International Journal of Scientific Research in Science and Technology
Print ISSN: 2395-6011 | Online ISSN: 2395-602X (www.ijsrst.com)
doi : https://doi.org/10.32628/IJSRST

Diabetes Mellitus : The Epidemic for Next Generation

[1]Reeshita Jhanak, IIMT college of Pharmacy Greater Noida, Uttar Pradesh
[2]Riya Raha, IIMT college of Pharmacy Greater Noida, Uttar Pradesh

ARTICLEINFO

Article History:

Accepted: 05 May 2023
Published: 20 May 2023

Publication Issue
Volume 10, Issue 3
May-June-2023

Page Number
264-273

ABSTRACT

Diabetes mellitus (DM), additionally recognized virtually as diabetes is a complicated metabolic sickness characterised with the aid of using hyperglycemia, a physiologically odd situation represented with the aid of using endured extended blood glucose levels. Hyperglycemia effects from anomalies in both insulin secretion or insulin movement or each and manifests in a persistent and heterogeneous way as carbohydrate, fat, and protein metabolic dysfunctions. The structural and practical disruptions in organ machine vasculature result in micro- and macrovascular headaches. Organ damage, dysfunction, and, ultimately, organ failure represent those headaches and have an effect on frame organs, which encompass, in particular, eyes, kidneys, coronary heart, and nerves. The cerebrovascular disease, peripheral arterial disease, and coronary coronary heart disease, collectively termed as atherosclerotic cardiovascular disease, are of not unusualplace incidence in diabetes and represent one of the main reasons of diabetes-related morbidity and mortality.

Keywords – Diabetes mellitus, hyperglycemia, insulin, GLUT4, TIOM

I. INTRODUCTION

Diabetes with its ever-growing international incidence has emerged as one of the maximum crucial and difficult fitness troubles confronting the human populace of the prevailing international. The growth in the superiority of diabetes in maximum areas throughout the globe has been parallel to the fast monetary development, main to urbanization and adoption of present day way of life habits. [1] In the 12 months 2019, the variety of person humans elderly 20–seventy nine years with diabetes has been anticipated to be approximately 463 million, which represents 9. 3% of the whole international person populace. By the 12 months 2030, this variety has been anticipated to growth to 578 million, representing 10.2% of the whole international person populace and similarly growth to seven hundred million via way of means of the 12 months 2045, which represents 10.9% of the whole international person populace. In the 12 months 2019, the superiority of diabetes amongst males and females has been anticipated to be 9.6% and 9.0%, respectively, of the whole respective gender international population. [2] Furthermore, withinside the 12 months 2019, about 4.2 million person humans elderly 20–ninety nine years died because of diabetes, and its related headaches and fitness expenditure ondiabetes

anticipated to at the least 760 billion USD, which represents 10% of the whole spending on adults. Diabetes all through being pregnant has been anticipated to have affected greater than 20 million stay births (1 in 6 stay births) withinside the 12 months 2019. [3]

II. PATHOPHYSIOLOGY OF DIABETES

A multitude of systems and pathways work together in the human body to achieve and maintain a healthy physiological state. The ability of the organism to maintain a consistent stable condition, or homeostasis, is at the heart of these activities. The development of an injury or a diseased condition in numerous organs is caused by a disruption in homeostasis. OM impairs a person's ability to control the amount of glucose in their blood, leading in a variety of severe and small consequences. The regulation of glucose levels in the blood is mostly dependent on a negative feedback loop, which is activated by the release of insulin and glucagon. When blood glucose levels are high, the B-cells of the pancreatic islet of Langerhans are triggered to release insulin, a 51-amino-acid polypeptide made up of two chains (A and B) linked by di-sulphide bridges. The pro-hormone convertases (PC I and PC2), as well as exo-protease carboxypeptidase, produce insulin from pro-insulin. [4] Insulin and Cs peptide are produced by the motion of the enzymes. [4] Insulin binds to the tyrosine kinase insulin receptor, which is made up of extracellular and intramembrane subunits linked by disulfide bonds. Insulin stimulates the phosphorylation of the B-subunit of the tyrosine kinase insulin receptor by interacting to it. Insulin indicators the liver to transform the extra glucose to glycogen for storage; it additionally triggers different cells withinside the body (adipose/ skeletal muscle cells) to take in extra glucose through the translocation of glucose transporter (GLUT4) to the molecular surface.

