Published in final edited form as:

Pediatr Diabetes. 2017 September ; 18(6): 422–427. doi:10.1111/pedi.12410.

Ketone production in children with type 1 diabetes, ages 4 to 14 years, with and without nocturnal insulin pump suspension

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Abstract

Objective—To compare the frequency of elevated morning blood ketone levels according to age in 4–14 year olds with type 1 diabetes following overnight use of an automated low glucose insulin suspension system, or following control nights when the system was not used.

Research Design and Methods—For 28 children ages 4–9 years and 54 youth ages 10–14 years, elevation of morning blood ketone levels was assessed using the Precision Xtra Ketone meter following 1,155 and 2,345 nights, respectively. Repeated measures logistic regression models were used to compare age groups for blood ketone level elevation following control nights (system not activated) and following intervention nights with and without insulin suspension.

Results—Elevated morning blood ketones (≥ 0.6 mmol/L) were present following 10% of 580 control nights in the 4–9 year olds compared with 2% of 1162 control nights in 10–14 year olds ($P < 0.001$). Likewise, the frequency was greater following intervention nights in the younger age group (13% of 575 nights versus 2% of 1183 nights, $P < 0.001$). A longer duration of pump suspension resulted in a higher percentage of mornings with elevated blood ketones in the younger age group ($P = 0.002$), but not in the older age group ($P = 0.63$). The presence of elevated morning ketone levels did not progress to ketoacidosis in any subject.

Conclusions—Elevated morning blood ketones are more common in younger children with type 1 diabetes with or without nocturnal insulin suspension. Care providers need to be aware of the differences in ketogenesis in younger age children relative to various clinical situations.

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*Full listing of the members of the study group is included

Keywords

Type 1 Diabetes; Ketosis; Pediatric; Insulin Pump

Introduction

For patients with type 1 diabetes, prompt detection of ketosis is important in the prevention of diabetic ketoacidosis (DKA). A number of reports have shown under experimental conditions, primarily in adults, that insulin delivery can be stopped for several hours before elevated blood ketone levels develop (1–9). In patients with type 1 diabetes, aged 15–45 years, we previously described the frequency of elevated blood ketone levels in the morning after 1,954 nights in participants in a randomized trial evaluating an automated nocturnal predictive low glucose suspend (PLGS) system (5, 10). Results showed that the frequency of elevated blood ketone levels was similar (all $\approx 1\%$) after control nights, or after intervention nights when an insulin pump suspension occurred or did not occur. Even with 2–3 hours of overnight insulin suspension, the presence of blood ketone levels ≥ 0.6 mmol/L was uncommon ($\approx 1\%$) in this age group. However, the development of ketosis in younger patients with type 1 diabetes using insulin pumps with interruption of insulin delivery has not been well studied. Determining the risk for ketosis is necessary in order to evaluate the safety of such systems for use in young children, and to improve these systems for use in the pediatric population.

Elevated blood ketones occur in children with and without diabetes mellitus as a result of fasting and of insulinopenia, and may occur in increased quantities in younger children (11–14). Younger children have now been studied as an extension of the predictive low glucose suspend (PLGS) system investigations described above (15), providing a large dataset for an adjunctive comparison of morning blood ketone levels in two groups of children, ages 4–9 and 10–14 years.

Study Design and Methods

The data utilized for the analyses reported herein were collected as part of a multi-center randomized controlled random order intervention crossover design trial to assess the efficacy and safety of an overnight PLGS system, the primary results of which have been published (15). The protocol, conducted at three clinical centers, was approved by each Institutional Review Board and written informed consent was obtained from each participant or parent, with assent obtained as required. An independent data and safety monitoring board provided oversight. The study is listed on clinicaltrials.gov (NCT01823341). Key aspects of the study protocol are described below.

