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Original Investigation

Bioimpedance and Fluid Status in Children and Adolescents Treated With Dialysis

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Background: Assessment of hydration status in patients with chronic kidney failure treated by dialysis is crucial for clinical management decisions. Dilution techniques are considered the gold standard for measurement of body fluid volumes, but they are unfit for day-to-day care. Multifrequency bioimpedance has been shown to be of help in clinical practice in adults and its use in children and adolescents has been advocated. We investigated whether application of multifrequency bioimpedance is appropriate for total-body water (TBW) and extracellular water (ECW) measurement in children and adolescents on dialysis therapy.

Study Design: A study of diagnostic test accuracy.

Setting & Participants: 16 young dialysis patients (before a hemodialysis session or after peritoneal dialysis treatment) from the Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, and the Emma Children's Hospital−Academic Medical Center, Amsterdam, the Netherlands.

Index Test: TBW and ECW volumes assessed by multifrequency bioimpedance.

Reference Tests: TBW and ECW volumes measured by deuterium and bromide dilution, respectively.

Results: Mean TBW volumes determined by multifrequency bioimpedance and deuterium dilution were 19.2 ± 8.7 (SD) and 19.3 ± 8.3 L, respectively; Bland-Altman analysis showed a mean bias between the 2 methods of −0.09 (95% limits of agreement, −2.1 to 1.9) L. Mean ECW volumes were 8.9 ± 4.0 and 8.3 ± 3.3 L measured by multifrequency bioimpedance and bromide dilution, respectively; mean bias between the 2 ECW measurements was +0.6 (95% limits of agreement, −2.3 to 3.5).

Limitations: Participants ingested the deuterated water at home without direct supervision by investigators, small number of patients, repeated measurements in individual patients were not performed.

Conclusions: Multifrequency bioimpedance measurements were unbiased but imprecise in comparison to dilution techniques. We conclude that multifrequency bioimpedance measurements cannot precisely estimate TBW and ECW in children receiving dialysis.

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INDEX WORDS: Hydration status; fluid status; body composition monitor (BCM); hemodialysis; peritoneal dialysis; pediatric; children; adolescents; multi-frequency bioimpedance measurement; total body water (TBW); extracellular water (ECW); body composition; stable isotopes; deuterium dilution; isotope ratio mass spectrometry; bromide dilution; fluid overload; renal failure.

Children and adolescents with chronic kidney failure treated with dialysis have cardiovascular disease–associated mortality rates many-fold higher than that of their age-matched peers, and many of them will die prematurely due to cardiovascular events in early adulthood.[1-3] Among the multiple etiologic factors involved, body fluid balance alterations may have a prevailing effect on cardiovascular disease development. Fluid balance alterations during dialysis treatment entail hypertension and fluid overload on the one hand and hypotensive episodes on the other. Although both have been found to be important risk factors for cardiovascular disease,[4,5] their prevention remains a challenge in the day-to-day management of dialysis patients.[5-7]

Several noninvasive techniques for the assessment of hydration status exist. These include various

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biochemical markers (eg, atrial and brain natriuretic peptide levels) and ultrasonography parameters (eg, inferior vena cava diameter and continuous blood volume measurements). None of these methods has been proven to be sufficiently accurate and practical for bedside use.[8] To this day, assessment of a patient's hydration status is mostly based on the clinician's judgment and is often fraught with inaccuracies.[9]

Multifrequency bioimpedance measurement has been claimed to be a reliable noninvasive technology for estimating body water compartments in adults.[10-12] Its application in pediatric dialysis has also been advocated.[13] However, no validation studies in children with chronic kidney failure exist. Given the fact that body composition in children and adolescents differs from that in adults, we set out to verify whether application of multifrequency bioimpedance is appropriate for estimation of total-body water (TBW) and extracellular water (ECW) in children and adolescents receiving dialysis.

METHODS

Participants

The study was performed at the pediatric dialysis units of the Fondazione Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, and the Emma Children's Hospital-Academic Medical Center, Amsterdam, the Netherlands, October 2013 to March 2014. Persons aged 5 to 17 years who were receiving maintenance dialysis were eligible for participation. Exclusion criteria were acute illness (as judged by the attending pediatrician); the presence of pins, stents, pacemakers, prostheses, or amputations; treatment with medications containing bromide; and overnight enteral nutrition. The medical ethics committees of both hospitals approved the study (approval number NL45187.018.13). Written informed consent was obtained from the parents of children younger than 12 years and from both participants and parents for persons 12 years and older.

