



Measurement of muscle mass in humans: validity of the 24-hour urinary creatinine method^{1,2}

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ABSTRACT Measuring muscle mass is an important component of the nutritional assessment examination and a suggested index of this body space is the 24-h urinary excretion of creatinine. The method originated from studies in a variety of animal species in whom early workers found a parallelism between total body creatine and urinary excretion of creatinine. Assuming that nearly all creatine was within muscle tissue, that muscle creatine content remained constant and that creatinine was excreted at a uniform rate, an obvious "corollary" was that urinary creatinine was proportional to muscle mass. The so-called "creatinine equivalence" (kg muscle mass/g urinary creatinine) ranged experimentally from 17 to 22. One of the limiting factors in firmly establishing this constant and its associated variability was (and is) the lack of another totally acceptable noninvasive technique of measuring muscle mass to which the creatinine method could (or would) be compared. An improved understanding of creatine metabolism and a variety of clinical studies in recent years has tended to support the general validity of this approach. However, specific conditions have also been established in which the method becomes either inaccurate or invalid. While creatinine excretion may serve as a useful approximation of muscle mass in carefully selected subjects, there remains a need for accurate and practical indices of muscle mass for use in the individuals in whom the method cannot be reliably applied. *Am J Clin Nutr* 1983;37:478-494.

KEY WORDS Muscle mass, urinary creatinine

Introduction

Muscle is roughly 80% water and 20% protein, and a 70-kg man has about 28 kg of this tissue (1). Muscle thus represents 4 to 6 kg of the body's total 10 to 12 kg of protein (2). Expressed in terms of metabolizable energy, this amounts to 20,000 to 30,000 kcal, of which 70 to 80% can be utilized during periods of negative energy balance (3). It is not surprising therefore, that quantifying muscle mass has been an important focus of nutritionists studying or caring for patients suffering from protein-energy malnutrition (4, 5). Unfortunately, this quantification of muscle tissue has lacked the accuracy enjoyed by other body compartments, because there is as yet no simple, accurate, and inexpensive method of measuring muscle mass in living

human subjects. Several methods have been suggested (Table 1), but none of these has a clearly demonstrated validity. This review focuses on one of these methods: the urinary creatinine method of measuring muscle mass.

Overview of the method

Myers and Fine (22) were the first to show that urinary creatinine output was directly

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TABLE 1
Techniques for in vivo measurement of muscle mass*

Method	Comment	Reference
Anthropometry	Limited accuracy; measures individual muscle groups, but not total muscle mass. Assumes muscle size proportional to muscle composition.	3, 6
Ultrasound	Replaces skinfold caliper for measuring thickness of fat layer.	7
Radiographic	Computerized tomography allows measurement of limb muscle cross sectional area. Cost, radiation dose, availability of scanners limit widespread application. Cannot measure total body muscle mass.	6
Isotopic methods ¹⁵ N-creatinine and ¹⁴ N-creatinine	Based on isotope dilution principle; requires muscle biopsy. Some workers argue that biopsy of one muscle group inadequate for accurate results.	8, 9 10
Total body water and extra-cellular volume	Method based on experimental observations in the rat.	11
Total body water and total body potassium	Method provides adipose, muscle and muscle-free lean tissue.	12
Neutron activation analysis	Limited number of instruments in operation. Values for total body muscle mass somewhat lower than anatomical dissections.	13-15
Nuclear magnetic resonance	As for radiography above, can visualize limb muscle cross sectional area. May also provide muscle composition data. Method largely untested in man.	16
Chemical markers 24-h urinary creatinine	Subject of current review.	
Urinary 3-methyl histidine	Appropriate method in healthy subjects ingesting meat-free diet. Not applicable in most disease states because of variable 3-methyl histidine turnover rate.	17, 18
Combined methods Creatinine and total body potassium	Method based on prediction equations developed in rat studies. Calculated variables include muscle protein, nonmuscle protein and total body protein.	19
Skeletal measurements plus total body potassium	Three component analysis includes adipose, muscle, and muscle free lean tissues.	20

* Modified from Reference 21.

proportional to the total body creatine content in three species: human, dog and rabbit. Palladin and Wallenburger (23) later extended this observation to rat, sheep, and guinea pig. Bürger (24), assuming that nearly all body creatine was within muscle, and that muscle possessed a constant creatine content, proposed that urinary creatinine was proportional to muscle mass. Bürger's calculation of the creatinine equivalence (kg muscle mass/g urinary creatinine) is presented in the experimental studies sections below.

Four assumptions are entailed in the extrapolation of urinary creatinine to muscle mass: 1) creatine is almost totally within skeletal and smooth muscle; 2) on a creatine-free diet, the total creatine pool and the average concentration of creatine per kg of muscle remains constant; 3) creatine is converted nonenzymatically and irreversibly to creatinine at a constant daily rate; and 4) creatinine, once formed, undergoes renal excretion at a constant rate. Mathematical expression of these assumptions is outlined in Table 2,

TABLE 2
Quantification of the creatinine-muscle mass method*

A) Assuming daily Crn excretion is the result of breakdown of a fraction K of Cr each day:

$$\text{Crn (moles/day)} = K (\text{day}^{-1}) \times \text{Cr (moles/kg)} \times M (\text{kg}) \quad (1)$$

B) Converting to gram equivalents for molar amounts of Cr and Crn and rearranging equation to solve for M:

$$M (\text{kg}) = \frac{\text{Crn (g/day)}}{K (\text{day}^{-1}) \times \{\text{Cr}/1.16\} (\text{g/kg})} \quad (2)$$

C) Since there are two species of tissue creatine, Cr and P-Cr, the measured fractional conversion K really reflects a combination of breakdown of Cr at fractional rate K_1 and P-Cr at fractional rate K_2 , we then modify equation (2) to:

$$M (\text{kg}) = \frac{\text{Crn (g/day)}}{\frac{K_1 (\text{day}^{-1}) \times \text{Cr (g/kg)}{1.16} + \frac{K_2 (\text{day}^{-1}) \times \text{P-Cr (g/kg)}{1.59}} \quad (3)$$

* Abbreviations: Cr = creatine concentration in skeletal muscle, Crn = total urinary creatinine, M = total muscle mass, and P-Cr = phosphocreatine concentration in skeletal muscle.

