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RESPONSES TO FASTING AND GLUCOSE LOADING IN A COHORT OF WELL CHILDREN WITH SPINAL MUSCULAR ATROPHY TYPE II

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Abstract

Objective—To examine the impact of fasting and glucose tolerance on selected metabolic variables in children with spinal muscular atrophy (SMA) type II in a well state because of reports of glucose regulation abnormalities in SMA.

Study design—In this prospective pilot study, 6 children with SMA type II ages 7–11 years participated in an oral glucose tolerance test and a supervised medical fast during two overnight visits at the University of Utah. At baseline, a dual energy x-ray absorptiometry (DXA) scan was performed to determine body composition. Labs were obtained at baseline and in response to the

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respective interventions. Data analysis was descriptive. Pre- and post-fasting data were evaluated using Wilcoxon signed ranks.

Results—All children were variably obese at baseline, based on DXA scan. All 6 participants demonstrated hyperinsulinemia, and 3 of 6 participants met formal American Diabetes Association criteria for impaired glucose tolerance. Homeostatic insulin resistance calculations indicated that 5 of 6 participants were insulin resistant. All participants tolerated a monitored fast for 20 hours without hypoglycemia (blood glucose<54 mg/dL). Free fatty acids significantly increased between pre- and post-fasting, while several plasma amino acids significantly decreased during fasting.

Conclusions—Children with SMA type II, determined to be obese using objective variables, are at increased risk for impaired glucose tolerance, whether or not they visually appear obese. Further studies are needed to determine the prevalence of impaired glucose tolerance and tolerance for fasting within the broader heterogeneous SMA population and to develop appropriate guidelines for intervention.

Spinal muscular atrophy (SMA) is an autosomal recessive motor neuron disease resulting in progressive muscular weakness and atrophy. SMA is classified into clinical subtypes based on maximum achieved motor milestones.[1–3] Children with SMA type II typically present between 6–18 months of age; they achieve the ability to sit but never walk independently.[3,4] Bulbar, feeding, and respiratory insufficiency occur at some point in the majority of patients with type II.[5,6] Despite advances in life expectancy, attributed to advances and standardization of medical care [7–9], there is limited knowledge of altered metabolism and nutrition in SMA.

Patients with SMA have documented decreased lean muscle mass and increased fat mass in comparison with healthy peers regardless of body mass index.[10,11] Increased visceral fat mass is a risk factor for insulin resistance and decreased glucose sensitivity in adults and children[12,13] and has been associated with peripheral neuropathy.[14–17] Healthy individuals rely on glycogen stores in the liver and muscle for short-term energy needs.[18,19] Little is known about how diminished lean mass affects fat lipolysis and protein catabolism during periods of fasting in children and adults with severe neuromuscular disease. Impaired fatty acid metabolism has been observed in children with SMA during fasting.[20,21] Poor tolerance for fasting (hypoglycemia, coma) has been observed in adults with various neuromuscular diseases including SMA.[22,23] SMA and survival motor neuron (SMN) gene depleted mice demonstrated pancreatic defects and altered glucose metabolism affecting glucose sensitivity.[24,25] Pancreatic tissue from infants with SMA type I recapitulated some of these findings.[24] Given the convergence of such data, further study is warranted. The primary aims for this study were to explore whether children with SMA type II demonstrate impaired glucose tolerance after glucose loading or intolerance of fasting in a well state.

METHODS

Participants were admitted to the University of Utah Center for Clinical and Translational Science (CCTS) in Salt Lake City, Utah, for two overnight inpatient visits. These visits consisted of an oral glucose tolerance test (OGTT) visit and a fasting visit, separated by 8 weeks.

Participants were 7–11 years of age, consumed at least 50% of their caloric intake by mouth, and met clinical diagnostic criteria for SMA type II. Homozygous *SMN1* deletion was documented in all participants; *SMN2* dosage of 3 copies was confirmed at the Ohio State University Molecular Diagnostic Laboratory for all 6 participants. Participants were excluded if they were acutely ill, taking oral hypoglycemic agents, or diagnosed previously with impaired glucose tolerance. Parental consents and assents were obtained for all participants under University of Utah IRB (64793).

