Applying an Artificial Neural Network to Predict Total Body Water in Hemodialysis Patients

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Key Words
Neural network · Anthropometry · Body water · Hemodialysis · Bioelectrical impedance

Abstract
Background: Estimating total body water (TBW) is crucial in determining dry weight and dialytic dose for hemodialysis patients. Several anthropometric equations have been used to predict TBW, but a more accurate method is needed. We developed an artificial neural network (ANN) to predict TBW in hemodialysis patients. ***Methods:*** Demographic data, anthropometric measurements, and multifrequency bioelectrical impedance analysis (MF-BIA) were investigated in 54 patients. TBW measured by MF-BIA (TBW-BIA) was the reference. The predictive value of TBW based on ANN and five anthropometric equations (58% of actual body weight, Watson formula, Hume formula, Chertow formula, and Lee formula) was evaluated. ***Results:*** Predictive TBW values derived from anthropometric equations were significantly higher than TBW-BIA (31.341 ± 6.033 liters). The only non-significant difference was between TBW-ANN (31.468 ± 5.301 liters) and TBW-BIA ($p = 0.639$). ANN had the strongest Pearson's correlation coefficient (0.911) and smallest root mean square error (2.480); its peak centered most closely to zero with the shortest tails in an empirical cumulative distribution plot when compared with the other five equations. ***Conclusion:*** ANN could surpass traditional anthropometric equations and serve as a feasible alternative method of TBW estimation for chronic hemodialysis patients.

Introduction

Water is the body's most important chemical compound. Balancing ideal total body water (TBW) is essential in normal subjects and hemodialysis patients. Accurate estimation of TBW in hemodialysis patients is important in helping to achieve ideal body weight at the end of every dialysis session. The reference technique for TBW measurement is deuterium oxide dilution, which is impractical due to radiation exposure, equipment needs, and high cost. Multifrequency bioelectrical impedance analysis (MF-BIA), a simple and safe method, is increasingly used to measure different body fluid compartments. MF-BIA distinguishes between extracellular and intracellular water volume by assessing body resistance to an alternating current. In one meta-analysis, MF-BIA proved to be accurate for estimating TBW in

healthy subjects, obese adults, and patients with chronic renal failure [1].

An artificial neural network (ANN) is a connectionist model composed of non-linear computational elements ('neurons') arranged in highly interconnected layers with a structure that simulates the biological nervous system [2]. Individual network neurons receive inhibitory and excitatory inputs from other neurons. ANN has the advantage of recognizing relationships between inputs (data from cases) and outputs (known outcomes) that may not be obvious with conventional statistical methods [3]. Furthermore, ANNs can improve accuracy through learning algorithms and have been applied to evaluation of dialytic adequacy [4–8], diagnosis and prognosis of nephropathies [9–13], and issues of renal transplantation [14–16].

Because MF-BIA equipment is limited in dialysis units and frequent measurements by MF-BIA may bother patients, many nephrologists prefer to use predictive equations for TBW estimation in these patients. Several anthropometric equations are available including TBW as 58% of body weight and the Watson [17], Hume [18], Chertow [19], and Lee formulas [20]. Because most anthropometric equations for TBW have considerable inter- and intraindividual variability compared with measured values by radiotracer or BIA, we developed an ANN-based model to predict TBW in hemodialysis patients and compared its predictive performance with those of conventional anthropometric equations.

Patients and Methods

Participants

The Ethics Committee on Human Studies at Tri-Service General Hospital (Taipei, Taiwan) approved the study, and all patients provided signed informed consent. Patients were selected with the following criteria: age >18 years; clinically stable end-stage renal disease (ESRD) on maintenance hemodialysis for more than 6 months; no hospitalization within 6 months; absence of heart, liver, infection, or other major disease per history and physical examination; no limb amputation or paralysis; no active physical exercise in the previous 48 h. The final population had 54 stable hemodialysis patients. All patients had 3 × weekly 4-hour hemodialysis sessions using cellulose acetate hollow fiber (blood flow 250–400 ml/min; dialysate flow 500 ml/min).

