

How to use a controlled fast to investigate hypoglycaemia

S Sreekantam,¹ M A Preece,² S Vijay,¹ J Raiman,¹ S Santra¹

¹Department of Metabolic Medicine, Birmingham Children's Hospital, Birmingham, UK
²Department of Newborn Screening and Biochemical Genetics, Birmingham Children's Hospital, Birmingham, UK

Correspondence to

Dr S Santra, Department of Metabolic Medicine, Birmingham Children's Hospital, Birmingham B4 6NH, UK; saikat.santra@bch.nhs.uk

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ABSTRACT

Controlled fasts can play a valuable role in the diagnosis and management of hypoglycaemia in paediatric clinical practice, but are no substitute for the collecting of appropriate critical samples at the time of hypoglycaemia for metabolic and endocrine studies. Fatty acid oxidation defects, hyperinsulinism and adrenal insufficiency should always be excluded prior to organising controlled fasts. Controlled fasts are safe if conducted in an experienced setting with strict protocols in place. Failure to adhere to protocol can defeat the purpose of the study and can potentially be dangerous. Proper planning in conjunction with the laboratory and close supervision by staff experienced in controlled fasts is crucial to ensure the best quality information is yielded from these procedures.

INTRODUCTION

Hypoglycaemia is not infrequent in paediatric clinical practice and can potentially result in significant morbidity and mortality.^{1–3} Some metabolic and endocrine disorders can cause recurrent hypoglycaemia in childhood and these might be potentially preventable.

Controlled fasts are used to evaluate hypoglycaemia safely in a hospital setting. The aim of this article is to help paediatricians understand the role of controlled fasts in the investigation and management of hypoglycaemia.

WHAT IS THE DEFINITION OF HYPOGLYCAEMIA?

There is no agreement between paediatricians and among paediatric textbooks about the lowest safe blood glucose levels in childhood. The definition of hypoglycaemia should ideally be based upon the lowest levels at which normal neurological function is affected. This varies between individuals, and depends on several factors including the rate of fall in blood glucose, the properties of the glucose transporter GLUT1 (which

transports glucose across the blood-brain barrier), variation in individual neural susceptibility to low glucose concentrations and the ability of neurons to use ketone bodies for energy production. Nevertheless, it has been shown that neurological dysfunction in newborns and children does not occur until plasma glucose levels fall below 2.6 mmol/L,^{4 5} and this can be used as reasonable value for defining significant hypoglycaemia in childhood. In practice, we recommend prompt treatment of hypoglycaemia if plasma glucose falls below 3 mmol/L in asymptomatic patients and in patients with symptomatic hypoglycaemia regardless of the result.^{6–9}

Metabolic and endocrine disorders causing hypoglycaemia in childhood (boxes 1 and 2) and tests recommended for investigation of hypoglycaemia (table 1) are outlined below.

PHYSIOLOGICAL BACKGROUND

Normal adaptive mechanisms during fasting

During fasting, blood glucose levels are sustained as a result of adaptive hormonal and metabolic counter regulatory mechanisms.

In the early fasting state, insulin levels decrease and levels of the counterregulatory hormones glucagon, growth hormone and cortisol increase. Glucagon stimulates glycogenolysis to release glucose from liver glycogen. When glycogen stores are depleted, glucose is formed from amino acids and glycerol by gluconeogenesis.

Insulin inhibits lipolysis which is activated in the fasting state to release free fatty acids, which are subsequently β -oxidised resulting in the generation of ketones. An increase in metabolites such as free fatty acids may precede hypoglycaemia. Ketone bodies, namely acetoacetate and 3-hydroxybutyrate are used as an alternative source of energy.¹⁰

The occurrence and intensity of ketonaemia is proportionate to the extent of hypoglycaemia.^{10 11}



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Box 1 Metabolic causes of hypoglycaemia in childhood

