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COMPREHENSIVE REVIEW OF DIABETES: UNDERSTANDING THE PATHOPHYSIOLOGY, MANAGEMENT STRATEGIES, AND EMERGING TREATMENTS

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ABSTRACT

The abstract highlights the significant global burden of diabetes mellitus, with an alarming projection of doubling by the year 2000. In the United States, around 12 million individuals were affected by diabetes in 1990, with an increasing trend annually. Cardiovascular disease stands out as the leading cause of morbidity and mortality among diabetes patients, with over 1 million diabetics hospitalized for cardiovascular or ischemic heart disease in 1987 alone, resulting in over 100,000 deaths. Studies have revealed that post-acute myocardial infarction, mortality rates are notably higher in patients with non-insulin dependent diabetes mellitus (NIDDM) compared to non-diabetic counterparts with similar infarcts. Additionally, research indicates a more than 8-fold increase in age-adjusted cardiovascular mortality rates in diabetics compared to non-diabetic individuals, mainly due to elevated incidence of coronary heart disease. Notably, diabetes emerges as an independent risk factor for cardiovascular disease, beyond traditional risk factors such as serum cholesterol, blood pressure, and smoking. The molecular genetics of diabetes is discussed, emphasizing the extensive research conducted in recent years on mutations and single nucleotide polymorphisms in genes involved in glucose metabolism and pancreatic cell function. Despite significant advances in molecular understanding, the mechanisms of diabetes development and complications remain incompletely understood, indicating the need for further extensive research to improve diagnosis, therapy, and minimize chronic complications.

KEYWORDS: Diabetes mellitus, Cardiovascular disease, Non-insulin dependent diabetes mellitus (NIDDM), molecular genetics, single nucleotide polymorphisms, chronic complications.

INTRODUCTION

The term "diabetes mellitus" originates from the Greek word for siphon, "diabetes," referring to passing through, and the Latin word "mellitus," meaning sweet. Apollonius of Memphis first used the term around 250 to 300 BC. Ancient civilizations like the Greeks, Indians, and Egyptians noted the sweet nature of urine in this condition, leading to the term Diabetes Mellitus. In 1889, Mering and Minkowski discovered the pancreas'srole in diabetes pathogenesis. Then, in 1922, Banting, Best, and Collip purified insulin from cow pancreas, providing an effective treatment. Despiteprogress, diabetes remains a prevalent chronic disease globally, ranking as the seventh leading cause of death in the US.

Diabetes mellitus (DM) is a metabolic disorder characterized by elevated blood glucose levels. It encompasses several categories, such as type 1, type 2, maturity-onset diabetes of the young (MODY), gestational diabetes, neonatal diabetes, and secondary causes stemming from endocrinopathies or steroid use. The primary subtypes, Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM), typically arise from deficient insulin secretion (T1DM) and (or) impaired insulin action (T2DM). T1DM usually manifests in children or adolescents, whereas T2DM is associated with middle-aged and older adults who develop prolonged hyperglycemia due to lifestyle and dietary factors. The pathogenesis and management of T1DM and T2DM differ significantly, leading to distinct etiologies, presentations, and treatment approaches.

Type 1 diabetes mellitus (T1D) is an autoimmune condition characterized by the destruction of insulin-producing pancreatic beta cells. It exhibits heterogeneity in metabolic, genetic, and immunogenetic features, as well as age-related variations, necessitating a personalized approach to treatment. The loss of insulin

secretion can occur rapidly or gradually. Adults with T1D often retain some insulin production (as evidenced by detectable/higher c-peptide levels), while diabetic ketoacidosis is more prevalent among youth with T1D.[1] Detectable c-peptide levels are associated with improved glycemic management.[2] Additionally, the presence of other autoimmune disorders, obesity, comorbidities, and the development of diabetes-related complications vary among individuals.[3]

Effectively managing T1D involves administering multiple daily insulin injections (MDI), using insulin pump therapy, or adopting automated insulin delivery systems, coupled with continuous glucose monitoring (CGM) whenever possible. If CGM is unavailable, individuals should be capable of performing capillary blood glucose monitoring (BGM). Self-management education, training, and support, along with addressing psychosocial concerns, are crucial for optimizing outcomes.[4] A collaborative multidisciplinary approach, involving medical providers, nurse and dietitian educators, pharmacists, and specialists like podiatrists, mental health professionals, social workers, ophthalmologists, and cardiologists, is recommended to meet individual needs.[5]

Etiology

Type 1 diabetes mellitus (T1DM) is characterized by the autoimmune destruction of beta cells in the pancreas, resulting in the absolute absence or extreme reduction of insulin production. In contrast, Type 2 diabetes mellitus (T2DM) presents with a more gradual onset, driven by an imbalance between insulin levels and sensitivity, leading to functional insulin deficiency. Insulin resistance, a hallmark of T2DM, typically arises from a combination of factors such as obesity and aging. Both types of diabetes have a significant genetic component, influencing disease risk. Ongoing exploration of the human genome has identified various loci associated with diabetes susceptibility. Polymorphisms, particularly within the major histocompatibility complex (MHC) and human leukocyte antigen (HLA), play a role in predisposing individuals to T1DM.[6] T2DM, on the other hand, involves a complex interplay between genetic predisposition and lifestyle factors. Strong evidence indicates a higher hereditary influence on T2DM compared to T1DM, with the majority of affected individuals having at least one parent with the condition.[7]

Monozygotic twins with one affected twin have a 90% likelihood of the other twin developing Type 2 diabetes mellitus (T2DM) during their lifetime.[8] Approximately 50 polymorphisms have been identified thus far, contributing to the risk or protection against T2DM. These genetic variants influence pathways involved in pancreatic development, insulin synthesis, secretion, amyloid deposition in beta cells, insulin resistance, and regulation of gluconeogenesis. For instance, a genome-wide association study (GWAS) identified genetic loci like the transcription factor 7-like 2 gene (TCF7L2), which increases T2DM risk.[9],[10] Other loci implicated in T2DM development include NOTCH2, JAZF1, KCNQ1, and WFS1.[11],[12] Maturity-onset diabetes of the young (MODY) is a heterogeneous disorder characterized by non-insulin-dependent diabetes diagnosed at a young age, typically under 25 years. It follows an autosomal dominant inheritance pattern and lacks autoantibodies typical of Type 1 diabetes mellitus (T1DM). Mutations in genes such as hepatocyte nuclear factor-1-alpha (HNF1A) and the glucokinase (GCK) gene are associated with MODY, occurring in a significant percentage of cases.[13],[14]

The etiology of gestational diabetes, which arises during pregnancy, remains unclear. Some theories suggest a role for HLA antigens, particularly HLA DR2, 3, and 4, while others implicate factors like excessive proinsulin levels or hormonal changes affecting beta-cell function and insulin sensitivity.[15] Various endocrinopathies, including acromegaly, Cushing syndrome, glucagonoma, hyperthyroidism, hyperaldosteronism, and somatostatinomas, can lead to glucose intolerance and diabetes mellitus due to the excessive secretion of hormones with glucogenic properties. Idiopathic hemochromatosis, characterized by excessive iron deposition in the pancreas, can also result in diabetes mellitus by causing beta-cell destruction.

In Type 1 diabetes (T1D), autoimmune processes gradually destroy beta cells within the pancreatic islets over a period of months or years, resulting in a severe deficiency of insulin.

While the precise cause of T1D remains elusive, there is strong evidence indicating a genetic predisposition, particularly linked to specific HLA (DR and DQ) alleles, with a more pronounced association observed in youth-onset T1D compared to adult-onset cases.[16] Additionally, multiple other genes contribute to the heritability of T1D.[17] It is widely believed that in individuals at risk, various factors such as viral infections, environmental elements, dietary factors, and stressors may trigger the autoimmune destruction of beta cells. Studies have identified a heightened risk of T1D development associated with infections from viruses such as Coxsackie, enteroviruses, cytomegalovirus, rubella, influenza B, mumps, and more recently, SARS-CoV-2 (COVID-19).[18],[19],[20] Findings from studies like The Environmental Determinants of Diabetes in the Young (TEDDY) have explored factors like breastfeeding and dietary introductions, with varying conclusions on their impact on T1D risk.[21]The presence of circulating pancreatic islet autoantibodies indicates an increased risk of or actual development of T1D. The type and prevalence of these autoantibodies vary with age, with IAAs primarily detected in children[22] and GAD65 being the most common autoantibody detected in adults.[23] The number and concentration of detectable antibodies correlate with the risk of developing

T1D.Diabetes mellitus (DM) is broadly categorized into three main types based on etiology and clinical presentation: Type 1 diabetes, Type 2 diabetes, and gestational diabetes (GDM). Less common types include monogenic diabetes and secondary diabetes.[24],[25],[26],[27]

Type 1 Diabetes Mellitus (T1DM)
T1DM constitutes 5% to 10% of diabetes cases and is characterized by the autoimmune destruction of insulin-producing beta cells in the pancreas, resulting in an absolute insulin deficiency. Genetic predisposition combined with environmental factors such as viral infections, toxins, or dietary elements are implicated as triggers for autoimmunity. While T1DM predominantly affects children and adolescents, it can manifest at any age.

Type 2 Diabetes Mellitus (T2DM)
T2DM comprises approximately 90% of diabetes cases and is marked by diminished responsiveness to insulin, known as insulin resistance. Initially, compensatory increases in insulin production maintain glucose homeostasis, but over time, insulin production declines, leading to T2DM. While traditionally seen in individuals over 45 years old, T2DM is increasingly prevalent in younger populations due to rising levels of obesity, physical inactivity, and high-calorie diets.

Gestational Diabetes Mellitus (GDM)
GDM, characterized by hyperglycemia first detected during pregnancy, affects pregnant women primarily during the second and third trimesters. Approximately 7% of pregnancies are complicated by GDM, with increased risks of future development of T2DM for both mother and child.

GDM may lead to complications such as hypertension, preeclampsia, hydramnios, and increased operative interventions, with infants at risk of macrosomia, congenital anomalies, respiratory distress syndrome, and subsequent obesity.

Monogenic diabetes
Monogenic diabetes results from a single genetic mutation in an autosomal dominant gene and includes conditions like neonatal diabetes mellitus and maturity-onset diabetes of the young (MODY). Accounting for 1 to 5% of diabetes cases, MODY typically presents before age 25 and is familial in nature.

Secondary diabetes
Secondary diabetes arises from complications of other diseases affecting the pancreas (e.g., pancreatitis), hormonal disturbances (e.g., Cushing's disease), or drug use (e.g., corticosteroids).