Oral Glucose Tolerance Test Visit

The first visit consisted of body composition analysis using dual energy x-ray absorptiometry (DXA) and a formal oral glucose tolerance test (OGTT). The evening prior, participants consumed a standardized meal and snack (14% protein, 54% carbohydrate, and 32% fat).

Following a 10-hour overnight fast, baseline blood samples were collected for: hemoglobin A1c, Insulin Growth Factor (IGF)-1, blood glucose, insulin, glucagon, plasma quantitative amino acids (PQAA), and cortisol. Samples were analyzed by ARUP Laboratories (Salt Lake City, UT) using standardized clinical protocols. For safety purposes, baseline and final glucose labs were also analyzed at bedside (YSI 2300 STAT PLUS, YSI Incorporated, Yellow Springs, Ohio). Participants consumed an oral glucose load of 1.75g glucose/kg body weight (maximum dose 75 g) following baseline lab collection. Subsequent blood samples were collected at 30, 60, 90, 120, and 180 minutes and analyzed for: glucose, insulin, glucagon, PQAA, and cortisol. The first and last urine voids were collected and assessed for urinary ketones using Ketostix reagent strips (Bayer HealthCare, Mishawaka, Indiana). OGTT test results were evaluated using American Diabetes Association guidelines and reference values for non-obese children.[26, 27]

DXA and Anthropometrics

Norland DXA (XR-36 software version 3.3.1, Fort Atkinson, Wisconsin) for small subjects was used to assess whole body composition (percent body fat). Body fat percentiles developed for 8–11 year olds using 1999–2004 National Health and Nutrition examination Survey (NHANES) data from whole body DXA scans (Hologic; Bedford, Massachussetts) were used to determine over fat (>85th percentile) and obese (greater than 95th percentile) classifications based on sex.[28]

Additional anthropometric measures included: segmental length, arm span, weight, abdominal circumference, chest circumference, ulnar length, mid-arm circumference, and triceps skinfold thickness. Length and circumference measures were obtained using a nonstretchable tape measure to the nearest mm. Triceps skinfold thickness was measured using the Lange skinfold caliper (Santa Cruz, CA) to the nearest mm on the right side. Measurements were obtained by trained study staff using standard assessment methods.[29]

Body mass index (BMI) for age percentiles were determined using Center for Disease Control (CDC) growth charts.

Per CDC criteria, a BMI for age greater than the 85th percentile was considered overweight; a BMI greater than the 95th percentile was considered obese.

Three-day dietary record

A three-day dietary record for two weekdays and one weekend day was obtained from participants prior to their OGTT visit. Diet records were analyzed using Food Processor nutrition analysis software (version 10.5.2, 2009 ESHA Research, Salem, Oregon).

Insulin resistance and hyperinsulinemia standards

Homeostatic model assessment for insulin resistance (HOMA-IR) was used to evaluate insulin resistance. Insulin resistance was calculated as equaling fasting glucose (mg/dL) x fasting insulin (μU/mL)/ 405.[30] Insulin resistance levels were compared with HOMA-IR cut-off values in obese children and adolescents (2.67 for prepubertal children, 3.82 for pubertal females, and 5.22 for pubertal males).[31] Insulin levels at 0, 30, 60, 90, and 120 minutes during the OGTT were totaled.[32] Hyperinsulinemia was defined as an insulin sum greater than 300 μU/mL.[31]

Fasting Visit

During the second visit, participants underwent a medically supervised 20 hour fast after receiving the same standardized evening meal with snack. Initial fasting lab samples were analyzed for: insulin, glucose, epinephrine, norepinephrine, cortisol, glucagon, free fatty acids, and PQAA. Blood samples were collected every two hours for glucose, insulin, and cortisol. Additional samples were collected every 4 hours for glucagon, free fatty acids, and PQAA. Epinephrine and norepinephrine samples were collected at 4 hours, 12 hours, 16 hours, and at 20 hours after beginning the fast. Glucose labs were analyzed at the bedside using YSI monitors. All other labs were analyzed by ARUP Laboratories. Each void was tested for urinary ketones using Ketostix. For initial and final voids, urine samples were collected and sent to ARUP Laboratories for complete urinalysis.

