Diabetes Mellitus

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1 Introduction

Diabetes mellitus (DM) is a metabolic disease of inadequate control of blood levels of glucose. It has many subclassifications, including type 1, type 2, maturity-onset diabetes of the young (MODY), gestational diabetes, neonatal diabetes, and steroid-induced diabetes. Type 1 and 2 DM are the main subtypes, each with different pathophysiology, presentation, and management, but both have a potential for hyperglycemia.

Type 1 DM classically results from defective insulin secretion. Type 2 DM results from defective insulin action (but serum levels of insulin are normal or increased). 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 T1DM and T2DM is drastically different, and therefore each type has various etiologies, presentations, and treatments.

2 Classification

2.1 Type 1 Diabetes Mellitus

Type 1 diabetes mellitus (T1DM) accounts for 5% to 10% of DM and is characterized by **autoimmune destruction** of insulin-producing beta cells in the islets of the pancreas. As a result, there is an absolute deficiency of insulin. A combination of genetic susceptivity and environmental factors such as viral infection, toxins, or some dietary factors have been implicated as triggers for autoimmunity. T1DM is most commonly seen in children and adolescents though it can develop at any age.

T1DM can be considered an autoimmune disease that leads to the destruction of insulin-producing pancreatic beta cells. Individuals with T1DM require life-long insulin replacement with multiple daily insulin injections daily, insulin pump therapy, or the use of an automated insulin delivery system. Without insulin, diabetic ketoacidosis (DKA) develops and is life-threatening.

2.2 Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (T2DM) accounts for around 90% of all cases of diabetes. In T2DM, the response to insulin is diminished, and this is defined as insulin resistance. During this state, insulin is ineffective and is initially countered by an increase in insulin production to maintain glucose homeostasis, but over time, insulin production decreases, resulting in T2DM. T2DM is most commonly seen in persons older than 45 years. Still, it is increasingly seen in children, adolescents, and younger adults due to rising levels of obesity, physical inactivity, and energy-dense diets.

2.3 Other uncommon types

DM has other uncommon categories, latent autoimmune diabetes of adults (LADA), maturity-onset diabetes of the young (MODY), gestational diabetes, neonatal diabetes, and secondary causes due to endocrinopathies, steroid use, etc.

3 Etiology

In the islets of Langerhans in the pancreas, there are two main subclasses of endocrine cells: insulin-producing 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.

In T1DM, there is autoimmune destruction of the beta cells in the pancreatic islets over months or years, causing an absolute deficiency of insulin. Although the exact etiology of T1DM is still unknown, researchers believe there is a genetic predisposition

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

Pathophysiology In T1DM, there is cellular-mediated, autoimmune destruction of pancreatic beta cells. The rate of destruction is generally rapid in children. Autoantibodies against islet cells and insulin may be detected in the serum of such patients. With the progressive destruction of beta cells, there is little or no secretion of insulin. These patients are generally not obese.

T2DM is an insulin-resistance condition with associated beta-cell dysfunction. Hyperglycemia alone can impair pancreatic beta-cell function and contributes to impaired insulin secretion. Consequentially, there is a vicious cycle of hyperglycemia leading to an impaired metabolic state. Initially, there is a compensatory increase in insulin secretion as a response to hyperglycemia, which maintains glucose levels in the normal range. As the disease progresses, beta cells become exhausted and depleted, and insulin secretion is unable to maintain glucose homeostasis, producing hyperglycemia. Most of the patients

with T2DM are obese or have a higher body fat percentage. This adipose tissue itself promotes insulin resistance through various inflammatory mechanisms, including increased fatty acids release and adipokine dysregulation. Lack of physical activity, presence of hypertension or dyslipidemia also increases the risk of developing T2DM.

Clinical manifestations Initial presentation of diabetes can vary from patient to patient:

- Classic initial symptoms can be seen in a patient presenting with polyuria, polydipsia, polyphagia, and weight loss.
- However, a more life-threatening presentation is diabetic ketoacidosis (DKA).
- Clinical finding in a routine determination of blood parameters.

Type 1 diabetes, especially in children, classically presents with hyperglycemic symptoms: polydipsia, polyuria, polyphagia, nocturnal enuresis, blurred vision, unintentional weight loss, fatigue, and weakness. If diagnosed properly and treated promptly, emergency situations can be avoided, such as DKA.

However, if hyperglycemic is not evaluated and treated promptly, it can become a medical emergency: DKA in Type 1 diabetes and hyperglycemic hyperosmolar syndrome in Type 2 diabetes. Hyperglycemia can cause osmotic diuresis, which can cause dehydration, hypotension, electrolyte abnormalities and even higher glucose levels. This uncontrolled hyperglycemia can worsen those abnormalities, and metabolic acidosis, and increased body ketone concentration can appear. All of these mechanisms can develop diabetic ketoacidosis (DKA). DKA requires hospitalization and treatment with intravenous fluids, insulin, potassium, and careful monitoring. This is the form of presentation of one-third of children/teenagers with Type 1 diabetes.

The most common form of presentation in Type 2 diabetes is a laboratory finding. However, some patients with uncontrolled hyperglycemia can develop hyperglycemic hyperosmolar syndrome. Essentially it is the same as DKA, with no increased ketone concentration (hyperosmolar hyperglycemic nonketotic syndrome). However, hyperosmolar hyperglycemic syndrome (HHS) is a serious and potentially fatal complication of Type 2 diabetes. The mortality rate can be as high as 20%, which is about 10 times higher than the mortality seen in diabetic ketoacidosis. Clinical outcome is determined by several factors: age, the degree of dehydration, and the presence of other comorbidities.

For both DKA and HHS, certain conditions o factors might trigger their development. The most frequent reason for this complication is infection. The infectious process in the respiratory, gastrointestinal, and genitourinary systems can act as the causative factor. The reason for this is the insensible dehydration and the release of endogenous catecholamines. This leads to the release of counterregulatory hormones with the resultant effect of an increased level of blood glucose, causing osmotic diuresis and more dehydration, with the final result being DKA or HHS. Decreased cerebral blood flow from severe dehydration can cause focal neurological deficit and coma.

4 Diagnosis

The diagnosis of diabetes mellitus 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 greater than 6.5% (HbA1c exceeding 6.5%). Hemoglobin A1C is also called glycated hemoglobin.

5 Treatment and 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 metformin, glucagonlike-peptide-1 agonist (GLP-1), dipeptidyl peptidase IV inhibitors (DPP-4), 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. 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. Urine microalbumin testing can also assess for early renal changes 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.