ORIGINAL RESEARCH

Longitudinal Changes in Body Composition in Patients After Initiation of Hemodialysis Therapy: Results From an International Cohort

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Objective: In patients with advanced kidney disease, metabolic and nutritional derangements induced by uremia interact and reinforce each other in a deleterious vicious circle. Literature addressing the effect of dialysis initiation on changes in body composition (BC) is limited and contradictory. The aim of this study was to evaluate changes in BC in a large international cohort of incident hemodialysis patients.

Methods: A total of 8,227 incident adult end-stage renal disease patients with BC evaluation within the initial first 6 months of baseline, defined as 6 months after renal replacement therapy initiation, were considered. BC, including fat tissue index (FTI) and lean tissue index (LTI), were evaluated by Body Composition Monitor (BCM, Fresenius Medical Care, Bad Homburg, Germany). Exclusion criteria at baseline were lack of a BCM measurement before or after baseline, body mass index (BMI) < 18.5 kg/m^2, presence of metastatic solid tumors, treatment with a catheter, and prescription of less or more than 3 treatments per week. Maximum follow-up was 2 years. Descriptive analysis was performed comparing current values with the baseline in each interval (delta analysis). Linear mixed models considering the correlation structure of the repeated measurements were used to evaluate factors associated with different trends in FTI and LTI.

Results: BMI increased about 0.6 kg/m^2 over 24 months from baseline. This was associated with increase in FTI of about 0.95 kg/m^2 and a decrease in LTI of about 0.4 kg/m^2. Female gender, diabetic status, and low baseline FTI were associated with a significant greater increase of FTI. Age $>$ 67 years, diabetes, male gender, high baseline LTI, and low baseline FTI were associated with a significant greater decrease of LTI.

Conclusions: With the transition to hemodialysis, end-stage renal disease patients presented with distinctive changes in BC. These were mainly associated with gender, older age, presence of diabetes, low baseline FTI, and high baseline LTI. BMI increases did not fully represent the changes in BC.

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Introduction

THE PREVALENCE OF protein-energy wasting is very high in dialysis patients[1] because of the synergic contribution of decreased protein and/or energy intake, chronic inflammation, physical inactivity, concurrent acute or chronic conditions or illness, and catabolism induced by hemodialysis process.[2] On the basis of the repetitive and prolonged nature of these processes, a deterioration of the nutritional status should be concurrent, and longitudinal studies should capture their close association.

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However, the initiation of hemodialysis might also improve nutritional state, for example, by improving appetite due to the partial reversal of the uremic state and correction of metabolic acidosis. Pupim et al.[3] in 2002 showed that the initiation of hemodialysis was associated with significant improvement of most nutritional markers, including albumin, prealbumin, dietary protein intake derived from nitrogen appearance rate, and body composition (BC) such as fat mass (1.29 ± 2.20 kg). Vendrely et al.,[4] in a study evaluating the fat and lean body mass development during the first year on hemodialysis in 15 patients previously treated with supplemented very low–protein diet and 15 patients on less restricted diet, found a significant increase in fat mass (12.6 ± 18.7% and 16.6 ± 16.1%, respectively). Lean mass remained stable overall in the 2 groups of patients. On the other hand, other studies showed that lean body mass significantly decreased after 24 months.[3,5] The increase in albumin and creatinine levels during the first 6 months of hemodialysis also reported by Goldwasser et al.[6] can be explained by the decline of renal function and the progressive retention of proteins and creatinine. A study by Raffaitin et al.[7] on a group of 10 diabetic patients starting dialysis and monitored by means of dual X-ray absorptiometry (DXA) confirmed a significant decrease in lean tissue mass and serum albumin over a period of 2 years.

A more recent study from Mathew et al.,[8] evaluating 41 prevalent hemodialysis or peritoneal dialysis patients surviving 24 months after their baseline anthropometric evaluation, showed a significant increase in triceps and biceps skin fold thicknesses and mid-arm circumference. Finally, Kalantar–Zadeh et al.[9] evaluated the body fat in 535 prevalent hemodialysis patients by near infrared interactance. After 6 months, they found that the 411 patients still on follow-up were stratified as follows: 27.5% with significant fat loss and 29.9% with significant fat gain. Similarly, Johansen et al.,[10] evaluating 54 prevalent hemodialysis patients with 4 measurements of fat mass and lean mass by DXA over a year, did not find any significant trend.

