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ARTICLE

Poor Specificity of Low Growth Hormone and Cortisol Levels During Fasting Hypoglycemia for the Diagnoses of Growth Hormone Deficiency and Adrenal Insufficiency

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What's Known on This Subject

Insulin excess and deficiencies of GH and cortisol are important causes of pediatric hypoglycemia. Measures of insulin, GH, and cortisol are recommended at the time of hypoglycemia for diagnostic purposes, but the utility of GH and cortisol levels have not been established.

What This Study Adds

Despite the recommendation that GH and cortisol be measured at the time of hypoglycemia, these measures are not reliable in diagnosing deficiencies of either of these hormones. This study establishes that fasting hypoglycemia is not an adequate diagnostic test for sufficiency of these hormones.

ABSTRACT

OBJECTIVES. Fasting tests are used to identify the cause of hypoglycemia in children. The purposes of this study were to (1) determine whether growth hormone and cortisol levels obtained at the time of hypoglycemia in such tests can identify children with growth hormone and/or cortisol deficiency and (2) identify potential clinical factors that influence growth hormone and cortisol responses to hypoglycemia.

STUDY DESIGN. The design consisted of chart review of all diagnostic fasting tests conducted over a 3-year period ($n = 151$). A normal growth hormone level was defined as ≥7.5 ng/mL, and a normal cortisol level was defined as ≥18 μg/dL.

RESULTS. During the fasting tests, 84 children (median age: 1.3 years [2 days to 14.3 years]), became hypoglycemic, with blood glucose ≤50 mg/dL. Diagnoses included normal, ketotic hypoglycemia, hyperinsulinism, fatty acid–oxidation defects, glycogen-storage disease, and late dumping hypoglycemia. A total of 70% had growth hormone and cortisol levels less than the "normal" thresholds regardless of diagnosis. Of various factors (age, diagnosis, fast duration, duration blood glucose level of <60 mg/dL, and blood glucose nadir), only age was positively associated with cortisol, and none were consistently related to growth hormone.

CONCLUSIONS. A singe low growth hormone or cortisol value at the time of fasting hypoglycemia has poor specificity for the respective diagnoses of growth hormone deficiency and adrenal insufficiency. *Pediatrics* 2008;122:e522–e528

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Key Words
hypoglycemia, children, fasting test, growth hormone deficiency, adrenal insufficiency

Abbreviations
GH— growth hormone
GHD— growth hormone deficiency
BG— blood glucose

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FASTING TESTS ARE routinely used to evaluate children with hypoglycemia. These tests take advantage of normal fasting adaptation, a process characterized by increasing serum free fatty acid and ketone levels.[1–6] Deviations from expected levels of these alternative fuels provide important clues for the diagnosis of a metabolic defect. Fasting tests have also been used to uncover hormonal defects such as congenital hyperinsulinism and hypopituitarism, important considerations in children with hypoglycemia. Although insulin is routinely measured at the time of hypoglycemia, this measure is not a reliable marker for hyperinsulinism. Instead, the diagnosis frequently depends on other findings at the time of hypoglycemia: suppressed ketones, suppressed free fatty acids, and a glycemic response to glucagon.[7–9]

Growth hormone (GH) and cortisol measurements have also conveniently been included in the "critical" sample obtained at the time of hypoglycemia during a fasting test as a means to exclude deficiencies of these hormones.[10] This practice is based on the insulin-induced hypoglycemia of the insulin-tolerance test, a potent stimulus for GH[11] and cortisol[12,13] secretion. Moreover, because GH is "tonically elevated" in the newborn period, experts recommend that GH be measured in the neonate with hypoglycemia and that concentrations of <20 μg/L suggest GH deficiency (GHD).[14,15]

However, clinical experience suggests that, at the time of hypoglycemia, GH and cortisol concentrations are frequently not above the thresholds defined as normal for provocative studies. The purposes of this study were to (1)

determine whether GH and cortisol concentrations during fasting hypoglycemia are commonly low in the absence of true hormone deficiencies and (2) identify clinical factors that might influence GH and cortisol at the time of hypoglycemia.

