ESTIMATION OF BODY PROTEIN DEFICIT IN PROTEIN MALNOURISHED POPULATIONS BY CREATININE EXCRETION MEASUREMENTS

Guillermo Arroyave

Jefe, División de Química Fisiológica

Instituto de Nutrición de Centro América y Panamá (INCAP)

Guatemala, C.A.

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Estimation of Body Protein Deficit in Protein Malnourished Populations by Creatinine Excretion Measurements

GUILLERMO ARROYAVE

The dynamics of the development of the severe forms of protein-calorie malnutrition in children, and the interrelationship between these syndromes and the chronic subacute malnutrition states which prevail among the population groups in underdeveloped areas, have been graphically represented by Scrimshaw and Béhar (1). Figure 1 illustrates their concept.

A child developing protein-calorie malnutrition will lose body weight, or will fail to gain weight as he grows older, in such a way that at any time he will occupy a point along the line *N-M* of the triangle more or less removed from the apex *N* which represents the zone of normality. *M* in turn represents the extreme marasmus or complete exhaustion of calorie-protein "reserves." Under some circumstances children who are lying at some point of, or falling progressively along, line *N-M*, may abruptly fall away from it towards line *K-M*. This side *K-M* of the triangle represents a spectrum of severe malnutrition forms as they occur in children, ranging from "pure" kwashiorkor on extreme *K* to pure marasmus on extreme *M* as mentioned previously. The many forms with mixed characteristics fall intermediate to those two extremes.

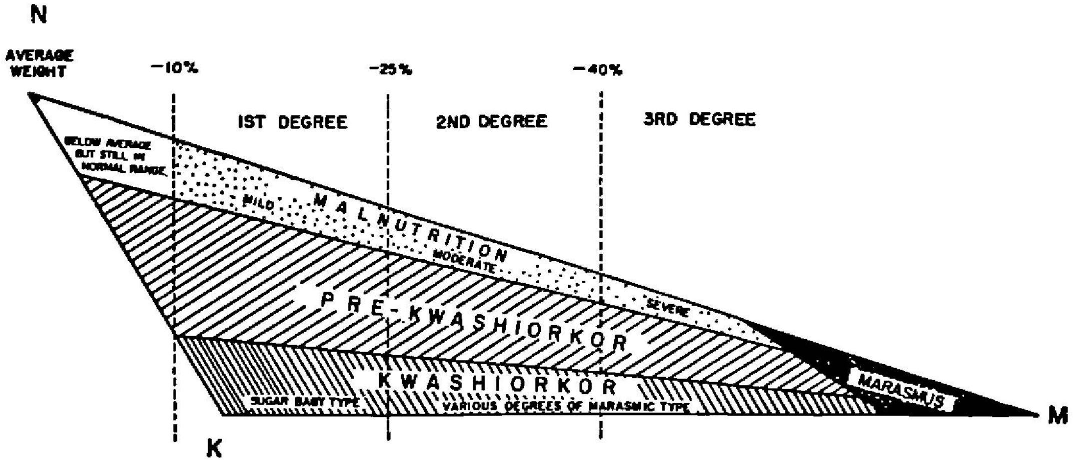

Fig. 1.—Development of the different types of protein malnutrition in children (1).

GUILLERMO ARROYAVE, Chief, Division of Physiological Chemistry, Institute of Nutrition of Central America and Panama, Guatemala, C. A. INCAP Publication I-304.

The causes which carry a child from line *N-M* to line *K-M* may be varied. From the evidence available, one may propose as the most common factors for the precipitation of kwashiorkor, a) the force-feeding of a diet high in carbohydrates and poor in proteins and b) stresses, such as infections and diarrhea, which result in sudden increased losses of nitrogen from the body.

The discussion which follows will relate particularly to children whose nutritional status corresponds to the zone in the upper middle part of the "triangle of malnutrition" of Scrimshaw and Béhar. They represent the vast majority of children, principally of preschool age, in the technically underdeveloped areas of the world.