In summary, the number of studies evaluating changes in nutritional parameters after the initiation of dialysis is limited and largely based on longitudinal studies in prevalent patients, often with contradictory results. This observational study in a large cohort of incident hemodialysis patients regularly monitored with bioimpedance spectroscopy aims to assess changes in BC in the initial phase of renal replacement therapy (RRT).

Methods

The study population was extracted from a database of 49,846 patients on hemodialysis treatment in 417 NephroCare centers throughout 21 countries in Europe, Latin America, and South Africa between January 1, 2007 and January 1, 2014. Patients were included if they were no longer than 6 months on RRT before admission to the unit (incident patients only) and if they underwent evaluation of BC using the Body Composition Monitor (BCM; Fresenius Medical Care (FMC), Germany). Baseline was defined as 6 months after hemodialysis initiation. Baseline values were defined as the mean of all measurements in the last 5 months before baseline (baseline period, Fig. 1). Patients were followed for a maximum of 2 years. Patients without at least 1 BCM measurement before and after baseline (defined as 6 months after RRT initiation) were excluded. To focus on a homogenous well-treated hemodialysis population and avoid including patients already having a poor outcome at study start, patients were also excluded who were malnourished (body mass index [BMI] < 18.5 kg/m^2), had metastatic solid tumors, were receiving less or more than 3 treatments per week, or were treated with a catheter at baseline.

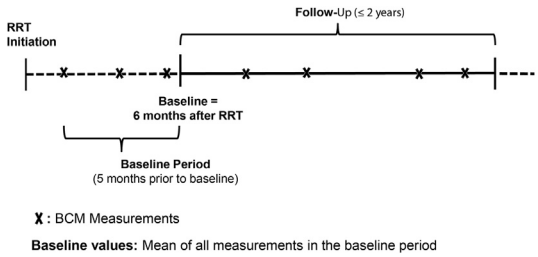

Figure 1. Study design. Hypothetical BCM measurement times are indicated with "x" as Body Composition Monitor (BCM) measurements were not done at strictly regular intervals. Body composition measurement was conducted with the BCM (FMC, Bad Homburg, Germany). RRT, renal replacement therapy.

Anonymized patient data were accessed through the European Clinical Database, which has been described elsewhere.[11,12] All patients consented that their data may be used for scientific research in anonymized form.

Lean tissue index (LTI) and fat tissue index (FTI) were calculated as the ratio of the respective tissue masses divided by the height in meters squared. The definition of the age- and gender-dependent reference groups of LTI and FTI, respectively, was based on an evaluation of 1,000 healthy individuals: "normal" LTI and FTI were defined as levels between the 10th and 90th percentile of the normal LTI or FTI distribution, respectively, whereas "low" is defined as under the 10th percentile and "high" as above the 90th percentile of the respective normal distributions.[13]

LTI and FTI were evaluated at intervals defined according to the network policy using the BCM (FMC), which is based on multifrequency bioimpedance spectroscopy at 50 different frequencies ranging between 5 and 1,000 kHz. BCM measures overhydration, total body water (in liters), extracellular water (in liters), intracellular water (in liters), fat tissue mass (in kilograms), lean tissue mass (in kilograms), and body cell mass. BCM has been validated against the following gold standard reference methods: bromide dilution for extracellular water, total body potassium for intracellular water, deuterium dilution for total body water, DXA for lean tissue mass, 4 compartment modeling, air displacement