- ▶ Glycogenoses
 - Glycogen storage diseases (I, III, VI, IX)
 - Glycogen synthase deficiency (GSD 0)
- ▶ Glucose transporter defects
 - Fanconi-Bickel syndrome
- ▶ Gluconeogenesis disorders
 - Fructose-1,6-bisphosphatase deficiency
 - Glucose-6-phosphatase deficiency (GSD 1)
- ▶ Fatty acid oxidation disorders
 - Primary carnitine deficiency and carnitine cycle defects
 - MCADD, LCHADD, VLCADD
 - Multiple acyl-CoA dehydrogenase deficiency
- ▶ Ketone synthesis defects
 - HMG-CoA synthase and lyase deficiencies
- ▶ Ketone utilisation defects
 - SCOT, ACAT1, MCT1 deficiencies
- ▶ Hereditary fructose intolerance
- ▶ Mitochondrial respiratory chain defects
- ▶ Liver disease (eg, galactosaemia)
- ▶ Other conditions associated with hypoglycaemia: tyrosinemia type 1 and organic acidaemias (not common)

Ghosh *et al.*⁹

ACAT1, acetoacetyl-CoA thiolase; HMG-CoA lyase, hydroxymethylglutaryl-CoA lyase; HMG-CoA synthase, hydroxymethylglutaryl-CoA synthase; LCHADD, long chain hydroxy acyl-CoA dehydrogenase deficiency; MCADD, medium chain acyl-CoA dehydrogenase deficiency; MCT1, monocarboxylase transporter 1; SCOT, succinyl-CoA oxoacid transferase; VLCADD, very long chain acyl-CoA dehydrogenase deficiency.

In the fed state, insulin levels increase which switches off lipolysis leading to a fall in the level of ketone bodies.

A typical example of the metabolic changes seen during a prolonged fast in a 3-year-old child is shown in [figure 1](#).

Consequently, a disturbance of any component of these responses has the potential to lead to hypoglycaemia. For instance in hyperinsulinism, high levels of insulin inhibit mobilisation of free fatty acids from adipose tissue and subsequent β -oxidation to ketones. These children typically have low levels of free fatty acids and ketone bodies at the time of hypoglycaemia. Defective β -oxidation of fatty acids in fatty acid oxidation defects explains the high levels of free fatty acids and hypoketotic hypoglycaemia noted in these children. In hepatic glycogen storage disorders, inability to mobilise glucose from liver glycogen explains the hypoglycaemia and very short fasting tolerance seen in these patients ([figure 2A,C](#)).

Box 2 Endocrine causes of hypoglycaemia in childhood

- ▶ Hyperinsulinaemic hypoglycaemia
 - Hyperinsulinism-hyperammonaemia syndrome
 - Congenital hyperinsulinism
 - Dumping syndrome
 - Insulinoma
 - Beckwith-Wiedemann syndrome
 - Exogenous insulin (diabetes, factitious hyperinsulinism)
- ▶ Adrenal insufficiency
 - Primary adrenal insufficiency
 - X-linked adrenoleukodystrophy
 - Withdrawal of exogenous corticosteroids
 - Hypopituitarism
- ▶ Growth hormone deficiency
 - Hypopituitarism
 - Isolated growth hormone deficiency
- ▶ Other causes
 - Idiopathic ketotic hypoglycaemia

Ghosh *et al.*⁹

The duration of fasting prior to hypoglycaemia can often provide clues to an underlying metabolic or endocrine disorder as shown in [table 2](#).

TECHNOLOGICAL BACKGROUND**Prerequisites for a controlled fast**

It is important to exclude fatty acid oxidation defects and hyperinsulinism before subjecting a child to a controlled fast. Fasting children with fatty acid oxidation defects and hyperinsulinism can be potentially life threatening as these subjects cannot produce ketone bodies. Blood acylcarnitine analysis should always be performed and confirmed to be normal before a controlled fast. Hyperinsulinism can be diagnosed based on high glucose requirements and detectable levels of insulin at the time of hypoglycaemia.

Suspected adrenal insufficiency should be assessed by a short Synacthen test prior to the fast.

Setting

Controlled fasts should be performed according to a strict protocol in a hospital setting under close supervision. The protocol should define the threshold for termination of the fast and initiation of appropriate treatment.

