

TOTAL BODY WATER AND INTRACELLULAR WATER RELATIONSHIPS WITH MUSCLE STRENGTH, FRAILTY AND FUNCTIONAL PERFORMANCE IN AN ELDERLY POPULATION. A CROSS-SECTIONAL STUDY

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Abstract: *Background:* As a person ages, total body water (TBW), intracellular water (ICW), muscle mass and muscle strength tend to decline. The decline in ICW may reflect losses in the number of muscle cells but may also be responsible for less hydrated muscle cells. *Aim:* To assess whether TBW and ICW are associated with muscle strength, functional performance and frailty in an aged population, independently of muscle mass. *Methodology: Design:* An observational cross-sectional study of community-dwelling individuals aged 75 years and older. TBW, ICW, fat mass, lean mass and muscle mass were assessed by bioelectrical impedance analysis, frailty status was measured according to Fried criteria, handgrip strength was measured using the hand-held JAMAR dynamometer, and functional performance was measured according to the Barthel index and gait speed. *Results:* A total of 324 subjects were recruited (mean age 80.1 years, 47.5% women). TBW and ICW were closely correlated with muscle mass in both sexes. ICW was also associated with Barthel score, gait speed and frailty in both sexes and with handgrip in men. Considerable variability in ICW was observed for the same muscle mass. Multivariate analysis showed a positive effect of ICW on handgrip, functional performance and gait speed and a protective effect of ICW on frailty, independently of age, sex, body mass index and number of comorbidities. *Conclusions:* In elderly individuals with similar muscle mass, those with higher ICW had a better functional performance and a lower frailty risk, suggesting a protective effect of cell hydration, independently of muscle mass.

Key words: Total body water, intracellular water, ageing, muscle mass, muscle strength, frailty, functional performance.

Introduction

Water is the main component of human body and represents approximately 60% of body weight in adult men and 50%-55% in adult women (1). Water content in lean body mass and in adipose tissue is about 73% and 10%, respectively. Older persons, women and obese individuals have lower total body water (TBW) because of their lower lean body mass. Water is distributed in the body as intracellular water (ICW) and extracellular water (ECW), which mainly includes plasma fluid and interstitial fluid. Fluid exchange between compartments is regulated by osmotic and hydrostatic pressure, with water flowing according to changes in extracellular fluid osmolarity (2). Water has fundamental functions in the body: a) it provides structure for cells and body fluids; b) it acts as a reaction medium and solvent and also as a reactant in body metabolism; c) it transports nutrients in the blood and interstitial fluid and transports waste in the urine; and d) it helps control body temperature through sweat evaporation (3). Water losses mainly occur in urine and sweat, but also through the faeces, skin and respiration. Water inputs mainly come from diet (food and fluids) but small quantities also come from body metabolic activity. Water balance in the body is tightly regulated by the kidneys, which can concentrate or dilute urine depending on metabolic wastes and water intake (2).

The water content of muscle, which represents the major component of body weight, is about 76%, so water losses may affect muscle function. It is known that moderate acute water losses (2%-3% of body weight) can produce fatigue and weakness, and can also alter mental state, inducing memory loss and affecting mental and psychomotor skills (4, 5). However, the effects of small but gradual losses of water observed with age are not well known. Water loss may be the result of a parallel decline in muscle mass, but may also be a contributor to muscle function impairment due to muscle cell dehydration (6). We hypothesize that the slow and gradual water losses that occur with age may be partially responsible for muscular weakness, functional impairment and frailty. The aim of this study was to assess if TBW and ICW are associated with muscle weakness, frailty and impaired functional performance in an aged population, independently of muscle mass, age, sex and body mass index (BMI).

Methodology

Study design and population

An observational cross-sectional study was performed of community-dwelling subjects aged 75 years and older. A sample was randomly selected from the database of 3 primary care centres in the city of Mataró (Barcelona, Spain).