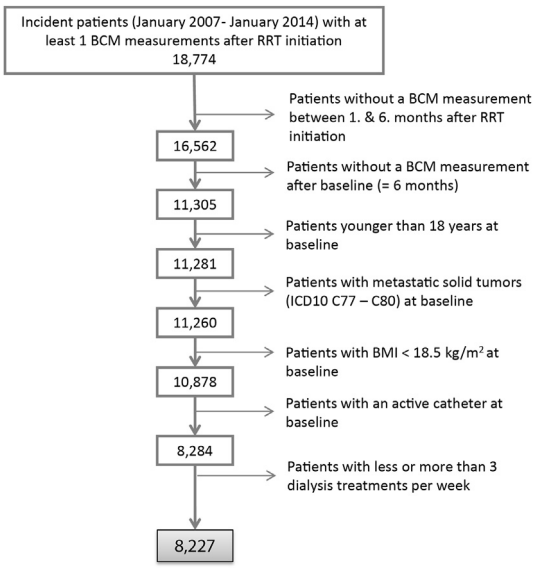

Figure 2. Patient selection. Body composition measurement was conducted with the Body Composition Monitor (BCM; FMC, Bad Homburg, Germany). BMI, body mass index; ICD, International Classification of Diseases; RRT, renal replacement therapy.

plethysmography, under water weighing for adipose tissue mass, magnet resonance tomography for body cell mass and an expert clinical assessment for overhydration.[14]

Statistical Analysis

The outcomes BMI, LTI, and FTI were analyzed to evaluate the nutrition status of the patients. Descriptive analysis was performed comparing current values for each patient with their baseline values for each 1-month interval (delta analysis). In cases without a measurement in the interval, the value of the previous interval was used (last observation carried forward).

To analyze differences between certain patient groups in the development of BMI, LTI, and FTI, linear mixed models were used. We applied an autoregressive process of first order as covariance structure to consider the specific structure of the repeated measurements in irregular intervals. For each outcome (BMI, LTI, and FTI) a separate mixed model with an adjustment for the three cardiovascular comorbidities chronic ischemic heart disease (International Classification of Diseases [ICD]-10 code I25), heart failure (ICD-10 code I50), and peripheral artery diseases (PAD; ICD-10 codes I70-I79) were fitted. In each model, the time (in days) was included as covariate. In addition, the factors gender, age (in tertiles: 18-56; 57-66; ≥67), diabetes, LTI- and FTI-reference groups ("low," "normal," "high") were included as main effects and as interactions with time. The main effects show average differences in the BC between certain subgroups. Interaction terms between the factors and the time are used to identify whether the changes in BMI, FTI, and LTI differ in these subgroups over time during the 2 years of follow-up.

Table 1. Patient Characteristics at Baseline

List of Variables	
General characteristics	
Area (N)	
West Europe	2,459
East Europe	4,922
Latin America and South Africa	846
Age (y; mean ± SD)	61.46 ± 14.65
Age groups (%)	
≥18 - <57 y	33.27
≥57 - <67 y	27.15
≥67 y	39.58
Gender (female, %)	36.38
Body composition	
Dialysis post weight (kg; mean ± SD)	71.93 ± 15.05
BMI: body mass index (kg/m^2; mean ± SD)	26.78 ± 5.15
LTI: lean tissue index (kg/m^2; mean ± SD)	13.10 ± 2.84
LTI-reference groups (%)	
Low LTI	42.68
Normal LTI	54.30
High LTI	3.03
FTI: fat tissue index (kg/m^2; mean ± SD)	12.76 ± 6.01
FTI-reference groups (%)	
Low FTI	7.80
Normal FTI	72.14
High FTI	3.03
Pre-dialysis overhydration (L; mean ± SD)	2.02 ± 1.74
Post-dialysis overhydration (L; mean ± SD)	−0.18 ± 1.94
Comorbidities	
Charlson Comorbidity Index (%)	
2	46.36
3	15.24
4	21.16
≥5	17.24
Diabetes (%)	32.88
Chronic ischemic heart disease (%)	13.57
Heart failure (%)	8.12
Arrhythmia (%)	8.64
Peripheral artery disease (%)	13.68
Stroke (%)	8.21
Cirrhosis (%)	0.82
Malignancies (%)	6.70
Respiratory diseases (%)	6.32
Laboratory values	
Albumin (g/dL; mean ± SD)	3.81 ± 0.41
CRP (mg/L; median; interquartile range)	6.0 (2.47-14.45)
Hemoglobin (g/dL; mean ± SD)	10.90 ± 1.24
Creatinine pre (mg/dl; mean ± SD)	7.10 ± 3.99
Phosphate (mg/dL; mean ± SD)	4.81 ± 1.23
Total cholesterol (mg/dL; mean ± SD)	174.34 ± 44.07
Equilibrated Kt/V (mean ± SD)	1.36 ± 0.30

CRP, C-reactive protein; SD, standard deviation.

