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REVIEW COMPLETE STUDY OF DIABETES DISEASE

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ABSTRACT

Evaluation of health-related quality of life (HRQoL) among people with diabetes has been growing in Iran over the last decade. The main aim of the current study was to systematically review the characteristics of these studies and examine quality of their findings. Persian (SID, Magiran) and English (Pubmed, Medline, Web of Science, CINAHL, Scopus, PsycINFO and ERIC) databases were systematically searched using the search terms: "diabetes" AND "quality of life" AND "Iran". The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. A total of 46 studies passed the inclusion criteria and were included in the review. The included studies were conducted in 20 out of 30 provinces of the country. Most studies investigated HRQoL among people with type 2 diabetes.

The Short Form Health Survey (SF-36) and WHO quality of life instruments (WHOQOL) were the main instruments used in these studies. Studies showed that people with diabetes had lower HRQoL than people without diabetes. Better socioeconomic status and better control of cardiovascular risk factors were associated with better HRQoL among the patients with diabetes. In general, the predictors of HRQoL among Iranian patients were similar to their international counterparts implying that diabetes patients share many common features. The reviewed studies suffer from major methodological and reporting flaws which limit validity and generalizability of their findings.

INTRODUCTION

Diabetes mellitus, commonly known as diabetes, is a chronic metabolic disease characterize high levels of sugar (glucose) in the blood. It occurs when the body cannot produce enough insulin or cannot effectively use the insulin it produces. Insulin is a hormone made by the pancreas that helps glucose enter cells to provide energy. Without proper insulin function, glucose remains in the bloodstream, leading to high blood sugar levels and, over time,causingdamage to various organs

Types of Diabetes

There are mainly three types of diabetes:

a) Type 1 Diabetes
- Also known as insulin-dependent diabetes.
- The body's immune system destroys insulin-producing cells in the pancreas.
- Usually diagnosed in children or young adults.
- Patients require daily insulin injections.

b) Type 2 Diabetes
- The most common type of diabetes.
- Occurs when the body becomes resistant to insulin or doesn't produce enough.
- Often linked to obesity, lack of exercise, and unhealthy diet.
- Can be managed with lifestyle changes, oral medicines, or insulin.

c) Gestational Diabetes
- Develops during pregnancy and usually disappears after childbirth.
- Increases the risk of developing Type 2 diabetes later in life.

Causes and Risk Factors

- Genetic factors (family history of diabetes)
- Obesity and unhealthy eating habits
- Physical inactivity
- High blood pressure and cholesterol
- Stress and hormonal imbalance

