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Masqueraders: how to identify atypical diabetes in primary care

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Abstract: Diabetes mellitus is a complex set of conditions that impacts 34 million Americans. While type 1 diabetes, type 2 diabetes, and gestational diabetes are most frequently encountered, there are many other types of diabetes with which healthcare providers are less familiar. These atypical forms of diabetes make up nearly 10% of diabetes cases and can masquerade as type 1 or 2 diabetes mellitus (T1DM or T2DM), and the treatment may not be optimized if the diagnosis is not accurate. Atypical forms include monogenic diabetes (formally known as maturity-onset diabetes of the young [MODY]), latent autoimmune diabetes of the adult (LADA), ketosis-prone diabetes, and secondary diabetes. This paper will detail the defining characteristics of each atypical form and demonstrate how they can masquerade as type 1 or 2 diabetes mellitus. Gestational diabetes mellitus will not be discussed in this article.

Keywords: atypical diabetes; latent autoimmune diabetes of the adult; monogenic diabetes; secondary diabetes.

Diabetes mellitus is a collection of heterogeneous metabolic disorders characterized by hyperglycemia (i.e., all disorders have elevated glucose in common). According to the Center for Disease Control and Prevention, there are over 34 million Americans with diabetes mellitus, of which Type 2 diabetes mellitus (T2DM) makes up about 90% and Type 1 diabetes mellitus (T1DM) is less than 5% [1]. However, the pathophysiology, clinical presentation, and optimal treatment vary greatly between the diabetes types. An accurate diagnosis of the type of diabetes is important in order to provide appropriate care to our patients. Broadly, the authors recommend a focus on the core etiology and initial clinical presentation of each diabetes type: autoimmune, metabolic, or genetic.

T1DM is an autoimmune disorder that results in beta cell destruction and absolute insulin deficiency. Because it is autoimmune, it may be associated with personal or family history of other autoimmune conditions, but 90% of people with T1DM do not have a family history of diabetes mellitus [2]. T1DM is acute in its presentation because patients will present with weight loss and the three "polys": polyuria, polydipsia, and polyphagia. Many people with T1DM are diagnosed when they present with diabetic ketoacidosis (DKA) [3].

T2DM is a complex metabolic condition with at least eight pathophysiologic pathways [4]. The eight pathophysiologic pathways include impaired insulin secretion, increased glucagon secretion, increased hepatic glucose production, decreased incretin effect, neurotransmitter dysfunction, increased lipolysis and reduced glucose uptake in fat cells, increased glucose reabsorption in the kidneys, and decreased glucose uptake in the muscles [4]. Other metabolic conditions, such as dyslipidemia and hypertension, are closely associated with T2DM. Unlike T1DM, most people with T2DM have a family history of this condition [4]. T2DM is an indolent condition and is diagnosed during routine blood testing or with the treatment of a diabetes-related complication. Another key distinguishing feature is that 30% of people with T2DM have a complication at the time of diagnosis [5]. For this reason, people with T2DM should be screened at the time of diagnosis, whereas those with T1DM can be screened for complications 5 years postdiagnosis [6].

Although T1DM and T2DM account for approximately 90% of individuals with diabetes, atypical forms may represent up to 10% of cases [7]. These include maturity-onset diabetes of the young (MODY), latent autoimmune diabetes of the adult (LADA), ketosis prone diabetes (KPD), and secondary diabetes. For each type, we will highlight the epidemiology, pathogenesis, clinical presentation, and treatment considerations. Table 1 summarizes the different

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Table 1: Different types of atypical diabetes and how it masquerades as Type 1 or Type 2.

What masquerades as T1DM	Key differences	What masquerades as T2DM	Key differences
KPD	Episodes of ketoacidosis, possible remission for months to years after initial episode, 4 main subtypes	LADA	Slower progression, insulin is not needed immediately, earlier presentation of complications
MODY	Autosomal dominant inheritance, C-peptide is within normal range	Secondary diabetes	Often diagnosed after the age of 50, presence of chronic recurrent pancreatitis or cystic fibrosis, no autoimmunity but insulin is not produced sufficiently, insulin is necessary

KPD, ketosis prone diabetes; LADA, latent autoimmune diabetes of the adult; MODY, maturity-onset diabetes of the young; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

atypical forms of diabetes and how they can masquerade as T1DM or T2DM.