Table 1

Total body water (TBW) and intracellular water (ICW) for the overall sample and by sex: correlations with muscle mass, muscle strength, Barthel index score and gait speed, and association with frailty

	Muscle mass		Handgrip (kg)		Barthel index		Gait speed (m/s)		Frailty		
	r	p	r	p	r	p	r	p	Yes	no	p
<i>All individuals</i>											
TBW (%)	0.89	<0.001	0.62	<0.001	0.34	<0.001	0.34	<0.001	49.1%	53.3%	<0.001
ICW (%)	0.60	<0.001	0.40	<0.001	0.33	<0.001	0.31	<0.001	48.9%	51.4%	<0.001
<i>Women</i>											
TRW (%)	0.80	<0.001	0.13	0.116	0.22	0.006	0.16	0.042	47.4%	48.6%	0.117
ICW (%)	0.44	<0.001	0.13	0.102	0.25	0.002	0.25	0.002	48.7%	50.2%	0.027
<i>Men</i>											
TBW (%)	0.71	<0.001	0.02	0.766	0.16	0.034	0.21	<0.001	54.5%	56.9%	0.110
ICW (%)	0.60	<0.001	0.20	0.010	0.24	0.002	0.26	0.001	49.4%	52.4%	0.018

Muscle mass as % of total body weight. r: Pearson correlation coefficient.

Selected subjects were invited to participate if they were not institutionalized, did not have active malignancy, dementia or serious mental illness and had a life expectancy greater than 6 months. Recruitment took place from January to July 2014. Study design details have been reported elsewhere (7). The hospital research ethics committee approved the study protocol (code 64/13) and all participants signed an informed consent form before inclusion.

Study factors and data collection

The main study factors included TBW, ICW, muscle mass, muscle strength and functional performance. TBW (in absolute litres or as % of total body weight), ICW (in absolute litres or as % TBW) and fat mass, lean mass and muscle mass (in absolute kg or as % of total body weight) were assessed by bioelectrical impedance analysis (BIA) (Bioelectrical Impedance Analyser, EFG3Electrofluidgraph, Akern SRL). Frailty status (robust, pre-frail or frail) was assessed according to Fried criteria (8), muscle strength was estimated from handgrip strength (assessed in kg by a hand-held JAMAR dynamometer), and functional performance was assessed according to the Barthel index score, the timed up-and-go test (TUG) and gait speed. Other study variables included socio-demographic characteristics, co-morbidities, geriatric syndromes and chronic medication. Information on comorbidities and medications was obtained from patient electronic medical records held by the corresponding centres. All other information was obtained directly from the patient by trained healthcare professionals.

Statistical analysis

The Pearson correlation coefficient (r) was used to assess TBW and ICW correlations with other continuous variables such as muscle mass, Barthel index score and gait speed. Frail and non-frail subjects were compared using the X² test or

Fisher's exact test for categorical variables and the t-test or Mann-Whitney U test for numerical variables. Linear regression analyses were performed and beta coefficients estimated to assess the effect of TBW and ICW on handgrip, Barthel index score and gait speed. The odds ratio (OR), calculated using logistic regression, was used as a measure of TBW and ICW associations with frailty. Regression analyses were used to adjust the effect of TBW and ICW for age, sex, muscle mass, BMI and number of co-morbidities. To assess the effect of ICW on strength, performance and frailty adjusted for muscle mass, a stratified analysis was also conducted of two muscle mass groups categorized according to the 50th percentile (p50) cut-off. To assess interactions according to sex, all analyses were performed on the full sample and separately for men and women. Statistical significance was set to p<0.05.

Results

A total of 324 community-dwelling elderly subjects were recruited with a mean age of 80.1 (SD 3.5) years, 154 (47.5%) of whom were women. TBW represented 56.7% and 48.4% of total body weight in men and women, respectively, and ICW represented 52.2% and 49.9% of TBW in men and women, respectively. TBW (as % of total body weight) was uncorrelated with age (r=-0.059, p=0.290), in both men (r=-0.138, p=0.075) and women (r=0.054, p=0.508). ICW (as %TBW) was negatively correlated with age in the overall sample (r=-0.260, p<0.001) and in men (r=-0.439, p<0.001), but not in women (r=-0.096, p=0.239). While TBW was negatively correlated with BMI (r=-0.607, p<0.001) in both men (r=-0.531, p<0.001) and women (r=-0.748, p<0.001), ICW was uncorrelated with BMI (r=0.077, p=0.166) in both men (r=0.134, p=0.083) and women (r=0.174, p=0.032).

