Serum ferritin as an index of iron nutrition in rural and urban South African children

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1. Serum ferritin concentrations were measured in 378 Zulu children aged 1–4 years living in Nqutu, KwaZulu and in 342 children of mixed race (Cape coloureds) aged between 1 and 16 years living near Johannesburg.

2. The pattern of serum ferritin concentrations encountered in the children at different ages tended to parallel the changes in iron stores which are known to occur during development.

3. Serum ferritin concentrations showed a significant direct correlation with age, haemoglobin, serum Fe and percentage saturation of transferrin values.

4. Anaemia was most prevalent in the younger children. Of the rural and urban children aged 13–24 months 60 and 53 % respectively were anaemic while only 11 % of those over 24 months had haemoglobin concentrations that were below normal.

5. The prevalence of anaemia among children who had serum ferritin values below 12 μg/l was only slightly higher than that for the groups as a whole (38·8 % *v*. 24·3 %), while the prevalence in those with values of 12 μg/l or more was only slightly less (18·2 %). However, when a ferritin concentration of less than 12 μg/l was associated with a percentage saturation of transferrin of less than 16 %, the prevalence of anaemia was 70·0 %, and only 10·2 % of children in whom both values were within the normal range were anaemic.

6. Since 67 % of children had either a normal serum ferritin and a normal percentage saturation of transferrin or both values below the normal range, the two measurements taken together provided a useful means of separating the children who had significant Fe deficiency from those whose Fe stores were sufficient to make the appearance of anaemia unlikely.

Iron deficiency still represents the most important cause of anaemia in the developing areas (Cowan & Bharucha, 1973) as well as in the more sophisticated Western countries (Hallberg, 1970). Methods of detecting Fe deficiency therefore have an important place in the control of nutritional anaemia. For this purpose the measurement of the haemoglobin concentration or packed cell volume is not satisfactory as an index of Fe nutrition, since it fails to identify lesser extents of Fe deficiency, where Fe stores are depleted but haemoglobin synthesis is not yet impaired or only slightly impaired. In addition, it does not distinguish between Fe deficiency and other causes of anaemia, such as folate deficiency. More direct methods of identifying Fe deficiency have been available for some time. They include the measurement of the plasma Fe concentration and the percentage saturation of transferrin as well as the estimation of the size of the body store of Fe in various ways, but all of them either lack specificity or are not suitable for application on a large scale. Recently immunoradiometric methods for measuring the serum ferritin concentration have been developed

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(Addison, Beamish, Hales, Hodgkins, Jacobs & Llewellin, 1972; Miles, Lipschitz, Bieber & Cook, 1974), and the results of several studies indicate that there is normally a close relationship between the values obtained and the size of the body Fe stores in healthy individuals (Jacobs, Miller, Worwood, Beamish & Wardrop, 1972; Walters, Miller & Worwood, 1973; Lipschitz, Cook & Finch, 1974). The assay has the further advantage of requiring only very small quantities of plasma or serum, and is therefore ideal for field studies. In the present investigation we measured serum ferritin concentrations and compared them with other indices of Fe status in two randomly-selected groups of children, one living in a rural area of KwaZulu, Natal and the other near Johannesburg.

EXPERIMENTAL

Subjects

Two groups of children, one rural and one urban, were studied during the course of a nutrition survey (Margo, Baroni, Green & Metz, 1977; Margo, Baroni, Wells, Green & Metz, 1977). The rural group comprised 378 black (Zulu) children aged between 1 and 5 years living in the Nqutu district of KwaZulu (mean altitude approximately 1200 m). They were well children aged between 1 and 4 years who were attending clinics for measles immunization; there were 183 boys and 195 girls.

The urban children were Cape coloured residents of Western Township in Johannesburg (altitude 1700 m). These included 273 children aged between 1 and 17 years, living at randomly-selected addresses in the community. Subsequently an additional sixty-nine 1-year-old children drawn randomly from birth notifications were added in order to augment the size of the sample of children in this age-group. There were 166 boys and 176 girls.

Informed consent was obtained from the parents and the study was carried out in accordance with the principles of the Declaration of Helsinki (Ethics in Medical Progress, 1966). Approval was also obtained from the Committee for Research on Human Subjects of the Faculty of Medicine, University of the Witwatersrand, before embarking on the survey.

Isotopic and chemical methods

Blood samples were obtained from non-fasting subjects. Serum ferritin concentrations were measured by the method of Miles *et al.* (1974) on 0·1 ml serum. The serum Fe concentration was measured using the International Committee for Standardization in Hematology (1971) method which was scaled down to use a volume of 0·25 ml serum/test, and the unsaturated Fe-binding capacity by a modified radioisotope dilution technique (Williams & Conrad, 1972). The haemoglobin concentrations and packed cell volumes were measured using a Coulter Counter (model 'S'; Coulter Electronics, Hialeah, Florida, USA).

