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Hypoglycemia in Mitochondrial Disorders

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HYPOGLYCEMIA IN MITOCHONDRIAL DISORDERS

A

THESIS

Presented to the Faculty of

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Allison Rachel Moats, BS, MA

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HYPOGLYCEMIA IN MITOCHONDRIAL DISORDERS

Allison Rachel Moats, BS, MA

Advisory Professor: Myla Ashfaq, MS, CGC

INTRODUCTION: The electron transport chain (ETC) in mitochondria functions to produce energy in the form of adenosine triphosphate (ATP). Defects in the mitochondrial or nuclear DNA that codes for components of the ETC lead to mitochondrial disorders (MTDs). MTDs are multi-system conditions affecting the heart, muscles, and especially brain. The endocrine system is commonly affected in MTDs, and diabetes and hyperglycemia are established secondary diagnoses. Rates of non-iatrogenic hypoglycemia have not been studied in individuals with MTDs. This study aims to investigate the frequency of hypoglycemia in patients with MTDs.

METHODS: Individuals diagnosed with a ‘definite’ or ‘probable’ MTD according to the modified Walker criteria at The University of Texas, Mitochondrial Center of Excellence were included in this study. Exclusion criteria included diagnosis of diabetes or adrenal insufficiency or past or present use of hydrocortisone or prednisone. Patient charts were reviewed retrospectively for blood glucose values. Individuals with at least two values were recorded. Patients were classified as neonatal (≤ 28 days of life) or non-neonatal (> 28 days of life) at the time of measurement. Data analysis included descriptive statistics, mixed-model regression, and two-sample tests of proportion. All data analysis was done using Stata® (v.13, College Station, TX). Statistical significance was assumed at $p < 0.05$.

RESULTS: Of the 116 patients included in this study, 22 (18.97%) experienced at least one episode of hypoglycemia. This is significantly higher ($p < 0.05$) than the 6% non-diabetic, general population rate of hypoglycemia. Neonatal readings were also found to be 30mg/dL lower than non-neonatal readings, on average, a significant difference ($p < 0.05$).

CONCLUSION: Patients with MTD are more likely to experience hypoglycemia compared to the general population with especially low blood glucose readings during the neonatal period. This demonstrates hypoglycemia may be contributing to the high rate of neurological symptoms reported in MTDs and supports that MTDs should be on the differential diagnosis in cases of hypoglycemia, especially during the neonatal period. Additional and earlier monitoring of blood glucose could reduce negative outcomes such as decreased cognitive outcome, developmental delays, seizures, or brain damage in patients with MTDs.

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INTRODUCTION

Mitochondria are organelles that engage in symbiotic relationships with eukaryotic cells: mitochondria provide energy in the form of adenosine triphosphate (ATP) for the cells in exchange for nutrients and proteins.¹ Mitochondria are constructed from proteins coded for by mitochondrial DNA (mtDNA) and nuclear DNA (nDNA). The vast majority of ATP generated by mitochondria is created through the electron transport chain (ETC), a series of components that facilitate the exchange of electrons from chemical donors to chemical acceptors via reduction-oxidation reactions.² When the ETC malfunctions, ATP yield decreases significantly leading to systemically low energy levels and multisystem malfunction. ETC dysfunction can be caused by errors in either mtDNA or nDNA due to both contributing to the structural composition of mitochondria. However, the majority of cases of ETC dysfunction are caused by mtDNA mutations.³ Individuals with ETC dysfunction are referred to clinically as having a mitochondrial disorder (MTD).¹

MTDs affect a multitude of organ systems due to systemically low levels of ATP. The heart, muscle, and brain are frequently affected tissues. Hallmark features of MTDs include depletion of mitochondrial material, ragged red fibers in the muscles, strokes, lactic acidosis, neuropathy, epilepsy, and encephalomyopathy.¹ Prevalence of MTDs is known to be 1/4,300³, but because of the variable expressivity in these conditions, diagnosis can be complicated. Unlike other medical settings where genetic testing is able to give etiological information, this is not necessarily the case with MTDs. Only a small portion of the genetic etiologies of these conditions are understood at this time¹, and in some cases, genetic yield is as low as 5%.⁴ Genetic information is most useful when considered in combined with other MTD symptoms. The modified Walker criteria are a set of guidelines using a combination of clinical,

