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ORIGINAL ARTICLE

Sequential body composition analysis by bioimpedance early post-kidney transplantation

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Summary

Background: While chronic renal failure patients present disturbed body water composition, few studies have been done on its behavior following kidney grafting (Tx). We report the changes associated with a successful Tx on body composition evaluated by bioelectrical impedance analysis (BIA). *Methods*: Twelve Tx (seven males, five females) were studied. The BIA was assessed before Tx, at month 1 and at month 3 post-Tx. Total body water (TBW), extracellular water (ECW), intracellular water (ICW), Na:K exchange rate (Nae:Ke) and phase angle (PA) were studied. An healthy group and a HD group were evaluated three times in a year interval. *Results*: Comparing before Tx with month 1 post-Tx, TBW, ECW and Nae:Ke increased, while ICW and PA decreased significantly. Comparing month 1 with month 3 post-Tx, ECW decreased, while ICW and PA increased. On comparing month 1 post-Tx with the healthy group, Nae:Ke was greater and PA was lower at month 1. *Conclusions*: The BIA showed that the different body water compartments of Tx recipients quickly match the constitution of normal individuals, overcoming drug therapy side effects.

Introduction

Kidney plays a critical role in maintaining overall fluid balance, not only by its modulation of body water, but also by its role in sodium and intravascular volume control. Maintaining the daily sodium balance is the main feature of this regulation because sodium influences both the extracellular volume and the distribution of water between intracellular and extracellular compartments. During the development of chronic renal failure, the ability in maintaining sodium balance becomes increasingly impaired and directly results in changes of the extracellular fluid [1]. The extreme situation is exemplified by end-stage renal disease (ESRD) patients treated by hemodialysis who suffer from intermittent fluctuations in hydration status and plasma electrolyte concentrations. Depending on the patient's fluid intake and residual renal function, hemodialysis must usually remove 1–4 l of fluid over an average of 4 h period, with rapid transcellular shifts of water between the intracellular (ICW) and extracellular water (ECW) compartments, such that by the end of hemodialysis, a new equilibrium is established in which plasma volume is partially restored at the expense of tissue interstitium fluids [2].

Successful kidney transplantation in a patient with ESRD restores near normal renal function and is expected to correct the metabolic abnormalities of renal insufficiency [3,4], and to normalize body electrolyte composition. Other authors have studied with different methodologies the composition of body solid compartments post-transplantation and its relationship to immunosuppressive therapy [5–8]. They reported a

weight gain, especially during the first 6 months after transplantation, predominantly due to an increase in fat-mass, which was already evident within the first 3 months [5], and that may result from the recovery of well-being, from the removal of dietary restrictions, and following an increase in appetite [6]. However, as a rule, the transplant patient does not achieve normal renal function as compared to what is observed with two native healthy kidneys. Moreover, immunosuppressive drugs currently in use on kidney transplantation are endowed with the capacity to interfere with kidney handling of water and electrolytes, even when they are not nephrotoxic. While the diffuse effects of glucocorticoids on the body reflect the variable mineralocorticoid potency of different steroids, which is rather important with the doses used during the first weeks post-transplantation, calcineurin inhibitors induce changes upon the glomerular hemodynamics and, among others, on renal tubular handling of potassium and magnesium [7,9]. The calcineurin inhibitors' vasoconstriction effect is in part induced by the powerful vasoconstrictor endothelin, but NO, renin-angiotensin system, arachidonic acid metabolism alteration and activation of the sympathetic nervous system also play a significant role [10]. Actually, the majority of kidney transplant patients develop hypertension and a tendency for sodium and water retention [7], probably as a consequence of calcineurin inhibitor effects, although other causes may be involved.

Bioelectrical impedance analysis (BIA) offers a variety of applications for the noninvasive measurement of the body composition, total body water (TBW), and compartmentalization of body fluids. The BIA has been recently applied to the dialysis population by several groups of investigators [8,11–15] with the therapeutic aim of better definition of euvolemic state or ''dry weight'', in order to prevent symptoms of hyper and hypovolemic status.

