Kidney International, Vol. 67 (2005), pp. 2056–2062

Validation of estimates of total body water in pediatric dialysis patients by deuterium dilution

SUSAN R. MENDLEY, NANCY L. MAJKOWSKI, and DALE A. SCHOELLER

University of Maryland School of Medicine, Baltimore, Maryland; Children's Memorial Hospital, Chicago, Illinois; and University of Wisconsin, Madison, Wisconsin

Validation of estimates of total body water in pediatric dialysis patients by deuterium dilution.

Background. Current K-DOQI recommendations call for an assessment of dialysis adequacy that depends critically on an estimate of total body water (TBW). Such estimates are problematic in children since the range of patient size is large, and often formulas derived in normals are not validated in end-stage renal disease. Gold standard methods of TBW measurement, such as deuterium dilution (^2H_2O), are not appropriate in the clinical setting, yet noninvasive methods such as bioimpedance analysis (BIA) and dual energy x-ray absorptiometry (DEXA) have not been independently validated.

Methods. We studied 14 stable pediatric dialysis patients on 1 to 3 occasions using ^2H_2O dilution, BIA, DEXA, and anthropometry to measure TBW. We compared our data set to previously published formulae for TBW to determine root mean square error (RMSE) and skew of the estimate.

Results. TBW prediction based upon the anthropometric formula proposed by the Pediatric Peritoneal Dialysis Consortium provided the best fit to our independent data set with RMSE = 2.15 L, and no skew by Bland-Altman analysis. Other formulas produced large, clinically relevant errors; obese subjects confounded many estimates. TBW calculated from hydrated lean body mass from DEXA scan was reliable with RMSE = 1.03 L and no skew. BIA-derived estimates can be useful, although the magnitude of RMSE ranged from 1.45 to 6.24 L, and one formula produced skewed results.

Conclusion. Techniques for estimating TBW in pediatric dialysis patients must be validated by independent data sets before being incorporated into clinical and research practice.

Kinetic modeling of hemodialysis (HD) and peritoneal dialysis (PD) prescriptions requires a meaningful estimate of total body water. Current Kidney-Dialysis Outcomes Quality Initiative (K-DOQI) recommendations are to determine the adequacy of peritoneal dialysis by calculation of volume-normalized clearance as Kt (clearance time-product)/V, where the volume of distribution of urea (Vd_{urea}) is considered equal to total body water (TBW) [1]. The estimate of TBW used in the denominator of this calculation dramatically affects the calculated Kt/V, leading to widely fluctuating measurements of dialysis adequacy. Further, kinetically derived Vd_{urea} in hemodialysis patients can be complemented by a reliable anthropometrically derived TBW to determine access recirculation or other causes of inadequate dialysis delivery [2]. Thus, prediction of body water in a variety of patient populations has received increased effort and scrutiny; however, studies in children with end-stage renal disease (ESRD) are particularly difficult because of small patient numbers.

The gold standard for measurement of TBW is isotope dilution, but this method is only appropriate in research settings. Estimates of TBW in children derived from measurements made by isotope dilution have been proposed, including that of Mellits and Cheek [3], and that of Friis-Hansen [4]. However, these estimates were derived in normal children, not those with renal failure in whom conventional assumptions of fluid balance may not apply. The most recent K-DOQI recommendations [1] include use of the Mellits and Cheek formulas for children with ESRD despite the lack of validation in this population. A reanalysis of the data set originally published by Mellits and Cheek has been performed in an attempt to improve the reliability of the original estimates [5]. The Pediatric Peritoneal Dialysis Study Consortium (PPDSC) has performed measures of total body water in a group of children with ESRD ages 4 months to 19 years receiving chronic PD, and they have published formulas for male and female subjects that permit calculation of TBW from height and weight [6]. Their comparison of measured TBW by deuterium oxide (^2H_2O) dilution and Mellits and Cheek data in a set of subjects receiving PD showed a clinically important difference in calculated Kt/V. Even the reanalyzed Mellits and Cheek data performed only slightly better than the original estimate. Other investigators have studied TBW by bioimpedance

Key words: total body water, children, dialysis adequacy, body composition, dual energy x-ray absorptiometry, bioimpedance analysis.

Received for publication September 24, 2004
and in revised form December 6, 2004
Accepted for publication December 15, 2004

analysis (BIA) and ^2H_2O dilution in a sample of children receiving chronic PD and hemodialysis [7]. We now provide an independent data set of total body water in children with ESRD to demonstrate the validity of the assumptions in the PPDSC model, as well as estimates proposed by other groups.

In clinical research and clinical practice, attempts have been made to utilize noninvasive methods of body water assessment, such as BIA and dual energy x-ray absorptiometry (DEXA), to estimate total body water [8]. These methods offer convenience and the possibility of applying individualized measurement of TBW when research measures such as isotope dilution are unfeasible. Chertow et al validated BIA as a surrogate for ^2H_2O in assessing TBW in adults with ESRD receiving long-term HD [9]. Pediatric studies of these methods have been performed in normal subjects and in a variety of disease states [10–13].