A review of the literature on protein malnutrition suggests that many of the biochemical manifestations that characterize the severe forms do not come about gradually during the development of the malnutrition state. They seem to appear rather suddenly and, for all practical purposes, simultaneously with the clinical manifestations. Severe hypoalbuminemia, decrease in some blood plasma enzymes such as cholinesterase, alkaline phosphatase and amylase, decrease in duodenal enzymes, impairment in the absorption and blood transport of vitamin A are examples of this type of biochemical change, described as characteristic of kwashiorkor in children.

A more fundamental phenomenon resulting from restricted intake of protein is a relatively reduced amount of body proteins. As discussed by Waterlow et al. (2), if the restriction in protein intake is imposed onto a subject who has been maintained previously on an adequate diet, the body becomes "depleted," that is, it loses a variable amount of body proteins, depending on the degree and duration of the dietary restriction.

In the growing animal, and particularly in children, a chronic intake of a poor protein diet — as is the case in most tropical and subtropical areas — results, physically, in the failure of growth and maturation, with retardation in height, weight, and bone development. The retardation in weight is usually more marked than that of height, particularly where both calories and proteins are in short supply.

As a result these children have a smaller absolute amount of body protein than do "control" children who are adequately nourished. It has been well documented, however, that in depletion proteins are lost in different proportions from the different organs and tissues of the body. Classic experiments with rats (3, 4) on diets lacking in proteins gave results which illustrate this point as shown in Table 1.

Examination of the data in Table 2 (5) reveals that in the malnourished child also the different organs are sacrificed to different

Table 1. — The Percentage of Original Organ Protein Lost in Fasting Rats (3)

Organ	7-day fast
Liver	40
Prostate	29
Kidney	20
Muscle, Skin, Skeleton	8
Brain	5

Table 2. — Weight of Body Components in Atrophic Infants (5)

Part of body	Percent of normal weight
Whole body	52
Brain	90
Kidneys	80
Heart	60
Fat	5
Skeleton	85
Muscle	30
Surface area	70

extents. Apart from adipose tissue, muscle is the organ quantitatively most affected. These data support the concept that under conditions of inadequate protein intake muscle tissue is sacrificed to supply amino acids for the protection of more "vitally essential" tissues.

We have postulated (6) that in uncomplicated protein undernutrition in children, leading to marasmus, this mechanism of reutilization by other tissues of the amino acids from the catabolism of muscle proteins operates with efficiency. The serious and acute metabolic impairments which characterize kwashiorkor apparently result from the failure of this mechanism. This agrees with the clinical observation that one of the most striking features of undernourished children in the technically underdeveloped areas of the world is the prominence of the bony skeletal angles as a result of reduced adipose tissue and skeletal muscle. Nevertheless, even in children with clinical marasmus, plasma albumin, as well as the functional integrity of other tissues such as the liver and the endocrine glands, may be maintained (1).

In public health nutrition terms, the concepts discussed in the previous paragraphs may offer a solution to a practical question which confronts nutrition workers in areas where protein deficiency may be prevalent, that is, the assessing of the extent of protein "depletion" or protein "deficit" of the body by methods that can be applied *in vivo*. This has been properly emphasized by Waterlow et al. in their recent review of protein malnutrition in man (2).

It may be assumed that if the protein requirement of a child has been met, his skeletal musculature will be fully developed and well maintained. If the converse is true, then estimating muscle mass will give some indication of adequacy of protein intake.

It has been recognized for a long time that the absolute amount of creatinine excreted by an individual per unit of time is a direct function of the amount of muscle mass in his body. This concept received recent support in the work of Miller and Blyth (7) who found in adults a good correspondence between 24-hour creatinine excretion and lean body mass determined by either basal oxygen consumption or body specific gravity measurements. Also in adult subjects, further supporting evidence has been contributed by researches showing agreement between measurements of total exchangeable potassium and lean body mass or excretion of creatinine (8, 9). A study in children by Kennedy (10) fails to demonstrate a correlation between creatinine excretion and muscle mass, as determined by anthropometric measurements or total exchangeable potassium. Since Kennedy's study was done in hospitalized sick children, some of whom were suffering from serious chronic diseases, it is necessary to await further research on healthy children in order to draw any general conclusions.

