

Blood glucose, lactate and pyruvate in kwashiorkor

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1. The blood sugar, lactate and pyruvate levels of sixty-nine Ugandan children, during treatment for kwashiorkor, have been studied. 2. The majority of untreated cases had low levels of blood glucose but high levels of lactate and pyruvate. Children with the lowest glucose levels had the lowest serum protein values and gained weight more slowly. 3. The response of the blood glucose to glucagon or adrenaline was twice as great at the end of treatment as at the beginning. 4. In children whose treatment was successful the lactate and pyruvate levels gradually fell to the normal range. There was a rise in the blood glucose value but after 3 weeks the level was still below that found in normal African children. In a few children who died or whose treatment was complicated by pyrexia and general apathy there was a rapid fall in lactate and pyruvate concentration to abnormally low levels.

Biochemical research on children with kwashiorkor (protein deficiency) has mainly been concentrated on abnormalities of protein and amino acid metabolism, and carbohydrate metabolism has largely been ignored. It is, however, the ingestion of a predominantly carbohydrate diet, deficient in protein, which is the dietary cause of kwashiorkor.

A small proportion of the Ugandan children admitted for treatment of kwashiorkor develop convulsions of the type found in hypoglycaemia. The prognosis of these children is poor. This investigation was planned to find out how many children with kwashiorkor had low levels of glucose in their blood. The level of blood lactate and pyruvate was also studied to see whether there were additional abnormalities in carbohydrate metabolism.

EXPERIMENTAL

Sixty-nine malnourished children were studied, of whom two died. They were aged from 1 to 4 years and showed, to a varying degree, the clinical signs of kwashiorkor described by Dean (1960). The children were underweight for their age; the feet and hands and often the thighs were swollen with oedema. The hair was abnormally pale in colour and pulled out easily, there was also pallor of the face. The children were miserable and apathetic. In the most severe cases there were skin lesions, deep cracks, some of them bleeding, around the ears and mouth and in the groins. With successful treatment the oedema disappeared within 2 weeks and the skin lesions improved rapidly, the children started to gain weight and their mental apathy disappeared. Eleven Africans, the children of professional parents living in Kampala, were studied in their own homes and used as the controls.

The children with kwashiorkor were treated for 2–3 weeks with a diet of calcium caseinate, dried skim milk, cane-sugar and cottonseed oil together with supplementary

sodium, potassium and magnesium so that the proportions were approximately the same as those present in human milk (Dean & Swanne, 1963).

Blood samples were collected on admission to the ward after a fasting period of at least 8 h and at successive intervals during treatment after an overnight fast. In a few very ill children, not included in the results, it was considered unwise to permit fasting and it was necessary to exclude them from this investigation. The blood sugars measured in the two children just before death were not fasting samples. The blood was taken from the internal jugular vein; 3 ml were placed immediately in an equal volume of ice-cold perchloric acid for determination of lactic and pyruvic acids, 100 μ l were added to 1.1 ml physiological saline for glucose determination, and serum was separated from the remaining blood. It was only possible to get permission to take blood samples by finger-prick from the control children, and analysis was limited to glucose. The samples were taken before breakfast.

In seven children the responses to glucagon or adrenaline were measured at the beginning and end of treatment. Adrenaline, 0.03 mg/kg, was given subcutaneously and glucagon (Ely Lilly and Co.), 0.1 mg/kg, intravenously. Blood samples were taken by finger-prick immediately before the hormone injection and at 30, 60, and 120 min afterwards.

Glucose was determined by the enzymic method of Marks (1959) and pyruvic and lactic acids with the 'enzyme test methods', TC-C 15973 and TC-B 15972, manufactured by C. F. Boehringer und Soehne GmbH, Mannheim, Germany. The amino acid ratio in the serum was measured by the method of Whitehead (1964) and the total proteins by a specific gravity method (Philips, Van Slyke, Dole, Emerson, Hamilton & Archibald, 1945).

RESULTS

For descriptive purposes the children have been divided into four groups, A, B, C and D, by the level of glucose found in the blood on admission. Table 1 shows the levels of glucose so found, the total proteins and the amino acid ratio in the serum and the percentage weight for age of sixty-seven children on admission to the ward for treatment of kwashiorkor. Of the sixty-seven children with kwashiorkor only thirteen had a blood glucose value above 60 mg/100 ml. Of the eleven control children ten had fasting blood sugar values above 60 mg/100 ml and the other child had a value of 58 mg/100 ml. The mean level was 73 mg/100 ml.