Surprisingly, little detailed information is available on changes in body composition after renal transplantation [16]. There is no report on the rate and effectiveness of kidney transplantation in restoring normal total body water, electrolyte body composition, and water distribution between extra and intracellular compartments. Also, the influence on body composition parameters by the degree of renal function recovery and therapeutic drugs side effects have not been analyzed. In this study, we report the influence of renal function recovery post-transplantation on body water composition during the early period, when the doses of calcineurin inhibitors and steroid are at their highest, as well as the comparison of Tx patients with either normal controls or chronic HD-treated patients.

Subjects and methods

Subjects

We have included 12 nondiabetic first cadaver kidney recipients, seven males and five females, with a mean age of 31.8 ± 8.4 years and a mean height of 165.4 ± 9.1 cm. All the patients underwent hemodialysis treatment for a period between 6 and 60 months pre-transplant, and were studied when there were no major infection episodes or other clinical events. The etiology of their chronic renal failure was not determined in five cases, IgA nephropathy in three cases, Alport nephropathy in two cases, hypertension and reflux nephropathy, one case each. Every patient was treated from the beginning with methylprednisolone, cyclosporine microemulsion, and either azathioprine or mycophenolate mofetil. The blood pressure was controlled by calcium channel blockers (amlodipine, nifedipine), β-adrenergic blockers (atenolol, metoprolol), and angiotensin–convertin enzyme inhibitor (captopril). None received diuretic therapy or lipid lowering drugs. At month 1 and at month 3 post-transplantation, creatinine clearance (crCl) was always greater than 60.0 ml/min/1.73 m^2. The hemodialysis group included 12 nondiabetic patients, seven males and five females, with a mean age of 38.3 ± 7.1 years and a mean height of 165.4 ± 7.2 cm. They were on regular hemodialysis from 6 up to 60 months, with blood access by arteriovenous fistulae, no dry weight changes greater than 5% in the last three months before each evaluation, residual creatinine clearance lower than 5.0 ml/min/1.73 m^2, HBV and HCV negatives, plasma albumin greater than 3.5 g/dl and total cholesterol greater than 180.0 mg/dl. All patients were on the waiting list for kidney transplantation. Patients with cardiac, pulmonary or hepatic failure, with cancer, diabetes mellitus or with previous graft failure were not considered. Patients with body mass index (BMI) values outside the range 18.0–30.0 kg/m^2 were excluded. In the healthy group we have included 10 subjects, six males and four females, with a mean of age 34.7 ± 5.9 years and a mean height of 172.1 ± 7.7 cm. All subjects were judged to be healthy by history and chemical laboratory profiles. Every subject displayed a plasma creatinine (Pcr) < 1.2 mg/dl and crCl > 90.0 ml/min/1.73 m^2. The characteristics of each group were given in Table 1.

Methods

Body composition assessment by BIA

Body composition was assessed by BIA instruments with the following characteristics: resistance between 0 and 1000 Ω, reactance between 0 and 500 Ω, precision of 1% and frequency of 50 kHz. The BIA plethysmograph (BIA-101; RJL/Akern Systems®, Detroit, MI) recorded the

Table 1. Groups characteristics at the selection timing.

	Tx group	HD group	Healthy group
n (M/F)	12 (7/5)	12 (7/5)	10 (6/4)
Age (years)	31.8 ± 8.4	38.3 ± 7.1	34.7 ± 5.9
Height (cm)	165.4 ± 9.1	165.1 ± 7.2	172.1 ± 7.7
Weight (kg)#	63.2 ± 6.3	62.1 ± 8.4	76.1 ± 13.2*
BMI (kg/m^2)	23.3 ± 2.8	22.8 ± 2.7	25.6 ± 3.1
Pcr (mg/dl)	1.30 ± 0.19†/1.28 ± 0.22‡	10.13 ± 0.99§	0.87 ± 0.10
crCl (ml/min/1.73 m^2)	70.03 ± 5.49†/75.12 ± 10.11‡	NA	123.44 ± 17.54
SBP (mm Hg)	137 ± 9†/128 ± 12‡	150 ± 15§/135 ± 19¶	126 ± 10
DBP (mm Hg)	80 ± 7†/73 ± 11‡	83 ± 10§/76 ± 9¶	73 ± 5

Results are presented as mean ± SEM. NA, not applied.
n, number; M, male; F, female; HD, hemodialysis; Tx, transplant.
#Post-HD weight at HD group and Tx group (before Tx).
*$P < 0.05$ as compared with Tx group.
†Month 1 post-Tx.
‡Month 3 post-Tx.
§Before HD.
¶After HD.

resistance and reactance values that, when inserted in the BIA software together with the sex, age, weight and height is capable of automatically performing the calculations for TBW, ECW, ICW, Nae:Ke, phase angle (PA), body cellular mass (BCM), fat-mass (FM), fat-free mass (FFM) and basal metabolism (BM) [17].