Controlled fasts should be planned in advance in conjunction with the laboratory. The protocol for the controlled fast should be individualised based on several factors including the clinical presentation, age of the patient and the reason for the fast. The duration of the fast depends on the age of the child ([table 3](#)) and the start time set such that in the event

Interpretations

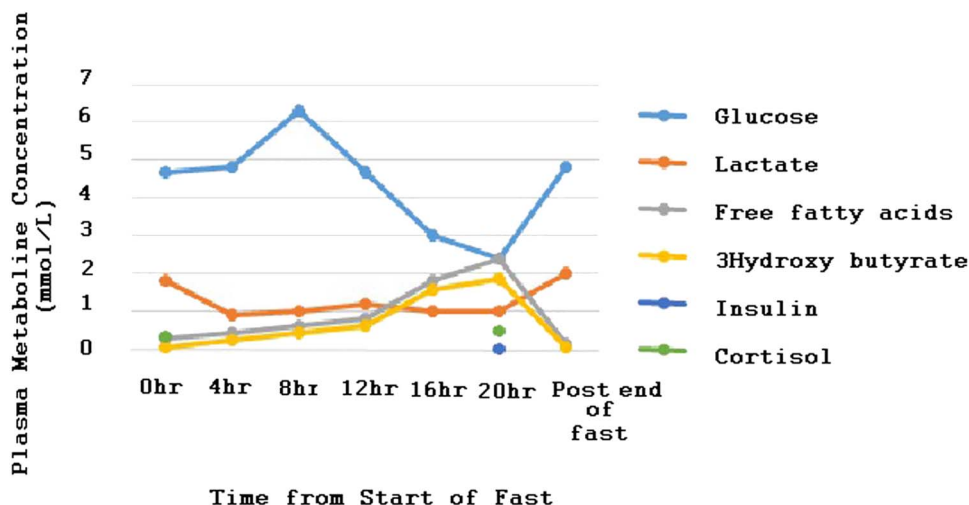


Figure 1 Typical metabolic responses to a 20 hour fast in a normal 3 year old boy.

of hypoglycaemia occurring, it is expected to do so during routine working hours with optimal staff levels available, for example, a child aged 8–12 months starting fasting at midnight.

Patients may therefore need admission overnight according to the planned duration of the fast. The patient should be examined to ensure fitness to undergo the fast. If there are signs of intercurrent illness, the fast is better deferred until the child is well. A secure intravenous cannula must be inserted before commencing the fast to enable easy and prompt sampling without distressing the child and also to enable dextrose to be given quickly if hypoglycaemia needs treating.

During the fast, only plain water should be allowed if the child is thirsty. Specimens should be taken regularly along with bedside glucose measurements as per an individualised protocol (table 4). The clinical condition should be monitored carefully for signs of hypoglycaemia. For children admitted the night before, hourly sampling can commence at the start of the working day, that is, 08:00–16:00.

When to stop the fast?

If the patient is hypoglycaemic or symptomatic, an urgent lab glucose along with the end of fast samples should be collected and the fast terminated. In our practice, we terminate controlled fasts in an asymptomatic child if the glucometer reading and/or the true laboratory glucose reading is ≤ 3.0 mM.

If the patient is symptomatic, intravenous glucose should be given after the collection of end of fast samples as a slow bolus in a dose of 200 mg/kg (2 mL/kg of 10% dextrose), followed by a continuous infusion of glucose at 5–8 mg/kg/min until the patient is stable enough to tolerate oral feeds.

If the patient is asymptomatic, a meal or a high carbohydrate drink can be given.

Post end of fast samples should be taken 1–1.5 hours later.

Why collect postprandial samples?

Collection of postprandial samples is important as it can provide useful diagnostic information.

Postprandial hyperglycaemia and fasting hypoglycaemia are seen in Fanconi-Bickel syndrome, characterised by mutations within *GLUT2*, the gene encoding the facilitative glucose transporter in hepatocytes, pancreatic β -cells, enterocytes and renal tubular cells. Analysis of postprandial glucose, lactate and ketones can be helpful in diagnosing rare metabolic conditions like glycogen synthase deficiency (GSD type 0), where postprandial lactate and glucose are usually elevated and ketone body utilisation defects like succinyl-CoA oxoacid transferase deficiency, where ketones are not always suppressed after feeding. Abnormalities in the postprandial metabolites warrant further metabolic input and investigations.

EXAMPLES OF CONTROLLED FAST INTERPRETATION

1) Glycogen storage disease type 1

A baby boy A aged 9 months with suspected glycogen storage disorder was electively admitted for a controlled fast to determine his safe fasting tolerance.

