Serum albumin and transferrin in protein-energy malnutrition

Their use in the assessment of marginal undernutrition and the prognosis of severe undernutrition

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1. Deficits in weight- and length-for-age, and serum albumin and transferrin concentrations were determined for children who were either marginally undernourished (twenty-five children) or suffering from either marasmus (thirty-two children) or kwashiorkor (twenty-six children) defined according to the Wellcome Classification (Waterlow, 1972). The measurements were also made in eight children with kwashiorkor after the loss of oedema, and in sixteen children who were recovering from either marasmus or kwashiorkor.

2. The mean concentration of serum albumin was similar for children from the 'undernourished' group and from the group with marasmus, but was significantly reduced in those with kwashiorkor.

3. The concentration of serum transferrin was significantly reduced in both the group of children with marasmus and those with kwashiorkor. The serum transferrin concentration was significantly lower in children with kwashiorkor when compared with the level in those with marasmus.

4. Seventeen children (seven with kwashiorkor and ten with marasmus) died. These children were neither lighter nor shorter than the severely malnourished children who survived. The concentration of serum albumin was not lower in the children who died than in those who survived.

5. In contrast to the results for serum albumin concentrations, the children who died had significantly lower levels of serum transferrin than those who survived.

6. There was a significant linear relationship between serum transferrin concentrations and the deficits in length-for-age ($P < 0.05$) and weight-for-length ($P < 0.001$) in the marginally undernourished children. The deficit in weight-for-length was also linearly related to the serum transferrin concentrations ($P < 0.001$) in children recovering from severe malnutrition.

7. It is suggested that the measurement of serum transferrin concentrations provides an index of severity in severely malnourished children, and should prove useful in field assessments of nutritional status.

In the last 15 years there has been a continuing interest in biochemical indices of nutritional status. The search for these indices has been directed towards two main objectives: (1) an index which aids the identification of early undernutrition in situations where anthropometric measurements may be unreliable; (2) an index which allows the clinician to estimate the severity and prognosis for recovery of a recognizable form of severe protein-energy malnutrition (PEM).

The development of field tests, particularly by workers in Uganda (Whitehead, 1968, 1969), has been based on various measurements of either protein metabolism or protein intake. Plasma amino acid concentrations (Whitehead & Dean, 1964; Rutishauser & Whitehead, 1969); plasma albumin concentrations (Whitehead, Frood & Poskitt, 1971) and the excretion of amino acids or their metabolites (Whitehead, 1968; Rutishauser & Whitehead, 1969) have been applied with varying success, because these different tests have a number of disadvantages (Whitehead, 1969).

Measurements of muscle wasting from changes in the excretion of creatinine (Viteri & Alvarado, 1970), as well as the concentrations of serum albumin (Lunn, Whitehead, Hay & Baker, 1973) and serum transferrin (MacFarlane, Ogbeide, Reddy, Adcock, Adeshina, Gurney, Cooke, Taylor & Mordie, 1969) have been proposed as indices of the severity of PEM. The concentration of serum transferrin predicts prognosis for recovery from kwashiorkor (MacFarlane *et al.* 1969; MacFarlane, Reddy, Adcock, Adeshina, Cooke & Akene, 1970; Gabr, El-Hawary & El-Dali, 1971) and has recently been recommended as one of a series of indicators of the severity of this condition (Stephens, 1974).

However, interest in the assessment of the severity of PEM has been mainly concentrated on the study of children with kwashiorkor, and apart from results obtained for a limited number of children with marasmus (Antia, MacFarlane & Soothill, 1968) there are no other reports of serum transferrin concentrations in this group, In view of the fact that marasmus may be becoming more prevalent (McClaren, 1966) it is timely to assess the use of the measurement of the serum transferrin concentration as an index of severity in cases of marasmus.

There are very large reductions in serum transferrin concentrations in kwashiorkor, and there are progressive reductions in the concentration of this protein in the serum of monkeys during the development of severe PEM (Kuma, Chase & O'Brien, 1972). It would seem worth while therefore to study the use of the measurement of serum transferrin concentration as a method for the early detection of undernutrition.

