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Effectiveness of a Diabetic Ketoacidosis Prevention Intervention in Children With Type 1 Diabetes

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Background

Diabetic ketoacidosis (DKA) is the leading cause of morbidity and mortality in young people with type 1 diabetes (T1D), impacting hundreds of thousands of Americans each year and causing 50% of the deaths in people with diabetes under 24 years old.[1,2]. While the incidence of DKA in patients with undiagnosed diabetes is relatively difficult to influence, the majority of patients with DKA have known diabetes. It is estimated that up to 50% of these cases of DKA may be preventable with appropriate education and regimen adherence[2]. Despite the high frequency of DKA admissions among this population, few of the studied interventions have been successful in preventing DKA incidence and subsequent hospitalization. With the increasing incidence of T1D in the United States[3], it is becoming increasingly important to find innovative approaches to DKA prevention that are successful in reducing the incidence of T1D's most lethal complication.

Burden of T1D and DKA in the United States

T1D is far less common than type 2 diabetes (T2D), making up only 5% of the burden of disease in the United States, but the prevalence has increased over the last few decades. In 2001, the prevalence was 1.48 per 1,000 population, but it had risen to 1.93 per 1,000 by 2009, representing 30% increase in the prevalence of T1D over 8 years. The etiology of this increase in prevalence, which has been seen worldwide, is not well understood[3]. While several trials have been initiated to prevent T1D in patients with a high genetic risk, there are currently no known methods to prevent the disease[4].

With the inability to prevent T1D itself, prevention must instead be at the level of disease management. The aim must be to prevent the dangerous complications of T1D, of

which DKA is the most concerning in the acute setting. The incidence of DKA in the US is between 3 and 8 per 1,000 patients with diabetes, and 80% of these occur in individuals with a known history of diabetes[5]. Understandably, the prevention strategies differ greatly depending on whether or not the individual is known to have diabetes. It is relatively difficult to influence DKA incidence among individuals who have not yet been diagnosed with diabetes, though this has been accomplished in the past[6]. Although some studies have shown that some interventions are able to systematically impact the incidence of DKA in people with known diabetes, hospital admissions for DKA have not decreased, and indeed may have increased over the past few decades[5]. This remains an important target in reducing the burden of diabetes both on individual patients and on the healthcare system.

While mortality rates for youth with diabetes have declined as outpatient diabetes regimens have improved, people with diabetes still have a 2- to 6-fold higher mortality when compared with age-matched controls without diabetes[7]. The majority of this increase is attributable to DKA; in one study, DKA was responsible for 54% of deaths in males and 76% of deaths in females under the age of 30[8]. While many patients and providers are more concerned with the danger of serious hypoglycemia (SH) in patients with type 1 diabetes, DKA is actually associated with a much higher mortality. The risk of death is not the only danger of DKA, however. The complications associated with DKA include cerebral edema, which occurs in 0.4-3.1% of cases. Cerebral edema can cause significant, permanent neurological sequelae in the majority of patients who experience it[9]. DKA is also associated with adult respiratory distress syndrome, comorbid lactic acidosis, thromboembolic complications, and non-traumatic rhabdomyolysis. These

complications can lead to death, extended hospitalizations, and long-term sequelae for those patients that experience them; thus, the impact of DKA is not necessarily complete when the acute episode has resolved.

The burden on the healthcare system is also quite significant. It is estimated that a single episode of DKA costs about $11,000 to treat, and the total cost of all episodes of DKA in the United States in 2004 was more than $1.8 billion[2,7]. This represents over a quarter of the total cost of T1D in America. The cost savings associated with the prevention of DKA are substantial and can justify prevention programs that are relatively expensive[10]. Additionally, interventions that allow for the management of mild DKA in the outpatient setting, rather than requiring inpatient admission, can have a large impact on the cost to the healthcare system.

The public health implications of a reduction in DKA incidence and hospitalization within the United States are enormous. There are more than 800,000 individuals with T1D in the US at this time, and currently there is a 0.8% chance of developing DKA for each person each year[11]. The morbidity and mortality of DKA is very high; DKA is responsible for more deaths among young people with T1D than any other complication of the disease. The implications on the cost of the disease are also quite significant; an episode of DKA nearly doubles the annual cost of diabetes. An intervention that could influence the incidence and severity of DKA could have a substantial impact on the mortality of the disease itself and on the overall cost of this disease to the healthcare system. DKA incidence is an important target for the healthcare system and represents an opportunity to greatly influence the morbidity, mortality, and cost of T1D in the United States.

Pathophysiology of DKA

DKA occurs when there is an absolute or relative insulin deficiency in the body. This is why it occurs more frequently in those with T1D: they do not have any endogenous insulin production. In patients with known T1D, DKA can develop secondary to interruptions in insulin provision for any reason, which will be discussed below. Absolute insulin deficiency is not required, however. In periods of acute illness or stress, insulin requirements increase significantly due to the release of counter-regulatory hormones. These hormones, which include glucagon, catecholamines, and cortisol, increase both endogenous glucose production and release and production of ketone bodies secondary to lipolysis. This causes an increased insulin requirement, and the baseline insulin levels may not be sufficient to prevent ketoacidosis. Thus, close monitoring of glucose and ketone levels and appropriate adjustments to insulin dosages are important tenets of sick day management. The increase in counter-regulatory hormones can also occur in those with type 2 diabetes in the setting of acute illness. In this way, patients with T2D can also develop DKA, though it is far less common in this population, occurring only in those with very low residual insulin production. In the patient with no physiologic stressors, only a small amount of insulin is required to prevent ketoacidosis, and people with T2D usually have sufficient insulin levels to avoid this complication[5].

Proximal causes of DKA can be divided into those related to decreased insulin provision and those related to increased endogenous insulin requirements[1]. Interruptions in insulin can be either intentional or accidental. One concern with the introduction of continuous subcutaneous insulin infusion (CSII), known as insulin pump therapy, was

that a kink in the catheter or the cannula being inadvertently removed might lead to DKA. The rates of DKA might be increased in patients using insulin pumps, even though they may have better overall control. Additionally, the use of the newer, shorter-acting insulin analogs in insulin pumps may lead to the development of DKA after a shorter period of insulin interruption than is seen with regular insulin[5]. These concerns were later found to be purely theoretical; DKA rates in patients using CSII are actually lower than in patients using multiple daily injection (MDI) regimens[12]. In patients using injection therapy, unintentional insulin interruption can occur secondary to errors in insulin administration[1].

Some patients with T1D, especially adolescents and young adults, intentionally withhold insulin. Comorbid psychological illness is common in diabetes; some studies have shown that people with diabetes are 2-3 times as likely to be depressed as the general population[13]. Withholding insulin can lead to weight loss; the body will use its fat stores for energy when it cannot use sugar due to insulin deficiency. Thus, purposeful insulin omission can be considered a disease-specific form of disordered eating behavior. Up to 20% of episodes of DKA in this population may be associated with disordered eating, and this should be considered and screened for in young women with repeated admissions for DKA[5]. Additionally, young people adjusting to life with diabetes can have periods of rebellion against the disease, during which they do not perform the actions they know are necessary for self-care due to resentment and denial[13].

