Chronic Cellular Dehydration in the Aged Patient

Patrick Ritz and the Investigators of the Source Study and of the Human Nutrition Research Centre-Auvergne

Background. As a reduction of water spaces is expected in the elderly because of fat-free mass loss, disease is often associated with increased hydration. The present study compared water spaces and cellular hydration in adults, healthy and diseased aged patients.

Methods. An open study was conducted in 6 geriatric wards and a nutrition laboratory involving 85 aged persons. Total body water (TBW, H\textsubscript{2}O dilution), extracellular water (ECW, Bromide dilution), and fat-free mass (FFM, body density and Siri’s equation) were measured directly whereas intracellular water (ICW = TBW – ECW) and body cell mass (FFM – ECW) were obtained by calculations.

Results. FFM, TBW, and ICW were higher in adults than in the 2 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 TBW was composed of ICW, in diseased patients compared with the 2 other groups. The proportion of ICW in body cell mass was also lower in diseased patients.

Conclusions. Diseased elderly persons display reduced ICW and expanded ECW. A cellular dehydration is suggested.

Hydration at the cellular level is an important factor in health and disease and is a key metabolic signal because 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 elderly persons (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 elderly persons (8). However, increases in the relative amounts of ECW (9) and large between-subject variations in the ratio of TBW to FFM, a proxy measurement of cellular hydration (10,11), have been reported in elderly subjects. Furthermore, ICW has been shown to be decreased in clinical situations where TBW is increased, such as uremia, post-trauma, or cirrhosis (12). In all the studies listed above, the changes in intracellular water could arise from the loss of body cell mass and/or cellular dehydration. Cellular dehydration has been described in critically ill patients (2).

Because little is known about cellular hydration in elderly persons, 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 FFM) in subjects of varying age and health status.

Materials and Methods

Subjects
A total of 186 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 of age, (ii) healthy elderly volunteers (HE, n = 68) >60 years of age, and (iii) aged patients (AP, n = 83). Healthy subjects were free of any disease or treatment that might interfere with hydration. AP were recruited consecutively in six geriatric wards. All patients were eligible, but those requiring intensive care (those with sepsis, acute organ failure, or those having undergone surgery), 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.

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 and colleagues (13).
Body fat was calculated from skinfold thickness according to Durnin and Womersley (14) using Siri’s (15) three-compartment equation

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

where d is total body density estimated from skinfold thickness, and w is the ratio of TBW to weight. FFM, calculated from body weight and percentage of fat, was the sum of body cell mass, extracellular fluid (98% of which is ECW), and extracellular solids. A proximal measurement of body cell mass was therefore calculated as the difference between FFM and ECW.

**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 and colleagues (16,17). Another sample was collected 4 and 5 hours postdose. All samples were kept at \(-20^\circ\) until analysis. Tracer concentrations were measured by isotope ratio mass spectrometry (\(^{18}\)O) (16) and high pressure liquid chromatography (17,18). TBW was calculated from \(^{18}\)O enrichments (19), and ECW was calculated from bromide concentrations (18). ICW was calculated as the difference between TBW and ECW.

**Statistical Methods**

Results are expressed as mean ± SEM. Comparisons of means were performed by one-way analysis of variance (ANOVA) after checking for normality of distributions. The post hoc test was Fisher PLSD. Analysis of covariance (ANCOVA) was performed as described by Zar (20). Significance was accepted at the .05 level. Calculations were performed with the Statview 4.0 Statistical Package (Abacus Concept, Berkeley, CA), except for ANCOVA, which was conducted with homemade software.

**RESULTS**

The physical characteristics of the volunteers and patients are shown in Table 1. HA had significantly more FFM and less fat mass than subjects from the other two groups. AP had significantly lower weight and FFM than HE.

**Water Spaces in Absolute Values**

TBW and ICW were significantly higher in HA than in HE and were higher in HE than in AP. ECW was significantly higher in HA than in HE and was similar between HA and AP. ECW was significantly higher in AP than in HE.

**Proportions of ECW and ICW in TBW**

Figure 1 shows a significant linear relationship between ECW (A) or ICW (B) and TBW in all categories of subjects. The slopes of these relationships did not differ significantly between the three groups. Adjusted means were not significantly different between HA and HE for both ECW and ICW. However, ICW, adjusted for differences in TBW, was lower in AP than in the other two groups. Conversely, adjusted ECW was higher in AP 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 HA and HE (t = .57) but was significantly lower in AP than in the other two groups (p < .0001). Even when differences in ECW where taken into account, AP had a lower ICW per unit of FFM minus ECW, a proximal measurement of body cell mass (p < .0001).

**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 HA and HE, which suggests that cellular hydration is preserved during healthy aging. However, in AP, a higher proportion of TBW was composed of ECW and a lower proportion of ICW. This study also suggests chronic cellular dehydration in AP because the proportion of ICW to FFM was decreased.