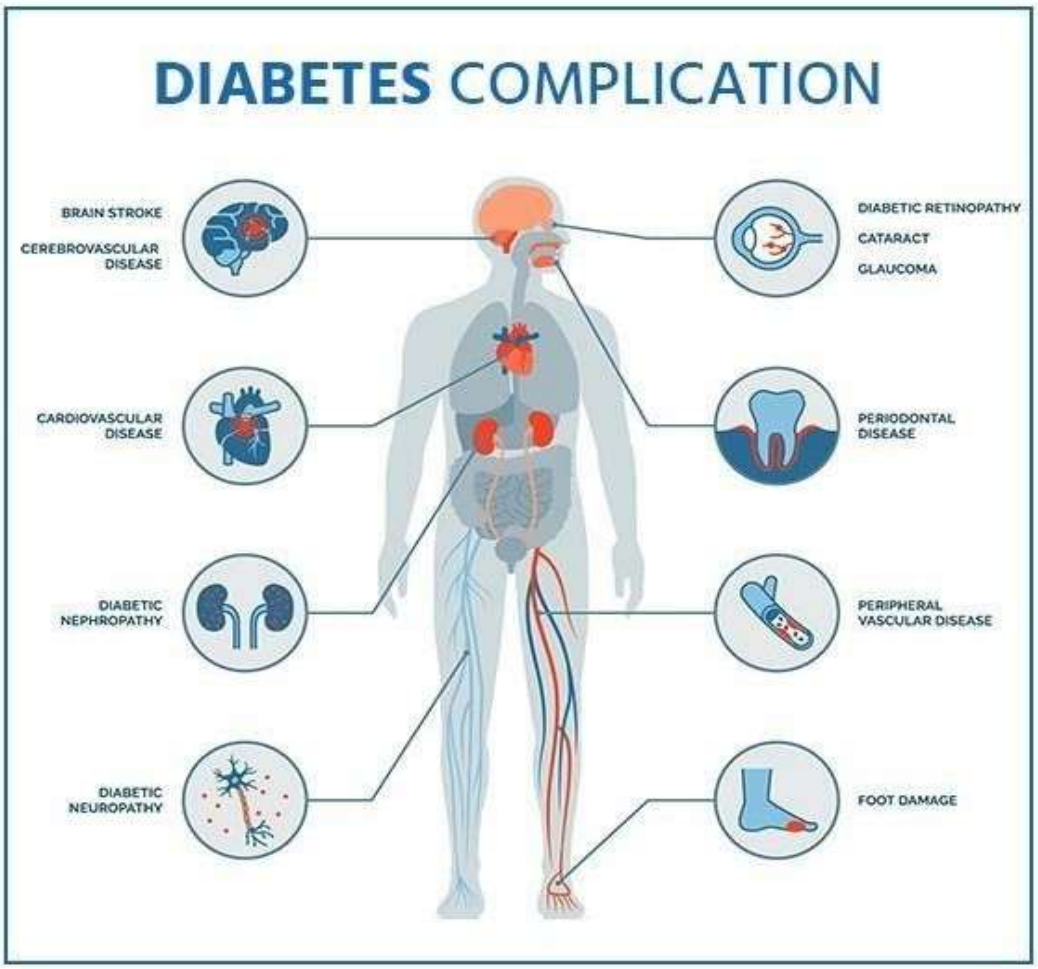
Prevention

- Maintain a healthy weight
- Eat balanced meals rich in fiber and low in refined sugars
- Engage in regular physical activity
- Avoid smoking and limit alcohol
- Regular medical check-ups, especially for high-risk individuals

Recent Advances in Diabetes Research

- Development of artificial pancreas and insulin pumps
- Use of stem cell therapy for regenerating insulin-producing cells
- Continuous glucose monitoring systems (CGMS) for better blood sugar tracking
- Advances in gene therapy and personalized medicine

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Diabetes I s a long-term health disease that impacts the body and converts food into energy, resulting in high blood sugar levels. It primarily affects the endocrine system but can also impact the heart, kidneys, nerves, and eyes.

Diabetes mellitus (DM) is a metabolic disease, involving inappropriately elevated blood glucose levels. DM has several categories, including type 1, type 2, maturity-onset diabetes of the young (MODY), gestational diabetes, neonatal diabetes, and secondary causes due to endocrinopathies, steroid use, etc. The main subtypes of DM are Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM), which classically result from defective insulin secretion (T1DM) and/or action (T2DM). T1DM presents in children or adolescents, while T2DM is thought to affect middle-aged and older adults who have prolonged hyperglycemia due to poor lifestyle and dietary choices. The pathogenesis for

Etiology

In the islets of Langerhans in the pancreas, there are two main subclasses of endocrine cells: insulinproducing beta cells and glucagon secreting alpha cells. Beta and alpha cells are continually changing their levels of hormone secretions based on the glucose environment. Without the balance between insulin and glucagon, the glucose levels become inappropriately skewed. In the case of DM, insulin is either absent and/or has impaired action (insulin resistance), and thus leads to hyperglycemia. T1DM is characterized by the destruction of beta cells in the pancreas, typically secondary to an autoimmune process. The result is the absolute destruction of beta cells, and consequentially, insulin is absent or extremely low.

T2DM involves a more insidious onset where an imbalance between insulin levels and insulin sensitivity causes a functional deficit of insulin. Insulin resistance is multifactorial but commonly develops from obesity and aging.

The genetic background for both types is critical as a risk factor. As the human genome gets further explored, there are different loci found that confer risk for DM. Polymorphisms have been known to influence the risk for T1DM, including major histocompatibility complex (MHC) and human leukocyte antigen (HLA).

T2DM involves a more complex interplay between genetics and lifestyle. There is clear evidence suggesting that T2DM is has a stronger hereditary profile as compared to T1DM. The majority of patients with the disease have at least one parent with T2DM.

Monozygotic twins with one affected twin have a 90% likelihood of the other twin developing T2DM in his/her lifetime. Approximately 50 polymorphisms to date have been described to contribute to the risk or protection for T2DM. These genes encode for proteins involved in various pathways leading