Clinical summary

Illustrative case of monogenic diabetes

A 22-year-old female with no medical history presented to an occupational health clinic to obtain clearance for work-related travel. She denied any specific complaints, and her physical exam was within the normal limits with no signs of insulin resistance. Her body mass index (BMI) was 23 kg/m^2. She reported that multiple relatives in every generation were diagnosed with mild diabetes at a young age. Because routine urine analysis indicates glycosuria, she started checking her blood glucose utilizing a relative's glucose meter. Her glucose checks revealed mild fasting and post-prandial hyperglycemia. Her A1c (glycated hemoglobin) was 7.1%, her C-peptide was 1.4 ng/dL (normal range, 0.8–3.5 ng/dL) with corresponding fasting blood glucose of 128 mg/dL, and her GAD-65 Ab and islet antibodies were negative. She was started on glipizide with improvement in blood glucose to normal ranges. She was referred for genetic testing to confirm MODY.

Illustrative case of latent autoimmune diabetes of the adult (LADA)

A 38-year-old male with a medical history of T2DM was referred for worsening of A1c from 7.2% in March 2018 to 9.9% just 3 months later in June 2018. He was diagnosed with T2DM a year earlier when he was hospitalized for spine surgery. His blood glucose was elevated, and he was started on metformin postdischarge. Due to worsening of A1c, oral medications were titrated with addition of sulfonylurea and maximizing the metformin dose but with no significant improvement. He denied having a family history of diabetes. He presented with blood glucose varying from 70 to 420 mg/dL. On examination, he had no evidence of insulin resistance (acanthosis nigricans); his BMI was 21.5 kg/m^2. Labs indicated his C-peptide was 0.5 with corresponding plasma glucose of 239 mg/dL, elevated GAD-65 autoantibody titer (77 units/mL), and negative islet-cell antibody (ICA). He was started on basal-bolus insulin regimen, and his metformin and sulfonylurea were discontinued. His blood glucose readings improved, and his A1c improved to 7.1% in September 2018 and has remained in the target range with his A1c at 6.7% as of February 2021.

Illustrative case of ketosis prone diabetes (KPD, flatbush diabetes)

A 17-year-old black male with no medical history presented to the emergency room with vomiting for 1 day. He reported having a history of polyuria, polydipsia, and polyphagia for 2 weeks. He has a family history of T2DM in his maternal grandmother. On physical examination, his BMI was 30 kg/m^2, and he had acanthosis nigricans on the back of his neck. Initial labs indicated plasma glucose of 1,228 mg/dL (normal range, 100–125 mg/dL), bicarbonate of 17 mEq/L (normal range, 23–30 mEq/L), anion gap of 20 mEq/L (normal range, 3–10 mEq/L), arterial pH of 7.22 (normal range, 7.35–7.45), and beta-hydroxybutyrate elevated at 77.20 mmol/L (normal, less than 0.4 mmol/L). The patient was diagnosed as having DKA and had an A1c of 12.2%. He was diagnosed with new-onset diabetes with DKA. He was treated for DKA and discharged home on long-acting insulin glargine, rapid-acting insulin aspart, and metformin. When the patient was seen in follow-up 1 month after discharge, he was noted to have pre-meal and bedtime

blood glucose within the target range and episodes of hypoglycemia between 61 and 67 mg/dL. A1c at this visit is 5.0%. Insulin glargine and aspart doses were reduced by 50%. On a 3-month follow-up visit, the A1c was 4.5%. Insulin was discontinued and metformin continued. The stimulated (mixed meal challenge) C-peptide was 9.45 ng/dL with corresponding glucose of 122 mg/dL; the GAD-65 Ab and islet-cell autoantibodies were negative. At 1-year follow-up, the patient continued to have A1c in the normal range on metformin and with lifestyle modifications.