METHODS

Chart Review

The Children's Hospital of Philadelphia, Division of Endocrinology, is a major referral center for the diagnosis and management of congenital hyperinsulinism and other forms of hypoglycemia. A total of 151 fasting tests conducted during the evaluation of hypoglycemia (January 2002–December 2005) were reviewed. Only tests that were terminated for blood glucose (BG) levels of ≤50 mg/dL were included in the final analyses. All GH and cortisol data, final diagnosis, age, duration of fast, BG nadir, medications, and growth were extracted from patient charts. The duration of time BG was ≤60 mg/dL before it reached ≤50 mg/dL was also recorded as a marker of tempo and rapidity of hypoglycemia onset; some children linger with BG in the 50s, whereas others have fairly long fasting durations with a BG level of >70 mg/dL and then acutely have hypoglycemia. GH data were excluded for octreotide treatment. Cortisol data were excluded for oral glucocorticoid treatment.

Fasting Tests

All patients were admitted to the Children's Hospital of Philadelphia. The fast start was defined as the time a feed or meal was completed. Bedside BG levels were measured frequently on a SureStep meter (Lifescan, Milpitas, CA). Blood ketone levels were measured at the bedside by using the Precision Xtra BG and ketone monitoring system (Abbott, Alameda, CA). The test was terminated for BG levels of ≤50 mg/dL (verified in the laboratory), for blood ketone levels of ≥2.5 mM, or if the child was able to fast for a defined period of time (age <1 month 12 hours; 1 month to 1 year ≥18 hours; 1–3 years ≥24 hours; and age >3 years ≥36 hours). At the termination of the test, blood was drawn to test BG, GH, cortisol, insulin, free fatty acids, β-hydroxybutyrate, and lactate; glucagon-stimulation testing was performed for BG levels at ≤50 mg/dL. Testing for acylcarnitine profiles and urine organic acids was performed.

A child who became hypoglycemic was considered normal if he or she was able to fast for the predefined period before becoming hypoglycemic and had normal fasting adaptation as defined by serum β-hydroxybutyrate ≥2.5 mM, a free fatty acids level of >1 mM, lactate at <2 mM, normal acylcarnitine and urine organic acid levels, and no response to glucagon. Ketotic hypoglycemia is essentially normal but shortened fasting adaptation in the setting of normal growth; this "diagnosis" is made when other diagnoses have been excluded.

Definitions

Hypoglycemia was defined as a BG level of ≤50 mg/dL. GH concentrations ≥7.5 ng/mL excluded GHD; this threshold is based on GH responses established as normal for standard GH-provocative studies.[16] Similarly, a normal cortisol level was defined as ≥18 μg/dL[17–20] on the basis of thresholds established for insulin-tolerance and standard corticotropin-stimulation tests.[17–20]

TABLE 1 **Patient Characteristics ($N = 84$)**

Variables	GH Available	Cortisol Available
Total (female), *n*	68 (37)	76 (39)
Age	2 (2 d to 14.3 y)	1.8 (2 d to 14.3 y)
<1 mo (2–26 d), *n*	4	8
>1 mo, *n*	64	69
Final diagnosis, *n*		
Normal	15	15
Ketotic hypoglycemia ($n = 16$)	16	15
Hyperinsulinism		
Congenital ($N = 37$)	24	33
Perinatal-stress induced ($N = 5$)	4	4
Late dumping syndrome ($N = 3$)	2	2
Glycogen storage disease type 1 ($N = 1$)	1	1
Fatty acid–oxidation defect ($N = 4$)	3	4
Isolated GH deficiency ($N = 2$)	1	1
Isolated corticotropin deficiency ($N = 1$)	1	1
Blood glucose nadir, median (range), mg/dL	45 (25–50)	
Fasting duration, median (range), h	14.3 (10 min–33)	
Time BG < 60 mg/dL, median (range), h	1 (0–9.5)	

Statistical Analyses

Means and SDs or medians and ranges, depending on normality, were used to summarize continuous variables; proportions were used for categorical variables. Continuous data were compared by using *t* tests or the Wilcoxon rank-sum test. The χ^2 test was used to compare binomial proportions. Two-sided tests were used, and $P < .05$ was considered significant. Nonnormally distributed continuous data were transformed to improve fit. Linear regression was used to identify factors important for GH and cortisol responses by using Stata 9 (Stata Corp, College Station, TX).

