ARTICLE

Delayed Management of Insulin-Dependent Diabetes Mellitus in Children

Emir Tas, MD, Katrin Wooley, APRN, MNSc, CPNP-AC, Vildan Tas, MD, & Yu-Chi Annie Wang, MD

ABSTRACT

Introduction: Diabetic ketoacidosis (DKA) is a common presentation for pediatric new-onset insulin-dependent diabetes mellitus (IDDM). Delayed diagnosis is the major risk factor for DKA at disease onset.

Method: Two pediatric endocrinologists independently reviewed the admission records to assess the appropriateness of preadmission management in various health care settings.

Results: Eighteen percent (n = 45) of patients with new-onset IDDM had a delayed diagnosis. Twenty-eight were misdiagnosed (respiratory [n = 9], nonspecific [n = 7], genitourinary [n = 4], gastrointestinal [n = 8] issues) and 17 were mismanaged. One child died within 4 hr of hospitalization, presumably because of a hyperosmolar coma. Forty-six percent (n = 21) of patients with delayed diagnosis presented with DKA, comprising 18% of all DKA cases.

Discussion: A significant number of patients with new-onset IDDM were either misdiagnosed or mismanaged. All providers must be appropriately trained in diagnosing new-onset IDDM and follow the standard of clinical care practices. J Pediatr Health Care. (2022) *XX*, 1–7

KEY WORDS

Children, diabetes, incidence, diabetic ketoacidosis, delayed management

Emir Tas, Attending Physician, Division of Endocrinology and Diabetes, Arkansas Children's Hospital, and Assistant Professor, Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock, AR

Katrin Wooley, Advanced Nurse Practitioner, Department of Pediatrics, University of Arkansas for Medical Sciences, and Division of Endocrinology and Diabetes, Arkansas Children's Hospital, Little Rock, AR

Vildan Tas, Assistant Professor, Department of Pediatrics, University of Arkansas for Medical Sciences, and Attending Physician, Division of General Pediatrics, Arkansas Children's Hospital, Little Rock, AR

Yu-Chi Annie Wang, Attending Physician, Division of Endocrinology and Diabetes, Arkansas Children's Hospital, and Associate Professor, Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock, AR

This work was supported by the Center for Childhood Obesity Prevention through the National Institute of General Medical Sciences of the National Institutes of Health under award no. P20GM109096.

Conflicts of interest: None to report.

Correspondence: Emir Tas, MD, Division of Endocrinology and Diabetes, Arkansas Children's Hospital, Slot 512-6, 1 Children's Way, Little Rock, AR 72202; e-mail: etas@uams.edu.
J Pediatr Health Care. (2022) *00*, 1–7

0891-5245/$36.00

https://doi.org/10.1016/j.pedhc.2022.07.004

INTRODUCTION

Diabetes is one of the most common chronic illnesses in pediatrics with an increasing incidence in recent years, exacerbated during the COVID-19 pandemic (Chao, Vidmar, & Georgia, 2021; Klingensmith et al., 2016; Lawrence et al., 2021; Nagl et al., 2022; Zylke & DeAngelis, 2007). An accurate and timely diagnosis is imperative to prevent acute complications such as diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS). DKA at disease onset is estimated to be present in 15% to 67% of patients with type 1 diabetes (T1D) and 4% to 25% of patients with type 2 diabetes (T2D; Dabelea et al., 2014; Wolfsdorf et al., 2018; Zeitler et al., 2018). The exact prevalence of HHS is not known because of its relative rarity. However, both complications are associated with increased morbidity and, although rare, mortality.

