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Estimation of glomerular filtration rate in anorectic adolescents

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Abstract. Severe malnutrition has been associated with a decrease in fat and lean body mass, as well as in renal function. This study was designed to evaluate the estimation of glomerular filtration rate (GFR, ml/min per 1.73 m^2) in malnourished teenagers, by using the formula GFR = kL/P_{cr} (where L is body height, P_{cr} is plasma creatinine concentration and k is a proportionality constant relating muscle mass to body size that has been found to equal 0.7 in adolescent boys and 0.55 in girls). Body composition was estimated using anthropometric measurements and urinary creatinine excretion ($U_{cr}V$). Malnourished female patients showed depletion of fat and muscle, whereas males had primarily decreased muscle mass. There was a good correlation (r = 0.74) between anthropometric [arm muscle volume (AMV)] and chemical $U_{cr}V$ estimates of muscle mass. However, our previously validated estimate of GFR did not give reliable results in this group of malnourished teenagers, probably because their muscle mass was so greatly altered by the severity of malnutrition. Therefore, we used anthropometric measurements and P_{cr}, to estimate GFR by multiple linear regression. The best prediction was obtained by using AMV/P_{cr} and the observed/expected (for age, height and sex) weight ratio (WR):

$$\text{GFR (ml/min)} = 0.06\ \text{AMV}/P_{cr} + 131\ \text{WR} - 79,\quad r = 0.82,\ n = 13.$$

We confirm that malnutrition in adolescents is associated with decreased GFR and conclude that the resulting variability in body composition limits the possibility of estimating GFR from P_{cr} and height. A somewhat better estimate may be obtained from simple anthropometric measurements and P_{cr}.

Key words: Kidney function – Glomerular filtration rate – Creatinine – Malnutrition – Muscle mass – Anthropometry

Introduction

Previous studies have shown that malnutrition is associated with a decrease in muscle mass, lean body mass [1, 2], and fat mass, and may be associated with a decrease in glomerular filtration rate (GFR) [3, 4].

Age-dependent changes in normal values of plasma creatinine (P_{cr}) during normal growth limit its use as an estimate of renal function in children [5, 6]. Previous studies from several laboratories have shown that GFR can be accurately estimated from the simple formula: GFR = kL/P_{cr}, where GFR is the glomerular filtration rate in ml/min/1.73 m^2, L is the body length or height in centimeters, and P_{cr} is the plasma creatinine concentration [5–13]. The proportionality constant, k, corresponds to the excretion of creatinine per unit of body size (mg/100 min/cm/1.73 m^2) and depends on the percentage of body weight that is muscle and on the units in which P_{cr} is expressed (mg/dl or μmol/l)[1]. The value of k should be determined for each laboratory, because the P_{cr} val-

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[1] Conversion factor: μmol/l = mg/dl × 88.4.

ue depends on the technique used [6]. In our laboratory k equals 0.55 in adolescent girls and 0.70 in adolescent boys with grossly normal body habitus (P_{cr} in mg/dl) [8]. Compared with these children, malnourished and obese patients have a smaller percentage of muscle mass and therefore excrete less creatinine per unit of body size [1, 2, 9].

This study was designed to evaluate the prediction of GFR from the value of P_{cr} and body length in malnourished teenagers and to propose an alternative estimate of GFR using P_{cr} and anthropometric measurement(s).

Patients and methods

Twenty-two female and 5 male malnourished teenagers with anorexia nervosa (DSM III) (19 females, and 2 males), bulimia (1 female), non-specified eating disorder (2 females, 1 male), and Crohn's disease (2 males) were studied. One male and 4 female patients were studied subsequently during refeeding, and because of major changes in body habitus, each follow-up study was considered as independent. Creatinine clearance (C_{cr}) and anthropometric data were measured in all 27 studies and inulin clearance in 10 (9 females, 1 male). Another group of 7 anorectic patients under therapy was used to test the validity of a new formula for estimation of GFR (see Results).