The protocol was approved by the Children's Hospital of Philadelphia Institutional Review Board.

RESULTS

During the 4-year interval, 84 of 151 fasting tests were terminated for BG concentrations of ≤50 mg/dL. Characteristics of children with GH ($n = 68$) and cortisol ($n = 76$) data available are shown in Table 1. Most were infants and young children. The majority were diagnosed as normal or as having ketotic hypoglycemia or hyperinsulinism. Two children with Nissen fundoplications had late dumping syndrome (postprandial hypoglycemia). Diagnoses among children <4 weeks of age varied: normal ($n = 1$), Glycogen storage disease type 1 ($n = 1$), and hyperinsulinism–congenital ($n = 5$) and perinatal stress-induced ($n = 1$). Formal GH-provocative studies were performed for 4 children; their final diagnoses included GHD ($n = 1$), ketotic hypoglycemia ($n = 1$), and hyperinsulinism ($n = 2$). Formal tests of the hypothalamic-pituitary-adrenal axis were performed for 8 children; the final diagnoses included normal ($n = 2$),

hyperinsulinism (n = 4), isolated GHD (n = 1), and isolated corticotropin deficiency (n = 1).

A 15-month-old girl with isolated congenital GHD had a GH concentration of 4 ng/mL obtained at hypoglycemia and a peak GH response to arginine and clonidine stimulation studies of 4.7 ng/mL. A second child with an established diagnosis of isolated congenital GHD at the time of fasting did not have GH measured because she was receiving GH treatment. This child had a cortisol concentration of 16.3 μg/dL at hypoglycemia; stimulation studies revealed that the peak cortisol level was 31 μg/dL. One child was diagnosed with isolated corticotropin deficiency on the basis of clinical presentation, cortisol level of <0.1 μg/dL at hypoglycemia, and undetectable cortisol and low corticotropin (3–4 pg/mL) responses to two corticotropin releasing hormone stimulation tests. Four children were classified as having fatty acid–oxidation disorders on the basis of having excessive free fatty acids and suppressed ketones.

The median BG level at test termination was 45 mg/dL, with 23 children having BG levels of ≤40 mg/dL. Fasting duration was varied. A total of 50% of children fasted for <14.5 hours, and 4 children fasted only 10 minutes. Once BG levels were at <60 mg/dL, 50% of children became hypoglycemic within an hour.

GH at the Time of Hypoglycemia

GH was obtained at the time of hypoglycemia in 68 children. GH was not obtained because of octreotide treatment (n = 9) or previously normal GH levels at the time of hypoglycemia (n = 6) or during stimulation studies (n = 1).

A total of 70% of the children in whom GHD was not previously excluded had GH concentrations of <7.5 ng/mL at the time of hypoglycemia (specificity of a low GH for GHD = 30%). Only 1 child, however, had GHD. Moreover, GH levels of <7.5 ng/mL were not limited to specific diagnoses (Fig 1). Children with normal fasting adaptation, ketotic hypoglycemia, hyperinsulinism, fatty acid–oxidation defects, glycogen-storage disease, and dumping would be diagnosed as having GHD if based exclusively on GH levels at the time of hypoglycemia. In fact, despite limiting analyses to normal or ketotic children (n = 31), 80% had GH levels of <7.5 ng/mL. Two of 4 children who became hypoglycemic within 10 minutes of fasting had GH levels of <7.5 ng/mL. Nine of 16 children with BG levels of ≤40 mg/dL had GH levels of <7.5 ng/mL, and GH with a BG nadir at ≤40 mg/dL (11.3 ± 13.6 ng/mL) was not significantly different from GH when the BG nadir was at >40 mg/dL (5.6 ± 6.2 ng/mL) (P = .13).