The results of this are shown in table 5 and figure 2C. Looking at the results of the fast, it is clear that baby A had a low plasma glucose of 2.7 mmol/L at 2 hours 15 min from the commencement of the fast. The results also illustrate how important it is to get a true glucose sample and not to rely completely on bedside glucometer readings. Had the true glucose not been checked, this child may have been assumed to be safe to fast for 30 min longer than he actually is. His safe fasting tolerance is only 2 hours.

There is no appreciable ketotic response which is also frequently seen in GSD type 1.

2) Ketotic hypoglycaemia

A boy aged 3 years with recurrent episodes of hypoglycaemia secondary to illness was admitted for a controlled fast the results of which are shown in table 6 and figure 2B.

Table 1 Tests recommended for investigation of hypoglycaemia/hypoglycaemia screen

| Test | Sample requirements (can vary—confirm with your laboratory) | Metabolic/endocrine conditions screened for by this test | Collection at the time of hypoglycaemia | Notes |
|---------------------------------|---|--|---|---|
| Glucose | Blood Fluoride oxalate | All | Essential | To confirm genuine hypoglycaemia |
| Insulin and C peptide | Blood Serum | Hyperinsulinism (including factitious) HIHA | Essential | Will require immediate freezing—discuss with laboratory. Intraosseous samples not suitable |
| Free fatty acids/NEFA | Blood Fluoride oxalate | Hyperinsulinism (low) | Essential | |
| 3HB/ketones | Blood Fluoride oxalate | Hyperinsulinism (low) Fatty acid oxidation disorders (low) Ketogenesis defects (low) Ketolysis defects (high) | Essential | Ratio of FFA/3HB indicative of disorder of FAO or ketone metabolism |
| Organic acids | Urine | FAOD Organic acidaemias | Essential | Ideally collect the next urine passed |
| Blood gas | Blood | Organic acidaemias Causes of lactic acidosis | Preferable | |
| Lactate | Blood Fluoride oxalate | Glycogen storage disorders Gluconeogenic defects Mitochondrial disease | Preferable | |
| Amino acids | Blood | Organic acidaemias Liver dysfunction | Preferable | |
| Ammonia | Blood | HIHA | Preferable | |
| Growth hormone | Blood Serum | GH deficiency Hypopituitarism | Preferable | Low levels of GH at the time of hypoglycaemia warrant liaison with endocrinology and further confirmatory testing |
| Cortisol | Blood | Adrenal insufficiency Hypopituitarism | Preferable | F/U short Synacthen test±VLCFA in boys |
| Acylcarnitines | Blood/DBS | FAOD Organic acidaemias | Not essential | |
| Thyroid-stimulating hormone | Blood | Hypopituitarism | Not essential | Interpret with caution in sick children and in conjunction with other pituitary tests |
| Liver function | Blood | Liver failure (including metabolic causes such as galactosaemia, tyrosinaemia type 1, mitochondrial disorders) | Not essential | |
| Renal function/ electrolytes | Blood | Adrenal insufficiency | Not essential | |

3HB, 3-hydroxybutyrate; DBS, dried blood spot; F/U, follow-up; FAOD, fatty acid oxidation defects; GH, growth hormone; HIHA, hyperinsulinism-hyperammonaemia syndrome; NEFA, non-essential fatty acids; UCED, urea cycle enzyme defects; VLCFA, very long chain fatty acids.

Acylcarnitines, urine organic acids and plasma quantitative amino acids were unremarkable.

Interpretation: The results of the fast indicate that the subject was hypoglycaemic at 16 hours after the commencement of the fast. At the time of hypoglycaemia, there is an appropriate increase in the levels of free fatty acids and ketone bodies indicative of normal lipolysis and β -oxidation of fatty acids during fasting. The postprandial samples show a decrease in the levels of free fatty acids and ketone bodies, which again is in keeping with the normal physiological response.

The results also demonstrate a normal response in the levels of insulin, C peptide and growth hormone at the time of hypoglycaemia.

We can now conclude that the subject has idiopathic recurrent ketotic hypoglycaemia of childhood having excluded an underlying metabolic or endocrine cause for hypoglycaemia.