Although the common presenting symptoms of childhood diabetes (polyuria, polydipsia, nocturia, weight loss) still holds and manifests for up to several weeks in children with T1D, they could be indolent and nonspecific, particularly in patients with T2D. With the rise of obesity in

children, the distinction between T1D and T2D can be more challenging (Stierman et al., 2021). Misdiagnosis or delayed referral are common and major risk factors for DKA at diagnosis (Rewers et al., 2008; Sundaram, Day, & Kirk, 2009; Wersäll, Adolfsson, Forsander, Ricksten, & Hanas, 2021). Most commonly misdiagnosed conditions include respiratory illnesses, gastrointestinal problems, urinary tract infections, and other nonspecified illnesses (Muñoz et al., 2019; Pawłowicz, Birkholz, Niedźwiecki, & Balcerska, 2009). Medical providers must be aware of the changing face of pediatric diabetes through education and awareness for timely diagnosis and initiation of appropriate treatment. A growing body of literature suggests that targeted awareness campaigns may allow for earlier diagnosis, thus reducing DKA at diagnosis. This study aimed to describe the characteristics of patients with new-onset insulin-dependent diabetes (IDDM) requiring hospital admission and analyze misdiagnosed and mismanaged cases in various health care settings before diabetes was diagnosed. As a secondary aim, we will compare the characteristics of the patients admitted with DKA or not.

METHODS

Participants

Children and adolescents (aged < 18 years) admitted to the Arkansas Children's Hospital and Arkansas Children's Northwest as new patients for the management of IDDM between January 1, 2021 and December 31, 2021, were included in this retrospective analysis. For this analysis, IDDM collectively refers to all patients (with T1D or T2D) who required insulin treatment for metabolic control on admission. Patients who did not require hospital admission, those with known T1D or T2D (i.e., diagnosed elsewhere), steroid-induced diabetes, and cystic fibrosis-related diabetes, and those with out-of-state zip code residential addresses were excluded from statistical analysis. The study was approved by the University of Arkansas for Medical Sciences Institutional Review Board.

Collection of Clinical Data

Electronic medical records were reviewed. Following data were collected on admission: demographics (age, sex, race/ethnicity, zip code), health insurance status (public vs. private), weight, height, laboratory values (venous pH, serum glucose, β-hydroxybutyrate, hemoglobin A1c [HbA1c], and pancreatic auto-antibodies), and whether the patient received hypertonic saline or a head computed tomography for suspected cerebral edema, and finally, based on the caregiver's report, whether the patient was seen by a health care provider (HCP) in the last 30 days before admission. In addition, two pediatric endocrinologists independently reviewed the referral documents in electronic medical records to verify caregivers' reports, assess the appropriateness of preadmission management, and determine whether there was a delay in the diagnosis or management of IDDM patients before hospital admission.

Inappropriate management was defined as (1) inability to recognize new-onset diabetes (i.e., misdiagnosis) or (2) inaction or erroneous action (i.e., mismanagement) resulting in delayed delivery for appropriate care despite correctly diagnosing diabetes. Weight and height data were used to calculate age and sex-specific body mass index percentiles. Obesity is defined as body mass index ≥ 95th percentile for age and sex. DKA was defined as venous pH < 7.30, and classified as mild (pH 7.20−7.29), moderate (pH 7.10 −7.19), or severe (pH < 7.10). Diabetes type was determined on the basis of auto-antibody (glutamic acid carboxylase-65 and islet antigen-2) results. Subjects with at least one positive pancreas auto-antibodies were classified as T1D. Residential zip codes were used to classify patients according to the health unit zones (Northwest, Northeast, Central, Southwest, Southeast) determined by the Arkansas Department of Health.

Statistical analysis

Summary statistics were presented as mean ± *SD* for continuous variables and count (%) for categorical variables. Categorical proportions (e.g., sex, insurance status, etc.) were compared among groups using Fisher's exact test. For a three-group comparison, one-way analysis of variance was conducted, followed by all-pairwise comparisons for post-hoc analysis. For a two-group comparison, Student's *t* test was used for normally distributed variables and a Mann-Whitney test for variables not normally distributed (as defined by $p < .05$, determined by the Kolmogorov-Smirnov test). A p value < .05 considered significant. SPSS (version 28, IBM Corp., Armonk, NY) was used for all calculations.