Increased insulin requirements can occur for a variety of reasons. Stress, infection, trauma, surgery, and serious medical problems like myocardial infarction can lead to an increase in counter-regulatory hormones, as mentioned above, which in turn causes increased glycogenolysis and gluconeogenesis as well as lipolysis and

ketogenesis. Cytokines released by immune cells during infections can also play a role in this process[1]. Standard insulin dosages are not adequate to account for the effects of these increased counter-regulatory hormones during acute illness. Without an awareness of these potential increased insulin requirements and an appropriate adjustment of insulin dosages, DKA can easily develop in patients with acute illnesses or injuries.

Finally, there are some drugs which can affect carbohydrate metabolism and give rise to the development of DKA; these include corticosteroids, thiazides, sympathomimetic agents, and pentamidine[5]. There may be clinical scenarios in which it is necessary to prescribe these medications to patients with diabetes, with the benefits outweighing the potential risks. It is important for patients to be informed of their potential effects on blood glucose and the necessary physicians should be consulted to modify medication regimens accordingly.

Diagnosis and Treatment of DKA

The symptoms of DKA include the symptoms of hyperglycemia (polyuria, polydipsia) and severe dehydration, but patients also may present with abdominal pain, nausea, vomiting, or Kussmaul breathing[9]. DKA is diagnosed in patients who have the triad of hyperglycemia, ketosis, and acidemia. The diagnostic criteria are defined as blood glucose > 250 mg/dL, blood pH < 7.3, serum bicarbonate < 15 mEq/L, moderate ketonemia (or ketonuria), and an increased anion gap[5]. The American Diabetes Association recently released a new set of criteria to grade patients into mild, moderate, or severe DKA based on levels of biochemical markers within these categories. The authors hoped the guidelines could be used to identify cases of mild DKA with minimal

acidosis, as the level of acidosis is not necessarily correlated with the degree of hyperglycemia and ketosis[14].

Providers must have a high level of clinical suspicion for DKA in patients with T1D presenting with abdominal pain and nausea or vomiting, or any mental status changes. Clinicians in the emergency department should have a low threshold for checking a fingerstick glucose level. Once DKA has been diagnosed, management in the emergency department includes gradual rehydration, insulin therapy, and continued frequent monitoring of vital signs and electrolytes[15]. Fluid replacement is extremely important in the management of DKA, but must be undertaken gradually to avoid predisposing the patient to cerebral edema, the most dangerous complication of DKA. Isotonic fluids have been shown to be the best option, and the initial bolus of 10-20 mL/kg of normal saline or Ringer's lactate should be given over the first 1-2 hours. Conventional wisdom has long suggested that giving more than 40 mL/kg during the first four hours of treatment may contribute to the development of cerebral edema[9]. However, recent studies have shown that cerebral hypoperfusion may play a role in the development of cerebral injuries, and there is an ongoing trial to determine which rehydration rate confers optimal long-term neurological outcomes[16].

Insulin therapy should not begin until after the initial fluid bolus has been completed. Insulin will restore physiological utilization of glucose and stop ketogenesis, but it should also be given slowly. While it is important to correct the hyperglycemia, correction of the acidemia is more important and takes a longer amount of time. Regular insulin should be started on a continuous drip at 0.1 units/kg/hr. Once the blood glucose has decreased to 250 mg/dL, dextrose should be added to the IV fluids to prevent

hypoglycemia before the acidemia has resolved. The insulin drip can be reduced to 0.05 units/kg/hr at this time as well[9]. IV insulin can be discontinued when the blood pH is greater than 7.3, serum bicarbonate is greater than 18 mEq/L, blood glucose is lower than 200 mg/dL, and the patient is ready to eat. At this point, the patient should be switched to subcutaneous insulin. While patients with known T1D can be transitioned back to their outpatient regimen, which should be examined to ensure that it is sufficient, people who have been newly diagnosed with diabetes should be started on an intensive injection regimen such as basal-bolus therapy, in which a long-acting insulin analog of approximately 0.4-0.5 units/kg/day is given to cover basal insulin needs and pre-meal doses of rapid-acting insulin are given to cover meals. Alternatively, a split-mixed dose regimen may be initiated with a total daily dose of around 1.0 mg/kg/day, depending on the needs of the patient. IV insulin should be continued for 1-2 hours after giving the subcutaneous insulin to avoid repeated hyperglycemia[5].

Electrolyte management during this period is also extremely important. Extracellular potassium levels are usually elevated, but the total body potassium is often depleted. To address this, if potassium is normal or low, potassium chloride should be added to all IV fluids following the initial bolus of 20-40 mEq/L. Potassium should be monitored every four hours and replacement should be initiated if the serum level drops below 5 mEq/L. The other electrolyte disturbances seen during DKA, such as hypophosphatemia, will usually be corrected by insulin therapy and resolution of normal metabolism, and do not require specific intervention[5].

The most dangerous complication of DKA is cerebral edema, which is due, in part, to shifts in intracellular and extracellular fluid secondary to hyperosmolality during

the rehydration process. There may also be associations with vasogenic edema; there is some evidence that brain ischemia leads to dysfunction in the blood-brain barrier and vasogenic edema, which in turn can perpetuate cerebral edema[17]. Many of the tenets of DKA therapy, including rehydration over a period of many hours and lowering glucose at a moderate rate, are designed in such a way to avoid the development of cerebral edema. Clinically, patients present with signs of increased intracranial pressure, with decreasing levels of consciousness, headache, seizures, and urinary incontinence[5]. Treatment, which includes IV mannitol or hypertonic saline, must be initiated immediately to avoid brain herniation or respiratory arrest. Patients may also be intubated and hyperventilated to induce cerebral vasoconstriction[9]. Steroid and diuretic therapy, mainstays of the treatment of other causes of cerebral edema, are not indicated in these patients. The effects of cerebral edema can be severe; nearly a quarter of patients die and 86-93% of surviving patients will have permanent neurological damage[2,9].

Other complications of DKA are less severe, but still cause significant morbidity and can extend hospital stays. Hypoglycemia secondary to aggressive insulin therapy, which is reported in up to 10% of patients, is dangerous in this setting because patients may not experience the usual symptoms. Adult respiratory distress syndrome (ARDS) occurs when therapy leads to interstitial edema of the lung and decreasing partial pressure of oxygen. Ketoacidosis can be compounded with comorbid lactic acidosis due to profound dehydration and increased generation of lactate to use as a precursor for gluconeogenesis. Dehydration can also lead to increased risk of thromboembolism, as can inappropriate activation of the coagulation system, and some patients will have

subclinical rhabdomyolysis. Clinicians must be aware of these complications and monitor for them on presentation and throughout treatment of the patient with DKA[5].

Clearly, the workup and treatment for DKA are extensive and complex; diagnosis requires interpretation of multifactorial laboratory data, and the treatment requires slow, stepwise changes to avoid dangerous complications such as cerebral edema. Once DKA has been diagnosed, the patient will require a multi-day hospitalization and may even be admitted to the intensive care unit. The complications of treatment can also be quite severe, and may prolong hospitalization or require extensive follow-up. It is important, then, to focus on DKA prevention so that these expensive and lengthy treatments, as well as the morbidity and mortality, can be avoided.