Study participants were post hoc grouped in two age cohorts based on observed and predicted frequency of morning ketone ≥ 0.6 mmol/L (Supplemental Figure 1). The younger cohort included 28 individuals with type 1 diabetes (50% male, 93% Caucasian) age 4 to 9 years, with median type 1 diabetes duration of 4 years, median body mass index (BMI) percentile 67 (interquartile range 51–79), and mean $\pm$ standard deviation ($\pm$ SD) glycated hemoglobin level of $7.9\% \pm 0.4\%$ (Table 1). The older cohort included 54 individuals with

type 1 diabetes (52% male, 96% Caucasian) age 10 to 14 years, with median type 1 diabetes duration of 5 years, median BMI percentile 69 (interquartile range 43–84), and mean ($\pm$ SD) glycated hemoglobin level of $7.7\% \pm 0.6\%$.

The pump suspension system consisted of a MiniMed Paradigm® REAL-Time Veo™ System and Enlite™ glucose sensor (Medtronic Diabetes, Northridge, CA), in which the continuous glucose monitor (CGM) and pump communicated with a bedside laptop computer which contained a Kalman-filter based hypoglycemia prediction algorithm (referred to as “the system”). On control nights, there was no automated suspension of insulin delivery. On intervention nights, insulin delivery was suspended when the glucose level was predicted to be below 80 mg/dL in the next 30 minutes. Basal insulin delivery resumed with the first rise in glucose during insulin suspension. Maximum pump suspension was 120 minutes within a 150 minute window, with a maximum cumulative total of 180 minutes each night. A bedside laptop computer contained a randomization schedule which determined whether the hypoglycemia prediction algorithm would be in operation that night (intervention night) or would not be activated (control night), to which the participant was blinded, with half of the 42 nights being intervention nights and half control nights. Participants were instructed to measure blood glucose (with Bayer Contour® Next Link and Bayer Contour® Next USB, Bayer HealthCare LL, Whippany, NJ) and blood ketone (with Precision Xtra meter, Abbott Diabetes Care, Alameda, CA) each morning after waking up and stopping the system, which transmitted the results to the study coordinating center. Ninety percent of the blood ketone values were taken between 6:00AM and 10:00AM, and the percent did not differ by treatment arm.

Blood ketone levels > 0.6 mmol/L were considered abnormal (16). Families were instructed not to activate the PLGS system if the participant was ill or if blood glucose was outside the range 90–270 mg/dL at bedtime. Families of participants with morning blood ketone values > 1.0 mmol/L were contacted by research staff the same morning, and in all cases the results returned to normal within a few hours. During the day, the participant used the CGM device and pump as it would be prescribed for usual diabetes management (without the algorithm being active).

Statistical Methods

The current analysis included 3,500 out of 3,606 randomized nights where a blood ketone measurement was available the following morning.

Cubic spline smoothing was used to estimate the probability of elevated morning blood ketone levels (> 0.6 mmol/L) as a function of patient age. Separate curves were fit for mornings following control and intervention nights. Repeated measures regression models were used to test the effect of age on the duration of pump suspension and morning glucose levels. Separate repeated measures logistic regression models were used to test the effect of age and BMI percentile on elevated morning blood ketone levels (> 0.6 mmol/L) and of age on the frequency of pump suspension; and to assess the effect of pump suspension, pump suspension duration, and morning glucose levels on elevated morning blood ketone levels (> 0.6 mmol/L). All separate control and intervention models included random subject effects and a within participant autocorrelation structure to account for correlated data due to

multiple mornings from the same participant. All reported P-values are two-sided. Statistical analyses were conducted using SAS version 9.4 software (SAS Institute Inc., Cary, NC).

Results

Analyses utilized the data from 575 intervention nights (PLGS system active, including nights with and without pump suspension) and 580 control nights (standard pump and CGM use without automated PLGS system active) in 4–9 year olds and 1183 intervention nights and 1162 control nights in 10–14 year olds.

