

ORIGINAL ARTICLE

An inadequate glycaemic response to glucagon is linked to insulin resistance in preterm infants?

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Arch Dis Child Fetal Neonatal Ed 2003;88:F62–F66

Aims: To define clinical, metabolic, and hormonal characteristics of preterm infants relative to glucagon responsiveness.

Methods: Two phase study of 78 preterm infants (25–36 weeks gestation) on regular four hourly feeds anticipating discharge home at 36 weeks mean corrected gestation. In phase 1 infants were fasted until hypoglycaemic, or maximally for eight hours. Endocrine and metabolic profiles were obtained at completion. Phase 2 was performed the following day. A feed was omitted and replaced by a bolus dose of intravenous glucagon (100 µg/kg). Main outcome measures were measurements of blood glucose and lactate concentrations, taken immediately pre-glucagon, and thereafter every 15 minutes for 60 minutes. A rise in glucose concentration of >1 mmol/l (55 infants) was defined as an adequate response to glucagon. An inadequate glycaemic response was <1 mmol/l (23 infants).

Results: Several differences in fasting blood glucose and hormone concentrations were identified in infants with an inadequate glycaemic response to glucagon compared to those with an adequate response: relative fasting hyperglycaemia (mean 3.7 v 3.3 mmol/l, $p = 0.008$); fasting hyperinsulinaemia (mean 4.3 v 2.6 mU/l, $p = 0.014$); an increased insulin:glucagon ratio (0.19 v 0.11, $p = 0.014$), and a lower insulin sensitivity QUICKI index (0.19 v 0.22, $p = 0.04$). There was no distinctive phenotype to reliably predict response to glucagon.

Conclusion: Some preterm infants show an inadequate glycaemic response to glucagon and have features suggestive of insulin resistance. The potential long term implications of such insulin resistance may have appreciable public health consequences.

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Accepted 9 July 2002

The human brain is dependent on a continuous supply of blood glucose for metabolic needs, but has minimal glycogen reserves, and a limited supply of alternative substrates. Blood glucose concentrations are therefore normally maintained within a controlled range. Acute hypoglycaemia impairs cerebral function and recurrent exposure to hypoglycaemia in the early postnatal period may have long term consequences on motor and cognitive development.^{1,2}

In utero the fetus receives a constant supply of maternal glucose via the placental unit. At birth this supply abruptly terminates and the infant must adapt to a state of independent and appropriate hepatic glucose production. The maintenance of blood glucose concentrations in the immediate newborn period is dependent on the mobilisation of hepatic glycogen stores, the establishment of an adequate nutritional intake, and the maturation of key liver enzyme systems controlling gluconeogenesis and glycogenolysis.³ Hepatic glucose-6-phosphatase is a rate limiting enzyme for pathways of glycogenolysis and gluconeogenesis,⁴ and is expressed at only low levels⁵ in the human fetus in utero. In most term infants, hepatic glucose-6-phosphatase activities increase to adult concentrations within a few days of delivery.⁵ In many preterm infants this increment in enzyme activity fails to occur.^{6,7} The delayed postnatal appearance of hepatic glucose-6-phosphatase in preterm infants makes them potentially vulnerable to repeated hypoglycaemic episodes and the resultant cerebral damage, and puts them at risk of sudden and unexpected death.^{2,8–10}

Genetic deficiencies of hepatic glucose-6-phosphatase (type I glycogen storage diseases) are characterised by fasting hypoglycaemia, and an attenuated hepatic response to glucagon.¹¹ Genetic deficiencies, or delayed development of hepatic glucose-6-phosphatase activities, as observed postnatally in preterm infants, can result in vulnerability to hypoglycaemia.

In a series of 78 preterm infants, ready for hospital discharge, we have shown that 18% were vulnerable to hypoglycaemia after missing a single feed.¹² Glucagon stimulates hepatic glycogenolysis and gluconeogenesis and through these mechanisms glucose is released into the circulation.¹³ In type I glycogen storage disease the response to glucagon is abnormal, with a blunted glycaemic response and an exaggerated rise in plasma lactate concentrations.¹¹ We proposed that an attenuated glucose response to glucagon stimulation should also occur in our group of preterm infants reported previously as vulnerable to hypoglycaemia.¹² We now report the results of glucagon stimulation in this group of infants.