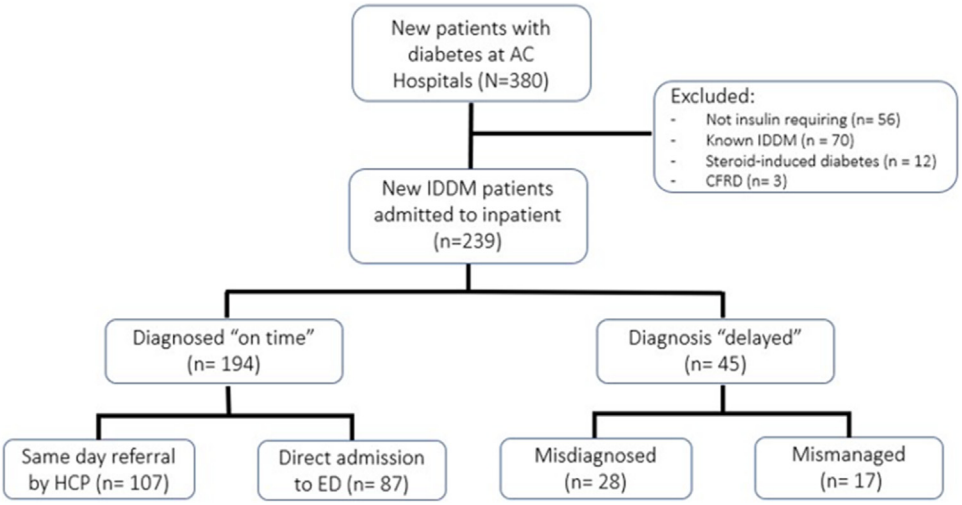
RESULTS

Characteristics of Patients with New-Onset Diabetes

Three hundred eighty patients were diagnosed with new-onset diabetes in our centers in 2021. Of these, 141 were excluded from the final analysis: 56 patients were managed in the outpatient setting and did not need insulin, 70 were previously diagnosed with IDDM elsewhere and already been on insulin treatment, 12 had steroid-induced diabetes, and three had cystic fibrosis-related diabetes. Our analysis included 239 children and adolescents with diabetes requiring hospital admission to initiate insulin treatment for the first time, including T1D and T2D (Figure). In our practice, we admit all pediatric patients with presumed T1D to the hospital for intensive diabetes teaching, but admission for presumed T2D patients is restricted to those with a baseline HbA1c of ≥ 9%.

Using the 2020 U.S. census data, we calculated an approximate average annual incidence of 22.7 new cases of T1D per 100,000 children and 11.4 new cases of T2D per 100,000 children in Arkansas. Our findings for both T1D and T2D annual incidence rates are similar to that previously reported for five different geographic regions combined in the United States (Lawrence et al., 2021; Mayer-Davis et al., 2017). As the state's only pediatric hospital system, Arkansas

FIGURE 1. Consort flowchart of the study participants. AC, Arkansas Children's; CRFD, cystic-fibrosis-related disease; ED, emergency department, IDDM, insulin-dependent diabetes mellitus; HCP, health care provider.



Children's Hospital and Arkansas Children's Northwest receive referrals from all over the state. Considering that some patients with T2D were managed as an outpatient (i.e., HbA1c < 9% at diagnosis), our calculated annual incidence rate for T2D is likely underestimated. Sixty-four percent of all patients (n = 153) were evaluated by an HCP within the last 30 days preceding the diagnosis of new-onset IDDM, and 107 were referred to the nearest emergency department (ED) for further evaluation.

The average age of all patients was 11.7 years (ranging from 1 to 17 years). The study cohort was 46% female, 77% non-Hispanic White and 10% Hispanic, 61% had public insurance, 67% T1D, and 38% obese. The average HbA1c of all patients was 11.8%. Twenty (8.4%) patients received a hypertonic solution or computed tomography of the head for suspected cerebral edema.