Following control nights, the frequency of morning blood ketones ≥ 0.6 mmol/L decreased with increasing participant age ($P < 0.001$, Supplemental Figure 1), and was 10% in 4–9 year olds versus 2% in 10–14 year olds (Table 2). The difference in frequency of elevated morning blood ketones between the two age groups was not affected by adjusting for duration of sleep (time between system activation and deactivation), which on average was longer in the younger age group (median hours of system use per night 9.9 versus 9.3). Preceding control nights, the frequency of bedtime snacking was 41% for the 4–9 year olds and 43% in the 10–14 year olds. The subsequent frequency of morning blood ketones ≥ 0.6 mmol/L was similar with and without a bedtime snack in the 4–9 year olds (9% vs. 11%) and in the 10–14 year olds (1% vs. 2%). The frequency of morning blood ketones ≥ 0.6 mmol/L was not significantly associated with participant BMI percentile ($P = 0.15$).

Similar to control nights, following intervention nights, the frequency of morning blood ketones ≥ 0.6 mmol/L decreased with participant age ($P < 0.001$, Supplemental Figure 1), and was 13% in 4–9 year olds versus 2% in 10–14 year olds (Table 2). The frequency of nights with one or more pump suspensions did not vary with age ($P = 0.72$), and occurred during 375 of the 575 nights (65%) in the 4–9 year old group and during 815 of the 1,183 nights (69%) in the 10–14 year old group. Among nights with one or more pump suspensions, total duration of overnight pump suspension slightly increased with age ($P = 0.03$), and the median total suspension duration was 50 minutes (IQR 22 to 99) for 4–9 year olds compared with 59 minutes (IQR 24 to 114) for 10–14 year olds.

The frequency of blood ketones ≥ 0.6 mmol/L was 11% following intervention nights without pump suspension and 14% following intervention nights with at least one pump suspension ($P = 0.09$) in 4–9 year olds and 3% versus 2%, respectively, in 10–14 year olds ($P = 0.20$). The probability of morning blood ketones ≥ 0.6 mmol/L increased with pump suspension in the 4–9 year olds ($P = 0.002$), but no significant relationship was observed in 10–14 year olds ($P = 0.63$, Figure 1). Among intervention nights, the younger age group had a higher percent of mornings with blood ketones ≥ 0.6 mmol/L following pump suspensions > 120 minutes (23%) compared to nights with no suspension (11%) or suspensions lasting 61–120 minutes (11%). This did not occur with the 10–14 year old age group (ketones ≥ 0.6 on 2% of mornings with > 120 minute suspension), or the previously described 15–45 year old group ($\approx 1\%$ of mornings) (10).

Following control nights, morning blood glucose concentration did not vary with age ($P = 0.92$). Mean ($\pm$ SD) glucose was 159 ± 65 mg/dL for 4–9 year olds compared with 156

± 66 mg/dL for 10–14 year olds; and similarly ($P=0.10$) following intervention nights, it was 165 ± 58 mg/dL for 4–9 year olds compared with 170 ± 61 mg/dL for 10–14 year olds (Table 1). As seen in Table 3, there was an association between morning blood glucose and blood ketone values >0.6 mmol/L among both age groups following control and intervention nights (all four $P<0.001$).

There were no cases of ketoacidosis or visits to a medical-care facility as a result of the study.

Exploratory Subgroup Analyses

Among $N=878$ intervention nights for subjects with $HbA1c <7.8\%$ (median $HbA1c$), the frequency of mornings with elevated blood ketone was 5.4% following nights with pump suspension compared with 3.8% after nights without pump suspension ($P=0.02$). The frequency increased with duration of pump suspension ($P<0.001$). Among $N=880$ intervention nights for subjects with $HbA1c \geq 7.8\%$, the frequency of mornings with elevated blood ketone was 5.5% with suspension and 6.9% without pump suspension ($P=0.73$). The association of ketone frequency with duration of pump suspension had a P -value of 0.24 .

Among $N=921$ intervention nights for subjects with <0.8 units of insulin per kilogram per day (median daily insulin dose), the frequency of mornings with elevated blood ketone was 7.4% following nights with pump suspension compared with 5.4% after nights without pump suspension ($P=0.06$). The frequency increased with duration of pump suspension ($P<0.001$). Among $N=837$ intervention nights for subjects with ≥ 0.8 units of insulin per kilogram per day, the frequency of mornings with elevated blood ketone was 3.4% following nights with pump suspension versus 5.5% without suspension ($P=0.35$). The association of ketone frequency with duration of pump suspension had a P -value of 0.25 .