Epidemiology
Globally, diabetes mellitus (DM) affects 1 in 11 adults, with 90% of cases being Type 2 diabetes mellitus (T2DM). The onset of Type 1 diabetes mellitus (T1DM) gradually increases from birth, peaking between ages 4 to 6 years and again from 10 to 14 years.[28] Approximately 45% of children develop T1DM before age ten.[29] The prevalence of T1DM among individuals under age 20 is around 2.3 per 1000. Unlike most autoimmune diseases, there are no significant gender differences in childhood T1DM incidence. However, in some populations, such as older males of European origin over 13 years old, there may be a higher likelihood of developing T1DM compared to females, with a ratio of 3:2 male to female. T1DM incidence rates have been increasing globally, with Europe, Australia, and the Middle East experiencing annual rises of 2% to 5%.[30],[31],[32] In the United States, T1DM rates have increased by approximately 2% yearly across most age and ethnic groups, with higher rates observed among Hispanic youth.[33] The exact reasons for these trends remain unclear, although some data sources, such as the United States Military Health System repository, suggest a plateauing trend from 2007 to 2012, with a prevalence of 1.5 per 1000 and an incidence of 20.7 to 21.3 per 1000.[34]

The onset of Type 2 diabetes mellitus (T2DM) typically occurs later in life, but the rise in adolescent obesity has contributed to its emergence in younger populations. In the United States, T2DM affects around 9% of the total population, with approximately 25% prevalence among those over 65 years old. Globally, the International Diabetes Federation estimates that 1 in 11 adults aged 20 to 79 had DM in 2015, with projections indicating an increase from 415 to 642 million by 2040, particularly in populations transitioning from low to middle-income levels.[35] T2DM prevalence varies across ethnic groups, with Blacks, Native Americans, Pima Indians, and Hispanic Americans experiencing 2 to 6 times higher rates compared to Whites in the United States.[36],[37]

While ethnicity is a significant factor in T2DM prevalence, environmental influences also play a crucial role in disease risk. For instance, Pima Indians in Mexico have a lower likelihood of developing T2DM compared to their counterparts in the United States, with prevalence rates of 6.9% versus 38%, respectively.[38]

Type 1 diabetes (T1D) is among the most common chronic conditions affecting children, although it can manifest at any age. In adults, new-onset T1D may be mistaken for Type 2 diabetes (T2D) and is actually more prevalent than T1D onset during childhood.[39] There has been a steady rise in the incidence and prevalence of T1D, constituting approximately 5% to 10% of all diabetes cases. A systematic review and meta-analysis revealed a global T1D prevalence of 9.5%, with an incidence of 15 per 100,000 people.[40] Geographic variations in incidence are considerable, with the highest rates observed in Finland and other Northern European countries, which are around 400 times greater than the lowest reported incidences seen in regions like China and Venezuela.

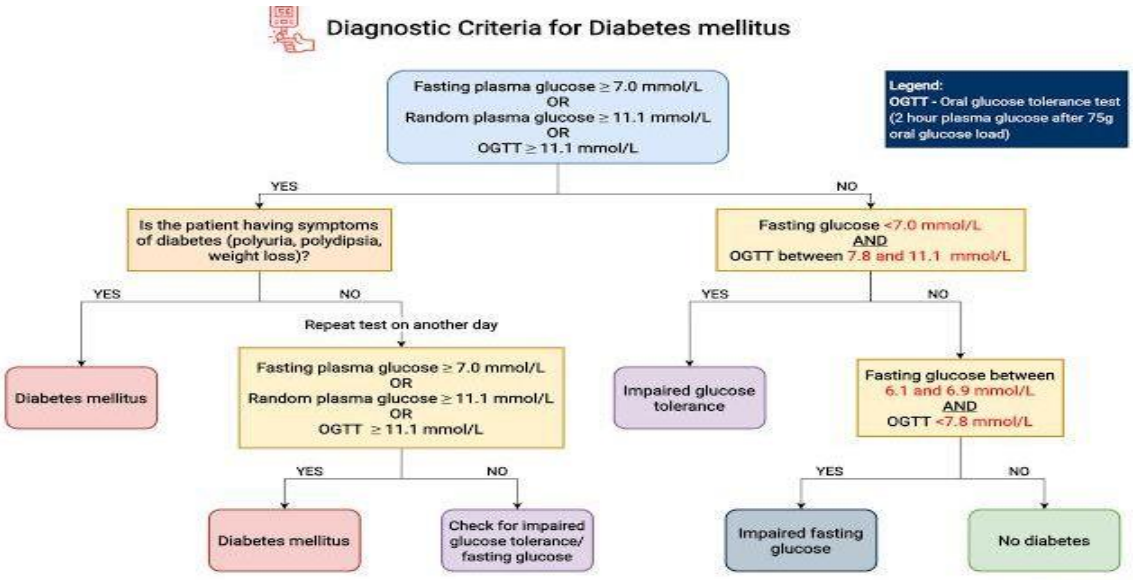
Diabetes presents a global epidemic, with changing lifestyles and increasing rates of obesity contributing to its prevalence. In 2017, the global prevalence of diabetes reached 425 million. According to the International Diabetes Federation (IDF), approximately 10% of the American population had diabetes in 2015, with 7 million cases going undiagnosed. The prevalence of diabetes rises with age, affecting about 25% of individuals over 65 years old.[41]

Pathophysiology

In individuals with diabetes mellitus (DM), hyperglycemia is a common occurrence with multifactorial origins contributing to its pathology. Elevated blood glucose levels can impair pancreatic beta-cell function, leading to reduced insulin secretion. This creates a cycle where hyperglycemia perpetuates metabolic dysfunction. While blood glucose levels exceeding 180 mg/dL are typically considered hyperglycemic, the absence of a clear cutoff point reflects the diverse mechanisms involved. Hyperglycemia triggers osmotic diuresis by saturating glucose transporters in the nephron, resulting in increased urine output and thirst. Symptoms of polyuria and polydipsia are often evident when serum glucose levels exceed 250 mg/dL. Insulin resistance, driven by excess fatty acids and proinflammatory cytokines, further exacerbates glucose dysregulation by impairing glucose transport and promoting fat breakdown. Inadequate insulin response or production prompts an inappropriate increase in glucagon levels, exacerbating hyperglycemia. While insulin resistance characterizes Type 2 diabetes mellitus (T2DM), the full spectrum of the disease arises when insufficient insulin production fails to compensate for resistance. Chronic hyperglycemia induces nonenzymatic glycation of proteins and lipids, a process measured by glycosylated hemoglobin (HbA1c) levels.

Glycation leads to microvascular damage in organs such as the retina, kidneys, and peripheral nerves, with higher glucose levels accelerating this process. Consequently, diabetic complications such as retinopathy, nephropathy, and neuropathy ensue, often resulting in preventable outcomes like blindness, dialysis, and amputation, respectively.[42]

The development of Type 1 diabetes (T1D) progresses through three stages. In Stage 1, individuals are asymptomatic but exhibit normal fasting glucose, normal glucose tolerance, and the presence of ≥2 pancreatic autoantibodies. Stage 2 diagnostic criteria include the presence of pancreatic autoantibodies (typically multiple) and dysglycemia, characterized by impaired fasting glucose (fasting glucose 100 to 125 mg/dL), impaired glucose tolerance (2-hour post-75 gm glucose load glucose 140 to 199 mg/dL), or an HbA1c level between 5.7% to 6.4%. Symptoms remain absent at this stage. Stage 3 marks the onset of diabetes, defined by hyperglycemia (random glucose ≥200 mg/dL) accompanied by clinical symptoms, fasting glucose ≥126 mg/dL, glucose ≥200 mg/dL two hours post-glucose load during an oral glucose tolerance test, and/or HbA1c ≥6.5%. When classic symptoms of hyperglycemia are absent, it's recommended to conduct two tests simultaneously or at different times to confirm the diagnosis.



[Fig. 1:-Adopted from gramproject.com ... https://images.app.goo.gl/cmYmCXW7ztXJcvvp8].

In cases of acute symptom onset with hyperglycemia, particularly in youth-onset T1D, reliance on HbA1c may be misleading, necessitating the use of glucose criteria for diagnosis.[43] T1D, particularly in children, typically presents with sudden hyperglycemic symptoms, including polydipsia, polyuria, polyphagia, nocturnal enuresis, blurred vision, unintentional weight loss, fatigue, and weakness. Without prompt evaluation and treatment, it can escalate into a medical emergency. Electrolyte abnormalities may also be present, and if left

untreated, diabetic ketoacidosis (DKA) may develop, necessitating hospitalization and treatment with intravenous fluids, insulin, potassium supplementation, and close monitoring. Nearly one-third of youth diagnosed with T1D present with DKA.[44] In adult-onset diabetes, symptoms onset is more variable compared to youth, and DKA is less common. Distinguishing between T1D and Type 2 diabetes can be challenging. GAD65 should be the initial antibody tested when T1D is suspected in adults. If negative and/or if available, IA2 and/or ZNT8 should also be measured. C-peptide levels can aid in differentiating between diabetes types. A random C-peptide drawn concurrently with serum glucose levels can provide valuable information. In cases where diabetes duration exceeds three years, a c-peptide level >600 pmol/L strongly suggests Type 2 diabetes, while a low (<200 pmol/L) or undetectable c-peptide confirms the diagnosis of T1D.[45]

Obesity precipitates peripheral insulin resistance, fostering hyperglycemia as a consequence. This resistance manifests across various organs and tissues, eventually culminating in beta-cell failure.[46] Notably, insulin resistance may persist for a substantial duration before the diagnosis of Type 2 diabetes mellitus (T2DM).[47] It's crucial to highlight that visceral obesity, rather than Body Mass Index (BMI) alone, could serve as a more accurate predictor for insulin resistance-related complications like T2DM and hypertension.[48]

Certain ethnicities exhibit heightened predisposition to insulin resistance and beta-cell dysfunction independent of obesity. Additionally, hormonal shifts during puberty induce transient insulin resistance, heightening the risk of hyperglycemia and T2DM development.[49] Hyperglycemia triggers osmotic diuresis, resulting in polyuria and increased thirst, ultimately leading to moderate to severe dehydration. Prolonged hyperglycemia can precipitate two distinct emergent conditions in children with T2DM:[50]

1. Diabetic Ketoacidosis (DKA): This condition is notably more prevalent in children with T2DM compared to adults. Insulin deficiency impairs glucose utilization, prompting the body to metabolize fat for energy, leading to ketosis, acidosis, and electrolyte imbalances, which may progress to coma and even fatality.
2. Hyperglycemic Hyperosmolar State (HHS): Characterized by hypertonicity, severe hyperglycemia (>600 mg/dl), and profound dehydration, HHS ensues from relentless osmotic diuresis and intravascular volume depletion.

History and Physical

During the patient history assessment, inquiries regarding family history, autoimmune disorders, and insulin resistance play pivotal roles in diagnosing diabetes mellitus (DM). While often presenting asymptomatically, patients may manifest symptoms such as polyuria, polydipsia, and weight loss. Physical examination of individuals with hyperglycemia may reveal poor skin turgor due to dehydration and a distinctive fruity breath odor indicative of ketosis. In diabetic ketoacidosis (DKA), clinicians may observe Kussmaul respirations, fatigue, nausea, and vomiting. Funduscopic examination may unveil hemorrhages or exudates on the macula, while frank diabetic retinopathy may feature dilated or occluded retinal venules. Ophthalmologists also monitor for neovascularization, which can precipitate retinal hemorrhages and macular edema, ultimately leading to blindness. While Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM) may present similarly, clinical history and examination aid in differentiation. T2DM patients typically exhibit signs of insulin resistance, including acanthosis nigricans—hyperpigmented, velvety patches in neck, axillary, or inguinal folds. Those with prolonged hyperglycemia may experience blurry vision, recurrent yeast infections, numbness, or neuropathic pain. Clinicians should routinely inquire about recent skin changes in the feet and conduct a diabetic foot examination, including the monofilament test, during each visit. At the initial outpatient consultation, gathering a comprehensive medical, surgical, psychosocial, and family history—including pregnancy and contraception—is imperative. Additionally, inquiries about prior diabetes education, blood glucose and ketone monitoring, continuous glucose monitoring (CGM), insulin administration, hypoglycemia recognition/treatment, glucagon use, dietary habits, physical activity, smoking, alcohol consumption, understanding of sick-day management, problem-solving abilities, and immunization history should be incorporated into the assessment.

