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Bioimpedance Spectroscopy Measurements for Body Fluids Assessment in Iraqi Maintenance Hemodialysis Patients

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***Abstract**: The challenge of estimating the hydration status (HS) has always been serious struggle for the physicians when treating patients with end stage renal disease (ESRD) whom undergoing maintenance hemodialysis (HD). Bioimpedance Spectroscopy (BIS) is cheap, easy and noninvasive method that has been successfully proposed for the determination of body fluid compartments, the intra cellular water (ICW), the extra cellular water (ECW) and the total body water (TBW), which can be utilized in calculating the amount of fluid excess or deficit by adapting the physiological body model.*

We explored the usefulness of the BIS in assessing the HS of 75 subjects Iraqi ESRD patients undergoing maintenance HD in the unit of the nephrology and renal transplantation center, Baghdad, Iraq by evaluating the HS from first BIS measurements session and adjusting the HD parameters accordingly for 4-6 weeks duration after then second follow up BIS measurement session was conducted. Water compartments and HS results were analyzed and compared with the previous measurements session.

It was evidently observed that the HS values of patients groups out of normo-hydration range were shifted toward the normo-hydration state.

These findings suggest that the use of BIS can contribute in a useful, easy and better way to HS assessment in HD patients in Iraq and thus preventing the occurring of the pathological consequences correspond to inaccurate assessment of the patients HS.

1. Introduction

The high morbidity and mortality rate in HD patients are evidently related in a major way to the cardiovascular pathology arises from the associated hypertension and cardiac damage [1]. Many studies showed that the hypertension remains a struggle despite the antihypertensive drug use and sever damage to the cardiac walls (e.g. left ventricular hypertrophy LVH) often developed and worsen throughout the renal replacement therapy [2]. That being said, other studies have shown that the blood pressure in such patients depends mainly on volume; consequently, strict HS control contribute in maintaining blood pressure to acceptable limits without using drugs which lead to lessening in cardiovascular system associated pathology and suppress mortality risk [3, 4]. Therefore physicians always aim to estimate and achieve patient dry weight, which is defined as the least achievable weight by ultrafiltration which maintains the patient blood pressure within the normal range in the inter-dialytic period without using blood pressure drugs [5, 6], during the HD session. However they are only counting on their experience and clinical observation which was reported to be subjected to high level of misjudgment by some studies [7], [8]. The gold standard technique for direct measuring of the body fluid compartment being the dilution method is difficult to be applied as routine procedure due to the facts of being invasive procedure and patients have to wait about 3 hours in order to obtain equilibrium of the diluting substances in the body in addition to the high cost of the materials and complicated associated blood samples analysis [9].

Bioimpedance techniques, are simple, affordable and noninvasive, have been used to measure and assess body fluids compartments utilizing various hypothesis and theories [10]. Its principle is based on the fact that the volumes of body fluids can be obtained by injecting low current (I) to the body and measuring the voltage (V) in order to calculate the bioimpedance (Z) as per Ohm's low (equation 1) [11]

$$\bar{Z} = \frac{\bar{V}}{\bar{I}} \qquad (1)$$

The bioimpedance (Z) is a complex number of the two components: the real part which is the resistance (R) and the imaginary part being the reactance (X_c). The TBW can then be calculated by assuming the body is comprises of five cylinders from equation (2) [12]

$$V_c = \rho \left(\frac{Ht^2}{R}\right) \qquad (2)$$

Where Vc is the volume of the cylinder in liter which is equivalent to the TBW, ρ is the resistivity in ohm centimeter, R is the resistance in ohm and Ht corresponds to the body height in centimeter.

This study uses the BIS technique which measures the tissue electrical impedance response to low injected AC current (as low as 50 μA) with a spectrum of 50 frequencies ranging from 5 Hz to 1 MHz where the high frequencies measurements correspond to ECW as the current cannot penetrate the cell membrane which acts as the capacitive barrier against electrical charges whereas the low frequencies measurements correspond to the TBW as the current can penetrate through the cell membrane (figure 1) [13]–[15].