TABLE 3
Measured turnover rates and creatine and creatinine concentrations for equations in Table 2.*

Term	Unit	Value	Subjects	Method	Reference
K_1	Day ⁻¹	0.011		In vitro	25
K_2	Day ⁻¹	0.0264		In vitro	25
K	Day ⁻¹	0.0164	One adult man	¹⁵ N-creatine	26
		0.014–0.017	7 patients with muscular and neurological disease and one with refractory anemia	¹⁴ C-creatine	27
		0.015–0.026	8 children recovering from protein-energy malnutrition	¹⁵ N-creatine	8
		0.0169 ± 0.006†	13 young men	¹⁵ N-creatine	28
		0.0138–0.0188	4 adults; 2 had endocrine diseases, and 2 were normal	¹⁴ C-creatine	9
Total Cr‡	g/kg WWM	3.91	5 normal subjects; on general diet	Biopsy	29
	g/kg NCP	22.08	5 normal subjects; on general diet	Biopsy	29
		21.2	11 normal subjects; on general diet	Biopsy	30
Cr/P-Cr	g/kg WWM	1.53/2.39	11 normal subjects; on general diet	Biopsy	30
	g/kg NCP	8.3/12.9	11 normal subjects; on general diet	Biopsy	30
	g/kg WWM	1.19/2.74	from ref 26, assume that 70% of total Cr is P-Cr		31

* Abbreviations: Cr, creatine; K, fractional breakdown rate of total body creatine to creatinine; K_1 , K_2 , breakdown rate of creatine and phosphocreatine; P-Cr, phosphocreatine.

† Mean ± SD for n = 13.

‡ Creatinine + phosphocreatine.

and estimated values of the quantities required to apply the formulae are presented in Table 3.

In this review, the first section examines creatine biosynthesis and metabolism in the context of the above four assumptions. In the second section, physiological and dietary fac-

tors that may influence the validity of the creatinine-muscle mass method are evaluated. Section three presents studies aimed at establishing the creatinine equivalence, and the final section provides a summary and recommendations for evaluating selected patients.

Creatine-creatinine metabolism

Biosynthesis of creatine

Creatine is a nitrogenous organic compound, which participates in cellular energy metabolism (Fig 1), and is found primarily in muscle. Bloch and Schoenheimer (32) first proposed that creatine was derived from three amino acids: arginine, glycine, and S-adenosyl methionine. Within several years of Bloch's studies, Borsook and Dubnoff (33) elucidated the first of two biosynthetic steps: the synthesis of guanidoacetate (glycocyamine) from glycine and arginine (Fig 1). This reaction, under control of the rate limiting enzyme glycine amidinotransferase (transamidinase), is found in human kidney, liver, pancreas, brain, spleen, and mammary gland (31). The predominant biosynthetic site in humans is the kidney. The rate of creatine synthesis is closely regulated by feedback in-

hibition of transamidinase. On a creatine-free vegetarian diet, this pathway is fully activated, and adequate guanidoacetate is synthesized from amino acid precursors. Creatine ingested from meat partially or totally represses transamidinase, freeing the precursor amino acids for other metabolic reactions, notably growth.

The activity of transamidinase is also modulated by sex hormones (31). Testosterone stimulates the de novo synthesis of transamidinase, which in turn increases the production rate of guanidoacetate and creatine. Krisko and Walker (34) suggest that the higher creatinine coefficient (mg creatinine/kg body weight) found in men as compared to women might be explained on this basis.

Creatine is formed in the next reaction by transfer of a methyl group from S-adenosyl-methionine to guanidoacetate (Fig 1). Contrary to the previous reaction, this step is

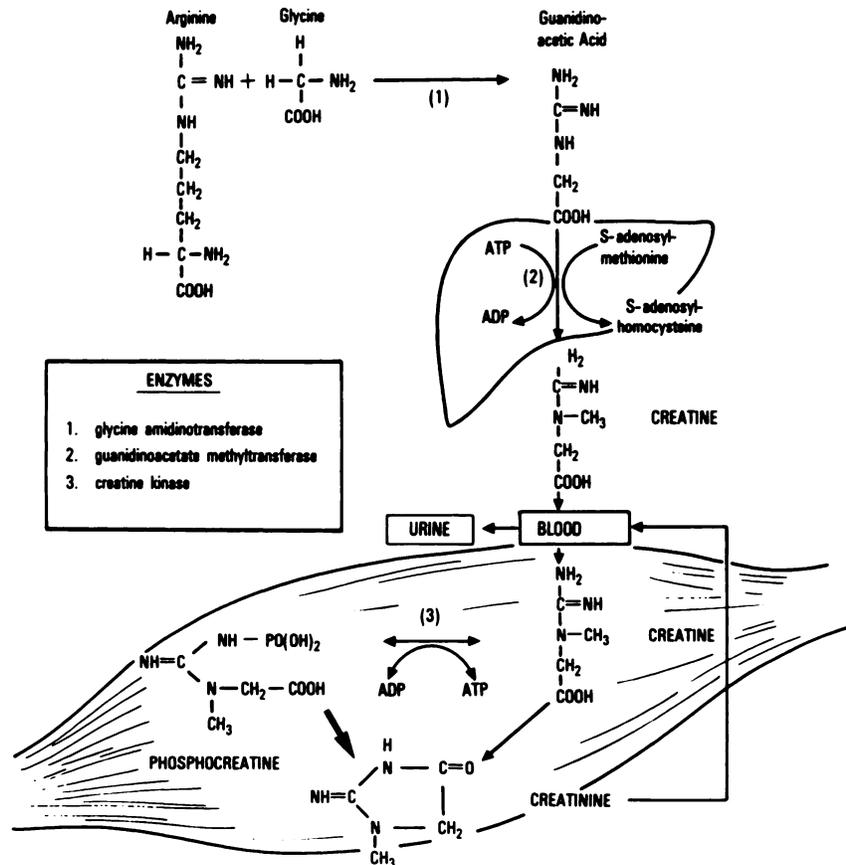


FIG 1. Principal pathways in creatine metabolism.

irreversible, not rate limiting, and occurs primarily in liver tissue (31).