The impact of patient-specific factors on GH response was examined (Table 2). Only age was negatively associated with GH (P = .04). However, when data were reanalyzed after exclusion of an outlier, an infant with a GH concentration of 52.2 ng/mL, no association was found between age and GH at the time of hypoglycemia (P = .10). When data were analyzed with inclusion of only normal or ketotic children (median age: 2.4 years [range: 11 days to 8.4 years]), a negative association of age with GH was found (P = .01). However, GH levels of <7.5 mg/dL were not limited to a specific age range. In addition, at fasting test termination, children who did not become hypoglycemic displayed a wide spectrum of GH concentrations (6 ± 10 ng/mL, n = 54) that were not different from (1) children whose fasts were terminated for hypoglycemia (mean ± SD = 7.1 ± 8.7 ng/mL; P = .6), or (2) the subset of 16 children with BG nadirs of ≤40 mg/dL (P = .09). The percentage with GH levels of <7.5 ng/mL was not different between hypoglycemic and nonhypoglycemic groups (P = .5).

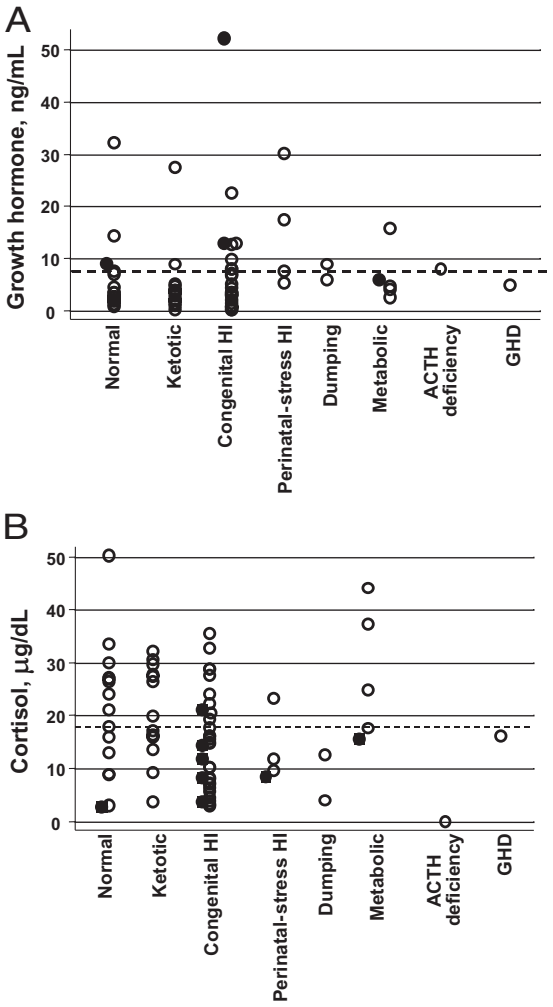

FIGURE 1
GH and cortisol at time of hypoglycemia according to final diagnosis. A, GH concentrations according to diagnosis in children undergoing diagnostic fasts (n = 68). A GH concentration of ≥7.5 ng/mL was defined as normal. B, Cortisol concentrations according to diagnosis in children undergoing diagnostic fasts (n = 76). A cortisol concentration of ≥18 ng/mL was defined as normal. Metabolic refers to patients with fatty acid–oxidation disorders (n = 4) or glycogen-storage disease type 1 (n = 1). Infants <4 weeks of age are indicated by closed circles, and children >4 weeks of age are indicated by open circles.

Cortisol at the Time of Hypoglycemia

Cortisol was obtained at the time of hypoglycemia in 76 children. In the remaining children, cortisol was not measured because it was previously documented as normal at the time of hypoglycemia (n = 3) or during

TABLE 2 **Relationship of Clinical Factors With GH and Cortisol Levels at Time of Fasting Hypoglycemia**

Variables		β-coefficient	P	R^2
Dependent	Independent			
Log_GH				
	Log_age	−0.19	.04	0.05
	Log_age (minus an outlier)	−0.15	.10	0.03
	Log_age (normal or ketotic only)	−0.39	.01	0.17
	Diagnosis		.1	
	Normal			
	Ketotic			
	Hyperinsulinism			
	Log_fast_duration	−0.06	.6	0.01
	BG_nadir³	0	.07	0.03
	Log_BG≤60	0.22	.12	0.02
	Sqrt_cortisol	0.09	.44	0.01
Sqrt_Cortisol				
	Log_age	0.26	.006	0.09
	Log_age (minus outliers)	0.26	.009	0.08
	Log_age (normal or ketotic only)	0.68	<.001	0.33
	Diagnosis			0.09
	Hyperinsulinism	−0.76	.05	
	Diagnosis adjusted for age			0.13
	Hyperinsulinism	−0.53	.18	
	Log_age	0.21	.07	
	Log_fast_duration	0.31	.012	0.07
	Log_fast_duration adjusted for age			0.11
	Log_fast_duration	0.22	.08	
	Log_age	0.20	.04	
	BG_nadir³	0	.63	0.003
	Log_BG≤60	0.03	.83	0.001