3) Fatty acid oxidation disorder

A girl aged 7 years with very long chain acyl-CoA dehydrogenase deficiency was electively admitted for

Interpretations

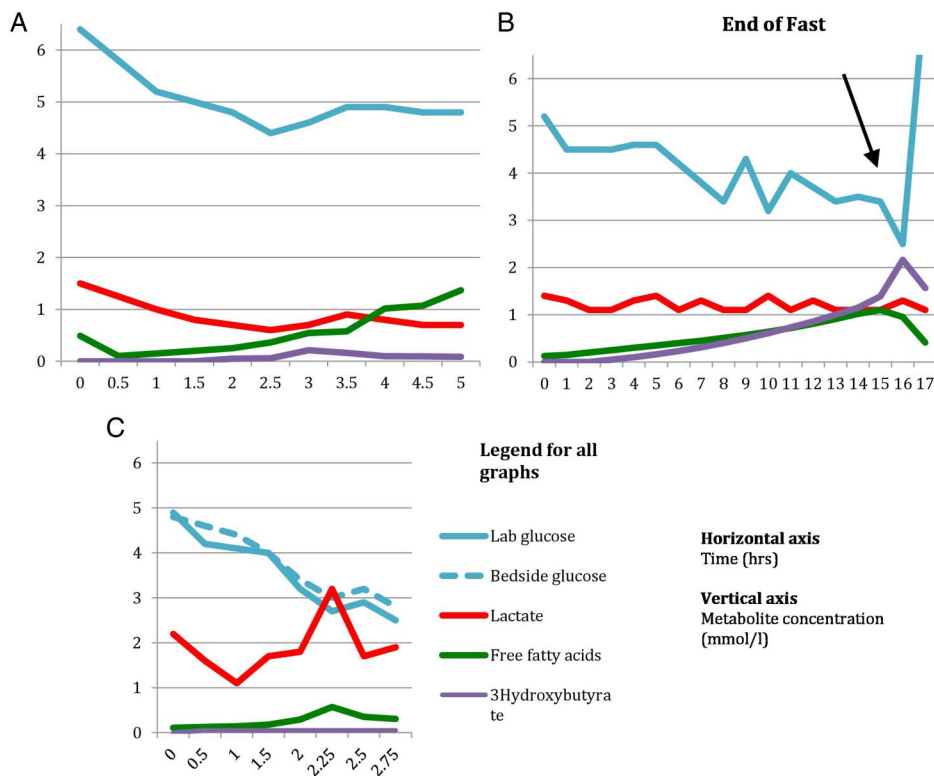


Figure 2 Controlled fasts scenarios.

Table 2 Changes in predominant fuel supply during fasting

| Duration of fasting (hours) | Predominant fuel | Conditions associated with impaired fasting tolerance of this duration |
|-----------------------------|-----------------------------------|--|
| 0–2 | Glucose | Hyperinsulinism |
| 2–6 | Glycogen | GSD |
| 6–12 | Gluconeogenesis | GSD 0 Disorders of gluconeogenesis |
| 12–24 | β -Oxidation of fatty acids | FAOD GH/cortisol deficiency |

De Leon *et al.*¹²

FAOD, fatty acid oxidation disorder; GH, growth hormone; GSD, glycogen storage disorder.

a 6-hour controlled fast for assessment of her safe fasting tolerance.

The results of the fast are shown in [table 7](#) and [figure 2A](#).

Interpretation: Though this subject did not go hypoglycaemic during the fast, the free fatty acids show a significant rise from 4 hours onwards without corresponding ketone production. The normal molar ratio of free fatty acids to 3-hydroxybutyrate is <2. It is clear that the ratio is very high in this subject (15.7 at 5 hours).

The free fatty acids (in this patient, likely to be all long chain fatty acids) can form toxic intermediates, which can cause potentially life-threatening encephalopathy, liver failure and arrhythmias.

Therefore, the safe fasting tolerance is only 4 hours in this subject.

CLINICAL QUESTIONS

Should a controlled fast be performed in any child with suspected hypoglycaemia without a documented hyposcreen?

In children with documented or suspected hypoglycaemia, ideally the aetiology of hypoglycaemia is best investigated by analysing hormone and metabolite concentrations in blood and organic acids in urine at the time of hypoglycaemia. While many metabolic disorders can still be diagnosed from random samples, diagnosis of some, especially endocrine disorders, becomes difficult if the required samples are not taken at the time of hypoglycaemia. Under such circumstances, a controlled fast may help to elucidate the underlying cause of hypoglycaemia. If there is no clear evidence of a metabolic or endocrine defect from the baseline tests, the decision to do a controlled fast should be based on the age of the child, presence of symptoms and the frequency of attacks.

