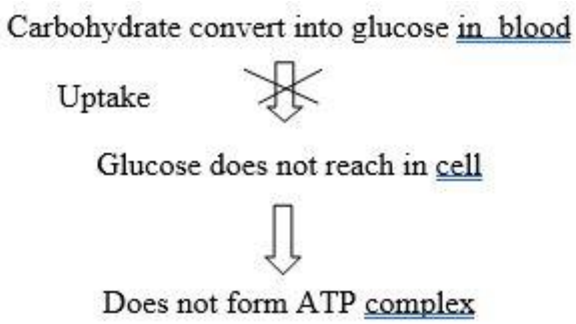
Table 1: Oral anti diabetic drugs

Name Of Drug	Daily Dose Range (mg/day)
Metformin	500/200
Linagliptin	5
Glimepiride	1/6
Pioglitazone	15/30
Vildagliptin	50/100
Teneligliptin	20
Gliclazide	60
Sitagliptin	50/100
Voglibose	0.2/0.6
Canagliflozine	100
Acarbose	25/50
Empagliflogin	10
Injectable Antidiabetic Medications	
Glargine	10/16
Lispro insulin	16/80
Regular insulin	14/34
Combination of insulin: Lispro /lispro protamine 25/75	12/70
Combination of insulin :Regular /NHP (30/70)	10/70

5. Mechanisms of action Glucose form in our body:



5.1 Mechanisms of action of DM:



In our body carbohydrate convert into glucose .By using uptake process glucose reach into cell and form ATP by glucose cycle. But there are uptake process does not work properly because of deficiency of insulin that's why glucose does not reach into cells and does not form ATP complex. In a blood there are glucose level rise in excessive amount and cause Hypoglycemia.

5.2 Insulin:

It helps to uptake process that is glucose reach into cells. Regulating the metabolism of carbohydrates is insulin, a polypeptide hormone. It assists in transferring blood glucose into the body's cells, where it is digested to provide energy. It keeps the amount of glucose in the bloodline. Insulin increases the uptake of glucose by muscle, liver, and fat cells, hence lowering blood glucose concentrations when they rise. These tissues transform extra glucose into glycogen. Blood glucose is converted back to glycogen and released as blood glucose concentration falls. By boosting DNA replication and protein synthesis, it contributes to the control of amino acid absorption. Insulin enables fat cells to absorb lipid from the blood, facilitating the production of fatty acids. Moreover, it reduces lipolysis, gluconeogenesis, and proteinolysis.

6. Conclusion:

The growing trend in DM cases suggests that the condition will continue to worsen for many more years. DM has now become a public clinical challenge that needs immediate attention. As of right now, DM has no long-term treatment. The management of DM has shown encouraging outcomes from a variety of treatment plans. Nevertheless, diabetes mellitus (DM) is still a severe problem that could endanger public health, even with the promise of these massive treatment programs. For a clinical management plan to be strong, effective, and safe, the issues with each of these approaches must be resolved. Encouraging proper education and support for improving diet, increasing physical activity, and reducing body weight is necessary for optimal metabolic regulation of blood pressure, glucose, and body weight.

In order to effectively and successfully manage the control of this disease, it is necessary to prioritize public policies that support health care resources and access, to promote a patient-centered care approach, and to establish environmental infrastructures that promote health.

References:

1. Giovanni, P.; Howes, M.J.R.; Edwards, S.E. Medicinal plants used in the traditional management of diabetes and its sequelae in Central America: A review. J. Ethnopharmacol. 2016, 184, 58-71. [CrossRef] [PubMed]
2. International Diabetes Federation. Data from: IFD Diabetes Altas Globally, IDF Diabetes Atlas, 8th ed, 2017. Available online: https://diabetesatlas.org/upload/resources/previous/files/8/ADFIle - Dia (accessed on 11 May 2022)
3. WHO. Global Report on Diabetes; WHO: Geneva, Switzerland, 2016. Available online: http://www.who.int/diabetes/global- report/en/ (accessed on 11 May 2022).
4. Wu, Y.; Ding, Y.; Tanaka, Y.; Zhang, W. Risk Factors Contributing to Type 2 Diabetes and Recent Advances in the Treatment and Prevention. Int. J. Med. Sci. 2014, 11, 1185-1200. [Cross Ref]
5. Group, T.D.P. Incidence and trends of childhood Type 1 diabetes worldwide 1990-1999. Debate. Med. 2006, 23, 857-866. [Cross Ref]
6. Rask-Madsen, C.; King, G.L. Vascular complications of diabetes: Mechanisms of injury and protective factors. Cell Metab, 2013, 17,20-33. [Cross Ref] [PubMed]
7. Diabetes Control and Complications Trial Research Group; Nathan, D.M.; Genuth, S.; Lachin, J., Cleary, P., Crofford, O.; Davis, M Rand, L.; Siebert, C. The effect of Intensive Treatment of diabetes on the development and progression of ling-term complications in insulin-dependent diabetes mellitus. N. Engl. J. Med. 1993, 329, 977-986. [PubMed]
8. Callejas, D.; Mann, C.J.; Ayuso, E.; Lage, R.; Grifoll, I.; Roca, C.; Andaluz, A.; Ruiz-de Gopegui, R.; Montané, J.; Muñoz, S.; et a Treatment of diabetes and long-term survival after insulin and glucokinase gene therapy. Diabetes 2013, 62,1718-1729
9. Palmer, S.C.; Mavridis, D.; Nicolucci, A.; Johnson, D.W.; Tonelli, M.; Craig, J.C.; Maggo, J.; Gray, V.; De Berardis, G.; Ruospo, M.; et al. Comparison of clinical outcomes and adverse events

associated with glucose-lowering drugs in patients with type 2 diabetes a meta-analysis. J. Am. Med. Assoc. 2016, 316, 313-324. [Cross Ref] [PubMed]

10. Defronzo, R.; Fleming, G.A.; Chen, K.; Bicsak, T.A. Metformin-associated lactic acidosis: Current perspectives on causes and risk Metab. Clin. Exp. 2016, 65, 20-29. [CrossRef]
11. Banting, F.G.; Best, C.H. Pancreatic extracts. J. Lab. Clin. Med. 1990, 115, 254-272. [PubMed]
12. Control, T.D.; Trial, C. Hypoglycemia in the diabetes control and complications trial. Diabetes 1997, 46, 271-286. [Cross Ref]
13. Group, T.D.R. Weight gain associated with intensive therapy in the diabetes control and complications trial. Diabetes Care 1988,11, 567-573. [CrossRef]
