Chronic cellular dehydration in the aged patient.

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OBJECTIVES : Investigate body water space and cellular hydration in elderly patients.

DESIGN : Open study.

SETTING : Geriatric wards and nutrition laboratory.

PARTICIPANTS : Aged diseased persons (n = 85, 80.5 ± 1.0 yrs, mean ± SEM) healthy elderly persons (n = 68, 66.1 ± 0.6 yrs) and healthy adults (n = 35, 38.1 ± 1.4 yrs).

MEASUREMENTS : Total body water (TBW, $H_2\,^{18}0$ dilution), extracellular water (ECW, Bromide dilution), intracellular water (ICW = TBW – ECW) fat-free mass (FFM, Siri's equation).

RESULTS : FFM, TBW, and ICW were highest in adults than in the two other groups and in the elderly than in aged patients. ECW was higher in aged patients than in healthy elderly participants. The proportion of TBW made of ECW or ICW was the same in adults and in healthy elderly persons. A higher proportion of TBW was composed of ECW, and a lower proportion of ICW in diseased patients compared to the two other groups. The proportion of ICW in body cell mass was also lower in diseased patients.

CONCLUSIONS : Diseased elderly persons display reduced intracellular water and expanded extracellular water. A cellular dehydratation is suggested.

INTRODUCTION

Hydration at the cellular level is an important factor in health and disease, and a key metabolic signal as overhydration can trigger anabolism and cell shrinkage leads to catabolism (1,2). Cellular dehydration promotes the toxicity of drugs with an intracellular distribution. It is widely believed that nearly all diseases result in increased hydration of the body, particularly in the critically ill (3-6). However, dehydration is a frequent life-threatening disorder in the elderly (7).

Total body water (TBW) is the sum of extracellular water (ECW) and intracellular water (ICW), which is mainly contained in fat-free mass (FFM). There is unfortunately no direct means of measuring ICW, which is calculated by subtracting ECW from TBW. Because of the well-known age-related decline in FFM, TBW and ICW are decreased in the elderly (8). However, increases in the relative amounts of ECW (9), and large between-subject variations in the ratio of TBW over FFM, a proxi-measurent of cellular hydratation (10,11) have been reported in the elderly. Furthermore, intracellular water has been shown to be decreased in clinical situations where total body water is increased, such as uremia, post-trauma, or cirrhosis (12, 13). In all the studies listed above, the changes in intracellular water could arise from loss of body cell mass and/or cellular dehydration. Cellular dehydration has been described in the critically ill (13).

As little is known about cellular hydration in the elderly, the present study investigated water spaces (as measured by state-of-the-art tracer dilution techniques) and cellular hydration (i.e. the proportion of ICW in body cell mass) in subjects of varying age and health status.

MATERIALS AND METHODS

1 - Subjects

One hundred and eighty-six volunteers participated in this study after giving written informed consent. The protocol was approved by the local ethics committee and the French Ministry of Health. Subjects were divided into three groups : i) healthy adults (HA, n = 35) < 55 years, ii) healthy elderly volunteers (HE, n = 68) > 60 years, iii) aged patients (AP, n = 83). Healthy subjects were free of any disease or treatment that might interfere with hydration. Aged patients were recruited consecutively in six geriatric wards. All patients were eligible, but those requiring intensive care (sepsis, surgery, acute organ failure), showing massive overhydration (ascites), receiving artificial nutrition, or at the end of life were excluded. On the basis of plasma sodium concentration and/or edema, 23 patients were considered dehydrated, 27 overhydrated, and 33 normally hydrated. The group of elderly patients was therefore fairly representative of the population in a geriatric ward. The proportion of dehydrated patients was slightly less than expected because cognitive impairment related to dehydration made it impossible to obtain written informed consent.

2 - Anthropometric measurements

Body weight was measured in light clothing to the nearest 0.1 kg on Seca scales (Seca, Les Muraux, France). Height was measured to the nearest 0.2 cm, except for patients unable to stand, for whom calculations were based on knee-height according to Chumlea (14). Body fat was calculated from skinfold thickness according to Durnin and Womersley (15) using Siri's three-compartment equation (16) :

$$\% \text{ fat} = 100 \times (2.11/d - 0.78\, w - 1.354)$$

where d is total body density estimated from skinfold thickness and w the ratio of total body water to weight. Fat-free mass was calculated from body weight and % fat. Fat-free mass was the sum of body cell mass, extracellular fluid (98% of which is extracellular water), and extracellular solids. A proxi measurement of body cell mass is therefore the difference between fat-free mass and extracellular water.