EXPERIMENTAL

Subjects. Three groups of children between the ages of 5 and 40 months were studied. The first group was drawn from an area of Ibadan where undernutrition of varying severity is prevalent. The children in this group were studied when they were recruited for a study of growth and development. This group was classified here as undernourished although there were well-nourished children in the group (Fig. 1).

The other groups of children were unselected cases of severe PEM who were referred to us by the General Out-patient Clinic of the University College Hospital, Ibadan. They were classified as having marasmus or kwashiorkor according to the Wellcome Classification (Waterlow, 1972).

The total number of children in the study was eighty-three: twenty-five undernourished, twenty-six with kwashiorkor, thirty-two with marasmus. Preliminary results obtained for sixteen of the severely malnourished children during their recovery from PEM, and for eight children who were studied after the loss of oedema and body-weight, are also given.

The mothers or guardians of the children were informed of the object of the study and their full consent was obtained.

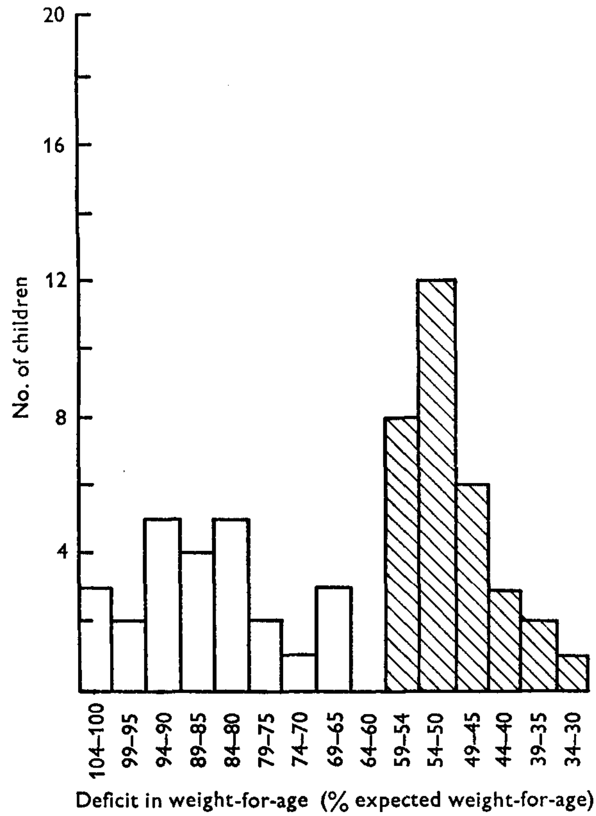

Fig. 1. The distribution of the deficit in weight-for-age (% expected weight-for-age, based on local standards (Janes, 1975)) of twenty-five undernourished children (□) and thirty-two children with marasmus (grouped according to the Wellcome Classification (Waterlow, 1972) of protein-energy malnutrition) (▧), aged between 5 and 40 months.

Procedures. The severely malnourished children who required emergency treatment were admitted to hospital and a blood sample was obtained before they received any treatment. The other severely malnourished children were treated on an out-patient basis. Blood samples from these children and from those in the 'undernourished' group were taken after an overnight fast. These samples were obtained at the Institute of Child Health, Ibadan.

At each visit a full physical examination was made and any new medical problems were treated. A variety of anthropometric measurements were then made by the same individual on every occasion. A 10 ml blood sample was then taken from the femoral vein. The blood was then allowed to clot in an air-conditioned room, the serum separated by centrifugation and stored at −18° until analysed.