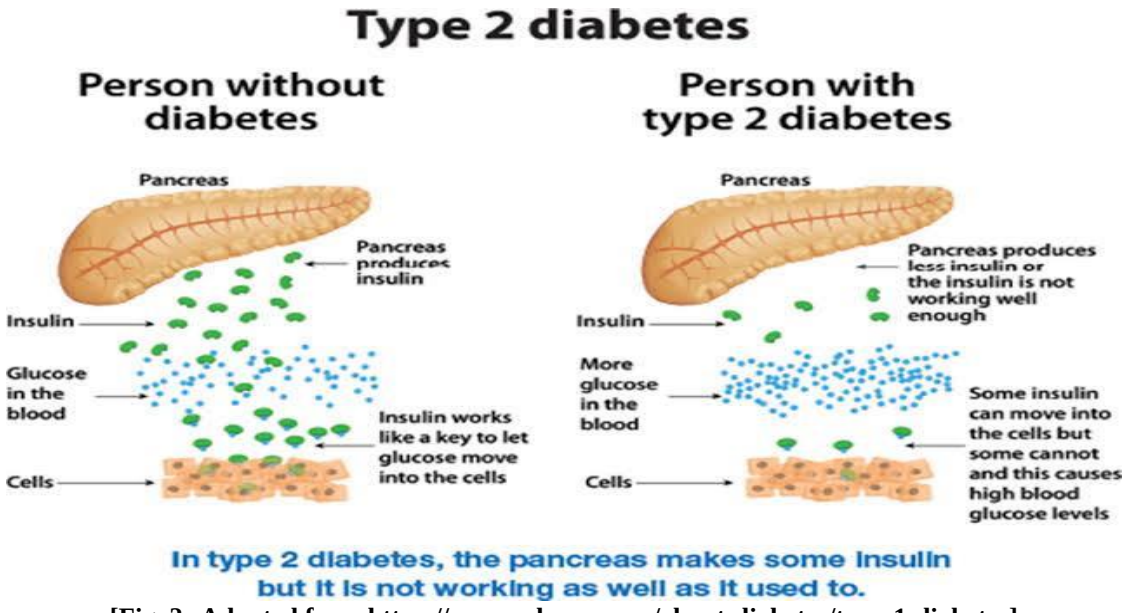
Particular emphasis should be on gathering information regarding the date of diagnosis, prior treatments, current medications, presence of hypoglycemia unawareness, and history of acute and chronic complications. Chronic complications encompass a range of conditions including skin disorders, dental issues, retinopathy, macular edema, neuropathy, kidney disease, cardiovascular ailments, peripheral arterial disease, stroke, foot ulcers, amputations, hearing loss, and sleep disorders. Given the heightened risk of autoimmune disorders among individuals with Type 1 diabetes, inquiries should extend to conditions such as autoimmune thyroid disease and celiac disease. Clinicians must conduct measurements of height, weight, and blood pressure while paying particular attention to skin examination, especially at insulin injection or infusion sites. Lipodystrophy warrants education on the significance of alternating injection/infusion sites. Comprehensive physical examinations should include assessment of the thyroid, heart, chest, abdomen, and foot examination to ascertain pedal pulses, foot deformities, pre-ulcerative lesions, ulcerations, calluses, and onychomycosis.

Additionally, testing for vibratory and protective sensations is essential, with abnormal findings on a 10-g

monofilament exam indicating an elevated risk of ulceration. Screening for psychosocial issues necessitates the utilization of various measures such as the Patient Health Questionnaire (PHQ-2/PHQ-9) for Depression and Generalized Anxiety Disorder (GAD-7). Assessment of diabetes distress and social determinants of health is imperative. Given the higher prevalence of eating disorders among individuals with Type 1 diabetes, especially in young women, clinical evaluation is warranted. Cognitive testing should also be considered early, particularly in cases where cognitive decline is suspected.[51] Continuous monitoring of data from Continuous Glucose Monitors (CGMs), blood glucose meters, insulin pumps, and automated insulin delivery systems is indispensable. These data should be downloaded, analyzed, and discussed at each visit and between visits as needed to tailor treatment regimens to achieve glycemic targets. CGMs, in particular, offer valuable insights by measuring glucose levels in interstitial fluid and transmitting readings to a receiver at frequent intervals. They enable users to monitor trends, set low and high glucose alarms, and share readings with relatives, friends, or caregivers. By providing real-time information, CGMs empower users to make informed decisions regarding insulin therapy and dietary management to mitigate glycemic fluctuations and prevent hypoglycemia.

Data from Continuous Glucose Monitors (CGMs) can be uploaded and stored in cloud-based systems, providing valuable insights into glycemic control. These data encompass various parameters, including Time in Range (TIR), Time Below Range (TBR), Time Above Range (TAR), and glycemic variability (% CV). TIR targets may vary depending on individual circumstances, such as pregnancy or frailty, and should be adjusted accordingly. Analyzing these data helps identify factors contributing to hypo- and hyperglycemia, facilitating informed decisions regarding insulin dosing, diet, and physical activity. Minimizing hypoglycemia is a primary goal, as a higher percent TIR is associated with reduced diabetes-related complications.[52],[53] Additionally, parameters such as HbA1c, TIR, and TBR show improvement with the integration of CGM into therapy regimens. The Glucose Management Indicator (GMI) offers further insight by correlating average sensor readings with estimated HbA1c levels.[54] In the absence of CGM data, blood glucose (BG) measurements at various intervals, including fasting, pre-meal, postprandial, bedtime, and occasionally during the night, guide insulin dosing. Insulin dosing data from connected insulin pens and pumps should also be considered during discussions. Patients with diabetes mellitus typically present with symptoms such as increased thirst, frequent urination, fatigue, infections, and delayed wound healing. Some may experience numbness, tingling, or blurred vision. Modest hyperglycemia can progress to severe hyperglycemia or diabetic ketoacidosis (DKA), particularly during infections or stress. Approximately 30% of patients with Type 1 diabetes mellitus (T1DM) may present with DKA coma as the initial manifestation. It is crucial to monitor parameters such as height, weight, BMI, retinopathy, peripheral pulses, and signs of neuropathy during physical examinations.

Children with Type 2 diabetes mellitus (T2DM) are often asymptomatic and may be diagnosed through screening. However, typical symptoms such as polyuria, polydipsia, polyphagia, and weight loss may manifest in some cases. Children, especially those of ethnic minority descent, may present with DKA or Hyperglycemic Hyperosmolar State (HHS). Physical examination findings may include acanthosis nigricans, prompting screening recommendations by the American Diabetes Association (ADA) for high-risk children.



[Fig. 2:-Adopted from https://www.ndss.com.au/about-diabetes/type-1-diabetes]

Treatment and Management

Treatment and management of diabetes require a comprehensive approach, emphasizing patient education and engagement. Successful disease management involves adherence to dietary restrictions, regular exercise, and diligent glucose monitoring.[55] Lifelong treatment aims to maintain glucose levels within the target range of 90 to 130 mg/dL and HbA1c below 7%, although overly aggressive management can increase the risk of hypoglycemia, which may have serious consequences For Type 1 diabetes mellitus (T1DM), insulin administration through daily injections or an insulin pump is essential due to the absence of endogenous insulin production. In Type 2 diabetes mellitus (T2DM), initial treatment may involve lifestyle modifications such as diet and exercise. Pharmacological therapies target insulin sensitivity or increase insulin secretion. These include metformin, sulfonylureas, meglitinides, alpha-glucosidase inhibitors, thiazolidinediones, glucagon-like peptide-1 (GLP-1) agonists, dipeptidyl peptidase IV (DPP-4) inhibitors, amylinomimetics, and sodium-glucose transporter-2 (SGLT-2) inhibitors. Metformin is commonly prescribed as first-line therapy for its ability to lower basal and postprandial glucose levels. Insulin therapy may be necessary for T2DM patients with inadequate glucose control, particularly in advanced stages of the disease.

Bariatric surgery may be considered for morbidly obese patients unresponsive to other treatments and with significant comorbidities.[56] Regular screenings are crucial to detect microvascular complications associated with diabetes. Diabetic retinal exams assess for retinopathy, while neurologic examinations with monofilament testing identify patients at risk for neuropathy-related complications. Patients should perform daily foot inspections to detect lesions, as neuropathy may obscure sensation. Neuropathic pain management may require medications such as low-dose tricyclic antidepressants, duloxetine, anticonvulsants, topical capsaicin, and analgesics. Urine microalbumin testing evaluates renal function, with albuminuria greater than 30mg/g creatinine indicating early renal changes. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are preferred agents to delay progression to macroalbuminuria in patients with both Type 1 and Type 2 diabetes mellitus, due to their antiproteinuric effects.

The FDA has granted approval for pregabalin and duloxetine to treat diabetic peripheral neuropathy, while tricyclic antidepressants and anticonvulsants have shown variable success in managing diabetic neuropathic pain. The ADA recommends regular blood pressure screening for diabetics, aiming for a systolic blood pressure of 130 mmHg and a diastolic blood pressure of 85 mmHg.[57] Pharmacologic therapy for hypertensive diabetics typically involves angiotensin-converting enzyme inhibitors. Lipid monitoring is also advised, with a target LDL-C level of less than 100 mg/dL in the absence of cardiovascular disease (CVD) and less than 70 mg/dL if atherosclerotic cardiovascular disease (ASCVD) is present. Statins are the first-line treatment for dyslipidemia in diabetics. Low-dose aspirin may be beneficial for diabetic patients at high risk of cardiovascular events, although its role in reducing such events remains uncertain.[58],[59],[60] Individuals with Type 1 diabetes (T1D) require insulin therapy, glucose monitoring (preferably through continuous glucose monitoring, CGM), and diabetes self-management education and support. Treatment options include multiple daily insulin injections (MDI) using basal and bolus insulins, continuous subcutaneous insulin infusion via an insulin pump, or automated insulin delivery systems. Hypoglycemia is a common adverse effect of insulin therapy, necessitating education on its signs and symptoms and appropriate management with glucose administration. Glucagon should be available for emergency use in cases of severe hypoglycemia. Sick day instructions should be provided, covering hyperglycemia management and ketone testing. Initial insulin dosing is calculated.[61] based on the individual's weight and adjusted according to various factors such as diet, physical activity, and glucose monitoring results.

Individuals with Type 1 diabetes (T1D) should ideally consult with a dietitian to learn carbohydrate counting and utilize an insulin-to-carbohydrate ratio for mealtime dosing. For those unable to count carbohydrates, a consistent carbohydrate diet is beneficial. Estimating the glucose reduction from one unit of rapid-acting insulin, termed the correction or insulin sensitivity factor, is also advisable for addressing hyperglycemia.