An acylcarnitine profile should always be analysed prior to organising a controlled fast as fasting can be dangerous in children with fatty acid oxidation defects. Impaired ketogenesis in these children results in accumulation of fatty acids and toxic acylcarnitine metabolites, which can lead to encephalopathy and death if not treated promptly. There are case reports of children with medium chain acyl-CoA dehydrogenase deficiency, who have died as a result of prolonged

Table 3 Duration of fasts according to age distribution¹

| Age | <6 months | 6–8 months | 8–12 months | 1–2 years | >2 years |
|------------------|-----------|------------|-------------|-----------|----------|
| Duration of fast | 8 hours* | 12 hours | 16 hours | 18 hours | 20 hours |

Morris *et al.*¹

*Duration of fast in infants <6 months of age should be determined based on weight and input from specialists.

Table 4 Example of specimens taken during a controlled fast

| Specimen | Test | Baseline sample | Postprandial sample | Samples at regular intervals | End of fast samples | Post end of fast samples |
|----------|--|-----------------|---------------------|------------------------------|---------------------|--------------------------|
| Blood | Bedside glucose (1 hourly) | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Lab glucose and lactate | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Free fatty acids | ✓ | ✓ | ✓ | ✓ | ✓ |
| | 3-Hydroxybutyrate | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Insulin | | | | ✓ | |
| | Growth hormone | | | | ✓ | ✓ |
| | Cortisol | ✓ | | | ✓ | |
| | Amino acids | ✓ | | | ✓ | |
| | Liver function tests | ✓ | | | ✓ | |
| | Ammonia and TCO ₂ | ✓ | | | ✓ | |
| | Carnitine and acylcarnitine | ✓ | ✓ | | ✓ | |
| Urine | Amino acids and organic acids Collect aliquots of all urine passed from the beginning of the fast and the first and second urines after the end of the fast. Label carefully with the time and store separately in fridge so that the end of fast specimens can be identified and analysed. | | | | | |

Urine amino acids: helpful in diagnosing aminoacidopathies.

Postprandial samples: samples taken 1–2 hours postcommencement of the fast. These samples are physiological postprandial samples as the fast commences after the patient is given a meal.

Post end of fast samples: samples taken after termination of controlled fast.

Table 5 Results from a controlled fast in a 9-month-old with glycogen storage disease type 1

| Time | Lab glucose (mmol/L) | Bedside glucose (mmol/L) | Lactate (mmol/L) | Free fatty acids (μmol/L) | 3-Hydroxybutyrate (μmol/L) |
|----------------|----------------------|--------------------------|------------------|---------------------------|----------------------------|
| Baseline | 4.9 | 4.8 | 2.2 | 111 | <50 |
| 30 min | 4.2 | 4.6 | 1.6 | 126 | <50 |
| 60 min | 4.1 | 4.4 | 1.1 | 143 | <50 |
| 90 min | 4.0 | 4.0 | 1.7 | 180 | <50 |
| 2 hours | 3.2 | 3.4 | 1.8 | 291 | <50 |
| 2 hours 15 min | 2.7 | 3.0 | 3.2 | 573 | <50 |
| 2 hours 30 min | 2.9 | 3.2 | 1.7 | 350 | <50 |
| 2 hours 45 min | 2.5 | 2.8 | 1.9 | 308 | <50 |

controlled fasts and those with very long chain acyl-CoA dehydrogenase deficiency, where fasting provoked rhabdomyolysis.¹ Fatty acid oxidation defects can now be diagnosed with the help of tandem mass spectrometry which is a much safer method.