Synthesized creatine is released into the circulation, where the next step is active uptake against a concentration gradient by muscle and other tissues (31, 35). During the transport process, creatine binds to a specific membrane site which recognizes the formamidine moiety of the molecule. This active uptake of creatine replaces about 2% of the total amount of creatine in muscle each day (31). The rate of creatine uptake is influenced by at least three factors; the process is retarded by cooling and anaerobiosis and enhanced by insulin (35).

About 98% of the total body creatine pool (120 g in a 70 kg adult man) (36) is within muscle. This creatine pool is slowly saturable (37) and has a relatively slow daily turnover rate of about 1.5 to 2% (37). Although the creatine concentration per kg of muscle varies from muscle to muscle, the average concentration is 3 to 5 g/kg of wet fat-free tissue (Table 3). The functions of muscle creatine are enumerated in Table 4.

Other tissues (brain, kidney, and liver) and fluids (blood and urine) contain measurable amounts of creatine. Because creatine in these tissues represent only a small percentage of the total body creatine pool (<2%), their overall contribution to creatine turnover is small.

Creatine uptake by muscle and other tissues is relatively complete, and blood levels rarely exceed 0.3 mg/dl (25). Urinary losses of creatine are usually negligible, unless blood levels become excessively high or renal tubular reabsorption is impaired.

Dehydration of creatine to creatinine

Early workers searched for the enzyme "creatase" or "creatinase" that converted creatine to creatinine. Hahn and Meyer (38)

subsequently showed that creatine was converted to creatinine in liver and kidney extracts at the same rate as in a buffered phosphate solution of the same pH. These investigators concluded that the creatine to creatinine conversion was brought about purely on a physiochemical basis. This irreversible reaction is now firmly established. Within muscle, creatine exists in two forms: creatine and phosphocreatine (39). Creatine dehydrates to creatinine at a rate of 1.1% per day, while phosphocreatine conversion is 2.64% per day (Table 3). Because urinary creatinine is derived from these two sources, the *in vivo* measurement of creatine turnover rate provides a value between 1.1 and 2.64%.

Among healthy male subjects, a rather constant creatine turnover rate of 1.6 to 1.7% per day was obtained (Table 3) (26, 28, 40). However, the observed range of values between 1.4 and 2.6% per day in children recovering from protein-energy malnutrition (8) and adult patients (9, 27) (Table 3) would limit the accuracy in predicting muscle mass from 24-h urinary creatinine in these subjects. Because the creatine pool is large, small changes in turnover rate result in large differences in daily urinary output of creatinine. For example, using the two turnover rates of 1.5 and 2.6% in equation 2, and assigning a hypothetical creatinine excretion and muscle creatine concentration of 1.6 g/day and 3.9 g/kg, respectively, calculated muscle mass is 31.7 g and 18.3 kg, or a difference of 42%. Assuming that intracellular pH and temperature remain constant, one explanation for differences in creatine turnover rate between subjects is the natural differences in the creatine to phosphocreatine ratio.

Excretion of creatinine in the urine

Once formed, creatinine diffuses from the cell and ultimately appears in the urine after glomerular filtration, and to a small extent, tubular secretion (41). The effect of renal insufficiency on creatinine excretion is discussed in the next section.

Physiological and pathological conditions that modulate output of creatinine

Folin's "law" (42) states that on a creatine-free diet, the output of creatinine is constant from day to day for each individual. Some variability is, however, recognized in the

TABLE 4
Functions of muscle creatine (3)

- | |
|--|
| 1) High energy intermediate in excitation—contraction coupling:
Phosphocreatine + ADP $\xrightarrow{1}$ creatine + ATP
Enzyme 1 is creatine phosphokinase, and enzyme 2 is creatine phosphorylase. |
| 2) Modulate glycolysis. |
| 3) Increase intracellular flux of potassium and phosphorous. |
| 4) Acts as a cofactor in muscle growth. |

healthy subject; more importantly, some pathological states can alter normal creatinine output.

Normal day to day variability

Normally, urinary creatinine excretion varies daily, the causes of which are largely unknown. The constancy of 24-h creatinine excretion reported in the early Folin studies, and later reinforced by Rose (43), has been repeatedly challenged through the years. Careful studies in reliable subjects have shown a daily variation from 4 to 8% in creatinine excretion, which cannot be explained by minor variations in physical activity and diet (44, 45).

Exercise

Extremely strenuous exercise can increase urinary output of creatinine by 5 to 10% (46, 47). Figure 2 demonstrates this effect in normal subjects marching for 3 h at two different speeds. The increase in daily creatinine output was about 10%. The mechanism(s) of these exercise-induced changes in urinary creatinine output are unknown.

Emotional stress

Creatinine excretion has been studied in a wide variety of stressful conditions and psy-

chiatric illnesses (48, 49). Scrimshaw et al (48) concluded that the variability (and not the absolute amount) in creatinine output increases during stress, but the underlying cause(s) of this phenomenon are poorly understood.

Diet

Urinary creatinine excretion is influenced to some extent by three dietary constituents: protein (50), creatine, and creatinine.

Dietary protein is the main source of the amino acid precursors of creatine. The activity of the first enzyme in creatine biosynthesis, transaminidase, is influenced by dietary protein intake (50, 51). For example, Van Pilsum (51) fed rats a protein-free diet for 12 days, and found an 85% reduction in transaminidase activity. The level of protein intake per se appears to have a small effect on urinary creatinine excretion (50, 52), but few studies have rigorously examined this relation independently from other dietary factors, notably creatine and creatinine. Bleiler and Schedl (52) studied six men who ingested a natural food, 120-g protein diet (Fig 3). The meal contained the usual amount of dietary creatine. The six men were then divided into three groups, and switched to a creatine-free diet; the two subjects in each group received 140, 70, and 20 g of protein, respectively. Over 8 to 11 wk, urinary creatinine excretion fell in each of the respective groups by 26, 32, and 40%. The men were then switched to another creatine-free 120-g protein diet, and the creatinine excretion increased over 3 wk in the three groups by 7.7, 10, and 13%, respectively. The large reduction in creatinine excretion from the basal diet occurred because the men were ingesting a meat-free diet (discussed below), although the total protein intake appears to have had some effect. An important consideration is that the men on the 20-g protein diet were probably in negative nitrogen balance, and some loss in muscle mass may have contributed to the larger decrease in urinary creatinine seen in this group.