Initially, this factor can be calculated as 1800 divided by the total daily dose (TDD) of insulin, requiring subsequent adjustments based on glucose monitoring results. Care must be taken to avoid insulin stacking, which can lead to hypoglycemia. Insulin needs fluctuate throughout life and in specific circumstances.[62] Increased insulin doses are typically necessary during puberty, pregnancy, steroid use, and obesity development. Conversely, insulin requirements decrease during aerobic exercise and the "honeymoon period" post-diagnosis, characterized by temporary beta-cell function recovery. Various types of insulin are available for injection therapy. Rapid-acting insulin (lispro, apart, glulisine) typically onset in 12 to 30 minutes, peak in 1 to 3 hours, and last 3-6 hours. Long-acting insulin, preferred for basal therapy, includes U-100 and U-300 glargine and degludec, lasting up to 42 hours. Intermediate insulin (NPH, NPL) has an onset in 1 to 2 hours, peak action at 2 to 8 hours, and duration of 12 to 24 hours. Insulin pumps deliver insulin continuously for basal needs and boluses to manage mealtime glucose fluctuations. Physical activity is beneficial for those with T1D, improving insulin sensitivity, cardiovascular health, lipid profiles, and reducing complications risk.

Understanding how different activities affect glucose levels and balancing carbohydrate intake with insulin doses during exercise is crucial. Annual eye and foot exams are recommended for T1D individuals. Other specialists may be needed, including nephrologists, ophthalmologists, and cardiologists. Pancreatic or islet cell transplantation may be considered for select cases.[63] For both T1DM and T2DM, diet and exercise are fundamental.[64],[65],[66] Metformin is the first-line therapy for T2DM, followed by other medications targeting insulin sensitivity or secretion. Recent studies highlight the cardiovascular benefits of certain medications like SGLT2 inhibitors and GLP-1 receptor agonists. Annual lipid and eye exams, blood pressure monitoring, and urine albumin testing are essential for diabetic management. Lifestyle modifications and medication adjustments should be made based on individual needs and risk factors.[67],[68],[69],[70]

Differentiai diagnosis

In addition to Type 1 diabetes (T1DM), Type 2 diabetes (T2DM), and Maturity-Onset Diabetes of the Young (MODY), various conditions affecting the pancreas can lead to diabetes mellitus (DM). Exocrine pancreatic disorders.[71] such as cystic fibrosis, hereditary hemochromatosis, pancreatic cancer, and chronic pancreatitis are notable examples. Hormonal syndromes like pheochromocytoma, acromegaly, and Cushing syndrome can impair insulin secretion. Drug-induced insulin resistance is also a consideration and may involve medications such as phenytoin, glucocorticoids, and estrogen. Gestational diabetes,[72] thyroid disorders, and pancreatic diabetes are among other conditions in the differential diagnosis of DM. Additionally, steroid-induced diabetes is a potential consideration.

The potential differential diagnoses for diabetes mellitus encompass a range of conditions with similar presentations:[73],[74]

1. Diabetes insipidus
2. Factitious illness
3. Maturity-Onset Diabetes of the Young (MODY)
4. Psychogenic polydipsia
5. Renal glycosuria

Additional considerations include

1. Drug-induced symptoms caused by corticosteroids, neuroleptics, pentamidine, etc.
2. Genetic abnormalities affecting beta-cell function and insulin action
3. Metabolic syndrome (syndrome X).[75]
4. Infectious causes
5. Endocrine disorders like acromegaly, Cushing's disease, pheochromocytoma, hypothyroidism, etc.[76]
6. Complications related to iron overload (hemochromatosis)
7. Conditions impacting the exocrine pancreas such as pancreatitis, cystic fibrosis, etc.[77]

For pediatric Type 2 diabetes mellitus, the differential diagnosis includes

1. Atypical diabetes mellitus (ADM)
2. Maturity-Onset Diabetes of the Young (MODY)
3. Diabetes resulting from DNA mutations
4. Exocrine pancreatic diseases
5. Diabetes induced by drugs or chemicals
6. Diabetic ketoacidosis (DKA)
7. Endocrine disorders
8. Genetic abnormalities affecting beta cells
9. Genetic defects in insulin action

Type 1 diabetes mellitus (T1DM)

Prognosis

The prognosis of diabetes mellitus is closely tied to glucose management, with chronic hyperglycemia significantly elevating the risk of complications. Studies like the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study underscore the link between sustained hyperglycemia[78],[79] and increased microvascular complications in both Type 1 and Type 2 diabetes. However, individuals who can achieve normal glucose levels, particularly during the progression from pre-diabetes to diabetes, often experience a more favorable prognosis, potentially slowing disease advancement.[80] Improved management strategies, including better control of glucose, blood pressure, and lipids, as well as enhanced foot care, have contributed to a reduction in the morbidity and mortality associated with Type 1 diabetes. While serious diabetes-related complications still occur, their incidence has decreased, and their onset has been delayed for many individuals. Despite a higher mortality rate among those with Type 1 diabetes compared to the general population, overall mortality rates have declined. Diabetes mellitus is also linked to an increased risk of atherosclerotic cardiovascular disease (ASCVD). Managing blood pressure, using statins, engaging in regular exercise, and quitting smoking are crucial in reducing this risk.[81] The excess mortality associated with Type 2 diabetes varies widely but is estimated to be around 15% higher on average. In the United States, the prevalence of vision-threatening diabetic retinopathy among adults with diabetes is approximately 4.4%, while the prevalence of end-stage renal disease is around 1%.

Currently, advancements in pharmacotherapy for hyperglycemia, alongside strategies to lower LDL cholesterol and manage blood pressure using ACE/ARB therapy and other antihypertensive medications, combined with aspirin for secondary prevention, have significantly improved the management of vascular complications. This comprehensive approach has led to a notable reduction in both morbidity and mortality rates.[82],[83] In contrast, long-term prognosis studies for pediatric Type 2 diabetes mellitus (T2DM) are lacking, sparking considerable concern within the medical community due to the potential for enduring complications. While many children and adolescents can achieve effective glycemic control and maintain healthy

lifestyles through appropriate treatment, lifestyle adjustments, and regular monitoring, the condition still poses significant health risks if left uncontrolled. The persistent threat of complications such as cardiovascular disease, kidney issues, and retinopathy underscores the importance of vigilant management. The long-term outlook for pediatric T2DM hinges on various factors, including the child's adherence to treatment plans, commitment to a healthy lifestyle, and access to consistent medical care. Early diagnosis, comprehensive education, and robust support systems are pivotal in enhancing the prognosis and mitigating the risk of severe complications in pediatric patients with T2DM.

Complications

Complications of diabetes, regardless of its type, encompass microvascular, macrovascular, and neuropathic issues. These complications vary depending on the degree and duration of poorly controlled diabetes and may include nephropathy, retinopathy, neuropathy, and ASCVD events, particularly when comorbidities like dyslipidemia and hypertension are present.[84] Cardiovascular disease (ASCVD) stands as one of the most severe consequences of diabetes, with approximately two-thirds of diabetic individuals succumbing to myocardial infarctions or strokes.[85] In Type 2 diabetes mellitus (T2DM), even fasting glucose levels exceeding 100 mg/dL significantly heighten the risk of ASCVD, often preceding overt hyperglycemia.[86],[87] Diabetic retinopathy is a prevalent cause of blindness among adults aged 20 to 74 in the United States, leading to 12,000 to 24,000 new cases of blindness annually. Treatments mainly involve laser surgery and glucose control Renal disease emerges as another significant contributor to morbidity and mortality in diabetes patients, being the primary cause of end-stage renal disease (ESRD) in the U.S. Persistent albuminuria, particularly microalbuminuria (30 to 300 mg/day), serves as an early indicator of diabetic nephropathy, while macroalbuminuria (exceeding 300 mg/24hr) accelerates progression to ESRD.[88] Diabetes also ranks as the leading cause of limb amputations in the United States, primarily attributable to vasculopathy and neuropathy associated with the condition. Regular foot exams are essential for patients with neuropathy to prevent infections from unnoticed wounds. The duration of diabetes remains a crucial risk factor for diabetic retinopathy, with onset typically occurring around five years after Type 1 diabetes diagnosis and often present at the time of Type 2 diabetes diagnosis. Moreover, evidence suggests a potential link between T2DM and cancer development, notably bladder cancer in individuals using pioglitazone.[89] Conversely, patients using metformin have shown improved cancer-specific survival rates in prostate, pancreatic, breast, and colorectal cancers, although the exact mechanism by which metformin modulates cancer in diabetic patients remains unclear.[90]

Individuals with gestational diabetes face an elevated risk of cesarean delivery and chronic hypertension. Pregnant patients with Type 2 diabetes generally have a more favorable outlook concerning neonatal and pregnancy complications compared to those with Type 1 diabetes. Neonates born to mothers with diabetes typically exhibit hypoglycemia and macrosomia.[91] The most acute complication of diabetes is diabetic ketoacidosis (DKA), primarily associated with Type 1 diabetes. This condition often arises due to inadequate dosing, missed doses, or concurrent infection. In DKA, insulin deficiency leads to the inability of tissues to utilize glucose from the bloodstream, prompting the metabolism of lipids into ketones as an alternative energy source. This process results in systemic acidosis, manifesting as a high anion-gap metabolic acidosis. Hyperglycemia and ketosis trigger diuresis, acidemia, and vomiting, leading to dehydration and life-threatening electrolyte imbalances. In Type 2 diabetes, hyperosmolar hyperglycemic syndrome (HHS) poses a significant concern.

While presenting similarly to DKA with symptoms like excessive thirst, elevated blood glucose, dry mouth, polyuria, tachypnea, and tachycardia, HHS typically lacks excessive urinary ketones due to the continued production of insulin by pancreatic beta cells. Treatment for both DKA and HHS involves insulin administration and aggressive intravenous hydration, with careful management of electrolytes, particularly potassium. The major acute complications of diabetes encompass hypoglycemia and severe hyperglycemia, including diabetic ketoacidosis. Chronic complications include nephropathy, neuropathy (both peripheral and autonomic), retinopathy/macular edema, heart disease (including coronary artery disease, heart failure, and cardiomyopathy), peripheral arterial disease, cerebrovascular disease (including stroke and transient ischemic attack), hearing loss, and diabetic foot diseases such as foot ulcers and amputations. Persistent hyperglycemia in uncontrolled diabetes leads to various complications, both acute and chronic, making diabetes one of the primary causes of cardiovascular disease (CVD), blindness, kidney failure, and lower limb amputations. Chronic microvascular complications encompass nephropathy, neuropathy, and retinopathy, while macrovascular complications include coronary artery disease (CAD), peripheral artery disease (PAD), and cerebrovascular disease. Middle-aged individuals with diabetes have an estimated annual risk of experiencing a CVD event ranging from 1.4% to 4.7%.[92] Children with Type 2 diabetes face significant long-term complications, often occurring earlier in the disease course compared to adults, including renal and neurological complications leading to dialysis, amputation, and blindness within 10 years of diagnosis. For adult patients with Type 2 diabetes, life expectancy is significantly reduced compared to those without the condition. Pediatric patients with Type 2 diabetes also exhibit higher rates of hypertension and albuminuria

compared to their peers without diabetes. Additionally, adult Type 2 diabetes patients are at higher risk of developing cancers and other non-vascular complications. However, data on life expectancy associated with pediatric Type 2 diabetes remains scarce.[93]

CONCLUSION

The conclusion underscores the growing epidemic of diabetes mellitus and the devastating complications it can cause if not effectively treated. Despite the challenges, comprehensive diabetes care can significantly improve outcomes, delaying the progression of complications and enhancing quality of life while reducing healthcare costs. Insulin remains a cornerstone treatment for all types of diabetes, but lifestyle interventions such as diet, exercise, and education are equally crucial. Addressing obesity and promoting lifestyle changes are essential strategies. Additionally, newer medications like GLP-1 analogs and DPP-4 inhibitors offer promising options, particularly for obese individuals. While current therapies cannot cure diabetes, ongoing research and emerging technologies provide hope for a better future for those living with the condition. The paper emphasizes the challenges of managing diabetes, highlighting its serious complications and the importance of maintaining strict control over blood glucose levels to mitigate them. While tight control is crucial, it can pose the risk of hypoglycemia, which can be more severe than high blood glucose levels. Researchers are therefore exploring alternative treatment methods to address this issue.