Statistical methods

Since the data, when classified into separate race, sex and age groups, were not normally distributed, non-parametric statistical methods of analysis were employed. Comparisons between groups were performed using the Mann-Whitney U test (Mann & Whitney, 1947), while Spearman rank correlation coefficients were obtained using the Statistical Package for the Social Sciences (SPSS) program on an IBM 370 computer.

RESULTS

The results for the rural children were divided into two age-groups and those for the urban children into five age-groups (Table 1). The lower limit of the normal range for haemoglobin concentration was arbitrarily defined by adding 5 g/l to the values given by the WHO

Table 1. *Measurements of body iron status in rural and urban children* at different ages*

(Median values are given with their 10th–90th percentiles)

	Rural children				Urban children									
Age (months) ...	13–24		25–60		13–24		25–60		60–96		97–144		145–220	
Sex ...	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
No. of subjects ...	61	70	122	125	35	48	39	25	20	23	39	34	33	46
Haemoglobin (g/l):														
Median values	112	112	122	125	111	114	128	131	131	133	138	134	148	141
10th–90th percentile	99–124	99–126	113–136	113–136	97–126	101–127	116–135	120–144	123–142	124–150	124–150	130–145	135–163	131–152
Values below normal (%)†	59·0	60·0	18·0	13·0	54·3	52·1	5·1	0	5·0	8·7	12·8	0	12·1	4·3
Percentage saturation of transferrin														
Median values	17·0	14·0	16·0	19·0	12·5	15·0	19·0	26·0	26·5	28·0	28·0	26·0	24·0	30·0
10th–90th percentile	8·0–29·6	8·4–23·6	10·0–28·0	11·0–30·0	5·9–32·5	3·0–27·9	7·8–34·2	13·0–38·0	13·0–38·5	19·0–44·2	17·4–38·0	12·7–40·1	15·0–42·8	14·3–42·7
Values below normal (%)‡	44·3	58·6	50·8	33·6	62·9	54·2	38·5	28·0	20·0	8·7	5·1	14·7	12·1	10·9
Serum ferritin (μg/l)														
Median values	17·6	19·0	28·1	30·0	11·5	14·9	16·4	20·1	29·5	35·2	45·5	43·6	71·4	24·9
10th–90th percentile	7·4–43·6	5·0–42·7	13·1–67·7	12·5–75·6	2·5–46·0	2·6–36·2	2·5–58·4	3·8–60·8	2·5–81·5	17·8–98·5	3·4–91·3	2·5–91·7	7·8–148·0	2·5–90·9
Values below normal (%)§	36·1	37·1	26·2	18·4	54·3	43·8	38·5	32·0	20·0	17·4	17·9	17·6	18·2	28·3
Percentage saturation of transferrin and serum ferritin values below normal (%)	18·0	30·0	19·7	12·0	37·1	29·2	15·4	12·0	0	0	2·6	5·9	6·1	6·5

* For details of subjects, see p. 384.

† Lower limits of normal for haemoglobin concentrations (g/l): 115 for children under 6 years; 125 for males of 6–14 years and for females older than 6 years; 135 for males older than 14 years (WHO (1968) criteria adjusted for altitude).

‡ Lower limit of normal for percentage saturation of transferrin 16 (Bainton & Finch, 1964).

§ Lower limit of normal for serum ferritin concentrations 12 μg/l (Cook *et al.* 1974).