One hundred ninety-four patients (81.2%) were diagnosed on time, and 45 (18.8%) had delayed diagnoses. Diagnosed on-time group comprised 107 same-day-referred patients and 87 who presented directly to the ED. Delayed diagnosis group subcategorized further into delayed/misdiagnosed (n = 28; 11.7%), and delayed/mismanaged (n = 17; 7.1%) subgroups. Three groups did not differ regarding the distribution of sex, race, ethnicity, insurance data, obesity status on admission, T1D percentage, mean HbA1c level, or health unit zones (Table 1).

Cases With Delayed Diagnosis

Misdiagnosed cases (n = 28; 11.1% of all cases) were assessed by an HCP for various symptoms and diagnosed with diseases other than diabetes. These included nonspecific or constitutional conditions (n = 7), respiratory illnesses (n = 9), gastrointestinal problems (n = 8), and genitourinary issues (n = 4). The average HbA1c of this group was 12.1%. Twenty (71%) patients in this group presented with DKA. Five (18%) patients received hypertonic saline infusion because of concerns for cerebral edema. Seventeen (61%) patients had T1D. Four subjects were prescribed steroid treatment 2−7 days before hospital admission for new-onset IDDM. One obese patient died 4 hr after presenting to the ED, presumably because of a hyperosmolar hyperglycemic coma. Serum glucose level was > 1,600 mg/100 mL on admission and 1,140 mg/100 mL when death was announced. This subject was diagnosed with strep throat infection at a local urgent care facility 2 days before admission and given a dose of intramuscular penicillin and dexamethasone. This group's median time between HCP evaluation and hospital admission was 4 days (range 1−29 days).

Mismanaged cases (n = 17; 7.1% of total cases) were correctly diagnosed with diabetes, but the standard of care clinical guidelines were not followed for these patients, resulting in delayed management. In 12 patients, HCP opted to place an outpatient diabetes clinic referral while monitoring for worsening symptoms. In comparison, HCP started oral medication in five patients and placed a referral. Three patients in the latter group were also given a prescription for basal insulin, but none started this treatment because they lacked knowledge of insulin administration. The average HbA1c of this group was 11%. Only one patient in this group presented with DKA. Eight (47%) patients had T1D. This group's median time between HCP evaluation and hospital admission was 13 days (range 2−30 days; Table 2).

Compared with the mismanaged group, patients in the misdiagnosed group were younger (11.0 ± 5.1 vs. 14.4 ± 2.9 years; p = .02), had unfavorable serum markers on admission (lower pH, higher serum glucose, and β-hydroxybutyrate), and significantly higher risk of DKA on admission

TABLE 1. Characteristics of all new-onset insulin-dependent diabetes mellitus patients, categorized on the basis of the timing of diagnosis (on-time vs. delayed)