14. Meek, T.H.; Morton, G.J. The role of leptin in diabetes: Metabolic effects. Diabetologia 2016, 59, 928-932. [Cross Ref] [PubMed]
15. https://my.clevelandclinic.org/health/diseases/7104-diabetes
16. https://www.mayoclinic.org/diseases conditions/diabetes/symptoms-causes/syc-20371444
17. https://images.app.goo.gl/kGvHijSX6USG6peM6
18. https://images.app.goo.gl/wXgzjWRGA9P8qGsh7
19. https://images.app.goo.gl/mqrnVFhqfnQnDEfw9
20. Herman, W.H.; Ye, W.; Griffin, S.J.; Simmons, R.K.; Davies, M.J.; Khunti, K.; Rutten, G.E.H.M.; Sandbaek, A.; Lauritzen, T.; Borch-Johnsen, K.; et al. Early detection and treatment of type 2 diabetes reduce cardiovascular morbidity and mortality: A simulation of the results of the Anglo-Danish-Dutch study of intensive treatment in people with screen-detected diabetes in primary care (ADDITION-Europe). Diabetes Care 2015, 38, 1449-1455. [CrossRef] [PubMed]
21. Franz, M.J. Lifestyle modifications for diabetes management. Endocrinol. Metab. Clin. North Am. 1997, 26, 499-510. [Cross Ref]
22. Chong, S.; Ding, D.; Byun, R.; Comino, E.; Bauman, A.; Jalaludin, B. Lifestyle changes after a diagnosis of type 2 diabetes. Diabetes Spectr. 2017, 30, 43-50. [Cross Ref]
23. Cotter, A.P.; Durant, N.; Agne, A.A.; Cherrington, A.L. Internet interventions to support lifestyle modification for diabetes management: A systematic review of the evidence. J. Diabetes Its Complicat. 2014, 28, 243-251. [Cross Ref]
24. Veiseh, O.; Tang, B.C.; Whitehead, K.A.; Anderson, D.G.; Langer, R. Managing diabetes with nanomedicine: Challenges and opportunities. Nat. Rev. Drug Discov. 2014, 14, 45-57. [CrossRef]
25. Disanto, R.M.; Subramanian, V.; Gu, Z. Recent advances in nanotechnology for diabetes treatment. Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol. 2015, 7, 548-564. [Cross Ref] [PubMed]
26. Lemmerman, L.R.; Das, D.; Higuita-Castro, N.; Mirmira, R.G.; Gallego-Perez, D. Nanomedicine-Based Strategies for Diabetes: Diagnostics, Monitoring, and Treatment. Trends Endocrinol. Metab. 2020, 31, 448-458. [CrossRef] [PubMed]
27. Weir, G.C.; Bonner-Weir, S. Five stages of evolving beta-cell dysfunction during progression to diabetes. Diabetes 2004, 53 (Suppl.3).[CrossRef] [PubMed]
28. Scognamiglio, V. Nanotechnology in glucose monitoring: Advances and challenges in the last 10 years. Biosens. Bioelectron. 2013 47, 12-25. [Cross Ref]
29. Garber, A.J.; Abrahamson, M.J.; Barzilay, J.1.; Blonde, L.; Bloomgarden, Z.T.; Bush, M.A.; Dagogo-Jack, S.; DeFronzo, R.A.; Einhorn, D.; Fonseca, V.A.; et al. Consensus statement by the American association of clinical endocrinologists and American college of endocrinology on the