Measurements

Demographic and anthropometric data recorded for all patients included age, gender, body weight (BW), body height (BH), and history of diabetes mellitus (DM). All anthropometric measurements were performed by the same operator. All patients were clothed in underwear with bare feet for measurements, with BW measured to the nearest 0.1 kg using a digital scale and BH measured to the nearest 0.1 cm using a linear height scale. Mean values from two measurements were employed as data. The five prediction equations used consisted of TBW calculated as 0.58% body weight (TBW-58), Watson formula (TBW-W), Hume formula (TBW-H), Chertow formula (TBW-C), and Lee formula (TBW-L). Details of equations are given in the Appendix.

Segmental resistance of arms, trunk, and legs was measured at 5, 50, 250, and 500 kHz with a multifrequency bioelectrical impedance analyzer (Inbody 3.0, Biospace Co. Ltd, Seoul, Korea) with all patients standing upright. The instrument uses eight-polar tactile electrodes: two in contact with the palm and thumb of each hand and two with the anterior and posterior aspects of the sole of each foot. The patient stands with soles in contact with foot electrodes and grasps hand electrodes. A microprocessor controls the sequence of measurements, and TBW (TBW-BIA) is calculated from the sum of each body segment using built-in software. Measurement was performed within 30 min after a dialysis session without food or drink intake to prevent change of BW [21].

ANN Analysis

A commercial software package, Statistica 7.0 (StatSoft, Inc., Tulsa, Okla., USA), generated various formulations of ANN models. A built-in intelligent problem solver of neural network module was adopted to choose the most excellent neural network [22–24]. Demographic variables (age, gender and DM) and anthropometric variables (BW and BH) were used as continuous or nominal input variables into the ANN model and TBW-BIA was entered as a continuous output variable for supervised training algorithm. From the perspective of resampling method, a leave-one-out, cross-validation technique was adopted to partition the original dataset in several different ways and compute an average score over different partitions [25]. This technique was intended to avoid possible bias introduced by relying on any one particular division into test and train components. The method splits n patterns into a training set of n – 1 and a test size of 1, averaging the squared error on the left-out pattern over n possible ways of obtaining such a partition. During the training process, the intelligent problem solver decided an appropriate architecture, using a combination of heuristic strategies and an optimization approach [26]. It guided a large number of experiments, which were used to determine the best architecture. It could allow simultaneously comparison of different types of networks (linear network, three-layer and four-layer multilayered perceptron networks, radial basis function network, probabilistic and generalized regression neural networks) and automatically selected the smoothing factor and the number of units for these networks. For all types of networks, we set up the number of hidden units as 1 for minimum and 14 for maximum. To compare the performance of networks with different input variables, the intelligent problem solver balanced error against type and diversity as criteria to select retained networks, in which case it preserved networks with a range of types and performance/complexity trade-offs. If the network file is full and the new model is inferior to the candidate for replacement, the network set will be increased in maximum size to accommodate the new networks. After the network was allowed to run and a prediction was made, the predicted outcome (TBW-ANN) was correlated with the observed outcome; and if the network predicted the outcome incorrectly, by a process of back propagation, hidden weights within the network were readjusted until the predicted outcome was accurate. At last, the intelligent problem solver retained the best network, architecture, and the optimum set of

input variables in order of descending importance in predicting the outcome according to the least standard deviation (SD) ratio, i.e. the ratio of prediction error SD to original output data SD.

For comparison, we also developed an anthropometric equation (TBW-T) using multiple stepwise linear regression (variable entered if $p < 0.05$ and variable removed if $p > 0.1$) with the same variables in the ANN model. Due to limitation in linear regression analysis, we transferred the categorical variable into numerical type (i.e. male, female, DM, and non-DM as 1, 0, 1, 0, respectively).