Before discussing in more detail the usefulness of this method in assessing the relative protein depletion of population groups, it is pertinent to mention some of its practical limitations. The relationship between the amount of lean body mass and creatinine excretion per unit of time does not hold under certain pathological conditions, such as renal diseases and excessive muscular wastage. These conditions, however, are uncommon in population groups and are easily recognizable clinically. A more important consideration is the evidence that the type of diet modifies the amount of creatinine excreted. In the studies of Best et al. (11), the rate of creatinine excretion during the period of 6 to 10 a.m. was lowered about 10 percent when all the protein was omitted from the preceding day's meal and from breakfast on the day of the study. The implication of these results is, however, twofold. On the one hand the study demonstrates that there is an effect of diet on the creatinine output, but on the other hand it suggests that, in population groups, the effect may not be so significant since an "all or none" situation with respect to protein intake is not generally encountered when comparing groups of people. Furthermore, Addis et al. (12) had previously reported that the influence of diet on the excretion of endogenous creatinine is absent in the morning period from 7 to 12 noon after a creatinine-free breakfast. The fasting overnight period seems sufficient to obtain basal conditions as far as creatinine is concerned. A creatinine-free breakfast could contain cereals, eggs, and toast, but not meats, viscera, or bacon.

A further consideration regarding the practical application of this method is the constancy of the creatinine excretion. A perusal of the literature reveals that in most instances the *individual* variation in 24-hour creatinine excretion from day to day usually shows an average coefficient

Table 3. — Urinary Creatinine Excretion per Minute Estimated in 3- and 24-Hour Specimens

Group	No.	3-hour periods		24-hour periods	
		mg/min		*mg/min*	
		$\bar{x}$	SD	$\bar{x}$	SD
Adult males	12	1.14	0.16	1.13	0.12
Adult females	12	0.66	0.10	0.68	0.09
Children	15	0.26	0.12	0.27	0.12

of variation of around 10 percent (11-16) or less. It is to be noted, however, that since this variation is random, the reliability of the average value for a group of people will obviously increase as the number of individuals studied becomes larger.

The collection of 24-hour specimens is rather difficult under field conditions. Therefore the usefulness of carefully timed shorter collection periods should be considered. In general, in individual studies, the accuracy of the values obtained may be expected to decrease with decreases in the length of the collection period (15, 16). On the other hand, Best et al. (11), studying diurnal trends in creatinine excretion, found that the values obtained from 6 to 10 in the morning were not only the closest to the 24-hour average figures but also varied least from day to day. In our laboratories we have shown that the calculated creatinine excretion in milligrams per minute is the same for a group of individuals including adults and children, whether from a 3-hour specimen (8-11 a.m.) or from a 24-hour period of collection. These results are illustrated in Table 3. It is apparent therefore, that urine collections for as short a period as 3 to 4 hours in the morning are suitable to estimate the characteristic 24-hour creatinine excretion of groups of individuals.

Stearns et al. (17) make use of urinary creatinine excretion as an estimate of muscle growth and development of children as related to their protein nutritional status. Figure 2 gives the mean 24-hour creatinine excretion per kilogram of body weight for boys from 6 months to 11 years old. These values of urinary creatinine for the specific ages, expressed per kilogram of body weight, are taken by Stearns and co-workers as representative of the mean proportion of skeletal muscle to total body weight.