Illustrative case of secondary diabetes

A 43-year-old male presented with a 1-month history of polyuria, polydipsia, and weight loss. As part of his evaluation, he was found to be hyperglycemic with a glucose of 420 mg/dL, and he had ketosis but minimal acidosis. His medical history included alcohol abuse and recurrent pancreatitis with four previous hospitalizations. He had been sober for 9 months and was told that there is permanent damage to his pancreas. After the patient was stabilized on treatment, he was evaluated for type 1 diabetes. His C-peptide was low but detectable at 0.45 ng/dL, with a corresponding glucose value of 160 mg/dL, and his auto-antibody panel (GAD-65, ICA, insulin autoantibodies [IAA]) was negative. Due to the significant hyperglycemia and pancreatitis, he was managed on a basal and bolus insulin regimen.

Discussion

Maturity-onset diabetes of the young (MODY)

Monogenic diabetes includes both MODY and neonatal diabetes mellitus. Neonatal diabetes will not be discussed in this manuscript. Approximately 500,000 people in the United States have MODY [8]. While its name reflects the clinical presentation, MODY, it does not accurately depict pathogenesis or the necessary treatment. MODY is caused by the autosomal-dominant transmission of a single mutated gene. To date, there have been 14 genetic mutations linked to MODY [9]. The most common forms of MODY are HNF1A MODY-3 and GCK MODY-2 gene mutations and result in abnormal vesicle packaging or release of insulin, which leads to a milder form of diabetes [9]. Because it is not a metabolic disease similar to T2DM, people with MODY are not likely to have dyslipidemia. They are more likely to be thin and without the comorbidities seen with T2DM. As a result, many people with MODY are misdiagnosed with T1DM and are started on insulin, many for the rest of their life. However, C-peptide levels are measurable and indicative of some production of insulin while they do not have GAD-65 antibodies [10].

A physician should consider MODY if an asymptomatic person presents with mild hyperglycemia and has a strong family history of similar diabetes presentation (with at least three generations represented in an autosomal-dominant pattern). The autosomal-dominant transmission identifies MODY as the form with the strongest familial pattern [9]. People with MODY will not have measures of autoimmunity or dyslipidemia, and they should have measurable insulin production. People with monogenic diabetes are often identified at the time of other screening such as a physical exam or during obstetrical care.

Monogenic diabetes is typically more difficult to diagnose because patients are often underweight to normal-weight children or young adults, although age is not predictive [9, 10]. They usually do not experience insulin resistance or metabolic syndrome, as in the case of typical T2DM. Therefore, there is the assumption that they have T1DM. However, if correctly diagnosed, these patients can be taken off insulin. Table 2 demonstrates the clinical comparison between MODY, T1DM, T2DM, KPD, and secondary diabetes.

Latent autoimmune diabetes of the adult (LADA)

LADA is a form of T1DM that is most commonly diagnosed between 30 and 50 years of age in people with a normal BMI (less than 25) [10]. Because it is an autoimmune disease, one of the main risk factors for LADA is a personal or family history of autoimmune disorders. The Immunology of Diabetes Society defines LADA by three criteria: adult-age onset, no need for immediate insulin therapy, and presence of islet-cell autoantibody [10, 11]. The impairment of beta cells in patients with LADA is a slower process compared to T1DM, which is why patients with LADA do not need insulin right away. By definition, people with LADA can go at least 6 months after diagnosis before they are so insulinopenic that they require insulin to live [11]. Because it is an autoimmune disease, metabolic syndrome characteristics are seen less commonly with LADA. An interesting finding with LADA is the earlier presentation of microvascular complications, such as neuropathy and retinopathy [11], as compared to T1DM, which may be due to a longer period of subclinical hyperglycemia. Many individuals with LADA are misdiagnosed with T2DM

Table 2: Clinical comparison between MODY, T1DM, T2DM, KPD, and secondary diabetes.