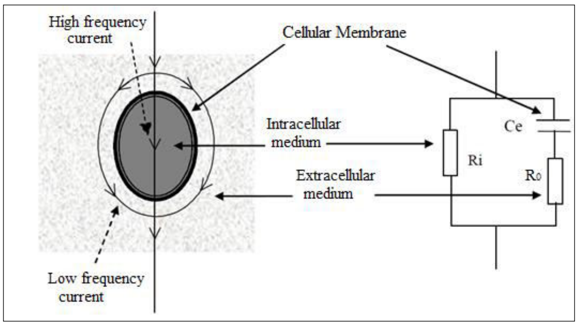

Figure (1) Electrical Equivalent Model for a biological cell in suspension in the ECW (Fricke's Model). R_i: intra-cellular resistance, R_0: extra-cellular resistance, Ce: capacitance

The 50 measurements of the resistance and reactance are then applied to the Cole-Cole model (Figure 2) with Hanai mixture theory where the resistance at zero frequency (R_0), which corresponds to the ECW resistance, and the resistance at infinity frequency (R_∞), which corresponds to the TBW resistance, are extrapolated mathematically using cole fitting equation [16] (equation 3) .

$$Z(\omega) = R_\infty + \frac{R_0 - R_\infty}{1 + (j\omega\tau)^\alpha} \qquad (3)$$

Where Z is the bioimpedance complex value at the applied angular frequency ω, j equal to √-1, τ is the characteristic time constant and α is the exponent factor of shape which represents the distribution influences seen in biological cell suspensions and tissues [17]

The ICW resistance Ri can then be calculated from equation (4).

$$\frac{1}{R_i} = \frac{1}{R_\infty} - \frac{1}{R_0} \qquad 4$$

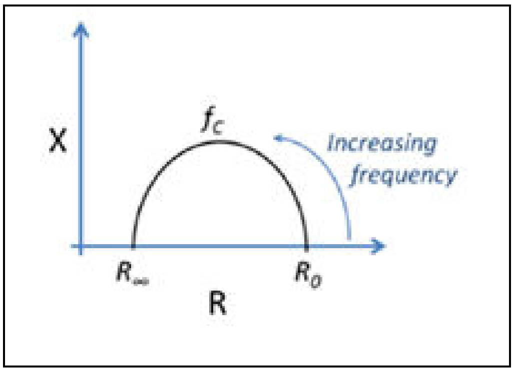

Figure (2) Cole-Cole Model

ECW volume, ICW volume and TBW volume are calculated from equations 3, 4 and 5 respectively [17]

$$ECW = \left(\frac{\rho_{ECW} K_B H^2 \sqrt{W}}{\sqrt{D} R_0}\right)^{\frac{2}{3}} \qquad 5$$

$$ICW = ECW\left[\left(\frac{\rho_{TBW} R_0}{\rho_{ECW} R_\infty}\right)^{\frac{2}{3}} - 1\right] \qquad 6$$

$$TBW = ECW + ICW \qquad 7$$

where ρ_{ECW} is the extracellular resistivity (female: 39 Ω cm, male: 40.5 Ω cm), ρ_{ICW} is the intracellular resistivity (female: 264.9 Ω cm, male: 273.9 Ω cm), H is the body height (cm), W is the body weight (kg), D is the body density (1.05 kg L−1) and K_B = 4.3 is a shape factor correcting for a whole body measurement between wrist and ankle, relating the relative proportions of the leg, arm, trunk and height [18]. ICW was calculated according to the published second generation mixture theory equation [19].

The water compartments estimations for both healthy and ESRD humans using BIS technique has been validated against the gold standard technique by many studies [20]–[22]

Based on the physiological tissue model introduced by Chamney et al [23], HS is assessed by calculating the excess or deficit fluid from equation 6

HS = (1.136ECW)–(0.430ICW)–(0.114W) 6

Where M denotes the patient weight in kg. The cutoff range for normo-hydration state was set between -1 L and 2.5 L [24]–[26].

2. Materials and Methods

Study participants were recruited from patients undergoing maintenance HD treatment in the HD department of the Kidney Transplant Center in Ghazi Al-Hariri Specialized Hospital in Baghdad, Iraq. Seventy five (75) patients were in the treatment schedule, patients who fit the study criteria, being older than 18 years, and diagnosed as ESRD with HD therapy schedule twice weekly, were voluntarily enrolled. Patients being scheduled for renal transplant procedure for less than three months or with pacemaker, amputation, serious trauma or end-stage life-limiting pathology were excluded.