Children with blood glucose values less than 40 mg/100 ml (A) had on the average lower serum protein levels than those with higher blood glucose values. The difference between groups A and B was significant ($t = 2.9$, $P < 0.01$) and also between A and D ($t = 3.53$, $P < 0.001$). The serum amino acid ratios were equally high in all groups on admission. There was no difference in the expected weight for age using a local standard (Rutishauser, 1965). These values do not represent the actual amount the children were underweight because of the presence of oedema. There is no satisfactory way of quantifying the degree of oedema but an approximate idea can be obtained from the difference between the weight on admission and the minimum weight during the first 2 weeks of treatment. This difference was on the average 5% of the initial body-weight and there was no difference between the various blood glucose groups.

Table 1 also shows the fasting concentrations of glucose at the end of 2-3 weeks' treatment, together with the corresponding total serum proteins, amino acid ratios and the mean daily weight gain. In the children with the lowest blood sugar values on admission (A) the mean value rose from 31 to 46 mg/100 ml (significant, $t = 4.46$, $P < 0.001$), and in group B there was a similar improvement ($t = 2.3$, $P = 0.025$), but the level remained below that found in the controls. In the remaining children, however, there was no improvement and in those with normal glucose levels on admission (D) there was a significant fall ($t = 4.2$, $P < 0.001$). It is remarkable that although the initial glucose levels were so different the final ones were so nearly the same.

Table 1. Relationship between the glucose concentration in blood and the nutritional status of children during treatment for kwashiorkor (mean values and standard deviations)

Blood glucose group (mg/100 ml)	No. of patients	On admission				On discharge			
		Blood glucose (mg/100ml)	Serum protein (g/100ml)	Amino acid ratio	Wt for age (%)	Blood glucose (mg/100ml)	Serum protein (g/100ml)	Amino acid ratio	Mean wt gain (g/day)
A, < 40	16	31 ± 9	3.9 ± 0.5	6.2 ± 2.1	79 ± 13	46 ± 10	6.4 ± 0.6	2.2 ± 0.7	4 ± 32
B, 40-49	17	45 ± 4	4.5 ± 1.1	6.1 ± 2.9	81 ± 14	51 ± 10	6.5 ± 0.7	2.3 ± 0.7	31 ± 22
C, 50-59	21	54 ± 3	4.5 ± 0.8	6.0 ± 1.5	77 ± 12	51 ± 12	6.5 ± 0.5	2.2 ± 0.5	20 ± 29
D, 60 and above	13	69 ± 11	4.5 ± 0.4	6.1 ± 2.4	77 ± 11	51 ± 12	6.7 ± 0.7	2.2 ± 0.5	20 ± 45

The children who had the lowest initial glucose levels (A) gained least weight. Over the treatment period the gain was 4 g/day compared with a mean increase of 24 g/day in the other three groups (significant, $t = 2.1$, $P < 0.05$). As the standard deviations show, the individual weight gain varied widely in all groups. This was probably because the net weight gain was affected by two opposing factors, the synthesis of new tissues and loss of oedematous fluid and it was not possible to differentiate between them. The measurements of serum proteins and the amino acid ratios failed to show any difference between the four groups, and the improvement was similar in each group.

Table 2 shows the effect of glucagon or adrenaline injections on the fasting values for blood glucose in seven children on admission to the ward and again at the end of treatment. This experiment was made to discover whether an impaired glycogenolysis might be a factor in the development of the low values for blood sugar. With both adrenaline and glucagon there was a rise in the level of blood glucose, but the response at the end of treatment was about twice that on admission. Before treatment the blood glucose value never rose above 80 mg/100 ml but after treatment the highest concentration was always over 100 mg/100 ml. This maximum occurred between 0.5 and 1 h after injection, but after 1.5 h the value had returned to the fasting level.

Table 3 shows changes in the concentrations of lactate and pyruvate at the beginning and end of treatment in twenty-seven children. In four groups the mean lactate level on admission was above the normal fasting one of 9 mg/100 ml quoted by Huckabee (1961), but there was no relationship between the hyperlactaemia and the hypoglycaemia. On treatment, there was a fall in lactate concentration in all groups to a

mean level of 10.0 mg/100 ml ($t = 4.6$, $P < 0.001$). The blood pyruvate value was also elevated on admission (0.55–1.90 mg/100 ml). Normal mean values given in the literature range between 0.43 mg/100 ml (Bauer, 1956) and 0.64 mg/100 ml (Gastaldi, 1955). The pyruvate values were within this range after treatment and the improvement was statistically significant ($t = 4.6$, $P < 0.001$).