The paper aims to provide an overview of the current state of diabetes research, emphasizing its significance as a prominent area of study in the new century. The author encourages new researchers to tackle the challenges associated with diabetes research.

1) Sapra A, Bhandari P	Type 1 diabetes mellitus (T1D) is an autoimmune condition characterized by the destruction of insulin-producing pancreatic beta cells.	2023
2) Ehrmann D, Kulzer B Roos T, Al-Khatib M	Detectable c-peptide levels are associated with improved glycemic management.	2020
3) Jeyam A, Colhoun H McGurnaghan S Chalmers J	The presence of other autoimmune disorders, obesity, comorbidities, and the development of diabetes-related complications vary among individuals	2021
4) Holt RIG, DeVries JH Hess-Fischl A, Weinstock RS	T1D involves administering multiple daily insulin injections (MDI), using insulin pump therapy, or adopting automated insulin delivery systems, coupled with continuous glucose monitoring (CGM) whenever possible	2022
5) ŠkrhaJ Jr, ADA	A collaborative multidisciplinary approach, involving medical providers, nurse and dietitian educators, pharmacists, and specialists like podiatrists, mental health professionals, social workers, etc.	2022
6) Zheng Y, Ley SH,	Insulin resistance, a hallmark of T2DM, typically arises from a combination of factors such as obesity and age.	2018
7) Rajaei E, Jalali MT, Shahrabi S, Asnafi AA	Strong evidence indicates a higher hereditary influence on T2DM compared to T1DM.	2019
8) Klein BE, Klein R, Moss SE, Cruickshanks KJ.	Monozygotic twins with one affected twin have a 90% likelihood of the other twin developing Type 2 diabetes mellitus (T2DM) during their lifetime	1996
9) Barnett AH, Eff C, 10) Leslie RD, Pyke DA, Saxena R, Voight BF	A genome-wide association study (GWAS) identified genetic loci like the transcription factor 7-like 2 gene (TCF7L2), which increases T2DM risk	1981 2007
11) Shields BM, Hicks S, Shepherd MH, Ellard S MODY, 12) Kühl C.	Other loci implicated in T2DM development include NOTCH2, JAZF1, KCNQ1, and WFS1.	2010, 1998
13) Leslie RD, Evans- MC, Buzzetti R, 14) Kim SS, Hudgins AD	Mutations in genes such as hepatocyte nuclear factor-1-alpha (HNF1A) and the glucokinase (GCK) gene are associated with MODY,	2021

	occurring in a significant percentage of cases.	
15) Krischer JP, Liu X, Lernmark Å	HLA antigens, particularly HLA DR2, 3, and 4, while others implicate factors like excessive proinsulin levels or hormonal changes affecting beta-cell function and insulin sensitivity	2022
16) Zorena K, MichalskaM, Kurpas M, Kurpas M.	In Type 1 diabetes (T1D), autoimmune processes gradually destroy beta cells within the pancreatic islets over a period of months or years, resulting in a severe deficiency of insulin.	2022
17) RahmatiM, Keshvari M, Mirnasuri S, Smith L.	Additionally, multiple other genes contribute to the heritability of T1D	2022
18) LampousiAM, Carlsson S, 19) Krischer JP, Liu X, 20) Malek R, Hannat S,	T1D development associated with infections from viruses such as Coxsackie, enteroviruses, cytomegalovirus, rubella, influenza B, mumps, and more recently, SARS-CoV-2 (COVID-19)	2021, 2019
21) Choi YJ, Chung YS	Young (TEDDY) have explored factors like breastfeeding and dietary introductions, with varying conclusions on their impact on T1D risk	2016
22) Picke AK, Campbell G, Napoli N, Rauner M.	The presence of circulating pancreatic islet autoantibodies indicates an increased risk of or actual development of T1D	2019
23) Felner EI, Klitz W, Lazaro AM, Stastny P.	GAD65 being the most common autoantibody detected in adults	2005
24) Dabelea D, Bell RA, 25) Gale EA, Gillespie KM, 26) Mamoulakis D, Galanakis E 27) Tuomilehto J.	Type 1 diabetes, Type 2 diabetes, and gestational diabetes (GDM). Less common types include monogenic diabetes and secondary diabetes.	2007, 2001, 2013.
28) PattersonCC, Dahlquist GG	Type 1 diabetes mellitus (T1DM) gradually increases from birth, peaking between ages 4 to 6 years and again from 10 to 14 years.[28]	2009
29) Vehik K, Hamman RF	Approximately 45% of children develop T1DM before age ten	2007
30) Rush T, McGeary M, 31) Zheng Y, Ley SH, 32) Harris MI, Flegal KM,	T1DM incidence rates have been increasing globally, with Europe, Australia, and the Middle East experiencing annual rises of 2% to 5%	2018, 1998,
33) Carter JS, Pugh JA.	T1DM rates have increased by approximately 2% yearly across most age and ethnic groups, with higher rates observed among Hispanic youth	1996
34) Schulz LO, Bennett PH	United States Military Health System repository, suggest a plateauing trend from 2007 to 2012, with a prevalence of 1.5 per 1000 and an incidence of 20.7 to 21.3 per 1000	2006
35) Leslie RD, Evans-Molina C.	The United States, T2DM affects around 9% of the total population, with approximately 25% prevalence among those over 65 years old.	2021
36) Mobasseri M, Shirmohammadi M, 37) Carrillo-Larco RM, Barengo NC	T2DM prevalence varies across ethnic groups, with Blacks, Native Americans, Pima Indians, and Hispanic Americans experiencing 2 to 6 times higher rates compared to Whites in the United States.	2019, 2020
38) Unger RH, Orci L	T2DM compared to their counterparts in the United States, with prevalence rates of 6.9% versus 38%, respectively. T2DM compared to their counterparts in the United States, with prevalence rates of 6.9% versus 38%,	2010

	respectively.	
39) Dabelea D, Rewers A	Type 1 diabetes (T1D) is among the most common chronic conditions affecting children, although it can manifest at any age.	2020
40) Flint A, Arslanian S.	There has been a steady rise in the incidence and prevalence of T1D, constituting approximately 5% to 10% of all diabetes cases.	2011
41) Caprio S, Pierpont B	The prevalence of diabetes rises with age, affecting about 25% of individuals over 65 years old.	-
42)	Glycation leads to microvascular damage in organs such as the retina, kidneys, and peripheral nerves, with higher glucose levels accelerating this process.	2018
43) Yapanis M, James S	HbA1c may be misleading, necessitating the use of glucose criteria for diagnosis.	2022
44) Beck RW, Bergenstal RM	Electrolyte abnormalities may also be present, and if left untreated, diabetic ketoacidosis (DKA) may develop, necessitating hospitalization and treatment with intravenous fluids, insulin, potassium supplementation, and close monitoring.	2019
45) Bergenstal RM, Beck RW	Type 2 diabetes, while a low (<200 pmol/L) or undetectable c-peptide confirms the diagnosis of T1D	2018
46) Umpierre D, Ribeiro PA	Obesity precipitates peripheral insulin resistance, fostering hyperglycemia as a consequence. This resistance manifests across various organs and tissues.	2011
47) Knowler WC, Barrett-Connor E.	Insulin resistance may persist for a substantial duration before the diagnosis of Type 2 diabetes mellitus (T2DM)	2002
48) DeBoer, IH, Bangalore S	Body Mass Index (BMI) alone, could serve as a more accurate predictor for insulin resistance-related complications like T2DM and hypertension.[48]	2017
49)	hormonal shifts during puberty induce transient insulin resistance, heightening the risk of hyperglycemia and T2DM development	2000
50) Ogawa H, Nakayama M	Hyperglycemia triggers osmotic diuresis, resulting in polyuria and increased thirst, ultimately leading to moderate to severe dehydration.	2008
51) Saito Y, Morimoto T	Type 1 diabetes, especially in young women, clinical evaluation is warranted. Cognitive testing should also be considered early, particularly in cases where cognitive decline is suspected	2011
52) Silver B, Ramaiya K 53) Hirsch IB, Juneja R	Minimizing hypoglycemia is a primary goal, as a higher percent TIR is associated with reduced diabetes-related complications.	2018, 2020
54) Lai LL, Wan Yusoff WNI	The Glucose Management Indicator (GMI) offers further insight by correlating average sensor readings with estimated HbA1c levels	
55) Eckstein ML, Williams DM	Successful disease management involves adherence to dietary restrictions, regular exercise, and diligent glucose monitoring	2019
56) Massey CN, Feig EH	Bariatric surgery may be considered for morbidly obese patients unresponsive to other	2019

	treatments and with significant comorbidities.	
57) Shah SR, Iqbal SM	The FDA has granted approval for pregabalin and duloxetine to treat diabetic peripheral neuropathy, while tricyclic antidepressants and anticonvulsants have shown variable success in managing diabetic neuropathic pain	2019
58) Zhonghua nei ke za zhi, 59) Flint A, Arslanian S, 60) Cha E, Paul S	atherosclerotic cardiovascular disease (ASCVD) is present. Statins are the first-line treatment for dyslipidemia in diabetics.	2018, 2011
61) Albert PE, Mateu OV, Martínez-Espinosa RM,	Hypoglycemia is a common adverse effect of insulin therapy, necessitating education on its signs and symptoms and appropriate management with glucose administration.	2018
62) Cha E, Paul S	Type 1 diabetes (T1D) should ideally consult with a dietitian to learn carbohydrate counting and utilize an insulin-to-carbohydrate ratio for mealtime dosing.	2018
63) Vaughan EM, Johnston CA 64) Holman RR, Paul SK, 65) Petersmann A, Müller-WD 66) Kerner W, Brückel J	insulin, preferred for basal therapy, includes U-100 and U-300 glargine and degludec, lasting up to 42 hours. Intermediate insulin (NPH, NPL) has an onset in 1 to 2 hours, peak action at 2 to 8 hours, and duration of 12 to 24 hours.	2017, 2008, 2019, 2014
67) Cepeda Marte JL, Ruiz-MC 68) Steffensen C, Dekkers OM 69) Heron M, 70) Albers JW, Herman WH	Metformin is the first-line therapy for T2DM, followed by other medications targeting insulin sensitivity or secretion.	2019, 2017, 2010
71)	Insulin pumps deliver insulin continuously for basal needs and boluses to manage mealtime glucose fluctuations. Physical activity is beneficial for those with T1D, improving insulin sensitivity, cardiovascular health, lipid profiles, and reducing complications risk.	1998
72)	Drug-induced insulin resistance is also a consideration and may involve medications such as phenytoin, glucocorticoids, and estrogen.	1998
73) Perreault L, Pan Q, 74) Ruiz PLD, Chen L	The potential differential diagnoses for diabetes mellitus encompass a range of conditions with similar presentations. 1. Diabetes insipidus 2. Factitious illness 3. Maturity-Onset Diabetes of the Young (MODY)	2012, 2022
75) Qin Z, Zhou K	Additional considerations include: 1. Drug-induced symptoms caused by corticosteroids, neuroleptics, pentamidine, etc. 2. Genetic abnormalities affecting beta-cell function and insulin action 3. Metabolic syndrome (syndrome X).	2020
76) Nowakowska M, Zghebi SS	Endocrine disorders like acromegaly, Cushing's disease, pheochromocytoma, hypothyroidism, etc.	2020
77) Yamazaki D, Hitomi H	Conditions impacting the exocrine pancreas such as pancreatitis, cystic fibrosis, etc.	2018
78) Wannamethee SG, Shaper AG 79) Rao Kondapally SS, Kaptoge S	diabetes mellitus is closely tied to glucose management, with chronic hyperglycemia significantly elevating the risk of complications.	2011
80) Stern MP	pre-diabetes to diabetes, often experience a more favorable prognosis, potentially slowing	1996