Morris *et al.*¹ reviewed 138 controlled fasts organised over a 30-month period in a tertiary metabolic centre. 54 (39%) resulted in hypoglycaemia and a

specific endocrine or metabolic cause was identified in 30 (21% of all fasts) patients. The diagnostic yield was highest in young children, specific defects being identified in 14 of the 32 children fasted at the age of <1 year. As expected, disorders were identified more frequently if hypoglycaemia had been documented at the referring hospital than if it was merely suspected. The diagnostic yield now would be expected to be

Interpretations

Table 6 Results from a controlled fast in a 3-year-old with ketotic hypoglycaemia

| Date | Time | Glucose (mmol/L) | Lactate (mmol/L) | Free fatty acids (μmol/L) | 3-Hydroxybutyrate (μmol/L) |
|-------------------|------------------|------------------|------------------|---------------------------|----------------------------|
| 24/3/15 | 13:00 (baseline) | 5.2 | 1.4 | 125 | <50 |
| Start of the fast | 19:00 | 4.7 | | | |
| | 20:00 | 4.5 | | | |
| | 21:00 | 4.5 | | | |
| 25/3/15 | 00:00 | 4.6 | | | |
| | 01:00 | 4.2 | | | |
| | 03:00 | 3.4 | | | |
| | 04:00 | 4.3 | | | |
| | 05:00 | 3.2 | | | |
| | 06:00 | 4.0 | | | |
| | 07:00 | 3.7 | | | |
| | 08:00 | 3.4 | | | |
| | 09:00 | 3.5 | | | |
| | 10:00 | 3.4 | 1.1 | 1103 | 1390 |
| 16 hours | 11:00 | 2.5 | 1.3 | 955 | 2161 |
| Postprandial | 12:45 | 7.9 | 1.1 | 411 | 1569 |

| Date | Time | Cortisol (nmol/L) | Growth hormone (mU/L) | Insulin (mIU/L) | C peptide (nmol/L) | Ammonia (μmol/L) | TCO ₂ (mmol/L) |
|---------|------------------|-------------------|-----------------------|-----------------|--------------------|------------------|---------------------------|
| 24/3/15 | 13:00 (baseline) | 123 | 2 | | | 48 | 24.3 |
| 25/3/15 | 09:00 | 458 | 4.6 | | | 53 | 17.8 |
| | 11:00 | 674 | 7.4 | <10 | <94 | 61 | 16.9 |
| | 12:45 | | 1.7 | | | | |

Table 7 Results of a controlled fast in a 7 year old with VLCADD deficiency

| Time | Glucose (mmol/L) | Lactate (mmol/L) | Free fatty acids (μmol/L) | 3-Hydroxybutyrate (μmol/L) |
|----------------|------------------|------------------|---------------------------|----------------------------|
| Baseline | 6.4 | 1.5 | 489 | <50 |
| 1 hour | 5.2 | 1.0 | | |
| 1 hour 30 min | 5.0 | 0.8 | | |
| 2 hours | 4.8 | 0.7 | | |
| 2 hours 30 min | 4.4 | 0.6 | 361 | 58 |
| 3 hours | 4.6 | 0.7 | 544 | 211 |
| 3 hours 30 min | 4.9 | 0.9 | 577 | 160 |
| 4 hours | 4.9 | 0.8 | 1015 | 96 |
| 4 hours 30 min | 4.8 | 0.7 | 1071 | 94 |
| 5 hours | 4.8 | 0.7 | 1370 | 87 |

VLCADD, very long chain acyl-CoA dehydrogenase deficiency.

Clinical bottom line

- ▶ Diagnosis of endocrine disorders causing hypoglycaemia may be missed if samples are not taken at the time of hypoglycaemia.
- ▶ In the absence of a hypoglycaemia screen, a controlled fast should be undertaken based on the individual clinical situation. It can be valuable in determining the maximum safe interval between feeds and prevent further hypoglycaemic episodes.
- ▶ Acylcarnitine profile should be confirmed to be normal prior to organising a controlled fast.

lower due to the wider availability of metabolic tests such as acylcarnitine profiles that can diagnose inborn errors of metabolism without the need for controlled fasting.

Controlled fasts can also help the family and clinician in determining the safe fasting tolerance of the child when well and tailor dietary management.

Is a controlled fast indicated in a neonate with high glucose requirement and in whom the opportunity was missed to do a hypoglycaemia screen?

The normal glucose requirement in a neonate is 4–8 mg/kg/min. Hyperinsulinism should be considered in a neonate when the glucose requirement is >10 mg/kg/min. It should be considered in any neonate with persistent or frequent hypoglycaemic episodes.