Discussion

In this study, the 4–9 year old age group had a substantially higher frequency of elevated morning blood ketones than the 10–14 year old age group following both control nights and intervention nights, indicating that the effect was inherent with age and not related to system use. The frequency of morning blood ketones did not change when study participants consumed a bedtime snack. The incidence of elevated ketones in the 10–14 year old age group was similar to that previously described for a 15–45 year old age group (5, 15). The cut point between 9 and 10 years was based on observation of the data which showed a consistently low morning ketosis rate from 10 to 14 and an increasing rate starting with age 9 years.

Similarly, in a previous report of 8-point 24 hour blood glucose and ketone profiles in 45 children with type 1 diabetes, younger children, ages 4–7 years, had a higher incidence of ketonemia (>0.2 mmol/L) compared with adolescents, ages 14–19 years. The authors also found ketonemia to be more common in the morning following an overnight fast than during the rest of the day ($P<0.001$) (14).

With fasting (or reduction of insulin infusion as glucose levels fall), counter regulatory hormones rise to ensure adequate supplies of glucose, fatty acids and ketones (11–14). The mobilized fatty acids and ketones serve as alternate fuels for muscle thereby sparing glucose for brain metabolism (13). It is also known that glucose production as a function of body weight does not reach adult levels until mid-adolescence (11, 12). Similarly, muscle primarily provides gluconeogenic precursors during fasting and muscle mass is lower relative to body weight in younger children (12). Decreased gluconeogenic substrates (such as alanine) have been observed in younger children with prolonged fasting (17). Thus, the increased ketone production would be expected to be a normal physiologic mechanism in younger children.

The etiology of increased utilization of fat for energy with resultant increased ketone production with prolonged pump suspensions is likely a normal physiologic protective measure, as discussed above, in the younger children. This could also be expected to occur with various clinical conditions, such as with insulin infusion set failures or with childhood illnesses.

The association between elevated morning blood glucose and ketone levels (> 0.6 mmol/L) observed in both age groups is likely the result of two factors. As insulin availability decreases, glucose utilization is reduced and physiologic ketone production, as discussed above, is increased. Insulin levels were not measured in the current study. The second possible factor relates to insulin resistance with increased fatty acid levels causing reduced glucose utilization. The association between blood glucose and ketone levels is important, as most families do not routinely measure ketones, but are instructed to do so with elevated blood glucose levels (18). Although the same factors occur with diabetic ketoacidosis, the conditions were not severe enough to result in ketoacidosis in any of the participants in this study.

Limitations of this study include the lack of a non-diabetic control group where ketones were measured. In addition, information was not collected to know if any families increased their child's morning insulin dose during the study.

Although the data shown in this paper were obtained during a randomized controlled trial that included insulin suspension to prevent hypoglycemia, the findings from the control nights are pertinent for all youth with type 1 diabetes regardless of insulin regimen. In this protocol, families were asked not use the system if the subject was ill. As ketone formation increases with illness, it is possible that even greater ketogenesis will result. For patients using insulin pumps with a feature that suspends insulin delivery to prevent hypoglycemia, further study may be indicated to determine if the duration of pump suspension should be different for younger aged children. It is important for care-providers to be aware of the physiologic differences between young children and adults. The rate of adverse of events when using technology approved for adults "at the discretion of the physician" may be higher when treating young children because of their different physiology.

It is important for physicians to be aware of the likelihood of more frequent, physiologic, elevation of ketone production in younger children. Since ketone testing is not routinely

completed upon waking in routine clinical care, ketone levels have not been well documented after periods of sleep and presumed fasting. The presence of ketones in 4–9 year olds, independent of system use, is likely to reflect ketone levels in a similar aged non-diabetic pediatric population. The clinical significance of unexplained morning ketones may be minimal, as all instances of ketones ≥ 1.0 mmol/L returned to normal within hours without incident.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to recognize the efforts of the participants and their families and thank them. We also would like to recognize Martin Cantwell, BSC, Medtronic Diabetes, Northridge, CA and Denny Figuerres, Jaeb Center for Health Research, Tampa, FL for their significant engineering contributions.