Prevention of DKA

Given the high contribution of DKA to the overall morbidity and mortality associated with T1D in children and adolescents, prevention programs have long been a focus among researchers. Prevention among patients with undiagnosed diabetes, or primary prevention of DKA, requires awareness campaigns among generalist providers and the general public. DKA prevention among patients with known diabetes, or secondary prevention, can be targeted to the specific families, and should address the issues that caused DKA in this patient previously. For example, a patient who is known to develop DKA frequently when sick should have the sick day guidelines reinforced, while a patient with concern for intentional insulin omission may need psychotherapy or counseling.

When designing and delivering DKA prevention interventions, it is important to define the population that the intervention will target. Some programs, like those focused

around education about diabetes management, are appropriate for all patients. But others may only be useful or cost-effective if they are limited to a specific population that will benefit most. One study showed that 20% of patients with T1D account for 80% of the hospitalizations for DKA, suggesting that there are certain populations for whom more aggressive prevention efforts may be warranted[18].

Primary prevention of DKA is more difficult to achieve than secondary prevention because it requires dissemination of information to the general public as well as primary care physicians. Families must be aware of the symptoms to look out for so that they seek care prior to the onset of DKA, and pediatricians must have a high level of suspicion for T1D when seeing a child with these concerning symptoms. The best-known study of primary DKA prevention occurred in Parma, Italy in the 1990s[6]. Researchers designed informational posters which were displayed in primary and secondary schools throughout the province; a total of 177 primary and secondary schools were covered. Additional posters were sent to pediatricians' offices, along with pocket cards with diagnostic guidelines for the healthcare professionals and supplies for testing fingerstick blood glucose levels. A telephone hotline was set up for families or physicians to call with questions and to get in touch with endocrinologists directly about a potential case of diabetes. 438,232 children age 6-14 lived in the three provinces studied, of whom 148 developed T1D over the 8-year period. The incidence of DKA in patients presenting with diabetes in Parma was only 12.5%, compared with 83% in a neighboring province without these interventions[6]. This primary prevention program was very successful in reducing the number of new-onset diabetes cases that presented in DKA, but this may not be the case if it were to be implemented in other settings. Italy has one of the highest

incidences of type 1 diabetes in the world[19], and primary prevention programs are only likely to be effective (and cost-effective) in areas with a relatively high prevalence of diabetes. In areas with a lower prevalence of diabetes, secondary prevention of DKA is more important.

Many DKA prevention programs do indeed focus on secondary prevention in patients with known diabetes. Office-based education programs are popular because they are low-cost and do not require additional time or commitment from families. One early study looked at a DKA prevention program in Los Angeles that involved focused teaching for families on the early symptoms of DKA, sick day guidelines, and having a provider available for consultation 24-hours per day. This program was able to reduce the incidence from 12 events to 4 events per 100 patient-years in the population of approximately 1,000 patients at their pediatric endocrinology practice; DKA incidence was the only outcome measured[15]. The tenets of this program were quite novel at the time, but have been widely adopted in the ensuing years. Having a provider available 24-hours per day for consultation, for example, has become standard of care for pediatric endocrinology practices.

Another intervention involved the creation of Care Ambassadors, who worked with families to remind them about appointments, and documenting the follow-ups as they occurred. 171 subjects (age 10-15) were randomized to standard care (n=82) or the Care Ambassador intervention (n=89). The Care Ambassadors helped families to schedule appointments, reminded them about the appointments when they were coming up, and followed up with families about any missed appointments, either over the phone or via mail. The data collected included HbA1c levels, hospital and emergency room

utilization, and frequency of severe hypoglycemia. Subjects were followed for two years. Hospital and emergency room usage was reduced by 50% in the intervention group, including for cases of DKA. There was no impact on HbA1c levels in aggregate, though those assigned to Care Ambassadors were less likely to have HbA1c values > 9.6[20]. Thus, we have examples of office interventions that effectively reduce the incidence and severity of DKA in people with known diabetes, and may positively influence other aspects of their diabetes management.

Many providers have worked to define the guidelines for sick day management, as errors in dosing insulin when endogenous requirements increase may result in DKA[1,21]. The tenets of these guidelines are consistent throughout the literature: monitor blood glucose and blood or urine ketones frequently, never stop insulin administration completely, watch for dehydration, treat the underlying sickness, and follow guidelines for adjusting insulin dosages[1]. Providers should review these recommendations with patients at least yearly, and be available by phone 24/7 to guide changing medication dosages in families that are uncomfortable making such changes on their own[21]. This can be cost-effective even though the program is expensive, because the prevention of even a single hospitalization for DKA can result in significant cost savings for the healthcare system. In 2008, revenues for a DKA hospitalization were over $5,000 in the United States[10].

As mentioned above, there are certain patients with recurrent DKA admissions that require more intensive or costly interventions. In one study, Ellis et al randomized families of 127 adolescents (10-17 years) with poorly controlled T1D to standard diabetes care or multisystemic psychotherapy (MST) for two years. MST is a home-based family

therapy, and those randomized to the intervention group received MST for six months to see if it would reduce incidence of DKA. The focus of MST was on alleviating barriers to adherence, including family-based issues, school-based issues, and health care system factors. Overall, the program was successful in its aims – the intervention group had significantly lower number of DKA admissions for 24 months following the intervention. Additionally, a decreased HbA1c was seen in the intervention group at termination of therapy, but this was not maintained six months after the therapy ended. More important than any of these outcomes, however, is the fact that the program was also cost-effective. While this program was relatively expensive (nearly $7,000 per family) it saved money overall due to decreased DKA admissions[10]. Such interventions must be targeted to the appropriate population (in this case, adolescents with chronic poor metabolic control) to be cost-effective. Another, more extreme intervention involved removing patients from dysfunctional families and placing them in foster care or residential treatment programs. The incidence of DKA was reduced from 1.14 to 0.29 episodes per patient per year. Obviously, it is important to carefully target such interventions to families that are unable to safely care for their children in the current environment[15].

No studies have been designed specifically to assess the impact of continuous glucose monitor (CGM) usage on DKA, but the issue of DKA has been addressed in studies on the utility of CGMs. People with diabetes who use CGMs have a much lower incidence of DKA than subjects who do not use them, but it is unknown whether this is due to confounding (because individuals using CGMs are more likely to manage their diabetes more carefully) or whether it is an effect of the technology itself[7]. One major randomized control trial assigned 322 children and adults to CGM treatment or a control

group of intensive diabetes management. There was only one episode of DKA in the study, in a subject in the control group, but the study was not powered to detect the difference in such rare events[22]. Still, it seems likely that CGM usage itself does lower incidence of DKA, as CGM devices alert patients to episodes of hyperglycemia early on so that they can be treated before serious DKA develops.

Researchers have found many successful ways to prevent DKA in patients with T1D. Office-based educational initiatives, with low cost and widespread applicability, are remarkably effective at reducing DKA incidence and hospital admissions. Patients requiring more targeted interventions may benefit from family psychotherapy or even placement in the foster care system. Yet despite having so many successful options for preventing DKA in various circumstances, rates of DKA have not decreased over the last few decades[23]. In a busy practice setting, it is difficult for clinicians to adhere to educational guidelines. Perhaps the lack of reimbursement from insurance companies discourages providers from taking the time to discuss sick day management with their patients. Maybe these methods have not been adopted by enough practices in the US to have an impact on national incidence rates. In any case, despite the evidence that secondary prevention strategies are effective in reducing DKA incidence, they have not been successfully incorporated into routine clinical use.