Table 2. *Rise in blood concentration of glucose (mg/100 ml) in response to adrenaline or glucagon injections in children with kwashiorkor*

Child no.	Hormone	Before treatment	After treatment
1	Adrenaline	25	62
2		19	56
3		38	67
4		36	90
5		36	60
6	Glucagon	31	87
7		48	67

Table 3. *Relationship between blood concentrations of glucose, lactate and pyruvate in children during treatment for kwashiorkor (mean values and standard deviations)*

Blood glucose group (mg/100 ml)	Lactate (mg/100 ml)			Pyruvate (mg/100 ml)		
	No. of patients	On admission	On discharge	No. of patients	On admission	On discharge
A, < 40	6	16.0 ± 6.8	12.0 ± 2.8	8	1.0 ± 0.6	0.6 ± 0.1
B, 40–49	7	14.4 ± 4.2	9.2 ± 2.4	7	0.8 ± 0.2	0.6 ± 0.1
C, 50–59	7	15.2 ± 7.0	10.7 ± 3.9	7	0.7 ± 0.1	0.5 ± 0.1
D, 60 and above	4	18.9 ± 9.5	7.8 ± 2.7	5	1.0 ± 0.3	0.5 ± 0.1

In addition to the results given in Tables 1 and 3, which are confined to the beginning and end of treatment, determinations of glucose, lactate and pyruvate were made in several children at different stages during treatment. Fig. 1 shows the course of events in a child who made good clinical progress. The glucose level rose gradually from 41 to 66 mg/100 ml over the 14-day period of treatment, and lactate and pyruvate showed a gradual fall in concentration. The results given in Fig. 2 for another child are quite different. He was admitted to the ward as a case of uncomplicated kwashiorkor and had elevated levels of lactate and pyruvate, but on day 4 of treatment he developed a fever and became more apathetic. These clinical signs were associated with a fall in blood lactate and pyruvate to very low levels. Clinical, haematological and bacteriological investigations, however, could establish no reason for the pyrexia although his temperature rose to 103.4 °F. The blood was free of malarial parasites, the white cell count was normal (5300/mm³) and the sickling test was negative. No pathogens were isolated from blood, stool or sputum cultures, salmonella agglutination tests were negative and the stools were free of parasites. X-ray examination 2 days before the onset of the fever showed no active pulmonary lesion. No virus agglutination tests were carried out. He had four loose stools daily and became moderately dehydrated. He was given half-strength Darrow's solution orally and a 3-day course

of chloramphenicol. As his clinical condition improved the lactate and pyruvate values rose to more normal levels. The blood glucose levels changed little during the fever but fell towards the end for no apparent reason. Of the children investigated, four others showed similar biochemical changes associated with fever. In two of them the temperature rose to 103°F but in the others only to 100°F.

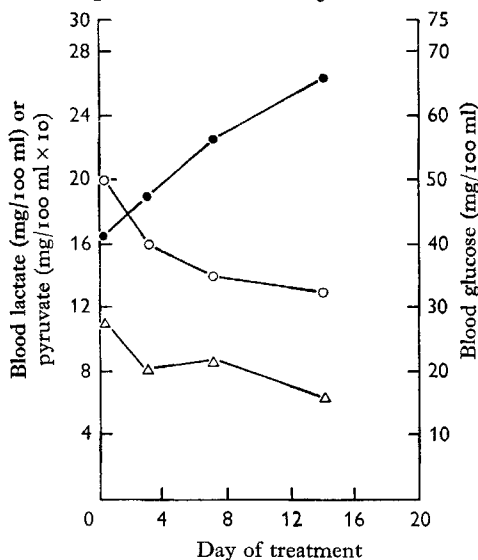


Fig. 1

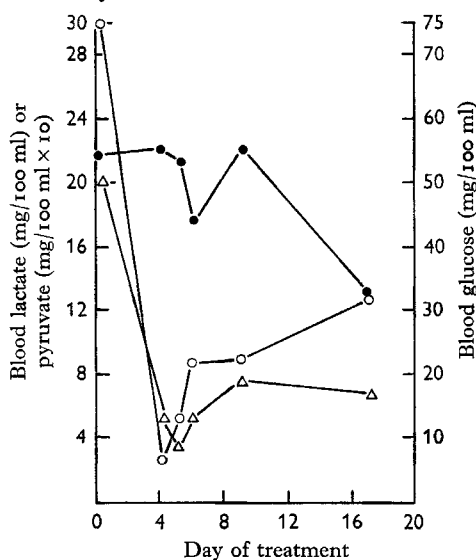


Fig. 2

Fig. 1. Variation in blood concentrations of glucose, lactate and pyruvate in a child recovering from kwashiorkor. ●—●, glucose; ○—○, lactate; △—△, pyruvate.

