Creatine Excretion and Body Composition

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Knowledge of body composition is of importance in studying nutrition. The procedures used for the study of body composition, however, are not simple because they require expert personnel, costly apparatus and time. It is therefore, particularly difficult to measure body composition in a large number of subjects. It is obvious that there would be a great advantage in having a simple technic adaptable to nutritional surveys. Theoretically, measuring the urinary excretion of creatinine would serve this purpose, since the variation in urinary creatinine excretion in persons with approximately normal body weight depends largely but not entirely on the variations in body mass.[1] Furthermore, since 98 per cent of creatine is in the skeletal muscle[2] and since it has been demonstrated that muscle creatine is the precursor of urinary creatinine,[3] we can safely conclude that the excretion of creatinine could serve as an index of muscular mass. To test the hypothesis that urinary creatinine can be used in the prediction of body compartments we have measured urinary excretion of creatinine and related these data to body mass and body compartments on the same subjects.

MATERIAL AND METHODS

The subjects were twenty-two residents of an altitude of 14,900 feet above sea level, with the following physical characteristics: age, seventeen to forty years (mean, twenty-eight years); height, 149.3 to 165.5 cm. (mean, 157 cm.); weight, 44 to 62 kg. (mean, 53.5 kg.).

Total body water (A) was estimated by the antipyrine dilution method described by Soberman et al.[4] Antipyrine concentration in plasma as well as in the solution injected was determined by the method of Brodie et al.[5] Extracellular fluid (E) was calculated from the maximum volume of sucrose distribution following the technic of calibrated infusion described by Deane et al.[6] The concentrations of sucrose in plasma, urine and infused solution were determined by the resorcinol method described by Roe and modified by Schreiner,[7] using cadmium sulfate to obtain the plasma filtrate. The intracellular fluid volume (I) is represented by the difference between total body water and extracellular fluid. Fat body mass (F), as a proportion of total body weight, was calculated from the following equation given by Keys and Brozek[8]:

$$F = 1 - A - 0.563 \quad (A - E)$$

Fat-free body mass was calculated as the difference between body weight and body fat.

A factor of correction for the extracellular fluid was not calculated because the sucrose space found in sea-level subjects in this laboratory,[9] as well as by Deane[10] agrees with the figures accepted as representative of the extracellular fluid volume by Keys and Brozek.[8] According to Deane,[11] the volumes of distribution of inulin and sucrose more closely approximate the extracellular fluid volume in man than do the volumes of distribution of test substances formerly used.

Creatinine was determined in urine excreted in a four hour period. The subjects were catheterized with a multiple-eyed catheter and the urine sample was collected between 6:00 and 10 a.m. because creatinine excretion during this period reflects the twenty-four hour excretion, and variation in the excretion of creatinine is least in the morning.[12] The concentration of creatinine was determined by Jaffe's reaction, as modified by Bonsnes and Taussky.[13]

The statistical analyses were calculated by standard methods. The significance of the coefficients of correlation was found from Snedecor's tables.[14]

RESULTS

Correlation Analysis

The subject's physical characteristics, cre-

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TABLE I
Mean Values and Standard Deviation of Creatinine Excretion and Body Composition in Twenty-Two Adult Men

Age (yr.)	27.7 ± 7.6
Height (cm.)	157.0 ± 4.6
Body weight (kg.)	53.5 ± 5.6
Creatinine excretion (mg./hr.)	45.0 ± 7.1
Total body water (L.)	31.8 ± 3.4
Extracellular fluid (L.)	9.4 ± 1.3
Intracellular fluid (L.)	22.4 ± 2.7
Body fat (% body weight)	16.9 ± 6.7
Body fat (kg.)	9.2 ± 4.1
Fat-free body mass (kg.) observed*	44.4 ± 4.9
Fat-free body mass (kg.) predicted†	44.4 ± 4.2
% deviation of predicted from observed	−0.08

* Calculated from fat-free body mass = body weight − body fat.

† Predicted from fat-free body mass = 17.6 + 0.596 mg. creatinine/hour.

atinine excretion and body compartments are summarized in Table I. Primary or zero order coefficients of correlation and some partial or first order coefficients of correlation are presented in Tables II and III.

Creatinine excretion showed a high statistically significant correlation with body weight, fat-free body mass and fluid spaces. Correlation with height was of statistical significance.

The highly significant correlation between creatinine excretion and body weight depends mostly on total body water, or fat-free body mass since the correlation between creatinine excretion and body weight becomes extremely small when either total body water or fat-free body mass is held constant. Extracellular and intracellular water have some influence on the relationship between creatinine excretion and body weight. On the other hand, this relationship is apparently strengthened when body fat is held constant.

The correlation between the excretion of creatinine and height remained highly significant when body fat was maintained constant and lost its statistical significance when each influence of the other measured factors was removed separately.