Statistical Analysis

Data were analyzed using MedCalc 8.0 (MedCalc Software, Mariakerke, Belgium) and expressed as mean ± SD. Correlations between variables and TBW-BIA were analyzed. TBWs derived from MF-BIA, anthropometric equations, and ANN were compared with Wilcoxon test. To test the performance of estimates, each calculated TBW derived from anthropometric equations and ANN was compared with TBW-BIA using Pearson's correlation coefficient (r), folded empirical cumulative distribution plot [27], and root mean square error (RMSE). Significance was defined as $p < 0.05$.

Table 1. Baseline characteristics of study population

Characteristic		r	p value[a]
Age, years	58.81 ± 14.25	–0.053	0.703
Males/females	34/20	0.706	<0.0001
Diabetes, %	31.50	0.350	0.010
Body height, cm	163.67 ± 9.23	0.790	<0.0001
Body weight, kg	61.83 ± 11.20	0.734	<0.0001

[a] The p value denotes that each variable correlated with TBW-BIA using Pearson's correlation coefficient (r).

Table 2. Results of TBW by MF-BIA, anthropometric equations, and ANN

Prediction	TBW, liters	p value[a]
TBW-BIA	31.341 ± 6.033	–
TBW-58	35.860 ± 6.494	<0.0001
TBW-W	33.971 ± 5.498	<0.0001
TBW-H	34.553 ± 5.944	<0.0001
TBW-C	33.095 ± 5.948	<0.0001
TBW-L	33.053 ± 6.209	<0.0001
TBW-ANN	31.468 ± 5.301	0.639

[a] The p value denotes that each predictive TBW was compared with TBW-BIA using Wilcoxon test.

Results

Participant characteristics are presented in table 1. Age range was 19–85 years and male-to-female ratio was 1.7:1. All variables significantly correlated with TBW-BIA except age. Among variables, gender, BH, and BW, were strongly correlated ($p < 0.0001$). Our new regression-based equation was TBW-T = –29.222 + 0.267 × BH + 0.246 × BW + 2.581 × gender, with gender = 1 if male and 0 if female ($r = 0.794$, $p < 0.001$; RMSE = 2.741). The p values of BW, BH, and gender were <0.0001, 0.0003, and 0.042, respectively. Two variables, age and DM, were excluded during stepwise process.

The final ANN was a generalized regression neural network (SD ratio = 0.414) with one input layer of 5 nodes, two hidden layers of 36 and 2 nodes, and one output layer with 1 node (fig. 1). In order of descending importance, input nodes were BW, gender, DM, BH, and age. Table 2 shows results of measured TBW-BIA (31.34 ± 6.03 liters) and calculated TBWs by anthropometric equations and ANN. TBWs derived from anthropometric equations

Table 3. Pearson's correlation coefficient, data of folded empirical cumulative distribution plot, and RMSE for anthropometric equations and ANN compared with MF–BIA

	TBW-58	TBW-W	TBW-H	TBW-C	TBW-L	TBW-ANN
r	0.734	0.894	0.897	0.898	0.899	0.911
Folded empirical cumulative distribution plot						
Median	–3.514	–2.313	–2.800	–1.261	–1.148	–0.350
Lowest value	–22.060	–13.144	–16.019	–12.605	–15.430	–5.616
Highest value	4.462	2.650	0.857	3.441	2.070	6.260
RMSE	6.412	3.685	4.196	3.205	3.225	2.480