Fig. 2. Variation in blood concentrations of glucose, lactate and pyruvate in a child whose recovery from kwashiorkor became complicated by pyrexia on day 4. ●—●, glucose; ○—○, lactate; △—△, pyruvate.

During the course of this study two other children who were being investigated died within 48 h of admission. Before death these children were in a similar clinical state to the one with the fever just described; their temperatures ranged from 100 to 103°F but no reason for the pyrexia could be found. Immediately before death the lactate and pyruvate concentrations in their blood were below 5 mg/100 ml and 0.4 mg/100 ml respectively. They differed from the children who recovered in that their blood glucose levels were also low, less in fact than 5 mg/100 ml.

DISCUSSION

This study has been confined to children with kwashiorkor and well-nourished healthy children from the same African population. The results show that many of the malnourished children did not have normal concentrations of blood sugar. Slone, Taitz & Gilchrist (1961) investigated blood sugar levels in South African Bantu children and found values similar to those described here. Measured by a less specific method, the mean level of glucose in their kwashiorkor group was 51 mg/100 ml and that of the controls 76 mg/100 ml. Bowie (1964), however, found normal levels in

another group of South African children with kwashiorkor, 82 mg/100 ml as against a control mean value of 83 mg/100 ml. Recently Baig & Edozien (1965) reported that the blood sugar levels in Nigerian children with kwashiorkor were only slightly reduced and Rao (1965), working in India, found normal blood glucose levels in his cases of kwashiorkor. No explanation for these differences can be given at present, but all children diagnosed as suffering from kwashiorkor evidently do not have the same metabolic abnormalities.

Slone *et al.* (1961) found no correlation between the degree of hypoglycaemia and the severity of malnutrition. In the Ugandan children statistical analysis of the results showed that the children with the lowest blood sugar values had lower serum protein levels, and they gained weight more slowly on treatment.

The rise in blood glucose concentration after adrenaline or glucagon injections even in the untreated child demonstrated that some glycogen stores were present. This is in agreement with the findings of Waterlow & Weisz (1956) in Jamaica who found that glycogen levels in the liver were actually elevated in kwashiorkor. The response on discharge was, however, much greater than in the untreated child, and it seems probable that one of the reasons for the low blood sugar levels in our children with kwashiorkor was a subnormal response to adrenaline and glucagon. Treatment probably restored the enzyme mechanisms necessary for this reaction, and as a result the children with low blood glucose levels on admission maintained higher levels at the end. The effect of an 8 h fast on the liver glycogen, especially in a malnourished child, is not known. It is possible that this was a factor in the different response to adrenaline and glucagon at the beginning and end of treatment. At the end of 2-3 weeks' treatment the blood glucose values were still below those found in the healthy children. This probably means that it is necessary to continue treatment for a longer period before the recovery from this metabolic abnormality is complete. Why the blood glucose levels in children with normal values on admission should fall with treatment cannot be explained. This phenomenon is being investigated.

The elevated levels of lactate and pyruvate demonstrate a second abnormality of carbohydrate metabolism. It is unlikely that this hyperlactaemia was a result of tissue hypoxia because Huckabee (1961) has shown that this raises the blood concentration of lactate much more than of pyruvate. It is more probable that there was a metabolic 'block' in the pathway responsible for the oxidation of pyruvate via the citric acid cycle and the accumulating pyruvate was converted into lactate. A deficiency of thiamine might have caused this, or of pantothenic acid, the precursor of co-enzyme A. These vitamins are normally added to the therapeutic diet, but their omission in a few children did not prevent the correction of this metabolic abnormality. Another possibility is that the pyruvate has to compete for co-enzyme A with an excess of free fatty acids formed either in the course of fat synthesis or arising from fat oxidation. An accumulation of pyruvate would also occur if the progress of metabolites round the tricarboxylic acid cycle was delayed. The diversion of two-carbon units towards synthesis of fat is the probable reason for its deposition in the tissues and liver in kwashiorkor. This problem merits more detailed investigation.

A further clue to the reason for the high levels of lactate and pyruvate on admission

is provided by their changes during treatment. In children whose treatment progressed satisfactorily the lactate and pyruvate values fell only gradually, but in the children who died or developed a high temperature and became very apathetic the fall in concentration was rapid and to very low levels. Recently Edwards (1964) suggested, from work on calves, that the brain could metabolize lactate as well as glucose. Neligan (1964) reported that hypoglycaemic fits occurred only in children with low values for both blood glucose and blood lactate. It is possible that the modified metabolism which resulted in the elevated levels of lactate and pyruvate in most of the children on admission to the ward was in fact a protective mechanism. Certainly, low levels of lactate and pyruvate when combined with a low level of blood glucose indicated that the prognosis was bad.

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