The degree of malnutrition was assessed by the ratio (WR) of the observed body weight over the expected weight for height and sex [14]: patients with a WR below 0.80 were considered to have severe malnutrition, whereas those with a WR of 0.80–0.89 were considered to have mild malnutrition [15]. The data were also compared with those of a control group of comparably aged and normally grown teenagers (9 males, 27 females), taken from the renal outpatient clinic, with normal C_{cr} (>90 ml/min/1.73 m^2) [5].

Muscle mass was first estimated from urinary excretion of creatinine using Talbot's coefficient; i.e., the daily excretion of 1 g creatinine is equivalent to 17.9 kg muscle mass [6, 16]. The calculated muscle mass was expressed, either as a percentage of body mass to give percent muscle mass (MM%), in mg/day/cm of height to give the creatinine-height index (CHI) [16], or in mg/cm/100 min/1.73 m^2 to give the value of k, which was obtained by the formula: $k = GFR*P_{cr}/L$ [5–9].

Muscle mass was estimated secondly from the value of arm muscle area (AMA, cm^2) and arm muscle volume (AMV, cm^3), calculated from mid-arm circumference, triceps skinfold thickness and upper arm length, as previously described (see Appendix) [9, 17].

Subcutaneous fat was estimated from the tricipital and subscapular skinfold thicknesses: the sum of both measurements was compared with normal values reported by Novak [18] in well-nourished adolescents. Fat mass as a percentage of body weight was calculated from the nomogram established by Parizkova using these two measurements [19].

Renal function studies were performed after an overnight fast and a 5 ml/kg oral water load in the morning. Three 20-to 40-min urine collections were obtained for C_{cr} studies. A modified Technicon Auto Analyzer technique was used for the measurement of creatinine to the nearest 0.05 mg/dl as previously described [5–9, 20, 21]. Inulin was injected intravenously (100 mg/kg) as a single injection of a 10% solution during the C_{cr} study. The clearance was calculated by the double slope analysis of the semi-logarithmic plot of concentration vs time [9, 22].

Statistical analysis included one-way analysis of variance, multiple range test, unpaired *t*-test and single or multiple regression analysis. The value of $P < 0.05$ was chosen for asserting statistical significance. The results are presented as mean ± SE.

Results

The mean age at the time of study was 14.3 ± 1.0 years in males and 16.8 ± 0.5 in females (Table 1). The median Tanner stage in girls was 5 (range 2–5). One of the female patients with anorexia

Table 1. Characteristics of the sample of malnourished adolescents and controls matched for age and sex

	n	Age (years)	Height (cm)	Weight (kg)	P_{cr} (mg/dl)	P_{cr}[1] (μM/l)	C_{cr} (ml/min/ 1.73 m^2)	C_{cr} (ml/min)
Females								
Malnutrition								
severe	17	16.9 ± 0.7	162 ± 2*	38.9 ± 1.1*	0.75 ± 0.05	66.3 ± 4.4	109 ± 7*	83 ± 6*
mild	9	16.6 ± 0.8	160 ± 1	42.9 ± 1.2*	0.75 ± 0.05	66.3 ± 4.4	131 ± 7	104 ± 7
Controls	26	17.2 ± 0.7	157 ± 1	53.8 ± 1.5	0.80 ± 0.05	70.7 ± 4.4	122 ± 5	108 ± 5
Males								
Malnutrition								
severe	4	14.8 ± 1.5	153 ± 7	30.5 ± 5.5*	0.55 ± 0.15	48.6 ± 13.3	114 ± 12	73 ± 9*
mild	2	13.5	145	32.6	0.60	53.0	178	116
Controls	9	14.2 ± 0.3	159 ± 2	48.9 ± 3.0	0.75 ± 0.05	66.3 ± 4.4	147 ± 9	125 ± 9
F vs M controls	***	NS	NS	NS	NS	NS	*	NS

Mean ± SE; severe and mild malnutrition: patients with an observed/expected weight ratio <0.80 and 0.80–0.89, respectively; F vs M controls: female controls versus male controls