histological, enzymological, functional, and metabolic criteria in addition to genetic information to diagnose MTD as ‘definite’, ‘probable’, or ‘possible’.⁴ Clinical presentations can sometimes be separated into specific mitochondrial syndromes such as mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS); myoclonic epilepsy with ragged red fibers (MERRF); and neuropathy, ataxia, and retinitis pigmentosa (NARP). However, if the clinical presentation does not fit a specific mitochondrial syndrome, the patient may remain in an unspecified MTD category.¹ Despite these differences in presentation, MTDs consistently cause symptoms in systems requiring high loads of ATP such as the nervous and endocrine systems.¹

The nervous system is the most frequently affected system, and forty-five percent of children with MTDs demonstrate neurological symptoms.¹ Similarly, endocrine system-related symptoms (*e.g.*, hypothyroidism, hypoparathyroidism, adrenal insufficiency, and diabetes) are commonly found in these individuals, specifically diabetes.^{1,5} Mitochondria and their ATP production in pancreatic islet β -cells are vital to the secretion of insulin in response to glucose stimulation.⁶ This balance is compromised in patients with MTD and leads to the 22.3% prevalence of diabetes and concomitant hyperglycemia in patients with MTDs.⁵ In addition to hyperglycemia, patients with MTDs and diabetes who manage their diabetes with insulin are known to experience iatrogenic hypoglycemia.^{7,8}

Unlike hyperglycemia, non-iatrogenic hypoglycemia, another sign of endocrine dysfunction, has not been well-documented in patients with MTDs. One case report described three unrelated individuals with MTDs who had hypoglycemia as their only presenting feature⁹. Otherwise, this correlation has not been studied. A recent study found the non-diabetic population rate of hypoglycemia to be 6%¹⁰, and learning whether the rate in the MTD population is significantly different or not is important due to the serious complications that can result from hypoglycemia. These complications can be divided into two categories: 1)

neurogenic, which affect the autonomic nervous system and range from sweating and shakiness and 2) neuroglycopenic, which affect the central nervous system, are much more severe, and can lead to severe cognitive impairment.^{11,12} Episodes of hypoglycemia that occur during periods of critical brain development are particularly damaging, and 25-50% of patients with neonatal hypoglycemia have developmental delay.¹² If MTDs do increase rates of hypoglycemia, the related complications may, in turn, be contributing to the high rate of children with MTDs having neurological symptoms.¹ This retrospective chart review aimed to determine how the frequency of hypoglycemia in a cohort of patients with MTDs without diabetes compared to the general population rate of 6.0%.¹⁰

METHODS

This study followed all regulations established by the Institutional Review Board of the University of Texas at Houston Health Science Center (HSC-MS-09-0057). The University of Texas, Mitochondrial Center of Excellence (UTMCE) patient database was used for this retrospective chart review.

Data Collection

The electronic medical records (EMR) for patients seen at the UTMCE between November 1997 and December 2018 were reviewed for those who had genetic testing to determine the etiology of their MTD. They were then filtered for those who met ‘definite’ or ‘probable’ MTD diagnosis based on the modified Walker criteria.⁴ The charts for patients meeting these criteria were systematically reviewed for measurements of serum glucose (SG) recorded in milligrams/deciliter (mg/dL) either from clinic-requested labs or inpatient testing at Children’s Memorial Hermann Hospital. Other information abstracted from the EMR included demographics (*i.e.*, sex, ethnicity, place of residence); the patient’s mitochondrial syndrome if known; and whether the patient’s pathogenic variant is in the mtDNA, nDNA, or is unknown. Patients were separated into one of 12 categories based on their mitochondrial syndrome. Patients included in this study fell within the categories: combined oxidative phosphorylation deficiencies (COXPD), depletion syndrome, Kearns-Sayre syndrome, Leigh syndrome, MELAS, MERRF, MNGIE, NARP, an MTD plus another diagnosed condition (mito+), or an unspecified MTD.

Exclusion Criteria

Patients were excluded from the study if they had a medical condition known to influence SG either through its natural history or treatment, such as diabetes and adrenal

insufficiency, or if the patient had past or present use of steroids (*i.e.*, hydrocortisone and prednisone). Patients with fewer than two SG measurements were also excluded. Any values greater than 500mg/dL were excluded due to questionable reliability of the glucometer above this cutoff. Any patient meeting one or more of the exclusion criteria was removed from the study.