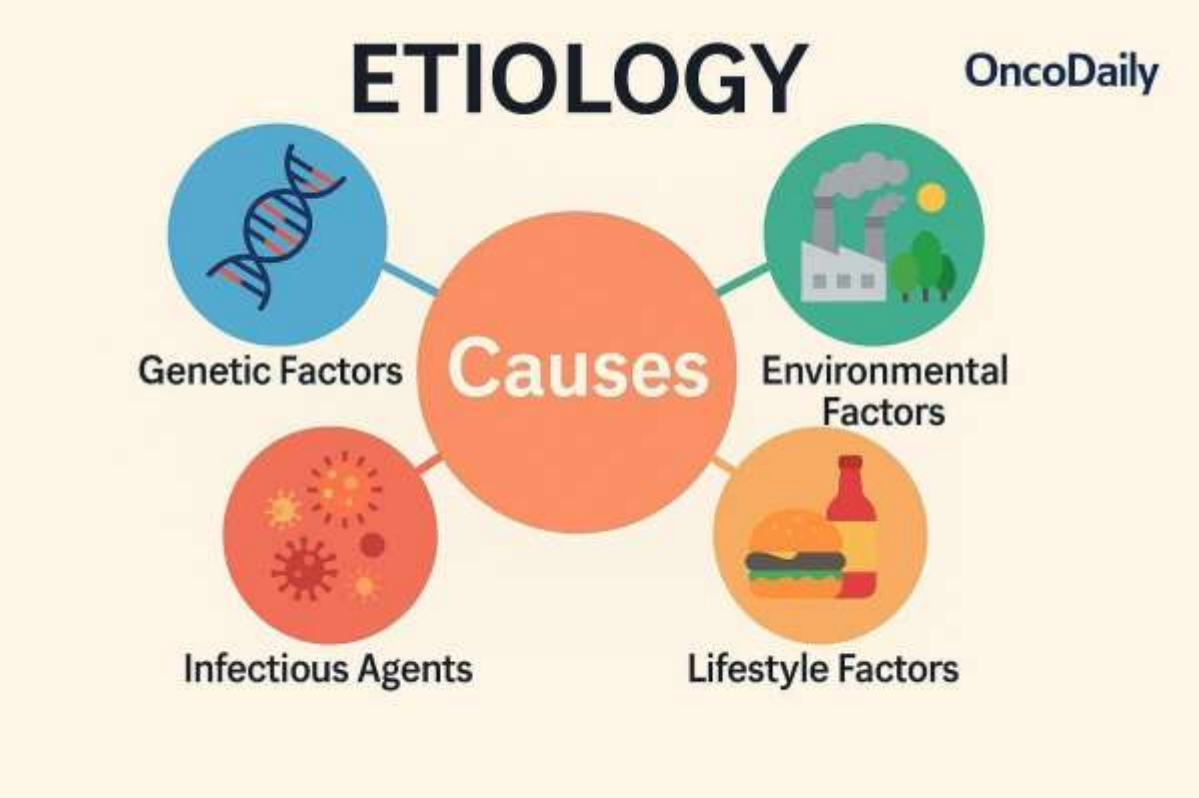
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to DM, including pancreatic development, insulin synthesis, secretion, and development,
amyloid deposition in beta cells, insulin resistance, and impaired gluconeogenesis regulation. A genome-wide association study (GWAS) found genetic loci for transcription factor 7-like 2 gene (TCF7L2), which increases the risk for T2DM. Other loci that have Implications in the development of T2DM include NOTCH2, JAZF1, KCNQ1, and WFS1.

MODY is a heterogeneous disorder identified by non-insulin-dependent diabetes diagnosed at a young age (usually under 25 years). It carries an autosomal dominant transmission and does not involve autoantibodies as in T1DM. Several genes have implications in this disease, including mutations to hepatocyte nuclear factor-1-alpha (HNF1A) and the glucokinase (GCK) gene, which occurs in 52 to 65 and 15 to 32 percent of MODY cases, respectively.[8][9] The genetics of this disease are still unclear as some patients have mutations but never develop the disease, and others will develop clinical symptoms of MODY but have no identifiable mutation.

Gestational diabetes is essentially diabetes that manifests during pregnancy. It is still unknown why it develops; however, some speculate that HLA antigens may play a role, specifically HLA DR2, 3, and 4. Excessive proinsulin is also thought to play a role in gestational diabetes, and some suggest that proinsulin may induce beta-cell stress. Others believe that high concentrations of hormones such as progesterone, cortisol, prolactin, human placental lactogen, and estrogen may affect beta-cell function and peripheral insulin sensitivity.

Several endocrinopathies, including acromegaly, Cushing syndrome, glucagonoma, hyperthyroidism,
hyperaldosteronism, and somatostatinomas, have been associated with glucose intolerance and diabetes mellitus, due to the inherent glucogenic action of the endogenous hormones excessively secreted in these conditions. Conditions like idiopathic hemochromatosis are associated with diabetes mellitus due to excessive iron deposition in the pancreas and the destruction of the beta cells



The quest to understand why diseases arise has transformed dramatically over centuries. In ancient and medieval eras, the predominant explanation for illness was the miasma theory, which held that foul air or "noxious vapors" emanating from decaying matter caused disease. Simultaneously, Hippocratic and Galenic traditions attributed sickness to imbalances of the four humors—blood, phlegm, yellow bile, and black bile—guiding treatments like bloodletting and purgation.