The highly significant correlation between creatinine excretion and total body water did not depend on body weight, on height, extracellular fluid or on body fat; this correlation became less significant when the influence of intracellular fluid was removed, and disappeared when the effect of fat-free body mass was removed. When body weight, total body water or fat-free body mass was held constant, the highly significant correlation between creatinine excretion and extracellular fluid was reduced to insignificance. The relationship became significant after the removal of the influence of height, or intracellular fluid, and was essentially unaltered when the effect of the body fat was removed.

The highly significant correlation between creatinine excretion and intracellular fluid was not reduced when the effects of body weight, height, extracellular fluid or body fat were removed, and was reduced to insignificance when fat-free body mass or total body water was held constant.

The highly significant correlation between creatinine excretion and fat-free body mass depended to a great extent on total body water owing to the high functional relationship between fat-free body mass and total body water It did not depend on body weight, height, extracellular fluid or body fat. This relationship became significant after removal of the influence of intracellular fluid. A similar coefficient of correlation was found by Miller and Blyth,[15] in whose studies fat-free body mass was determined following densitometric analysis.

Regression Analysis

The high correlation between creatinine excretion and the various body compartments suggests that creatinine excretion could serve as an excellent standard of reference for determination of body composition. The best empiric criterion for the validity of any method for the determination of any body space is the accuracy with which body composition can be predicted when the standard is known. We have therefore calculated the regression equations to predict fat-free body mass or total body water, given the creatinine excretion.

Creatinine excretion had a high degree of correlation with total body water. The coefficient of determination estimates that 76

TABLE II
Coefficients of Correlation Between Indicated Variables*

Data	Weight	Height	Creatinine	A	E	I	F
Height	0.69†	...	...	...	...	...	...
Creatinine	0.72†	0.54‡	...	...	...	...	...
A	0.74†	0.53‡	0.87†	...	...	...	...
E	0.75†	0.57†	0.61†	0.72†	...	...	...
I	0.59†	0.41	0.83†	0.95†	0.46‡	...	...
F	0.52‡	0.34	−0.06	−0.19	0.24	−0.36	...
FFM	0.70†	0.50‡	0.87†	0.99†	0.65†	0.97†	−0.25

* A, total body water; E, extracellular fluid; I, intracellular fluid; F, fat body mass; FFM, fat-free body mass.
† $P < 0.01$.
‡ $P < 0.05$.

TABLE III
Partial Coefficients of Correlation Between Creatinine and Body Compartments, Keeping Constant Various Factors

Factor Held Constant	Partial Coefficients of Correlation						
	Weight	Height	A	E	I	F	FFM
Weight	...	0.07	0.72*	0.16	0.72*	−0.73*	0.73*
Height	0.58*	...	0.82*	0.44†	0.79*	−0.30	0.82*
A	0.25	0.18	...	−0.04	0.04	0.23	0.03
E	0.50†	0.28	0.78*	...	0.78*	−0.26	0.78*
I	0.51†	0.38	0.47†	0.47†	...	0.46†	0.47†
F	0.88*	0.59*	0.88*	0.65*	0.87*	...	0.88*
FFM	0.33	0.24	0.14	0.13	−0.13	0.33	...

* $P < 0.01$.
† $P < 0.05$.

per cent of the variation in creatinine excretion is associated with variation in total body water. The following regression equation was calculated:

A (liters) = 12.9 + 0.421 mg. creatinine/hour ± 1.70

The regression coefficient of this equation is highly significant.

Fat-free body mass correlated to a high degree with creatinine excretion. The coefficient of determination was 75 per cent. The following equation defines the regression line:

Fat-free body mass = 17.6 + 0.596 mg. creatinine/hour ± 2.44

The coefficient of regression of this equation is highly significant.

COMMENTS

Creatinine excretion can serve as an excellent standard of reference for predicting fat-free body mass or total body water as the highly significant correlation coefficients which we find in this study indicate. In general, the data suggest that there is an important relationship between creatinine excretion and fat-free body mass and, of course, between creatinine excretion and total body water, since fat-free body mass and total body water are nearly perfectly correlated. This is attributable to the fact that the total body water forms part of the fat-free body mass. This relationship between total body water and creatinine does not depend on body weight or on body fat. We also note that total body water, as well as fat-free body mass, had a great influence on the correlation between creatinine excretion and body weight, height, extracellular or intracellular water, since these correlations became extremely small when either of the two factors (total body water or fat-free body mass) was held constant. The strong relationship between creatinine excretion and total body water is probably traceable to the fact that the creatinine is distributed uniformly in the water of the body.[16–18] But it must be pointed out that although the coefficient of determination estimates that 75.7 per cent of the variation in creatinine excretion is associated with variations in total body water it does not prove any direct causal relationship in a physiologic sense. The high correlation between creatinine excretion and total body water may be indirect and result from the correlation of both variables with fat-free body mass. It is noteworthy that, according to partial correlations, the intracellular fluid has some influence on the relationships between creatinine excretion and total body water, but extracellular fluid has almost none. The reason for this could be that $C = I/0.70$,[8] a space that is intimately tied to creatinine formation,[2,3] or because $A = I + E$, and the intracellular fluid comprises the largest part of the total body water.