SUBJECTS AND METHODS

We recruited a consecutive series of preterm infants (78 infants, 25–36 weeks gestation) who were admitted to the Neonatal Intensive Care Unit, Ninewells Hospital, Dundee and who survived to discharge home at 36 weeks mean corrected gestation. There were no exclusion criteria (table 1). Infants were on no medications apart from iron and vitamin supplementations, which are given routinely in this hospital. The study protocol was approved by the Tayside Medical Research Ethics Committee. Informed written parental consent was obtained.

Extensive epidemiological data were collected on each infant; these included maternal health, both generally and in pregnancy, as well as any prescribed drugs in pregnancy; disorders of pregnancy; details of delivery and resuscitation; neonatal morbidity; and any medications prescribed.¹⁴

An extensive range of anthropometrical measurements was obtained at the time of the study. Birth weight ratios¹⁵ and study weight ratios¹² were calculated for each infant using reference values attained from the Scottish Morbidity Record

Table 1 Clinical characteristics of infants studied

	Adequate glycaemic response group (n=55)	Inadequate glycaemic response group (n=23)	p value
<i>At birth</i>			
Birth weight (kg)	1.69 (0.05)	1.61 (0.09)	0.46
Birth weight ratio	0.88 (0.02)	0.93 (0.04)	0.19
Gestation (weeks)	32.6 (0.35)	31.6 (0.47)	0.12
<i>At study</i>			
Corrected gestation (weeks)	36.6 (0.26)	36.7 (0.35)	0.72
Weight (kg)	2.21 (0.04)	2.27 (0.05)	0.42
Study weight ratio	0.79 (0.01)	0.81 (0.02)	0.68
Occipito-frontal circumference (cm)	32.0 (0.56)	32.8 (0.22)	0.39
Crown-heel length (cm)	44.7 (0.25)	44.7 (0.39)	0.78
Sum of skinfold thickness (mm)	23.3 (0.62)	23.5 (1.02)	0.80

An adequate glycaemic response to glucagon >1 mmol/l; inadequate response <1 mmol/l increment in blood glucose.

Results expressed as mean (SEM).

(SMR) 2 as supplied by the Information and Statistics Division of the Common Services Agency, Edinburgh. Measurements included: crown-heel length; crown-rump length; occipital-frontal circumference; mid-arm and leg circumferences; and waist, chest, and hip circumferences. Ponderal indices, placental:birth weight ratios, and mid-arm circumference:occipito-frontal circumference ratios were calculated. Skin fold thickness was measured using Holtain calipers and a standardised technique and one operator, at the following sites: biceps, triceps, anterior and posterior thigh, supra-iliac crest, and infra-scapular; the sum of these measurements was used as a proxy for total body fat.

This was a two phase study in the days immediately preceding discharge home at a corrected gestation of 36 weeks. All infants were on four hourly feeds. In phase 1 infants were fasted until hypoglycaemic, or maximally for eight hours; an endocrine and metabolic profile was obtained at completion. The results from this phase of the study have been published elsewhere.¹² Phase 2 was performed the following day. A scheduled feed was omitted and replaced by a bolus dose of intravenous glucagon (100 µg/kg). Blood was obtained through a heparinised indwelling cannula, and glucose and lactate concentrations were measured immediately pre-glucagon, and thereafter every 15 minutes for 60 minutes.

Blood glucose and lactate concentrations were analysed immediately using an on-site Yellow Springs analyser (Yellow Springs Instrument Co., Yellow Springs, Ohio, Model 23A). Hypoglycaemia was defined as a blood glucose measurement of <2.6 mmol/l. In the absence of published data in preterm infants, an adequate response to glucagon was arbitrarily defined as a rise in blood glucose concentration in excess of 1 mmol/l and an inadequate response a rise of less than 1 mmol/l, in an attempt to identify infants clinically most at risk of hypoglycaemia post-discharge. Infants with an inadequate response and those with an adequate response to glucagon were compared (table 1). Case records were retrospectively reviewed for the frequency of biochemical hypoglycaemia in the early postnatal period. The glucagon stimulation test was repeated at 40 weeks gestation corrected age in those infants who had an inadequate response to the initial test. Infants who had an inadequate response to this second glucagon stimulation test had a further glucagon stimulation test at 3 months corrected postnatal age. Constraints on blood volumes required limited investigations. Hormones and β-hydroxybutyrate concentrations were only measured at completion of phase 1 of the study and were analysed by the Department of Biochemical Medicine, Ninewells Hospital, Dundee. β-Hydroxybutyrate (detection limit (dl) 0.05 mmol/l, coefficient of variance (cv) 5.1%) concentrations were measured on plasma (separated and frozen immediately) by microenzymatic methods using a Cobas fast centrifugal analyser.¹⁶ Com-

mercial immunological assay kits were used to measure the following: cortisol (dl 5.5 nmol/l, cv 4.5%), Chiron; insulin (dl 1.0 mU/l, cv 5%), Abbott Laboratory; glucagon (dl 1.5 pmol/l, cv 10%), Diagnostic Products Corporation; human growth hormone (dl 0.01 mU/l, cv 6%), Diagnostic Products Corporation.