Feeding the two dietary amino acid precursors of creatine, arginine, and glycine, enhances transaminidase activity and increases urinary excretion of guanidoacetate. The activation of transaminidase results in a higher rate of creatine production, as well as enlarge-

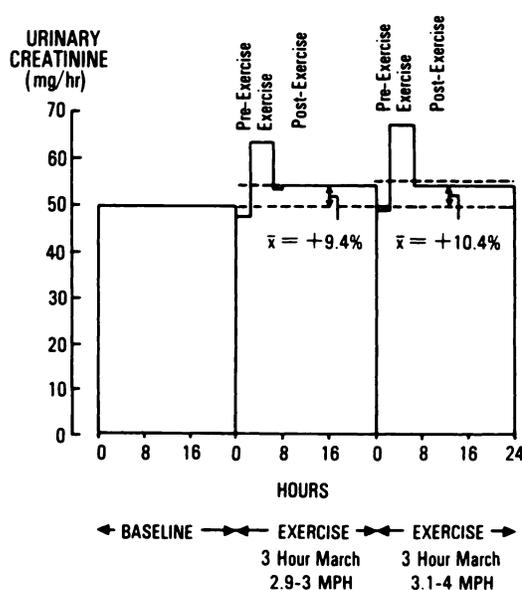


FIG 2. Exercise-induced increase in creatinine excretion. Figure 2 was prepared from the data presented in Reference 47.

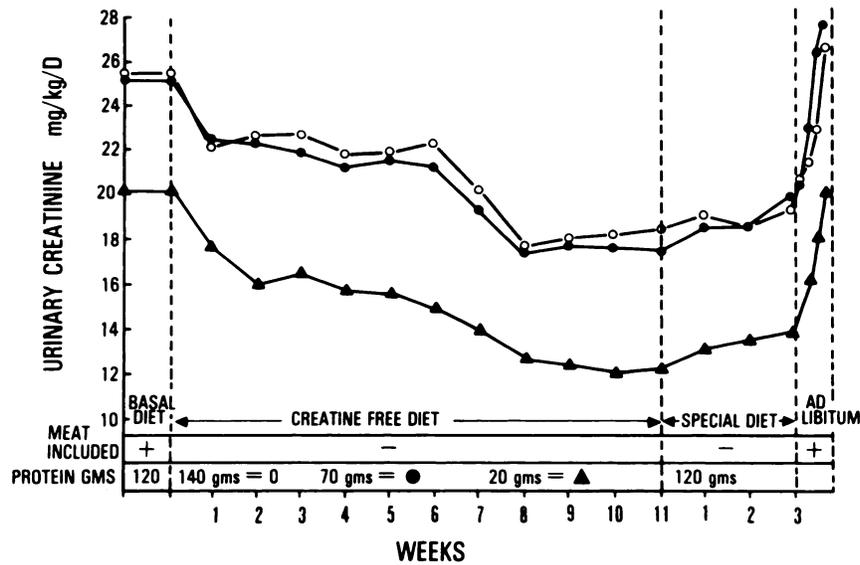


FIG 3. Influence of dietary protein and creatine on urinary creatinine excretion. Figure 3 was prepared from the data presented in Reference 52.

ment of the creatine pool independent of changes in muscle mass. Crim and coworkers (28, 40) fed normal volunteers a creatine-free diet for 71 days, adding during the last 10 days isonitrogenous amounts (4 g nitrogen/day) of either an equimolar mixture of arginine and glycine or alanine. There was a small but significant increase in creatinine excretion in two of the four subjects fed arginine-glycine; no significant changes were observed in the other two subjects, or in the alanine fed group.

The second dietary constituent that influences urinary creatinine excretion is preformed creatine. The amount of dietary creatine directly influences the size of the creatine pool, which in turn is proportional to the output of creatinine in the urine. The "average" daily American diet includes about 200 g (7 oz) of meat (53), which contains 700 mg creatine and 37 mg creatinine (54). Cooking the meat at 77°C reduces creatine content to 570 mg and increases creatinine to 160 mg. Thus, average daily dietary intake of creatine and creatinine replaces about one-third to one-half of the daily urinary creatinine losses.

The influence of dietary creatine on urinary creatinine excretion has been examined by a number of investigators. Switching from an ad libitum diet, to a meat-free protein source (casein), Bleiler and Schedl (52)

showed a reduction in urinary creatinine over 6 wk from 1.9 to 1.5 g/day (-21%). These investigators further demonstrated a rapid increase in urinary creatinine when subjects were switched from a creatine-free 120 g/day protein diet to an ad libitum general diet (Fig 3). Crim et al (40) shifted from a 9-day low creatine diet (0.23 g/day), to a 10-day high creatine diet (10 g/day), and found a prompt 10 to 30% increase in urinary creatinine excretion (Fig 4). In a subsequent creatine-free period, Crim showed that nitrogen and potassium balance remained positive despite declining creatinine excretion, indicating a degree of independence between creatinine excretion and muscle or lean body mass. The independence between creatinine excretion and muscle or fat free body mass is also observed when switching from a general hospital diet which includes meat, to a creatine-free hyperalimentation formula and vice versa. The undernourished cancer patient presented in Figure 5A was undergoing enteral hyperalimentation. Switching from a solid food diet that included meat, to a creatine-free formula caused a gradual reduction in urinary creatinine excretion. The decline in urinary creatinine output, however, was paralleled by strongly positive nitrogen balance, enlarging fat free body mass and an increasing arm muscle area. The reverse of



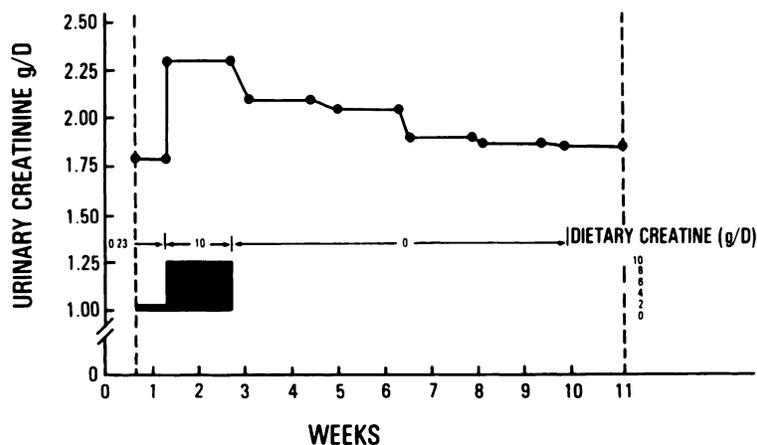


FIG 4. Influence of dietary creatine intake on urinary creatinine excretion. Figure 4 was prepared from the data presented in Reference 40.

this effect is seen in the anorexia nervosa patient depicted in Figure 5B, who was switched from a creatine-free hyperalimentation formula to a general hospital diet that included meat.