	disease advancement.	
81) Forbes JM, Cooper ME	Despite a higher mortality rate among those with Type 1 diabetes compared to the general population, overall mortality rates have declined.	2013
82) Tseng CH, 83) Yin M, Zhou J	LDL cholesterol and manage blood pressure using ACE/ARB therapy and other antihypertensive medications, combined with aspirin for secondary prevention, have significantly improved the management of vascular complications.	2011, 2018
84) Murphy HR, Steel SA	Complications of diabetes, regardless of its type, encompass microvascular, macrovascular, and neuropathic issues	2011
85) Karslioglu FE, Donihi AC	Cardiovascular disease (ASCVD) stands as one of the most severe consequences of diabetes, with approximately two-thirds of diabetic individuals succumbing to myocardial infarctions or strokes.	2019
86) Akalu Y, Birhan A 87) Patoulias D, Papadopoulos C	Type 2 diabetes mellitus (T2DM), even fasting glucose levels exceeding 100 mg/dL significantly heighten the risk of ASCVD, often preceding overt hyperglycemia.	2020
88) Valaiyapathi B, Gower B	Diabetic retinopathy is a prevalent cause of blindness among adults aged 20 to 74 in the United States, leading to 12,000 to 24,000 new cases of blindness annually.	2020
89) Dart AB, Martens PJ	Diabetes also ranks as the leading cause of limb amputations in the United States, primarily attributable to vasculopathy and neuropathy associated with the condition.	2014
90) Dart AB, Sellers EA	Patients using metformin have shown improved cancer-specific survival rates in prostate, pancreatic, breast, and colorectal cancers, although the exact mechanism by which metformin modulates cancer in diabetic patients remains unclear.	2012
91) Kianmehr H, Zhang P	gestational diabetes face an elevated risk of cesarean delivery and chronic hypertension.	2022
92) Rao Kondapally SS, Kaptoge S	Acute and chronic, making diabetes one of the primary causes of cardiovascular disease (CVD), blindness, kidney failure, and lower limb amputations. Chronic microvascular complications encompass nephropathy, neuropathy, and retinopathy, while macrovascular complications include coronary artery disease (CAD), peripheral artery disease (PAD).	2011
93) Cioana M, Deng J, Nadarajah A	Pediatric patients with Type 2 diabetes also exhibit higher rates of hypertension and albuminuria compared to their peers without diabetes.	2021

REFERENCE

1. Sapra A, Bhandari P. Diabetes. [Updated 2023 Jun 21]. In: Stat Pearls [Internet]. Treasure Island (FL): [Stat Pearls Publishing;], 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK551501/
2. Ehrmann D, Kulzer B, Roos T, Haak T, Al-Khatib M, Hermanns N. Risk factors and prevention strategies for diabetic ketoacidosis in people with established type 1 diabetes. [The lancet. Diabetes & endocrinology.], 2020; 8(5): 436-446. doi: 10.1016/S2213-8587(20)30042-5. Epub
3. Jeyam A, Colhoun H, McGurnaghan S, Blackbourn L, McDonald TJ, Palmer CNA, McKnight JA, Strachan MWJ, Patrick AW, Chalmers J, Lindsay

RS, Petrie JR, Thekkepat S, Collier A, MacRury S, McKeigue PM, SDRNT1BIO Investigators. Clinical Impact of Residual C-Peptide Secretion in Type 1 Diabetes on Glycemia and Microvascular Complications. [Diabetes care], 2021: 44(2): 390-398. doi:10.2337/dc20-0567. Epub 2020 Dec 10

4. Holt RIG, DeVries JH, Hess-Fischl A, Hirsch IB, Kirkman MS, Klupa T, Ludwig B, Nørgaard K, Pettus J, Renard E, Skyler JS, Snoek FJ, Weinstock RS, Peters AL. Correction to: [The management of type 1 diabetes in adults]. A consensus report by the ADA and the EASD. Diabetologia, 2022; 65(1): 255. Doi: 10.1007/s00125-021-05600-6. Epub
5. Škrha J Jr. ADA [Standards of Medical Care in Diabetes] 2022 – whats new? Vnitrni lekarstvi, 2022; 68(2): 85-88.
6. Zheng Y, Ley SH, Hu FB. [Global etiology and epidemiology of type 2 diabetes mellitus and its complications]. Nature reviews. Endocrinology, 2018; 14(2): 88-98. doi: 10.1038/nrendo.2017.151. Epub 2017 Dec 8
7. Rajaei E, Jalali MT, Shahrabi S, Asnafi AA, Pezeshki SMS. [HLAs in Autoimmune Diseases]. Dependable Diagnostic Biomarkers? Curr Rheumatol Rev, 2019; 15(4): 269-276.
8. Klein BE, Klein R, Moss SE, Cruickshanks KJ. [Parental history of diabetes in a population-based study]. Diabetes Care, 1996; 19(8): 827-30.
9. Barnett AH, Eff C, Leslie RD, Pyke DA. Diabetes in identical twins. A study of 200 pairs. [Diabetologia], 1981; 20(2): 87-93.
10. Saxena R, Voight BF, Lyssenko V, Burtt NP, de Bakker PI, Chen H, Roix JJ, Kathiresan S, Hirschhorn JN, Daly MJ, Hughes TE, Groop L, Altshuler D, Almgren P, Florez JC, Meyer J, Ardlie K, Bengtsson Boström K, Isomaa B, Lettre G, Lindblad U, Lyon HN, Melander O, Newton-Cheh C, Nilsson P, Orho-Melander M, Råstam L, Speliotes EK, Taskinen MR, Tuomi T, Guiducci C, Berglund A, Carlson J, Gianniny L, Hackett R, Hall L, Holmkvist J, Laurila E, Sjögren M, Sterner M, Surti A, Svensson M, Svensson M, Tewhey R, Blumenstiel B, Parkin M, Defelice M, Barry R, Brodeur W, Camarata J, Chia N, Fava M, Gibbons J, Handsaker B, Healy C, Nguyen K, Gates C, Sougnez C, Gage D, Nizzari M, Gabriel SB, Chirn GW, Ma Q, Parikh H, Richardson D, Ricke D, Purcell S. Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of Bio-Medical Research [Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels]. Science, 2007; 01, 316(5829): 1331-6.
11. Shields BM, Hicks S, Shepherd MH, Colclough K, Hattersley AT, Ellard S MODY: how many cases are we missing? [Diabetologia], 2010; 53(12): 2504-8.
12. Kühl C. [Etiology and pathogenesis of gestational diabetes]. Diabetes Care, 1998; 21, 2: B19-26.
13. Leslie RD, Evans- MC, Freund-BJ, Buzzetti R, Dabelea D, Gillespie KM, Goland R, Jones AG, Kacher M, Phillips LS, Rolandsson O, Wardian JL, Dunne JL. [Adult-Onset Type 1 Diabetes]: Current Understanding and Challenges. Diabetes care, 2021; 44(11): 2449-2456. doi: 10.2337/dc21-0770. Epub
14. Kim SS, Hudgins AD, Yang J, Zhu Y, Tu Z, Rosenfeld MG, DiLorenzo TP, Suh Y. A comprehensive integrated post-GWAS [analysis of Type 1 diabetes reveals enhancer-based immune dysregulation]. PloS one, 2021; 16(9): e0257265. doi: 10.1371/journal.pone.0257265. Epub 2021 Sep 16
15. Krischer JP, Liu X, Lernmark Å, Hagopian WA, Rewers MJ, She JX, Toppari J, Ziegler AG, Akolkar B, TEDDY Study Group. Predictors of the Initiation of Islet Autoimmunity and Progression to Multiple Autoantibodies and Clinical Diabetes; [The TEDDY Study]. Diabetes care, 2022; 1, 45(10): 2271-2281. doi: 10.2337/dc21-2612. Epub
16. Zorena K, Michalska M, Kurpas M, Jaskulak M, Murawska A Kurpas M [Environmental Factors and the Risk of Developing Type 1 Diabetes-Old Disease and New Data]. Biology, 2022; 16, 11(4): doi: 10.3390/biology11040608. Epub 2022 Apr 16.
17. Rahmati M, Keshvari M, Mirnasuri S, Yon DK, Lee SW, Il Shin J, Smith L. The global impact of COVID-19 pandemic on the incidence of pediatric new-onset type 1 diabetes and ketoacidosis: [A systematic review and meta-analysis]. Journal of medical virology, 2022; 94(11): 5112-5127. doi: 10.1002/jmv.27996. Epub 2022 Jul 22.
18. Lampousi AM, Carlsson S, Löfvenborg JE. [Dietary factors and risk of islet autoimmunity and type 1 diabetes]: a systematic review and meta-analysis. Ebio-Medicine, 2021; 72: 103633. doi: 10.1016/j.ebiom.2021.103633. Epub 2021 Oct 14.
19. Krischer JP, Liu X, Lernmark Å, Hagopian WA, Rewers MJ, She JX, Toppari J, Ziegler AG, Akolkar B, TEDDY Study Group. Characteristics of children diagnosed with type 1 diabetes before vs after 6 years of age in the [TEDDY cohort study]. Diabetologia, 2021; 64(10): 2247-2257. doi: 10.1007/s00125-021-05514-3. Epub 2021 Jul 22
20. Malek R, Hannat S, Nechadi A, Mekideche FZ, Kaabeche M. Diabetes and Ramadan: A multicenter study in Algerian population. [Diabetes research and clinical practice], 2019; 150: 322-330. doi: 10.1016/j.diabres.2019.02.008. Epub 2019 Feb 16
21. Choi YJ, Chung YS. Type 2 diabetes mellitus and bone fragility: Special focus on bone imaging. [Osteoporosis and sarcopenia], 2016; 2(1): 20-24. doi: 10.1016/j.afos.2016.02.001. Epub 2016 Mar 3
22. Picke AK, Campbell G, Napoli N, Hofbauer LC, Rauner M. Update on the impact of type 2 diabetes mellitus on bone metabolism and material properties. [Endocrine connections], 2019; 1, 8(3): R55-R70. doi: 10.1530/EC-18-0456. Epub
23. Felner EI, Klitz W, Ham M, Lazaro AM, Stastny P, Dupont B, White PC. Genetic interaction among