Table 1 shows TBW and ICW correlations with muscle

TOTAL BODY WATER & INTRACELLULAR WATER

mass, handgrip, Barthel index score and gait speed, as well as their relationship with frailty for both the overall sample and the sample stratified by sex. Evident is the high correlation of muscle mass with TBW and ICW in both men and women, and a significant ICW association with Barthel index score, gait speed and frailty in both sexes and also with handgrip in men.

Figure 1 plots muscle mass and ICW, showing that, for both men and women with a similar muscle mass, ICW is highly variable. Figure 2 plots muscle strength and ICW by muscle mass and sex groups. Table 2 reports results for the effect of TBW and ICW on handgrip, Barthel index score, gait speed (linear regression analysis) and frailty (logistic regression analysis) adjusted for age, sex, muscle mass or BMI and number of co-morbidities. Evident are the positive effect of ICW on handgrip and functional performance and the protective effect on frailty.

Figure 1

Relationship between muscle mass and intracellular water (ICW) stratified by sex

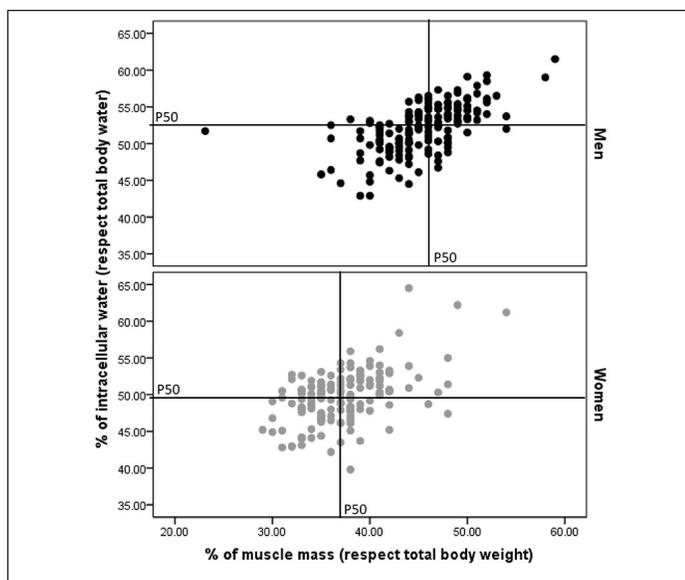


Table 3 compares handgrip, Barthel index score, gait speed and frailty status for groups with a similar muscle mass but different ICW. It shows that, in individuals with above-median muscle mass, those with $ICW > p50$ have a higher Barthel index score and lower TUG test than those with $ICW < p50$.

Discussion

The main results of the present study indicate that, for community-dwelling elderly subjects: a) TBW is closely correlated with muscle mass and is also positively correlated with Barthel index score and gait speed in both men and women; b) ICW is correlated with muscle mass, Barthel index score and gait speed in both men and women and is also

correlated with handgrip in men; c) frail compared to non-frail men and women have lower ICW percentages, indicating that ICW has a protective effect on frailty; d) ICW, when adjusted for age, BMI and co-morbidities, has a positive effect on Barthel index score, gait speed and frailty in women and on handgrip and Barthel index score in men; and e) for a muscle mass above p50, higher ICW is associated with better functional performance. These results point to a relevant role of intracellular water in muscle functioning and suggest that its determination could be a relevant marker of functional capacity and performance in elderly subjects.

Water is an essential nutrient for life, but as a person ages, TBW tends to decline because of a decrease in fat-free mass and muscle mass. Different studies have proposed poor physical activity, malnutrition (7), anabolic hormonal decline (9), insulin resistance (10) and inflammation (11) as the main factors responsible for muscle wasting with age (12). However, other factors may influence TBW in elderly individuals, such as decreased water intake secondary to a reduced thirst sensation (13), age-related dysphagia or dysphagia secondary to stroke or neurodegenerative diseases (14), and increased water excretion due to medication or an impaired kidney capacity to concentrate urine (15). Decreased water intake or excessive water excretion may lead to dehydration. However, age-related dehydration does not seem to affect ECW and ICW compartments equally. Increased ECW relative to ICW with age has been described and proposed as a biomarker of muscle ageing (6). This idea is reinforced by the observation of increased relaxation time for fast-twitch muscle fibres in elderly people attributed to increased extracellular space (16).