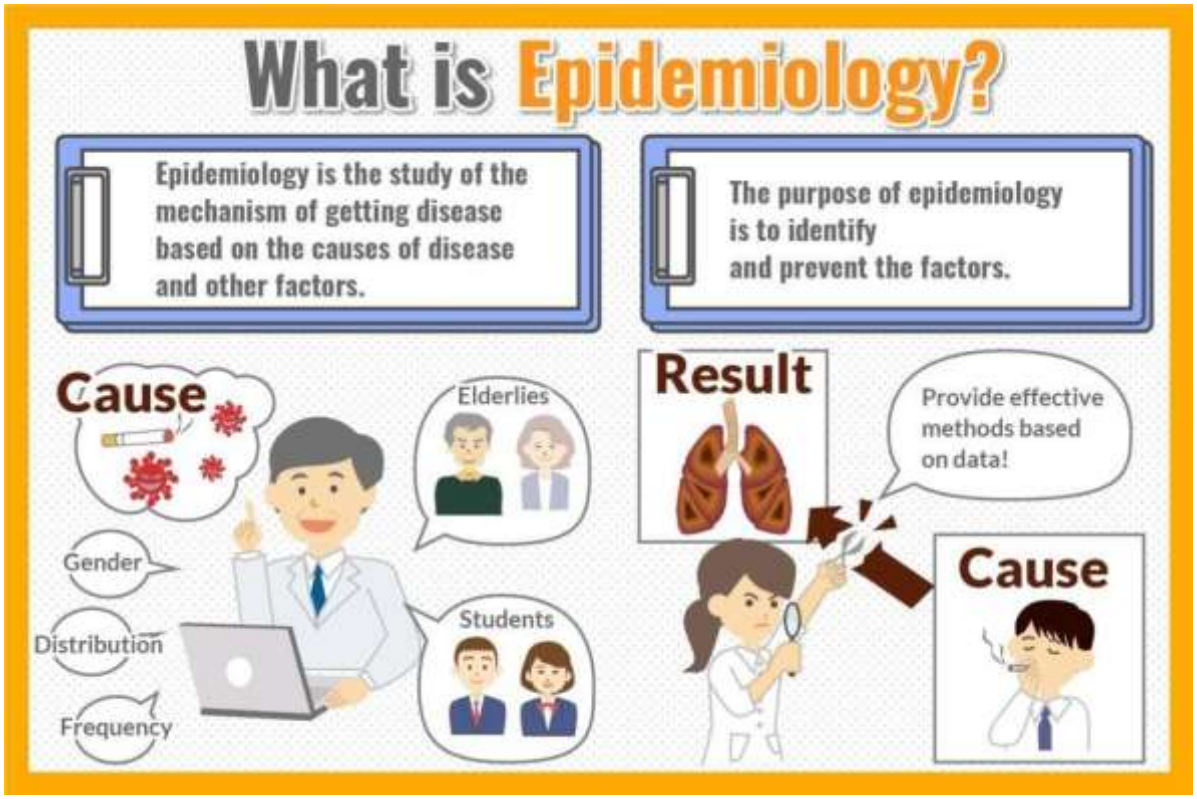
Epidemiology

Globally, 1 in 11 adults has DM (90% having T2DM). The onset of T1DM gradually increases from birth and peaks at ages 4 to 6 years and then again from 10 to 14 years. Approximately 45% of children present before age ten years. The prevalence in people under age 20 is about 2.3 per 1000. While most autoimmune diseases are more common in females, there are no apparent gender differences in the incidence of childhood T1DM. In some populations, such as in older males of European origin (over 13 years), they may be more likely to develop T1DM compared to females (3:2 male to female ratio). The incidence of T1DM has been increasing worldwide. In Europe, Australia, and the Middle East, rates are rising by 2% to 5% annually. In the United States, T1DM rates rose in most age and ethnic groups by about 2% yearly, and rates are higher in Hispanic youth. The exact reason for this pattern remains unknown. However, some metrics, such as the United States

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Military Health System data repository, found plateauing over 2007 to 2012 with a prevalence of 1.5 per 1000 and incidence of 20.7 to 21.3 per 1000.

The onset of T2DM is usually later in life, though obesity in adolescents has led to an increase in T2DM in younger populations. T2DM has a prevalence of about 9% in the total population of the United States, but approximately 25% in those over 65 years. The International Diabetes Federation estimates that 1 in 11 adults between 20 and 79 years had DM globally in 2015. Experts expect the prevalence of DM to increase from 415 to 642 million by 2040, with the most significant increase in populations transitioning from low to middle-income levels. T2DM varies among ethnic groups and is 2 to 6 times more prevalent in Blacks, Native Americans, Pima Indians, and Hispanic Americans compared to Whites in the United States. While ethnicity alone plays a vital role in T2DM, environmental factors also greatly confer risk for the disease. For example, Pima Indians in Mexico are less likely to develop T2DM compared to Pima Indians in the United States (6.9% vs. 38%).



Pathophysiology

A patient with DM has the potential for hyperglycemia. The pathology of DM can be unclear since several factors can often contribute to the disease. Hyperglycemia alone can impair pancreatic betacell function and contributes to impaired insulin secretion.

Consequentially, there is a vicious cycle of hyperglycemia leading to an impaired metabolic state. Blood glucose levels above 180 mg/dL are often considered hyperglycemic in this context, though because of the variety of mechanisms, there is no clear cutoff point.

Patients experience osmotic diuresis due to saturation of the glucose transporters in the nephron at higher blood glucose levels. Although the effect is variable, serum glucose levels above 250 mg/dL are likely to cause symptoms of polyuria and polydipsia.