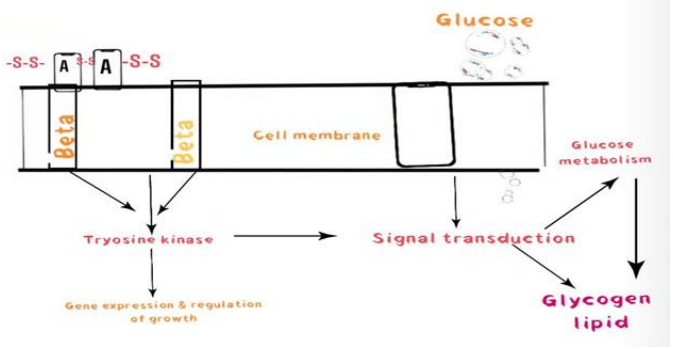

Figure 1. Insulin action. The binding of insulin to the a subunits of the insulin receptor activates the tyrosine kinase in the f subunit promoting autophosphorylation of the subunit. Insulin signals the liver to convert the excess glucose to glycogen for storage; Other cells in the body (adipose skeletal muscle cells) are also triggered to take up more glucose via the glucose transporter (GLUT4), which is brought to the cell surface in response to action insulin.

This helps to bring circulation glucose levels back to normal. When blood glucose levels are low, pancreatic cells are prompted to produce glucagon. To establish homeostasis, glucagon instructs the liver to convert stored glycogen into glucose, which is then released into the bloodstream. There is an abnormality in the synthesis or secretion of insulin in diabetes, as shown in Type I diabetes mellitus (T10M) and pancreatic duct stenosis, or the development of insulin resistance or subnormal production in Type 2 diabetes (T20M) and certain secondary diabetes[5].

Acute Neurological Disorders Associated with Diabetes Mellitus

In patients with acute diabetic ketoacidosis, neurological symptoms of fatigue, headache, and declining level of consciousness leading to coma develop as glucose values exceed 20 mmol/liter (360 mg/dl) over hours to days. Neurological symptoms improve with rehydration, insulin therapy, and the correction of acidosis and other electrolyte abnormalities. In some patients, however, there may be deterioration of the level of consciousness associated with cerebral edema during the correction

of high glucose levels. Nonketotic hyperglycemia is associated with high glucose levels (433 mmol/l (600 mg/dl)) without acidosis, but may be complicated by confusion, coma, or focal (stroke-like) neurological abnormalities. Abrupt lowering of glucose levels below normal levels (o2.7 mmol/l (50 mg/dl)) may be associated with anxiety, tremulousness, confusion, sweating, tachycardia, and eventual loss of consciousness. [5] Seizures are a common complication of hypoglycemia, and some patients may also have focal (stroke-like) neurological abnormalities on examination. If uncorrected, permanent injury to cerebral cortical neurons may ensue, resembling the injury that occurs following ischemic and hypoxic brain injury (as occurs during acute and severe reductions in the blood or oxygen supply to the brain). Hypoglycemia may arise from insulin overdose (intentional or nonintentional), insulin-secreting tumors (insulinomas), liver disease, and other less common disorders [6].

Chronic Neurological Disorders Associated with Diabetes Mellitus

Atherosclerosis, Stroke, and Leukoencephalopathy Chronic diabetes mellitus is associated with accelerated atherosclerosis. Diabetics have a two- to fourfold greater risk of fatal cardiovascular events (strokes and myocardial infarction). Because of both atherosclerosis and the detrimental effects of hyperglycemia in increasing the extent and severity of infarction, diabetes is linked to more frequent and severe cerebral infarction (stroke). [6] Stroke occurs most commonly from narrowing or ulceration (erosion) of the inside wall of an atherosclerotic artery (generating unstable thrombi that are shed farther downstream as clots known as emboli) or occlusion of large vessels supplying the brain. Narrowing of the internal carotid artery at or beyond the bifurcation of the common carotid artery into its external and internal divisions is particularly common, and may be treated surgically if the narrowing is greater than 67% and causes symptoms. In addition, infarctions may occur from atherosclerosis of the vertebrobasilar arterial supply of the brain or the aortic arch. [5] Strokes cause partial or complete motor paralysis, loss of sensation, loss of vision, and impairment of speech. Cerebral infarction or stroke may also occur because of coronary artery disease that results in abnormalities of cardiac wall motion or rhythm, which in turn cause local clots or emboli to dislodge and occlude cerebral vessels. Over time, diabetes causes changes in brain structure and function. White matter abnormalities, also known as leukoencephalopathy, and general cerebrum shrinkage are prominent among these alterations. In certain cases, these alterations may be linked to cognitive impairment and dementia. Microangiopathy, or damage to small cerebral blood vessels, and direct damage to neurons and axons of the brain may be among the mechanisms[7].