Serum albumin concentration was determined by the method of Doumas, Watson & Briggs (1971) and serum transferrin concentration by an immunodiffusion method (Mancini, Carbonara & Heremans, 1965) using a kit supplied by Travenol Laboratories Ltd, Thetford, Norfolk. The diffusion stage was carried out at 4° for 18 h in all instances, the maintenance of a constant temperature during this stage being of

Table 1. *Ages (months), deficits in weight- and length-for-age (% expected values), and serum albumin and transferrin concentrations (g/l) for undernourished (UN) children, and children with marasmus (MAR)‡ and kwashiorkor (KW)‡, aged between 5 and 40 months*

(Mean values and standard deviations; deficits in weight- and length-for-age were assessed by comparison with local standards (Janes, 1975))

Group ...	UN		MAR		KW	
No. of children ...	25		32		26	
	Mean	SD	Mean	SD	Mean	SD
Age	16·9	8·0*†	21·1	7·4	24·6	5·8
Weight-for-age	85·1	12·5*†	50·9	6·6**	70·9	7·8
Length-for-age	93·2	3·7†	85·1	5·0***	91·4	3·7
Weight-for-length	94·0	11·4*†	65·6	8·2**	82·2	6·4
Serum albumin	37·0	6·0***	33·6	8·6***	21·7	6·8
Serum transferrin	2·56	1·02***†	1·31	1·04**	0·51	0·30

Mean values were significantly different from that of the KW group: * $P < 0·05$, ** $P < 0·01$, *** $P < 0·001$.

Mean values were significantly different from that of the MAR group: † $P < 0·05$.

‡ Grouped according to the Wellcome Classification (Waterlow, 1972) of protein-energy malnutrition.

Table 2. *Ages (months), deficits in weight- and length-for-age (% expected values), and serum albumin and transferrin concentrations (g/l) for children (a) who survived and (b) who died as the result of either marasmus‡ (MAR) or kwashiorkor‡ (KW)*

(Mean values and standard deviations; deficits in weight- and length-for-age were assessed by comparison with local standards (Janes, 1975))

Group ...	MAR				KW			
	Survived		Died		Survived		Died	
No. of children ...	22		10		19		7	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	19·8	8·0	24·2	5·3	25·3	5·4	22·7	6·0
Weight-for-age	52·4	5·3	47·2	8·5	70·3	7·6	72·5	8·5
Length-for-age	85·6	5·1	83·8	4·7	90·8	3·6	93·0	3·9
Weight-for-length	66·8	6·9	62·9	6·9	81·8	11·7	82·0	5·5
Serum albumin	35·0	9·1	30·8	6·4*	21·6	5·7	21·9	11·0
Serum transferrin	1·58	1·14	0·73	0·38*†	0·57	0·40	0·34	0·04*

Mean value (*a*) for 'died KW' group significantly different from that for the 'survived KW' group; (*b*) for 'died MAR' group significantly different from that for 'died KW' group: * $P < 0·001$.

Mean value significantly different from that for the 'survived MAR' group: † $P < 0·05$.

‡ Grouped according to the Wellcome Classification (Waterlow, 1972) of protein-energy malnutrition

critical importance. The sera used for the estimation of transferrin had been thawed once.

The deficits in weight- and length-for-age were assessed by comparison with local standards (Janes, 1975). Differences between mean values were assessed by Student's *t* test for groups with either equal or unequal variance.