Data Classification

SG measurements were categorized as neonatal or non-neonatal depending on if the patient was within the first 28 days of life or older than 28 days of life at the time of the measurement. For this study, we defined hypoglycemia in the neonatal period as SG less than or equal to 45mg/dL and hypoglycemia in the post-neonatal period as SG less than or equal to 60mg/dL. A more stringent cutoff for neonatal hypoglycemia than the 55-60 mg/dL previously suggested¹² was used as it is difficult to distinguish the difference between iatrogenic hypoglycemia and post-birth-transitional hypoglycemia. To facilitate the visualization of trends toward hypoglycemia, a category of low normal SG was defined as measurements up to 10mg/dL higher than hypoglycemia in the respective age groups (*i.e.*, neonatal and non-neonatal low normal SG ranged from 46-50mg/dL inclusive and 61-70mg/dL inclusive, respectively). Hyperglycemia in any age group was defined as SG greater than or equal to 200mg/dL. This is the cutoff for hyperglycemia following the administration of an oral glucose tolerance test⁷. This stringent value was used to denote measurements that are truly abnormally high.

Data Analysis

This cohort was evaluated using descriptive statistics. Categorical data were described using frequencies and percentages, and medians with interquartile ranges were used to describe continuous variables. Contingency tests, such as Chi² and Fisher's Exact, were used to compare categorical variables across groups. Additional statistical analysis between groups included a

random effects regression models, a mixed-effects regression analysis group, and two-sample tests of proportion. All data analysis was done using Stata® (v.13, College Station, TX). Statistical significance was assumed at $p < 0.05$.

RESULTS

At the time of data collection, the UTMCE patient database contained 799 patients. Two hundred sixty-three had undergone genetic testing, and of those, 168 met the criteria of having a ‘definite’ or ‘probable’ MTD based on the modified Walker criteria.⁴ After excluding patients with a diagnosis of diabetes or adrenal insufficiency, past or current use of hydrocortisone or prednisone, or fewer than two SG measurements, 116 patients were included in the study. These patients had a combined total 1,787 SG measurements.

Population Demographics and Serum Glucose Measurements

In the cohort, 60/116 (51.72%) were female. The average age was 11.8 years (range=0 days–65years). The majority of the patients reported Caucasian ethnicity (73/116, 62.93%). The most common mitochondrial syndromes were depletion syndrome (11.21%), Leigh syndrome (24.14%), and MELAS (10.34%). There were eight patients in the mito+ category. Nearly 82% of the patients had a pathogenic mutation found with most being in the mtDNA (51/116, 42.97%). A total of 1,787 SG readings were collected with an average of 15.41 readings per patient. Of the 116 patients, nine (7.76%) had SG drawn during the neonatal period with 99/1,787 (5.54%) total neonatal readings. All 116 patients collectively contributed to the 1,688/1,787 non-neonatal readings (94.46%). Patient demographics can be found in Table 1, and SG measurement information can be found in Table 2.

Statistical Analysis

Of the total 1,787 SG readings collected, 51/1,787 (2.85%) were hypoglycemic. The majority of readings (95.86%) were either normal or low normal, and 23/1,787 (1.29%) were hyperglycemic (Table 2, Figure 1). The neonatal cohort was separated for individual analysis, and the remaining cohort (*i.e.*, non-neonatal cohort) was also analyzed independently. The neonatal cohort had 17/99 (17.17%) hypoglycemic, 15/99 (15.15%) low normal, and 67/99