Diabetes is due to either the pancreas not producing enough insulin, or the cells of the
body not responding properly to the insulin produced. There are three main types of
diabetes mellitus:

- Type 1 DM results from the body's failure to produce enough insulin. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes". The cause is unknown
- Type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly. As the disease progresses a lack of insulin may also develop. This form was previously referred to as "non-insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes". The primary cause is excessive body weight and not enough exercise.
- Gestational diabetes, is the third main form and occurs when pregnant women without a previous history of diabetes develop a high blood glucose level.

- Diabetes is due to either the pancreas not producing enough insulin, or the cells of the body not responding properly to the insulin produced. There are three main types of diabetes mellitus:
- Type 1 DM results from the body's failure to produce enough insulin. This form was previously referred to as "insulin-dependent diabetes mellitus"
- (IDDM) or "juvenile diabetes". The cause is unknown
- Type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly. As the disease progresses a lack of insulin may also develop. This form was previously referred to as "non insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes". The primary cause is excessive body weight and not enough exercise.
- Gestational diabetes, is the third main form and occurs when pregnant women without a previous history of diabetes develop a high blood glucose level.
- Diabetes is due to either the pancreas not producing enough insulin, or the cells of the body not responding properly to the insulin produced. There are three main types of diabetes mellitus:
- Type 1 DM results from the body's failure to produce enough insulin. This form was previously referred to as "insulin-dependent diabetes mellitus"
- (IDDM) or "juvenile diabetes". The cause is unknown
- Type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly. As the disease progresses a lack of insulin may also develop. This form was previously referred to as "non-insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes". The primary cause is excessive body weight and not enough exercise.
- Gestational diabetes, is the third main form and occurs when pregnant women without a previous history of diabetes develop a high blood glucose level[8].

III.CLASSIFICATION OF DIABETES MELLITUS

It is critical to appreciate that on is a broad term used for a group of diseases that lead to prolonged hyperglycemia. The categorization of diabetes is based on the differences in the processes that cause each kind to develop.

Type I Diabetes Mellitus: T1DM, formerly referred to as insulin based diabetes or juvenile onset diabetes is an autoimmune sickness that entails the destruction of the cells through activated C04+ and C08+ T cells and macrophages infiltrating the pancreatic islets. [9] T1DM usually begins in childhood or in adulthood. (Some patients have a different kind of T1DM called idiopathic diabetes, which does not include autoimmunity). It is seen in African and Asian populations, and is significantly less common than autoimmune T1DM. Although the origin and pathophysiology are unknown, the patients lack insulin production and are prone to ketoacidosis in the absence of antibodies against thirteen cells. [10] Every other kind of T1DM is fulminant Type I Diabetes Mellitus, which involves the rapid and virtually complete loss of thirteen cells.

Type 2 Diabetes Mellitus: T2DM is distinguished by the approach of inadequate insulin production and secretion as a result of insulin resistance. It is generally identified after the fourth decade of life, and debts for approximately 90% of all diabetes worldwide. [11] The occurrence and prevalence of T2DM are placed to increase with age. T2DM is divided into two subgroups: diabetes with and without weight concerns. Obese T2DM patients often have increased resistance to endogenous insulin due to changes in mobile receptors, which is linked to the distribution of stomach fat.