The third component of the diet that influences creatinine excretion, mentioned above, is creatinine. Dietary creatinine undergoes intestinal absorption and prompt renal excretion (25, 55).

When applying the creatinine muscle mass method to assess muscle mass in human subjects, most, if not all these dietary factors can be eliminated if subjects are placed on a low creatine, meat-free diet with 60 to 80 g of protein per day. Most relevant, however, is that the diet be constant, and not changed from one type to another during the period of study.

Menstrual cycle

Studies by Smith (56) demonstrated a rise and fall in creatine and creatinine excretion during the menstrual cycle, but changes were apparently unrelated to estrogen levels. He showed in repeated studies that creatinine excretion increased by 5 to 10% late in the second half of the menstrual cycle, and then decreased in the days preceding or during menstrual flow.

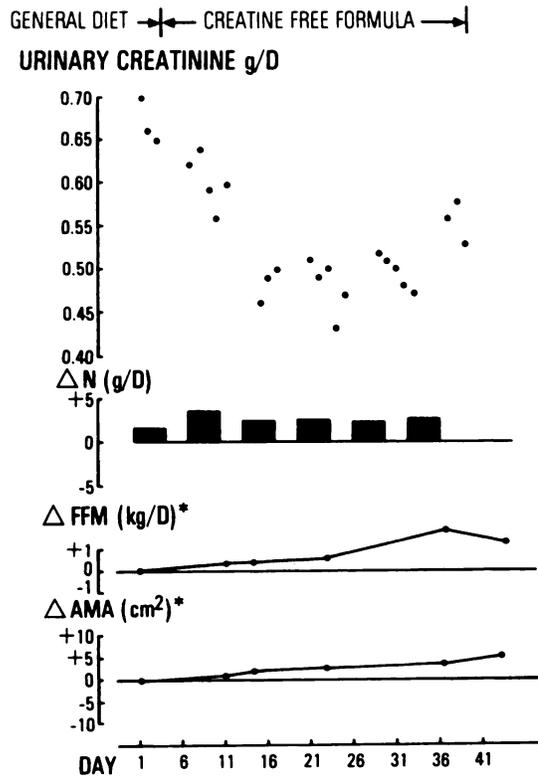
Aging

In the adult, fat free body mass declines with increasing age, and most of this loss in

lean tissue can be attributed to the atrophy of skeletal muscle (57). Creatinine excretion also declines with age, and this presumably reflects the diminution in muscle mass (57). Dietary factors might also account for some of the decrease in urinary creatinine with age, as the elderly tend to eat less meat. It is unknown if the reduction in creatinine excretion found in the elderly is in proportion to the loss in muscle mass, and it also has not been established how each of the terms in equation 3 (Table 2) is specifically influenced by senescence. The age dependency of the creatinine equivalence is therefore unknown.

Infection, fever, and trauma

Waterlow et al (58) found increased creatinine turnover in rats suffering from lung abscesses, and concluded that the creatinine equivalence may no longer be valid in the presence of infection. The severe battle casualties studied by Frawley et al (59) showed an increase in creatinine excretion, but the daily output appeared to be independent of type, degree, or location of injury. Schiller et al (60) confirmed the studies of both Waterlow and Frawley by demonstrating a rise in creatinine excretion with both fever and severe trauma. In some patients, an increase of 20 to 100% in urinary creatinine excretion occurred in the immediate posttraumatic period (60-62). Therefore, in the acute phase of injury, other available indices of muscle mass (Table 1) should be applied.



A * Cumulative

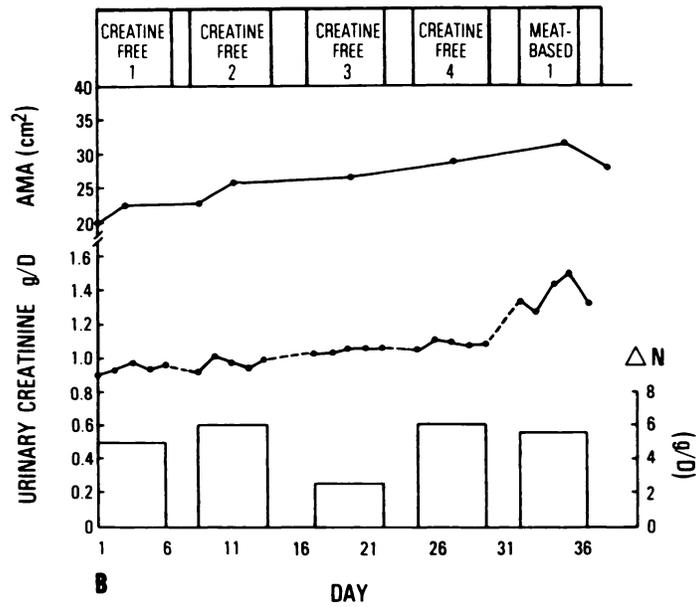


FIG 5. Influence on creatinine excretion when switching to and from a creatine-free hyperalimentation formula when the hospital diet contains meat. The undernourished cancer patient (A) and the anorexia nervosa patient (B) were undergoing enteral hyperalimentation. Abbreviations: FFM, fat free body mass; N, nitrogen.