Hyperinsulinism is a predominant cause of profound hypoglycaemia in the neonatal period, which, if untreated, can lead to significant morbidity and mortality. Studies have shown that recurrent spontaneous hypoglycaemia may not be accompanied by recognised neuroglycopenic symptoms in infants with congenital hyperinsulinism.⁵ Therefore, it is important to have a high index of suspicion of hyperinsulinism in a neonate with hypoglycaemia and high glucose requirement.

Hyperinsulinism is diagnosed by the finding of detectable insulin levels, low free fatty acid concentrations and low ketones at the time of hypoglycaemia. Hence, a hypoglycaemia screen would be ideal in diagnosing hyperinsulinism.

A controlled fast is not necessarily indicated in neonates with hyperinsulinism in whom the diagnosis can

Clinical bottom line

- ▶ Hyperinsulinism should be considered in any neonate with persistent or frequent hypoglycaemic episodes and in whom the glucose requirement is >10 mg/kg/min.
- ▶ Close liaison with an endocrinologist is useful in managing hypoglycaemia secondary to hyperinsulinism, especially the refractory cases who may need specific therapy as diazoxide and chlorthalidate.

be made based on the high glucose requirement and widely available assays to measure insulin at the time of hypoglycaemia. Fasting can be dangerous in these subjects as they cannot produce ketones, which can be used as alternative sources of energy supply. Specialist endocrine input should be sought in all cases of suspected hyperinsulinism, who did not have a hyposcreen, to guide further management.

Is a controlled fast indicated in a child with hypoglycaemia secondary to illness?

Hypoglycaemia secondary to an intercurrent illness like diarrhoea and vomiting in a child is a common scenario in paediatric emergency department. Ideally, every attempt should be made to collect crisis samples at the time of hypoglycaemia and the next available urine collected for analysis of ketones and organic acids.

However, it is important to establish whether children are ketotic at the time of hypoglycaemia. In the review by Morris *et al.*,¹ 32 (59%) children who became hypoglycaemic during the fast had ‘ketotic hypoglycaemia’.

Idiopathic ketotic hypoglycaemia (IKH) is the most frequent term used to describe recurrent hypoglycaemia in children aged between 1 and 5 years.¹³ The clinical pattern was characterised by Colle and Ulstrom as the tendency of affected children to become ketotic and hypoglycaemic during a low calorie ketogenic diet.¹¹ It is due to the failure of hepatic glucose production to meet the body’s increase in glucose demand during illness or fasting.^{13 14} IKH typically improves with age and is not usually observed after children reach puberty.

Recurrent episodes necessitate baseline metabolic investigations including an acylcarnitine profile prior to controlled fast. In cases with recurrent episodes or symptomatic hypoglycaemia, metabolic specialist opinion should be sought regarding further management. X-linked adrenoleukodystrophy should always be considered in a boy with recurrent episodes of hypoglycaemia and low cortisol levels.

Controlled fasts should be considered in children with clinical features of a primary endocrine or metabolic defect or in those with recurrent symptomatic hypoglycaemia.

Controlled fasts can also be helpful in determining the fasting tolerance in suspected cases of primary endocrine or metabolic disorder.

Clinical bottom line

- ▶ IKH is common in childhood but it is a diagnosis of exclusion.
- ▶ In the absence of a hyposcreen, the decision to undertake a controlled fast should be taken based on individual clinical situation and after close liaison with metabolic specialists.

SUMMARY

Controlled fasts can play a valuable role in the diagnosis and management of hypoglycaemia in paediatric clinical practice, but are no substitute for the collecting of appropriate critical samples at the time of hypoglycaemia for metabolic and endocrine studies. Fatty acid oxidation defects, hyperinsulinism and adrenal insufficiency should always be excluded prior to organising controlled fasts.

Controlled fasts are safe if conducted in an experienced setting with strict protocols in place. Failure to adhere to protocol can defeat the purpose of the study and can potentially be dangerous.

Proper planning in conjunction with the laboratory and close supervision by staff experienced in controlled fasts is crucial to ensure the best quality information is yielded from these procedures.

Contributors SSr: written the article. SSa: contributed to design and presentation of the data, gave ideas for the scenarios, critically reviewed the paper and finalised it. JR: reviewed the clinical questions and also helped with the design and presentation of the data. SV: reviewed the paper. MAP: reviewed relevant literature, contributed to design and presentation of the data and offered ideas for the scenario.

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S Sreekantam, M A Preece, S Vijay, J Raiman and S Santra

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