stimulation studies ($n = 4$) or because of sampling error ($n = 1$). Four children with normal fasting tolerance were treated with inhaled glucocorticoids: 2 had cortisol levels of >18 μg/dL at the time of hypoglycemia, whereas the other 2 had cortisol levels of <18 μg/dL but normal responses to provocative studies.

Cortisol concentrations of <18 μg/dL at the time of hypoglycemia were found in 61% of children (the specificity of a low cortisol level for adrenal insufficiency is 40%). Only 1 child had documented adrenal insufficiency (isolated corticotropin deficiency). Cortisol levels of <18 μg/dL were not limited to specific diagnoses (Fig 1). Inclusion of only normal or ketotic diagnoses reduced the percentage of children with cortisol concentrations of <18 μg/dL to 47%. Three of the 4 children who became hypoglycemic within 10 minutes of fasting had cortisol concentrations of <18 μg/dL. Eleven of 23 with BG levels of ≤40 mg/dL had cortisol concentrations of <18 μg/dL, and cortisol concentrations did not differ between the subset of hypoglycemic children with nadir BG levels of ≤40 mg/dL (17.9 ± 10.7) and those with nadir BG levels of >40 mg/dL (17.4 ± 10.5) ($P = .85$).

The impact of patient-specific factors on cortisol responses was examined (Table 2). Age was positively associated with cortisol ($P = .006$) even after exclusion of 2 outliers. This relationship persisted with restriction of data to those from children diagnosed as normal or ketotic. Congenital hyperinsulinism predicted lower cortisol but after adjustment for age, neither hyperinsulinism ($P = .18$) nor age ($P = .07$) was significant. For the entire group, duration of fasting was positively associated with cortisol. However, after adjustment for age only, the relationship between age and cortisol persisted ($P = .04$), likely reflecting the tendency toward longer fasting durations in older children because they frequently have normal fasting adaptation or ketotic hypoglycemia.

No relationship was found between GH and cortisol or with either of these outcomes and BG nadir or duration of BG levels <60 mg/dL. Three patients with GH levels of <7.5 ng/mL had GH obtained 30 to 70 minutes after hypoglycemia; all remained at <7.5 ng/mL. None had nadir BG levels of ≤40 mg/dL. In contrast, 2 of 4 children, in whom repeat sampling was performed 10 to 70 minutes after hypoglycemia, had cortisol levels of >18 μg/dL; 1 had a BG nadir at ≤40 mg/dL.

DISCUSSION

The results of this study demonstrate that GH and cortisol concentrations obtained at the time of hypoglycemia in children undergoing fasting tests are frequently below the thresholds established as normal. This finding raises the possibility that a large percentage of children would erroneously be diagnosed as adrenally insufficient or as having GHD on the basis of the "critical" sample alone.

Because most children did not undergo formal provocative studies to exclude either GHD or cortisol deficiency, the possibility exists that some children with values below the threshold defined as normal did, indeed, have deficiencies of these hormones. Misclassification is primarily a concern here for the children diagnosed with ketotic hypoglycemia because this "diagnosis" is made when other etiologies have been excluded. Because outside the neonatal period a child's growth provides an important clue to the diagnosis of GHD, GH results are interpreted in light of the child's growth. Growth was normal in the ketotic cohort except in 1 child in whom GHD was subsequently excluded through provocative studies. Normal growth renders GHD in this subset of children highly improbable. In addition, normal growth is reassuring in the context of a low cortisol level because corticotropin deficiency in the absence of GHD is rare. Adrenal insufficiency attributable to exogenous glucocorticoid is an obvious exception. Children on oral glucocorticoids were excluded from this study, and children treated with inhaled glucocorticoids underwent provocative studies to exclude adrenal insufficiency. Addison's disease is also unlikely to be missed, because children with this disease do not typically present with isolated hypoglycemia but with a constellation of findings and symptoms including hyperpigmentation, weight loss, nausea, electrolyte abnormalities, and hypotension.