Daniels and Hejinian (18) several years ago reported some figures for the 24-hour creatinine excretion of infants under 1 year old expressed, not per kilogram of body weight, but rather per centimeter of body height. The interpretation of the latter expression as an index of relative lean body mass development seems more straightforward than the use of

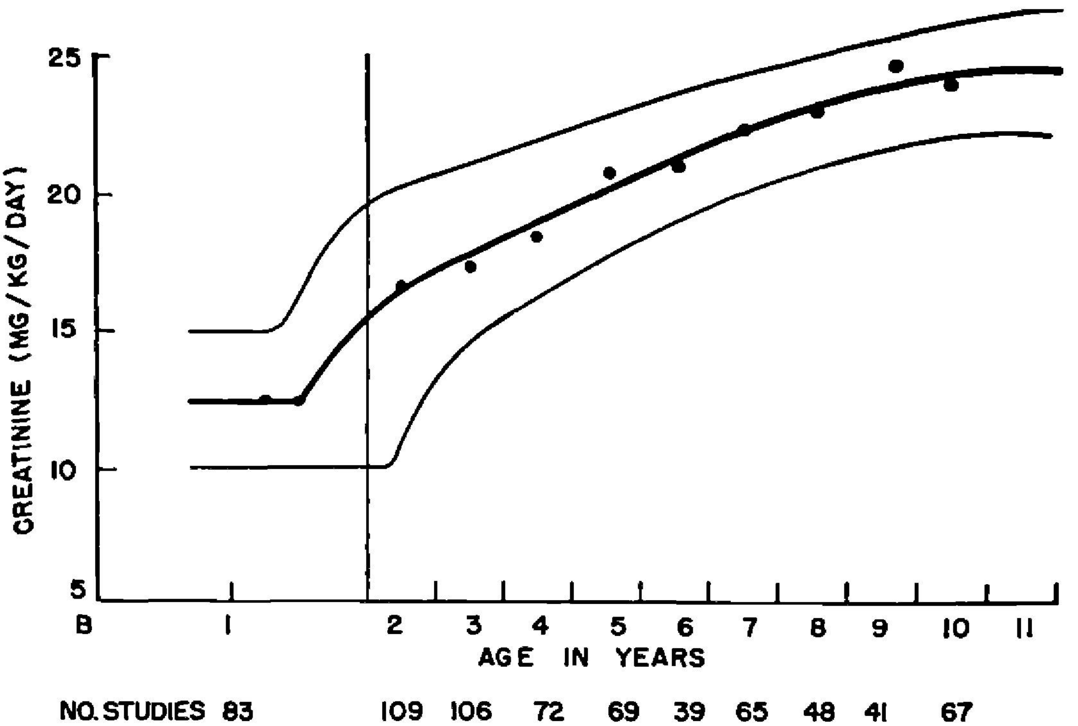

Fig. 2. — Mean creatinine per kilogram for boys of each age group studied. The fine lines represent standard deviation for the given age. This figure indicates relative growth of the skeletal musculature in relation to total body growth (17).

body weight, since the variations of adipose tissue do not influence it. In fact the ratio of urinary creatinine excretion to body height may represent an approximate expression of muscle mass development in relation to skeletal development.

Both our studies at the Institute of Nutrition of Central America and Panama (INCAP) (19) and those of Standard, Wills, and Waterlow (20) suggest that the lean body mass of children with inadequate nutrition can be reduced far beyond the extent to which height or even weight are in deficit.

Table 4. — 24-Hour Creatinine Output of Malnourished Babies at Different Stages of Recovery (20)

Days after hospitalization	No. cases	Creatinine output	
		mg/day/cm height	*mg/day/kg weight*
Under 20	19	0.79 ± 0.051[a]	9.4 ± 0.55
20–39	13	1.04 ± 0.056	11.9 ± 0.69
40–59	13	1.48 ± 0.120	14.3 ± 0.86
Over 60	8	1.86 ± 0.120	15.0 ± 0.60

[a] Mean ± SEM.