In non-overweight T2DM there's a few insulin resistance on the put up receptor degrees further to a deficiency in insulin manufacturing and release. Since weight problems and aberration of metabolic elements are vital to the prevalence of TIDM, In emerging abroad locations, truly good modifications in weight loss programme and lifestyle lead to the greatest prevalence of diabetes in those countries.[12]

IV.OTHER CLASSIFICATION OF DIABETES MELLITUS

Gestational Diabetes

GDM stands for gestational diabetes mellitus, which describes the onset of diabetes throughout pregnancy and its resolution at the conclusion of the pregnancy. During pregnancy and the gestational period, females go through a great deal of glucose fluctuations and often experience accelerated starvation. A temporary status of insulin resistance is caused by an increase in insulin secretion by the placenta and a deterioration in insulin sensitivity at the end of the first trimester. Although this form of diabetes resolves at the end of the gestational period, certain complications may develop which may be irreversible. For-example gestational diabetes markedly increases the risk of mortality in both mother and fetus and is a potential teratogen. Furthermore, diabetic nephropathy in GDM can lead to pre-eclampsia, which is linked to a variety of fetal development disorders such as intrauterine growth retardation (lUGR), preterm delivery, and stillbirth.[13]

Maturity Onset Diabetes of the Young

Maturity Onset Diabetes of the Young (MODY) O is a monogenic-kind of diabetes. It represents a completely small percent of patients with diabetes and is usually identified through the second one decade of the patient's life. The improvement of the six forms (1-6) of MODY are connected with mutations in some of genes together with hepatocyte nuclear issue 4a (HNF-4a), glucokinase gene (MODY 2) HNF-Ia, insulin promoter issue-I (lPF-I), HNF-1[three and NEURODI. The maximum not unusual place mutation is withinside the HNF-J a gene. This mutation bills for almost 70% of all MODY patients. MODY 2 and MODY three are the maximum not unusual place shape of disease, in which MODY three is characterized through essential illness in insulin secretion. Although infrequent, it's far vital to set up the proper analysis for MODY and decide the motive of diabetes so as to offer the maximum suitable treatment. Other secondary sorts of diabetes are brought about through pancreatitis, Cushing's syndrome, Klinefelters syndrome and hyperthyroidism. Certain capsules and chemical compounds together with thiazide diuretic, [three-blocker, calcineurin, protease inhibitors and abnormal antipsychotic capsules also can motive secondary diabetes. [14]

V. DIAGNOSIS OF DIABETES

A consensus declaration posted with the aid of using the World Health Organization (WHO) in 2006 posted the modern diagnostic standards for diabetes [15] that are in settlement with the ones of the American Diabetes Association (ADA) as said of their consensus declaration [16] and the standards from the Canadian Diabetes Association (CDA). [17]

These are:

- A fasting plasma glucose126 mg/dL (7.0 mmol/ L) on two occasions or more or
- A 2-hour plasma glucose200 mg/dL (11.1 mmol/ L) after 75 g glucose load (oral glucose tolerance test, OGTT) or
- A random plasma glucose200 mg/dL (11.1 mmol/L).

Characteristic	*Physician Diagnosis of Diabetes mellitus*	*No Physician Diagnosis of Diabetes mellitus*
Sex		
Female	20.6	20.5

Male	80.5	80.4
Age, y		
<19	10	5.4
25-30	20	19.8
30-39	30	26.8
40-49	38	25.4
50-59	40	14.3
>60	50	15.8
Symptoms		
Nausea	80.6	67.7
Vomiting	40.7	18.8
Weight gain	66	57
Joint pain	88.4	88.5
Mussel pain	89.4	72.3
Dizziness	82.2	71.5
Severity of Diabetes mellitus		
Extensive Serve	45.9	21.8
Serve	43.8	50.3
Moderate	9.7	26.1
Mild	0.6	1.7