The BIA instrument was used according to the manufacturer's instruction and always by the same operator. To improve the accuracy and precision, patients' vertical stature was measured to the nearest 0.5 cm and weight was measured to the nearest 0.1 kg [18]. The measurements were made in a room without exposure to hot or cold temperatures, or humidity [18,19], and the subjects were instructed to avoid heavy exercise 12 h before testing [17–19]. The electrodes were used only once, no body part was in contact to metals, and skin was clean and dry. Patients with skin diseases, that may modify electrode–skin electrical transmission, with amputations and with regional alterations in skeletal muscle tissue were excluded [18]. Females were not analyzed during their menstrual period.

The measurements were taken on subjects approximately 2 h after eating a breakfast-like light meal. Subjects lay clothed, but without shoes and socks, in the supine position on a stretcher, with the limbs not touching the body, abducted to 30 ° [20]. An inner electrode was attached to the dorsal surface of the wrist on the arm without arteriovenous fistulae [18]. An outer electrode was placed on the dorsal surface of the third metacarpal bone. A second pair of electrodes was positioned on the anterior surface of the ipsilateral ankle and the dorsal surface of the third metatarsal bone [12]. A single frequency (50 kHz) low-amplitude current was introduced via the electrodes on the hand and the foot. The voltage drop was detected by the electrodes at the wrist and the ankle. The procedure was performed in less than 5 min [12].

In the transplant group, the first BIA measurement was performed immediately after the hemodialysis session just before transplant surgery, while the other measurements were performed at month 1 and month 3 after renal transplantation. At month 1, all patients had adequate diuresis, free of oedema, and were clinically stable; same conditions were applied to month 3 procedures. For the hemodialysis group, we have done the assessment before and 15 min after HD session, three times during a year, on a right side without vascular access. We presented the average value for each patient. The healthy subjects were analyzed three times a year and the mean was calculated for each parameter.

Laboratory assessment

Pcr, cyclosporine level (CsA), crCl, osmolarity (Osmo), glucose fasting levels (Gluc), serum albumin (Alb), total cholesterol (Chol), triglycerides (Tgs) and hematocrit (Hct) were evaluated for the transplant group. crCl was assessed by Cockroft–Gault formula [21], while the trough CsA level was measured in whole blood by TDx monoclonal, from Abbott®, Abbott Park, Ill. We have monitored the blood pressure with a digital instrument (Arlington, TX).

Ethics and statistical analysis

The protocol was approved by the local Commission of Ethics and informed consent was obtained from each individual.

Results are given as mean ± standard error of the mean. Kolmogorov–Smirnov test was used to study the normal distribution of the sample for all variables. Paired

Student's *t*-test was used to evaluate the body composition differences between post-hemodialysis, month 1 and month 3 inside the transplant group, while one way ANOVA test was performed to study the difference between the transplant group and the nontransplant groups. Pearson correlation was used to study the influence of methylprednisolone and cyclosporine on body composition parameters. We have considered the level of significance when $P < 0.05$.

Results

Biochemistry results

Biochemistry results are displayed in Table 1, for Tx, HD and healthy groups, respectively. The group of patients on regular hemodialysis presented urea reduction rate (URR) of 72.6 ± 6.1%. Among Tx groups, there exist no differences for biochemistry values when month 1 with month 3 were compared. However, as expected, at month 3, methylprednisolone and CsA doses were lower than at month 1.

Concerning biochemistry parameters among the healthy group, no significant changes were found when comparing the three separated evaluations.

The BIA results for Tx, HD and healthy group are presented in Table 2.