Patient Demographics				
	Category	n (%)	p-value	p-value
			<i>Hypoglycemia</i>	<i>Hyperglycemia</i>
Sex			0.210	0.487
	<i>Female</i>	60 (51.72)		
	<i>Male</i>	56 (48.28)		
Ethnicity			0.391	0.789
	<i>African American</i>	5 (4.31)		
	<i>Asian</i>	2 (1.72)		
	<i>Hispanic</i>	14 (12.07)		
	<i>White</i>	73 (62.93)		
	<i>Other</i>	18 (15.52)		
	<i>Unknown</i>	4 (3.45)		
Mitochondrial Condition			0.423	0.780
	<i>COXPD</i>	3 (2.59)		
	<i>Depletion Syndrome</i>	13 (11.21)		
	<i>Kearns-Sayre Syndrome</i>	4 (3.45)		
	<i>Leigh Syndrome</i>	28 (24.14)		
	<i>MELAS</i>	12 (10.34)		
	<i>MERRF</i>	2 (1.72)		
	<i>MNGIE</i>	1 (0.86)		
	<i>NARP</i>	2 (1.72)		
	<i>Mitochondrial Disorder+</i>	8 (6.90)		
	<i>Unspecified</i>	43 (37.07)		
Pathogenic Mutation			0.356	0.637
	<i>mitoDNA</i>	51 (43.97)		
	<i>nDNA</i>	21 (18.10)		
	<i>Unknown</i>	44 (37.93)		
Total n=116				

*Mitochondrial Disorder+ = meeting the Walker Criteria diagnosis of mitochondrial disorder + a second diagnosis including: dopa dystonia (2), Friedreich’s ataxia (1), malignant hyperthermia (1), multiple sclerosis (1), partial ornithine carbamoyltransferase (1), spondyloepimetaphyseal dwarfism (1), and a 651kb interstitial deletion on chromosome 22 (1).

Table 1: Patient Demographics

Summary of Number of Blood Glucose Measurements						
	Category	n (%)	Range	Recurrence (%)	Frequency (%)	p-value
Numbers Per Patient						
	<i>Mean</i>	15.41	2–99			
	<i>Median</i>	8.5				
Whole Cohort Totals						
	<i>Hypoglycemia</i>	51 (2.85)	1–11	33.36	1.1–40	
	<i>Low Normal</i>	97 (5.43)				
	<i>Normal</i>	1,616 (90.43)				
	<i>Hyperglycemia</i>	23 (1.29)	1–6	41.67	1.1–50	
Total n=1,787						
Totals by Age						
†Neonatal Cohort (n=9)	<i>Hypoglycemia</i>	17 (17.17)	2–11	100	8.33–19.05	<i>p</i> <0.05* <i>p</i> <0.05**
	<i>Low Normal</i>	15 (15.15)				
	<i>Normal</i>	67 (67.68)				
	<i>Hyperglycemia</i>	0 (0.00)				
Total n=99 (5.54)						
Non-Neonatal Cohort (n=107)	<i>Hypoglycemia</i>	34 (2.01)	1–9	17.76	1.1–40	
	<i>Low Normal</i>	82 (4.86)				
	<i>Normal</i>	1,549 (91.77)				
	<i>Hyperglycemia</i>	23 (1.36)				
Total n=1,688 (94.46)						

*Between rate of neonatal hypoglycemia and rate of non-neonatal hypoglycemia in this study by Chi² and mixed-effect regression model