In the study of Standard et al. (20), the 24-hour creatinine output was measured in hospitalized malnourished infants at intervals during recovery. The creatinine excretion per centimeter of body length more than doubled 2 months after admission of the children. Relative to body weight a lesser increase was recorded as illustrated in Table 4. The authors' interpretation is that the simple measurement of weight may seriously underestimate the degree of protein depletion.

Our study (19) reported observations on the creatinine excretion per centimeter of body height in children from three groups varying in their nutritional status from "excellent" to acute kwashiorkor. A marked deficit in height and weight was found among the poorly nourished children as seen in Fig. 3. The results on creatinine excretion per 24 hours are given in Fig. 4. The figures for the adequately nourished Guatemalan children were of the same order of magnitude as those for North Ameri-

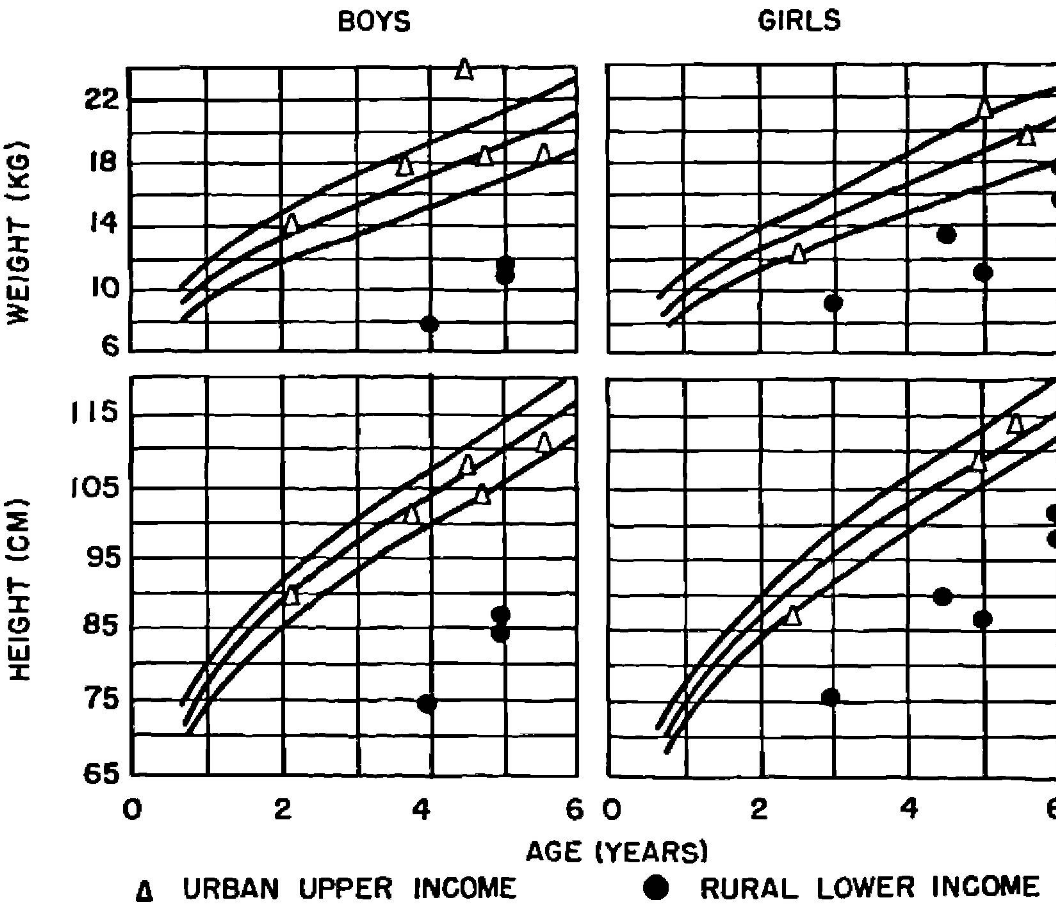

Fig. 3.—Body weights and heights of preschool children of two different socio-economic groups in Guatemala. For comparison, standards for height and weight adopted by INCAP for Central America are reproduced in solid lines (19).

can children as calculated from the data of Stearns and others (17), indicating that the groups had the same relative amount of lean body mass.