Data Collection and Statistical Methods

Study data were collected and managed using REDCap (Research Electronic Data Capture) .[33] Descriptive statistics were used to evaluate pilot data using Microsoft Excel (Version 14). Pre- and post-fasting data were evaluated using Wilcoxon sign ranks. Significance was set at $P<0.05$ for all comparisons; no adjustments were made for multiple testing as this analysis was considered to be exploratory in a relatively small sample size.

RESULTS

Sex, ethnicity, race, and age were reported on the parental consent form for each participant. Six participants were enrolled in the study: 4 males and 2 females. All six participants completed both study visits. Participants were between 7 to 11 years old (mean age 8.9±1.7 years). Ethnicity and race included: 5 Non-Hispanic Caucasian, and 1 Hispanic African American. Four participants (3 males, 1 female) were considered prepubertal. One female and one male were considered pubertal based on age and Tanner stage. Only one patient had a gastrostomy tube. Tube placement was for supplemental nighttime feeds and consisted of

less than 50% of total caloric intake. Per patient and parental report, participants did not have issues with swallowing, with one exception after an illness. However, a videofluoroscopic swallow study performed prior to study enrollment for this participant was normal. Three of 6 participants were taking valproic acid and l-carnitine as a putative disease- modifying therapy for SMA.

Several participants employed the use of respiratory therapies. Two participants, A and B, used BiPAP 6–12 hours daily. The other 4 participants reported never using BiPAP. Participant B used cough assist daily. All 6 participants reported the use of cough assist or vest therapy as needed during illness.

Frequency and duration of physical activity was reported. At the first visit, 5 participants reported at least 30 minutes of range of motion activity daily. All participants spent at least 30 minutes in a stander at least twice a week. Other physical activity included swimming 1–2 times/week for at least an hour for two participants. One innovative physical activity reported by one participant included a supported harness system attached to a treadmill for supported walking. Only one participant, F, reported at least an hour of physical activity daily.

DXA and Anthropometrics

DXA results, BMI, and BMI classification for each participant are included in Table I. Five of 6 participants were classified as overweight or obese based on BMI for age percentile greater than the 85th percentile. DXA scan results presented average lean body mass of 10.44 ± 6.93 kg. Average total fat mass was 24.82 ± 4.65 kg. Percent body fat, calculated using DXA scan results, averaged 71.6±13.1% body fat. Using NHANES DXA scan comparative data from children 8–11 years of age for body composition reference range criteria, all study participants' percent body fat exceeded the 95th percentile and thus are considered obese.

Oral Glucose Tolerance

Baseline hemoglobin A1c and IGF-1 values (Table I) were within normal ranges with the exception of participant B. This participant's hemoglobin A1c level was slightly elevated and considered to be in the pre-diabetic range. Participant D reached laboratory criteria for hypoglycemia following completion of the OGTT with a YSI glucose level of 52.4 mg/dL (2.9 mmol/L), but remained clinically asymptomatic. However, an increased amplitude of hand tremor (polyminimyoclus) was evident as she fed herself her lunch. Interestingly, this participant was the only child unable to consume the prescribed amount of glucose drink (leaving 5 ml). Glucose ranges during the OGTT are summarized in Figure 1. Glucose values were above documented normal blood glucose reference values in normal children during OGTT. Oral glucose tolerance testing indicated that 3 of 6 participants exhibited impaired glucose tolerance. Two of the 3 participants with OGTT determined impaired glucose tolerance had been on stable doses of valproic acid for several years. None of these children had a family history of diabetes.