three genomic regions creates distinct contributions to early- and late-onset type 1 diabetes mellitus. [Pediatric diabetes], 2005; 6(4): 213-20.
24. Dabelea D, Bell RA, D'Agostino RB Jr, Imperatore G, Johansen JM, Linder B, Liu LL, Loots B, Marcovina S, Mayer-Davis EJ, Pettitt DJ, Waitzfelder B. Writing Group for the SEARCH for Diabetes in Youth Study Group, [Incidence of diabetes in youth in the United States]. JAMA, 2007; 27, 297(24): 2716-24.
25. Gale EA, Gillespie KM. [Diabetes and gender]. Diabetologia, 2001; 44(1): 3-15.
26. Mamoulakis D, Galanakis E, Bicouvarakis S, Paraskakis E, Sbyrakis S, Epidemiology of childhood type I diabetes in Crete, 1990-2001. [Acta paediatrica] (Oslo, Norway, 1992). 2003.
27. Tuomilehto J. [The emerging global epidemic of type 1 diabetes]. Current diabetes reports, 2013; 13(6): 795-804. doi: 10.1007/s11892-013-0433-5. Epub
28. Patterson CC, Dahlquist GG, Gyürüs E, Green A, Soltész G, EURODIAB Study Group., [Incidence trends for childhood type 1 diabetes in Europe] during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. Lancet (London, England), 2009; 13.
29. Vehik K, Hamman RF, Lezotte D, Norris JM, Klingensmith G, Bloch C, Rewers M, Dabelea D. [Increasing incidence of type 1 diabetes in 0- to 17-year-old Colorado youth]. Diabetes care, 2007; 30(3): 503-9.
30. Rush T, McGeary M, Sicignano N, Buryk MA. A plateau in new onset type 1 diabetes: [Incidence of pediatric diabetes in the United States Military Health System]. Pediatric diabetes, 2018; 19(5): 917-922. doi: 10.1111/pedi.12659. Epub 2018 Mar 8
31. Zheng Y, Ley SH, Hu FB, Global etiology and epidemiology of type 2 diabetes mellitus and its complications. Nature reviews. [Endocrinology], 2018.
32. 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 U.S. adults]. The Third National Health and Nutrition Examination Survey, 1988-1994. Diabetes care, 1998; 21(4): 518-24.
33. Carter JS, Pugh JA, Monterrosa A, [Non-insulin-dependent diabetes mellitus in minorities in the U.S]. Annals of internal medicine, 1996; 1.
34. Schulz LO, Bennett PH, Ravussin E, Kidd JR, Kidd KK, Esparza J, Valencia ME. [Effects of traditional and western environments on prevalence of type 2 diabetes in Pima Indians in Mexico and the U.S]. Diabetes care, 2006; 29(8): 1866-71.
35. Leslie RD, Evans-Molina C, Freund-Brown J, Buzzetti R, Dabelea D, Gillespie KM, Goland R, Jones AG, Kacher M, Phillips LS, Rolandsson O, Wardian JL, Dunne JL.[Adult-Onset Type 1 Diabetes]. Current Understanding and Challenges. Diabetes care, 2021; 44(11): 2449-2456. doi: 10.2337/dc21-0770. Epub
36. Mobasseri M, Shirmohammadi M, Amiri T, Vahed N, Hosseini Fard H, Ghojazadeh M. [Prevalence and incidence of type 1 diabetes in the world]. a systematic review and meta-analysis. Health promotion perspectives, 2020; 10(2): 98-115. doi: 10.34172/hpp.2020.18. Epub 2020 Mar 30
37. Carrillo-Larco RM, Barengo NC, Albitres-Flores L, Bernabe-Ortiz A. The risk of mortality among people with type 2 diabetes in Latin America: A systematic review and meta-analysis of population-based cohort studies. [Diabetes/metabolism research and reviews], 2019; 35(4): e3139. doi: 10.1002/dmrr.3139. Epub 2019 Mar 4
38. Unger RH, Orci L, [Paracrinology of islets and the paracrinopathy of diabetes]. Proceedings of the National Academy of Sciences of the United States of America, 2010; 14.
39. Dabelea D, Rewers A, Stafford JM, Standiford DA, Lawrence JM, Saydah S, Imperatore G, D'Agostino RB Jr, Mayer-Davis EJ, Pihoker C, SEARCH for Diabetes in Youth Study Group. Trends in the prevalence of ketoacidosis at diabetes diagnosis: the SEARCH for diabetes in youth study. Pediatrics, 2014; 133(4): e938-45. doi: 10.1542/peds.2013-2795. Epub 2014 Mar 31Valaiyapathi B, Gower B, Ashraf AP. [Pathophysiology of Type 2 Diabetes in Children and Adolescents]. Current diabetes reviews, 2020; 16(3): 220-229. doi: 10.2174/1573399814666180608074510. Epub
40. Flint A, Arslanian S. [Treatment of type 2 diabetes in youth]. Diabetes care, 2011; 34, 2(2): S177-83. doi: 10.2337/dc11-s215. Epub
41. Caprio S, Pierpont B, Kursawe R. The "adipose tissue expandability" hypothesis: [a potential mechanism for insulin resistance in obese youth].
42. [Hormone molecular biology and clinical investigation], 2018; 29: 33(2):.pii: /j/hmbci.2018.33.issue-2/hmbci-2018-0005/hmbci-2018-0005.xml. doi: 10.1515/hmbci-2018-0005. Epub 2018 Mar 29
43. Yapanis M, James S, Craig ME, O'Neal D, Ekinci EI. [Complications of Diabetes and Metrics of Glycemic Management Derived From Continuous Glucose Monitoring]. The Journal of clinical endocrinology and metabolism, 2022; 17, 107(6): e2221-e2236. doi: 10.1210/clinem/dgac034. Epub
44. Beck RW, Bergenstal RM, Riddlesworth TD, Kollman C, Li Z, Brown AS, Close KL. Validation of Time in Range as an [Outcome Measure for Diabetes Clinical Trials]. Diabetes care, 2019; 42(3): 400-405. doi: 10.2337/dc18-1444. Epub 2018 Oct 23
45. Bergenstal RM, Beck RW, Close KL, Grunberger G, Sacks DB, Kowalski A, Brown AS, Heinemann L, Aleppo G, Ryan DB, Riddlesworth TD, Cefalu WT. GMI: A [New Term for Estimating A1C From Continuous Glucose Monitoring]. Diabetes care,

2018; 41(11): 2275-2280. doi: 10.2337/dc18-1581. Epub 2018 Sep 17
46. Umpierre D, Ribeiro PA, Kramer CK, Leitão CB, Zucatti AT, Azevedo MJ, Gross JL, Ribeiro JP, Schaan BD. Physical activity advice only or [structured exercise training and association with HbA1c levels in type 2 diabetes]. a systematic review and meta-analysis. JAMA, 2011; 4, 305(17): 1790-9. doi: 10.1001/jama.2011.576. Epub
47. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM, Diabetes Prevention Program Research Group. [Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin]. The New England journal of medicine, 2002; 7, 346(6): 393-403.
48. de Boer IH, Bangalore S, Benetos A, Davis AM, Michos ED, Muntner P, Rossing P, Zoungas S, Bakris G. [Diabetes and Hypertension]. A Position Statement by the American Diabetes Association. Diabetes care, 2017; 40(9): 1273-1284. doi: 10.2337/dci17-0026. Epub
49. American Diabetes Association. [Aspirin therapy in diabetes]. Diabetes care, 2000 Jan; 23 Suppl 1(): S61-2
50. Ogawa H, Nakayama M, Morimoto T, Uemura S, Kanauchi M, Doi N, Jinnouchi H, Sugiyama S, Saito Y, [Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes]. a randomized controlled trial. JAMA, 2008; 12.
51. Saito Y, Morimoto T, Ogawa H, Nakayama M, Uemura S, Doi N, Jinnouchi H, Waki M, Soejima H, Sugiyama S, Okada S, Akai Y, Japanese Primary Prevention of [Atherosclerosis With Aspirin for Diabetes Trial Investigators]. Low-dose aspirin therapy in patients with type 2 diabetes and reduced glomerular filtration rate: subanalysis from the JPAD trial. Diabetes care, 2011; 34(2): 280-5. doi: 10.2337/dc10-1615. Epub
52. Silver B, Ramaiya K, Andrew SB, Fredrick O, Bajaj S, Kalra S, Charlotte BM, Claudine K, Makhoba A. EADSG Guidelines: [Insulin Therapy in Diabetes]. Diabetes therapy : research, treatment and education of diabetes and related disorders, 2018; 9(2): 449-492. doi: 10.1007/s13300-018-0384-6. Epub 2018 Mar 5
53. Hirsch IB, Juneja R, Beals JM, Antalis CJ, Wright EE. [The Evolution of Insulin and How it Informs Therapy and Treatment Choices]. Endocrine reviews, 2020; 1, 41(5): 733-55. doi: 10.1210/endrev/bnaa015. Epub
54. Lai LL, Wan Yusoff WNI, Vethakkan SR, Nik Mustapha NR, Mahadeva S, Chan WK. Screening for non-alcoholic fatty liver disease in patients with type 2 diabetes mellitus using transient elastography. [Journal of gastroenterology and hepatology], 2019; 34(8): 1396-1403. doi: 10.1111/jgh.14577. Epub 2019 Jan 21
55. Eckstein ML, Williams DM, O'Neil LK, Hayes J, Stephens JW, Bracken RM. [Physical exercise and non-insulin glucose-lowering therapies in the management of Type 2 diabetes mellitus]. a clinical review. Diabetic medicine : a journal of the British Diabetic Association, 2019; 36(3): 349-358. doi: 10.1111/dme.13865. Epub 2018 Dec 7
56. Massey CN, Feig EH, Duque-Serrano L, Wexler D, Moskowitz JT, Huffman JC. [Well-being interventions for individuals with diabetes] A systematic review. Diabetes research and clinical practice, 2019; 147: 118-133. doi: 10.1016/j.diabres.2018.11.014. Epub 2018 Nov 27
57. Shah SR, Iqbal SM, Alweis R, Roark S. A closer look at [heart failure in patients with concurrent diabetes mellitus using glucose lowering drugs]. Expert review of clinical pharmacology, 2019; 12(1): 45-52. doi: 10.1080/17512433.2019.1552830. Epub 2018 Dec 3
58. Zhonghua nei ke za zhi. 2018 Dec 1:57(12):885-893, Chinese Diabetes Society, National Office for Primary Diabetes Care. [National guidelines for the prevention and control of diabetes in primary care, 2018]. doi: 10.3760/cma.j.issn.0578-1426.2018.12.003. Epub
59. Flint A, Arslanian S. [Treatment of type 2 diabetes in youth]. Diabetes care, 2011; 34, 2(2): S177-83. doi: 10.2337/dc11-s215. Epub
60. Bhatt M, Nahari A, Wang PW, Kearsley E, Falzone N, Chen S, Fu E, Jeyakumar Y, Zukowski J, Banfield L, Thabane L, Samaan MC. [The quality of clinical practice guidelines for management of pediatric type 2 diabetes mellitus] a systematic review using the AGREE II instrument. Systematic reviews, 2018; 15, 7(1): 193. doi: 10.1186/s13643-018-0843-1. Epub 2018 Nov 15
61. Albert PE, Mateu OV, Martínez-Espinosa RM, Molina Vila MD, Reig García-GM. New Insights about How to Make an [Intervention in Children and Adolescents with Metabolic Syndrome]. Diet, Exercise vs. Changes in Body Composition. A Systematic Review of RCT. Nutrients, 2018; 6, 10(7). doi: 10.3390/nu10070878. Epub 2018 Jul 6
62. Cha E, Paul S, Braxter BJ, Umpierrez G, Faulkner MS. [Dietary Behaviors and Glucose Metabolism in Young Adults at Risk for Type 2 Diabetes]. The Diabetes educator, 2018: 44(2): 158-167. doi: 10.1177/0145721718756057. Epub 2018 Mar 1
63. Vaughan EM, Johnston CA, Cardenas VJ, Moreno JP, Foreyt JP. [Integrating CHWs as Part of the Team Leading Diabetes Group] Visits: A Randomized Controlled Feasibility Study. The Diabetes educator, 2017; 43(6): 589-599. doi: 10.1177/0145721717737742. Epub 2017 Oct 19
64. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of [intensive glucose control in type 2 diabetes]. The New England journal of medicine, 2008; 9, 359(15): 1577-89. doi: 10.1056/NEJMoa0806470. Epub 2008 Sep 10