2.1. Session One:

Patients were interviewed and assessed by specialized HD nurse upon arrival. Each patient's records reviewed. The test explained for them and their verbal permission taken. Height, weight and blood pressure measurements were taken. Pre HD ECW, ICW and TBW were measured as well by BIS with the Xitron Hydra 4200, Xitron Technologies, San Diego, covering a frequency spectrum of 50 frequencies from 5 kHz to 1 MHz logarithmically spaced. The devices were calibrated using a testbox from the manufacturer. All subjects were in supine position for 10 minutes before conducting the measurement. A tetrapolar arrangement of gel electrodes (2.0 x 7.5 cm2) was applied to the subject's skin after alcohol preparation. Electrodes were placed (1) on the anteriodorsal surface of the right ankle over the axis of the medial and lateral malleoli, (2) on the dorsal surface of the right foot 2 cm proximal from the metatarsophalangeal joint of the third toe, (3) on the dorsal surface of the right wrist 7.5 cm proximal from the hand electrode and (4) on the dorsal surface of the right hand 1 cm proximal from the metacarpophalangeal joint of the third finger. The collected raw data for the resistance (R), reactance (X_c), time delay (T_d) and phase shift (θ) were applied to the Cole model to extrapolate the R_0 and R_∞ after then R_i was calculated (equation 4). ECW, ICW and TBW were then calculated by equations 5, 6 and 7 respectively. HS was assessed by calculating the excess or lacked fluid from the body composition model proposed by Chamney et al (equation 6). The model is based on the hypothesis of constant tissue hydration properties and that for the dialysis patients the excess fluid is mainly accumulate in the expanded extracellular volume [26].

Subjects were then divided into three groups based on the HS results: normal group (NG), dehydration group (DG) and fluid overload group (FOG). Subjects with HS showing over-hydration to more than 2.5 L were assigned to the FOG group where three HD session per week with higher ultrafiltration and lower sodium profile were prescribed for the duration until the next BIS measurement session. Subjects with HS showing dehydration of less than -1 L were assigned to the DG group. More fluid intake, lower ultrafiltration and higher sodium profile were prescribed to the group for the duration until the next BIS measurement session. The remaining subjects were assigned to the NG group in which the HS values lie within the range of the normo-hydration state and no alteration to the HD parameters were made.

2.2. Session Two:

Second follow up sessions were conducted to all groups after 4-6 weeks duration during which the required adjustment for HD sessions and sodium profiling for each of the study group were applied. The procedure from session one was repeated to assess the progress in the HS and body water compartments.

2.3. Statistical Analysis:

All data were reported as mean ± standard deviation (SD). Categorical variables are presented as ratio of whole. Intervention effects were assessed using simple t test. Comparisons for the univariate were performed via one way ANOVA. All statistical analyses were performed using Graph prism (Graphpad 5, San Diego, CA, USA).

3. Results

The baseline characteristics of the study group are shown in table (1) with the associated bioimpedance and body fluid compartments measurements. Total of 75 subjects whom diagnosed as ESRD patients were voluntarily enrolled with mean age (38.88 ± 13.07 years). There were (54 / 72%) males. The mean value of the systolic blood pressure (SBP) measurements of the entire study population was (133.2 ± 11.7 mmHG) and the mean diastolic blood pressure (DBP) value was (88.47 ± 10.9). The distribution of the hydration status of the entire study group is demonstrated in (figure 4). Referencing the HS measurements of session one, subjects were grouped into three categories: (52%) were in the normal range value and thus were enlisted in the NG whilst the dehydration and fluid overload values were seen in (20%) and (28%) of the patients respectively and were assigned to the DG and FOG accordingly. Age, height, body mass index (BMI) and body surface area (BSA) values are shown in table (1). R_i and R_0 calculations for the NG, DG and FOG were (1356 ± 351.5 Ω), (1162 ± 267.9 Ω) and (1101 ± 281.9 Ω), and (665 ± 146.4 Ω), (816.9 ± 233.1 Ω) and (469.9 ± 86.02 Ω) respectively. The water compartments for the three groups were as follows: TBW, ECW and ICW for the NG were (37.03 ± 10.19 L), (16.14 ± 4.48 L) and (20.88 ± 5.81 L) respectively whereas for the DG TBW, ECW and ICW were noticed to be (38.34 ± 7.66 L), (13.93 ± 3.10 L) and (24.41 ± 4.91 L) respectively. Whilst for the FOG TBW, ECW and ICW were (43.81 ± 7.548 L), (20.06 ± 2.76 L) and (23.76 ± 5.28 L) respectively. The water compartments ratios of the three groups are illustrated in figure (3).