Fasting insulin (I_0) and glucose (G_0) values were fitted to the Quantitative Insulin Sensitivity Check Index (QUICKI) equation ($QUICKI = 1/[\log(I_0) + \log(G_0)]$) to assess insulin sensitivity in this cohort of preterm infants.¹⁷ Statistical analysis was performed using SPSS for Windows (release 10.0; SPSS Inc., Chicago, Illinois, USA). Normally distributed data were analysed using parametric tests. Non-normal data were analysed using non-parametric tests. Statistical significance was taken at $p < 0.05$.

RESULTS

Fifty five infants had an adequate glycaemic response to glucagon (>1 mmol/l), and 23 an inadequate response (<1 mmol/l) at initial testing at 36 weeks mean corrected gestation. The infants with an inadequate glycaemic response had lower blood glucose values and higher lactate concentrations at 30 minutes following glucagon stimulation compared to the infants with an adequate glycaemic response (table 2).

No factors relating to antenatal health, pregnancy, delivery, or postnatal morbidity influenced the infants' response to glucagon stimulation between the two groups. In particular, there was no relation between antenatal steroid exposure and response to glucagon. No differences were identified in anthropometric measurements, or in ponderal indices, placental:birth weight ratios, or in combined skin fold thicknesses (table 1).

Differences in blood glucose and hormone concentrations, obtained from the controlled fast in phase 1 of the study, were observed between infants with an inadequate and adequate glycaemic response to glucagon. Infants with an inadequate response compared to those with an adequate response had the following: relative fasting hyperglycaemia (3.7 v 3.3 mmol/l, $p = 0.008$); fasting hyperinsulinaemia (4.3 v 2.6 mU/l, $p = 0.014$); an increased insulin:glucagon ratio (0.19 v 0.11, $p = 0.014$), and a lower QUICKI index (0.19 v 0.22, $p = 0.04$) indicating reduced insulin sensitivity (table 3). Human growth hormone concentrations were higher in infants with an adequate glycaemic response but there were no differences in β-hydroxybutyrate, cortisol, or glucagon concentrations (table 3).

Retrospective review of case records showed an increased frequency of biochemical hypoglycaemia in the early postnatal period in the group with the inadequate response to glucagon (7.76 v 4.02 episodes, $p = 0.017$).

The glucagon stimulation test was repeated at 40 weeks gestation corrected age in the 23 infants who had an

Table 2 Blood glucose and lactate concentrations in response to glucagon

	Adequate glycaemic response group (n=55)	Inadequate glycaemic response group (n=23)	p value
<i>Time (min)</i>	<i>Blood glucose (mmol/l)</i>	<i>Blood glucose (mmol/l)</i>	
0	3.25 (0.07)	3.61 (0.12)	0.08
15	4.40 (0.10)	4.00 (0.11)	0.02
30	4.91 (0.10)	4.14 (0.12)	<0.001
45	4.60 (0.12)	3.80 (0.12)	0.01
60	3.90 (0.11)	3.32 (0.14)	0.03
<i>Time (min)</i>	<i>Blood lactate (mmol/l)</i>	<i>Blood lactate (mmol/l)</i>	
0	1.15 (0.06)	1.32 (0.16)	0.09
15	1.29 (0.06)	1.55 (0.09)	0.012
30	1.10 (0.04)	1.45 (0.12)	0.01
45	1.19 (0.05)	1.31 (0.10)	0.015
60	1.03 (0.05)	1.17 (0.10)	0.08

An adequate glycaemic response to glucagon >1 mmol/l; inadequate response <1 mmol/l increment in blood glucose.

Results expressed as mean (SEM).