Characteristics	All (*n* = 239)	Delayed diagnosis (*n* = 45)			*p* Value
		Diagnosed on time (*n* = 194)	Misdiagnosed (*n* = 28)	Mismanaged (*n* = 17)	
Age (year) at diagnosis	11.7 ± 4.5	11.6 ± 4.5[a]	11 ± 5.1[a]	14.4 ± 2.9[b]	.01
Age categories, years					.04
0–5	38 (16)	32 (84)	6 (16)	0 (0)	
6–12	83 (35)	71 (85)	8 (10)	4 (5)	
13–18	118 (49)	91 (77)	14 (12)	13 (11)	
Female sex	110 (46)	89 (46)	12 (43)	9 (53)	.80
White race	185 (77)	150 (77)	22 (78)	13 (77)	.98
Hispanic ethnicity	23 (10)	20 (10)	2 (7)	1 (6)	.75
Public insurance	146 (61)	120 (62)	15 (54)	11 (65)	.67
Type 1 diabetes	159 (67)	131 (68)	17 (61)	8 (47)	.23
Obese on admission	91 (38)	71 (37)	11 (39)	9 (53)	.41
Body mass index status on admission					.72
Underweight	21 (9)	19 (10)	2 (7)	0 (0)	
Normal	100 (42)	82 (42)	11 (39)	7 (41)	
Overweight	27 (11)	22 (11)	4 (14)	1 (6)	
Obese	91 (38)	71 (37)	11 (39)	9 (53)	
Hemoglobin A1c on admission	11.8 ± 1.9	11.9 ± 1.9	12.1 ± 1.9	11 ± 1.8	.13
pH	7.25 ± 0.15	7.25 ± 0.15[a]	7.17 ± 0.17[a]	7.36 ± 0.04[b]	< .001
Glucose	432 ± 203	435 ± 193[a]	505 ± 261[a]	281 ± 125[b]	.001
β-hydroxybutyrate	4.4 ± 3.8	4.5 ± 3.8[a]	6.4 ± 3.6[b]	1.3 ± 1.7[c]	< .001
Diabetic ketoacidosis on admission	117 (48)	96 (49)[a]	20 (71)[a]	1 (6)[b]	< .001
Hypertonic solution on admission	20 (8.4)	15 (8)	5 (18)	0	.08
Computed tomography head-on admission	12 (5)	10 (5)	2 (7)	0	.56
County zone					.21
Northwest	73 (30)	59 (30)	8 (29)	6 (35)	
Northeast	28 (12)	21 (11)	4 (14)	3 (17)	
Central	88 (37)	74 (38)	11 (39)	3 (18)	
Southwest	33 (14)	28 (14)	4 (14)	1 (6)	
Southeast	17 (7)	12 (6)	1 (4)	4 (24)	

Note. Data are expressed as mean ± *SD* or n (%). Significant differences between groups were determined by one-way analysis of variance followed by post-hoc all-pairwise comparison. Labeled (a, b, c) means the difference between groups following post-hoc analysis. The same letter indicates no difference between the groups compared.

(relative risk, 12.1; 95% confidence interval, 1.8–82.4; $p = .01$). Groups did not differ in regard to demographics, HbA1c level on admission, and percentage of patients with T1D (61% vs. 47%; $p = .37$). Median time between HCP evaluation and hospital admission was shorter in the misdiagnosed group ($p = .01$)

DKA on Admission

Forty-nine percent ($n = 117$) of all patients presented with DKA. Compared with non-DKA group children with DKA were younger (11.1 ± 4.8 vs. 12.3 ± 4.2 years; $p = .02$) and they had higher HbA1c (12.4 ± 1.4 vs. 11.3 ± 2.2%; $p < .001$) and serum glucose (522 ± 219 vs. 346 ± 141 mg/100 mL; $p < .001$) on admission. There were more male patients in this cohort (55% vs. 41% in females; $p = .04$). Race, ethnicity, insurance status, or residential zones were comparable between groups. DKA frequency was significantly higher in the 0–5 year age group ($n = 26$; 68%) than the 6–12 year ($n = 41$; 49%) and 13–18 year ($n = 50$; 42%) groups ($p = .02$). There were more male patients with T1D ($n = 90$; 57%) than T2D ($n = 27$, 34%; $p < .001$). Those with T1D had a higher risk of DKA on admission than patients with T2D requiring admission (relative risk 1.49; 95% confidence interval, 1.05–2.10; $p = .02$). DKA prevalence on admission was comparable between the on-time and delayed/misdiagnosed groups, but was significantly higher than the delayed/mismanaged group (44% vs. 71% vs. 6%, respectively; $p < .001$).