Basal glucose and insulin levels were analyzed using the HOMA-IR assessment model. Values for determining prepubertal and pubertal insulin resistance for obese children were

used for comparison in Table I. Four of 6 and 5 of 6 participants were considered insulin resistant based on this model for basal glucose and insulin levels at the OGTT and fasting visits, respectively.

All of the participants demonstrated hyperinsulinemia during the OGTT. The sum of insulin levels at 0, 30, 60, 90, and 120 minutes were calculated for each participant (Figure 2).

Three-Day Dietary Records

Five participants submitted dietary records for review. The mean and standard deviation of caloric intake for patients was 1328.2±90.4 calories (39.9±10.8 kcal/kg body weight and 9.8 ±1.1 kcal/cm height). Protein intake was 55.3± 13.8 g (1.6± 0.4 g protein/kg body weight). Percent energy intake of fat and carbohydrates were 35.9± 2.4% and 47.9±6.0%, respectively. Fiber intake was 12.1±4.2 g.

Fasting

All participants completed 20 hours of medically supervised fasting without glucose levels falling below 54 mg/dL (3.0 mmol/L). Symptoms were monitored and recorded at least every 2 hours. The most commonly reported symptom was hunger/stomach ache for 4 participants. One participant complained of a mild headache at 16 hours that resolved by the 18 hour mark; one participant reported being tired at 20 hours. After the fast concluded, a noticeable increase in polyminimyoclonus amplitude was observed in one participant. Group mean insulin levels fell to within normative fasting insulin values after 14 hours of fasting. Figure 1 depicts insulin and glucose levels during OGTT and Fasting visits.

Many plasma metabolites and hormones changed significantly before and after fasting. (Pre- and post-fasting values are summarized in Table II; available at www.jpeds.com). At the end of fasting, insulin values were significantly decreased ($P<0.05$). Alanine, branched chain amino acids (BCAA), methionine, and phenylalanine were among the amino acids significantly decreased after fasting ($P<0.05$). Free fatty acids were significantly increased after fasting ($P<0.05$). Glutamine, cortisol, norepinephrine, and epinephrine values remained relatively unchanged. Mean and standard deviation values of epinephrine pre- and post-fast and norepinephrine pre-and post-fast were 56.0±6.5 pg/mL (n=3) and 69.0±24.2 pg/mL (n=4), 199.5±116.9 pg/mL (n=6) and 222.6 ±130.0 pg/mL (n=5), respectively. Ketones were present in the urine of 3 of the 6 participants at the end of the fasting visit.

Most glucagon levels obtained during the OGTT and fasting visits remained below detectable limits, <25 ng/L. Those glucagon values that were detectable did not demonstrate recognizable trends or associations with other study data.

DISCUSSION

Our pilot cohort study results suggest that obese children with SMA type II are at increased risk for insulin resistance and impaired glucose tolerance and demonstrate abnormal glucose metabolism in a well state. Specifically, the children in our study demonstrated hyperinsulinemia during the OGTT and insulin resistance based on HOMA-IR modeling. Half of the participants met diagnostic criteria for impaired glucose tolerance. Such findings

emphasize the importance of obesity assessment and future glucose metabolism research in patients with SMA.

Hyperinsulinemia in children with SMA has serious potential long-term health implications. Hyperinsulinemia may precede the glucose intolerance exhibited in diabetes by 10 years.[34,35] The development of type 2 diabetes often begins with hyperinsulinemia and normal or slightly elevated glucose that ultimately leads to impaired glucose tolerance and insulin resistance.[36] In the United States, approximately 1 in 433 youth have diabetes; type 2 diabetes comprises 0.24/1000.[37,38] Clinically, we are aware of 3 of 153 individuals with SMA type II in our natural history study database with documented type 2 diabetes. Two of them presented in childhood; one, an obese Hispanic girl, presented in diabetic ketoacidosis. LaMarca et al reported a 29-year- old male who likewise presented in diabetic ketoacidosis.[39] Several other children or adolescents have manifested hyper and hypoglycemia and/or metabolic acidosis in a catabolic setting, but have not been formally evaluated.