The excretion values per unit of body height for the rural, low socio-economic children, 3 to 6 years old, corresponded to those of younger, adequately nourished children, and in several instances were similar even to the figures given by Daniels and Hejinian (18) for infants 4 to 7 months old. They were also of the same order of magnitude as those found for children suffering from kwashiorkor. From these data two important inferences can be made. First, that the lower muscle mass per unit of height of the nutritionally underprivileged children in this study may be taken as an evidence of the retarded maturation, also suggested by the deficits in height and in weight. Data presented by Cravioto illustrate this point (21). He has compared the actual 24-hour creatinine excretion values of 22 malnourished Guatemalan children with the theoretical excretions calculated for their developmental age as judged by their height and not by their chronological age alone. The average figures obtained were very similar, 223 and 238 mg per 24 hours, respectively.

The second important inference that may be derived from our study is that "apparently healthy" preschool children in this and in nutritionally similar communities do not seem to differ from those children suffering from kwashiorkor, in terms of the magnitude of their protein depletion state. It is not surprising, therefore, that the acute clinical malnutrition

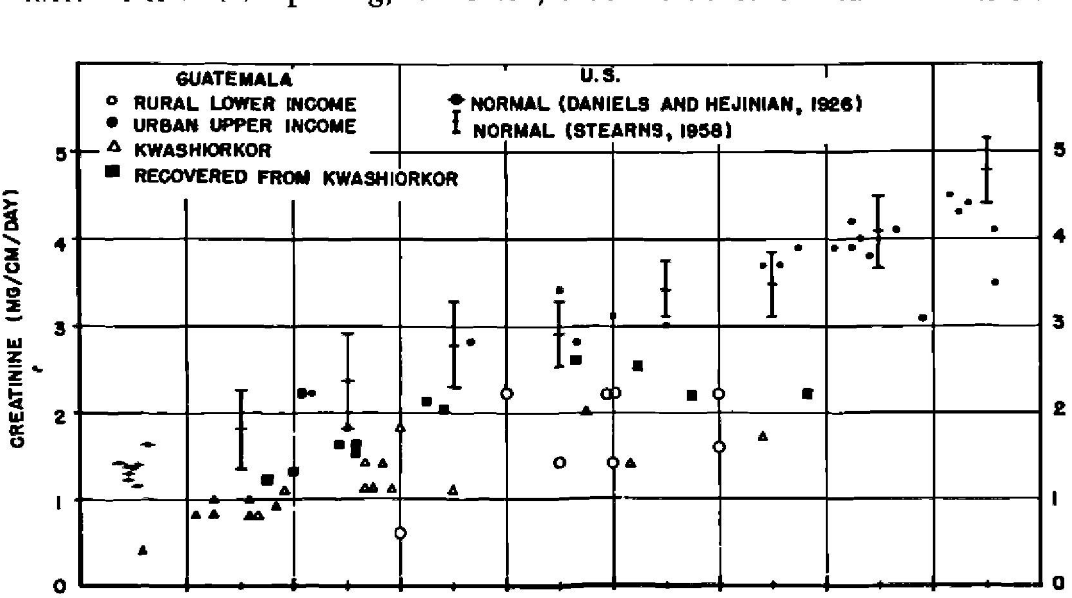

Fig. 4. — Urinary excretion of creatinine in relation to body height in children of different nutritional and socio-economic status (19).

syndrome ensues in these young subjects when superimposed factors such as infections or other stresses act upon them.

In summary, evidence has been presented that urinary creatinine excretion measurements in field studies are useful as an indirect biochemical estimate of muscle mass development. Data so obtained may be of great value in assessing the relative degree of protein depletion of population groups suffering from dietary protein shortage.

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