Adult diabetes mellitus: Thinking beyond type 2

Abstract: *Not all adults presenting with diabetes mellitus have type 2. NPs must become familiar with atypical presentations of type 1 and type 2 diabetes mellitus, especially in light of the current endocrinologist shortage. Two case studies illustrate variations of adult-onset diabetes along with discussion and diagnostic clues.*

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The CDC estimates that 12.3% of individuals in the United States age 20 and older have diabetes mellitus. Broken down by age group, 25.9% of those age 65 and older (typically Medicare eligible), and 16.2% of adults ages 45 to 64, have diabetes.[1] The vast majority of diabetes mellitus care (hereafter simply referred to as diabetes) is received in primary care settings, where the majority of NPs care for patients.[2,3] DesRoches and colleagues demonstrated that the "largest number of NPs per 1,000 Medicare beneficiaries were practicing in rural states," and NPs were more likely than physician colleagues to care for "underserved populations" as evidenced by an increased patient load with dual Medicare/Medicaid eligibility.[4]

Mundinger and colleagues first demonstrated equivalent primary care between NPs and their physician colleagues.[5] A recent systematic review and meta-analysis confirmed the same findings: Primary care NPs have consistently demonstrated equivalent primary care compared with physician primary care providers (PCPs).[6] Therefore, healthcare consumers have the choice of receiving care from NPs—who demonstrate equivalent care as discussed—but with the added advantage of holistic approaches to care, communication skills (particularly with patients), promotion of patient-centered self-management, and subspecialty expertise in chronic disease management.[7]

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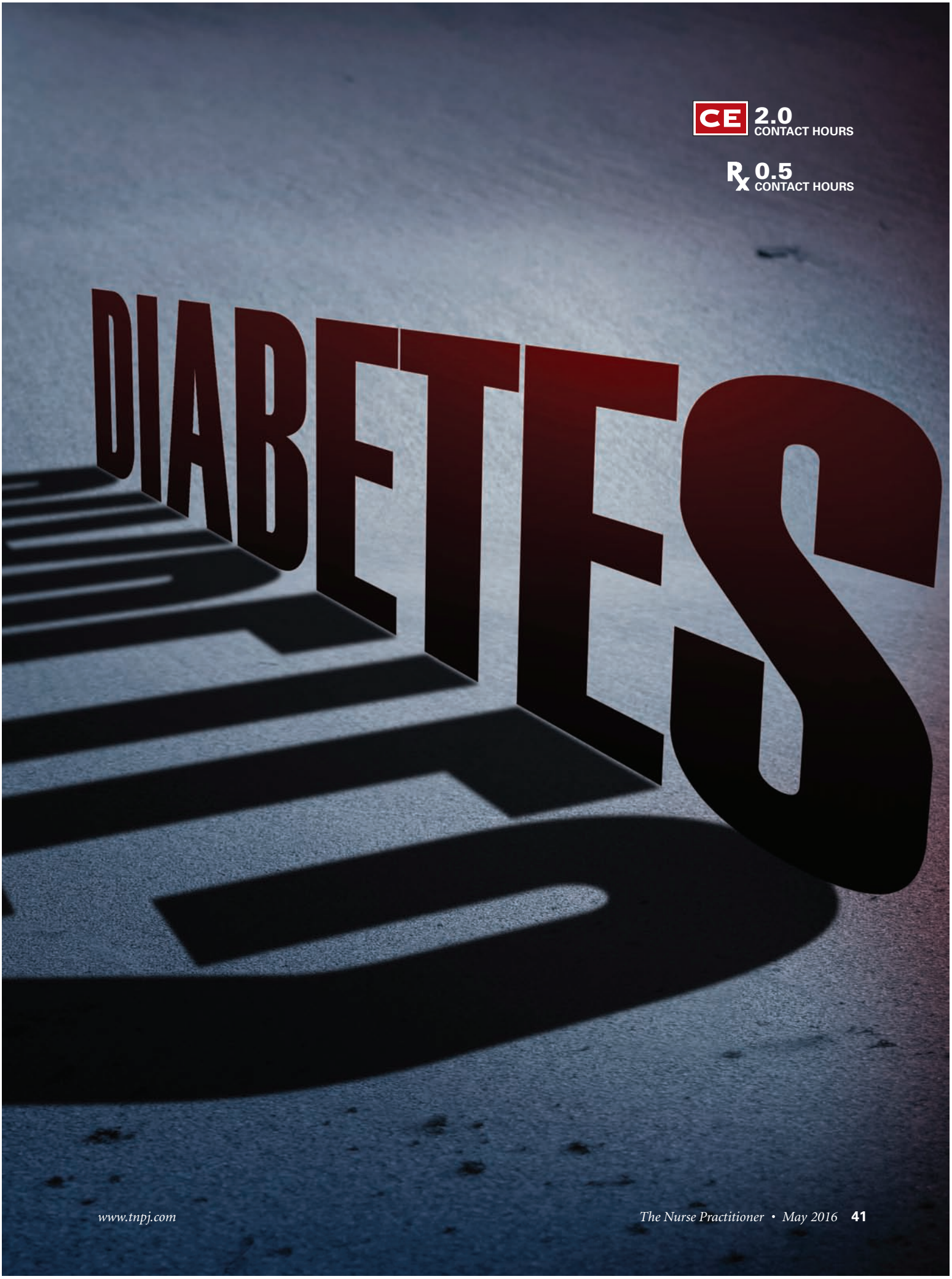
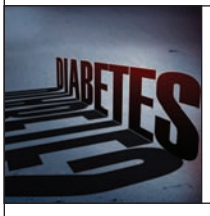