SBP measurements were (134 ± 11.5 mmHG), (140.2 ± 11.9 mmHG) and (125.4 ± 10.5 mmHG) for the NG, FOG and DG respectively, whereas DBP values were (88.27 ± 10.9 mmHG), (93.07 ± 10.1 mmHG) and (82.53 ± 9.7 mmHG) for the NG, FOG and DG respectively (table 1).

Table 1. Study Patients Demographics and Parameters from Session One

Variable	All Patients (N=75)	NG (N=39)	FOG (N=21)	DG (N=15)	P value
Age (years)	38.88 ± 13.1	37.15 ± 12.6	40.43 ± 10.0	41.2 ± 17.7	0.4911
Male (ratio)	54 (72%)	24 (61.53%)	18 (85.7%)	12 (80%)	> 0.9999
Weight (Kg)	73.53 ± 18.3	75.95 ± 20.3	70.57 ± 12.8	71.36 ± 19.3	0.4899
Height (m)	1.683 ± 0.1	1.672 ± 0.1	1.707 ± 0.1	1.68 ± 0.1	0.3673
BMI (Kg/m^2)	25.36 ± 5.7	26.31 ± 5.5	23.71 ± 3.3	25.2 ± 8.3	0.2445
BSA (m^2)	1.844 ± 0.3	1.868 ± 0.3	1.826 ± 0.2	1.806 ± 0.2	0.6927
ECW (L)	16.8 ± 4.4	16.14 ± 4.5	20.06 ± 2.8	13.93 ± 3.1	< 0.0001
ICW (L)	22.39 ± 5.7	20.88 ± 5.8	23.76 ± 5.3	24.41 ± 4.9	0.0502
TBW (L)	39.19 ± 9.4	37.03 ± 10.2	43.81 ± 7.5	38.34 ± 7.7	0.0243
HS (L)	1.068 ± 3.1	0.7 ± 1.3	4.526 ± 2.1	-2.809 ± 2.0	< 0.0001
SBP (mmHG)	133.2 ± 11.7	134 ± 11.5	140.2 ± 11.9	125.4 ± 10.5	0.0013
DBP (mmHG)	88.47 ± 10.9	88.27 ± 10.9	93.07 ± 10.1	82.53 ± 9.7	0.0147
R_0 (Ω)	640.8 ± 195.4	665 ± 146.4	469.9 ± 86.0	816.9 ± 233.1	< 0.0001
R_i (Ω)	1246 ± 335.0	1356 ± 351.5	1101 ± 281.9	1162 ± 267.5	0.0091
R_∞(Ω)	418.1 ± 110.9	443.9 ± 98.3	327.8 ± 64.9	477.5 ± 122.1	< 0.0001