In the present study, we measured TBW in children with ESRD treated by PD or HD utilizing ^2H_2O dilution, an accepted technique for accuracy and reliability [14]. Measured total body water in these subjects was compared to published formulas for children, looking at both closeness of estimate (error) and skew (different errors occurring in subjects of differing size). Further, we performed DEXA scans and BIA on the same subjects at the time of their TBW measurement and compared it to previously published estimates from normal children using formulas of Davies [15] and Kushner [16]. This allowed us to assess the reliability of each noninvasive method compared to the gold standard, deuterium dilution, for general clinical use and clinical research.

METHODS

After written informed consent was obtained from parents and subjects, we measured total body water in 14 stable pediatric patients with ESRD on 1 to 3 occasions. All prevalent PD and HD patients were offered participation. The preponderance of patients received PD, which reflected the practice in our center and most other pediatric dialysis centers. No subject had confounding residual renal function, and there was no urine output during the 4-hour study period in any child. Subjects were studied at their estimated dry weight (EDW), and assessed according to response to ultrafiltration (by blood pressure, symptoms, and clinical examination). Studies were performed in the General Clinical Research Center after overnight fast. Those receiving nightly peritoneal dialysis had a prolonged final drain prior to the study. Hemodialysis patients were studied on an interdialytic day to avoid body water space disequilibrium from dialysis and ultrafiltration. Simultaneous measurements of TBW were made by deuterium dilution, BIA, and DEXA during the same 4-hour period.

Table 1. Formulas for calculating total body water as referred to in text

Davies
$TBW = 0.6(Ht^2/resistance) - 0.5$
Kushner et al
$TBW = 0.593(Ht^2/resistance) + .065(Wt) + .04$
Wühl et al
$TBW = 0.144(Ht^2/resistance) + 0.4(Wt) + 1.99.$
Friis-Hansen
$TBW = 0.135(Wt)^{0.666}(Ht)^{0.535}$
Mellits and Cheek
Males
$TBW = -1.927 + 0.465(Wt) + 0.045(Ht)$, when $Ht \leq 132.7$ cm
$TBW = -21.993 + 0.406(Wt) + 0.209(Ht)$, when $Ht \geq 132.7$ cm
Females
$TBW = 0.076 + 0.507(Wt) + 0.013(Ht)$, when $Ht \leq 110.8$ cm
$TBW = -10.313 + 0.252(Wt) + 0.154(Ht)$, when $Ht \geq 110.8$ cm
Morgenstern et al recalculation of Mellits and Cheek
Infants 0–3 months
$TBW = 0.887(Wt)^{0.83}$
Children 3 months to 13 years
$TBW = 0.0846 \times 0.95^{[\text{if female}]} \times (Ht \times Wt)^{0.65}$
Children >13 years
$TBW = 0.0758 \times 0.84^{[\text{if female}]} \times (Ht \times Wt)^{0.69}$
PPDSC
Boys
$TBW = 0.074(Ht \times Wt)^{0.66}$
Girls
$TBW = 0.117(Ht \times Wt)^{0.59}$
Watson et al
$TBW = 2.447–0.09516(age)+ 0.1074(Ht)+0.3362(Wt)$

First, deuterium oxide (^2H_2O, isotopic purity ≥99.9%) (60 mg/kg) was administered as an oral liquid dose in the morning in the fasting state. Serum samples were collected at baseline, at 3 and 4 hours postdose, and kept frozen until analysis. Deuterium dilution space (N_D) was calculated from the enrichment of the second serum sample relative to the baseline serum sample, and was measured using isotope ratio mass spectrometry (Nuclide 3–60 HD). TBW was calculated from the isotope dilution space assuming $TBW = N_D/1.041$ [14].

Whole body DEXA (scanner model DPX-L, Lunar Radiation Corp, Madison, WI, USA) was performed between the baseline and 3-hour ^2H_2O sample collections so measurements would be simultaneous. Results were analyzed by the device proprietary software version 3.6, which allowed measurement of lean body mass, fat mass, and bone mineral content. Total body water was calculated from lean body mass obtained from DEXA scan, multiplied by an age-adjusted hydration constant [17].

Single frequency BIA (RJL Systems, Detroit, MI, USA) at 50 KHz was performed at the same time as DEXA scanning and ^2H_2O dilution. TBW was calculated according to the formulas of Kushner et al [16] and Davies [15], both intended to be applied in children, and by Wühl et al, derived in pediatric dialysis patients [7] (shown in Table 1).

Total body water was calculated from anthropometric formulas of Friis-Hansen [4], Mellits and Cheek [3],