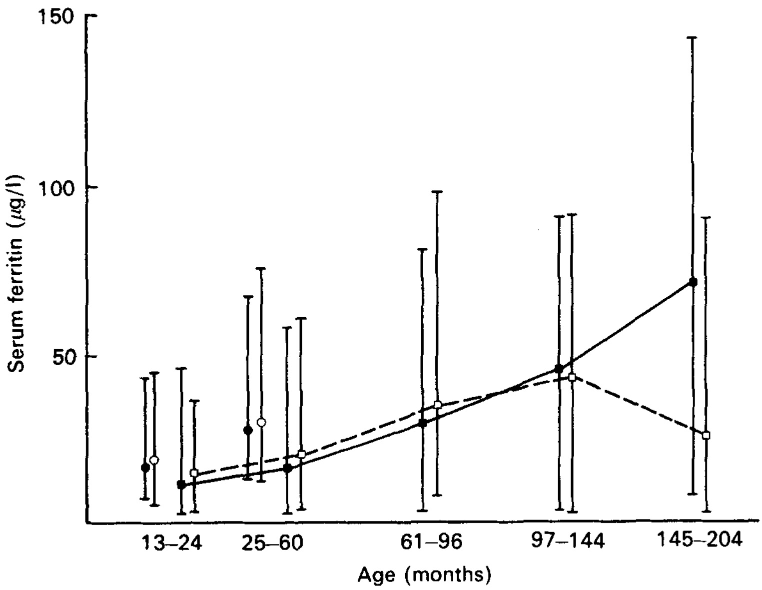

Fig. 1. Median serum ferritin concentrations (μg/l) and 10th–90th percentiles in rural male (●) and female (○) infants and in urban male (■) and female (□) children at various ages (months). For details of subjects, see p. 384.

Table 2. *Correlation of serum ferritin concentration with age, haemoglobin and percentage saturation of transferrin, using the Spearman correlation coefficients* (r_s) (*Siegel*, 1956) *for non-parametric data*

Group*		Age	Haemoglobin	Serum iron	Percentage saturation of transferrin
Rural children:					
♂	r_s	0·4061	0·3168	0·1780	0·2937
	P	<0·001	<0·001	<0·015	<0·001
♀	r_s	0·3839	0·3046	0·2531	0·4127
	P	<0·001	<0·001	<0·001	<0·001
Urban children:					
♂	r_s	0·5002	0·5104	0·2467	0·3276
	P	<0·001	<0·001	<0·001	<0·001
♀	r_s	0·2086	0·3239	0·2070	0·3039
	P	<0·005	<0·001	<0·005	<0·001

* For details of subjects, see p. 384.

Scientific Group (WHO, 1968), since the average altitude of the two locations was approximately half of that of Mexico City, where 10 g/l is added to sea-level values. Thus 115 g/l was taken to be the lower limit of normal for children up to the age of 6 years, 125 g/l for girls over 6 years and for boys between 6 years and 14 years, and 135 g/l for boys over 14 years. Values for percentage saturations of transferrin below 16% (Bainton & Finch, 1964) and serum ferritin concentrations of less than 12 μg/l (Cook, Lipschitz, Miles & Finch, 1974) were considered to be abnormal.

There were no significant differences between the values obtained in boys and girls, except that the serum ferritin concentrations in the 13–17-year-old boys were significantly higher than those in the girls ($P < 0·005$). The values obtained for each age-group in the two population groups were similar, although somewhat lower haemoglobin values and

Table 3. *The value of using percentage saturation of transferrin and serum ferritin concentrations in predicting the occurrence of haemoglobin concentrations which are below normal**

(Urban and rural groups† were pooled)

Age-group ...	All ages		1–2 years	
Group	No.	% anaemic	No.	% anaemic
All children	720	24·3	214	57·0
Normal percentage saturation of transferrin	456	11·4	98	30·9
Normal serum ferritin concentration	514	18·2	126	46·8
Normal percentage saturation of transferrin and serum ferritin concentration	365	10·2	69	26·1
Low percentage saturation of transferrin‡	264	45·9	116	79·2
Low serum ferritin concentration§	206	38·8	88	71·8
Low percentage saturation of transferrin and serum ferritin concentration	115	70·0	59	87·0

* Lower limits of normal for haemoglobin concentrations (g/l): 115 for children under 6 years; 125 for males of 6–14 years and for females older than 6 years; 135 for males older than 14 years (WHO (1968) criteria adjusted for altitude).

† For details of subjects see p. 384.

‡ Lower limit of normal for percentage saturation of transferrin 16% (Bainton & Finch, 1964).

§ Lower limit of normal for serum ferritin concentrations 12 μg/l (Cook *et al.* 1974).

higher ferritin concentrations were found in the rural children aged between 2 and 5 years. The haemoglobin levels, serum Fe concentrations and values for percentage saturation of transferrin increased progressively with increasing age. Serum ferritin concentrations increased progressively in the boys while the girls showed an increasing value until puberty which was followed by a decrease (Fig. 1). The serum ferritin concentrations were significantly correlated with the ages as well as with the haemoglobin, serum Fe and percentage saturation of transferrin values (Table 2).