Renal disease

As glomerular filtration rate falls in chronic renal failure, there is a decrease in the excretion of creatinine. Goldman (63) noted that the reduced output of creatinine is especially apparent when serum creatinine exceeds 6 mg/dl. Noting that muscle mass was not significantly decreased, Goldman suggested that the low output was due either to reduced creatinine production or an alternate excretory pathway. Jones and Burnett (64) investigated the "creatinine deficit" in patients with renal insufficiency, and found that 15.9 to 65.7% of creatinine formed in their subjects was metabolized or excreted via extrarenal routes. The studies of Mitch and coworkers (65, 66) also indicate metabolism rather than excretion of creatinine. These workers identified two pathways of creatinine catabolism; a recycling of creatinine to creatine, and intestinal degradation of creatinine to products other than creatine. In advanced renal disease, therefore, the creatinine equivalence method should be avoided.

Section summary

Table 5 summarizes factors other than muscle mass which influence daily creatinine excretion. The accuracy of predicting muscle mass from urinary creatinine excretion for each individual depends on the contribution of these seven factors, and on individual genetic differences in creatine metabolism. Little information is available on the latter subject.

TABLE 5
Factors that influence daily urinary creatinine excretion other than changes in muscle mass

Condition	Magnitude of effect
Normal daily variation	±4 to 8%
Very strenuous exercise	+5 to 10%
Emotional stress	±5 to 10%
Diet: switching from meat diet to creatine-free diet or vice versa	±10 to 30%
Menstrual cycle: minimum during menstrual flow, maximum second half of cycle	+10 to 15%
Renal disease: serum creatinine >2 mg/dl <6 mg/dl	*
≥6 mg/dl	↓†
Severe infection, high fever, trauma	+20 to 100%†

* Magnitude unknown.

† Magnitude and duration variable.

Experimental studies of the creatinine-muscle mass method

Although the assumptions of the creatinine-muscle mass method presented previously appear generally valid, the basic question has yet to be addressed: Does the 24-h urinary creatinine excretion correlate with muscle mass? If there was a simple answer to this question, our review would have little purpose. Since no one has yet examined the literature on this subject, we now proceed with this task. Our discussion is divided into animal and human studies.

Animal studies

Garn (67) has emphasized the advantages of animal studies. The investigator can create a homogeneous study group by selecting animals that are similar in age and genetic background, and who are subjected to the same activity level and diet. These ideal conditions are rarely obtainable in human studies. Furthermore, animal studies have an additional advantage: muscle mass can be measured very exactly by direct carcass analysis.

The murine studies of Chinn (68) are the most relevant animal experiments to our discussion. Chinn found that muscle protein (carcass analysis) could be predicted within ±4.17% from 24-h urinary creatinine in three groups of adult rats differing in muscle mass: normally fed males and females, and males fed 50% of their normal diet.

Similar rat studies by Meador et al (69) and Graystone (11) confirm that under controlled laboratory conditions, creatinine excretion closely parallels muscle mass.

Human studies

Apart from the biological and dietary variability present in human studies, the most significant problem is that an independent, completely valid, noninvasive measure of muscle mass is unavailable. The validity or real variability of the creatinine-muscle mass method is thus difficult if not impossible to assess.

An additional problem is the use of different definitions of muscle mass. The latter issue deserves additional comment. In referring to "creatinine equivalence," nonmuscle creatine pools, because of their small contribution to creatinine output, are neglected.

For the most part, so are nonskeletal muscle sources of creatinine, such as heart, uterus, aorta, and other tissues with smooth muscle. Generally, the creatine concentration in these muscles is less than striated skeletal muscle (25). In nearly all studies, the creatinine output is determined from values appropriate for skeletal muscle, thus introducing a probable small bias due to creatinine which originates outside skeletal muscle.

The units used to express the creatinine equivalence also differ among authors. Skeletal muscle is composed of intra- and extracellular fluids and solids. Some, but not all workers refer to fat-free wet muscle, which is 2 to 5% less than whole wet muscle mass (WWM). Creatinine reflects the intracellular space of muscle tissue, so in addition some investigators express results per kg of intracellular or non-collagenous proteins (NCP). The creatinine equivalence is therefore presented per kg WWM, per kg fat-free wet muscle, and per kg NCP.

The final difference between the reviewed studies was diet. The feeding programs were described as creatine-free, low creatine, or general diets.

Hunter (36), in his classic monograph on creatine and creatinine, relates Bürger's (24)

calculation of the creatinine equivalence: "A normal man of 63.1 kg was assumed, on the basis of Vierordt's (70) figures, to possess 25.4 kg of muscle. The creatine content of this mass was taken to be 88.4 g, and 2 g more were allowed for the other organs of the body. The creatinine output of the subject averaged 1.36 g daily. From these data Bürger calculates that one gram of urinary creatinine per day corresponds to 22.9 kg of whole wet muscle. This result seems to involve an arithmetical error, and is admittedly an approximation." Talbot (71), applying a similar approach to literature values for the creatinine coefficient and Vierordt's data for muscle mass, found "one gram of urinary creatinine per day corresponds (on a general diet) for the infant to 17.8 kg, and for the man, to 17.9 kg of (whole wet) muscle" (Table 6).

Total body muscle mass is not required to calculate the creatinine equivalence from Table 2 equations and the data presented in Table 3. Substitution of creatine and phosphocreatine concentrations and turnover rates into equations 2 and 3 produce values of 17.55, 17.9, and 18.45 kg WWM/g of creatinine, and 3.12 and 3.41 kg NCP/g creatinine (Table 7). These estimates would apply to patients on a general diet. Somewhat

TABLE 6
Studies reporting the "creatinine equivalence"

Author	Method of deriving muscle mass	Study diet	Creatinine equivalence			Subjects	
			Average (range)	Units*			
				WWM	FFWM		NCP
Bürger (24)	Vierordt's dissection tables (70)	Not stated; presumably general	22.9†	X		None	
Talbot (71)	Vierordt's dissection tables (70)	General	17.9, 17.8 (13.5-31.6)	X		Children, adults	
Picou et al (8)	¹⁵ N-creatinine	Meat-free	18.6 (13.8-31.9)	X		Children recovering from PEM‡	
Kreisberg et al (9)	¹⁴ C-creatinine	General	16.2 (14.5-18.6)		X	Adults with chronic disease	
Graystone (11)	Isotopic method based on constant developed in rats.	Low creatine	20		X	Normal children	
Current review (Table 7)	Calculated equivalence from equations 2 and 3	General	17.55, 17.9, 18.45, 3.12, 3.41		X	X	

* WWM; FFWM, fat-free wet muscle; and NCP, all in g/kg.