Improved access to care through the Affordable Care Act (ACA) has contributed to identifying previously undiagnosed diabetes.[8] Additionally, based on this author's experience in a private NP-managed diabetes clinic, expanding health coverage through the ACA has enabled patients with diabetes previously in safety-net care settings, those with significant gaps in health coverage, and those recently released from incarceration to enter the private primary care offices, often with significantly advanced disease. Diabetes cases continue to rise in other private sectors as well. Burgeoning diabetes caseloads, coupled with a nationwide shortage of endocrinologists, have created a critical need for expert-level diabetes care among NPs as well as an improved knowledge base for primary care NPs.[9]



T1DM and LADA are frequently associated with normal to low body weight and/or significant weight loss at presentation.

Approximately 90% of diabetes cases are type 2 diabetes mellitus (T2DM).[1] Of these cases, a substantial number of individuals (estimated at 10%) are positive for pancreatic autoantibodies characteristic of type 1 diabetes mellitus (T1DM).[10] T1DM, including both autoimmune and idiopathic, make up the second largest category behind T2DM. Although most commonly associated with childhood onset, literature from Sweden has reported that approximately 25% of T1DM cases are diagnosed as adults.[11] A vast number of less common types of diabetes, including secondary to exocrine pancreatic disease (such as cystic fibrosis), monogenic diabetes syndromes (such as maturity-onset diabetes), drug-induced diabetes, chemical-induced diabetes, and other variants, make up the remaining nongestational cases.[12]

This article highlights clinical presentations of two atypical types of adult diabetes: ketosis-prone diabetes (KPD) and latent autoimmune diabetes in adults (LADA). Diagnostic clues and testing are discussed in an effort to arrive at the best diagnostic classification, promoting the most appropriate glucose-lowering regimen for improved patient outcomes.

Case one

Mr. G, 30, is a Black male with class 3 obesity (body mass index [BMI] 45) who presents to the primary care office 1 week post ICU hospitalization for follow-up diabetic ketoacidosis (DKA), new-onset T2DM, and dental abscess. He has no history of unintended weight loss, but his history is positive for urinary frequency, thirst, blurred vision, and fatigue over the last few months. Severe dental pain precipitated the ED visit.

Mr. G's medical history is positive for obesity for many years, and his family history is positive for T2DM and obesity. Admission hospital labs were significant for large urine ketones, positive serum acetone, and hemoglobin A1C (A1C) of 12.7%. The dental abscess was treated with I.V. antibiotics, DKA was corrected, and he was subsequently discharged to primary care follow-up with a diagnosis of T2DM and treatment with basal insulin.

A diabetes-related autoantibody panel was run, including islet cell autoantibody (ICA), glutamic acid decarboxylase-65 autoantibody (GAD-65A), and insulin autoantibody (IAA). An insulinoma-associated-2 autoantibody (IA-2A) is also included in this panel for some labs, but not the lab used in this case. A fasting C-peptide and fasting blood glucose were also obtained. Results showed a normal C-peptide, elevated fasting blood glucose (235 mg/dL), negative ICA, negative GAD-65A, and negative IAA.

Case two

Ms. M, 49, is a White female who presents to her PCP with a 30-lb (13.6 kg) unintentional weight loss, palpitations, hot flashes, anxiety, and thirst over the last 6 months. She has no family history of diabetes, and her presenting BMI is 21.60. Initial labs included a fasting blood glucose level of 325 mg/dL and otherwise normal chemistry panel, small urine ketones, and an A1C of 12%. An urgent referral to the diabetes clinic was made. Labs from the diabetes clinic included a markedly elevated GAD-65A, markedly elevated antithyroid peroxidase (TPO) antibody, elevated thyroid-stimulating hormone (TSH) receptor antibody, suppressed TSH, free thyroxine (FT4) 1.5 ng/dL, and C-peptide 0.9 ng/mL.

