Archives of Disease in Childhood, 1984, **59**, 771–775

Hyperglycaemia in infantile gastroenteritis

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SUMMARY The prevalence and pathogenesis of hyperglycaemia were investigated in a consecutive series of 27 black infants admitted to hospital with gastroenteritis over a period of three months. Hyperglycaemia (plasma glucose concentration greater than 10 mmol/l) occurred in 15 (55%) of these patients. The pathogenesis was not clear but possible contributory factors included raised concentrations of the stress hormones pancreatic glucagon, growth hormone, and cortisol; hypokalaemia; and peripheral insulin resistance. Intravenous rehydration, without insulin, corrected the plasma glucose concentrations and restored the hormonal profile towards normal within 36 to 48 hours.

The association of hyperglycaemia with infantile gastroenteritis and dehydration is well recognised.[1 2] There is, however, little or no information on its prevalence or pathogenesis. In this study we have assessed the prevalence of hyperglycaemia in black South African children admitted to hospital with gastroenteritis and have investigated the changes in a number of blood electrolytes, substrates, and glucoregulatory hormones.

Patients and methods

Selection of patients. All the patients investigated were black and were admitted to the paediatric wards of Baragwanath Hospital. Those with gastroenteritis were admitted during the summer months, from February to April 1980. They were selected consecutively between 9 am and 3 pm daily except at weekends. All were dehydrated and needed intravenous rehydration treatment. Their ages ranged from 6 months to 2 years with a mean of 8·6 months. Twenty seven patients were studied and they fell into two groups:

(a) Fifteen who were found to be hyperglycaemic (random plasma glucose concentrations exceeding 10 mmol/l) on admission to hospital.

(b) Twelve who were normoglycaemic on admission to hospital.

Nine patients in group (a) and nine in group (b) were below the third centile on the Boston weight chart and were regarded as undernourished. Eight of the 18, four children in each group, were either frankly marasmic or suffering from kwashiorkor.

Two control groups were studied:

(c) Ten infants who suffered from pneumonia or bronchopneumonia and served as a 'stress' control group. Their ages ranged from 8 months to 2 years with a mean of 12·1 months. Five were below the third centile on the Boston weight chart, one of whom was marasmic.

(d) Ten infants admitted for minor surgical procedures such as circumcision or removal of extra digits. They served as a non-infected, fasting (6 to 8 hours) normal control group. Their ages ranged from 5 months to 2 years, with a mean of 11·9 months. All were well nourished.

Experimental protocol. *On admission* venous blood was drawn for the following investigations before starting intravenous treatment in groups (a), (b), and (c), and after a 6 to 8 hour fast in group (d): blood glucose, serum urea, sodium, potassium, chloride, pH, and base excess; plasma concentrations of insulin, C-peptide, human growth hormone, cortisol, pancreatic glucagon, free fatty acids, and ketones. Liver function tests including alanine aminotransferase, aspartate aminotransferase, and γ-glutamyl transferase were performed on five hyperglycaemic and five normoglycaemic patients with gastroenteritis. *After 24 hours* of intravenous treatment blood glucose, serum electrolyte, plasma insulin, C-peptide, human growth hormone, glucagon, and free fatty acid concentrations were estimated. *After 48 hours* blood glucose and free fatty acid concentrations were determined. *On recovery* blood glucose, plasma insulin, C-peptide, human growth hormone, cortisol, glucagon and free fatty acid concentrations were again measured. The study

was approved by the Human Research Committee of the University of the Witwatersrand.

Methods. Blood glucose was estimated by the glucose oxidase method. Urea, electrolytes, pH, and base excess were measured by routine laboratory techniques. A radioimmunoassay method was used for estimating insulin values,[3] while pancreatic glucagon, C-peptide, cortisol, and human growth hormone were determined by commercially available radioimmunoassay kits (Serona Biodata, Byk-Mallinckrodt, Sorin and Phadebas, respectively). Plasma free fatty acid was estimated by a modification of the Dole technique.[4] Ketostix strips (Ames) were used for the semiquantitative estimation of plasma ketones.

Statistical analysis of the data was performed using two tailed unpaired and paired Student's *t* tests as applicable.

Results

Biochemical and hormonal results on admission. Fifteen of the 27 infants with gastroenteritis who were investigated were hyperglycaemic on admission to hospital. Nine of these (60%) were hyponatraemic with serum sodium concentrations between 119 and 132 mmol/l, two had concentrations of 136 and 141 mmol/l, while four were hypernatraemic with serum sodium values between 150 and 163 mmol/l.