*, *** $P < 0.05$, < 0.001, unpaired *t*-test, or multiple range test ($P < 0.05$) if ANOVA significant

Table 2. Triceps and subscapular skinfold thickness measurements in adolescents: effects of malnutrition

	Triceps (mm)	Scapular (mm)	Sum of 2 Skinfolds (mm)	*n*
Females				
Malnutrition				
severe	6.7 ± 0.9*	6.0 ± 0.7*	12.7 ± 1.6*	14
mild	9.4 ± 1.9*	7.7 ± 0.9	17.1 ± 2.2*	7
Controls[a]	16.2 ± 0.8	9.5 ± 0.4	25.2 ± 1.2	21
Males				
Malnutrition[b]	5.6 ± 1.1*	4.9 ± 0.5**	10.5 ± 1.3***	5
Controls[a]	12.6 ± 1.2	8.5 ± 0.9	21.1 ± 2.0	21
F vs M controls	*	NS	NS	

[a] Data from Novak [18]
[b] Malnourished males are pooled because the skinfold measurements were almost identical in the two subgroups: 5.3 vs 6.0, 4.6 vs 5.5 and 9.9 vs 11.5 respectively (all NS by *t*-test)
*, **, *** $P < 0.05$, < 0.01, < 0.001, unpaired *t*-test, or multiple range test ($P < 0.05$) if ANOVA significant
For other abbreviations, see Table 1

nervosa had primary amenorrhea; the others had secondary amenorrhea. The mean WR (for height and sex) was 0.75 ± 0.05 and 0.75 ± 0.02 for males and females, respectively.

The triceps and subscapular skinfold thickness measurements were less than those of age- and sex-matched controls (Table 2) [18]. The measurements in females tended to decrease in parallel with the severity of malnutrition. Estimated fat mass as a percentage of body weight in malnourished females (14.2 ± 1.1%) was less than published values for non-athletic females (19%–28%) [23, 24]. Estimated fat mass as a percentage of body weight in malnourished males (10.7 ± 2.0%) was just below the normal range for non-athletic teenagers (11%–19%) [23, 24].

The urinary excretion of creatinine was significantly decreased in malnourished patients compared with controls (Table 3). AMA was less than the tenth percentile for age [25] in 13 of 19 female and in 3 of 3 male patients. There was a significant correlation between the two methods (urinary creatinine and anthropometry) for evaluating muscle mass:

$U_{cr}V$ (mg/day) = 26.3 AMA + 252 $r = 0.68$, $P < 0.001$, $n = 22$

$U_{cr}V$ (mg/day) = 1.1 AMV + 54 $r = 0.74$, $P < 0.001$, $n = 13$ (Fig. 1).

Table 3. Excretion of creatinine in adolescents: effects of malnutrition

	n	k[1] (mg/100 min/cm/1.73 m²)	$U_{cr}V$[1] (mg/day)	CHI[1] (mg/day/cm)	MM% (%)
Females					
Malnutrition					
severe	17	0.51 ± 0.03*	906 ± 64*	5.55 ± 0.36*	41.5 ± 2.5
mild	9	0.59 ± 0.03	1080 ± 63	6.75 ± 0.37*	44.9 ± 2.1
Controls	26	0.60 ± 0.02	1207 ± 47	7.69 ± 0.29	40.4 ± 1.3
Males					
Malnutrition					
severe	4	0.39 ± 0.06*	598 ± 193*	3.76 ± 1.01*	32.7 ± 4.4
mild	2	0.69	945	6.54	52.2
Controls	9	0.70 ± 0.07	1372 ± 161	8.59 ± 0.98	49.4 ± 3.9
F vs M controls		NS	NS	NS	NS

* $P < 0.05$, multiple range test, when ANOVA significant
For other abbreviations, see Table 1

