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Hypoglycaemic Response to Exogenous Insulin in Children with Protein Energy Malnutrition

FA AKESODE* AND AA BABALOLA†

Summary

Akesode FA and Babalola AA. Hypoglycaemic Response to Exogenous Insulin in Children with Protein Energy Malnutrition. *Nigerian Journal of Paediatrics* **1987; 14:45.** Response to an intravenous bolus of insulin was investigated in 38 children with protein energy malnutrition (15 with kwashiorkor, 12 marasmic kwashiorkor and 11 with marasmus) and a group of 14 well-nourished children (controls), by monitoring the subsequent changes in the blood sugar levels. The mean fasting blood sugar (FBS) in children with kwashiorkor was 3.15 mmol/l and in marasmic-kwashiorkor, 3.17mmol/l. The marasmic children and the controls had mean FBS of 3.86mmol/l and 4.28mmol/l respectively; one child among the marasmic group had a FBS below 2.22mmol/L. Children with kwashiorkor had a sluggish but prolonged hypoglycaemic response to insulin which was not seen in the controls or in other subgroups. It is speculated that the slow recovery of blood sugar from hypoglycaemic to normoglycaemic levels in patients with kwashiorkor might be due to a defect in the homeostatic glycogenolytic pathway.

Introduction

SIGNIFICANT concern has been expressed in the past about hypoglycaemia being responsible for some deaths recorded in protein energy malnutrition (PEM)[1]. Only recently, Laditan and Tindimwebwa[2] in a review of the present line of management of PEM at Ibadan, highlighted the lack of adequate documentation of blood sugar levels in their patients. They therefore, advocated that a vigorous search for hypoglycaemia should always be made among malnourished children. However, a significantly low fasting blood sugar has been found in PEM patients [1 3–5] although some workers have not observed this low fasting blood sugar[6]. Both in the latter report[6] and some other studies that have reported significantly lower fasting blood sugar in PEM victims than in normal controls, absolute hypoglycaemia (blood glucose below 2.22 mmol/l) has not been commonly encountered among PEM patients[3 5]. However, in Uganda, 23% of children with kwashiorkor were reported to have a mean blood sugar of 1.72 ± 0.5mmol/l[7].

College of Medicine, University of Lagos, Lagos.

Department of Paediatrics.
*Senior Lecturer
+Lecturer

Correspondence: Dr FA Akesode

Conflicting results from studies in PEM patients were probably due to the different diagnostic criteria used by the investigators before the introduction of the Wellcome classification[8].

The fasting blood sugar (FBS) in a PEM patient is a result of a balance between glycogenolysis, gluconeogenesis and the effect of insulin. The effectiveness of glycogenolysis and gluconeogenesis in PEM has been well studied, [3 4 6 7] so also has the insulin production in these patients[9]. The information about insulin sensitivity in PEM is scanty, the only existing publication on this subject, to the best of our knowledge was by Alleyne *et al*[4]. The aim of this study therefore, was to investigate insulin sensitivity in PEM patients.

Materials and Methods

Thirty-eight malnourished patients consisting of 15 kwashiorkor, 12 marasmic-kwashiorkor and 11 marasmic children were investigated in the paediatrics wards of the Lagos University Teaching Hospital. The classification of the various categories of malnutrition was according to that of Wellcome[8]. Fourteen clinically healthy and well-nourished children were also investigated as controls.

Most of the malnourished children and their age-matched controls were selected from the paediatric out-patients' clinic of the hospital; they were studied as day cases. The remaining subjects and controls were selected from among those who were on admission in the Paediatric Emergency Room; they were also investigated after initial resuscitation and recovery from such additional ailments like gastroenteritis and respiratory tract infections. Informed consent was obtained from the parents of all the subjects and controls.

The children were fasted from midnight to between 08.00 and 09.00 hours when insulin tolerance test was commenced. Fasting blood sample was obtained and intravenous saline infusion through a peripheral vein was commenced. The insulin was given to each child at a dose of 0.05 unit per kilogram body weight as recommended in the Residents' Handbook of Pediatrics of the Hospital for Sick Children, Toronto[10]. This dose was given intravenously as a bolus at zero hour and blood samples were subsequently withdrawn at 30-minute intervals over the subsequent 2 hours. The blood samples were placed in fluoride bottles and were sent to the laboratory for blood sugar determination, according to the enzymatic method of Trinder[11]. During this procedure, a rough estimate of blood sugar was obtained on every blood sample using blood dextrostix strip. The patient's pulse, respiration, muscle tone and level of consciousness were closely monitored throughout the duration of the procedure.