In our study, hemoglobin A1c levels did not accurately reflect the degree of glucose metabolism abnormalities discovered with OGTT and do not appear to be a sensitive screening measure to assess patients with SMA for glucose intolerance in this setting.

The 6 participants in this study were all considered to be obese based on DXA determined body composition. Alternatively, using BMI for age percentiles on the CDC growth chart, only half were considered obese. Obesity is the largest determinant for insulin resistance in youth[40] and the prevalence of metabolic syndrome rises with increased obesity.[41] Previous research has indicated that children with SMA have increased fat mass and diminished lean mass when compared with healthy peers regardless of BMI.[10,11] However, determining obesity in patients with SMA is difficult, because they may appear normal on growth charts and in person even in the setting of obesity. Based on previously published and unpublished research and clinical data, we suggest that children with SMA type II should be evaluated for obesity using appropriate anthropometrics/body composition analysis annually and especially with a BMI for age greater than the 25th percentile, gynecomastia, or increased abdominal fat and referred appropriately by their primary care provider.

Diet record analysis indicates that our patients are not eating excessive amounts of carbohydrates or calories in comparison with dietary reference intake (DRI) guidelines.[42] However, our cohort’s dietary fiber intake comprised half the amount of fiber recommendations (25–31 g). Decreased fiber intake is associated with increased obesity risk and impaired glucose metabolism in adolescents.[43] Decreased physical activity caused by decreased mobility and muscular weakness also puts patients with SMA and other neuromuscular diseases at increased risk of obesity. Only one of our participants met the Physical Activity Guidelines for Americans of one hour of physical activity daily.[44] All participants in this study were confined to an electric wheelchair for the majority of each day, with limited opportunities for exercise especially during school days. As they get bigger, the significant assistance and equipment required to safely permit regular daily physical activity becomes an increasing obstacle.

We suspect that being overly fat plays a role in the observed glucose metabolism abnormalities. However, we cannot preclude developmental pancreatic defects, as implicated in mouse model studies. Bowerman et al demonstrated abnormalities of glucose metabolism in a SMA and *SMN*-depleted mouse model that may be potentially relevant to disease pathogenesis in humans.[24,25] Their *SMN* 2B/− intermediate SMA mice were glucose intolerant; intolerance increased with age. These mice exhibited hyperglucagonemia, increased insulin sensitivity, and fasting hyperglycemia. Pancreatic islet cells in the SMA mice demonstrated a markedly increased proportion of glucagon-producing α cells and decreased number of insulin-producing β cells. This phenomenon was also observed in samples from 6 deceased human infants with SMA type I from our natural history cohort.[24] Aged *SMN*-depleted mice (*SMN*+/−), which may be similar to milder forms of SMA, demonstrated weight gain, hyperinsulinemia, increased number of β cells, increased hepatic insulin and glucagon sensitivity, and fasting hyperglycemia.[25]

In contrast, the children in this pilot study did not exhibit hyperglucagonemia, glucagon sensitivity, or increased insulin sensitivity. Baseline insulin and glucose values were sufficiently high to indicate insulin resistance and half of the OGTT results indicated impaired glucose tolerance. Similar to aged *SMN*-depleted mice, our cohort demonstrated increased weight gain and hyperinsulinemia. We hypothesize that the *SMN*-depleted mice more closely mimic milder variants of SMA and we could potentially see more pronounced abnormalities with age. Pancreatic abnormalities may also exist, but this has not been evaluated.

Prior published research indicates a poor tolerance for fasting in patients with neuromuscular disease. Orngreen et al examined this issue in adults with various neuromuscular diseases including 4 adult patients with SMA type II who developed hypoglycemia within 14–23 hours of fasting.[22] Bruce and Jacobsen studied two females with SMA type II with a history of hypoglycemia and coma. Both developed ketonuria during the course of a 12-hour fast, and one developed hypoglycemia.[23] The authors of both studies concluded that neuromuscular patients with lower lean body mass were at increased risk for hypoglycemia.