A number of other limitations deserve mention. Because the Children's Hospital of Philadelphia is a major referral center for congenital hyperinsulinism, our sample represents a significant referral bias and is not a simple random sample of all children with hypoglycemia. In fact, many children with hypoglycemia attributable to GHD and/or adrenal insufficiency would never be referred to Children's Hospital of Philadelphia but

would be diagnosed and treated locally. On the other hand, our normal and ketotic children are a representative sample of children with hypoglycemia because they were referred from the local community. Another issue is that GH and cortisol testing was not repeated for children who had had previously documented normal GH ($n = 6$) or cortisol ($n = 3$) levels at the time of hypoglycemia. Even with inclusion of these children, however, 65% of children would be misdiagnosed as having GHD and 58% would be misdiagnosed as being adrenally insufficient.

The basis for inadequate GH responses to hypoglycemia remains in question. The vagaries of GH-provocative studies are well known; 25% of children without GHD will have an abnormal GH response to a single GH-provocative study. In 1969, discrepant responses to arginine and insulin-provocative studies were recognized: 13 children with short stature had subnormal GH responses (<7 ng/mL) during an insulin-tolerance test, but 8 of them had normal responses to an arginine-provocative test performed on a separate day. One interpretation of these results is that hypothalamic sensitivity to different stimuli varies; perhaps for the children in the current study, hypoglycemia was not a potent stimulus. In addition, patients with recurrent hypoglycemia may be desensitized and unable to mount a GH response to hypoglycemia. The finding of GH levels at <7.5 ng/mL regardless of diagnosis argues against this desensitization as the sole explanation. Children who are considered normal and those who are ketotic have only occasional hypoglycemia but were just as likely to be misdiagnosed as having GHD as children with untreated congenital hyperinsulinism, a condition with which hypoglycemia is frequent.

Moreover, according to the consensus guidelines for the diagnosis of GHD published by the Growth Hormone Research Society in 2000, GHD in a neonate is suggested by a random GH level of <20 ng/mL.[14] This threshold is much higher than the one adopted for this study, and applying this threshold to our neonates would have led to the diagnosis of GHD in all but 1. Other studies have suggested that a random GH level of <20 ng/mL may be found in neonates with GHD,[21,22] consistent with our findings. Nonetheless, whereas GH concentrations are tonically elevated in the newborn period,[23,24] a consistent association between age and GH at the time of hypoglycemia was not found in our population. In fact, no relationship was found between age and GH even in the children who did not become hypoglycemic, suggesting that fasting is not a potent stimulus for GH secretion. These findings echo those of Nitzan et al[2] in 1 of the first studies of fasting adaptation in children: plasma GH obtained at the time of fasting ketosis was <7.5 ng/mL in 11 of 12 children and did not differ from GH values obtained in the well state. The findings in our study differ somewhat from reports of adequate GH in neonates with hyperinsulinism but inadequate responses in older children with various forms of hypoglycemia.[25]

With respect to age and cortisol, the pituitary-adrenal axis matures postnatally.[26] In support of a developmental component is the finding that age was positively associated with the "critical sample" cortisol. However, a cortisol level of <18 μg/dL at the time of hypoglycemia was observed in both neonates and older children, consistent with a previous report.[25] These findings suggest that blunted cortisol responses to hypoglycemia are not attributable solely to hypothalamic-pituitary-adrenal axis immaturity.