**Between rate of neonatal hypoglycemia and rate of non-diabetic hypoglycemia¹⁰

†Neonatal = ≤28 days of life

Table 2: Summary of Number of Blood Glucose Measurements

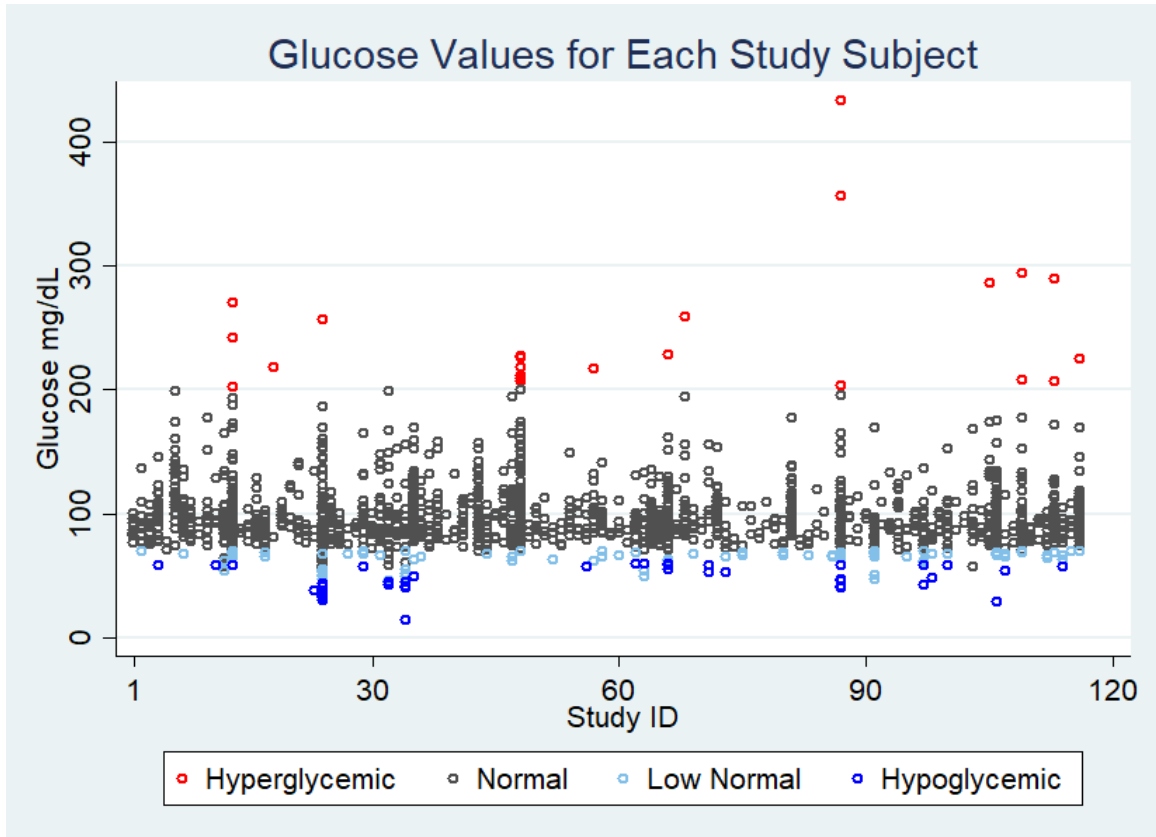


Figure 1: *Glucose Values for Each Study Subject*

(67.68%) normal measurements (Table 2, Figure 2). There was no neonatal hyperglycemia. The non-neonatal cohort had 34/1,688 (2.01%) hypoglycemic, 82/1,688 (4.86%) low normal, 1,549/1,688 (91.77%) normal, and 23/1,688 (1.36%) hyperglycemic SG measurements (Table 2, Figure 2).

The median SGs were calculated per patient, and when these values were averaged across the whole patient cohort, the mean was 90.32mg/dL (range=66–149.5mg/dL) (Table 3). The minimum and maximum values for each patient were also averaged across the cohort and can be found in Table 3. Similar calculations were done for the neonatal and non-neonatal cohorts and can also be found in Table 3.

Summary of Blood Glucose Values (mg/dL)				
	Category	n	Range	Total Readings
Averages				
Whole Cohort (n=116)	Median	90.32	66–149.5	1,787
	Low	70.64	14–108	
	High	135.36	67–433	
Averages by Age				
†Neonatal Cohort (n=9)	Median	79.33	68–86	99
	Low	29.00	14–43	
	High	204.00	156–257	
Non-Neonatal Cohort (n=107)	Median	90.62	66–149.5	1,688
	Low	71.74	29–108	
	High	133.54	67–433	