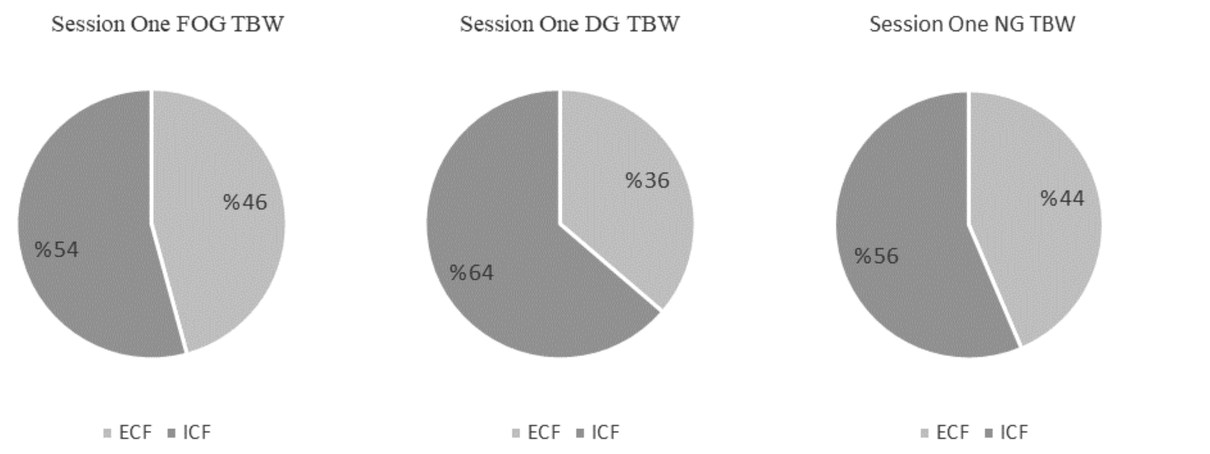

Figure (3) Session one water compartments

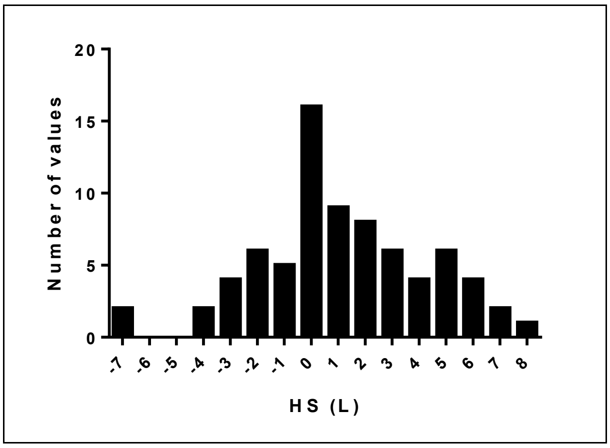

Figure (4) Frequency distribution of session one HS

Session two BIS measurements and the fluid compartments calculations were conducted after 4-6 weeks from session one. The overall measurements are shown in table (2).

Subjects of FOG were prescribed to have thrice-weekly HD sessions with increased ultrafiltration and decreased dialysate sodium during the duration between the two measurements sessions in order to increase fluid shifting toward the dialysate. For FOG, R_0 values were observed to be (650.5 ± 204.8 Ω). R_i measurements value (1147 ± 23 Ω). The TBW and ECW were deviated to values (TBW: 41.52 ± 5.85 L) and (ECW: 18.46 ± 2.80 L), whilst the ICW showed shifting to a value of (23.06 ± 3.54 L). The HS calculations were seen to have value of (3 ± 2.26 L).

DG second session BIS measurements were performed after 4-6 weeks from session one date as well. During the between BIS measurements sessions duration the group subjects were prescribed to have more fluid intake and their HD sessions were adjusted to no/low ultrafiltration and higher sodium dialysate. The R_0 measurements were observed to be shifted to (756.3 ± 235.7 Ω, P= 0.484), whilst R_i values were noticed to be (1129 ± 245.3 Ω, P= 0.724). The changes in the R_0 values resulted in shifting the water compartments to: ECW (14.79 ± 3.58 L, P=0.486), TBW (39.37 ± 8.22 L, P=0.725), ICW (24.58 ± 5.04 L, P=0.926), and HS (-1.90 ± 1.49 L).

NG session two results which was performed within the same time period of other groups, were observed to be: 669.7 ± 201.9 Ω, 1356 ± 453.3 Ω and 444.9 ± 133.4 Ω for the R0, Ri and R_∞, and 16.27 ± 4.45 L for the ECW, 21.13 ± 6.05 L for the ICW, and 37.4 ± 10.41 L for the TBW. The HS results were observed to be 0.731 ± 1.36 L (table 2).

Figure (5) demonstrate HS shifting between session one and session two BIS measurements for the sum of study group and the three categorical groups: NG, DG and FOG.