The blood glucose and other biochemical studies on admission are shown in Table 1. The mean blood glucose concentration in the hyperglycaemic group was six times the value in the normal group ($P<0.0005$). Plasma osmolarity was greatest in the hyperglycaemic patients. There was a significant metabolic acidosis in both gastroenteritis groups, being slightly greater in the hyperglycaemic groups ($P<0.1$). All but three infants with hyperglycaemia presented with hypokalaemia (potassium concentration<3·5 mmol/l); this differed from the normoglycaemic group whose serum potassium values were in the normal range ($P<0.05$).

The initial hormonal and free fatty acid concentrations are recorded in Table 2. The insulin values in both groups of patients with gastroenteritis were raised compared with both normal controls ($P<0.005$) and the pneumonia group ($P<0.05$). Mean C-peptide concentrations reflected the corres-

Table 1 *Acid base status and glucose, urea, and electrolyte concentrations in the four groups on admission to hospital (mean (SEM))*

Group		*Glucose (mmol/l)*	*pH*	*Base excess (mmol/l)*	*Osmolarity (mOsm/l)*	*Urea (mmol/l)*	*Sodium (mmol)*	*Potassium (mmol/l)*
Children with gastroenteritis	(a) Hyperglycaemia (n = 15)	20·0 (2·7)	7·1 (0·10)	−19·2 (1·6)	293 (8)	15·1 (3·0)	136 (4)	3·1 (0·3)
	(b) Normoglycaemia (n = 12)	5·9 (0·5)	7·2 (0·02)	−14·4 (1·3)	281 (6)	14·2 (2·6)	137 (3)	4·4 (0·5)
Controls	(c) Pneumonia (n = 10)	5·8 (0·3)	7·4 (0·30)	−3·0 (1·2)	286 (2)	4·7 (0·5)	140 (1)	4·7 (0·2)
	(d) Normal (n = 10)	3·4 (0·1)	7·4 (0·02)	−3·0 (0·9)	274 (2)	4·1 (0·5)	136 (1)	4·8 (0·2)

Table 2 *Hormonal and free fatty acid concentrations in the four groups on admission to hospital (mean (SEM))*

Group		*Insulin (mU/l)*	*C-peptide (μg/l)*	*Glucagon (ng/l)*	*Cortisol (nmol/l)*	*Growth Hormone (μg/l)*	*Free fatty acids (μmol)*
Children with gastroenteritis	(a) Hyperglycaemia (n = 15)	52 (9)	10·1 (2·1)	1300 (223)	1822 (166)	39 (11)	3117 (225)
	(b) Normoglycaemia (n = 12)	37 (5)	7·6 (2·5)	811 (68)	1435 (220)	21 (6)	2685 (239)
Controls	(c) Pneumonia (n = 10)	17 (6)	2·2 (0·3)	950 (490)	1270 (276)	11 (3)	1352 (153)
	(d) Normal (n = 10)	16 (4)	1·8 (0·3)	559 (74)	386 (83)	6 (1)	1344 (59)

ponding insulin concentrations. There was a tendency for concentrations of the counter regulatory hormones glucagon, human growth hormone, and cortisol to be higher in the hyperglycaemic than in the normoglycaemic patients with gastroenteritis, but these differences were not significant. Glucagon concentrations in the hyperglycaemic children were twice those of the normal controls ($P<0.025$). Cortisol concentrations were raised in all three groups of ill patients, the differences from the normal group being significant in each instance ($P<0.0005$). Concentrations of human growth hormone in both gastroenteritis groups were higher than those of the normal controls ($P<0.025$).

In both groups with gastroenteritis the initial mean plasma free fatty acid concentrations were at least twice those of the normal controls ($P<0.0005$) and the pneumonia patients ($P<0.0005$), the hyperglycaemic infants showing the highest values. Plasma ketones were detected in five infants with gastroenteritis, the amounts being mild in four and moderate in one. Four of these patients were hyperglycaemic with blood glucose concentrations between 12 and 13·7 mmol/l. Free fatty acid values were raised in all five cases.