Before Tx compared with month 1 post-Tx

We observed the following significant decreases at month 1 as compared to pre-Tx: R ($P = 0.002$), X ($P < 0.0001$), ICW ($P < 0.0001$), PA ($P < 0.0001$) and BCM ($P = 0.0056$), while the opposite was observed for TBW ($P = 0.0014$), ECW ($P < 0.0001$) and Nae:Ke ($P = 0.0003$), which were higher at month 1.

Before Tx compared with month 3 post-Tx

We observed the following significant decreases at month 3 as compared to pre-Tx: R ($P = 0.0016$), X ($P = 0.0003$), ICW ($P < 0.0001$), PA ($P < 0.0001$), and BCM ($P = 0.0212$), while the opposite was observed for weight ($P = 0.0105$), ECW ($P < 0.0001$) and Nae:Ke ($P = 0.0011$), which were higher at month 3.

Month 1 post-Tx as compared to month 3 post-Tx

A significant increase in weight ($P = 0.0058$), ICW ($P = 0.0199$) and PA ($P = 0.0224$) was found at month 3, while ECW was found to be lower ($P = 0.0199$) at month 3 (Figs 1 and 2).

Chronic HD patients as compared with early Tx

As anticipated, no differences were found on comparing post-HD patients with post-HD immediately before transplantation.

Of interest, when we compared before HD session of HD group with month 1 post-transplantation, no significant difference was observed. However, by comparing post-HD session of the HD group with month 1 post-transplant, we observed that R was lower ($P = 0.003$), X was lower ($P < 0.0001$), ICW was lower ($P < 0.0001$), PA was lower ($P < 0.0001$), ECW was greater ($P < 0.0001$) and Nae:Ke was greater ($P = 0.001$) at month 1 post-kidney transplantation. When we compared before HD

Table 2. Bioelectrical impedance analysis results for Tx, HD and healthy group.

	R (Ω)	X (Ω)	TBW (%)	ECW (%)	ICW (%)	Nae:Ke (ratio)	PA (°)
Tx group							
pre-Tx	550 ± 52*†	65 ± 8*†	57.8 ± 8.03*	42.4 ± 2.65*†	57.6 ± 2.65*†	0.97 ± 0.09*†	6.7 ± 0.76*†
Month 1	491 ± 60	45 ± 6	61.5 ± 9.20	48.8 ± 3.04**	51.3 ± 3.04**	1.28 ± 0.18	5.2 ± 0.52**
Month 3	482 ± 54	48 ± 6	60.0 ± 8.75	46.2 ± 2.19	53.8 ± 2.19	1.17 ± 0.16	5.7 ± 0.47
HD group							
pre-HD	486 ± 42	44 ± 4	61.3 ± 5.2	49.4 ± 3.0#	50.6 ± 3.0#	1.33 ± 0.1	5.1 ± 0.5#
post-HD	597 ± 61‡	66 ± 9§	57.4 ± 4.8	42.0 ± 1.8§	58.0 ± 1.8§	0.94 ± 0.1‡	6.7 ± 0.5§
Healthy group	509 ± 80	52 ± 6***	55.2 ± 3.8	45.9 ± 2.3***	54.2 ± 2.3***	1.08 ± 0.08¶	5.9 ± 0.5***¶

HD, hemodialysis; Tx, transplant; R, resistance; X, reactance; TBW, total body water; ECW, extracellular water; ICW, intracellular water; Nae:Ke, sodium/potassium exchangeable ratio; PA, phase angle.

*$P < 0.005$ as compared with month 1.

†$P < 0.005$ as compared with month 3.

‡$P < 0.005$ as compared with month 1.

§$P < 0.0001$ as compared with month 1

¶ $P < 0.05$ as compared with month 1.

#$P < 0.05$ as compared with month 3.

**$P < 0.05$ as compared with month 3.

***$P < 0.05$ as compared with pre-Tx.

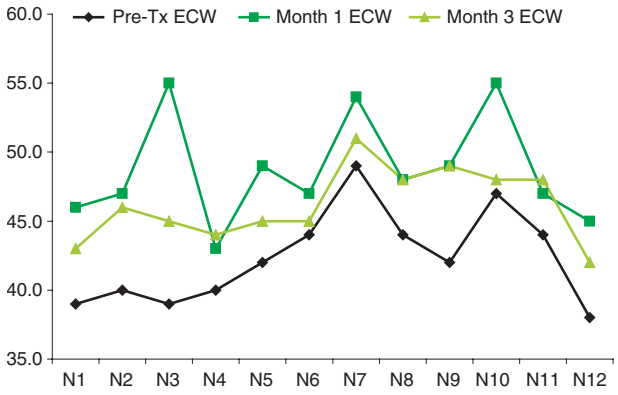

Figure 1 Extracellular water (ECW) fluctuations among transplant patients as comparing pre-Tx with month 1 and with month 3 post-Tx.