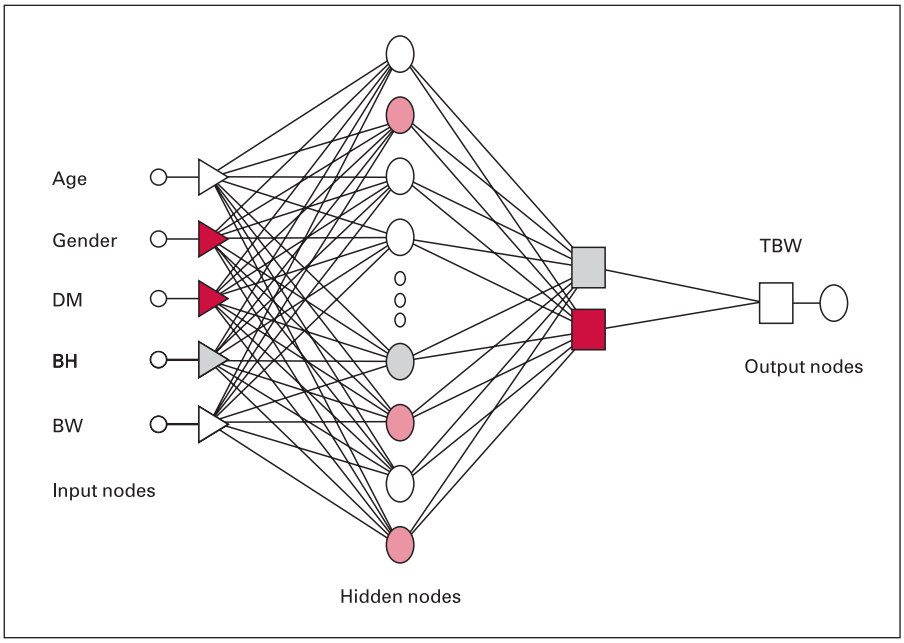

Fig. 1. Diagram of ANN model.

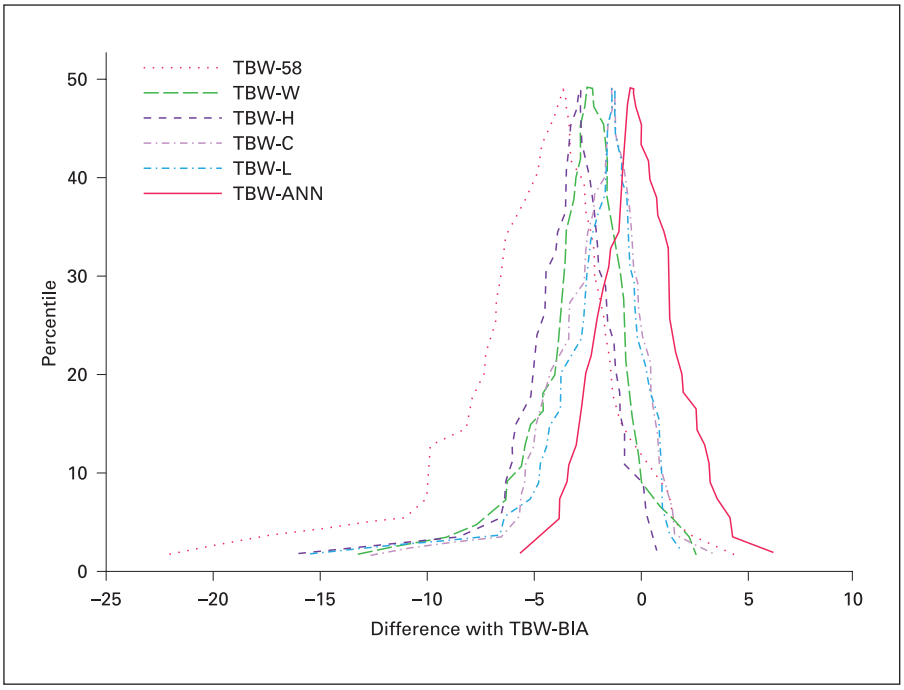

Fig. 2. Folded empirical cumulative distribution plot between TBW calculated by five anthropometric equations and ANN based on TBW-BIA in hemodialysis patients.

were all significantly higher than TBW-BIA. No statistical difference was found between TBW-ANN and TBW-BIA.