Statistical analysis was by the student's t test.

Results

Table I shows the ages, physical characteristics and serum protein levels. All the children were in the age range 0.8 to 2.1 years. The marasmic children had the least mean weight of 5.5 kg and mid arm circumference of 9.7 cm. However, the kwashiorkor children had the lowest mean serum total protein of 3.6mg/dl.

Table II compares the mean blood sugar changes after the intravenous insulin. The only PEM patient with a FBS lower than 2.22mmol/l belonged to the PEM sub-group of marasmus. The kwashiorkor group had a prolonged response to insulin in that the blood glucose continued to fall at 90 minutes and showed a rise only at 120 minutes. The marasmic-kwashiorkor group also showed a slow recovery. The marasmic group had a pattern of response which was similar to that of the controls. At 30 minutes, there was a drop of about 45% and by 60 minutes, the serum glucose level had started approaching the fasting level.

TABLE I

Mean Values of Age, Physical Characteristics and Serum Proteins in Children with PEM and Controls*

Groups	*Age (years)*	*Weight (kg)*	*Height (cm)*	*Mid-Arm Circumference (cm)*	*Total Serum Proteins (mg/dl)*
Kwashiorkor (n=15)	1.3(0.92-1.8)+	7.7(7.2-8.5)	75.7(73-77)	11.8(11.5-12)	3.6(2.5-4.11)
Marasmic-kwashiorkor (n=12)	1.4(0.8-2.1)	5.8(4.8-7.1)	70(65-75)	10.7(10-12)	4.9(4.0-5.8)
Marasmus (n=11)	1.1(0.8-1.4)	5.5(4.5-6.7)	72.7(68-80)	9.7(8.2-11.0)	5.7(4.7-7.8)
Controls (n=14)	1.1(0.8-1.4)	8.3(7.0-9.7)	73.2(70.7-75.0)	13.9(13.0-16.0)	6.2(5.6-6.8)

* PEM = Protein Energy Manultrition.
\+ Figures in parenthesis represent ranges.

TABLE II

Mean Blood Sugar (mmol/l) changes after Intravenous Insulin Administration

Groups	*Time (minutes)*				
	0	30	60	90	120
Kwashiorkor (n = 15)	3.15 (2.78 - 4.67)	2.17 (1.78 - 2.50)	2.02 (1.11 - 3.33)	1.82 (1.11 - 3.56)	2.44 (2.22 - 4.22)
Marasmic-kwashiorkor (n = 12)	3.17 (2.56 - 4.00)	1.82 (1.39 - 2.78)	1.85 (1.83 - 3.22)	2.04 (2.33 - 3.56)	2.61 (2.50 - 3.89)
Marasmus (n = 11)	3.86 (2.20 - 5.11)	2.11 (1.44 - 3.44)	3.17 (2.0 - 3.33)	3.33 (2.28 - 3.72)	3.33 (2.06 - 4.44)
Controls (n = 14)	4.28 (3.33 - 5.56)	2.54 (1.67 - 4.17)	3.34 (2.22 - 4.17)	3.71 (2.0 - 5.28)	4.0 (2.22 - 5.83)

Figures in parenthesis represent ranges.
Conversion: SI units to traditional units
1mmol/l = 18mg/dl.

Table III shows the maximum decline in blood sugar level for each group. In all groups, the lowest blood sugar level was recorded 30 minutes after intravenous insulin except in the kwashiorkor group which had the lowest level at 90 minutes. The percentage drop in mean blood sugar was however, similar in kwashiorkor (42.2%) and marasmic-kwashiorkor (42.6%) ($p>0.05$). There was no significant difference in the percentage drops between the controls and the marasmus group.

Table IV shows the extent of recovery to baseline, two hours after intravenous insulin bolus.

TABLE III

Maximum Decline in Blood Sugar Level following Intravenous Insulin in PEM Patients and Controls

Groups	*Pre Insulin Mean BS (mmol/l)*	*Lowest Mean BS (mmol/l)*	*% Drop in Mean BS from Pre-Insulin Level*
Kwashiorkor (n=15)	3.15	1.82++	42.2
Marasmic-kwashiorkor (n=12)	3.17	1.82+	42.6
Marasmus (n=11)	3.86	2.11+	45.3
Controls (n=14)	4.28	2.54+	40.7

BS = Blood Sugar
+Lowest BS recorded 30 minutes after intravenous insulin.
++ Lowest BS recorded 90 minutes after intravenous insulin.
Conversion: SI units to traditional units
Immol/l = 18 mg/dl.