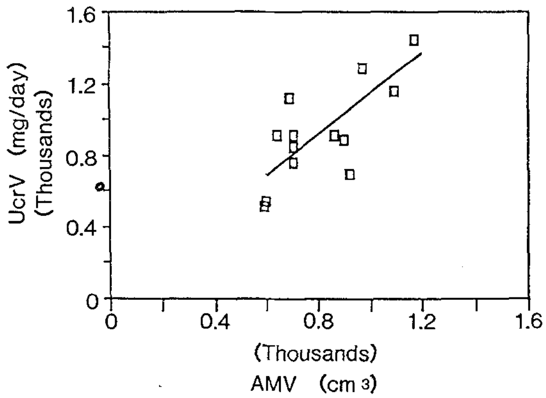

Fig. 1. Comparison between anthropometric assessment of muscle mass and urinary excretion of creatinine in malnourished adolescents before and during therapy: arm muscle volume (*AMV*) versus daily urinary excretion of creatinine ($U_{cr}V$): $U_{cr}V$ (mg/day) = 1.1 AMV + 54, r = 0.74, n = 13

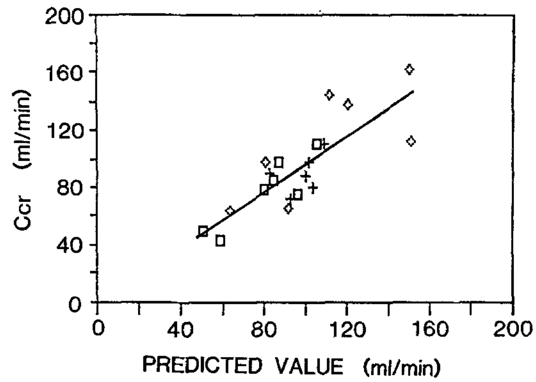

Fig. 2. Comparison between measured creatinine clearance (C_{cr}) and the value obtained by using the anthropometrically derived formula in anorectic patients. The regression line was obtained by combining studies performed at admission (*initial* □) with those performed during re-feeding (+): C_{cr} (ml/min) = 0.06 AMV/P_{cr} + 131 WR − 79, r = 0.82, n = 13. The corresponding values of predicted and observed C_{cr} for an independent group of malnourished patients in the process of re-feeding (◇) are superimposed on the graph

The mean value of k was lower in both severely wasted females and males than in controls (Table 3). The prediction of C_{cr} (ml/min/1.73 m^2) from kL/P_{cr} in malnourished teenagers was not as accurate as for children with normal body habitus [5, 8] using 0.55 in females and 0.7 in males. The correlation coefficient between C_{cr} and 0.55 L/P_{cr} in malnourished females was only 0.57 (n = 26, P <0.005), while there was no significant correlation between C_{cr} and 0.7 L/P_{cr} in malnourished males (r = 0.17, n = 6). The relative error of the predicted GFR was >25% in 6 of 26 (23%) females and 5 of 6 (83%) males. The mean ratio kL/P_{cr} : C_{cr} was 1.37±0.06 in females (significantly different from 1, P <0.005) and 1.64±0.27 in males (0.05< P <0.10), respectively.

On the other hand, absolute C_{cr} (ml/min) could be grossly predicted from AMV/P_{cr}, regardless of sex and nutritional status:

C_{cr} (ml/min) = 0.07 AMV/P_{cr} + 7.1, r = 0.64, P <0.02, n = 13.

Correction to 1.73 m^2 did not improve the correlation (r = 0.51).

The estimation of C_{cr} was then evaluated using a multiple regression analysis including additional anthropometric variables (weight, height, WR), age and sex. Only WR significantly improved this correlation:

C_{cr} (ml/min) = 0.06 AMV/P_{cr} + 131 WR −79, r = 0.82, n = 13 (Fig. 2).

The utility of this equation was tested in a group of 7 anorectic teenagers who were being re-fed (WR range 0.71-1.11). The correlation coefficient between the measured value of C_{cr} and the predicted value was 0.75, and the mean ratio of (using the above-described formula) predicted C_{cr}: observed C_{cr} was 1.01±0.09, not significantly different from 1.