The above findings are corroborated by the results of our study. We observed that muscle mass was strongly correlated with TBW and ICW. However, the correlation between ICW and muscle mass, in both men and women, was not very high, indicating variability in % ICW for the same muscle mass (as shown in Figure 1), that is, variability in muscle cell hydration. The observed effect of ICW on strength and performance may be partially attributed to reasons other than muscle mass, such as better quality and better hydrated muscle cells. Our results show an independent effect of ICW on muscle strength, functional performance, gait speed and frailty when adjusted for age, sex, BMI and co-morbidities. However, except for gait speed in men, this effect was not statistically significant when adjusted for muscle mass, probably because of a lack of statistical power. Noteworthy is the fact that, when adjusted for age, sex, muscle mass and co-morbidities, ICW had a protective effect on frailty, with $OR=0.89$ ($p=0.061$), suggesting an 11% reduction in frailty risk for each 1% increase in ICW. Yamada et al. (6) reported that thigh ECW/ICW ratio was a significant predictor of knee extension strength and gait speed independently of age, sex, BMI and skeletal muscle mass. These authors conclude that ECW space in skeletal muscle tissue increases with age and that the expanded ECW (or reduced ICW) can partially explain the reduction in muscle

Table 2

Adjusted effect of total body water (TBW) and intracellular water (ICW) on handgrip, Barthel index score, gait speed and frailty for the overall sample and by sex

	Handgrip (kg)		Barthel index		Gait speed (m/s)		Frailty	
	β	p	β	p	β	p	OR	p
<i>All individuals</i>								
TBW (%) ^a	0.139	0.114	0.139	0.143	0.004	0.285	0.96	0.429
ICW (%) ^a	0.197	0.021	0.299	0.001	0.013	<0.001	0.84	0.005
ICW (%) ^b	0.144	0.144	0.140	0.189	0.007	0.090	0.89	0.061
<i>Women</i>								
TBW (%) ^c	0.174	0.098	0.299	0.094	0.002	0.740	0.96	0.581
ICW (%) ^c	0.127	0.176	0.393	0.013	0.016	<0.001	0.84	0.017
ICW (%) ^d	0.059	0.579	0.170	0.340	0.009	0.090	0.88	0.089
<i>Men</i>								
TBW (%) ^c	0.115	0.409	-0.002	0.985	0.005	0.292	0.93	0.496
ICW (%) ^c	0.352	0.022	0.229	0.017	0.011	0.060	0.84	0.162
ICW (%) ^d	0.306	0.080	0.145	0.192	0.006	0.018	0.91	0.460

TBW as % of total body weight. ICW as % of total body water. β : linear regression coefficient. OR: odds ratio; a. Adjusted for age, sex, BMI and number of comorbidities; b. Adjusted for age, sex, muscle mass and number of comorbidities; c. Adjusted for age, BMI and number of comorbidities; d. Adjusted for age, muscle mass, BMI and number of comorbidities.

Table 3

Intracellular water (ICW) relationship with strength, functionality, performance and frailty stratified by muscle mass for the overall sample and by sex