In response to hypoglycemia induced by an insulin-tolerance test, cortisol and GH levels peak at 60 minutes but can peak as early as 30 and as late as 90 minutes.[27] Thus, the possibility that hormonal responses are delayed and consequently not identified by the critical sample should be considered. This retrospective review was not designed to study the possibility of delayed GH and cortisol peaks. The finding that 2 of 3 children with cortisol concentrations of <18 μg/dL had values above this threshold in delayed samples is noteworthy. To resolve this specific issue, cortisol has been measured every 10 minutes for 50 minutes after hypoglycemia in neonates with hyperinsulinism.[25] Cortisol concentrations at these delayed times remained below the defined normal threshold. Similarly, although some older children displayed enhanced responses 10 to 50 minutes after hypoglycemia, at least 4 had abnormal responses.[22] Given that insulin-tolerance test data in children who showed peak cortisol levels may not occur for 60 to 90 minutes,[27] additional evaluation of cortisol at these delayed times is warranted.

In contrast to the gradual onset of hypoglycemia that occurs with fasting in normal individuals, the insulin-tolerance test evokes a rapid decrease in BG. Thus, poor responses may reflect the prolonged BG decline before hypoglycemia.[28] Nonetheless, children with hypoglycemia within 10 minutes of fasting still had GH and cortisol concentrations below the defined normal thresholds, and responses were not associated with fast duration.

Another difference between insulin-tolerance and fasting tests is BG nadir. A BG nadir of 40 mg/dL or a 50% decrease in BG from baseline is required during the insulin-tolerance test to provoke GH and cortisol responses, and maximal stimulation of cortisol during an insulin-tolerance test may only occur below 40 mg/dL.[27] Because hypoglycemia has been defined as a BG level of ≤50 mg/dL, fasting tests were terminated once this threshold was met. BG levels were ≤40 mg/dL in 25% of the fasts, however, and BG nadir was not related to GH or cortisol response. In fact, inadequate GH and cortisol levels were present in 50% of children with BG levels at ≤40 mg/dL.

Inadequate responses in hyperinsulinism have been hypothesized to arise from (1) a direct effect of insulin on the hypothalamic-pituitary axis or (2) hyperinsulinism-causing mutations disrupting hypothalamic glucose-responsive cells.[25] Given that nearly 50% of our study population had ketotic hypoglycemia or was normal, these responses are unlikely to be a significant contributor to suboptimal responses.

The recommendation to measure GH and cortisol as part of the fasting test is worth reviewing. Fasting tests are designed to evaluate whether the mechanisms responsible for fasting adaptation (glycogenolysis, glu-

coneogenesis, fatty acid oxidation, and ketogenesis) are intact. Although hormonal regulation of these pathways is critical, at the time of hypoglycemia, an insulin level is not sensitive for the diagnosis of hyperinsulinism,[7] and GH and cortisol levels are not specific for deficiencies of these hormones. Whereas suppressed ketones and free fatty acids at hypoglycemia are indicative of hyperinsulinism, hypopituitarism in the neonate can mimic hyperinsulinism. A glucagon-stimulation test may help differentiate the two. In the older child, hypopituitarism resembles ketotic hypoglycemia (normal but shortened fasting adaptation). Thus, other assessments of GH sufficiency such as growth and growth factors are recommended in older children. The utility of measuring GH and cortisol during other times of the fasting test, such as early morning (when cortisol is known to peak) or an hour after sleep onset (when GH is known to peak) or after administration of glucagon (a known stimulant of GH secretion), is not known. In the absence of such data and a formal prospective study, measuring GH and cortisol levels at the time of hypoglycemia in children in whom sufficiency of these hormones is in question may still be helpful. GHD and adrenal insufficiency could be excluded in 30% to 40% of children by simply adding GH and cortisol measures to blood testing that is already being performed. This maneuver could prevent the need for more labor-intensive provocative studies in the subset of children for whom these diagnoses remain in question.

CONCLUSIONS

The results of this study demonstrate that GH and cortisol levels at the time of hypoglycemia cannot be used alone to diagnose deficiencies of either of these hormones. Although normal GH and cortisol levels at the time of fasting hypoglycemia can be useful to exclude deficiencies of these hormones, abnormal results cannot be used to establish the diagnosis of either GHD or cortisol deficiency. Additional testing to confirm a deficiency of GH or cortisol should be performed before embarking on treatment with either GH or glucocorticoids.

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Poor Specificity of Low Growth Hormone and Cortisol Levels During Fasting Hypoglycemia for the Diagnoses of Growth Hormone Deficiency and Adrenal Insufficiency

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