Diagnosis and diagnostic clues

Diabetes (nongestational) is diagnosed by repeat testing (in the absence of unequivocal hyperglycemia) based on a fasting plasma glucose of 126 mg/dL or greater, or an A1C of 6.5% or greater, or a 2-hour plasma glucose of 200 mg/dL or greater during an oral glucose tolerance test, or a random plasma glucose of 200 mg/dL or greater with symptoms of hyperglycemia.[12] The American Diabetes Association (ADA) classifies diabetes typology into four main categories based on underlying mechanisms: T1DM (indicating absolute insulin deficiency); T2DM (characterized by insulin resistance and progressive beta cell dysfunction); gestational diabetes

(typically diagnosed in the second or third trimester); and other cause of diabetes, as previously mentioned.[12]

Age of onset, body habitus, and presence/absence of ketones are not diagnostic criteria for diabetes. However, age at diagnosis can provide clues, since most autoimmune diabetes presents in either childhood (T1DM) or earlier adulthood in the slowly progressing form of T1DM known as LADA.

Body habitus offers a diagnostic clue because a large percentage of T2DM is associated with obesity. T1DM and LADA are more frequently associated with normal to low body weight and/or significant weight loss at presentation. Presence of ketones or DKA (a common problem in T1DM) provides an additional, although nondiagnostic, clue to diabetes classification.

Ketosis-prone diabetes

KPD is a subtype of T2DM seen in patients primarily of African, Hispanic, or Asian descent.[13] This nonautoimmune subtype presents acutely with very high blood glucose levels and ketones with or without acidosis, and is more common (although not exclusively) in obese males.[13] Glucose toxicity, manifested as extremely high blood glucose; unintentional weight loss; extreme, unquenchable thirst; urinary frequency; and fatigue at presentation are common. Umpierrez and colleagues demonstrated that the acute glucose toxic presentation of KPD blunts beta cell functioning, but is reversible.[14]

Choukem and colleagues further demonstrated a residual dual defect of reduced beta and alpha cell function, resulting in impaired insulin secretion and impaired glucagon suppression in patients with KPD even after normoglycemia was achieved.[15] Diagnostic clues to KPD include the symptoms of glucose toxicity discussed above, coupled with ketosis and/or DKA, negative diabetes-related autoantibodies, and a normal C-peptide.[16]

Reversible (yet still reduced) beta cell dysfunction suggests that exogenous insulin administration may not be necessary for an extended period of time.[14,15] Insulin therapy is used initially; however, based on this physiology, once acute glucose toxicity is stabilized with insulin therapy, lifestyle measures and metformin plus additional pharmaceutical intervention targeting beta and alpha cell dysfunction—such as glucagon-like peptide-1 (GLP-1) receptor agonists and/or sulfonylureas—would be appropriate based on glucose levels.[15]

Latent autoimmune diabetes in adults

LADA is an immune-mediated, antibody-positive type of diabetes.[17] Exact labeling has been somewhat confusing because many patients are initially diagnosed as T2DM until an astute clinician recognizes nonresponse to traditional T2DM therapy and checks islet cell antibodies. (See *Autoantibodies associated with autoimmune diabetes*.) Current guidelines classify LADA as a subtype of T1DM due to its autoimmune state.[12] The Immunology of Diabetes Society suggests three important criteria for LADA: age of at least 30, positive for at least 1 antibody, and not requiring insulin for glucose control the first 6 months of the disease state.[18] The ICD-10 Manual does not have a code for LADA; therefore, coding could fall under the E10 category, "type 1 diabetes mellitus."[19]

Progressive, immune-mediated beta cell destruction within the pancreas is accelerated, leading these patients to require insulin replacement. Unintended weight loss and ketosis are signs of significant beta cell destruction and should prompt a quick reanalysis of any previously diagnosed patient with T2DM. Clues to diagnosing LADA may include a "younger" adult (although late in life is still possible) inadequately responding to typical T2DM therapies; relatively normal body weight, personal or family history of autoimmune illnesses (such as autoimmune hypothyroidism or hyperthyroidism), Addison disease, or celiac disease; ketosis; and unintended weight loss (see *Atypical diabetes types*). Patients with LADA will typically (eventually) require basal (long-acting/background) and prandial (mealtime) insulin due to beta cell destruction. In addition, evidence suggests that earlier treatment with insulin therapy leads to improved metabolic control.[20,21]