Surprisingly, all participants in our study successfully completed the 20-hour fast without exhibiting laboratory evidence of hypoglycemia. One participant’s increased hand tremor may indicate subclinical symptoms/effects of fasting not been captured in the laboratory data. Age of participants may have been a factor because lean muscle mass decreases over time in SMA.[10] Thus, a longer period of fasting may have been necessary in this younger age group to demonstrate fasting issues. We observed a significant drop in alanine, BCAAs, and phenylalanine, and increases in plasma free fatty acids and urinary ketones during the fast. BCAA concentrations in healthy adults become elevated during fasting due to transamination of BCAA in the muscle.[43] We hypothesize that the decrease in BCAA in our cohort was due to the significantly reduced lean muscle mass in SMA. We also observed a significant decrease in alanine during fasting, a marker of energy metabolism. This decrease has also been noted by Orngreen for adult neuromuscular patients compared with healthy age-matched controls.[22] Interestingly, the insulin levels in neuromuscular patients in their study were significantly higher in the fed versus the fasted state, an increase not observed in

healthy adult controls. In our present study, insulin levels prior to fasting were also significantly higher in the fed versus fasted state.

Limitations of this study include the small number of participants in this pilot study which precluded recruiting a broad spectrum of patients with SMA type II. Patients with SMA type II requiring greater than 50% of calories via gastrostomy tube were specifically excluded to standardize intake. Due to this exclusion criterion and concerns of increased risks of decompensation in the setting of the prolonged fasting associated with this study, patients who were underfed or cachectic were less likely to participate. Thus, we cannot extend our observations to those patients. Additionally, study observations do not predict how our obese patients would fare with prolonged fasting in the setting of a catabolic state during illness or associated with several days of inadequate nutrition. DXA data obtained in this study used different DXA equipment than the NHANES data. We cannot preclude a potential contributing effect of valproic acid on weight and glucose metabolism abnormalities in 3 of 6 participants. Because all participants were considered obese by DXA determined body fat composition compared with healthy peers, implications from this study should be restricted to this cohort. The lack of appropriate age- matched controls limits our conclusions as to whether the metabolite changes observed in patients with SMA type II during fasting are clinically significant compared with healthy children. We were unable to obtain historical fasting reference data for these metabolites in healthy children for comparison.

In conclusion, all six children with SMA type II participating in this pilot study demonstrated hyperinsulinemia with insulin resistance and/or impaired glucose metabolism. Obesity is a growing problem in general, but especially in children with neuromuscular diseases including SMA, many of whom do not appear clinically obese. More research is needed to determine the extent of glucose metabolism and fasting abnormalities in children across the heterogeneous SMA population along with other neuromuscular diseases. Further studies are needed to determine the modifying impact that body composition may play in response to fasting and glucose loading in neuromuscular patients. Appropriate strategies for diagnosis, referrals for dietary counseling and clinical management of metabolism issues in children with SMA and other neuromuscular diseases warrant more attention to help ensure the best outcomes for our patients well into their adult years.

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ABBREVIATIONS AND ACRONYMS

SMA	Spinal muscular atrophy
DXA	Dual energy x-ray absorptiometry
OGTT	Oral glucose tolerance test

SMN	Survival motor neuron
HOMA-IR	Homeostatic model assessment for insulin resistance
BMI	Body mass index
PQAA	Plasma quantitative amino acids
BCAA	Branched chain amino acids