Table 3 Fasting concentrations of hormones and metabolites

	Adequate glycaemic response group (n=55)	Inadequate glycaemic response group (n=23)	p value
Cortisol (nmol/l)	206 (20)	192 (32.9)	0.72
Glucagon (pmol/l)	29 (1.7)	25 (2.0)	0.63
Growth hormone (mU/l)	53 (3.9)	37 (4.7)	0.025
Insulin (mU/l)	2.6 (0.29)	4.3 (0.76)	0.014
Insulin:glucagon ratio	0.11 (0.01)	0.19 (0.03)	0.014
QUICKI score	0.22 (0.007)	0.19 (0.009)	0.04
β -Hydroxybutyrate (mmol/l)	0.11 (0.012)	0.15 (0.019)	0.39

An adequate glycaemic response to glucagon >1 mmol/l; inadequate response <1 mmol/l increment in blood glucose.

Results expressed as mean (SEM).

QUICKI score: Quantitative Insulin Sensitivity Check Index equation (QUICKI = $1/[\log(I_{0.5}) + \log(G_{0.5})]$).

inadequate response to the initial test. Eighteen infants had an adequate glycaemic response (>1 mmol/l). Five infants had an inadequate response (<1 mmol/l) to this second glucagon stimulation test, but had an adequate glycaemic response (>1 mmol/l) to a third glucagon stimulation test at 3 months corrected postnatal age.

DISCUSSION

In one third of preterm infants, at a corrected gestation of 36 weeks, hepatic glucose production in response to exogenous glucagon was inadequate. Our arbitrary cut off for an adequate glycaemic response to glucagon (a rise in blood glucose concentration in excess of 1 mmol/l) was defined early in the study in an attempt to identify infants clinically most at risk of hypoglycaemia post-discharge home. The response to glucagon in preterm infants is under explored and no previous work to determine population norms for this group was available to otherwise determine a grouping strategy. Previous studies have been limited in actual number, and confined predominantly to term infants, particularly those who were growth restricted.^{18–21} In a group of 11 infants with comparable corrected gestational age to our group of infants at first test (36 weeks gestation) but at a median age of 24 hours postnatal age, a different pattern of response was evident to our infants, and only one infant failed to increase their concentration of blood glucose >1 mmol/l in response to glucagon.²² Glucagon stimulation in type 1a glycogen storage disease results in a typically flattened glucose response in combination with an exaggerated lactate response.¹¹ Our group of preterm infants with an inadequate glycaemic response had lower blood glucose concentrations and higher lactate concentrations 30 minutes following glucagon stimulation, similar to the pattern associated with type 1a glycogen storage

disease, but not as marked. Hepatic glucose-6-phosphatase deficiency, as we have shown previously in preterm infants,^{6,7,9} could contribute to such a response following glucagon administration.

An integrated endocrine response is required by the newborn infant to initiate the transition from maternal dependent glucose metabolism to independent glucose metabolism. A catecholamine surge at the time of delivery may initiate this response, together with changes in cortisol, glucagon, and insulin concentrations, which favour the induction of key gluconeogenic and glycogenolytic enzymes.^{13,23} All infants identified in our study with an inadequate response to glucagon eventually developed an adequate glycaemic response to glucagon. Previous studies in infants 0.5–12 months of age have shown a mean glycaemic response of 3 mmol/l in response to glucagon.²¹ We do not know whether these maturational patterns in our infants were influenced by the repeated doses of glucagon inherent in our testing protocol, or merely reflected variable development between infants. A similar conclusion can be made for the subgroup of infants initially identified as hypoglycaemic on fasting, where glycaemic control improved with time, as all infants had at least a single dose of prescribed glucagon.¹²

The first phase of this study showed that infants with a hypoglycaemic tendency on fasting had lower birth weights, and study weights, in spite of a higher postnatal energy intake, than normoglycaemic infants.¹² In infants where hypoglycaemia was severe and/or persistent, concentrations of cortisol, corticotropin, and blood lactate were higher than those in infants with transient hypoglycaemia, or normoglycaemia.¹² Low birth weight is associated with increased urinary cortisol and metabolites in children,^{24,25} and in adult men with higher plasma cortisol, increased cardiovascular risk,^{26,27} and impaired glucose tolerance.^{28,29} The mechanisms underlying the

association of type 2 diabetes, raised blood pressure, and dyslipidaemia (that is, the metabolic or insulin resistance syndrome) and their exacerbation by obesity are not known. Epidemiological studies have shown that low birth weight predicts subsequent insulin resistance, glucose intolerance, hypertension, and cardiovascular disease.³⁰ Events in early life may have long term effects on the hypothalamic-pituitary-adrenal axis, and exposure of pregnant rats to adverse influences during gestation results in the birth of small offspring with hypertension, insulin resistance, and increased cortisol secretion.³¹ Although our infants had severe growth restriction, and raised cortisol concentrations, there was no evidence of insulin resistance and hyperglycaemia, but on the contrary, hypoglycaemia on omission of a regular feed as the dominant clinical problem.