Returning to the case studies presented, case one, representing Mr. G, depicts KPD with antibody negative status and normal C-peptide. Basal and prandial insulin were used for 3 months, allowing the glucose toxicity to abate and pancreatic function to return. Over the subsequent months, metformin and a once-weekly GLP-1 agonist were added

Autoantibodies associated with autoimmune diabetes[21,22]

Islet cell autoantibody testing is very helpful in diagnosing autoimmune diabetes, such as LADA and T1DM. Autoantibodies include:

- Islet cell cytoplasmic autoantibodies (ICA) (normal <1:4; no antibody detected)
- Glutamic acid decarboxylase-65 autoantibody (GAD-65A) (normal 0.0–5.0 IU/mL)
- Insulinoma-associated-2 autoantibody (IA-2A) (normal 0.0–0.8 units/mL)
- Insulin autoantibodies (IAA) (normal 0.0–0.4 units/mL)
- Zinc transporter 8 (ZnT8A) autoantibodies: Available in research settings and in some facilities (normal 0.0–15.0 units/mL)

Atypical diabetes types[13-18]

Diabetes type	Ketosis	Antibodies	Obese	Acute onset	Family history of diabetes	C-peptide
KPD	+	–	+	+	+	↔
LADA	+	+	–	–	+	↓

Key: + = present, – = absent, ↔ = normal, ↓ = decreased.

while simultaneously titrating off insulin. Mr. G will remain vulnerable to ketosis in times of illness, and NPs must watch for further deterioration of beta cell function. His last A1C was within the ADA goal (less than 7%), at 6.8%.[12]

Case two, representing Ms. M, deals with a woman who for unclear reasons developed two autoimmune disease processes simultaneously: LADA, as evidenced by the markedly elevated GAD-65A antibody, low C-peptide, and ketonuria, in addition to Graves disease as evidenced by the markedly elevated TPO antibody, elevated TSH receptor antibody, and suppressed TSH. Although hot flashes could be related to perimenopause, they resolved with Graves disease treatment.

Insulin therapy is clearly indicated in case two; however, there is not one right way to initiate insulin. Evidence-based practice includes scientific evidence in addition to clinical experience and patient values and preferences.[23] Therefore, patient factors, such as meal patterns, willingness toward injection frequency, anxiety level, social support, education level, and insurance coverage, must all be considered in choosing an insulin regimen. The ADA suggests initiating insulin at 0.4 to 1.0 unit/kg/day with one-half to two-thirds used for basal (background) coverage, and the other one-third to one-half divided for meal coverage.[24]

Ms. M was started on a total daily insulin dose at 0.4 unit per kg body weight, with half (10 units) basal at bedtime and the other half as a prandial (mealtime) rapid-acting analogue insulin dose of 3 units before breakfast, lunch, and dinner. Fixed mealtime doses were chosen for Ms. M due to her high anxiety level with the initial diagnosis in addition to consistent, highly predictable meals.

Concomitant with the diagnosis and insulin initiation was an important standard of care in any patient with newly diagnosed diabetes (or in cases of diabetes where therapy has changed): referral to a certified diabetes educator (CDE) for comprehensive diabetes self-management education (DSME) and teaching of home blood glucose monitoring.[23] Education about carbohydrate counting may enable a more intensive insulin regimen based on meal carbohydrate content in the future. Ms. M's most recent A1C was 6.5%, her anxiety was markedly improved, and the patient's self-care and self-confidence were strong.

When to refer

Self-reflection in evaluating an NP's knowledge and management skills around diabetes care is helpful for personal growth and patient safety. A mentor early in the author's own career once warned of "not knowing what you don't know." A tongue twister, yes, but if an NP does not know of a disease process, it cannot be properly addressed. Engaging in continuing education through professional journal reading, conference attendance, and networking, along with active clinical practice, contributes to an NP's expanding knowledge base.

Patient safety is always first. In cases with a perplexing diagnosis or diabetes management, NPs should refer to a diabetes specialty-level NP clinician likely holding a CDE and/or board certified advanced diabetes management credential, or an endocrinologist. Preferable referral centers will have a nationally accredited DSME program for initial and ongoing support. Similarly, for those patients who are not responding to therapy, reevaluation of the diagnosis, including lifestyle and medication adherence, is crucial.

Moving forward

NPs must be alert for cases of atypical diabetes, such as KPD and LADA/slowly progressing T1DM, and proactively prepare to diagnose and treat such cases appropriately for improved outcomes. An urgent need exists for NPs with specialty level skills in diabetes management due to a confluence of factors, including the endocrinology physician shortage, epidemic obesity rates with resultant diabetes, and patient desire for NP care. The ADA (www.diabetes.org) and the American Association of Diabetes Educators (www.diabeteseducator.org) have additional resources for NPs ready to further enhance knowledge of diabetes care.

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