The value of GFR (ml/min) in severely wasted patients was lower than in controls (Table 1). Some of these differences disappeared when clearance was expressed in ml/min/1.73 m^2 (Table 1).

There was no difference by paired t-test between inulin clearance and creatinine clearance. The mean C_{cr} : C_{in} ratio was 1.00±0.07 (range 0.68−1.34, n = 10).

Discussion

We have confirmed, using indirect methods, that malnutrition is associated with a decrease in both fat mass and lean body mass [1, 2, 9, 26]. The degree of weight loss was generally commensurate with muscle wasting. We found a relatively greater decrease of muscle mass in severely malnourished males (more than 50% loss as estimated from $U_{cr}V$) than in females (25% loss). This might be related to the different pattern of tissue accretion during normal puberty; females during adolescence increase their percentage of fat up to 19%−28%, while males increase their percentage of muscle up to 45%−51% [8, 14, 17, 27, 28].

Creatinine excretion rate is a good predictor of muscle mass when, as in our study, creatine (meat) intake is limited and there is no acute infection, fever or trauma [29]. Moreover, creatinine excretion correlated well with anthropometric indices of arm muscle mass in malnourished patients (Fig. 1), confirming the results of previous studies [9, 29, 30].

The amount of urinary creatinine derived from muscle creatine metabolism depends on muscle mass, which is in turn closely related to lean body mass [16, 29]. During the process of normal human growth, muscle mass per kilogram of body mass increases progressively, proportional to the empirical constant k relating GFR (ml/min/1.73 m^2) to L/P_{cr} [6]. In our laboratory the value of k increases from 0.33 in low-birth-weight infants, to 0.45 in term infants, to 0.55 both in male and in female children and in adolescent females, and to 0.70 in adolescent males [5–9].

Malnutrition is associated with a decrease both in urinary creatinine excretion and body weight with sparing of height (or length); body surface area depends on both weight and length and therefore may decrease less than weight alone. Thus, in malnourished patients the decrease in the creatinine-height index (CHI, mg/day/cm) will tend to be greater than the reduction in k, which depends on creatinine excretion per surface area (mg/100 min/cm/1.73 m^2) and which is, in turn, greater than the decrease in the percentage of body weight that is muscle (MM%) (Table 3).

Re-feeding anorectic teenagers has been associated with a simultaneous increase in fat and lean body mass [1]. We have observed a trend towards an increase in body fat only during the process of re-feeding, irrespective of the degree of malnutrition, the initial body habitus, the quality of the diet or the amount of physical activity [31]. Perhaps after a longer period of therapy a more normal body habitus may be obtained.

In this study we have shown that C_{cr} in malnourished teenagers gives a good approximation of the true GFR (C_{in}), as shown previously in infants, children and adolescents [5–9]. The ratio of $C_{cr}: C_{in}$ was equal to 1, as observed previously for normal and mildly decreased values of GFR [32]. Therefore, the inaccuracies of the formula kL/P_{cr} to estimate GFR cannot be ascribed to poor agreement between C_{cr} and C_{in}.

Since the value of k decreased in these malnourished patients as a function of the severity of malnutrition and was variable because of the wide range in muscle mass per unit of body size, the prediction of GFR from the formula 0.55 or 0.7 L/P_{cr} was poor. It is possible that the prediction of GFR may be more satisfactory in specific subgroups with more homogeneous body composition, as found previously in preterm vs term infants [9]. For the present, we conclude that accurate evaluation of GFR in an adolescent with malnutrition requires a carefully performed clearance.

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Appendix

The upper arm muscle area (AMA, cm^2) was obtained by the formula [17]:

$$\text{AMA} = \frac{[\text{Arm muscle circumference (cm)} - 0.314 \times \text{triceps skinfold (mm)}]^2}{12.57}$$

The constant 12.57 equals 4 × pi.

The upper arm muscle volume (AMV, cm^3) was obtained by using the formula [9]:

AMV = AMA × Upper arm length (cm).

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