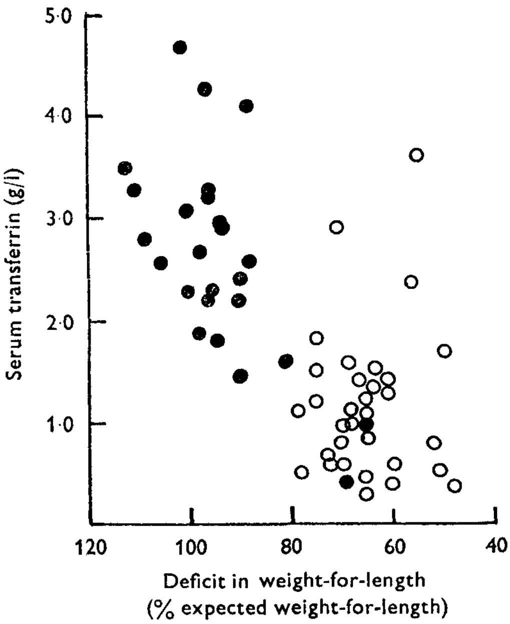

Fig. 2

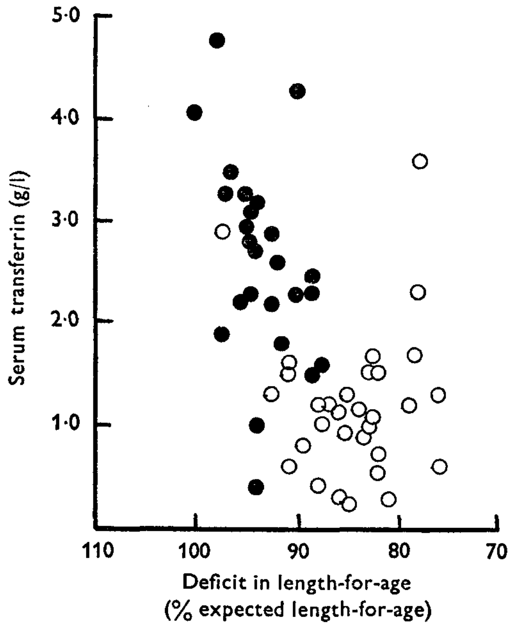

Fig. 3

Fig. 2. The relationship between the serum transferrin concentration (g/l) and the deficit in weight-for-length (% expected weight-for-length, based on local standards (Janes, 1975)) in twenty-five marginally undernourished children (●) and in thirty-two children with marasmus (grouped according to the Wellcome Classification (Waterlow, 1972) of protein-energy malnutrition) (○), aged between 5 and 40 months. 'Undernourished' group: *n* 25, slope 4·71, *r* 0·547, $P < 0·001$; 'marasmus' group: *n* 32, slope 1·20, *r* 0·185, not significant; combined values: *n* 57, slope 3·75, *r* 0·436, $P < 0·01$.

Fig. 3. The relationship between the serum transferrin concentration (g/l) and the deficit in length-for-age (% expected length-for-age, based on local standards (Janes, 1975)) in twenty-five marginally undernourished children (●) and in thirty-two children with marasmus (grouped according to the Wellcome Classification (Waterlow, 1972) of protein-energy malnutrition) (○), aged between 5 and 40 months. 'Undernourished' group: *n* 25, slope 11·03, *r* 0·403, $P < 0·05$; 'marasmus' group: *n* 32, slope 2·19, *r* 0·130, not significant; combined values: *n* 57, slope 9·29, *r* 0·580, $P < 0·001$.

RESULTS

During the study seventeen children (seven with kwashiorkor and ten with marasmus) died. The results obtained for these children are reported separately in Table 2. Of these, 70% died within 48 h of being admitted to hospital.

The ages, and deficits in weight- and length-for-age of the three groups of children, are given in Table 1. In agreement with our previous findings (Reeds & Laditan, unpublished results) the mean age of the group with marasmus was not significantly different from that of the group with kwashiorkor. The mean age of the 'undernourished' group was, however, significantly lower than that of either of the two groups of severely malnourished children. Deficits in weight- and length-for-age were similar to reported values (Shakir, Demarchi & El-Milli, 1972; Waterlow, 1972). The children who died were neither shorter nor lighter than those who survived (Table 2).

Table 3. *Deficits in weight-for-length (% expected value), and serum albumin and transferrin concentrations (g/l) for undernourished children (UN), children with marasmus* (MAR), children originally with kwashiorkor* after the loss of their oedema (KWM), and children gaining weight during their recovery from either marasmus or kwashiorkor (REC)*

(Mean values and standard deviations; deficits in weight-for-length were assessed by comparison with local standards (Janes, 1975)

Group ...	KWM		MAR		REC		UN	
No. of children ...	8		32		16		25	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Weight-for-length	69·9	8·4	65·6	8·2	89·0	10·2	94·0	11·4
Serum albumin	24·6	12·4	33·6	8·6	36·1	8·2	37·0	6·0
Serum transferrin	0·92	0·43	1·31	1·04	2·15	1·19	2·56	1·02

* Grouped according to the Wellcome Classification (Waterlow, 1972) of protein-energy malnutrition

Serum albumin concentrations were similar in the group with marasmus and the undernourished group, although there was a greater range of values in the group with marasmus (Table 1). Seven of the children with marasmus had concentrations of serum albumin lower than 25 g/l. As expected, the concentration of serum albumin was significantly reduced in the children with kwashiorkor. The children who died did not have significantly lower concentrations of serum albumin at first presentation at the hospital than those who survived.