Purpose and Study Design

This study is a pre-post observational cohort study designed to assess the efficacy of an in-office educational module on sick day management in improving knowledge about DKA and reducing emergency department and hospital visits among children ages 0-18 in a pediatric practice. Subjects were recruited in a convenience sample from

patients in the waiting room at an academic pediatric endocrinology practice. The surveys were completed by the patient if they were over the age of 13, or the parent if the child was 13 years of age or younger. Each patient/parent was given a pre-test about DKA and sick day management and sent home with a printed algorithm for sick day management after reviewing sick day guidelines with their clinician (see Appendix 2). Six months to one year later, patients/parents were given a post-test to assess retention of the information. They were also asked about the number of emergency room visits in the previous year. The rest of the patients' diabetes care continued as usual, with regular office visits and lab testing. Clinicians were not reminded to review the sick day guidelines with patients during further regularly scheduled visits. It was hypothesized that reviewing these guidelines with patients at a single visit and sending them home with a printed algorithm would lead to long-term retention of the information about sick day management, and that emergency department visits would decrease following the intervention.

While the success of in-office interventions has been evaluated previously (see above), this study differs in that it additionally investigated the extent to which knowledge was retained. The majority of prior studies have looked at outcomes, but have not determined the ways in which these outcomes have been achieved. By using a pre- and post-test to assess the extent to which the information taught to families was retained, we tried to determine if patients were simply following an algorithm or if they internalized a better understanding of the issues at stake in sick day management. Additionally, the intervention was designed to work within the context of a busy clinical practice. It did not require changing the structure of diabetes management in the practice

or setting up additional resources for patients. Instead, it only required an education session on the use of the algorithm tool, and the printing and distributing of the algorithm itself. It could be implemented in almost any office setting in the United States for a very low cost.

Methods

A convenience sample of subjects was recruited from the waiting room of the pediatric diabetes clinic at a large academic practice. Subjects were asked if they were interested in learning more about sick day management and DKA. Inclusion criteria included having been diagnosed with type 1 diabetes and being treated by one of the pediatric providers at the clinic. There were no exclusion criteria. Those subjects who agreed to participate in the study were given a pre-test (see Appendix 1) with multiple choice questions about DKA and sick day management. The questions were divided into "skills" and "understanding" subsets to reflect skills in managing diabetes during sick days and knowledge of issues contributing to causes of DKA. Two different versions of the pre-test were administered, one for patients on multiple daily injections and one for patients on insulin pumps. Subjects above the age of 13 completed the test themselves. For those aged 13 or below, a parent or guardian who accompanied them to the appointment completed the test. Additional information on the number of emergency room visits, frequency of diabetes sick days, and frequency of calls to the diabetes emergency line were collected, as well as information on perceived comfort and support in their understanding and management of DKA. Emergency line calls and diabetes sick day frequency were measured via a Likert scale of frequency, where zero was least frequent and five was most frequent. Gender, age, duration of diabetes, and age at

diagnosis of diabetes were recorded from the electronic medical record. Hemoglobin A1c (HbA1c) levels were recorded from that day's visit. ZIP codes were collected from the chart as well, and the median income of that ZIP code was recorded as a proxy for socioeconomic status.

After the information was collected, the sick day management algorithm (see Appendix 2) was reviewed with the patients and their families. The algorithm is a step-by-step overview of what should be done in case of unexpected high blood glucose (BG) or nausea and vomiting. Patients are reminded to check ketones, and to change insulin pump sets, correct for high BG levels, repeat BG checks, and to take in supplemental fluids and carbohydrates as needed. The final endpoint for non-resolving hyperglycemia or ketonuria is to call the diabetes emergency line and speak with the on-call provider, rather than directly proceed to the emergency room. Subjects were sent home with a magnet version of the algorithm to refer to on sick days. The correct answers to the pre-test were also reviewed with subjects, to reinforce their knowledge about DKA and the important steps that must be taken during sick day management.

The follow-up encounter occurred six months to one year following the initial encounter. Subjects who had been recruited for the first phase of the study were approached at their regularly scheduled office visits over a period of six months. Subjects were asked about their use of the algorithm since they had received it, as well as sick day frequency, frequency of calls to the diabetes emergency line, and number of emergency room visits. They also completed a post-test with the same questions that they had answered on the pre-test. Subjects were given the same version of the test that they took prior to the intervention, even if their diabetes management had changed from injections

to pump or vice versa. Similarly, if the subjects' parents completed the pre-survey, the parents also completed the post-survey, even if the subject turned 14 during the follow-up period. HbA1c levels were recorded from this visit as well. Some providers used this as an additional opportunity to review sick day management with the patients.

The primary outcome was ED visit frequency; it was hypothesized that they would decrease following the intervention. Secondary outcomes included frequency of reported sick days and calls to the emergency line, which were hypothesized to increase following the intervention, and HbA1c levels, which were hypothesized to decrease, as better sick day management in patients with frequent sick days would alter average blood glucose levels. Finally, test scores were hypothesized to be higher following the intervention, showing that patients had retained the knowledge that they learned. With an alpha value of 0.05 and a standard deviation (determined from previous analyses) of 0.437, the study has a power of 0.835 to detect a difference of 0.15 ED visits per person-year if follow-up is conducted with 75 patients.

Descriptive statistics, univariate analyses, and pre-post comparisons were performed using SAS (version 9.4, SAS Inc. Cary, NC). Baseline sample characteristics were compared between those patients who did follow up and those who did not follow up to ensure that the group that followed up was representative of the study population. Paired t-tests and Wilcoxon signed rank tests were performed for the parametric and non-parametric values, respectively, to see if there was any significant difference before and after the intervention in the subset of patients who did follow up. An analysis was also performed comparing those subjects who could locate and had used the algorithm with those who had not used the algorithm. Finally, the results were dichotomized into those

patients who were greater than 13 years of age (who had completed the tests themselves) and those patients who were 13 years of age or less (whose parents had completed the tests). While these were both post-hoc analyses and the study was not necessarily powered to look at these sub-groups, these exploratory analyses are important categorizations to examine to determine the appropriate next steps in this research. It is possible that instructing parents on the best practices to care for their children will have different results from empowering teenagers to take better care of themselves.

The intervention and algorithm were designed by the research team prior to the student's involvement, as were the pre-intervention survey and test. The post-intervention survey was designed by the student. Follow-up data was collected by clinicians and the research team after the student reviewed each week's clinic schedule for enrolled patients. The student designed the data analysis plan and conducted all data entry and statistical analyses.

Results

Of the 244 subjects that completed the intervention, 76 completed the follow-up 6-12 months later. Baseline data between the two groups was compared to ensure that those who were lost to follow-up (LTFU) were not significantly different from those who did follow-up (table 1). Gender breakdown, age, duration of diabetes, age at diagnosis of diabetes, income, scores on the pre-test (including understanding and skills sub-scores), and number of emergency department visits were not significantly different between the two groups. HbA1c, however, was significantly lower in the LTFU group than in the group that did follow up (8.05 vs. 8.55, p=0.034).