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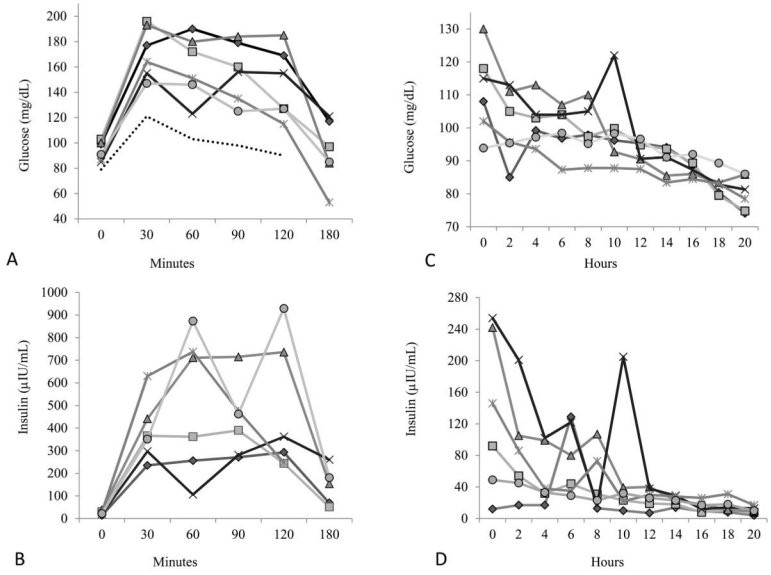

Figure 1.

(A) Individual plasma blood glucose levels during the oral glucose tolerance test in 6 children with SMA type II. The dashed bottom line represents the mean value for healthy children.[27] The dotted line at 140 mg/dL represents the cut-off for impaired glucose tolerance at 120 minutes. (B) Individual plasma insulin levels during the oral glucose tolerance test for the same 6 children. (C, D) Individual plasma blood glucose and insulin levels, respectively during the medically supervised 20-hour fast in 6 well children with SMA type II.

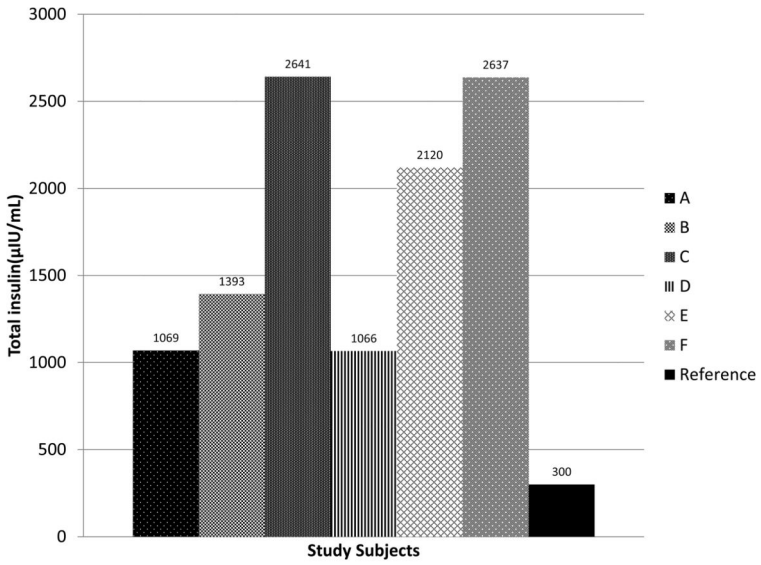

Figure 2.

The sum of insulin levels during the oral glucose tolerance test (at 0, 30, 60, 90, and 120 minutes) for 6 children with SMA type II. All of the participants exceeded established cut-off values for children for hyperinsulinemia.[31]

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Table 1

Baseline labs, body composition and insulin resistance measures for SMA type II pilot study(n=6)

Participant	BMI(kg/m^2)	BMI for age classification	Body fat (%)	HgA1c (%)	IGF-1 (ng/mL)	HOMA- IR OGTT	HOMA IR Fasting	120min Glucose (mg/dL)
A	15.6	Normal	56.66	5.3	477	3.42^B	1.65^B	**169**
B	18.9	Overweight	83.43	**5.7**	261	**7.89**^{C}	**4.45**^{C}	127
C^A	23.3	Obese	76.10	5.1	147	**9.38**^{C}	**8.94**^{C}	**185**
D^A	21.3	Obese	82.14	4.9	127	**3.78**^{C}	**8.50**^{C}	**155**
E^A	23.0	Obese	77.54	5.4	198	**6.23**^{C}	**6.48**^{C}	115
F	20.8	Overweight	53.52	4.9	234	4.94^B	**6.20**^{B}	127