As shown in table 3, all estimates of TBW significantly correlated with TBW-BIA ($r = 0.734$ to 0.911, $p < 0.001$). TBW-ANN had the highest correlation ($r = 0.911$) compared with the other five equations. ANN also had the smallest RMSE (2.480). In a folded empirical cumulative distribution plot based on TBW-BIA, ANN had the peak centered most closely to zero and had the shortest tails (fig. 2). Conversely, TBW-58 had the poorest correlation, peak farthest from zero and much larger tails, and maximal value of RMSE compared with others.

Discussion

MF-BIA is increasingly used clinically for estimating TBW because it is a portable, inexpensive, non-invasive technique for predicting TBW without radiation exposure. Although MF-BIA cannot measure TBW directly as do radiotracer techniques, several studies support its reliability in hemodialysis patients [28–30]. We constructed an ANN to predict TBW with data from demographic and anthropometric variables and relevant clinical history – without using radiotracers or MF-BIA. This ANN proved to have better performance in predicting TBW than conventional anthropometric equations. The mean value of TBW estimate derived from any anthropometric equation was significantly higher than measured TBW, but the difference was not significant from ANN prediction. Although all predictive models significantly correlated with TBW measured by MF-BIA, the five anthropometric equations and our newly developed linear equation fitted to a relatively lower correlation ($r = 0.734$ to 0.899) than ANN ($r = 0.911$). This may indicate that conventional anthropometric equations based on a linear relationship are not the best model to predict TBW in hemodialysis patients. Because many variables in body constitution research have an optimal estimate (e.g. body mass index), they correlate with output in a non-linear pattern [31]. Because a non-linear phenomenon seems to be essential in medicine, ANN has an advantage to predict complex non-linear relationships of biological processes between independent and dependent variables by (1) learning course and (2) including more processing elements in one or more hidden network layers. Furthermore, ANN approach can make use of combinations of categorical and continuous variables. No assumption of variable distribution is necessary, and correlative interactions among inputs are pruned during the network's training process. The performance of ANN will continuously improve over time because ANN can be constantly retrained as more cases accumulate. Such advantages make ANN a more robust application in the real world setting.

In our study, we displayed lack of agreement by presenting bias as the peak (median) and the difference as two tails (lowest and highest values) with a folded empirical cumulative distribution plot, which computed a percentile for each ranked difference between a new method and a reference method. ANN had the peak centered most closely to zero with shortest tails (fig. 2), demonstrating that ANN had least bias among tested models. Moreover, RMSE value can be used for goodness of fit of a model. Our ANN model had the lowest RMSE value compared with conventional anthropometric equations and our new linear equation, TBW-T (table 3).

While using MF-BIA as the reference method, all anthropometric equations including 58% of body weight and the Watson, Hume, and Chertow formulas overestimated TBW; these findings are similar to those from a Korean study [20]. In that study, the Watson formula performed better than the Hume or Chertow formula. The three formulas had a similar predictive performance in our study. We also found that the Lee formula had a better predictive ability than the other four anthropometric equations. The fact that the Watson and Hume formulas were based on data in non-dialysis subjects whereas the Chertow and Lee formulas were derived from hemodialysis patients may account for our finding that the Chertow and Lee formulas performed better than the Watson and Hume formulas. The Chertow formula was derived from measurements of TBW by BIA in a large population of hemodialysis patients with BIA performed before a dialysis session. At this moment, TBW is at its highest value in most patients because it is prior to fluid removal by dialysis. In contrast, the Lee formula was developed after a dialysis session. Finally, the Korean patients were Asian, as are our hemodialysis patients. Therefore, the Lee formula should be the most comparable with ours. Differences in body composition related to racial differences or body fat between the North American population from which the Chertow formula was derived and our Asian population may be clinically important. Therefore, all formulas should be carefully used when applied to patients of different race or ethnicity.