DISCUSSION

This study evaluated data from 239 pediatric patients with new-onset IDDM (T1D and T2D). We assessed the appropriateness of preadmission management of those evaluated by an HCP within 30 days before hospital admission. We found that 29% (45 out of 153) of patients assessed by an HCP were either misdiagnosed or mismanaged, leading to delayed delivery of appropriate care for diabetes and acute complications of diabetes (i.e., DKA). These cases comprised 19.6% ($n = 21$) of all DKA admissions and could

TABLE 2. Characteristics of mismanaged patients

ID	Sex	Race	Age, years	HCP	Action taken by HCP	Time until admission days)	DM type	HbA1c (%)	DKA	BMI	Insurance
10	M	W	16	PCP	Monitor for worsening of symptoms	29	2	13.5	No	Overweight	Public
21	M	W	17	PCP	Endocrine outpatient referral	22	2	11.5	No	Obese	Public
40	F	W	12	Urgent care	Follow-up with PCP	2	1	12.6	No	Normal	Private
59	M	W	12	PCP	Endocrine outpatient referral	28	2	8.3	No	Obese	Public
104	F	B	15	PCP	Endocrine outpatient referral	21	2	11.4	No	Obese	Public
107	F	W	15	PCP	Started metformin; endocrine outpatient referral	25	2	10.8	No	Obese	Public
110	F	B	15	PCP	Endocrine outpatient referral	30	2	9.7	No	Obese	Public
185	M	W	17	ED	Endocrine outpatient referral	2	1	11	No	Normal	Private
200	M	B	16	PCP	Monitor for worsening of symptoms	15	1	9.3	No	Obese	Public
238	F	B	11	PCP	Endocrine outpatient referral	28	2	10.2	No	Obese	Public
243	F	W	15	PCP	Monitor for worsening of symptoms	13	1	11.9	No	Normal	Private
244	F	W	17	PCP	Started metformin; endocrine outpatient referral	7	2	13.1	Yes	Normal	Public
255	M	W	13	PCP	Recommended to start basal insulin; endocrine outpatient referral	2	1	13.8	No	Normal	Private
260	M	W	7	PCP	Endocrine outpatient referral	2	1	9.6	No	Normal	Private
261	F	W	13	PCP	Started metformin; recommended to start basal insulin; endocrine outpatient referral	2	2	10.2	No	Obese	Public
269	M	W	13	PCP	Recommended to start basal insulin; endocrine outpatient referral	2	1	12.8	No	Obese	Public
307	F	W	15	PCP	Endocrine outpatient referral	2	1	7.3	No	Normal	Private

Note. *B,* Black; *BMI,* body mass index; *DKA,* diabetic ketoacidosis; *ED,* emergency department; *F,* female; *HbA1c,* Hemoglobin A1c; *M,* male; *PCP,* primary care physician; *W,* White; *HCP,* **health care provider.**

have been prevented. Moreover, one patient died shortly after ED admission, presumably because of a hyperosmolar hyperglycemic coma. He received a dose of intramuscular steroid treatment 2 days before presentation, possibly contributing to the severity of hyperglycemia and dehydration, exacerbating HHS.

We further showed that misdiagnosed cases were more likely to present with DKA at the onset of diabetes than those who were mismanaged. These two groups were comparable regarding the distribution of sex, race, ethnicity, type of diabetes, and obesity status, suggesting that the diagnostic or management choices of the providers were not affected by patient characteristics. The American Diabetes Association guidelines for managing pediatric T2D recommend the initiation of basal insulin in patients with HbA1c $\geq$ 8.5% (Arslanian et al., 2018). At our center, patients with HbA1c > 9% are generally admitted for basal/bolus insulin initiation education, given that antibody testing for the type of diabetes is not quickly available, and the diagnosis is sometimes not clear given the prevalence of obesity in the general population. Forty-seven percent of the mismanaged cases had T1D and outpatient referral only delayed time to insulin initiation; fortunately, only one patient presented in DKA. All but two mismanaged patients had an HbA1c significantly > 9%. The patients who do not meet the criteria for insulin initiation were not appropriately treated with metformin on a timely basis. As expected, the rate of DKA was higher in the misdiagnosed group, given that the diagnosis of diabetes was not entertained and the symptoms were inappropriately treated with a more significant delay in treatment.