Table 1: Subjects who followed up compared with lost to follow-up (LTFU)

	Followed up (n=76)	LTFU (n=168)	p-value*
Gender	55% male	52% male	0.614
Age	13.86	14.01	0.804
Duration of diabetes (years)	5.71	6.34	0.460
Age at diagnosis of diabetes (years)	8.15	7.79	0.547
Income (dollars)	83,511	90,262	0.214
HbA1c (%)	8.55	8.05	**0.034**
% correct	55.0%	56.3%	0.703
Understanding sub-score	53.2%	54.5%	0.730
Skill sub-score	56.4%	57.6%	0.777
ED Visits (visits per person-year)	0.22	0.22	0.993

*p-values from paired t-test, chi square test

For subjects who did complete the follow-up, test scores, HbA1c levels, ED visits, and sick day and emergency line call frequency were all compared before and after the intervention (table 2). HbA1c decreased (8.55 before vs. 8.35 after), though this was not statistically significant (p=0.336). The scores of the post-test were significantly higher than the pre-test; prior to the intervention, subjects averaged 55% correct, while after the intervention they averaged 61.6% correct (p=0.007). The sub-score for understanding about DKA was also significantly higher (59.2% after vs. 53.2% prior; p=0.019), while

the skills sub-score, though higher, did not achieve statistical significance (63.3% after vs. 56.4% prior; p=0.059). Emergency department visits were also lower (0.13 per person-year versus 0.22 per person-year), though this was not statistically significant (p=0.070). Subjects did call the emergency line more frequently (1.20 after vs. 0.86 prior; p=0.032), and recognized more diabetes sick days (1.57 after vs. 1.17 prior; p=0.014).

Table 2: Pre-Post comparisons (n=76)

	Mean before	Mean after	Difference	p-value*
HbA1c (%)	8.55	8.35	-0.20	0.336
% correct	55.0%	61.6%	6.6%	**0.007**
Understanding sub-score	53.2%	59.2%	6.1%	**0.019**
Skill sub-score	56.4%	63.3%	7.0%	0.059
ED Visits (visits per person-year)	0.22	0.13	-0.09	0.070
Diabetes sick day frequency (Likert scale)	1.17	1.57	0.39	**0.014**
Emergency line call frequency (Likert scale)	0.86	1.20	0.34	**0.032**

*p-values from paired t-test, Wilcoxon signed rank test

An analysis was performed to determine if there were different outcomes between those who did not use the algorithm magnet and those who knew where the magnet was

located in their home or had referenced it (those who had used the magnet). Initially, the baseline demographics were compared between these groups. Gender, age, duration of diabetes, age at diagnosis of diabetes, income, and HbA1c did not differ significantly between these groups (table 3), though HbA1c was non-significantly higher in the group that did not use the algorithm (8.77 vs. 8.32; p=0.290). In comparing the outcomes after the intervention in those who actually referenced the magnet (table 4), the differences in HbA1c and emergency department visits remained statistically non-significant. The percent correct on the post-test remained significantly higher following the intervention (66.2% after vs. 57.6% prior; p=0.029). The understanding and skills sub-scores, however, were not significantly different (p=0.117, p=0.125, respectively). Frequency of diabetes sick days (1.88 after vs. 1.26 prior; p=0.013) and emergency line calls (1.68 after vs. 1.09 prior; p=0.013) were significantly higher following the intervention in this group.

Table 3: Baseline characteristics of those who used the algorithm vs. all who followed up

	Didn't use algorithm(n=39)	Used algorithm (n=34)	Didn't answer (n=3)	p-value* (used vs didn't use)
Gender	56% male	53% male	66% male	0.766
Age (years)	13.54	14.18	14.33	0.543
Duration of diabetes (years)	5.68	5.91	3.73	0.827

Age at diagnosis of diabetes (years)	7.86	8.26	10.60	0.683
Income (dollars)	81,985	79,600	147,680	0.783
HbA1c (%)	8.77	8.32	8.37	0.290

*p-values from chi square test or ANOVA test

Table 4: Subjects who used the Algorithm (n=34)

	Mean before	Mean after	Difference	p-value*
HbA1c (%)	8.32	8.34	0.01	0.957
% correct	57.6%	66.2%	8.6%	**0.029**
Understanding sub-score	55.9%	62.4%	6.5%	0.117
Skill sub-score	58.8%	68.9%	10.1%	0.125
ED Visits (visits per person-year)	0.147	0.059	-0.09	0.183
Diabetes sick day frequency (Likert scale)	1.26	1.88	0.62	**0.013**
Emergency line call frequency (Likert scale)	1.09	1.68	0.59	**0.013**

*p-values from paired t-test, Wilcoxon signed rank test

One additional post-hoc analysis was performed, comparing those subjects over the age of 13, who completed the pre- and post-tests themselves, with those subjects age 13 or younger, whose guardians completed the pre- and post-tests. There were 42 subjects over the age of 13 (table 5). In this subgroup, HbA1c did not change over the course of the study (8.59 after vs. 8.54 prior; p=0.833). The scores on the post-test were not significantly higher either overall (60.9% after vs. 55.8% prior; p=0.089), or in either of the sub-scores (understanding: 58.6% after vs. 55.2% prior; p=0.280; skills: 62.6% after vs. 56.1% prior; p=0.209). Reported frequency of diabetes sick days was higher, though not significantly so (1.62 after vs. 1.26 prior; p=0.122), while emergency line call frequency remained significantly higher following the intervention (1.05 after vs. 0.60 prior; p=0.044). In this sub-group, emergency department visits did decrease significantly (0.10 per person-year after vs. 0.21 per person-year prior; p=0.024).

Table 5: Age>13 (n=42)

	Mean before	Mean after	Difference	p-value*
HbA1c (%)	8.54	8.59	0.06	0.833
% correct	55.8%	60.9%	5.1%	0.089
Understanding sub-score	55.2%	58.6%	3.3%	0.280
Skill sub-score	56.1%	62.6%	6.5%	0.209
ED Visits (visits per person-year)	0.21	0.10	-0.12	**0.024**

Diabetes sick day frequency (Likert scale)	1.26	1.62	0.36	0.122
Emergency line call frequency (Likert scale)	0.60	1.05	0.45	**0.044**

*p-values from paired t-test, Wilcoxon signed rank test

There were 34 subjects age 13 or younger (table 6). HbA1c decreased in this group, though not significantly (8.06 after vs. 8.57 prior; p=0.107). The subjects' parents had higher overall scores on the post-test (62.5% after vs. 54.2% prior; p=0.039) as well as higher understanding sub-scores (60.0% after vs. 50.6% prior; p=0.030), though the skills sub-scores were not significantly higher (64.3% after vs. 56.7% prior; p=0.158). Emergency department visits were unaffected by the intervention (0.18 per person-year after vs. 0.24 per person-year prior; p=0.535). Frequency of diabetes sick days (1.50 after vs. 1.06 prior; p=0.066) and calls to the emergency line (1.38 after vs. 1.18 prior; p=0.461) were both higher, though the differences were not statistically significant.