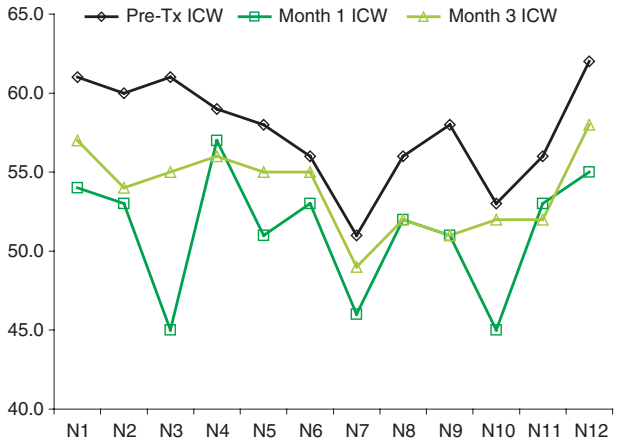

Figure 2 Intracellular water (ICW) fluctuations among transplant patients as comparing pre-Tx with month 1 and with month 3 post-Tx.

session with month 3 post-transplantation, only ECW was lower ($P = 0.018$), ICW was greater ($P = 0.018$), and PA was greater ($P = 0.031$) at month 3.

Healthy controls as compared with early Tx

When we compared before transplantation among the transplant group (i.e. post-HD session), with healthy individuals, we observed that body weight was lower ($P = 0.018$), X was greater ($P = 0.007$), ECW was lower ($P = 0.022$), ICW was greater ($P = 0.022$), and PA was greater ($P = 0.035$) among the pre-transplant group. When we compared month 1 post-transplant with the healthy group, we observed a lower body weight ($P = 0.019$), a greater Nae:Ke ($P = 0.021$), and a lower PA ($P = 0.048$) at month 1 post-transplantation. All other parameters were not different.

We tested the correlation between CsA level, CsA dose and mPred dose with TBW, ECW, ICW, Nae:Ke and PA at month 1 and at month 3 post-transplantation. At month 1, we observed a significant correlation between cyclosporine dose with TBW ($r = 0.712$, $P = 0.014$) and between cyclosporine dose with Nae:Ke ($r = 0.661$, $P = 0.027$). However, at month 3 no significant correlation was found.

Discussion

As far as we know, this is the first study of body water compartments composition by BIA during the first month of post-kidney grafting. Among kidney transplants, the study of body composition has been focused upon the changes observed in fat-mass and lean-body mass, which were patently clear when the doses of steroids were much higher than today with the use of calcineurin inhibitors [22]. However, body composition alterations are not just at fat or lean body mass compartments but, body hydration status which is profoundly affected in chronic renal patients is expected to be corrected following kidney transplantation. However, kidney transplant patients do not usually recover normal levels of glomerular filtration and they may undergo immunosuppressive drugs side effects. Actually, both corticosteroid and especially calcineurin inhibitors induce changes on glomerular and tubular functions that may prevent the full normalization of hydroelectrolytic balance.

Our patients when studied pre-Tx displayed a body water distribution similar to what has already been reported by others [23,24], namely increased TBW and ECW before HD session, which are both overcorrected by HD treatment. At post-HD, they presented lower Wt, ECW, Nae:Ke and greater ICW, PA, *R* and *X*, as compared with healthy controls. As a rule, our patients showed a mild degree of dehydration when they are sent to the operating theatre, especially at the ECW expense. This picture rapidly changed following the kidney grafting, which was characterized by ECW increase and ICW decrease, in a way that they were not any more different to normal. Briefly, our data highlight the well-known extracellular volume expansion pre-dialysis which is followed by an abnormal degree of extracellular volume contraction post-dialysis, and by a full recovery of normal ECW early post-transplantation.