Insulin resistance is attributable to excess fatty acids and proinflammatory cytokines, which leads to impaired glucose transport and increases fat breakdown. Since there is an inadequate response or production of insulin, the body responds by inappropriately increasing glucagon, thus further contributing to hyperglycemia. While insulin resistance is a component of T2DM, the full extent of the disease results when the patient has inadequate production of insulin to compensate for their insulin resistance.

Chronic hyperglycemia also causes nonenzymatic glycation of proteins and lipids. The extent of this is measurable via the glycation hemoglobin (HbA1c) test. Glycation leads to damage in small blood vessels in the retina, kidney, and peripheral nerves. Higher glucose levels hasten the process. This damage leads to the classic diabetic complications of diabetic retinopathy, nephropathy, and neuropathy and the preventable outcomes of blindness, dialysis, and amputation, respectively.

History and Physical

During patient history, questions about family history, autoimmune diseases, and insulinresistant are critical to making the diagnosis of DM. It often presents asymptomatically, but when symptoms develop, patients usually present with polyuria, polydipsia, and weight loss. On physical examination of someone with hyperglycemia, poor skin turgor (from dehydration) and a distinctive fruity odor of their breath (in patients with ketosis) may be present. In the setting of diabetic ketoacidosis (DKA), clinicians may note Kussmaul

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respirations, fatigue, nausea, and vomiting. Funduscopic examination in a patient with DM may show hemorrhages or exudates on the macula. In frank diabetic retinopathy, retinal venules may appear dilated or occluded. The proliferation of new blood vessels is also concern for ophthalmologists and can hasten retinal hemorrhages and macular edema, ultimately resulting in blindness. While T1DM and T2DM can present similarly, they can be distinguished based on clinical history and examination. T2DM patients are typically overweight/obese and present with signs of insulin resistance, including acanthosis nigricans, which are hyperpigmented, velvety patches on the skin of the neck, axillary, inguinal folds. Patients with a longer course of hyperglycemia may have blurry vision, frequent yeast infections, numbness, or neuropathic pain. The clinicians must ask the patient bout any recent skin changes in their feet during each visit. The diabetic foot exam, including the monofilament test, should be a part of the routine physical exam.

Evaluation

The diagnosis of T1DM is usually through a characteristic history supported by elevated serum glucose levels (fasting glucose greater than 126 mg/dL, random glucose over 200 mg/dL, or hemoglobin A1C (HbA1c exceeding 6.5%) with or without antibodies to glutamic acid decarboxylase (GAD) and insulin.

Fasting glucose levels and HbA1c testing are useful for the early identification of T2DM. If borderline, a glucose tolerance test is an option to evaluate both fasting glucose levels and serum response to an oral glucose tolerance test (OGTT). Prediabetes, which often precedes T2DM, presents with a fasting blood glucose level of 100 to 125 mg/dL or a 2-hour post-oral glucose tolerance test (postOGTT) glucose level of 140 to 200 mg According to the American Diabetes Association (ADA), a diagnosis of diabetes is through any of the following: An HbA1c level of 6.5% or higher; A fasting plasma glucose level of 126 mg/dL (7.0 mmol/L) or higher (no caloric intake for at least 8 hours); A two-hour plasma glucose level of 11.1 mmol/L or 200 mg/dL or higher during a 75-g OGTT; A random plasma glucose of 11.1 mmol/L or 200 mg/dL or higher in a patient with symptoms of hyperglycemia (polyuria, polydipsia, polyphagia, weight loss) or hyperglycemic crisis. The ADA recommends screening adults aged 45 years and older regardless of risk, while the United States Preventative Service Task Force suggests screening individuals between 40 to 70 years who are overweight.

To test for gestational diabetes, all pregnant patients have screening between 24 to 28 weeks of gestation with a 1-hour fasting glucose challenge test. If blood glucose levels are over 140mg/dL, patients have a 3-hour fasting glucose challenge test to confirm a diagnosis. A positive 3-hours OGTT test is when there is at least one abnormal value (greater than or equal to 180, 155, and 140 mg/dL for fasting one-hour, two-hour, and 3-hour plasma glucose concentration, respectively).

Several lab tests are useful in the management of chronic DM. Home glucose testing can show trends of hyper- and hypoglycemia. The HbA1c test indicates the extent of glycation due to hyperglycemia over three months (the life of the red blood cell). Urine albumin testing can identify the early stages of diabetic nephropathy. Since patients with diabetes are also prone to cardiovascular disease, serum lipid monitoring is advisable at the time of diagnosis. Similarly, some recommend monitoring thyroid status by obtaining a blood level of thyroid-stimulating hormone annually due to a higher incidence of hypothyroidism.

Treatment / Management

The physiology and treatment of diabetes are complex and require a multitude of interventions for successful disease management. Diabetic education and patient engagement are critical in management. Patients have better outcomes if they can manage their diet (carbohydrate and overall caloric restriction), exercise regularly (more than 150 minutes weekly), and independently monitor glucose. Lifelong treatment is often necessary to prevent unwanted complications. Ideally, glucose levels should be maintained at 90 to 130 mg/dL and HbA1c at less than 7%. While glucose control is critical, excessively aggressive management may lead to hypoglycemia, which can have adverse or fatal outcomes.