TABLE IV

Extent of Blood Sugar Recovery to Baseline 2 Hours after Intravenous Insulin Bolus

Groups	*Mean BS at zero hour (mmol/l)*	*Mean BS at 2 hours (mmol/l)*	*% Recovery of BS at 2 hours*
Kwashiorkor (n=15)	3.15	2.44	77.6
Marasmic-kwashiorkor (n=12)	3.17	2.61	82.5
Marasmus (n=11)	3.86	3.33	86.3
Controls (n=14)	4.28	4.0	93.5

BS = Blood Sugar
Conversion: SI units to traditional units
I mmol/l = 18mg/dl.

Discussion

The lower mean fasting blood sugar (FBS) in kwashiorkor and marasmic-kwarhiorkor patients relative to controls which was observed in this study is in accord with findings in most previous studies on PEM[3–7]. In none of the children suffering from kwashiorkor and marasmic-kwashiorkor was the FBS lower than 2.22mmol/l. Marasmic children in contrast to children with the other forms of PEM, had a mean FBS which compared well with that of normal controls; in respect of marasmic children, therefore, our results are in agreement with that of Rao[6].

Johnson, Agbedana and Adeyemo[5] in their study of 30 patients with PEM in Ibadan, reported only one patient, a child with kwashiorkor, whose FBS was below 2.22 mmol/l. It would appear therefore, that while fasting hypoglycaemia is uncommon in malnourished children, an occasional child within any of the PEM clinical subgroups is in fact, liable to significant hypoglycaemia after a short period of fasting. The reason for this may lie in defective gluconeogenesis since blood glucose tends to drop after fasting for a few hours if gluconeogenesis is defective. Slone Taitz and Gilchrist[3] have postulated impaired gluconeogenesis in kwashiorkor, based on reported finding of high blood amino acid and low blood urea levels in kwashiorkor patients during initial phase of hospital admission, Inadequate substrate generation may be another factor in the defective gluconeogenesis in this type of PEM. Inadequate generation would indeed, appear to be a more plausible reason for fasting hypoglycaemia in an occasional child with marasmus as enzyme activity such as that which subserves glycogenolysis has been found to be exaggerated in this type of PEM[6].

In the present study, children with kwashiorkor exhibited a sluggish but prolonged hypoglycaemic response to insulin which was not seen in the controls or other PEM subgroups. It is possible that this sluggish insulin effect in oedematous kwashiorkor patients might be due to defective glycolytic pathway rather than insulin distribution in a larger fluid space as suggested by Alleyne *et al*[4]. Our results have shown that PEM patients demonstrated definite

insensitivity to insulin. Previous studies have demonstrated intolerance in PEM patients [3 4 9 12] and it is likely that insulin insensitivity observed in this study coupled with diminished insulin secretion previously reported in PEM patients[5 12] account substantially for this intolerance.

The slow recovery of blood sugar from hypoglycaemic to normoglycaemic levels in kwashiorkor patients, might be due to increased half-life of insulin or to a defect in the homeostatic glycogenolytic pathway in these children. A previous observation of increased half-life of insulin in PEM[13] lends support to the former hypothesis. However, given the diminished insulin sensitivity in kwashiorkor, an intact glycogenolytic pathway in these children should have been able to effect a prompt correction of hypoglycaemia. Fatty degeneration in the liver of the child with kwashiorkor has been documented but glycogen storage has been shown to be normal[7]. The blood glucose response to glycogen[7 12] and epinephrine stimulation has been shown to be blunted in kwashiorkor and exaggerated in marasmus[6]. The lack of prompt and spontaneous recovery from hypoglycaemic state observed in kwashiorkor in contrast to marasmic patients in this study, is therefore, in agreement with the finding in previous studies that a defect in glycogenolytic pathway actually exists in kwashiorkor. This defect might be due to hypothalamo-endocrine insensitivity to the stress of hypoglycaemia with consequent inadequacy of hormonal back-up for glycogenolysis or to inadequate enzyme activity at the hepatocellular level. To the best of our knowledge, the hypothalamo-endocrine responsiveness of children with PEM to hypoglycaemia has not been properly documented, but efforts are presently being made to investigate this important pathway in PEM patients in our unit. An insensitive hypothalamo-endocrine pathway failing to sense and respond appropriately to hypoglycaemia would be an added factor to the sluggish self-correction of hypoglycaemia in children with kwashiorkor.

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