Table 6: Age<=13 (n=34)

	Mean before	Mean after	Difference	p-value*
HbA1c (%)	8.57	8.06	-0.51	0.107
% correct	54.2%	62.5%	8.3%	**0.039**
Understanding sub-score	50.6%	60.0%	9.4%	**0.030**
Skill sub-score	56.7%	64.3%	7.6%	0.158

ED Visits (visits per person-year)	0.24	0.18	-0.06	0.535
Diabetes sick day frequency (Likert scale)	1.06	1.50	0.44	0.066
Emergency line call frequency (Likert scale)	1.18	1.38	0.21	0.461

*p-values from paired t-test, Wilcoxon signed rank test

Discussion

The sick day management intervention successfully improved recognition of diabetes sick days, increased utilization of the emergency line, and subjects had improved scores on the post-test compared with the pre-test. Emergency department visits were decreased among all sub-groups, and this decrease was statistically significant for subjects > 13 years old. Subjects retained the information that they learned and applied it in recognizing their own diabetes sick days and calling the emergency line first rather than going directly to the emergency department.

The initial analyses were performed to determine if there were any systematic differences between those who were approached for a follow-up survey and those who were not. If the subjects who did not follow up did so because they were skipping appointments, they might be more likely to have poor control and thus more likely to have emergency department visits for DKA. The goal was to ensure that those who followed up were a representative sample of the entire study population. Table 1 shows

that the two groups were similar in nearly all of the baseline criteria measured. Even the pre-test scores and sub-scores were not significantly different. Emergency department visits were nearly identical. The one measure that was different between the two groups was HbA1c: the pre-intervention average for those who followed up was 8.55 while for those who did not follow up it was 8.05. Individuals with higher HbA1c levels have higher BG levels as well, and it is known that these patients might be expected to be more likely to develop DKA. If anything, the subjects who did follow up are more likely to experience DKA. Therefore, it does not appear that the intended target population of patients who are likely to develop DKA was missed due to poor follow-up.

Loss to follow-up is a multifactorial issue, and could be related to the design of the study. When the initial intervention was given, subjects were not told a specific date for the follow-up; instead, members of the research team approached them in the waiting room before their regularly scheduled doctor's appointments. The research team was not in the office every day, and could have missed subjects who came on days that they were not available. Additionally, if several subjects arrived at the same time, it is likely that only one received the follow-up survey. As was discussed above, patients who frequently miss appointments were less likely to be present for the follow-up appointment. Most of these are non-differential, and the statistical analysis of the data from the first survey seems to confirm that the group that followed up is a random, representative sample of the entire study population.

In this study, subjects served as their own controls; the control period of one year prior to the intervention was compared with the year following the intervention, to remove some of the possibility of confounding. Statistical analyses were performed with

paired t-tests to reflect this fact. It is unsurprising that there was no significant difference in HbA1c between the two time points, as this intervention was not designed to reduce HbA1c. There were, however, significant increases in pre- and post-test scores, both overall and for the understanding sub-score. The skills sub-score was not significantly impacted. Subjects thus retained information even up to a year after the intervention took place. The significant increase in understanding sub-score suggests that much of the information retained from the intervention related to what DKA is and how dangerous it can be. The fact that the skill sub-score was not significantly different is likely related to the power of the study to detect this difference (see below), as the p-value was borderline at 0.059, though it is possible that subjects simply may not have remembered the specific steps they should take to manage diabetes sick days.

The true significance of the improved test scores, however, lies in the ensuing behavior of the subjects. The intervention was designed to increase patient awareness of diabetes sick days, improve utilization of the emergency line, and decrease emergency room visits. It does seem that subjects recognized more diabetes sick days over the year following the intervention; it is unlikely that this group of patients suddenly started getting sick more frequently. It is more likely that a review of the definition of diabetes sick days helped them to more appropriately identify their occurrence. This is important because people with diabetes should be checking ketone levels when they are sick regardless of whether they have elevated BG levels.[1] Identification of these sick days is the first step in safer management. The frequency of calls to the emergency line also significantly increased. The algorithm directed subjects to call the emergency line in several different situations if basic home management was not effective in reducing BG

levels or ketones. While it is possible that subjects did not follow all of the recommendations on the algorithm every time they were ill, it seems that they remembered the importance of calling the emergency line for help. It is possible that these increased calls led to better home management of diabetes sick days and prevented families from having to bring their children to the emergency department. Proper management of ketonuria can help avoid decompensation to DKA and the need for more aggressive (and expensive) medical treatment in the emergency department or inpatient setting. That being said, there was not a significant decrease in self-reported emergency department visits. There were fewer visits per person-year (0.13 per person-year after vs. 0.22 per person-year before) following the intervention, but it was not statistically significant.

By examining the overall results, it was found that over 50% of the subjects had not used the algorithm, did not remember receiving the algorithm, or could not currently locate the algorithm. It was thus important to perform an analysis to examine whether there were different effects in the subgroup that could locate the algorithm or had used it in the intervening period. This analysis will provide the efficacy of this intervention under ideal adherence conditions, while the full sample analyses provided the effectiveness, which assesses the intervention in real-life settings.

First, the baseline demographics were compared between the group that did not use the algorithm (n=39), those that did use the algorithm (n=34), and those who did not answer the question (n=3). None of the differences were statistically significant, as can be seen in table 3; gender, age, age at diagnosis of diabetes, duration of diabetes, and income were all extremely similar, and the p-values were not significant. With these baseline

factors that were measured, there is no way to predict which subjects are more likely to use the algorithm following the intervention. It is interesting to note that subjects with lower HbA1c levels, and better control of their diabetes overall, were more likely to have used the algorithm, though this difference in HbA1c levels was not statistically significant.

In the group that did use the algorithm, the HbA1c was not significantly different following the intervention, and indeed was slightly higher. The overall scores on the pre- and post-tests remained significantly higher, but there were no differences in the understanding and skills sub-scores. This study was underpowered for subgroup analyses, however, so it is difficult to interpret these results accurately. It is possible that the sub-scores are actually different but with a smaller number of subjects in this group (39 versus 76 in the overall group), we cannot detect such a small change. The fact that the overall percent correct remains significantly higher suggests that this group of subjects also retained the information that they learned in the intervention and practiced by using the algorithm on sick days.

The reported frequency of diabetes sick days and calls to the emergency line remained significantly higher after the intervention in the group that used the algorithm as well. This group of subjects also recognized the signs of diabetes sick days more often, and called the emergency line more frequently. The absolute differences before and after the intervention are higher among these subjects (0.62 and 0.59, respectively), than among the group as a whole (0.39 and 0.34, respectively), though these numbers were not compared statistically. Still, it seems as though the subjects who used the algorithm may have had a greater gain in positive habits than the group as a whole.

Emergency department visits were not significantly lower in the subgroup of subjects who used the algorithm, and the absolute difference (-0.09 visits per person-year) is the same as in the overall group. The non-significant p-value, then, is likely not due to the smaller sample size in the subgroup. Instead, it seems that using the algorithm does not prevent any more emergency department visits than simply going through the brief in-office portion of the intervention. This was a bit unexpected, given that the algorithm was, in part, designed to get subjects to call the emergency line rather than go directly to the emergency department when feeling ill. One possible explanation is that the subjects retained the most important part of the intervention: to call the emergency line when they are not feeling well. While those who used the algorithm likely had already completed most of the home management when they called the line, those who did not use the algorithm were likely guided through the steps of the algorithm by the on-call provider to whom they spoke. Going through the in-office portion, then, may be the most effective part of this intervention, and referencing the algorithm at home is less effective at impacting the major endpoints.