Since T1DM is a disease primarily due to the absence of insulin, insulin administration through daily injections, or an insulin pump, is the mainstay of treatment. In T2DM, diet and exercise may be adequate treatments, especially initially. Other therapies may target insulin sensitivity or increase insulin secretion by the pancreas. The specific subclasses for drugs include biguanides (metformin), sulfonylureas, meglitinides, alpha-glucosidase inhibitors, thiazolidinediones, glucagonlike-peptide-1 agonist, dipeptidyl peptidase IV inhibitors (DPP-4), selective, amylinomimetics, and sodium-glucose transporter-2 (SGLT-2) inhibitors. Metformin is the first line of the prescribed diabetic medications and works by lowering basal and postprandial plasma glucose. Insulin administration may also be necessary for T2DM patients, especially those with inadequate glucose management in the advanced stages of the disease. In morbidly obese patients, bariatric surgery is a possible means to normalize glucose levels. It is recommended for individuals who have been unresponsive to other treatments and who have significant comorbidities.[29] The GLP-1 agonists liraglutide and semaglutide correlate with improved cardiovascular outcomes.

The SGLT-2 inhibitors empagliflozin and canagliflozin have also shown to improve cardiovascular outcomes along with potential renoprotection as well as prevention for the development of heart failure.

Regular screenings are necessary since microvascular complications are a feared complication of diabetes. Regular diabetic retinal exams should be performed by qualified medical personnel to assess for diabetic retinopathy. Neurologic examination with monofilament testing can identify patients with neuropathy at risk for amputation. Clinicians can also recommend patients perform daily foot inspections to identify foot lesions that may go unnoticed due to neuropathy. Low-dose tricyclic antidepressants, duloxetine, anticonvulsants, topical capsaicin, and pain medications may be necessary to manage neuropathic pain in diabetes. Urine microalbumin testing can also assess for early renal changes

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from diabetes with albuminuria greater than 30mg/g creatinine along with the estimated GFR. The antiproteinuric effect of the angiotensin-converting enzyme (ACE) inhibitors and the angiotensin receptor blockers (ARBs) makes them the preferred agents to delay the progression from microalbuminuria to macroalbuminuria in patients with both Type 1 or Type 2 diabetes mellitus.

The FDA has approved pregabalin and duloxetine for the treatment of diabetic peripheral neuropathy. Tricyclic antidepressants and anticonvulsants have also seen use in the management of the pain of diabetic neuropathy with variable success.

The ADA also recommends regular blood pressure screening for diabetics, with thgoal being 130 mmHg systolic blood pressure and 85 mmHg diastolic blood pressure.Pharmacologic therapy for hypertensive diabetics typically involves angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, beta-blockers, and/or calcium channel blockers. The ADA recommends lipid monitoring for diabetics with a goal of lowdensity lipoprotein cholesterol (LDL-C) being less than 100 mg/dL if no cardiovascular disease (CVD) and less than 70 mg/dl if atherosclerotic cardiovascular disease (ASCVD) is present.

Statins are the first-line treatment for the management of dyslipidemia in diabetics. The ADA suggests that low dose aspirin may also be beneficial for diabetic patients who are at high risk for cardiovascular events; however, the role of aspirin in reducing cardiovascular events in patients with diabetes remains unclear.

Differential Diagnosis

In addition to T1DM, T2DM, and MODY, any disorder that damages the pancreas can result in DM. There are several diseases of the exocrine pancreas, including:[34] Cystic fibrosis Hereditary hemochromatosis Pancreatic cancer

Chronic Pancreatitis
Hormonal syndromes that can lead to impaired insulin secretion include: Pheochromocytoma

Acromegaly Cushing syndrome
Drug-induced insulin resistance is also in the differential of classical diabetes. These drugs include: Phenytoin

Glucocorticoids Estrogen
Other diseases in the differential of diabetes mellitus include: Gestational diabetes

Thyroid Disorders

Pertinent Studies and Ongoing Trials
Various trials have been undertaken to understand the cardiovascular outcomes with antidiabetic medications. The LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), was a double-blinded trial comparing the use of liraglutide, which is a GLP - 1 agonist to placebo in around 10000 patients. After a follow-up period of about four years, liraglutide was shown to reduce mortality from cardiovascular causes as well as all-cause mortality. It also seemed to reduce the first occurrence of the first nonfatal myocardial infarction (MI) and stroke.

The EMPA-REG OUTCOME trial ([Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) have shown considerable reductions in mortality and heart failure hospitalization risks in patients with type 2 diabetes mellitus (T2D), by and cardiovascular disease with empagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor.