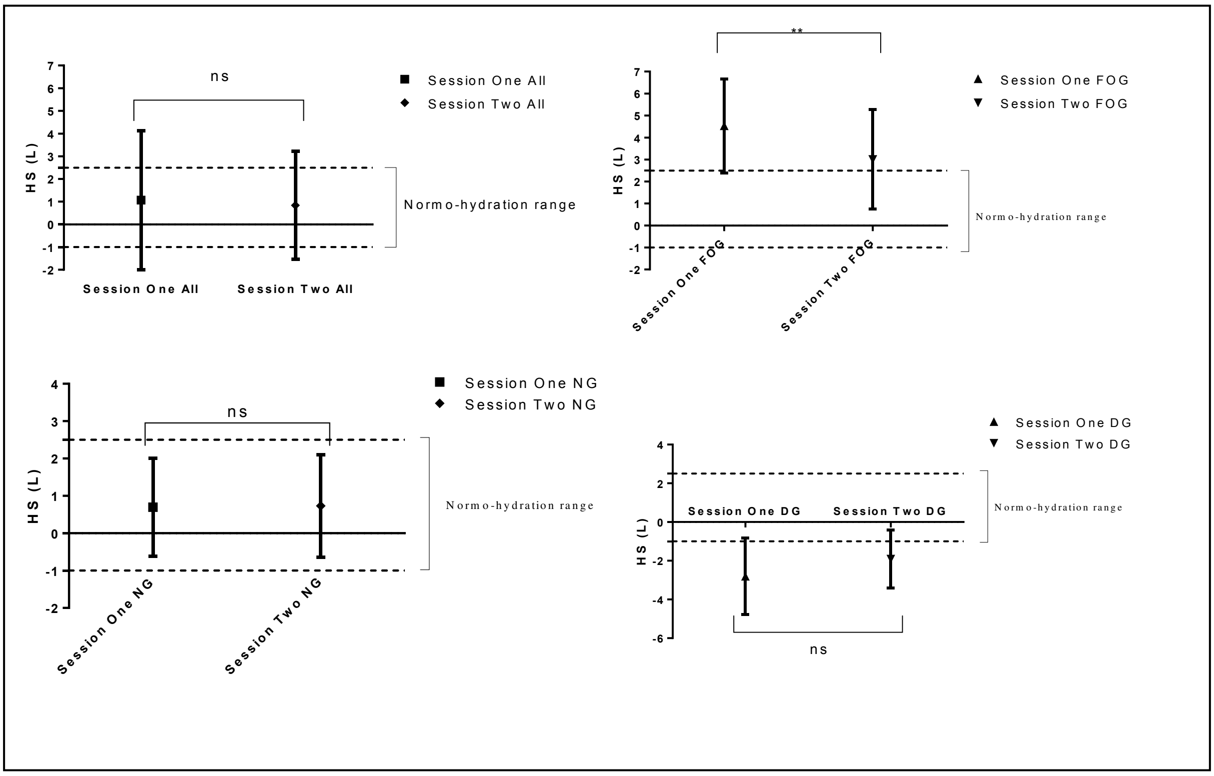

Figure (5) HS shifting between session one and session two

Table 2. Session Two Measurements

Variable	All patients	NG (N=39)	FOG (N=21)	DG (N=15)
Weight (kg)	73.56 ± 17.8	73.57 ± 17.8	69.73 ± 11.6	72.13 ± 17.9
BMI (kg/m^2)	25.43 ± 5.48	26.9 ± 5.3	23.82 ± 3.04	25.8 ± 7.4
SBP (mmHG)	133.8 ± 12.2	134.06 ± 11.18	139.24 ± 21.1	125.47 ± 10.07
DBP (mmHG)	88.3 ± 10.8	88.3 ± 10.7	92.36 ± 10.2	82.64 ± 9.2
ECW (L)	16.58 ± 4.05	16.27 ± 4.45	18.46 ±2.80	14.79 ± 3.57
ICW (L)	22.36 ± 5.38	21.13 ± 6.05	23.06 ± 3.54	24.58 ± 5.03
TBW (L)	38.94 ± 8.99	37.4 ± 10.41	41.52 ± 5.85	39.37 ± 8.21
HS (L)	0.8406 ± 2.374	0.731 ± 1.36	3.1 ± 2.16	-1.995 ± 1.46
R_0 (Ω)	650.5 ± 204.8	669.7 ± 201.9	539.2 ± 129.3	756.3 ± 235.7
R_i (Ω)	1252 ± 378.5	1356 ± 453.3	1147 ± 231	1129 ± 245.3
R_∞ (Ω)	423.64 ± 121.37	444.9 ± 133.4	365.4 ± 80.86	450 ± 119.2