BOLD Values out of normal reference range

^{A}Using valproic acid

^{B}Cut off value 3.82 for pubertal females, 5.22 for pubertal males[31]

^{C}Cut-off value2.67 for prepubertal children[31]

Table 2

Summary of pre and post fast plasma metabolites and hormones in 6 children with type II SMA after a 20 hour fast

	Fed State (Pre Fast)					Fasted State (Post Fast)					
Metabolite/hormone	**median**	**Q1**	**Q3**	**Min**	**Max**	**median**	**Q1**	**Q3**	**Min**	**Max**	**P value[A]**
Glucose (mg/dL)	111.5	102	118	98.9	130	79.9	74.8	85.8	74.1	86	0.03 *
Insulin (uIU/mL)	119	49	242	12	254	9.5	8	13	4	17	0.03 *
Cortisol (ug/dL)	6.9	1.8	12	1.6	14.1	4.7	4.5	4.9	3.6	9.7	0.56
Free fatty acids(mmol/L)	0.24	0.14	0.37	0.12	0.65	0.94	0.93	1.07	0.91	1.39	0.03 *
Glutamine (umol/L)	421.5	348	500	273	562	397	356	519	317	531	1
Alanine (umol/L)	508	378	723	314	773	185	167	240	151	275	0.03 *
Arginine (umol/L)	97	87	104	84	134	52.5	49	66	39	70	0.03 *
Asparagine (umol/L)	44	39	63	34	67	26.5	23	34	23	39	0.03 *
Citrulline (umol/L)	25.5	15	35	14	39	17.5	17	21	16	26	0.1
Cystine (umol/L)	29.5	23	34	19	42	35.5	32	39	24	41	0.31
Glutamic acid (umol/L)	69	40	93	26	110	44	19	84	13	85	0.03 *
Glycine (umol/L)	197	172	245	158	257	183.5	174	272	159	309	0.68
Histidine (umol/L)	72.5	67	77	57	87	62.5	59	69	58	88	0.43
Isoleucine (umol/L)	104	94	122	43	211	51.5	41	64	35	67	0.03 *
Methionine (umol/L)	38.5	21	42	17	43	14	14	15	12	20	0.03 *
Leucine (umol/L)	171	146	208	73	335	95	87	103	59	110	0.03 *
Lysine (umol/L)	204.5	153	226	123	289	107	97	111	85	148	0.03 *
Ornithine (umol/L)	57	52	77	36	88	29	25	35	21	37	0.03 *
Phenylalanine (umol/L)	80	58	87	52	88	40.5	38	50	30	51	0.03 *
Proline (umol/L)	331	241	444	213	533	99.5	96	119	86	126	0.03 *
Serine (umol/L)	134.5	121	144	109	147	117	106	128	100	130	0.07
Taurine (umol/L)	39	34	51	33	54	45.5	34	57	33	58	0.32
Threonine (umol/L)	135	111	165	93	182	64.5	59	85	45	104	0.03 *
Tryptophan (umol/L)	54.5	43	69	39	79	42	31	45	24	46	0.06

	Fed State (Pre Fast)					Fasted State (Post Fast)					
Metabolite/hormone	**median**	**Q1**	**Q3**	**Min**	**Max**	**median**	**Q1**	**Q3**	**Min**	**Max**	**P value[A]**
Tyrosine (umol/L)	113.5	65	125	52	127	35	33	43	29	52	0.03*
Valine (umol/L)	376.5	276	415	156	602	171.5	158	206	114	249	0.03*

[A] Wilcoxon Sign Rank test pre and post fasting

* $P < 0.05$