The CANVAS trial (Canagliflozin Cardiovascular Assessment Study) subsequently reported a reduction in 3-point major adverse cardiovascular events and heart failure (HF) hospitalization risk. The proposed mechanism through which SGLT2 inhibitors work helps patients with heart failure is via the promotion of natriuresis and osmotic diuresis and reduced preload. SGLT2 inhibition is also associated with the preservation of renal function. Based on data from mechanistic studies and clinical trials, large clinical trials with SGLT2 inhibitors are now investigating the potential use of SGLT2 inhibition in patients who have HF with and without T2 diabetes mellitus.

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Toxicity and Adverse Effect Management

One of the most common adverse effects of insulin is hypoglycemia. Gastrointestinal upset is the most common side effect of many of the T2DM medications. Metformin can lead to lactic acidosis and should be used with caution in patients with renal disease and discontinued if the estimated glomerular filtration rate (e-GFR) is under 30 mL/min. Sulfonylureas can lead to hypoglycemia and may promote cardiovascular death in patients with diabetes.[35] Thiazolidinediones have fallen out of favor in clinical practice due to their adverse effects, specifically resulting in fluid retention, worsening heart failure, and fractures.[36][37] DPP-4 may increase the risk for upper respiratory tract infections but may have less nausea and diarrhea compared to other drugs such as metformin.[38][39] SGLT-2 inhibitors can lead to increased urinary tract infections due to increased urinary glucose excretion.[40] Both SGLT2 inhibitors and GLP-1 Receptor agonists reduce ASCVD events and are now considered the second line to metformin in such patients.

Prognosis

Diabetes mellitus was the seventh leading cause of death in the United States in 2015.The prognosis of DM gets significantly influenced by the degree of glucose management. Chronic

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hyperglycemia significantly increases the risk of DM complications. The Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study found that individuals with T1DM and T2DM respectively had increased microvascular complications with chronic hyperglycemia.[42][43] Patients who can revert to normal glucose during the progression from pre-diabetes to frank DM had a good prognosis and may be able to slow disease progression.

Complications

Regardless of the specific type of diabetes, complications involve microvascular, macrovascular, and neuropathic issues. Microvascular and macrovascular complications vary according to the degree and the duration of poorly control diabetes and include nephropathy, retinopathy, neuropathy, and ASCVD events, especially if it is associated with other comorbidities like dyslipidemia and hypertension.[45] One of the most devastating consequences of DM is its effect on cardiovascular disease (ASCVD). Approximately two-thirds of those with DM will die from a myocardial infarction or stroke.[46] In T2DM, fasting glucose of more than 100 mg/dL significantly contributes to the risk of ASCVD, and cardiovascular risk can develop before frank hyperglycemia.

DM is also a common cause of blindness in adults aged 20 to 74 years in the United States. Diabetic retinopathy contributes to 12000 to 24000 new cases of blindness annually, and treatments generally consist of laser surgery and glucose control.

Renal disease is another significant cause of morbidity and mortality in DM patients. It is the leading contributor to end-stage renal disease (ESRD) in the United States, and many patients with ESRD will need to start dialysis or receive a kidney transplant.[49] If the albuminuria persists in the range of 30 to 300 mg/day (microalbuminuria), it seems to be a predictable earliest marker for the onset of diabetic neuropathy. Once macroalbuminuria (greater than 300 mg/24 hr) sets in, the progression to ESRD hastens up. The random spot urine specimen for measurement of the albumin-to-creatinine ratio is a quick, easy, predictable method that is the most widely used and preferred method to detect microalbuminuria. Two of three tests, done over a six month showing a persistent level greater than 30 mcg/mg creatinine, confirms the diagnosis of microalbuminuria.

DM is also the leading cause of limb amputations in the United States; this is primarily due to vasculopathy and neuropathy associated with DM.[49] Many patients who develop neuropathy need to have regular foot exams to prevent infection from wounds that go unnoticed.The duration of diabetes is the most crucial risk factor for the development of diabetic retinopathy. In people with type 1 diabetes, it typically sets in about 5 years after disease onset. Hence it is recommended to start the yearly retinal exams in these patients about five years after diagnosis. Among patients with type 2 diabetes, many patients might already have retinal changes at the time of diagnosis. Approximately 10% at ten years, 40% at 15 years, and 60% at 20 years will have nonproliferative retinal disease. In these patients, the recommendation is to start the yearly retinal screening at the time of diagnosis. Study after study has shown that reasonable glycemic control favorably affected the onset and progression of diabetic retinopathy. Uncontrolled blood pressure is an added risk factor for macular edema. Lowering the blood pressure in patients with diabetes thus also affects the risk of progression of the retinopathy. Injection of antibodies vascular endothelial growth factor (antiVEGF) agents are generally in use as the initial therapy in cases of macular edema. In cases of nonproliferative diabetic retinopathy, pan-retinal photocoagulation is being used. In cases of diabetic proliferative retinopathy, combined modalities of anti-VEGF agents and pan-retinal photocoagulation are now in use.

Sudden loss of vision can occur for several reasons in patients with diabetes mellitus, the most common being vitreous hemorrhage. Less common causes that merit consideration include vascular occlusion (central retinal vein or branch vein occlusion involving the macula), retinal detachment, end-stage glaucoma, and ischemic optic neuropathy.