DKA at diagnosis often results from misdiagnosis or delayed treatment (Wolfsdorf et al., 2018). Many studies have examined the factors associated with diabetic ketoacidosis in children and adults with T1D. Usher-Smith, Thompson, Sharp, and Walter (2011) Compiled data from more than 24,000 children from 31 countries. They showed that diagnostic error (i.e., misdiagnosis) and delayed treatment (i.e., mismanagement) along with younger age and lack of insurance coverage were associated with an increased risk of DKA (Usher-Smith et al., 2011). Similarly, Muñoz et al. (2019) surveyed the adult patients with T1D or the parents of children with T1D registered in the T1D Exchange clinic registry and online community. They found that about one-sixth of all children with T1D were initially misdiagnosed, with the rate of misdiagnosis being higher in the 0−6 years group (Muñoz et al., 2019). Flu/viral illnesses followed by nonspecific conditions and bacterial infections were among the most commonly misdiagnosed. In a retrospective analysis spanning more than 10 years in Malaysia, 38.7% of children with T1D were misdiagnosed and had a higher DKA admission rate than those diagnosed correctly (Mavinkurve et al., 2021). Another retrospective study from Poland showed a clinically significant delay in diagnosis of 14.1% of children (n = 67) with T1D, resulting in higher than average DKA admission rates in this population. Furthermore, most patients (79%) were evaluated by family physicians before a T1D diagnosis was established (Pawłowicz et al., 2009).

Given that diagnostic errors and delayed treatment are major risk factors for pediatric DKA, campaigns have been performed to increase awareness of pediatric diabetes in public and among medical providers with variable results. The Parma campaign in Italy, launched in the nineties, has shown a drastic decrease in DKA incidence at diabetes diagnosis (Cangelosi et al., 2017; Vanelli, Chiari, Lacava, & Iovane, 2007; Vanelli et al., 1999). Similar results were obtained in an awareness campaign in Australia that resulted in a 64% decrease in DKA rate at initial diagnosis (King et al., 2012). Both campaigns provided point-of-care equipment to check blood sugar and urine glucose or ketones at the doctor's offices. In contrast, no significant reduction in pediatric DKA rates was achieved in a Welch and Austrian study through informational posters only (Fritsch et al., 2013; Lansdown et al., 2012). These studies suggest that, in addition to increased awareness, empowering local providers with necessary tools such as point-of-care testing equipment is more likely to yield better results.

Despite increased alertness and ongoing efforts to reduce DKA rates among children with T1D, medical providers lack knowledge regarding presenting signs and symptoms in children with T2D, likely because of its gradual onset. In two previous studies conducted in Arkansas, authors demonstrated that up to 25% of youth with atypical diabetes had DKA at disease onset (Pihoker, Scott, Lensing, Cradock, & Smith, 1998; Scott, Smith, Cradock, & Pihoker, 1997). In our study, 33.7% (n = 27) of patients with T2D had DKA at diagnosis. Of these, eight were misdiagnosed, and one had delayed management as the cause of their DKA, which could have been prevented. Our results call for an urgent need to raise awareness among HCPs in our community regarding the frequency of IDDM being misdiagnosed as other illnesses and mismanaged even when the diagnosis is correctly made, and that T2D patients are at risk for DKA like patients with T1D.

In conclusion, delayed diagnosis of pediatric IDDM because of misdiagnosed or mismanaged cases in various health care settings has led to an increased number of patients presenting with DKA at diabetes onset. Identifying knowledge gaps among the medical providers caring for children in these settings and providing periodic and targeted education for the initial diagnosis and management of IDDM may prevent future preventable errors. Considering the medical, psychosocial, economic, and medicolegal consequences of delayed management of pediatric diabetes, it is paramount to address the barriers through a concerted effort. Primary care services for children are being rendered by various providers, including pediatricians, family practitioners, nurse practitioners, physician assistants, and internal medicine physicians. Given the heterogeneity of primary care providers, particularly in rural areas, educators in graduate schools should ensure the trainees are equipped with up-to-date knowledge, while medical and nursing societies, as well as state boards, ensure the currently practicing providers are aware and capable of implementing evidence-based

pediatric diabetes guidelines involving diagnosis and initial management.

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