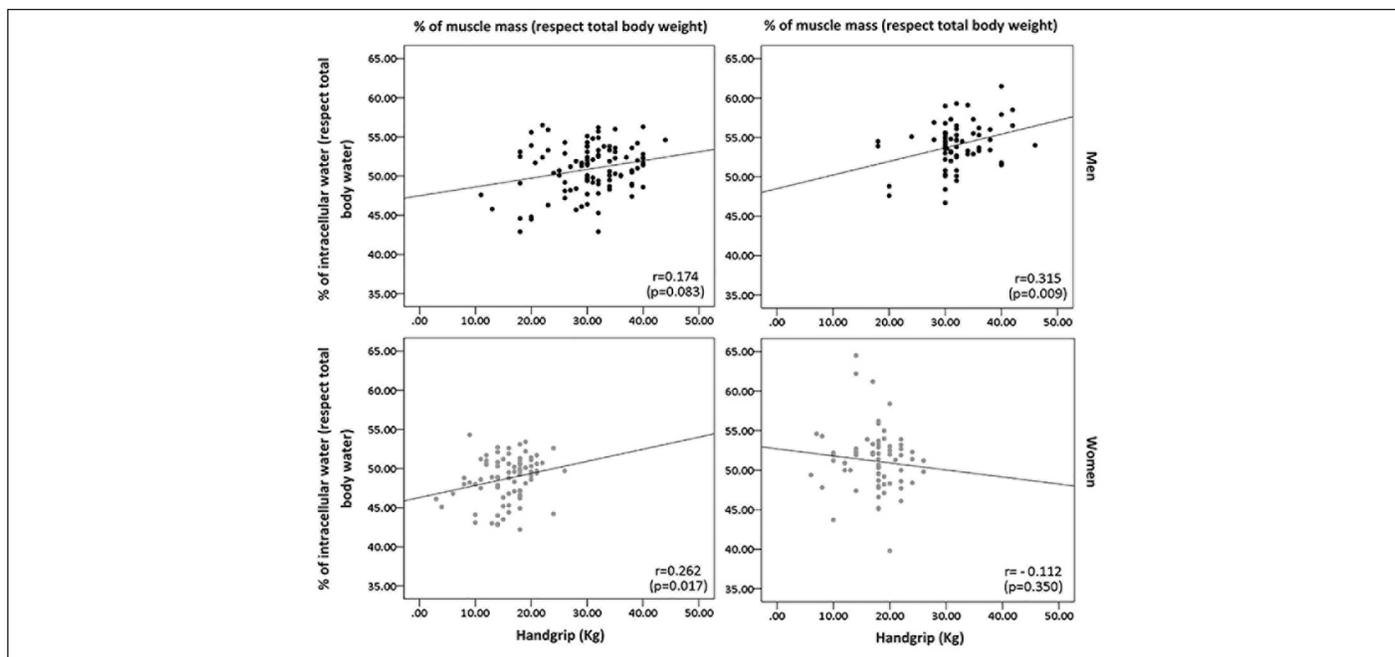
	Muscle mass <p50			Muscle mass \geq p50		
	ICW <p50	ICW \geq p50	p	ICW <p50	ICW \geq p50	p
<i>All individuals</i>						
Handgrip (kg)	24.1 (9.6)	23.7 (8.8)	0.875	22.3 (7.9)	25.4 (8.9)	0.096
Barthel index	95.1 (7.0)	95.8 (7.8)	0.158	96.3 (6.1)	98.6 (3.3)	0.016
Gait speed (m/s)	0.88 (0.2)	0.88 (0.2)	0.997	0.90 (0.2)	1.00 (0.2)	0.085
TUG (seconds)	9.7 (3.5)	9.4 (3.3)	0.613	9.2 (2.6)	8.0 (1.6)	0.004
Frailty (%)	21.3%	16.4%	0.430	14.3%	4.2%	0.067
<i>Women</i>						
Handgrip (kg)	15.3 (4.7)	16.7 (3.6)	0.164	17.7 (4.6)	17.1 (4.3)	0.357
Barthel index	93.0 (7.0)	93.0 (9.9)	0.346	95.0 (7.0)	98.0 (4.9)	0.122
Gait speed (m/s)	0.78 (0.2)	0.80 (0.2)	0.563	0.84 (0.2)	0.95 (0.2)	0.030
TUG (seconds)	11.0 (3.0)	10.4 (4.0)	0.142	9.7 (3.0)	8.4 (2.0)	0.017
Frailty (%)	33.3%	29.0%	0.685	22.2%	6.8%	0.065
<i>Men</i>						
Handgrip (kg)	30.4 (6.8)	30.9 (6.4)	0.737	30.6 (5.4)	32.4 (5.0)	0.244
Barthel index	96.6 (6.2)	98.7 (2.6)	0.151	98.3 (4.1)	99.4 (1.9)	0.261
Gait speed (m/s)	0.95 (0.2)	0.97 (0.2)	0.858	1.03 (0.3)	1.05 (0.2)	0.577
TUG (seconds)	8.9 (3.4)	8.4 (1.8)	0.888	8.1 (2.3)	7.7 (1.6)	0.499
Frailty (%)	12.7%	3.3%	0.150	0%	1.9%	---

p50: 50th percentile. TUG: timed up-and-go test; p50 of muscle mass for men =46%. p50 of muscle mass for women =37%. p50 of ICW for men =52.5%. p50 of ICW for women =50.0%

TOTAL BODY WATER & INTRACELLULAR WATER

Figure 2

Relationship between muscle strength (handgrip) and intracellular water (ICW) stratified by muscle mass (above or below p50) and sex



quality (muscle strength/skeletal muscle mass) observed with ageing. A study that assessed and compared body water compartments for healthy adults, healthy elderly and elderly patients, reported higher ECW in elderly patients compared to healthy elderly individuals. Another finding was that the proportions of water spaces remained constant from healthy adults to healthy elderly individuals, suggesting that cell hydration is preserved in the latter (17).