Index Tests

Volumes of TBW and ECW were measured by the multifrequency bioimpedance method using the Body Composition Monitor (BCM; Fresenius Medical Care, software version 3.2). The device had been tested by Fresenius and clinical engineers of the 2 centers. All BCM measurements were performed by a trained pediatrician (G.P.M. or M.J.S.O.) with the participant in supine position on a nonconductive bed, in resting conditions. Two nonrecyclable electrode strips ("pediatric" version for participants weighing $\leq$20 kg) were placed on the dorsal surface of the wrist (just proximal to the phalangeal-metacarpal joint and between the styloid processes of the ulna and radius) and foot (just proximal to the transverse metatarsal arch and between the malleoli) on one side of the body and connected to the BCM device. The device measures a person's impedance at 50 different frequencies of 5 to 1,000 kHz by currents that are introduced at the distal and recorded by the proximal electrodes. BCM measurements were performed twice in all patients.

Reference Tests

TBW volume was also measured by deuterated water (^2H_2O) dilution, following a single oral dose (60 mg/kg) of ^2H_2O (isotopic purity, 99.9%; Erasmus Medical Center Pharmacy, Rotterdam, the Netherlands). Measurement of deuterium enrichment was performed on saliva samples. Considering that deuterium dilution in body water can be delayed if alterations in ECW amount are present (eg, children presenting with edema),[14] samples were collected up to 6 hours after ^2H_2O ingestion, as previously described in patients receiving dialysis.[15] ECW volume was determined by sodium bromide dilution. For this purpose, participants ingested 1 oral dose (25 mg/kg) of sodium bromide (ACEF spa). Bromide dilution was determined in serum samples because ECW assessment by bromide dilution in saliva is considered inaccurate in pediatric patients.[16] Body weight was measured to the nearest 0.1 kg using a balance scale. Height was measured to the nearest 0.5 cm with the patient standing, back to a stadiometer. Balance scale and stadiometer calibration were tested by the clinical engineers of each hospital prior to the study.

Study Protocol

After enrollment, protocol procedures were carefully explained to participants and their parents. Prior to the study day, participants were provided with written protocol instructions, a diary for recording sampling and ^2H_2O intake and sample collection scheme, and kits to collect saliva (a stick with a sponge and airtight plastic containers [Salivette; Sarstedt]). Study procedures were reviewed with participants on this occasion. Measurements were performed on days of planned hemodialysis treatments or, for participants on peritoneal dialysis therapy, of outpatient visits. In the 48 hours preceding the test day, participants received an airtight glass bottle containing the ^2H_2O dose and were instructed to store it in the home refrigerator. On the afternoon before the test day, parents were again instructed by telephone regarding test procedures. Patients had to fast overnight prior to the measurement day. Participants treated by peritoneal dialysis were required to end the dialysis treatment with an empty abdomen.

On the morning of the test day and after an overnight fast, participants collected one saliva sample by keeping the sponge of a saliva collection stick in their mouth for at least 2 minutes. The sponge was transferred to an airtight plastic container, the plastic stick was cut off, and the container with the sponge was closed and stored in a box filled with ice. Following collection of the first saliva sample, patients ingested the oral ^2H_2O dose. Patients were instructed to rinse the empty dose container twice with 10 mL of tap water and ingest the content to ensure that all ^2H_2O was consumed. Also, it was required that the exact time of ^2H_2O ingestion be noted. Participants were then requested to visit the hospital 3 hours after ingestion of the ^2H_2O dose. Upon arrival, a second saliva sample and a baseline blood sample were obtained. Subsequently, an oral sodium bromide dose (dissolved in 10 mL of tap water) was administered. Again, the sodium bromide container was rinsed twice with 10 mL of water and the participant was required to ingest the content. The home saliva sample and diary were collected and procedure adherence was ascertained by investigators G.P.M. and M.J.S.O. Body weight and height were measured. During the following 3 hours, BCM measurements were performed and saliva samples were collected (at 4, 5, and 6 hours after ^2H_2O ingestion). Drinking small amounts of water was allowed (except during the 30 minutes prior to saliva collection) because patients also had to take medications during this time. At the end of this interval, a second serum sample was collected (in most cases coinciding with the start of a hemodialysis session), completing the measurement protocol. The timeline of procedures is summarized in Fig 1.

Sample Analysis and Calculations

Saliva and serum samples were stored at $-20^{\circ}C$ until analysis. All samples were analyzed at the stable isotope mass spectrometry laboratory of the Emma Children's Hospital-Academic Medical Center.