VI.ADVANCES IN DIAGNOSIS

The usual clinical presentation of type 1 diabetes, with relatively acute, severe hyperglycemia resulting in weight loss, polydipsia, polyuria, polydipsia, and potentially ketoacidosis, should not escape clinical notice. Glucose cut points are not normally required for diagnosis. Type 2 diabetes, on the other hand, has a more insidious onset, with glucose levels that rise slowly and are often asymptomatic, necessitating diagnostic cut points to identify people who need treatment as well as those who are at high risk of developing type 2 diabetes, allowing for targeted prevention. Glucose levels assessed in the fasting state or following a metabolic stress test, such as an oral glucose tolerance test, have traditionally been used to diagnose type 2 diabetes and identify those at high risk. The glucose levels chosen to diagnose diabetes are based on their association with risk of developing retinopathy. [18] More recently, HbA1c levels have been recommended for diagnosis of diabetes and prediabetes. [18] Improvements in the precision and standardization of the assay; recognition that chronic glycemia was at least as intimately related to risk of diabetic complications as blood glucose, which fluctuate constantly; and the relative ease of obtaining HbA1c samples, which do not require scheduled samples or an oral glucose tolerance test. Because acute glucose levels, whether measured fasting or after a glucose challenge, and chronic glycemia levels reflect different metabolic processes, several research evaluating their diagnostic capacities have found that the two tests classify slightly different individuals as diabetic. Regardless, each test identifies individuals who are at risk of microvascular problems, and depending on availability and other patient characteristics, fasting, 2-hour post–oral glucose tolerance test glucose levels, or HbA1c values can be used to make the diagnosis.[19] The reports for Type 2 diabetes testing and the frequency of screening are usually chosen to make screening efficient, and have not altered in over a decade. 18 Being 45 years old or older has been linked to an increased risk of type 2 diabetes; having a body mass index (calculated as weight in kilograms divided by height in meters squared) of 25 or higher; not being physically active; having a prior history of gestational diabetes; having hypertension, dyslipidemia, or cardiovascular disease; having a first-degree family member with diabetes; being African American, Latino, American Indian, Asian American, or Pacific Islander; or having tested positive for prediabetes. [20]

VII. SCREENING FOR DIABETES

The suggest time from onset to analysis of kind 2 DM is 4–7 years [21] and for the duration of this era of out of control hyperglycemia macro- and microvascular headaches can also additionally occur. Fasting or random plasma glucose, as well as the DCCT aligned HbA1c, are all appropriate screening examinations. If

any uncertainty exists, then a 2-hour OGTT have to be undertaken. HbA1c have to now no longer be used whilst sure hematologic situations exist including hemoglobinopathies wherein there may be an immoderate destruction of purple blood cells. To negate false-positives or -negatives, fasting plasma blood glucose or OGTT have to be used as an alternative. In the context of a expert neurology placing any affected person who affords with a likely hardship of diabetes (neurologic or otherwise) have to be screened.[22] The following is non-exhaustive listing of situations that the neurologist can also additionally come across which require screening for diabetes:

- Polyneuropathy (especially sensory)
- Any condition with an increased prevalence of IGT
- entrapment neuropathies
- Focal neuropathies such as oculomotor palsy or thoracic radiculopathy
- Lumbosacral radiculoplexopathy
- Mononeuritis multiplex
- Autonomic neuropathies
- Cerebrovascular disease
- Trinucleotide repeat sequence disorders (Friedreich's ataxia, myotonic dystrophy, Huntington's chorea)
- Mitochondrial disorders
- Stiff person syndrome or PERM
- Initiation of corticosteroid therapy.

VIII. FUTURE OF DRUGS AND THERAPIES FOR DIABETES MELLITUS

Growing information withinside the knowledge of diabetes and its pathophysiology has recommended drug agencies into the improvement of greater powerful drugs. Some of the brand new anti-diabetic drugs work at the incretin system and consist of injectable glucagon-like peptide-1 (GLP-1) agonists (Exenatide. Liraglutide, Albiglutide) and oral dipeptidyl peptidase-4 (DPP-4) inhibitors (Alogliptin, Linagliptin, Saxagliptin, 2021 Sitagliptin, Vildagliptin). GLP-1 agonists are thought to increase insulin secretion. The DPP-4 inhibitors inhibit the DPP-4 enzyme, and growth the circulating incretin hormone GLP-1.[23] Furthermore, sodium-glucose transport protein-2 (SGLT-2) inhibitors (Dapagliflozin, Remogliflozin, Sergliflozin) are being developed to prevent renal glucose re-absorption via the SGLT-2 transporter." [24]

Immunotherapies which target B-mobileular depletion and play immunosuppressive roles, including B-mobileular depletion the use of an anti-C20 antibody (Rituximab). T-mobileular depletion with a CD3-unique antibody (Otelixizumab) and inhibitors of T-mobileular costimulation (Abatacept), are being evolved for the treatment of TIDM. [25]