Similar results have been reported for young adult athletes. Silva et al. (18) reported that athletes who increase muscle strength by more than 3% over a full sport season showed significantly higher ICW and concluded that ICW is the main predictor of leg strength and jump performance in highly trained athletes. Moreover, athletes who showed a decrease in ICW during training sessions were also found to have reduced power and grip strength (19, 20). Proposed as a physiological explanation for this direct relationship is the so-called cell swelling theory (21, 22), which suggests that cell volume is a metabolic signal that regulates cellular function. The theory is based on in vivo evidence indicating that cellular swelling leads to anabolism, counteracts proteolysis and stimulates glycogen synthesis, whereas cellular shrinkage promotes catabolism and protein degradation. Since cell volume is influenced by extracellular osmolality, extracellular hypo-osmolality leads to cell swelling, whereas extracellular hyper-osmolality leads to cell shrinking. Keller et al. (23), who assessed the effect of acute changes in extracellular osmolality on protein, glucose and lipid metabolism in 10 male subjects, concluded that hypo-osmolality promotes lipolysis and counteracts proteolysis and glycogenolysis, while hyper-osmolality induces glycogenolysis.

The cell swelling theory is also supported by the idea that water, in binding to glycogen, ensures good availability of nutrients and optimal energy resource usage and has anabolic effect, whereas ICW depletion impedes nutrient availability and may produce an intracellular catabolic effect.

ICW evaluation may also be of interest for several critical conditions that can be considered in terms of accelerated model of frailty. In critically ill patients, for instance, ECW/ICW ratio trends could help manage sarcopenia subsequent to sepsis and assist with nutritional and functional monitoring (24, 25). In this kind of patient, biochemical or anthropometric evaluation are not useful in monitoring the effect of nutritional support and radiologic evaluation of muscle mass (26) is both static and laborious. BIA has been shown to be useful in assessing and monitoring nutritional status in critically ill patients (27). The ECW/ICW ratio in critically ill patients is increased, and when >1 , is associated with proteolysis and poorer evolution of patients with sepsis and trauma (28-30). All the above mentioned evidence would suggest that ICW plays an important role in cell functioning and that cell dehydration may partially be responsible for poor muscle strength. There are very few published studies reporting the effect of ICW on muscle function and frailty in elderly individuals, which required further large and prospective studies.

Among the limitations of this study is its cross-sectional design, which does not allow causal relationships to be established. Another limitation is the small sample size, which compromises its statistical power, especially for subgroup and multivariate analyses. Finally, although BIA was performed in standard conditions (an apparently well hydrated patient who

had rested for 15 minutes before testing, who was tested lying down, with all metallic elements removed), the reliability of this measurement may be compromised because of hours of food and liquid fasting, previous exercise, temperature, sweating or liquid retention.

In summary, the decline in TBW and in ICW in the elderly mainly reflects a decrease in muscle mass and is accompanied by a decrease in muscle strength and impaired functional performance. However, for individuals with a similar muscle mass, the fact that those with higher ICW have a better functional performance and a lower frailty risk would suggest that cell hydration has a protective effect that is independent of muscle mass. These results have two main potential clinical implications; a) ICW could be used as an indicator or a biomarker for frailty and muscular impairment, and b) physicians should keep in mind the importance of good hydration in the elderly, should recommend enough water intake and should assess possible effects of diseases, pharmacological treatments, diets, physical activity or environmental conditions on water balance to ensure good hydration. Further prospective and well-powered observational studies are needed to assess the role played by TBW and the ECW/ICW ratio in the genesis of frailty and disability in elderly individuals.

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Conflict of interest: All authors declare that they have no conflict of interest in relation with this study.

Ethical standard: This study complies with the current Spanish laws regarding confidentiality and clinical research.

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