3 - Body water spaces

After an overnight fast (≈ 12 hours), volunteers provided plasma and urine samples, for natural abundance determinations of ^{18}O-enrichments and bromide concentrations. They then received an oral dose of 2 % ^{18}O enriched water (≈ 50 g water) and potassium bromide (≈ 1 g bromide), as described by Vaché et al (17,18). Another sample was collected 4 and 5 hours post-dose. All samples were kept at - 20° until analysis. Tracer concentrations were measured by isotope ratio mass spectrometry (17) and HPLC (19). Total body water was calculated from ^{18}O enrichments (20), and extracellular water from bromide concentrations (19). Intracellular water was the difference between TBW and ECW.

STATISTICAL METHODS

Results are expressed as the mean ± SEM. Comparisons of means were performed by one-way analysis of variance after having checked for normality of distributions. The post-hoc test was Fisher PLSD. Analysis of covariance was performed as described by Zar (21). Significance was accepted at the 5 % level. Calculations were performed with Statview 4.0 Statistical Package (Abacus Concept, CA), except for analysis of covariance conducted with an homemade software.

RESULTS

The physical characteristics of volunteers and patients are shown in table 1. Healthy adults had significantly more fat-free mass and less fat mass than subjects from the other two groups. Aged patients had significantly lower weight and fat-free mass than healthy elderly volunteers.

Water spaces in absolute values (litres, Table 1). TBW and ICW were significantly higher in adults than in healthy elderly subjects, and in healthy elderly subjects than in aged patients. ECW was significantly higher in adults than in healthy elderly subjects, and similar between adults and aged patients. ECW was significantly higher in aged patients than in healthy elderly subjects.

Proportions of ECW and ICW in TBW. Figure 1 shows a significant linear relationship between ECW (Panel A) or ICW (Panel B) and TBW in all categories of subjects. The slopes of these relationships did not differ significantly between the 3 groups. Adjusted means were not significantly different between adults and healthy elderly subjects both for ECW and for ICW.

However, ICW adjusted for differences in TBW was lower in aged patients than in the other two groups. Conversely, adjusted ECW was higher in aged patients than in the other two groups.

Cellular hydration. Figure 2 shows the significant linear relationship between ICW and FFM in the three categories of subjects. The slopes of these lines did not differ. ICW adjusted for differences in FFM was not significantly different between adults and healthy elderly subjects ($t = 0.57$) but significantly lower in aged patients than in the other two groups ($p < 0.0001$). Even when differences in ECW where taken into account, aged patients had a lower ICW per unit of FFM – ECW, a proxi measurement of body cell mass ($p < 0.0001$).

LEGENDS FOR FIGURES

Figure 1 : Relationship between ECW (Panel A) or ICW (Panel B) and TBW in the three categories of subjects. Slopes were significantly different from zero (R^2 between 0.34 and 0.70 for ECW, and between 0.51 and 0.81 for ICW), and did not differ between groups. Adjusted mean ECW were higher, and ICW lower in aged patients than in the other two groups.

Figure 2 : Relationship between ICW and FFM in the three categories of subjects. Slopes were significantly different for zero (R^2 between 0.47 and 0.81), but did not differ between groups. Adjusted ICW for differences in FFM was significantly lower in aged patients than in the other two groups.

Table 1. Physical characteristics of the volunteers

	Healthy adults (n = 35)	Healthy elderly subjects (n = 68)	Aged patients (n = 83)	One-way ANOVA P
Age (yr)	$38.1 \pm 1.4^{a,3}$	$66.1 \pm 0.6^{b,3}$	$80.5 \pm 1.0^{c,3}$	< 0.0001
Weight (kg)	70.3 ± 1.5	$69.1 \pm 1.3^{b,3}$	$62.1 \pm 1.5^{c,3}$	0.0003
Height (cm)	$174.2 \pm 0.9^{a,3}$	$162.9 \pm 1.0^{b,2}$	$158.7 \pm 1.1^{c,3}$	< 0.0001
BMI ($kg.m^{-2}$)	$23.1 \pm 0.4^{a,3}$	$26.0 \pm 0.4^{b,1}$	24.5 ± 0.5	0.0009
FFM (kg)	$56.4 \pm 1.0^{a,3}$	$46.1 \pm 1.1^{b,3}$	$41.8 \pm 1.1^{c,3}$	< 0.0001
% fat	$19.6 \pm 0.7^{a,3}$	33.3 ± 1.1	$32.0 \pm 1.0^{c,3}$	< 0.0001
TBW (l)	$41.3 \pm 0.7^{a,3}$	$33.9 \pm 0.8^{b,3}$	$29.7 \pm 0.7^{c,3}$	< 0.0001
ECW (l)	$18.3 \pm 0.5^{a,3}$	$15.1 \pm 0.4^{b,2}$	17.1 ± 0.5	0.0002
ICW (l)	$23.1 \pm 0.7^{a,3}$	$18.8 \pm 0.5^{b,3}$	$12.6 \pm 0.5^{c,3}$	< 0.0001

Significant difference between healthy adults and elderly (a) or aged patients (c), between healthy elderly and aged patients (b). 1 < 0.05, 2 $p < 0.01$, 3 $p < 0.001$) – BMI : body mass index ; FFM : fat-free mass ; TBW : total body water ; ECW : extracellular water ; ICW : intracellular water ; ANOVA : analysis of variance.