65. Petersmann A, Müller-WD, Müller UA, Landgraf R, Nauck M, Freckmann G, Heinemann L, Schleicher E. Definition, Classification and Diagnosis of Diabetes Mellitus. Experimental and clinical endocrinology & diabetes: official journal, [German Society of Endocrinology and German Diabetes Association], 2019; 127(01): S1-S7. doi: 10.1055/a-1018-9078. Epub 2019 Dec 20
66. Kerner W, Brückel J, German Diabetes Association. Definition, classification and diagnosis of diabetes mellitus. [Experimental and clinical endocrinology & diabetes]. official journal, German Society of Endocrinology [and] German Diabetes Association, 2014; 122(7): 384-6. doi: 10.1055/s-0034-1366278. Epub 2014 Jul 11
67. Cepeda Marte JL, Ruiz-MC, Mota M, Pérez S, Recio N, Hernández D, Fernández J, Porto J, Ramos A. [Quality of life and metabolic control in type 2 diabetes mellitus diagnosed individuals]. Diabetes & metabolic syndrome, 2019; 13(5): 2827-2832. doi: 10.1016/j.dsx.2019.07.062. Epub 2019 Jul 30
68. Steffensen C, Dekkers OM, Lyhne J, Pedersen BG, Rasmussen F, Rungby J, Poulsen PL, Jørgensen JOL. [Hypercortisolism in Newly Diagnosed Type 2 Diabetes]. A Prospective Study of 384 Newly Diagnosed Patients. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolism, 2019; 51(1): 62-68. doi: 10.1055/a-0809-3647. Epub 2018 Dec 6
69. Heron M. Deaths: Leading Causes for 2015. [National vital statistics reports: from the Centers for Disease Control and Prevention]. National Center for Health Statistics, National Vital Statistics System, 2017; 66(5): 1-76.
70. Albers JW, Herman WH, Pop-Busui R, Feldman EL, Martin CL, Cleary PA, Waberski BH, Lachin JM, Diabetes [Control and Complications Trial /Epidemiology of Diabetes Interventions and Complications Research Group]. Effect of prior intensive insulin treatment during the DCCT on peripheral neuropathy in type 1 diabetes during the Epidemiology of Diabetes Interventions and Complications (EDIC) Study. Diabetes care, 2010; 33(5): 1090-6. doi: 10.2337/dc09-1941. Epub 2010 Feb 11
71. [Intensive blood-glucose control with sulphonylureas] or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet (London, England), 1998; 12.
72. [Intensive blood-glucose control with sulphonylureas] or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet (London, England), 1998; 12.
73. Perreault L, Pan Q, Mather KJ, Watson KE, Hamman RF, Kahn SE, Diabetes Prevention Program Research Group. [Effect of regression from prediabetes to normal glucose regulation on long-term reduction in diabetes risk]. results from the Diabetes Prevention Program Outcomes Study. Lancet (London, England), 2012; 16, 379(9833): 2243-51. doi: 10.1016/S0140-6736(12)60525-X. Epub 2012 Jun 9
74. Ruiz PLD, Chen L, Morton JI, Salim A, Carstensen B, Gregg EW, Pavkov ME, Mata-Cases M, Mauricio D, Nichols GA, Pildava S, Read SH, Wild SH, Shaw JE, Magliano DJ. [Mortality trends in type 1 diabetes]. a multicountry analysis of six population-based cohorts. Diabetologia, 2022; 65(6): 964-972. doi: 10.1007/s00125-022-05659-9. Epub 2022 Mar 22
75. Qin Z, Zhou K, Li Y, Cheng W, Wang Z, Wang J, Gao F, Yang L, Xu Y, Wu Y, He H, Zhou Y. The atherogenic index of plasma plays an important role in predicting the prognosis of type 2 diabetic subjects undergoing percutaneous coronary intervention: results from an observational cohort study in China. [Cardiovascular diabetology], 2020; 21, 19(1): 23. doi: 10.1186/s12933-020-0989-8. Epub 2020 Feb 21
76. Nowakowska M, Zghebi SS, Ashcroft DM, Buchan I, Chew-Graham C, Holt T, Mallen C, Van Marwijk H, Peek N, Perera-Salazar R, Reeves D, Rutter MK, Weng SF, Qureshi N, Mamas MA, Kontopantelis E. Correction to: [The comorbidity burden of type 2 diabetes mellitus]. patterns, clusters and predictions from a large English primary care cohort. BMC medicine, 2020; 25, 18(1): 22. doi: 10.1186/s12916-020-1492-5. Epub 2020 Jan 25
77. Yamazaki D ,Hitomi H, Nishiyama A, [Hypertension with diabetes mellitus complications]. Hypertension research: official journal of the Japanese Society of Hypertension, 2018.
78. Wannamethee SG,Shaper AG,Whincup PH,Lennon L,Sattar N, [Impact of diabetes on cardiovascular disease risk and all-cause mortality in older men]. influence of age at onset, diabetes duration, and established and novel risk factors. Archives of internal medicine, 2011; 14.
79. Rao Kondapally SS, Kaptoge S, Thompson A, Di Angel AE, Gao P, Sarwar N, Whincup PH, Mukamal KJ, Gillum RF, Holme I, Njølstad I, Fletcher A, Nilsson P, Lewington S, Collins R, Gudnason V, Thompson SG, Sattar N, Selvin E, Hu FB, Danesh J, (Emerging Risk Factors Collaboration. [Diabetes mellitus], fasting glucose, and risk of cause-specific death). NEJM, 2011; 3, 364(9): 829-841. doi: 10.1056/NEJMoa1008862. Epub
80. Stern MP, Do [non-insulin-dependent diabetes mellitus and cardiovascular disease] share common antecedents? Annals of internal medicine, 1996; 1.
81. Forbes JM, Cooper ME. [Mechanisms of diabetic complications]. Physiological reviews, 2013; 93(1): 137-88. doi: 10.1152/physrev.00045.2011. Epub
82. Tseng CH. [Diabetes and risk of bladder cancer]. a study using the NHIDT. Diabetologia, 2011; 54(8):

2009-15. doi: 10.1007/s00125-011-2171-z. Epub 2011 May 5
83. Yin M, Zhou J, Gorak EJ, Quddus F. [Metformin is associated with survival benefit in cancer patients with concurrent type 2 diabetes: a systematic review and meta-analysis. The oncologist], 2013; 18(12): 1248-55. doi: 10.1634/theoncologist.2013-0111. Epub 2013 Nov 20
84. Murphy HR, Steel SA, Roland JM, Morris D, Ball V, Campbell PJ, Temple RC, EASIPOD. [Obstetric and perinatal outcomes in pregnancies complicated by Type 1 and Type 2 diabetes], influences of glycaemic control, obesity and social disadvantage. Diabetic medicine: a journal of the British Diabetic Association, 2011; 28(9): 1060-7. doi: 10.1111/j.1464-5491.2011.03333.x. Epub
85. Karslioglu FE, Donihi AC, Korytkowski MT. [Diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome]. review of acute decompensated diabetes in adult patients. BMJ (Clinical research ed.), 2019; 29, 365: l1114. doi: 10.1136/bmj.l1114. Epub 2019 May 29
86. Akalu Y, Birhan A. [Peripheral Arterial Disease and Its Associated Factors among Type 2 Diabetes Mellitus] Patients at Debre Tabor General Hospital, Northwest Ethiopia. Journal of diabetes research, 2020; 2020(): 9419413. doi: 10.1155/2020/9419413. Epub 2020 Jan 29
87. Patoulias D, Papadopoulos C, Stavropoulos K, Zografou I, Doumas M, Karagiannis A. Prognostic value of arterial stiffness measurements in cardiovascular disease, diabetes, and its complications: [The potential role of sodium-glucose co-transporter-2 inhibitors]. Journal of clinical hypertension (Greenwich, Conn.), 2020; 22(4): 562-571. doi: 10.1111/jch.13831. Epub 2020 Feb 14
88. Valaiyapathi B, Gower B, Ashraf AP. [Pathophysiology of Type 2 Diabetes in Children and Adolescents]. Current diabetes reviews, 2020; 16(3): 220-229. doi: 10.2174/1573399814666180608074510. Epub
89. Dart AB, Martens PJ, Rigatto C, Brownell MD, Dean HJ, Sellers EA. Earlier onset of [complications in youth with type 2 diabetes]. Diabetes care, 2014; 37(2): 436-43. doi: 10.2337/dc13-0954. Epub 2013 Oct 15
90. Dart AB, Sellers EA, Martens PJ, Rigatto C, Brownell MD, Dean HJ. [High burden of kidney disease in youth-onset type 2 diabetes]. Diabetes care, 2012; 35(6): 1265-71. doi: 10.2337/dc11-2312. Epub 2012 Mar 19
91. Kianmehr H, Zhang P, Luo J, Guo J, Pavkov ME, Bullard KM, Gregg EW, Ospina NS, Fonseca V, Shi L, Shao H. [Potential Gains in Life Expectancy Associated With Achieving Treatment Goals in US Adults With Type 2 Diabetes]. JAMA network open, 2022; 1, 5(4): e227705. doi: 10.1001/jamanetworkopen.2022.7705. Epub 2022 Apr 1
92. Rao Kondapally SS, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, Whincup PH, Mukamal KJ, Gillum RF, Holme I, Njølstad I, Fletcher A, Nilsson P, Lewington S, Collins R, Gudnason V, Thompson SG, Sattar N, Selvin E, Hu FB, Danesh J, Emerging Risk Factors Collaboration. [Diabetes mellitus, fasting glucose, and risk of cause-specific death]. The New England journal of medicine, 2011; 3, 364(9): 829-841. doi: 10.1056/NEJMoa1008862. Epub
93. Cioana M, Deng J, Hou M, Nadarajah A, Qiu Y, Chen SSJ, Rivas A, Banfield L, Chanchlani R, Dart A, Wicklow B, Alfaraidi H, Alotaibi A, Thabane L, Samaan MC. [Prevalence of Hypertension and Albuminuria in Pediatric Type 2 Diabetes]. A Systematic Review and Meta-analysis. JAMA network open, 2021; 1, 4(4): e216069. doi: 10.1001/jamanetworkopen.2021.6069. Epub 2021 Apr 1