One additional subgroup analysis was performed, dichotomizing the subjects by age $\leq$13 and >13. Subjects aged 13 and younger had the surveys and tests filled out by their parents, while subjects older than 13 filled out the tests themselves. Furthermore, with the older subjects, an attempt was made to direct the educational intervention at the subjects themselves rather than at the parents or guardians. This was also a post hoc analysis, as this study was not designed to look at subgroups. It was important to perform this subgroup analysis, however, because the intervention was performed somewhat

differently in the two groups, and perhaps the intervention was more effective in one of these subgroups. If that is the case, that group should be targeted in any future studies.

The study had 42 subjects older than 13. Once again, HbA1c was not significantly affected by the intervention. Surprisingly, however, the pre- and post-test scores were also not significantly different, neither in the total percentage correct nor in the understanding or skills sub-scores. Perhaps these teenagers were not paying as close attention to the intervention as the parents of younger children did, or perhaps they simply did not retain the information as well or as concretely as the parents. Once again, statistical power could play a role.

As was stated above, however, it is more important to look at the impact of the intervention on clinical health behaviors and outcomes rather than on test scores, the clinical significance of which is unknown. Reported diabetes sick day frequency was not significantly increased, though the absolute difference is similar to that seen in the total group. In keeping with the lack of significance in the changes in test scores, it is possible that the teenaged group simply did not retain the definition of diabetes sick days as well as the parents of younger children. Emergency call line frequency, however, was significantly higher following the intervention. It is possible that this group of subjects remembered little from the intervention except to call the diabetes emergency line when they are sick, and this was the way in which the intervention had its impact.

Subjects older than 13 were the only subgroup in which emergency department visits were significantly lower. There were 0.21 visits per person-year in the year prior, and 0.10 visits per person-year in the year following the intervention ($p=0.024$). There are several possible explanations for this result. It could be solely due to chance, especially

given that this was a post-hoc analysis; the study needs to be replicated with a larger sample size before we can definitively conclude that this intervention reduces emergency department visits among older subjects. But it is possible that, when the teenagers began calling the emergency line more frequently, they were able to manage ketonuria at home under the guidance of their medical team, prevent it from developing into DKA, and were able to avoid an emergency department visit. Even if calling the emergency line is the only habit that the greater than 13 age group gained from this intervention, it was successful in reducing emergency department visits and likely reduced costs to the subjects' families as well as to the healthcare system as a whole.

There were 32 subjects aged 13 and younger in this study, and their parents filled out the surveys on their behalf. HbA1c values in this subgroup decreased slightly, but not significantly ($p=0.107$), which is expected given the nature of the intervention. Pre- and post-test scores were significantly higher in both the overall and understanding sub-scores; skill sub-scores were once again not significantly different. It is unsurprising that these adults had good recall of the information presented to them up to a year previously. It is likely that the parents paid close attention to the intervention when it was being presented, and they may have been more worried about the possibility of severe DKA than the teenagers who filled out the surveys themselves.

Unlike the overall analysis, however, the increased frequency of diabetes sick days and calls to the emergency line after the intervention was not statistically significant. For emergency line call frequency, the mean before the intervention was almost double the mean at the same time point for the older group of subjects. Thus it's possible that the parents were not as reluctant to ask for help or remembered about the availability of the

emergency line more regularly. Perhaps the parents were using the emergency line appropriately, and the intervention only invoked a slight increase in its usage. When teenagers take over their own care, they potentially do not utilize the resources available to them as readily as parents who are worried about their children, and this intervention increased their utilization. As in all of the subgroup analyses, this could also be an issue of statistical power, but it could also be that the parents for some reason did not internalize the definition of diabetes sick days as well as the older subjects did. It is also possible that the younger children do not always tell their parents about their symptoms and the parents are unaware of the true number of diabetes sick days.

It is also important to consider the different etiologies of diabetes sick days in these subgroups. The illnesses that younger children contract can be more severe, and the more frequent emergency department visits may be merited. Younger children also may not be able to identify when they are starting to get sick, and sick day management steps cannot be taken until later in the course of the disease. While adolescents may be able to force themselves to drink water when dehydrated and take other difficult management steps while sick, younger children may be unwilling to take such steps, and thus may require emergency department care or hospitalization. There are cases in which home management is insufficient, and there may be more of these in the group age 13 and under.

The subjects 13 years old or younger comprised the subgroup for whom emergency department visits decreased the least: a difference of only 0.06 visits per person-year. The fact that they were already calling the emergency line more regularly means that they were getting appropriate advice from the on-call provider about how to

manage sick day complications more often. Perhaps a larger percentage of the emergency department visits were merited in this subgroup, and the intervention was not able to have as much of an impact because parents were already following the advice of the on-call providers, which was similar to the information codified in the algorithm. It is also possible, however, that the intervention was not as effective in this subgroup for some reason.

While statistical significance was limited to the >13 years of age group, there were decreases in emergency department visits among all of the groups analyzed, and an estimate of the cost savings of this intervention can be quantified. In an analysis of all subjects, emergency department visits were decreased by 0.39 visits per person-year. Among the 76 subjects, this amounts to nearly 30 events avoided in the year of the study. It can be assumed that the baseline number of ED visits for non-DKA-related issues did not significantly change and that the majority of these emergency department visits avoided were secondary to DKA. Using the figure of $11,000 per DKA hospitalization from Bismuth and Laffel[2], cost savings to the healthcare system could be as high as $330,000. A formal cost effectiveness analysis will need to be conducted, but the initial calculations are quite promising.

There are some limitations inherent to the design of this study. First and foremost, it was not designed for subgroup analyses, and the data from the subgroup analyses cannot be considered definitive without repeating the study with a larger sample size. Both of the subgroup analyses have solid justifications (the analysis focusing on those who used the intervention to determine the efficacy of this intervention in addition to the effectiveness; the age dichotomization because the intervention was delivered differently

to these two groups) but issues of sample size and power could have led to increased type II error and some results being biased toward the null. Additionally, the study may have been under-powered even when conducting analyses of the full data set. With 76 subjects, a power of 0.8, a type I error of 0.05, and a standard deviation of 0.437, the detectable difference for emergency department visits would be +/- 0.142 per person-year. To look at one specific example, the difference in emergency department visits before and after the intervention when analyzing the entire sample was -0.09. With the sample size in this study, we cannot detect a difference this small. Thus, the insignificance of this result could be because the study was underpowered rather than because the intervention did not impact emergency department usage. This topic will need to be studied further with a larger sample size to determine whether or not the intervention truly impacts emergency department visits. Questions of power and sample size came up in all of the subgroup analyses, and several of the main analyses had borderline p-values, such as the skills sub-score on the pre-/post-test, and change in emergency department visits. This is a fundamental issue with the study, and it is difficult to interpret these results without further studies.