Hyperglycaemia in gastroenteritis related to nutritional status (Table 3)

When analysed according to their nutritional status, the mean blood glucose concentrations of the 18

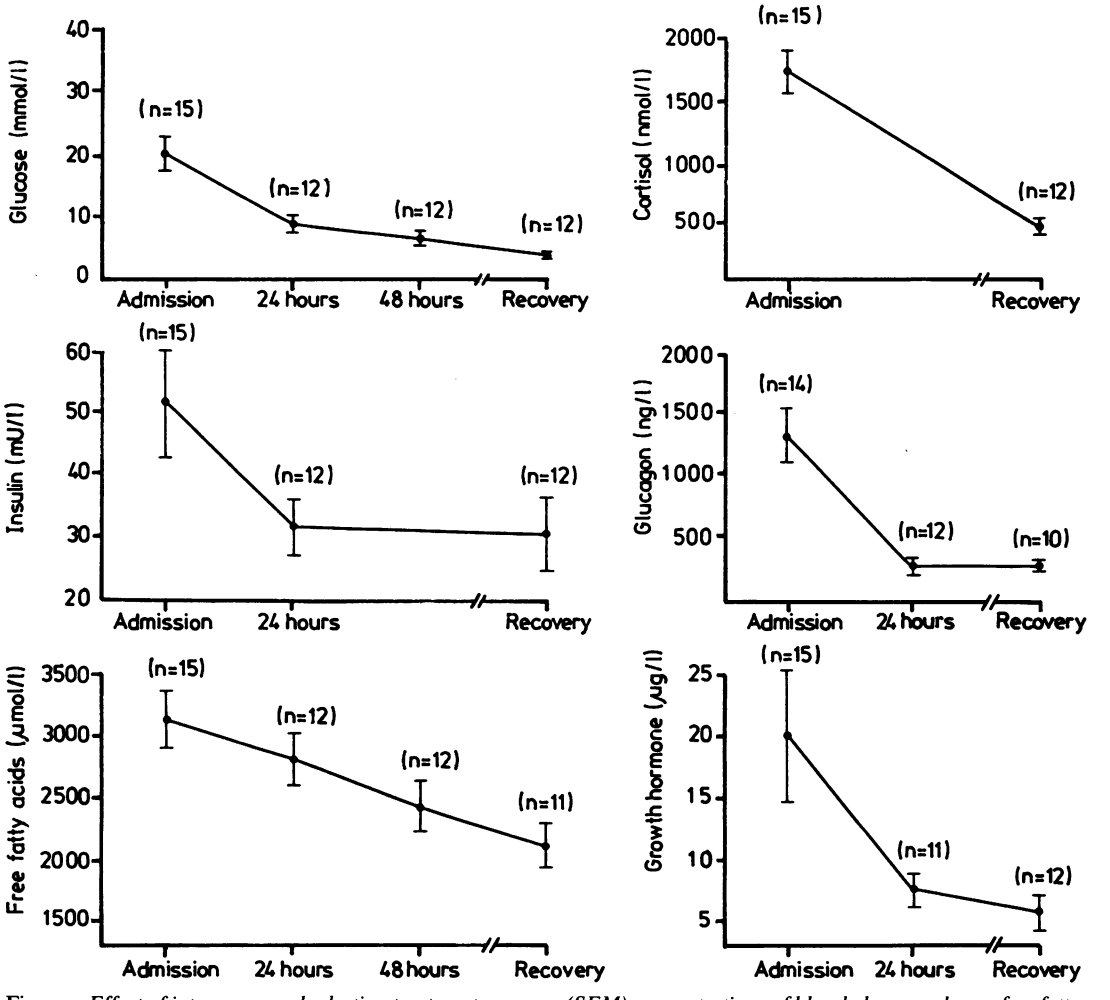

Figure *Effect of intravenous rehydration treatment on mean (SEM) concentrations of blood glucose, plasma free fatty acids and glucoregulatory hormones in hyperglycaemic infants with gastroenteritis.*

Table 3 *Blood glucose concentrations related to nutritional status in 27 children admitted to hospital with gastroenteritis (mean (SEM))*

Nutritional status	*No*	*Age (months)*	*Weight (kg)*	*Glucose (mmol/l)*	*No with hyperglycaemia*
Undernourished†	18	8·7 (0·7)	5·4 (0·3)	13·1 (2·7)	9
Well nourished	9	8·3 (2·8)	7·1 (0·7)*	15·2 (3·0)	6

* P<0·025. Other differences not significant.
† Below the third centile on the Boston weight chart.

undernourished children (including those with frank protein-energy malnutrition) were not significantly different from those who were found to be well nourished on admission.