†Neonatal = ≤28 days of life

Table 3: Summary of Blood Glucose Values

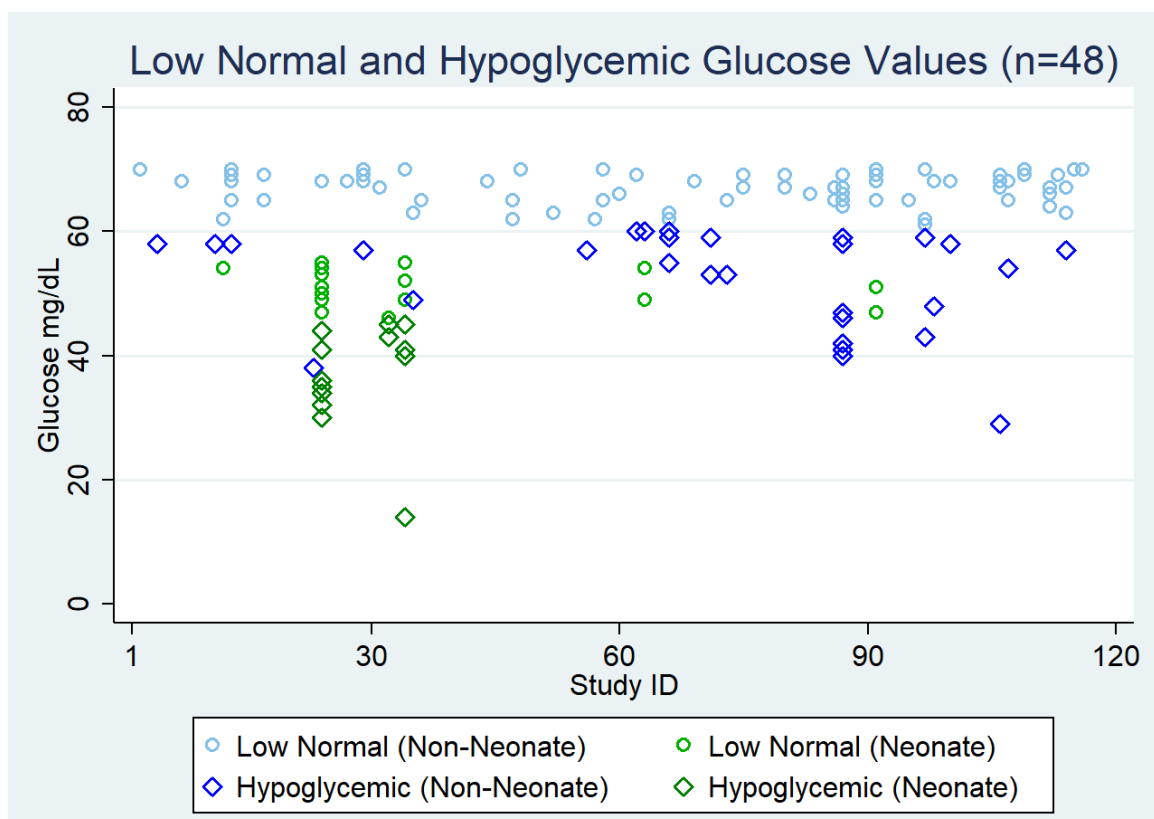


Figure 2: Low Normal and Hypoglycemic Glucose Values (n=48)

Of the 116 patients, 22/116 (18.97%) experienced at least one SG reading of hypoglycemia as their lowest reading (Table 4.1). Just over 13% (3/22) of these readings were neonatal (Table 4.2). An additional 26/116 patients (22.41%) experienced low normal SG as their lowest reading (Table 4.1), three of which were neonatal (11.54%) (Table 4.2). The remaining 68/116 patients (58.62%) had a normal SG as their lowest value (Table 4.1). In terms of their highest readings, 12/116 patients (10.34%) experienced hyperglycemia (Table 4.1), none of which were neonatal. The vast majority of patients had a normal value as their highest SG (103/116, 88.79%), and only one patient had a low normal reading as their highest SG (1/116, 0.86%) (Table 4.1).

Of the 22 patients with hypoglycemic measurements, one third experienced recurrent hypoglycemia defined as more than one hypoglycemic reading (Table 2). 100% of neonatal patients experienced repeat hypoglycemia (Table 2). Nearly half of patients with hyperglycemia experience recurrence of these (Table 2). By number of readings, there was a statistically significant increase in the rate of hypoglycemia in neonatal patients compared to non-neonatal patients (17.17% versus 2.01%; $p < 0.05$) (Table 2).

Using Chi² analyses, there were no statistically significant differences in the likelihood of having hypoglycemia depending on the patient's sex ($p = 0.210$), ethnicity ($p = 0.391$), specific diagnosis ($p = 0.423$), or the location of their pathogenic mutation ($p = 0.356$) (Table 1). There were also no statistically significant differences with hyperglycemia and any of these categories (sex $p = 0.487$; ethnicity $p = 0.789$; specific diagnosis $p = 0.780$; location of pathogenic mutation $p = 0.637$) (Table 1). When assessing for time trends using a random effects regression model, there was no statistically significant increases or decreases in SG readings for every day of life gained ($p = 0.1403$; 95% CI [-0.028]–0.199). Mixed-effects regression analysis showed a statistically significant difference in the SG readings based on whether the individual was a