comprehensive type 2 diabetes management algorithm-2018 executive summary. Endocr. Pract. 2018, 24, 91-120. [CrossRef]

30. Viswanathan, V.; Krishnan, D.; Kalra, S.; Chawla, R.; Tiwaskar, M.; Saboo, B.; Baruah, M.; Chowdhury, S.; Makkar, B.M.; Jaggi, S. Insights on Medical Nutrition Therapy for Type 2 Diabetes Mellitus: An Indian Perspective. Adv. Ther. 2019, 36, 520-547. [Cross Ref]
31. Dunbar, C.E.; High, K.A.; Joung, J.K.; Kohn, D.B.; Ozawa, K.; Sadelain, M. Gene therapy comes of age. Science 2018, 175. [Cross Ref]
32. Xu, R.; Li, H.; Lai-yin, T.; Hsiang-fu, K.; Lu, H.; Lam, K. Diabetes Gene Therapy: Potential and Challenges. Curr. Gene Ther. 2003,3, 65-82. [Cross Ref]
33. Wong, M.S.; Hawthorne, W.J.; Manolios, N. Gene therapy in diabetes. Self/Nonself 2010, 1, 165-175. [Cross Ref]
34. Mali, S. Delivery systems for gene therapy. Indian J. Hum. Genet. 2013, 19, 3-8. [Cross Ref]
35. Kaufmann, K.B.; Büning, H.; Galy, A.; Schambach, A.; Grez, M. Gene therapy on the move. EMBO Mol. Med. 2013, 5, 1642-1661.[Cross Ref]
36. Tsokos, G.C.; Nepom, G.T. Gene therapy in the treatment of autoimmune diseases. J. Clin. Investig. 2000, 106, 181-183. [Cross Ref]
37. Mccall, M.D.; Toso, C.; Baetge, E.E.; Shapiro, A.M.J. Are stem cells a cure for diabetes? Clin. Sci. 2009, 118, 87-97. [Cross Ref] Abdulazeez, S.S. Diabetes treatment: A rapid review of the current and future scope of stem cell research. Saudi Pharm. J. 2015, 23, 333-340. [CrossRef]
38. Bonner-Weir, S.; Baxter, L.A.; Schuppin, G.T.; Smith, F.E. A second pathway for regeneration of adult exocrine and endocrine pancreas: A possible recapitulation of embryonic development. Diabetes 1993, 42, 1715-1720. [Cross Ref]
39. Bonner-Weir, S.; Taneja, M.; Weir, G.C.; Tatarkiewicz, K.; Song, K.H.; Sharma, A.; O'Neil, J.J. In vitro cultivation of human islets from expanded ductal tissue. Proc. Natl. Acad. Sci. USA 2000, 97, 7999-8004. [Cross Ref] [PubMed]
40. Gao, R.; Ustinov, J.; Pulkkinen, M.A.; Lundin, K.; Korsgren, O.; Otonkoski, T. Characterization of endocrine progenitor cells and critical factors for their differentiation in human adult pancreatic cell culture. Diabetes 2003, 52, 2007-2015. [Cross Ret] [PubMed].
41. Schwartz TW. The processing of peptide precursors. In Okamoto, H. (ed.) Molecular biology of the islets of lang-erhans. Cambridge: Cambridge University Press, 1990:153-205.
42. Docherty K, Steiner DF. Post-translational proteolysis in polypeptide hormone biosynthesis. Annu Rev Physiol 1982; 44: 625-638.
43. Seidah NG, Chrétien M. Proprotein and prohormone convertases of the subtilisin family recent developments and future perspectives. Trends Endocrinol Metab 1992; 3(4): 133-140.
44. Chance RE, Ellis RM, Bromer WW. Porcine proinsulin: characterization and amino acid sequence. Science 1968;161(3837): 165-167.
45. Cutfield JF, Cutfield SM, Dodson EJ, Dodson GG, Em-din SF, Reynolds CD. Structure and biological activity of hagfish insulin. J Mol Biol 1979; 132(1): 85-100.
46. Bajaj M, Blundell TL, Pitts JE, et al. Dogfish insulin. Eur J Biochem 1983; 135(3): 535-542.
47. Pollock HG, Kimmel JR, Hamilton JW et al. Isolation and structures of alligator gar (lepisosteus spatula) insulin and pancreatic polypeptide. Gen Comp Endocrinol 1987; 67(3): 375-382.

48. Alberti KG, Zimmet PZ. Consultation W. Definition, di-agnosis and classification of diabetes mellitus and its com-plications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. Dia-bet Med 1998; 15(7): 539-553.
49. Bennett P. New data, fresh perspectives: diabetes atlas. Di-abet Voice 2007; 52(1): 46-48.
50. Modi P, Mihic M, Lewin A. The evolving role of oral insu-lin in the treatment of diabetes using a novel RapidMis-tTM System. Diabetes Metab Res Rev 2002; 18 (Suppl 1):
51. Cefalu WT. Concept, strategies, and feasibility of noninva-sive insulin delivery. Diabetes Care 2004; 27(1): 239-246.
52. Morihara K, Oka T, Tsuzuki H. Semi-synthesis of human insulin by trypsin-catalysed replacement of Ala-B30 by Thrin porcine insulin. Nature 1979; 280(5721): 412-413.
53. Markussen J. The advent of human insulin in diabetes therapy. Medicographia 1982; 4(1): 39-44.
54. Chan SJ, Weiss J, Konrad M, et al. Biosynthesis and periplasmic segregation of human proinsulin Esche-richia coli. Proc Natl Acad Sci USA 1981; 78(9): 5401-5405.
55. Markussen J, Havelund S, Kurtzhals P, et al. Soluble, fatty acid acylated insulins bind to albumin and show pro-tracted action in pigs. Diabetologia 1996; 39(3): 281-288.
56. Boothe J, Nykiforuk C, Shen Y, et al. Seed-based expression systems for plant molecular farming. Plant BiotechnolJ 2010; 8(5): 588-606.
57. Arakawa T, Yu J, Chong DKX, Hough J, Engen PC, Langridge WH. A plant-based cholera toxin B subunit–insulin fusion protein protects against the development of autoimmune diabetes. Nat Biotechnol 1998; 16(10):934-938.