Effects of intravenous rehydration on patients with hyperglycaemia (Figure)
One of the 15 hyperglycaemic patients died, one developed measles, and one was critically ill; these children were not studied further. Blood glucose concentrations in the remaining hyperglycaemic infants fell by half within 24 hours of starting intravenous rehydration treatment with half strength Darrow's and five per cent glucose solutions; normal values were reached within 48 hours.

Plasma insulin concentrations dropped steeply within 24 hours of treatment but remained slightly raised. Counter regulatory hormone values fell sharply within the first 24 hours. Levels of these hormones were all within normal limits on recovery. Plasma free fatty acid concentrations declined at a slower rate during treatment, and on recovery were still slightly high.

In the first 24 hours of treatment the blood urea concentrations declined from their initial value of mean (SEM) 15·1 (3) mmol/l to 6·6 (1·7) mmol/l (P<0·005), while potassium values rose from mean (SEM) 3·1 (0·3) to 4·1 (0·3) mmol/l (P<0·05).

Discussion

In this study hyperglycaemia was common in black infants with gastroenteritis, dehydration, and acidosis. It developed regardless of serum sodium concentrations, which is contrary to some previous reports in which its association with hypernatraemia and hyperosmolar states has been stressed.[1 5]

With regard to the pathogenesis of the hyperglycaemia, a diagnosis of moderately severe non-ketotic diabetes was initially considered but its frequent occurrence, response to rehydration without insulin treatment, and good prognosis made this possibility very unlikely. Dehydration and haemoconcentration do not seem to play a major role in causing the high blood glucose concentrations, since patients with similar degrees of dehydration had normal blood glucose values. Nor could we incriminate the feeding of glucose water and insufficiently diluted milk powders.[6] Most of the infants had vomited their feeds, and black tea or water were the main fluids administered before admission to hospital. Finally, on the negative side, the role of associated undernutrition was assessed but it did not emerge as a pertinent factor since the mean blood glucose concentration of undernourished infants was similar to that of the well nourished children.

The hyperglycaemia in our patients may have been due to a number of interrelated factors. Hypovolaemia and stress may be important. This could be mediated via the stress hormones glucagon, cortisol, and human growth hormone acting synergistically to raise blood glucose concentrations.[7] Impaired utilisation of glucose by peripheral tissues is also possible since both potassium depletion[8] and hypernatraemia[9] may cause such impairment. Finally, some degree of insulin resistance, as discussed later, may have contributed to the hyperglycaemia. These are tentative suggestions, however, and the precise mechanism of the hyperglycaemia remains uncertain.

Insulin concentrations were raised in the hyperglycaemic group, although probably not to the extent that might be expected for the degree in hyperglycaemia. The reasons for this increase remain obscure but some possibilities include the hyperglycaemia itself, raised free fatty acid concentrations,[10] and acute uraemia.[11] Impaired hepatic uptake or degradation is an unlikely reason since liver function tests were normal and concentrations of C-peptide, not metabolised by the liver, were also high. The evidence suggests, therefore, that the hyperinsulinaemia was due to increased secretion of the hormone. Low plasma concentrations of insulin before treatment were found in one previous report; however, only three patients were studied and the blood glucose concentrations were only slightly raised.[1]

Although the plasma insulin concentrations were raised in the hyperglycaemic patients, the action of insulin was impaired, as evidenced by the high blood glucose and free fatty acid values. Insulin resistance in these cases may have been due to circulating antagonists such as the raised counter regulatory or stress hormones, severe metabolic acidosis,[12] or an insulin receptor or post-receptor abnormality. Viral infections have been reported to cause insulin resistance by decreasing insulin receptors.[13] In a microbiological study performed on children with gastroenteritis during a similar period of the year at

this hospital, 15% of the cases were of viral aetiology.[14]

Very high concentrations of free fatty acid were encountered in both our hyperglycaemic and normoglycaemic infants with gastroenteritis. Hypovolaemia and liberation of stress hormones could again be the cause of this. Yet ketonaemia was not common. This could be due to high insulin concentrations in the portal vein resulting in an adequately insulinised liver, thereby suppressing hepatic ketogenesis.[15]

Fluid and electrolyte replacement is the only treatment necessary for correcting the hyperglycaemia and insulin is not indicated.

We thank Drs E U Rosen, R J Cohn, and M D Davis for their help and Mrs Anthea Botha, Mrs Jane Lamprey, and Mr Gopal Moodley for technical assistance. Financial assistance was provided by the South African Medical Research Council.

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Received 8 May 1984