Furthermore, evidence suggests that T2DM may also contribute to cancer development, specifically bladder cancer, in those using pioglitazone. Patients using metformin had improved cancer-specific survival in those with prostate, pancreatic, breast, and colorectal cancers. However, it is unclear how metformin plays a role in modulating cancer in patients with diabetes.

Those with gestational diabetes are at a higher risk for cesarean delivery and chronic hypertension. Pregnant patients with T2DM generally have a better prognosis in terms of neonatal and pregnancy complications compared to those with T1DM. Generally, neonates of DM mothers will present with hypoglycemia and macrosomia.

The most acute complication of DM is diabetic ketoacidosis (DKA), which typically presents in T1DM. This condition is usually either due to inadequate dosing, missed doses, or ongoing infection.[53] In this condition, the lack of insulin means that tissues are unable to obtain glucose from the bloodstream. Compensation for this causes the metabolism of lipids into ketones as a substitute energy source, which causes systemic acidosis, and can be calculated as a high anion-gap metabolic acidosis. The combination of hyperglycemia and ketosis causes diuresis, acidemia, and vomiting leading to dehydration and electrolyte abnormalities, which can be life-threatening. In T2DM, hyperosmolar hyperglycemic syndrome (HHS) is an emergent concern. It presents similarly to DKA with excessive thirst, elevated blood glucose, dry mouth, polyuria, tachypnea, and tachycardia. However, unlike DKA, HHS typically does not present with excessive urinary ketones since insulin still gets produced by pancreatic beta cells. Treatment for DKA or HHS involves insulin administration and aggressive intravenous hydration. Careful management of electrolytes, particularly potassium, is critical in the management of these emergent conditions.[

Deterrence and Patient Education

Healthcare professionals should take an active approach to educate patients with DM. It is misguided for patients to think that lifestyle changes for a limited time are appropriate, and

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instead, lifelong lifestyle changes may be necessary to control their DM adequately. A randomized, controlled trial identified that individualized education is more effective compared to group education in patients who had poorly controlled DM.[55] Often, nonclinician healthcare professionals (e.g., nurses, pharmacists) have extensive training in DM education and have more time for individualized education.

Pearls and Other Issues

Amino acid metabolism may play a critical role in the development of T2DM. Studies have shown that there is a 4-fold increase in isoleucine, phenylalanine, and tyrosine in individuals with hyperglycemia. Researchers found that these amino acids were elevated up to 12 years before the onset of the disease.[56] Recent studies have further elucidated the role of these metabolites in the development, screening, and treatment of metabolic syndrome (MetS), a cardiometabolic cluster that predisposes patients to T2DM and CVD. Studies have shown that choline, L-carnitine, and trimethylamine-N-oxide were associated with inflammatory pathways and increased the risk of metabolic dysfunction in nascent MetS patients, who meet classification for MetS but do not have T2DM and cardiovascular disease.

Literature has also shown increased levels of isoleucine and tyrosine and decreased levels of lysine and methionine. These metabolites appear to be early biomarkers of nascent MetS and significant contributors to the pro-inflammatory burden of Mets.Low levels of lysine, in particular, were associated with increased inflammation and elevated blood glucose. Thus, increased dietary lysine may promote anti-inflammatory effects.

In a recent investigation, researchers found phosphatidylcholine 34:2, PC(34:2), GABA, and dpyroglutamic acid (PGA) were significantly increased in nascent MetS and correlated positively with certain inflammatory parameters.[59][60] These findings further support the role of metabolites in the early development of T2DM and suggest that they may have a role in the pro-inflammatory state associated with diabetes.

Enhancing Healthcare Team Outcomes

Primary care clinicians are often the first to identify diabetes in their patients. Since DM is acomplex disease, it requires an interprofessional team approach to management. Nurse practitioners and physician assistants can be critical to ensuring proper patient follow-ups and monitoring the efficacy of treatments. Nutritionists and diabetes educators can also provide consultations to help educate patients on appropriate lifestyle modifications and at-home glucose management.

Ophthalmologists, neurologists, podiatrists, and nephrologists may also be part of the healthcare team to ensure that patients with DM have adequate screenings to prevent devastating microvascular complications. Endocrinologists may be consulted when patients have a complex presentation or are unresponsive to initial treatments. Of course, pharmacists play a crucial role in evaluating proper medication administration and preventing polypharmacy in DM patients who are often taking multiple medications for the frank disease and its complications; they can ensure optimal dosing and recommend the most efficient regimens to achieve glycemic control, and also educate the patient on the medications and disease process.

Sperl-Hillen et al. found that patients with suboptimally controlled diabetes had better glucose control outcomes when given individualized education compared to group education. These patients also had better psychosocial and behavioral outcomes.Consequentially this emphasizes the role of an interprofessional team approach, including clinicians, specialists, specialty trained diabetic nurses educators, and pharmacists who are conversing across disciplines to optimize patient-specific management leading to improved outcomes. [Level 5]

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