† According to Hunter (36) there is a calculation error in Bürger's data.

‡ Protein-energy malnutrition.

TABLE 7
Examples of creatinine equivalence calculated from Table 2 equations and Table 3 data

Example	Table 2 equation	K ₁ *	K ₂ *	K*	Total Cr	Cr/P-Cr	Creatinine equivalence†	
							Kg WWM/g Crn	Kg NCP/g Crn
A	3	0.011	0.0264			1.19/2.74‡	17.9	
B	2			0.0169	3.91‡, 22§		17.55	3.12
C	3	0.011	0.0264			1.53/2.39‡ 8.3/12.9§	18.45†	3.41

Abbreviations: K, K₁, and K₂ are fractional breakdown rates of respectively total creatine, creatine, and phosphocreatine (Cr, P-Cr); Crn is creatinine.

* Day⁻¹.

† General diet.

‡ g/kg wet wt.

§ g/kg NCP.

higher values would be expected on a creatinine-free diet.

The "Talbot" creatinine equivalence presented above was widely quoted throughout the next decade. Graystone (11) later modified this value to 20 kg of fat-free wet skeletal muscle per g of urinary creatinine (Table 6). The initial observation that led Graystone to revise the creatinine equivalence was made by Cheek et al (72), who noted that the calculated muscle mass in children was 20% of body weight; this percentage was less than the figure of 25% established by the 19th century German anatomists. Cheek's explanation for this discrepancy was that these children were on a low creatine diet, and he therefore proposed an upward adjustment of the creatinine equivalence in order to compensate for the apparent low predicted muscle mass. Support for the new creatinine equivalence was subsequently provided by Graystone's animal studies (11). Investigating the 7-wk-old rat, she found that 56.7% of intracellular water was in muscle tissue, and muscle is about the same proportion of body weight in the young rat and child. This fraction was then applied to intracellular water measured in children in order to calculate total muscle water. Since the ratio of muscle water to muscle solids was known in vivo, muscle mass could then be calculated. Creatinine collections in the same children then allowed computation of the creatinine equivalence for muscle mass. Results were 21.0 and 20.8 for boys and girls, respectively. These values did not differ significantly from Cheek's estimated value of 20, and thereafter the latter remained the creatinine equivalence (11). The low creatine diet ingested by these

children no doubt increased the creatinine equivalence compared to Talbot's data.

A more recent method of measuring muscle mass in children and adults is by isotopic dilution of creatine. Picou et al (8), applying this method to children who had recovered from protein-energy malnutrition, found that total WWM varied between 15 and 37% of body weight, with a mean of 28%. One g of urinary creatinine on a meat-free diet corresponded to anywhere from 13.8 to 31.9 kg of WWM, with a mean (\pm SD) of 18.6 ± 6.6 kg.

In the study of Kreisberg et al (9), total wet fat-free muscle mass was evaluated in four adult patients on a general diet by isotopic dilution of ¹⁴C-creatine. The calculated creatinine equivalence was 16.2 kg fat free wet muscle per g urinary creatinine (range 14.5 to 18.6). Greatrex et al (10) have criticized the isotopic creatine-muscle mass method on the grounds that creatine concentration varies from muscle to muscle, and a single biopsy does not adequately account for this variability.

All methods of assessing muscle mass presented above were indirect. Studies from our center in a wide variety of normal and undernourished subjects indicated that anatomic muscle mass correlated strongly with urinary creatinine excretion (73). Figure 6 shows arm muscle area (AMA) calculated from mid-arm circumference and triceps skinfold thickness, plotted against 24-h urinary creatinine excretion. The subjects (n = 25) were on low creatine balance diets for 7 days, and plotted creatinine values are the average of days 4 to 7. Patients with pendulous or excessively large skinfolds were excluded, because anthropometric measure-

ments of muscle mass in these individuals is inaccurate. Although AMA correlated well with creatinine excretion in this study ($r = 0.94$, $p < 0.001$), no creatinine equivalence could be calculated from this type of analysis.

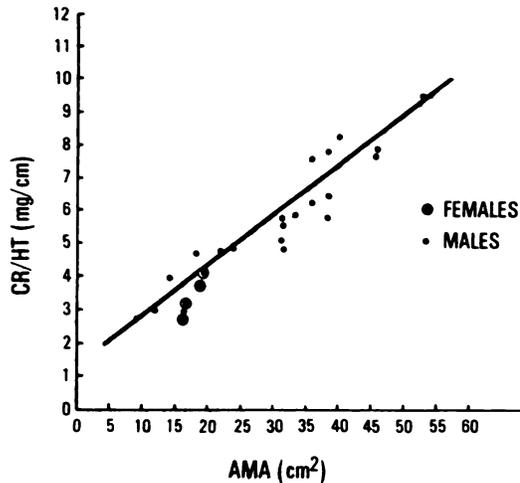


FIG 6. Correlation between urinary creatinine excretion (CR/HT) and AMA. The latter was measured anthropometrically. The data are for 25 subjects, $r = 0.94$, $p < 0.001$, $Y = 0.14 X + 1.32$. From Reference 73.

Figure 7 shows similar studies conducted longitudinally in patients losing ($n = 3$) or gaining weight ($n = 6$); again, the change in arm muscle area correlated reasonably well with the change in urinary creatinine. The data compiled in the Minnesota experiment (74) at 12 and 24 wk of semistarvation is also plotted in Figure 7, and agrees closely with our more recent data. The AMA, as calculated in the Minnesota experiment, included fat. We therefore assumed a base-line triceps skinfold thickness of 12 mm, and at 12 and 24 wk of semistarvation (S12 and S24) of 7 and 4 mm, respectively. Values for AMA were then recalculated according to the method of Heymsfield et al (73). Both the original and recalculated data provided qualitatively similar results. In a similar type of analysis, Standard et al (75) have shown a significant correlation ($r = 0.74$, $p < 0.001$) between muscle thickness and creatinine excretion in children recovering from protein malnutrition. The observed variability when comparing the two measures of muscle mass (anthropometric and biochemical) might be related to the inclusion of extracellular fluid and interfibrillar fat in the anthropometric