Table 4.1
Cross Tabulation of Blood Glucose Minimums and Maximums by Individual (Total)

Minimum Reading	Maximum Reading				Totals (%)
	<i>Hypoglycemia</i>	<i>Low Normal</i>	<i>Normal</i>	<i>Hyperglycemia</i>	
<i>Hypoglycemia</i>	0	0	18	4	22 (18.97)*
<i>Low Normal</i>	0	1	20	5	26 (22.41)
<i>Normal</i>	0	0	65	3	68 (58.62)
<i>Hyperglycemia</i>	0	0	0	0	0
Totals (%)	0	1 (0.86)	103 (88.79)	12 (10.34)	116

Table 4.2
Cross Tabulation of Blood Glucose Minimums and Maximums by Individual (†Neonatal)

Minimum Reading	Maximum Reading				Totals (%)
	<i>Hypoglycemia</i>	<i>Low Normal</i>	<i>Normal</i>	<i>Hyperglycemia</i>	
<i>Hypoglycemia</i>	0	0	3	0	3/116 (2.59)
<i>Low Normal</i>	0	0	3	0	3/116 (2.59)
<i>Normal</i>	0	0	3	0	3/116 (2.59)
<i>Hyperglycemia</i>	0	0	0	0	0
Totals (%)	0	0 (0)	9/116 (7.76)	0 (0)	9/116

*Denotes a statistically significant difference from general population values in non-diabetic patients¹⁰

†Neonatal = ≤28 days of life

Tables 4.1 & 4.2: Cross Tabulation of Blood Glucose Minimums and Maximums by Individual (Total & Neonatal)

Non-neonatal hypoglycemia = ≤60mg/dL, low normal = 61-70mg/dL, normal = 71-199mg/dL, and hyperglycemia = ≥200mg/dL. Neonatal hypoglycemia = ≤45mg/dL, low normal = 46-50mg/dL, normal = 51-199mg/dL, and hyperglycemia = ≥200mg/dL

neonate ($p < 0.05$, 95% CI [-36.802]–[-23.715]) showing that on average, neonatal readings are 30mg/dL lower than non-neonatal readings. In this model, there was no difference in SG readings for each year of life gained ($p = 0.222$, 95% CI [-0.247]–0.057) or between females and males ($p = 0.834$, 95% CI [-3.755]–4.654). A two-sample test of proportion showed a statistically significant increase in our cohort’s frequency of hypoglycemia (22/116=18.97%) compared to the previously found population rate of hypoglycemia in patients without diabetes of 6.0%¹⁰ ($p < 0.05$, 95% CI 0.43–0.186) (Table 2). A two-sample test of proportion also showed no statistically significant difference in our cohort’s frequency of hypoglycemia compared to the previously found population rate of hypoglycemia in patients with diabetes of 16.8%¹⁰ ($p = 0.8615$, 95% CI [-0.065]–0.078).

DISCUSSION

This study is the first to investigate the frequency of hypoglycemia in patients with MTDs diagnosed by the modified Walker criteria.⁴ The vast majority of SG measurements (95.86%) were either normal or low normal demonstrating the cohort experiences normal SG the majority of the time. This was reiterated by the cohort-wide and non-neonatal averages of mean, minimum, and maximum all being between 60mg/dL and 200mg/dL and, thus, higher than either the cutoff for hypoglycemia or lower than the cutoff for hyperglycemia. While the minimum and maximum for the neonatal cohort are both lower and higher than the normal cutoffs, respectively, these are likely a reflection of a smaller sample size and possibly unknown neonatal risk factors such as gestational age, maternal diabetes, and yet undiagnosed diabetes.¹²

Despite the majority of readings being normal, 18.97% of the cohort experienced hypoglycemia (Table 4.1). This rate was similar to the 16.8% rate previously reported in diabetic populations¹⁰ but is statistically higher than the 6.0% frequency found in a general, non-diabetic population.¹⁰ Recurrence of hypoglycemia was 33.36% in the full cohort and 100% in neonates. The frequency of recurrence of hyperglycemia was unexpected considering the population is void of individuals with diabetes, and rates of hyperglycemia are predicted to be low in unaffected populations as these readings may be used to diagnose diabetes.⁷ However, as this study is a retrospective chart review, the patients may be diagnosed with diabetes eventually. Regardless, increased rates of both hypoglycemia and hyperglycemia demonstrate endocrine malfunction.¹