In our own population, the accuracy of TBW-T was obviously lower than ANN model accuracy, with a lower correlation coefficient and higher RMSE value. In variable analysis, multiple stepwise linear regression only selected three variables (BW, BH, and gender), although there were four significant variables (BW, BH, gender, DM) in univariate correlation analysis. Age and DM were deleted during the multiple stepwise linear regression process. Similarly, ANN may identify input variables that are most valuable with regard to accuracy of prediction. In our study, the ANN model finally used all five variables to generate better accuracy than that achieved with the five anthropometric equations and our linear equation, TBW-T. Besides these, BH was more influential in the TBW-T equation but relatively less important in the ANN model; DM was still significant in our ANN

model. These findings suggest that applying variables in clinical medicine should not be easily explained as a linear relationship or deleted from a simple linear equation. Although variables adopted in the ANN model should not be illustrated as independent predictors as perceived by clinicians, they could be elucidated as part of the global function of the ANN, expressing the multidimensional and complicated variable nature of interconnections among clinical factors [23].

In contrast, Cooper et al. [28] used the radiotracer technique as reference method in patients with ESRD under hemodialysis or peritoneal dialysis and found that predicted TBW by the Watson equation was significantly underestimated while predicted TBW by the 58% BW approximation was significantly overestimated. Another study [32] used single frequency BIA to measure TBW and found that calculated TBW by the Watson formula was underestimated compared with measured TBW by BIA after dialysis, but it was not significantly different within 2 h after the end of a hemodialysis session. This is why we did all of our MF-BIA measurements within 30 min after the end of a dialysis session. However, incomparable study populations and different reference methods might contribute to discrepancies.

There are some limitations in this study. First, there are other potential determinants of body composition such as activity and diet. It would be feasible in the future to incorporate some of these factors into ANN analysis. Second, our sample size was relatively small, although the leave-one-out, cross-validation technique might have overcome this problem [25]. Third, our study was done at a single institution. Further studies in different centers can be designed to corroborate our findings and decrease possible inter-institutional variation. Finally, some clinicians may feel ANN is more onerous to use than some simpler equations (e.g., TBW as 58% of BW). Current hardware and software are more user-friendly, and the predictive ANN model is easier to use and more accurate than conventional anthropometric equations. Our future study will also focus on development of a web-based platform using ANN as a kernel engine for clinicians to do real-time estimation of TBW in their patients.

In conclusion, TBW estimated by anthropometric equations may be misleading. We demonstrated that the ANN approach outperforms conventional anthropometric equations and the ANN model may be a feasible alternative for TBW estimation in hemodialysis patients.

Acknowledgments

We are indebted to Mr. Sung-Yin Hsiao, who served in developing the software for the leave-one-out cross-validation technique. We are much indebted to Dr. Fu-Chiu Yu for his critique of the manuscript.

Appendix

Details of the anthropometric equations for estimation of TBW investigated in this paper are listed below.:

58% of BW (TBW-58) [BW, body weight]
TBW-58 = 0.58 × BW

Watson formula (TBW-W) [BH, body height; BW, body weight]
Male: TBW-W = 2.447 – (0.09156 × age) + (0.1074 × BH) + (0.3362 × BW)
Female: TBW-W = –0.2097 + (0.1069 × BH) + (0.2466 × BW)

Hume formula (TBW-H) [BH, body height; BW, body weight]
Male: TBW-H = (0.194786 × BH) + (0.296785 × BW) – 14.012934
Female: TBW-H = (0.34454 × BH) + (0.183809 × BW) – 35.270121

Chertow formula (TBW-C) [BH, body height; BW, body weight; DM, diabetes mellitus]
TBW-C = (–0.07493713 × age) – (1.01767992 × male) + (0.12703384 × BH) – (0.0412056 × BW) + (0.57894981 × BW) + (0.57894981 × DM) – (0.00067247 × BW2) – (0.03486146 × age × male) + (0.11262857 × male × BW) + (0.00104135 × age × BW) + (0.0186104 × BH × BW), where male = 1 and DM = 1.

Lee formula (TBW-L) [BH, body height; BW, body weight]
Male: TBW-L = –28.3497 + (0.243057 × BH) + (0.366248 × BW)
Female: TBW-L = –26.6224 + (0.262513 × BH) + (0.232948 × BW)

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