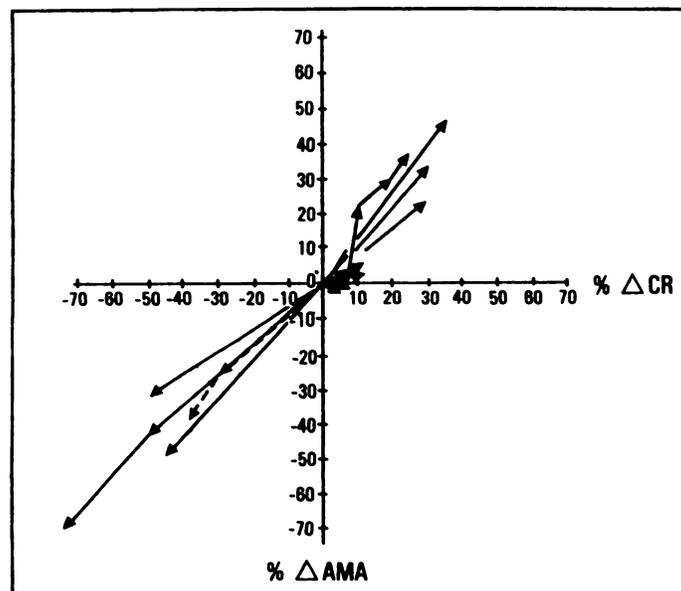


FIG 7. Longitudinal changes in arm muscle area (Δ AMA) and 24-h urinary creatinine excretion (Δ CR), both expressed as a percentage of base-line value. Subjects were losing weight secondary to cancer, or gaining weight during hyperalimentation. The *dashed line* represents the change in muscle mass observed during 12 and 24 wk of semistarvation in the Minnesota experiment (74).

method, the inaccuracies inherent in the anthropometric method (6, 73), and between subject differences in diet and creatine turnover rate.

From these human investigations it is concluded that: 1) studies differed in diet, health status of study subject, definition, and method of measuring muscle mass, 2) the creatinine equivalence in humans is not definitively established, 3) even if such an equivalence can be agreed upon, the SD around this average tentatively appears quite large, and 4) reliable estimates of the creatinine equivalence and associated variability will be forthcoming only when a definitive method of measuring muscle mass in vivo is available to clinical investigators. Such methods are now becoming available, but at the present are limited to only a few centers (2, 16).

Unlike muscle, lean body mass (LBM) can be measured accurately in the clinical setting; because muscle is roughly 30 to 50% of LBM, many workers have focused on the correlation of creatinine with accurately and easily measured LBM (76-79).

When LBM is correlated with creatinine, there is almost universal agreement that these two indices are closely related. Some variation in the predictive value of this relation is found by some authors, but the principal difference appears to be the precision with which urine samples were collected, and the number of urines analyzed.

Why should a precise relation between creatinine and LBM be found in the above mentioned human studies, while so much variability is found in the studies relating muscle mass directly to creatinine? Two possible explanations are offered. The first is that creatinine excretion may be a more accurate reflection of the total creatine pool (muscle plus other soft lean tissues), rather than the muscle creatine pool. The small contribution of nonskeletal muscle creatine to urinary creatinine has been discussed above. A second, and more likely explanation, is that LBM can be measured more accurately and reproducibly than muscle mass. A much larger number of subjects have therefore been examined, and usually under much more carefully controlled dietary conditions. It would therefore seem likely that a very carefully controlled study (diet, activity, absence of stress or dis-

ease, adequate number of urine collections) correlating creatinine with some as yet undeveloped or unverified accurate in vivo measure of muscle mass would provide a creatinine equivalence with minimum variability.

Conclusions and summary

The collective review of the literature allows us to draw the following conclusions.

1) If an individual consumes the same amount of a constant composition diet, creatinine output in the urine is proportional to muscle mass.

2) Changing from a meat diet to a creatine-free diet and vice versa causes readjustment over time in the size of the creatine pool. The result is a change in urinary creatinine excretion that is independent from changes in muscle mass. Diet therefore must remain reasonably constant.

3) Other than dietary factors, the variability in the creatinine-muscle mass relationship is due to normal daily variation in creatinine excretion; variability is increased by severe emotional stress, by sampling during different phases in the menstrual cycle, and by very vigorous exercise. Collecting several consecutive 24-h specimens, and ensuring a minimum of emotional stress and physical activity can eliminate some of the variation in creatinine excretion.

4) Severe renal insufficiency, acute infection, or the early phases of major injury are conditions in which creatinine output is not proportional to muscle mass. Quantifying muscle mass in these patients should be accomplished by other methods. A notable problem however, is that not all of the methods listed in Table 1 are clinically available, and of those that are, most have limitations that also limit their accuracy.

5) The creatinine equivalence is roughly 17 to 20 kg muscle per g of creatinine, but the variability and precision of these estimates remain uncertain. The value is higher on a creatine-free diet, and lower for a meat diet. Converting creatinine to muscle mass may thus serve as an approximation, but should not be considered a definitive appraisal of muscle mass.

6) In the evaluation of selected patients,

creatinine can be compared to serial samples collected over time to establish trends (assuming diet remains fairly constant), or compared directly to "standard" tables based on age, sex, stature, and diet (80, 81). The comparison to reference tables provides an estimate of the "percent of standard" muscle mass.

In summary, the use of urinary creatinine excretion as an index of muscle mass is conceptually interesting, and the method may provide useful information in carefully selected subject groups. There remains, however, a large group of individuals in whom the method cannot be reliably applied. For example, what set of reference values should be used in the athlete who ingests an unusually large amount of meat in his/her diet, or in the cancer patient with reduced food (ie, creatine) intake secondary to anorexia? How can change in muscle mass in the latter patient be accurately followed over time, when food intake may vary with exacerbation and remission of disease? There is little question that the assumptions of the creatinine-muscle mass method are invalid in the early phase of injury, and in the presence of fever and infection. Since undernutrition and muscle atrophy are often found in patients in whom the creatinine-muscle mass method is inaccurate, a priority research focus should be the development and validation of accurate and practical methods of measuring muscle mass in these individuals. 

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