When considering individual readings, the frequency of hypoglycemia in neonates is significantly increased compared to that in non-neonatal frequency. Neonatal SG is known to be lower than that of older children and adults¹², and this was reflected in this study by using a lower threshold for hypoglycemia in neonates. Regardless, a 30mg/dL decrease still exceeds the

established difference in cutoffs and indicates neonates with MTD may be predisposed to abnormally low hypoglycemia. However, other unknown neonatal risk factors may have played a role in these levels.¹²

Recently, a study looking at a group of patients with Prader-Willi syndrome found 12.6% frequency of hypoglycemia in the neonatal population.¹³ Prader-Willi syndrome is also commonly associated with endocrine dysfunction, and Harrington *et al.* suggested neonatal hypoglycemia may play a role in the diminished neurological abilities of these patients.¹³ Our population of non-diabetic patients with MTDs was three times more likely to experience hypoglycemia than the non-diabetic general population.¹⁰ Additionally, neonates were significantly more likely to experience SG readings 30mg/dL lower than their non-neonatal counterparts. These findings supports the notion that endocrine malfunction may be one of the first symptoms of MTD and may severely influence SG levels in neonates. Children with MTDs may experience diminished neurocognitive abilities due to hypoglycemia in early life or later undiagnosed hypoglycemia.^{1,13}

Study Limitations

There are several inherent limitations to a retrospective chart review. Information regarding whether the SG values were fasting or reactive was not available. Similarly, the nature of the EMR made it difficult to ascertain the full course of treatment for the episodes of hypoglycemia, making it impossible to determine if these occurrences would qualify as true, clinical hypoglycemic episodes or if they are artifact hypoglycemia. Information regarding when the patient may have started treatment for the symptoms of their disease was also not available, and we are unable to say whether this influenced their SG readings. Because this study is retrospective, patient outcomes, such as whether or not the patients develop diabetes, are not known. Lastly, birth information, such as weight or gestational age, for neonatal patients

was not collected. Without this information, the possibility of neonatal hypoglycemia being due to other neonatal risk factors¹² cannot be eliminated.

CONCLUSION

Based on the finding of 18.97% hypoglycemia in this non-diabetic, MTD population, glucose monitoring for low SG values should become standard of care. These data also support that endocrine malfunction may be one of the first symptoms of MTDs. Forty-five percent of children with MTDs demonstrate neurological symptoms¹, and this study demonstrates that it is reasonable to consider at least a portion of those childrens' symptoms may be due to aberrant glucose values, particularly during critical brain development. MTDs should be on the differential diagnosis in cases of hypoglycemia, particularly neonatal hypoglycemia. Thornton *et al.* previously published recommendation for the monitoring of neonates with recurrent episodes of hypoglycemia¹², and this study demonstrates that analysis for MTD by modified Walker criteria may be warranted in the presence of repeat neonatal hypoglycemia. Additionally, very low hypoglycemia may be another indication warranting MTD analysis, particularly if in the presence of repeat hypoglycemia. Identifying patients with MTD as early as possible to avoid the serious neurological complications that can result from uncontrolled glucose such as decreased cognitive abilities, developmental delay, seizures, or death is important for best health outcomes.^{11,12} Future longitudinal studies following patients from birth with information regarding whether the SG readings are fasting or reactive would help establish patterns throughout development and whether hypoglycemia leads to specific complications in the future

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VITAE

Allison Rachel Moats was born in Ravenna, Ohio, the daughter of Dr. Aaron and Shelly Moats. After completing her work at Ravenna High School in Ravenna, OH in June 2011, she entered Kent State University in Kent, Ohio. She received the degree of Bachelor of Science with a major in biological anthropology and minor in biology from Kent State University in May 2014. In August 2014, she entered Harvard University in Cambridge, Massachusetts. She received the degree of Master of Arts with a concentration in human evolutionary biology and developmental genetics from Harvard University in August 2016. For the next year, she conducted post-graduate studies at Kent State University. In August 2017, she entered The University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences.

Permanent Address:

500 Bennett Ave.
Ravenna, OH 44266