4. Discussion

Bioimpedance spectroscopy technique utilizes the tissue resistive behavior to obstruct current flow in a measurable way that is directly related to the amount of the tissue water content to the cellular level. With the cell membrane acting as a barrier preventing the flow of low frequencies current, the measureable tissue resistive behavior (i.e. bioimpedance) considered to be related to the extra cellular space vis-à-vis the ECW. Whereas the high frequencies current can break through the cell membrane providing measureable bioimpedance related to the TBW. Providing such noninvasive, relatively fast and easy to be applied tool to the dialysis centers healthcare delivery specialists that is capable of assessing the HS of the maintenance HD patients is remarkably vital for those patients group management since the uncontrolled fluid management considered as major factor contributing in cardiovascular disorders and high mortality rate in the dialysis center. However, several factors are considered as limitations for putting the ultimate confident in the accuracy of the BIS technique in Iraq. Firstly would be the sat local standard of twice weekly HD sessions whilst having additional third weekly HD session will minimize the excessive fluid overload risk for the patients. The assumption of the body comprising of five cylinders with uniform conductivity at any cross section, the base theory of the BIS measurement, is a major drawback for the technique as well. Another limitation is the fact that the measured whole body bioimpedance is mainly derived from the resistance of the extremities with percentage of more than 90% whist the amount of water volume in the extremities does not exceed 30% of the TBW and 70% in the trunk. Also any factor affecting the distribution of the water content among the body segments such as body position alteration or setting the measurement immediately post dialysis, will results in increasing the error in results, this can be overcame by using the segmental BIS technique.

Age, height, body mass index (BMI) and body surface area (BSA) values showed no significant differences among the three groups as seen in table (1). However it was noticed that the FOG blood pressure measurements higher than other groups. Session one R_0 measurement showing noticeable larger values in the DG than both NG and FOG and the latest showed the least values. This variation reflected on the ECW and TBW values of each of the categorical groups. It is well noticed that the ECW and TBW of the FOG showing expanded values than both the NG and DG, whereas the latest results were the least in values. Despite the appearing differences of the ECW and TBW yet it is not precisely indicating the level of the hydration of the body because of the variation in the ECW normal values due to the variations in body composition among the Iraqi population. Therefore to put an indicating reference for the hydration of the body a body composition model were used to measure the HS considering the weight in addition to the ECW and TBW with ideal value of (0 L) and normo-hydration range -1 to 2.5 L.

Results from session two BIS measurements revealed non-significance changes in weight and BMI among the three groups comparing to session one measurement. However it showed significant shifting in R_0 values among the DG and FOG patients. Changes of R_0 for FOG seen to be toward higher values ($P = 0.0009$) whereas for the DG toward lower values ($P = 0.2302$) comparing to session one BIS measurements. Same behavior was noticed for R_∞ showing higher values in DG ($P = 0.221$) and lower values in FOG ($P = 0.001$). Consequently, these changes reflected evident shifting in the concerned ECW and TBW toward lower values for the FOG (ECW P = 0.0002 and TBW P = 0.0015). Whilst DG ECW and TBW shifting was toward higher amounts (ECW P = 0.2101 and TBW P = 0.2922). On the other hand it was well observed that session two HS results were shifted toward the normo-hydration range for both the FOG (P = 0.0086) and DG (P = 0.2514) (figure 5). Ri values showed no significant difference between the two sessions among the three groups (P = 0.1356 for FOG, P = 0.3102 for DG and P = 0.9979 for NG) and were accordingly reflected on the ICW not significantly differences (P = 0.2228 for FOG, P = 0.678 for DG and P = 0.3439 for NG). Furthermore R_0 and R_∞ shifting for the NG patients between the two sessions were not significantly different (P = 0.7885 and P = 0.9223 respectively), accordingly the ECW and TBW differences were not significantly different as well (P = 0.5898 and P = 0.3644 respectively) (figure 5) and HS values remained within the range of the normo-hydration state (P = 0.8893). The blood pressure measurements were seen to be improved especially for the FOG, both SBP and DBP were noticed to be dropped toward the normal range values (P = 0.0672 and 0.1747) respectively.

The above findings indicate that BIS provided assistive guideline for the study group hydration evaluation and highlighted an interest on how the clinical decision outcome associated with BIS results provided better management for the study categorical group more effectively for the patients with accumulated fluid overload.

5. Conclusion

Bioimpedance spectroscopy (BIS) is noninvasive, safe, relatively cost effective, simple, portable and applicable technique that can conveniently assist healthcare delivery specialists in Iraq to achieve better estimation of the body fluid compartments of the ESRD patients whom undergo maintenance HD. Having accurate body fluids assessment is one of the essential parameters affecting the treatment delivery decision concerning the study pathological group in the Iraqi society. However, the varieties of factors that can affect the accuracy of the measurements of BIS such as misplacing the electrodes, high dependability on the surrounding electrical environment and the fact that all the measurements are being equated from several assumptions and modelling algorithms, require further investigations and experimental works to make the process of more precise and less sensitive to noise factors.

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