The fact that extracellular fluid does not influence the relationship between creatinine excretion and intracellular fluid may be possibly due to the fact that extracellular and intracellular fluids are different spaces.

Extracellular fluid does not influence the relationship between creatinine excretion and fat-free body mass, but total body water does. The data suggest that increases in fat-free body mass are related to increases in creatinine excretion, a phenomenon which is intimately tied to total body water, but is not necessarily associated with changes in the extracellular fluid volume.

Unlike the effect of body weight on the relationship of intracellular fluid and creatinine excretion, it was found that the highly significant correlation of extracellular fluid with creatinine excretion lost its statistical significance when body weight was maintained constant. We must also note that the highly significant correlation between creatinine excretion and body weight depended to a high degree on total body water and fat-free body mass, since this correlation lost its statistical significance when any one of these factors was held constant. It is suggested that variations in body weight may not be necessarily accompanied by variations in creatinine excretion if there are not concomitant variations in fat-free body mass. This is supported by the fact that the relationship between creatinine excretion and body fat gave a highly significant negative correlation when body weight was held constant. This can be explained by the fact that when body weight is held constant, variations in total body fat will be inversely related to fat-free body mass. This phenomenon is also corroborated by the fact that the correlation between creatinine excretion and total body weight increased when body fat was held constant. This is in accord with the fact that 98 per cent of creatine is in muscle[2] and that creatinine originates in skeletal muscle from creatine or muscle phosphocreatine.[2,3]

The significant correlation between creatinine excretion and height lost its statistical significance when any one of the factors studied, with the exception of body fat, was held constant. On the other hand, height had no influence on the relationship between creatinine excretion and body spaces, with the exception of extracellular fluid where height had a very small influence. This indicates that variations in height have no influence on creatinine excretion if, at the same time, there are no variations in the total body weight, or more exactly in fat-free body mass, and that variations in body weight or fat-free body mass will be accompanied by variations in creatinine excretion even though height is maintained constant.

The high correlation between fat-free body mass and creatinine excretion found by other investigators, who employed different methods from ours for the estimation of fat-free body mass,[15,19–21] has been confirmed in this study. The closeness of this correlation was unexpected since only four hour specimens of urine, primarily collected for sucrose measurements, were used for creatinine estimation, and dietary protein intake was not controlled. Although, Miller and Blyth[15] and Best[22] pointed out that creatinine excretion varied with dietary protein content and that there are considerable daily variations in creatinine excretion, other investigators found that the daily excretion of creatinine was constant over long periods, provided the collection of urine was accurate[23–25] and that it was little affected by diet.[25,26] McClugage et al.[24] found that the excretion of creatinine was independent of the other elements of nitrogen metabolism, of the total nitrogen excretion and presence of positive or negative nitrogen balance, and of the total urine volume. Recently Standard et al.[27] have also found that the increase in creatinine excretion did not differ significantly with the protein content of the food intake. These investigators found a correlation between increase in muscle thickness and increase in creatinine output. Moreover, the four hour urine collection, suggested by Best et al.[12] gave more constant results than a twenty-four hour collection for reasons which are not clear.[15]

The nonspecificity of the Jaffe reaction for creatinine determination constitutes a serious limitation to the procedure, since various plasma chromogen substances yield color with alkaline picrate. If it is true that only 75 to 80 per cent of the total plasma chromogen represents true creatinine in normal subjects, 90 to 100 per cent of the urinary chromogen is creatinine.[18,28–31] Sullivan and Irreverre[30] found that the various interfering substances in the Jaffe-Folin and Benedict-Behre procedures do not occur in normal urine. Moreover, the analytical results of Miller and Dubos[18] suggest that the kidneys do not remove the noncreatinine chromogenic materials from normal and nephritic plasma.

CONCLUSIONS

Creatinine excretion and body composition have been determined in twenty-two subjects residing at 14,900 feet above sea level.

A direct and intimate relationship exists between creatinine excretion and total body water as well as between creatinine excretion and fat-free body mass which is independent of body weight, height, extracellular fluid or body fat, and only slightly affected by intracellular fluid volume. The relationship between creatinine excretion and extracellular fluid depends on body weight, fat-free body mass and, most of all, total body water. Intracellular fluid and height influence this last relationship only slightly. This relationship is not altered by body fat. The relationship between creatinine excretion and intracellular fluid volume is not affected by body weight, height, body fat or extracellular fluid, but depends to a high degree on fat-free body mass.

Creatinine excretion is one of a number of reasonably useful tools for determining nutritional status. It may be used as a standard of reference for the determination of fat-free body mass; it is a simple technic which can be used in hospital, school, military and other surveys of nutrition.

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