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Table 1. Physical Characteristics of the Volunteers

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Healthy Adults (n = 35)</th>
<th>Healthy Elderly Subjects (n = 68)</th>
<th>Aged Patients (n = 83)</th>
<th>One-way ANOVA p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>38.1 ± 1.4***</td>
<td>66.1 ± 0.6***</td>
<td>80.5 ± 1.0***</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.3 ± 1.5</td>
<td>69.1 ± 1.3***</td>
<td>62.1 ± 1.5***</td>
<td>.003</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174.2 ± 0.9***</td>
<td>162.9 ± 1.0***</td>
<td>158.7 ± 1.1***</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.1 ± 0.4***</td>
<td>26.0 ± 0.4***</td>
<td>24.5 ± 0.5</td>
<td>.0009</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>56.4 ± 1.0***</td>
<td>46.1 ± 1.1***</td>
<td>41.8 ± 1.1***</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Fat (%)</td>
<td>19.6 ± 0.7***</td>
<td>33.3 ± 1.1</td>
<td>32.0 ± 1.0***</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>TBW (l)</td>
<td>413 ± 0.7***</td>
<td>339 ± 0.8***</td>
<td>29.7 ± 0.7***</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>ECW (l)</td>
<td>183 ± 0.5***</td>
<td>151 ± 0.4***</td>
<td>17.1 ± 0.5</td>
<td>.0002</td>
</tr>
<tr>
<td>ICW (l)</td>
<td>231 ± 0.7***</td>
<td>188 ± 0.5***</td>
<td>12.6 ± 0.5***</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

*Note: BMI = body mass index; FFM = fat-free mass; TBW = total body water; ECW = extracellular water; ICW = intracellular water; ANOVA = analysis of variance.*

†Significant difference between healthy adults and elderly patients.

‡Significant difference between healthy elderly adults and aged patients.

§Significant difference between healthy adults and aged patients.

*p < .05; **p < .01; ***p < .001.
The conclusions were made on the basis of measurements of ICW and FFM, ICW being calculated as TBW minus ECW. There is little doubt that $^{18}$O is the best probe for measuring TBW. 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 (18). Finn and colleagues (2), Kim and colleagues (21), and Brennan and colleagues (12) have shown that the intracellular penetrance of bromide was not appreciably changed in critically ill patients, AIDS patients, 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 HE and AP. This validates the altered fluid homeostasis found in AP. Our second important conclusion (genuine cellular dehydration) was made on the basis of FFM estimates. Most of the techniques for measuring FFM assume that its hydration (the ratio of TBW to FFM) is known and constant. Age-related changes in this ratio are debatable (10,11), and the ratio has been found to vary greatly between individuals, especially in diseased patients (5,10). Siri’s (15) three-compartment equation includes a measured “hydration component” that makes the estimate of the percentage of fat (hence FFM) accurate even in situations in which hydration of FFM is not standard (22). In young and old persons, the accuracy of Siri’s (15) model is 0.2% compared with state-of-the-art techniques. Therefore, our estimates of FFM are likely to be accurate.

Aging is associated with a decline in FFM (which contains most of the ICW) and an increase in fat mass (which contains very little water and shows a 4:1 ratio of ECW to ICW) (23). Therefore, a decrease in TBW, ECW, and ICW 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 HE 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 FFM (or per unit of a proximate measurement of body cell mass) was lower in AP than in HE. Because AP were older than HE, an effect of age independent of disease cannot be ruled out in the very elderly. However, this seems unlikely from the comparison between HA and HE.

Flear and Singh (24) 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 and colleagues (1) stated that factors such as inflammation, amino-acid starvation, and stress result in hormonal alterations (low insulin, high glucagon, and catecholamines) that could favor cell shrinkage. However, even if this theory were true, it would be difficult to tell the chicken from the egg. Cellular dehydration could be the key signal for catabolism and 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 (25–29). The more dramatic the wasting, the higher the ECW/ICW ratio appears to be (25,27). Furthermore, in some (26) but not all studies (29), nutritional repletion decreased the ECW/ICW ratio. In the present study, the simi-
larity of the percentage of fat in HE and AP excludes this explanation for differences in ECW. Therefore, the relationship between disease, wasting, and fluid homeostasis is probably more complex and requires further study.

In conclusion, AP displayed chronic cellular dehydration associated with relative extracellular overhydration, which did not seem to be related to aging per se because HE and HA had similar water space distributions. This is important because of the frequency of body fluid imbalance in elderly patients. Therefore, increased ECW might mask cellular dehydration whereas 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 elderly patients. 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. Improving cellular hydration could be viewed as a means of improving nutritional status.

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References


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