Both groups of severely malnourished children had significantly lower concentrations of serum transferrin than the undernourished group (Table 1). The mean value for the concentration of serum transferrin was significantly lower in the group with kwashiorkor than in the group with marasmus. Furthermore, the children who died had significantly lower concentrations of serum transferrin than those who survived (Table 2). The children with kwashiorkor who died still had significantly lower serum concentrations of transferrin than those with marasmus who died.

Serum albumin concentrations were not linearly related to deficits in either weight- or length-for-age ($r < 0{\cdot}1$) in any of the three groups of children. However, there was a significant linear relationship between serum transferrin concentrations and the deficits in both weight-for-length (r 0·547, $P < 0{\cdot}001$; Fig. 2) and length-for-age (r 0·403, $P < 0{\cdot}05$; Fig. 3) in the undernourished group. There was no significant linear relationship between the deficits in weight- and length-for-age and serum transferrin concentrations ($r < 0{\cdot}20$; Figs. 2 and 3) in the children with marasmus although there was a correlation when the results were pooled with the values for the undernourished group (Figs. 2 and 3). Serum transferrin concentrations were not linearly related to deficits in weight- and length-for-age in the children with kwashiorkor. They were linearly related in children who had lost their oedema and in children gaining weight during their recovery from either marasmus or kwashiorkor (Fig. 4). The slope of the regression line shown in Fig. 4 (4·40) was similar to that of the corresponding line for the undernourished group (4·71; Fig. 2).

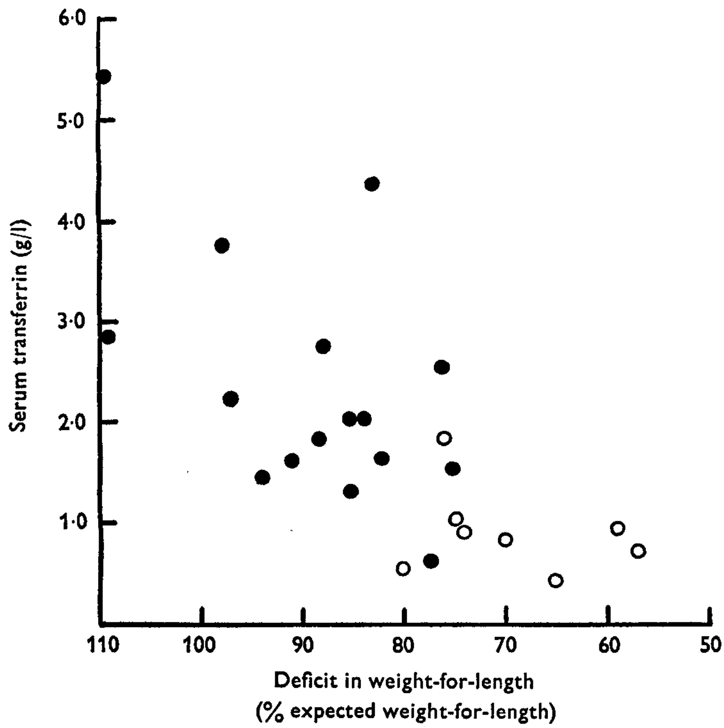

Fig. 4. The relationship between the serum transferrin concentration (g/l) and the deficit in weight-for-length (% expected weight-for-length, based on local standards (Janes, 1975)) in sixteen children gaining weight (●) during recovery from marasmus or kwashiorkor (grouped according to the Wellcome Classification (Waterlow, 1972) of protein-energy malnutrition), and in eight children originally with kwashiorkor after the loss of oedema and body-weight (○), aged between 5 and 40 months. Combined values: n 24, slope 4·40, r 0·733, $P < 0·001$.

DISCUSSION

The two serum proteins studied here are both synthesized in the liver. The rates of synthesis of both albumin (Rothschild, Oratz & Schreiber, 1972) and transferrin (Jeejeebhoy, Bruce-Robertson, Ho & Sodtke, 1972) are sensitive to the protein intake and it is to be expected that their serum concentrations will vary to some extent with the nutritional status of the individual.