Only about one third of the subjects completed the follow-up survey six months to one year following the intervention. While analyses were performed to ensure that those patients who did follow up were a representative population of the subjects in the initial phase of the study, there are many potential confounding factors that were not measured. The 76 subjects who did complete the follow-up survey could have been, in some way, systematically different from the group as a whole. This was partially ameliorated by the fact that each subject served as his or her own control, comparing the period prior to the

intervention to the period following the intervention. Thus, only the subjects who followed up were included in the means of the pre-intervention measures. While this does help the results to be more accurate, it would be better to have achieved better follow-up with the subjects.

Each subject serving as his or her own control is an excellent design for avoiding confounders, but the passage of time does complicate the interpretation of the results. It is unknown what would have happened in the ensuing year had the subjects not received the intervention. Perhaps as one subject aged, he or she would have started calling the emergency line more frequently regardless of the intervention. Maybe emergency department visits would have increased significantly as another subject aged, but instead they only increased slightly. It is impossible to know what would have happened without the intervention. Perhaps the study could be repeated as a randomized control trial with a comparable control group, though it would then be difficult to correct for all of the necessary confounders.

The use of self-report of emergency line calls and emergency department visits might be called into question; some might prefer to use physician records of such events. Previous studies, however, have shown that physicians do not always ask patients about these episodes and that their records may not be complete. Indeed, self-report is actually more accurate in determining the number of episodes, as patients are likely to remember significant events like emergency department visits[12].

The study was conducted at a single location, in an academic pediatric endocrinology practice in an urban area. These results cannot be generalized to the entire population of people with T1D, even those in the United States, because there may be

very different clinical settings and barriers to care. Interventions like this would need to be repeated in varied settings to ensure that they are effective in other contexts. Specifically, it would be difficult to extend these results to areas where emergency care is difficult to access or to any clinics without an emergency line.

Finally, most subjects had something between six months and one year between the initial intervention and the follow-up. Yet, they were asked about their emergency department visits, emergency line usage, and diabetic sick days over the past year. For many subjects, there was likely some overlap between the two one-year periods. This would have biased results towards the null, as events that occurred prior to the intervention would have been included in the post-intervention period. A design with discrete study visits, rather than finding subjects at their normal appointments, could have prevented this issue, but may have missed some of the less-adherent patients who could be uninterested in extra visits to the physician's office.

There are several future directions in which this research should proceed. The need for a similar study with a larger number of subjects has already been mentioned several times, as this would solve some of the problems with statistical power that were encountered in this study. The study could even be repeated in the same clinic setting and give new results; the clinic has now switched over to an electronic medical record, and all calls to the emergency line are recorded in each patient's medical record. Historical report was the best option for data collection at the time of the study, but in the future data could be pulled from the chart directly without having to rely on patient report for emergency line usage. Longer-term follow-up would also be interesting; the fact that the effects were seen a year after the intervention is encouraging, but it would be useful to

know how frequently this information should be presented to families and reinforced in order to continue to reduce emergency department visits and increase recognition of diabetes sick days. As mentioned above, a randomized control trial that randomizes subjects to standard care or to receive the intervention would be the study design that most definitively answers the question of this intervention's efficacy.

A physical, printed algorithm may not be the best way to reach the target population of this intervention. A study could be designed that targets subjects older than 13, perhaps with the algorithm in app form for smartphones so that it is always accessible. A qualitative study, with focus groups of subjects, could explore how people are using the algorithm and whether or not subjects approach sick day management differently, in order to discover why this intervention was effective. Finally, a cost effectiveness analysis should be undertaken to determine if such interventions save money for families and insurance companies. Such sessions are unlikely to be adopted in a widespread fashion unless insurance companies will reimburse for them, and this analysis would be the first step in securing such reimbursements.

In summary, this study was designed to investigate if a brief in-office intervention on sick day management, as well as a take-home algorithm, could help reduce risk of DKA by increasing recognition of diabetic sick days and calls to the emergency line and reducing emergency department visits. It was found that subjects retained the information they were taught, even up to a year after the intervention, and that they recognized sick days and called the emergency line more regularly. Teenage subjects had fewer emergency department visits following the intervention, though younger subjects did not. This intervention was successful in its aims, and could result in improved health

outcomes and decreased costs to the healthcare system. It should be examined in other contexts and in a targeted fashion for teenagers with diabetes to see if it is a generalizable intervention that could be routinely delivered to those patients at highest risk for DKA.

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Appendix 1: Pre- and Post-Tests

Part I: Understanding (*circle the **ONE BEST** answer*)

1. Which of these is a diabetes sick day?
    a. Being tired and having a headache
    b. Having a temperature of 99.5 but able to eat
    c. Having a cold with a little cough and a runny nose
    d. Vomiting or nauseated and can't eat

2. Ketones are:
    a. Acids that can be dangerous when they build up in the blood
    b. A sign that the body doesn't have enough insulin
    c. Made by the body when it uses fat for energy instead of sugar
    d. All of the above

3. What is true about ketones?
    a. They happen because there is not enough insulin in the body
    b. They don't happen when blood sugar is low or normal
    c. They are caused by eating too much
    d. All of the above

4. What makes diabetic ketoacidosis (DKA) a medical **emergency**?
    a. Ketones in the urine can hurt the kidneys
    b. Ketones make the blood like an acid so the body's organs shut down
    c. Blood sugar levels over 300 can cause long-term problems
    d. It can make it more likely to have a very bad low blood sugar reaction

5. What are the **specific** signs that you are in diabetic ketoacidosis (DKA)?
    a. Peeing and drinking more
    b. A headache, cough, and fever
    c. Vomiting, stomach pain, and difficulty breathing
    d. All of the above

Part II: Skills (*circle the **ONE BEST** answer*)

6. How often should you test blood sugars when sick?
    a. Before meals and at bedtime
    b. Every thirty minutes for one full day
    c. Every 2-3 hours until you feel better
    d. Every 2-3 hours until the blood sugar is below 300

7. What is **NOT** good to eat or drink while vomiting and blood sugar levels are low?
    a. Popsicles
    b. Sips of regular juice or soda
    c. Chocolate milk
    d. Lollipops

8. When should you **stop** giving insulin?
    a. When blood sugar is less than 100 mg/dL
    b. Never
    c. When vomiting and unable to eat
    d. When drinking lots of water

9. All of these are times to test for ketones **EXCEPT**:
    a. If your blood sugar is over 300 one time
    b. If blood sugar stays over 300 for a few hours
    c. If vomiting and blood sugar is over 300
    d. If vomiting, no matter your blood sugar level

10. (pump version) What should you do **FIRST** when you have ketones and a blood sugar over 300 first thing in the morning?
    a. Increase basal insulin rates and give correction by pump
    b. Give correction by injection and change pump site
    c. Drink water and exercise
    d. Go to the emergency room

10. (injection version) What should you do **FIRST** if blood sugar is 300 and there are small ketones and nausea first thing in the morning?
    a. Take morning insulin and recheck glucose and ketones in 2 hours
    b. Call the diabetes emergency line right away
    c. Drink lots of water and exercise
    d. Go directly to the emergency room

11. You should call the Diabetes <u>Emergency Line</u> if:
    a. Ketones are moderate or large
    b. Vomiting persists for 3 or more hours
    c. Blood sugar is running very low or very high for a few hours
    d. All of the above

Write the clinic's phone number and which button to push for the emergency clinician here: _____

Appendix 2: Sick Day Management Algorithms