Details of patient numbers per country and of countries per geographical region: West Europe = France (211), Italy (271), Portugal (1,216), Spain (742), and the United Kingdom (19); East Europe = Bosnia (219), Croatia (4), Czech Republic (421), Estonia (8), Hungary (241), Poland (931), Romania (1,129), Russia (727), Serbia (90), Slovakia (319), Slovenia (64), Sweden (4), and Turkey (765); Latin America and South Africa = Chile (33), Colombia (797), and South Africa (16).

All covariates were categorical and therefore were included in the model as dummy variables. The corresponding reference categories are reported in the tables in the Results section. Because of the high number of covariates, Akaike information criterion (AIC) was used to select covariates. AIC model selection balances between the goodness of fit and the complexity of the model and can therefore result in exclusion of some covariates that have a low impact on the outcome. The analysis was conducted with the statistical software SAS, version 9.4.

Results

Patient selection is shown in Figure 2. After the selection process, 8,227 patients of the original 49,846 patients were recruited. Baseline characteristics are summarized in Table 1. During the baseline period, patients had a median of 4 (interquartile range: 2-5) BCM measurements. On average, patients had a median of 7 (interquartile range: 3-14) BCM measurements after baseline, the last of which was in mean 319 days after baseline. Figure 3 shows the means of the delta analyses. In 2 years of follow-up, the BMI increased by ~0.6 kg/m^2 (or 2.2%). This change was mainly the result of an increase of 0.95 kg/m^2 (7.4%) in FTI and a decrease of 0.4 kg/m^2 (3.1%) in LTI. These changes in BMI, FTI, and LTI were significant for all intervals ($P < .001$, paired t-tests).

The results of the linear mixed models for the outcomes BMI, FTI, and LTI are summarized in Tables 2-4. All covariates are listed with the appropriate reference categories and the estimations for the specified groups, the standard errors, and the P values. The results for the time interactions are highlighted in the following section, these being most relevant to the study aim.

Results for BMI

After AIC selection, the model for BMI no longer contained PAD, heart failure, and the interaction term of diabetes and time (Table 2). Diabetes did not significantly affect the development of BMI. BMI increased more for females than for males, more for patients aged <57 years than for patients aged ≥67 years, and more for patients with normal LTI and normal FTI than for patients with high LTI and FTI at baseline. The model results can also be summarized as shown in Formula 1.

$$\begin{aligned} BMI(time) = {} & 25.78+0.0028\times time+\begin{cases} -0.27-0.001\times time & male \\ 0 & female \end{cases} \\ & +\begin{cases} 0.22-0.0009\times time & \geq 67 years \\ 1.02-0.0004\times time & [57;67) years \\ 0 & <57 years \end{cases} +\begin{cases} 0.86 & diabetes \\ 0 & no\ diabetes \end{cases} \\ & +\begin{cases} 0.35 & ischemic\ heart\ disease \\ 0 & no\ ischemic\ heart\ disease \end{cases} +\begin{cases} -2.06+0.0002\times time & low\ LTI \\ 2.76-0.0015\times time & high\ LTI \\ 0 & normal\ LTI \end{cases} \\ & +\begin{cases} -4.97+0.0005\times time & low\ FTI \\ 8.69-0.0015\times time & high\ FTI \\ 0 & normal\ FTI \end{cases} \end{aligned} \quad [1]$$

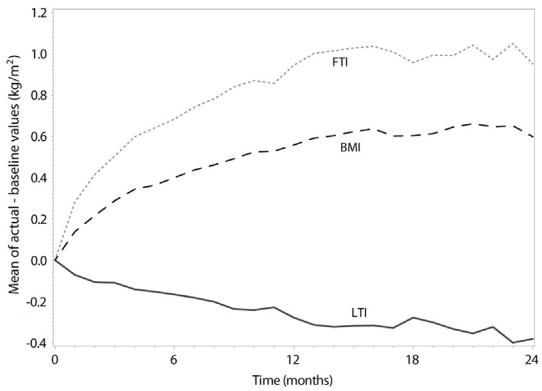

Figure 3. Delta analysis comparing current values of BMI, LTI, and FTI with baseline values. BMI, body mass index; FTI, fat tissue index; LTI, lean tissue index.