Authorship Contribution

The study was designed and conducted by the investigators. The writing group collectively wrote the manuscript and vouch for the data. R. P. Wadwa and H. P. Chase are the guarantor of this work and, as such, had full access to all the data in the study. R. P. Wadwa, H. P. Chase, B. A. Buckingham, D. M. Maahs, L. Messer, T. Ly, T. Aye, P. Clinton, and I. Hramiak researched data, contributed to discussion, and reviewed/edited manuscript. C. Kollman contributed to discussion, and reviewed/edited manuscript. R. P. Wadwa, H. P. Chase, D. Raghinaru, J. Lum and R. Beck wrote the manuscript, contributed to discussion, and reviewed/edited manuscript.

Disclosure

The project described was supported by the National Institute of Diabetes and Digestive and Kidney Diseases (R01DK085591), grants from JDRF (22-2013-266), and the JDRF Canadian Clinical Trial Network (CCTN) which is a public-private partnership including JDRF International, JDRF-Canada (JDRF-C) and the Federal Economic Development Agency for Southern Ontario (FedDev Ontario); and is supported by JDRF # 80-2010-585. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Diabetes and Digestive and Kidney Diseases or the National Institutes of Health.

Continuous glucose monitors and sensors were purchased at a bulk discount price from Medtronic MiniMed, Inc. (Northridge, CA). Home glucose meters and test strips were provided to the study by Bayer HealthCare LLC. Home ketone meters and test strips were provided by Abbott Diabetes Care, Inc. The companies had no involvement in the design, conduct, or analysis of the trial or the manuscript preparation.

RPW reports personal consulting fees from Medtronic, Novo Nordisk outside the submitted work; HPC reports grants from Dexcom during the conduct of the study, as well as a patent Kalman filter based hypoglycemia prevention algorithm is pending; DR has nothing to disclose; BAB reports grants from NIDDK, during the conduct of the study; grants, personal fees and non-financial support from Medtronic, personal fees from Sanofi, personal fees from Tandem, personal fees from Novo-Nordisk, personal fees from Animas, outside the submitted work. In addition, BAB reports a patent Kalman filter based hypoglycemia prevention algorithm is pending; DMM reports grants from American Diabetes Association-Medtronic; LM has nothing to disclose; TL reports honoraria from Medtronic outside of the submitted work; TA has nothing to disclose; PC has nothing to disclose; IH reports grants from JDRF-Federal Development funding during the conduct of the study, as well as grants, personal fees and non-financial support from Abbott, from AstraZeneca/Bristol Myers Squibb; personal fees and non-financial support from Boehringer Ingelheim, grants, personal fees and non-financial support from Eli Lilly, grants, personal fees and non-financial support from Janssen-Ortho/Johnson & Johnson (JNJ), personal fees and non-financial support from Medtronic, grants, personal fees, non-financial support and other from Merck, grants, personal fees and non-financial support from Novo Nordisk, grants from Pfizer, grants, personal fees and non-financial support from Sanofi Aventis, outside the submitted work; JL has nothing to disclose; CK reports consultant fees from Medtronic MiniMed, Inc.; RWB reports grants from NIH and from JDRF during the conduct of the study.

Abbreviations

DKA

diabetic ketoacidosis

PLGS

predictive low glucose suspend system

BMI

body mass index

± SD

standard deviation

CGM

continuous glucose monitor

referred to as “the system”

Kalman-filter based hypoglycemia prediction algorithm

IQR

interquartile range

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Figure 1. Percent of Mornings with Blood Ketones ≥ 0.6 mmol/L vs. Duration of Pump Suspension

Numbers above each bar indicate # mornings with blood ketone ≥ 0.6 mmol/L / # nights.