It was surprising in phase 2 of the study to find that infants selected on the basis of a glucagon stimulation test as showing an inadequate glycaemic response were no different in growth at birth, or at the time of study, or in plasma cortisol concentrations, from those infants with an adequate glucagon response. There was no distinctive phenotype, which could be used to reliably predict response to glucagon. In addition, infants with an inadequate glycaemic response had higher fasting blood glucose concentrations, insulin concentrations, and insulin:glucagon ratios, and lower QUICKI index features suggestive of insulin resistance. Current methods are limited to assess insulin sensitivity in preterm infants. The hyperinsulinaemic euglycaemic glucose clamp technique is the "gold standard" for quantifying insulin sensitivity in vivo because it directly measures the effects of insulin to promote glucose utilisation under steady state conditions.³² The glucose clamp technique is difficult to perform in preterm infants, as is the alternative of a minimal model analysis of a frequently sampled intravenous glucose tolerance test (FSIVGTT).³³ More recently a simpler method based on fasting glucose and insulin concentrations, the Quantitative Insulin Sensitivity Check Index (QUICKI), has been shown to correlate well with glucose clamp and minimal model analysis methods in adults and children.^{33,34} Infants with an inadequate glycaemic response compared to those with an adequate response had a lower QUICKI index (table 3) consistent with relative insulin resistance and in keeping with the relative fasting hyperglycaemia, fasting hyperinsulinaemia, and the increased insulin:glucagon ratio in these infants. As far as we are aware, this is the first application of the QUICKI index in preterm infants, but without direct comparison to established methods of assessing insulin resistance, interpretation of hormonal effects in infants must be made with caution. For example, we have recently shown a paradoxical association of increased amounts of prescribed insulin in preterm infants with increased hepatic glucose-6-phosphatase activity,¹⁴ which in normal adults and diabetics reduces enzyme activity,^{35,36} and reduces transcription of the human gene.³⁷

This study is limited by the lack of long term metabolic and hormonal data from these infants, but is suggestive that different hormonal dysfunctions are present in the low birth weight population, perhaps predisposing them in the long term towards different elements of the metabolic syndrome. Repeated episodes of early neonatal hypoglycaemia characterise groups of infants with fasting hypoglycaemia and raised cortisol concentrations,¹² and as in this study, with an inadequate response to glucagon linked to parameters suggestive of insulin resistance. This suggests preterm infants have variable hormonal responses in an attempt to correct recurrent neonatal hypoglycaemia. This is perhaps not surprising as we have already shown variable postnatal hepatic expression of glucose-6-phosphatase in preterm infants,^{6,7} but also in term infants,¹⁰ and varied metabolic responses to perinatal factors,³⁸ and to hypoglycaemia, particularly in the generation of alternative substrates such as lactate and ketone bodies.^{12,39} The lack of correlation between

fasting blood glucose concentrations and glycaemic response to glucagon means that it is likely that these infants have multiple and varied failures in developmental regulation of hormonal responses and in the expression of key genes in the process of hepatic gluconeogenesis. These regulatory defects are variable and the infants who were identified as hypoglycaemic on fast were not exclusively those with the inadequate responses to glucagon.

We have identified, in the postnatal period, a subset of preterm infants who show an inadequate glycaemic response to glucagon and features of insulin resistance. The long term implications of the findings of this study are not yet known. For instance we are unsure of whether the metabolic differences found in our groups of infants are transient or persistent. Clearly such metabolic and hormonal studies also need to be extended to infants born at term, and pilot work suggests similar patterns to this preterm group.

ACKNOWLEDGEMENTS

The work carried out was supported by grants from the Scottish Executive (AB, RH), British Diabetic Association (AB), Wellcome Trust (RH), Tenovus (Scotland) (AB, RH), Research Trust for Metabolic Diseases in Children (AB), Paediatric Metabolic Research Trust (RH), and Anonymous Trust (AB, RH).

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Arch Dis Child Fetal Neonatal Ed 2003 88: F62-F66
doi: 10.1136/fn.88.1.F62

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