Intracellular water volume, which is of great importance for nutrition evaluation, portrayed different changes with transplantation. ICW volume was significantly reduced pre-HD and following an appropriated ultrafiltration during dialysis, ICW was significantly raised above normal. On the contrary, ICW rapidly normalized following transplant and it kept within normal along the study

period. We know that the cell volume which increases at the early steps of renal involution may reverse to atrophy and cell death and to functional tissue loss at later stages of renal failure, probably following deranged cell volume regulatory mechanisms [25]. Moreover, within a uremic milieu, the cell is unable to uptake substrates with high osmolar activity such as amino acids and glicose, which would be used on proteins and glycogen synthesis [26]. These pathways may both be involved upon the ICW downregulation found at pre-HD. On the contrary, following the expected decrease of plasma osmolality during HD, an osmolar gradient is created which would cause a rapid movement of water from plasma into the interstitial and intracellular spaces, underling the ICW upregulation observed among our patients at post-HD [27]. This deregulated ICW behavior was full normalized post-kidney grafting and, of interest, we observed a progressive ICW increase between month 1 and month 3 post-Tx that was accompanied by muscle mass increase as assessed by anthropometrics measurements (data not presented) which may be an indirect evidence of abrogation of the inhibitory effect of intermittent cell swelling on proteolysis present among uremic patients [25]. Uremic patients display an abnormal PA which associates with abnormal ICW, and that may constitute a signal of perturbations of cell membrane integrity. PA was shown to correlate with mortality risk among dialysis patients [11,28]. Table 2 displays PA values on HD patients that, as compared with healthy people, were lower before and greater after dialysis session. However, early post-Tx PA progressively normalized and perfectly matched healthy controls by month 3, as shown in Table 2. It is important to point that neither HD group nor Tx group presented PA values <4.0°, that may predict a decrease in survival.

Of importance, our study further shows that one single functioning kidney, under the influence of drugs which have the potential to disturb the water and electrolyte balance, is able to fully recover a normal body composition for water and Nae:Ke. Actually, we did not anticipate that body water distribution in transplant patients would be so close to healthy controls, especially as crCl in the study group, although excellent, was clearly below normal (70.0 at month 1 and 75.1 ml/min/1.73 m^2 at month 3 for the transplant study group versus 123.4 ml/min/1.73 m^2 for the healthy group). Interestingly, plasma endogenous digitalis-like factors were found to be significantly raised post-kidney transplantation at crCl of 61.2 ± 24.6 ml/min [1] and a correlation between the accumulation of plasma endogenous digitalis-like factors with the degree of renal dysfunction has been reported [29]. One may speculate that the potential Na–K–ATPase inhibition by plasma endogenous digitalis-like factors may be counterbalanced by the fluid-retaining effects from both methylprednisolone and CsA. Furthermore, transforming growth factor beta 1 enhance glucocorticoid regulated kinase transcription, and this kinase stimulates two mechanisms for intracellular volume upregulation, the renal epithelial Na^+ channel ENaC and the thick ascending limb Na^+, K^+, $2Cl^-$ cotransporter BSC1 [25]. Actually, we observed a significant correlation between both TBW and Nae:Ke with CsA doses, while methylprednisolone dose did not show any correlation with TBW and Nae:Ke, which reproduces the findings reported by van den Ham *et al.* [6] among a stable renal transplant group studied by DEXA .

In summary, BIA of well-functioning kidney transplant recipients showed that the different body water compartments quickly approach/equalize the constitution of normal individuals which is never achieved by a hemodialysis session. Furthermore, our study suggest that with current doses of immunosuppressive drugs that have the potential to induce changes on renal handling of water and electrolytes, no significant changes of body water are observed since month 1 post-transplantation. Moreover, the ICW normalization very early post-transplantation, along with PA values which were perfectly identical among month 3 Tx and healthy controls surmises the full recovery of normal protein anabolism even under significant doses of corticosteroid therapy.

We feel important to stress that these results were observed among patients enjoying excellent graft function, but with crCl significantly lower than healthy subjects.

We are currently studying long-term kidney transplant patients with different graft function, searching for the glomerular filtration rate level which may mark the beginning of significant body water retention and cellular water disturbances, which could be of nutritional and clinical prognostic importance.

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