DISCUSSION

The main results of the present study are that water spaces differed between age and disease categories, but remained in the same proportion to TBW and FFM in adults and healthy elderly subjects which suggests that cellular hydration is preserved during healthy aging. However, in aged patients a higher proportion of TBW was composed of ECW, and a lower proportion of ICW. This study also suggests chronic cellular dehydration in aged patients since the proportion of ICW to FFM was decreased.

The conclusions reached were based on measurements of ICW and fat-free mass, ICW being calculated as TBW minus ECW. There is little doubt that ^{18}O is the best probe for measuring TBW (8, 20). However, the validity of bromide as an extracellular tracer may be questionable, especially in diseased patients. For our purposes, the usual 10 % intracellular penetrance of bromide was assumed (19). Finn et al (13), Kim et al (22) and Brennan et al (12) have shown that intracellular penetrance of bromide was not appreciably changed in the critically ill, AIDS, and uremia patients. Therefore, it is safe to consider that bromide is confined to ECW, provided that the 10 % correction is made. In any case, a slightly greater intracellular penetrance of bromide could not account for the 33 % difference in ICW observed between healthy elderly subjects and aged patients. This validates the altered fluid homeostasis found in aged patients. Our second important conclusion (genuine cellular dehydration) was based on fat-free mass estimates. Most of the techniques for measuring fat-free mass assume that its hydration (the ratio of TBW to fat-free mass) is known and constant. Age-related changes in this ratio are debatable (10, 11), and it has been found to vary greatly between individuals, especially in diseased patients (5, 10). Siri's three-compartment equation (16) includes a measured « hydration component » that makes the estimate of % fat (hence fat-free mass) accurate even in situations in which hydration of fat-free mass is not standard (23). In young and old persons, the accuracy of Siri's model is 0.2 % compared to state-of-the-art techniques. Therefore our estimates of FFM are likely to be accurate.

Aging is associated with a decline in FFM (24) (which contains most ICW) and an increase in fat-mass (which contains very little water, and shows a 4 : 1 ratio of ECW to ICW, (25)). Therefore, a decrease in TBW, ECW, and ICW (expressed in litres) in elderly subjects is to be expected. Expression of results relative to TBW (and not to body weight) avoids the influence of fatness. The present study shows that healthy elderly subjects did not display significant variations in the proportion of water spaces to TBW and FFM, i.e. there was no cellular dehydration.

Our study suggests that a genuine cellular dehydration occurs in aged patients. Even after accounting for the expected decrease in TBW, ICW expressed per unit fat-free mass (or per unit of a proxi measurement of body cell mass) was lower in aged patients than in healthy elderly subjects. As aged patients were older than healthy elderly subjects, an effect of age independent of disease cannot be ruled out in the very elderly. However, this seems unlikely from the comparison between adults and healthy elderly subjects.

Flear and Singh (26) have proposed the "sick cells" theory whereby cell membrane function is probably altered in disease, particularly regulation of osmolarity, causing fluid shifts. The determinants of this alteration are not known. Haussinger et al (1, 2) stated that factors such as inflammation, amino-acid starvation and stress result in hormonal alterations (low insulin, high glucagon and cathecholamines) that could favour cell shrinkage. However, even if this theory is true, it is difficult to tell the chicken from the egg. Cellular dehydration could be the key signal for catabolism, hence for metabolic adaptation to stress, or, cellular catabolism could draw osmolytes (glutamine, potassium, etc) and therefore water outside the cell.

An increase in ECW, together with a decrease in ICW (in proportion to TBW), could also result from malnutrition (27-31). The more dramatic the wasting, the higher the ratio

ECW/ICW appears to be [27-29]. Furthermore, in some (28) but not all studies (31) nutritional repletion decreased the ECW/ICW ratio. In the present study, the similarity of % fat in healthy elderly subjects and aged patients excludes this explanation for differences in ECW. Therefore the relationship between disease, wasting and fluid homeostasis is probably more complex requiring further studies.

In conclusion, aged patients displayed chronic cellular dehydration associated with relative extracellular overhydration, which did not seem to be related to aging per se since healthy elderly subjects and adults had similar water spaces distributions. This is an important issue because of the frequency of body fluid imbalance in elderly patients. Therefore, increased ECW might mask cellular dehydration, while cellular dehydration could predispose to fast dehydration in the case of water imbalance. This imbalance in body fluid is also important for the pharmacology of the elderly. Extracellular overhydration can dilute drugs artificially and bias plasma monitoring, whereas cellular dehydration could increase drug toxicity. Finally, cell shrinkage might be a catabolic signal (1). Improving cellular hydration could be viewed as a means of improving nutritional status.

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