Transplantation of entire pancreas or purified pancreatic islets remains an appealing remedy for TIDM." The primary constraint to each pancreas and islet mobileular transplant is the supply of appropriate donor tissue and rejection even withinside the presence of immunosuppressant, and lifetime use of those tablets minimizing the capacity of immune device to fight the antigens. Ongoing studies additionally goals at growing stem cells to generate insulin-generating ß cells the use of both embryonic stem cells or grownup pancreas precursor cells. These putative remedies are in particular vital to the 10% of TIDM sufferers who show erratic glycaemic manage or have hypoglycaemic unawareness. [26-31]

NAME	DRUG COMBINATION	SIDE EFFECTS	AGE	WEIGHT	DIABETIC	FAMILY HISTORY OF DIABETES	TAKING MEDICATION
Ashish Gupta	Admelog+ lantus	Drowsiness, hair loss, tiredness, Parkinson	57	68	Yes	No	Yes
Piyush Mittal	Alogliptin + Metformin	Depression, Drowsiness	63	71	Yes	No	Yes
Vishal Sharma	Chlorpropamide + metformin	Constipation, leg Swelling, Insomnia	36	76	Yes	No	Yes
Mukesh	Chlorpropamide + carbamazeinate	Anxiety, confusion, tiredness	33	71	Yes	No	Yes
Sanjeev Chauhan	Metformin + Dapagliflozin	Tiredness, dizziness	43	67	Yes	No	Yes
Prabha Chauhan	Glipizide + Metformin	nausea, vomiting, diarrhea, Joint pain	67	58	Yes	Yes	Yes
A.K Singh	Acarbone, Metformin + Glipizide	Leg cramps, fibrosis	56	86	Yes	No	Yes

IX. CONCLUSION

Diabetes is rising as a main worldwide fitness hassle with the quantity of human beings dwelling with diabetes anticipated to upward thrust to 380 million through 2025. Approximately 10% of this populace may have T1DM characterized through the modern lack of B cells and whole insulin deficiency. The ultimate 90% of the populace may have T2DM characterized through insulin resistance and impaired insulin secretion. Although present day control and remedy techniques are capable of assist sufferers with diabetes, new green remedies are needed. Recent traits for T2DM therapeutics consciousness on tablets to beautify insulin secretion/action, sensitisation and discount of hepatic glucose production. For T1DM capacity new remedies encompass entire. pancreas or pancreatic islet transplantation, B-mobileular regeneration and stem mobileular remedy. These treatments are urgently needed to lower blood glucose levels and inhibit long-term macrovascular (cardiovascular, cerebrovascular, peripheral vascular

disease, and lower-extremity amputation) and microvascular (neuropathy, nephropathy, and retinopathy) side effects, which are the primary causes of untimely mortality rates.

X. REFERENCES

[1]. Agrawal, Blas E, Kurup AS, editors. Equity, social determinants and public health programmes. World Health Organization; 2010.

[2]. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, Colagiuri S, Guariguata L, Motala AA, Ogurtsova K, Shaw JE. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas. Diabetes research and clinical practice. 2019 Nov 1;157:107843.

[3]. Atlas D. International Diabetes Federation. IDF Diabetes Atlas, 7th edn. Brussels, Belgium: International Diabetes Federation, 2015. Eur Respir J. 2006;27:188-207.

[4]. Pessin JE, Saltiel AR. Signaling pathways in insulin action: molecular targets of insulin resistance. The Journal of clinical investigation. 2000 Jan 15;106(2):165-9.

[5]. Zochodne, D.W. (2014). Encyclopedia of the Neurological Sciences || Diabetes Mellitus. , (), 992–994. doi:10.1016/B978-0-12-385157-4.00080-4

[6]. Phillips JM, Parish NM, Raine T, Bland C, Sawyer Y, De La Peña H, Cooke A. Type 1 diabetes development requires both CD4+ and CD8+ T cells and can be reversed by non-depleting antibodies targeting both T cell populations. The review of diabetic studies: RDS. 2009;6(2):97.

[7]. Harris MI, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, Little RR, Wiedmeyer HM, Byrd-Holt DD. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in US adults: the Third National Health and Nutrition Examination Survey, 1988–1994. Diabetes care. 1998 Apr 1;21(4):518-24.

[8]. Masharani U. Diabetes mellitus and hypoglycemia. Current medical diagnosis and treatment. 2005:1157-201.

[9]. de Souza Rugolo, Ligia Maria Suppo, Maria Regina Bentlin, and Cleide Enoir Petean Trindade. "Preeclampsia: effect on the fetus and newborn." NeoReviews 12, no. 4 (2011): e198-e206.