The highest prevalence of anaemia occurred among the 1–2-year-old children. In Table 3 the value of the percentage saturation of transferrin and the serum ferritin concentration for the prediction of anaemia is examined in all the children of both groups taken together as well as in the 1–2-year-old children of both groups where the highest prevalence rates of anaemia were encountered. Of note was the fact that neither measurement when considered alone was a good discriminant for detecting anaemia. While 38·8% of children with low serum ferritin concentrations were anaemic, 18·2% of those with normal levels also had low haemoglobin concentrations. Comparable figures for the percentage saturation of transferrin were 45·9% and 11·4% respectively. In contrast, 70% of children with low values for both measurements were anaemic, while the figure was only 10·2% when both were normal.

DISCUSSION

The serum ferritin concentration reflects the size of the body Fe stores under most circumstances (Jacobs *et al.* 1972; Walters *et al.* 1973; Lipschitz *et al.* 1974). Inappropriately high values have been reported in liver disease, acute infections and certain neoplastic conditions, but values lower than normal have been found only in association with Fe deficiency. While most of the surveys carried out to date have been done in adults, Siimes and his co-workers (Siimes, Addiego & Dallman, 1974) have reported the findings in a large group of infants and children living in California. They noted that changes in the serum ferritin concentration with age paralleled the known changes in Fe stores which occur during development (Lintzel, Rechenberger & Schairer, 1944; Siep & Halvorsen, 1956; Smith, Rosello, Say & Yeys, 1955). A similar pattern was encountered in the present investigation: the lowest median ferritin concentrations were observed in 1-year-old infants, and in the males there was a progressive increase in ferritin concentration with increasing age, while the females showed similar increments until the time of puberty after which the levels tended to decrease again.

The increasing median serum ferritin values and the progressive decrease in the prevalence of low serum ferritin concentrations with increasing age (Table 1) conform to current concepts of Fe nutrition in early life. The neonate's Fe endowment, which is not affected by maternal Fe storage status (Rios, Lipschitz, Cook & Smith, 1975), is more than enough for the first few months of life, but towards the end of the first year it has been fully deployed to meet the needs of a rapidly expanding red cell mass. As the rate of growth slows during the second year of life the demand for Fe decreases, and this combined with the introduction of a mixed diet, which allows for the absorption of greater amounts, alleviates the shortage. The prevalence of Fe deficiency is therefore highest between the ages of 6 months and 2 years (Smith *et al.* 1955). The adolescent growth spurt is the second critical period and in girls the onset of menstruation, with its attendant loss of Fe, markedly increases the Fe requirement. This was reflected in the present study by the significantly lower serum ferritin concentrations in the urban teenage girls as compared with the boys.

Further evidence supporting the relationship between the serum ferritin concentration and the body Fe stores in children was gained by comparing the serum ferritin concentrations with the other indices of Fe status. There was a statistically significant correlation between the serum ferritin concentration and the serum Fe concentration, the percentage saturation of transferrin and the haemoglobin concentration. It would therefore seem that a low serum ferritin concentration is indicative of reduced Fe stores in children as it is in adults.

Fe deficiency was the only identifiable factor responsible for the anaemia (Margo, Baroni, Green & Metz, 1977; Margo, Baroni, Wells *et al.* 1977), and significant correlations were found between the serum ferritin concentration and other measures of Fe status. A low serum ferritin concentration was nevertheless found to be a relatively poor predictor of the presence of anaemia as defined using arbitrary criteria (WHO, 1968) adjusted for altitude (Table 3). This can partly be ascribed to the fact that there is an overlap between the haemoglobin concentrations of normal and anaemic individuals (Garby, Irnell & Werner, 1969). Consequently, some non-anaemic individuals have values within the normal range (Cook, Alvarado, Gutnisky, Jamira, Labardini, Layrisse, Linares, Loria, Maspes, Restrepo, Reynafarje, Sánchez-Medal, Vélez & Viteri, 1971). In addition, the finding of a low serum ferritin concentration in non-anaemic individuals is not surprising, since there may be sufficient Fe for erythropoiesis but no stored surplus. A low percentage saturation of transferrin reflects more directly the balance between supply and demand, but it too did not prove to be a good predictor of anaemia. Interpretation of this measurement is complicated by the fact that the percentage saturation is diminished in other conditions, such as infection, where Fe release from reticulo-endothelial cells is impaired (Bothwell & Finch, 1962). By far the best separation of anaemic from non-anaemic children was achieved by the concurrence of a low serum ferritin and low percentage saturation of transferrin. Our findings thus support the conclusions of Cook, Finch & Smith (1976) that the accuracy of the detection of individuals with Fe-deficiency anaemia in a population is substantially improved if two independent measures of Fe deficiency are used in combination. The fact that the measurement in the present study had an even better predictive value than was reported by Cook *et al.* (1976) can be ascribed to the fact that Fe deficiency was virtually the only cause of anaemia in the groups we studied.

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