Characteristic	MODY	T1DM	T2DM	KPD	Secondary diabetes
Typical age at diagnosis	<25	5–25	12-Adulthood	12-Adulthood	Dependent on underlying cause
Parental history	60–90%	<10%	10–14%	Similar to T2DM	None
Inheritance type	Autosomal dominant	None	Polygenic	Polygenic	Dependent on underlying cause
Obesity; insulin resistance; metabolic syndrome	Uncommon	Uncommon	Common	Common	Uncommon
Beta cell antibodies	Absent	Present	Absent	Dependent on subtype	Absent
C-peptide	Normal	Undetectable	High-low	Initially low and subsequently normal	Low

KPD, ketosis prone diabetes; LADA, latent autoimmune diabetes of the adult; MODY, maturity-onset diabetes of the young; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

because of adult onset. However, a common feature is poor control on standard type 2 therapy or inadequate control until started on insulin.

Pieralice and Pozzilli [12] developed a predictive model for identifying LADA based on measurement of GAD-65 Ab and C-peptide measurement to confirm the diagnosis and determine the treatment protocol. Some of the clinical risks associated with LADA include BMI of less than 25 kg/m^2, younger than 50 years of age, acute hyperglycemia symptoms at onset, and personal or family history of autoimmune disorders. Patients with two or more of these risk factors should be considered high risk for LADA. A positive GAD-65 Ab measurement should be an indicator of LADA. A patient with mild risk and one risk factor along with a low C-peptide value should be an indicator to test GAD-65 Ab [12]. Similarly, the new The Rare and Atypical Diabetes Network (RADIANT) trial aims to create a descriptive guide detailing the genetic and clinical presentation for all of the atypical forms of diabetes, including LADA [13]. Table 3 demonstrates the clinical comparison between T1DM, LADA, T2DM, KPD, and secondary diabetes.

Ketosis prone diabetes (KPD)

KPD is a form of T2DM and is defined by recurrent episodes of ketoacidosis. The mechanism of development and the progression of the illness is not well understood [14], but glucose toxicity and lipotoxicity leading to beta cell desensitization has been hypothesized [15]. KPD is seen more often in overweight and obese black males with a family history of T2DM [16]. KPD is generally diagnosed when patients are admitted to the hospital with ketoacidosis. They present with acute-onset hyperglycemia and some impairment of beta cell function and insulin insensitivity. What is unique about KPDM is that after resolution of ketoacidosis, patients can often be in remission (normal glucose levels with no medications) for months to years after initial episode and diagnosis, although they are prone to recurrent spontaneous ketoacidosis. KPDM may not always be associated with measures of autoimmunity such as GAD-65 or anti-islet-cell autoantibodies.

Balasubramanyam et al. [17] and Sjöholm [18] have classified patients with KPD based on the presence or absence of autoantibodies and the presence or absence of beta cell function measured soon after resolution of initial DKA episode. There are four general subtypes of KPD in this Aβ classification scheme:

- A–β–, autoantibody negative and with absent β-cell function;
- A+β–, autoantibody positive and with absent β-cell function;
- A–β+, autoantibody negative and with present β-cell function;
- A+β+, autoantibody positive and with present β-cell function [17, 18].

A–β– and A+β– KPD have permanent and complete beta cell failure and thus require long-term insulin. A–β+ KPD have preserved beta cell function and do not require insulin for long-term survival. A+β+ KPD may either have preserved beta cell function or have progressive beta cell failure, which will determine long-term insulin requirement.

Secondary diabetes

Secondary diabetes results as a consequence of other medical issues that affect the pancreas. In conditions like

Table 3: Clinical comparisons between T1DM, LADA, T2DM, KPD, and secondary diabetes.