[10]. WHO (2006). Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycemia. Report of a WHO/IDF Consultation. World Health Organization, Geneva: 1–46.

[11]. American Diabetes Association (2010a). Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 33: S62–S69.

[12]. Cheng AY, Lau DC (2013). The Canadian Diabetes Association 2013 clinical practice guidelines – raising the bar and setting higher standards! Can J Diabetes 37: 137–138.

[13]. Harris MI, Klein R, Welborn TA et al. (1992). Onset of NIDDM occurs at least 4–7 yr before clinical diagnosis. Diabetes Care 15: 815–819

[14]. Herman WH. Response to Comment on Inzucchi et al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach. Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015; 38: 140–149. Diabetes Care. 2015 Sep 1;38(9):e143-.

[15]. Inzucchi SE. Diagnosis of diabetes. New England Journal of Medicine. 2012 Aug 9;367(6):542-50.

[16]. Gallwitz B. The evolving place of incretin-based therapies in type 2 diabetes. Pediatr Nephrol 2010; 25(7):1207-1217,

[17]. Riedel MJ, Kieffer TJ. Treatment of diabetes with glucagon-like peptide-1 gene therapy. Expert Opinion on Biological Therapy. 2010 Dec 1;10(12):1681-92.

[18]. Washburn WN. Evolution of sodium glucose co-transporter 2 inhibitors as anti-diabetic agents. Expert Opinion on Therapeutic Patents. 2009 Nov 1;19(11):1485-99.

[19]. Vardanyan M, Parkin E, Gruessner C, Rilo HL. Pancreas vs. islet transplantation: a call on the future. Current opinion in organ transplantation. 2010 Feb 1;15(1):124-30.

[20]. Kroon E, Martinson LA, Kadoya K, Bang AG, Kelly OG, Eliazer S, Young H, Richardson M, Smart NG, Cunningham J, Agulnick AD. Pancreatic endoderm derived from human embryonic stem cells generates glucose-responsive insulin-secreting cells in vivo. Nature biotechnology. 2008 Apr;26(4):443-52.

[21]. Gonez LJ, Knight KR. Cell therapy for diabetes: stem cells, progenitors or beta-cell replication? Molecular and Cellular Endocrinology. 2010 Jul 8;323(1):55-61.

[22]. Steven RG. Emerging epidemic: diabetes in older adults: demography, economic impact, and pathophysiology. Diabetes Spectrum 2006; 19: 221–228. CrossRef Google Scholar

[23]. Norris SL, Zhang X, Avenell A et al. Long-term effectiveness of lifestyle and behavioral weight loss interventions in adults with type 2 diabetes: a meta-analysis. Am J Med 2004; 117: 762. CrossRef PubMed Google Scholar

[24]. Mokdad AH, Ford ES, Bowman BA et al. Prevalence of obesity, diabetes, and obesity-related health risk factors. JAMA 2003; 289(l): 76–79. CrossRef PubMed Google Scholar

[25]. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352(9131): 854–865. Google Scholar

[26]. Patel A et al. ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008; 358(24): 2560–2572. CrossRef CAS PubMed Google Scholar

[27]. White NH, Danis RP. Davis MD et al. Long-term renal outcomes of patients with type 1 diabetes mellitus and microalbuminuria: an analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications cohort. Arch Intern Med 2011; 171(5): 412–420. CrossRef PubMed Google Scholar

[28]. Funnell MM, Brown TL, Childs BP et al. National standards for diabetes self-management education. Diabetes Care 2007; 30: 1630. CrossRef PubMed Google Scholar

[29]. Karter AJ, Parker MM, Moffet Hh et al. Longitudinal study of new and prevalent use of self-monitoring of blood glucose. Diabetes Care 2006; 29(8): 1757–1763. CrossRef PubMed Google Scholar

[30]. Goldstein DE, Little RR, Lorenz RA et al. Tests of glycemia in diabetes. Diabetes Care 2004; 27: 1761. CrossRef PubMed Google Scholar

[31]. Miller CK, Edwards L, Kissling G et al. Nutrition education improves metabolic outcomes among older adults with diabetes mellitus. Prev Med 2002; 34(2): 252–259. CrossRef PubMed Google Scholar