Table 1Demographic and Safety Glucose Data – *median (IQR), mean $\pm$ SD, or n (%)*

	Participants Age 4–9	Participants Age 10–14
Characteristic	Years (N=28)	Years (N=54)
Age (years)	7 (6, 8)	12 (11, 13)
Male	14 (50%)	28 (52%)
Race		
White non-Hispanic	26 (93%)	52 (96%)
Hispanic	2 (7%)	1 (2%)
Asian	0	1 (2%)
Diabetes duration (years)	4 (2, 5)	5 (3, 8)
Body-mass index percentile^a	67 (51, 79)	69 (43, 84)
HbA1c (%)	7.9 $\pm$ 0.4	7.7 $\pm$ 0.6
Number of nights		
Total	1,155	2,345
Control	580	1,162
Intervention	575	1,183
Overnight Sensor Glucose (mg/dL)		
Control	153 $\pm$ 48	146 $\pm$ 51
Intervention	161 $\pm$ 47	152 $\pm$ 49
Morning Blood Glucose (mg/dL)		
Control	159 $\pm$ 65	156 $\pm$ 66
Intervention	165 $\pm$ 58	170 $\pm$ 61

^aBody-mass index percentiles adjusted for age and gender were computed using the 2000 CDC population growth chart data (*Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, et al. CDC growth charts: United States. Adv Data 2000;1–27*)

Table 2

Distribution of Morning Blood Ketones (mmol/L) by Age and Treatment Group

Morning Blood Ketones	4–9 Years of Age		10–14 Years of Age	
	<i>Control</i>	<i>Intervention</i>	<i>Control</i>	<i>Intervention</i>
	N=580	N=575	N=1,162	N=1,183
0.0 mmol/L	83 (14%)	93 (16%)	438 (38%)	394 (33%)
0.1 mmol/L	208 (36%)	190 (33%)	556 (48%)	575 (49%)
0.2 mmol/L	133 (23%)	106 (18%)	112 (10%)	135 (11%)
0.3 mmol/L	47 (8%)	59 (10%)	23 (2%)	43 (4%)
0.4–0.5 mmol/L	50 (9%)	54 (9%)	14 (1%)	13 (1%)
0.6–0.9 mmol/L	38 (7%)	56 (10%)	14 (1%)	14 (1%)
1.0–3.0 mmol/L	20 (3%)	16 (3%)	4 (<1%)	9 (<1%)
>3.0 mmol/L	1 (<1%)	1 (<1%)	1 (<1%)	0
0.6 mmol/L	59 (10%)	73 (13%)	19 (2%)	23 (2%)

Table 3

Presence of Elevated Morning Blood Ketones (≥ 0.6 mmol/L) by Morning Blood Glucose, Treatment, and Age Group. ^{*}, [†]

	4–9 Years of Age		10–14 Years of Age	
	<i>Control</i>	<i>Intervention</i>	<i>Control</i>	<i>Intervention</i>
All	59/580 = 10%	73/575 = 13%	19/1162 = 2%	23/1182 = 2%
Morning Blood Glucose				
99 mg/dL	14/111 = 13%	8/53 = 15%	2/238 = <1%	2/120 = 2%
100 – 149 mg/dL	4/173 = 2%	21/206 = 10%	3/376 = <1%	3/366 = <1%
150 – 199 mg/dL	11/150 = 7%	21/177 = 12%	2/298 = <1%	2/368 = <1%
200 – 249 mg/dL	9/84 = 11%	8/87 = 9%	3/135 = 2%	2/207 = <1%
250 – 299 mg/dL	14/49 = 29%	7/35 = 20%	1/77 = 1%	3/86 = 3%
300 mg/dL	7/13 = 54%	8/17 = 47%	8/38 = 21%	11/35 = 31%

^{*} – Data presented in the format: # mornings with elevated ketones / # nights = percentage.

[†] – Test for association of elevated morning ketones with morning blood glucose: $p < 0.001$ in all four columns.