Characteristic	T1DM	LADA	T2DM	KPD	Secondary diabetes
Age of diagnosis	0–25	35–50	12-adulthood	12-adulthood	Dependent on the underlying cause
Time to insulin	Immediate	>6 months	Typically years	Immediately needed but subsequently dependent on the subtype	Dependent on the underlying cause
Autoantibodies	+++	++	None	+/− Depending on the subtype	None
Risk for other auto-immune Dx	++	+++	No added risk	No added risk	No added risk
Sensitivity to Insulin	+++	+++	Not sensitive	Not sensitive	+++
Lipids	Normal	Normal	High trigs Low HDL	High trigs Low HDL	Dependent on the underlying cause

KPD, ketosis prone diabetes; LADA, latent autoimmune diabetes of the adult; MODY, maturity-onset diabetes of the young; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

pancreatitis, pancreatic cancer, and cystic fibrosis, the beta islet-cell function becomes impaired [19]. This beta islet-cell impairment leads to a lack of insulin production and subsequent insulin dependence. Patients with secondary diabetes may initially present with the underlying primary problem, such as chronic or recurrent pancreatitis, pancreatic cancer, or new-onset T1DM. In the case of an older patient with pancreatic cancer presenting with weight loss or otherwise unexplained deterioration of glycemic control, secondary diabetes should certainly be considered. The key features that make this different is that they will look like they have T1DM and will not make sufficient insulin to control glucose, but there will be no measures or risk of autoimmunity. One important clinical warning is to make sure that physicians do not confuse secondary diabetes with T2DM. Those with secondary diabetes need insulin as treatment to live like T1DM. Another key finding is that any person who presents as new-onset T1DM after the age of 50 years should be evaluated for secondary forms of diabetes such as pancreatic cancer [19].

Other causes of secondary diabetes can be hereditary hemochromatosis, atypical antipsychotics, glucocorticoids, or posttransplant diabetes (also called new-onset diabetes after transplantation, or NODAT) due to immunosuppressive medications and endocrine disorders (Cushing's syndrome). These conditions will not be discussed in this manuscript.

Future directions in atypical diabetes

With awareness of atypical diabetes on the rise, there have been new efforts to accurately diagnose people with the other forms of diabetes. The RADIANT trial is a national multicenter trial with the aim to categorize people with atypical forms of diabetes. This National Institutes of Health (NIH)-funded trial seeks to provide a specific diagnosis to nearly 2,000 people with atypical diabetes. More information can be found at https://www.nih.gov/news-events/news-releases/nih-funds-first-nationwide-network-study-rare-forms-diabetes [13].

Conclusions

The atypical forms of diabetes mellitus are easily misdiagnosed due to their similarities with the more common T1DM and T2DM. As discussed in this article, patients with LADA may be misdiagnosed with T2DM and continued on oral medications for a prolonged duration if appropriate diagnosis is not made early. Similarly, young adults with MODY may be mislabeled and incorrectly diagnosed with T1DM and sometimes even T2DM and subsequently started on insulin for the remainder of their life. This article brings to light that all patients who present with DKA do not have T1DM. Providers must evaluate for KPD as a possible diagnosis especially in patients who initially present with DKA but do not have the typical physical characteristics of T1DM. If a patient presents with signs of insulin resistance (acanthosis nigricans) and a family history of T2DM, and a significant reduction in insulin requirement is noted, KPD should be considered. The authors encourage providers to consider secondary diabetes when patients with chronic pancreatitis have beta cell loss and thus are insulin dependent. Secondary diabetes can also occur due to immunosuppressants, steroids, endocrine disorders, or hemochromatosis. Appropriate treatment and proper

management of the atypical forms of diabetes are contingent upon the correct diagnoses. The authors recommend keeping an open mind when diagnosing diabetes to avoid misdiagnosis. Additional investigation should be considered if standard treatment is ineffective. The RADIANT trial will provide physicians with more resources and data to be able to make the correct diagnoses and begin appropriate treatment, specific to the atypical form of diabetes [13].

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Competing interests: Dr. Shubrook has served on the American Diabetes Association Primary Care Advisory Committee and serves as an Advisory Board member to NovoNordisk and Bayer. and Dr. Ahmed has served on the Diabeteswise.org advisory board.

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