The results of the present study suggest that the concentration of serum albumin is a poor indicator of a marginal reduction in nutritional status. The results of field studies carried out by Rutishauser & Whitehead (1969) also indicated that there was no simple relationship between the serum albumin concentration and the deficits in weight- and length-for-age in marginally undernourished children. Serum albumin was reduced in severely malnourished children with oedema, and Whitehead *et al.* (1971) and Lunn *et al.* (1973) have proposed that the concentration of serum albumin is an indicator of the likelihood of the development of oedema in severely malnourished children.

However, the results described in the present paper and those reported by Baertl, Placko & Graham (1974) suggest that there is a considerable overlap in the levels of serum albumin found in children with marasmus and kwashiorkor. Seven of the children with marasmus (present study) had serum albumin concentrations of less than 25 g/l, this level being regarded by Whitehead *et al.* (1971) as being critical for the subsequent development of oedema. It is possible that these children represented a group who were developing marasmic-kwashiorkor, as three of these children went on to develop oedema. As their weight-for-age was still less than 60 % of the standard value they would then have been classified as having marasmic-kwashiorkor.

Although the children with marasmus whose serum albumin concentrations were low tended to be lighter and shorter than those with normal concentrations of serum albumin, neither the serum albumin concentration nor the deficit in weight- and length-for-age predicted the likelihood of recovery from severe PEM. In contrast low serum transferrin concentrations were strongly associated with a poor prognosis in both groups of severely malnourished children. The association between low serum transferrin concentrations and death was not unexpected in the children with kwashiorkor as it has previously been found in studies in Ibadan (MacFarlane *et al.* 1969), in Egypt (Gabr *et al.* 1971) and in Zambia (Stephens, 1974). However, the children with marasmus who subsequently died also had lower serum transferrin concentrations than those who survived. Consequently it would seem appropriate to measure routinely the serum concentration of transferrin in all hospital cases of severe PEM.

The measurement of the concentration of serum transferrin would appear to be of use in the identification of early undernutrition. There was a significant linear relationship between serum transferrin concentrations and the deficits in weight- and length-for-age in marginally malnourished children, although there was no such relationship in the two groups of severely malnourished children. Although the finding of a linear relationship between serum transferrin concentrations and the deficits in weight- and length-for-age is contrary to the findings of Roode, Prinsbo, Laubscher, Hogewind & Kruger (1975) the children studied by these workers were not undernourished on an anthropometric basis. The results of the present study suggest that serum transferrin concentrations were not lower than the normal range until the deficit in weight-for-age decreased to less than 80 % of the standard value. This value is the upper limit of the range taken by the Wellcome Foundation Working Party (Waterlow, 1972) for undernutrition in their classification of types of PEM, and it is our experience that deficits in weight-for-length do not become high until the weight-for-age is at least 80 % of the standard value. Deficits in weight-for-age which are lower than this value are largely due to deficits in length and it is disputable whether nutritional intervention will produce a real catch-up of growth in terms of length.

The lack of a significant linear relationship between transferrin concentrations and deficits in weight- and length-for-age in the severely malnourished children is not surprising. The effects of dehydration and anaemia, both of which will tend to increase serum transferrin concentrations (Mosawe & Rwabwogo-Atenyi, 1973) will minimize the final reduction in the serum transferrin concentration in severe PEM. In addition the association of a very low level of serum transferrin with a poor prognosis for recovery is more significant in severely malnourished children than a linear relationship between the level of this protein and the deficits in weight- and length-for-age.

The reason why serum albumin and transferrin concentrations should behave differently in relation to nutritional status is unknown. Plasma albumin concentrations in severe PEM are maintained to some extent by a reduction in the rate of catabolism of albumin (James & Hay, 1968) but there appears to be no information about the rate of transferrin catabolism in either malnourished animals or humans. A study of this problem would be valuable in understanding the relationship between the nutritional status of the individual and the serum concentration of transferrin.

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