For example, the BMI for a female, aged between 57 and 66 years old, no diabetes, no ischemic heart disease, with low LTI and high FTI is given by Formula 2.

$$\begin{aligned} BMI(time) = {} & 25.78+0.0028\times time+1.02-0.0004 \\ & \times time-2.06+0.0002\times time+8.69-0.0015 \\ & \times time=33.43+0.0011\times time \end{aligned} \quad [2]$$

After 2 years of follow-up: $BMI(730)=33.43+0.0011\times 730=34.23$

Results for FTI

After AIC selection, heart failure and the interaction term between age and time were no longer in the model. In this model, age did not appear to affect FTI development as the interaction term between age and time was not significant (Table 3). FTI increased more

for females than for males, more for diabetic patients than for non-diabetic patients, more for patients with normal versus low baseline LTI, and more for patients with low baseline FTI. The increase of FTI over the time was smallest for patients with high FTI at baseline (Formula 3)

$$\begin{aligned} FTI(time) = {} & 11.53 + 0.003 \times time + \begin{cases} -3.29 - 0.001 \times time & male \\ 0 & female \end{cases} \\ & + \begin{cases} 2.44 & \geq 67\ years \\ 1.99 & [57;67)\ years \\ 0 & < 57\ years \end{cases} + \begin{cases} 0.72 + 0.0009 \times time & diabetes \\ 0 & no\ diabetes \end{cases} \\ & + \begin{cases} 0.25 & ischemic\ heart\ disease \\ 0 & no\ ischemic\ heart\ disease \end{cases} + \begin{cases} 0.15 & PAD \\ 0 & no\ PAD \end{cases} \\ & + \begin{cases} 0.88 - 0.0006 \times time & low\ LTI \\ -0.50 + 0.0001 \times time & high\ LTI \\ 0 & normal\ LTI \end{cases} + \begin{cases} -5.80 + 0.001 \times time & low\ FTI \\ 9.24 - 0.002 \times time & high\ FTI \\ 0 & normal\ FTI \end{cases} \end{aligned} \quad [3]$$

For example, the FTI for a female, aged between 57 and 66 years old, no diabetes, no ischemic heart disease, without PAD, with low LTI and high FTI is given by Formula 4.

$$\begin{aligned} FTI(time) = {} & 11.53 + 0.003 \times time + 1.99 + 0.88 - 0.0006 \\ & \times time + 9.24 - 0.002 \times time = 24.36 + 0.0013 \\ & \times time \end{aligned} \quad [4]$$

After 2 years of follow-up: $FTI(730) = 23.54 + 0.0004 \times 730 = 23.83$

Results for LTI

The same covariates were considered for the outcome LTI. After AIC selection, the model no longer contained chronic ischemic heart disease (Table 4). LTI decreased more for males than for females, more for patients aged ≥67 years than for patients aged <57 years, more for diabetic patients, and more for patients with high LTI or low FTI at baseline. The smallest decrease in LTI was observed for patients with low LTI or high FTI at baseline. The model results can also be summarized by Formula 5.

$$\begin{aligned} LTI(time) = {} & 13.91 - 0.0002 \times time + \begin{cases} 2.83 - 0.0002 \times time & male \\ 0 & female \end{cases} \\ & + \begin{cases} -2.69 - 0.0003 \times time & \geq 67\ years \\ -1.22 - 0.0002 \times time & [57;67)\ years \\ 0 & < 57\ years \end{cases} \\ & + \begin{cases} -0.16 - 0.0007 \times time & diabetes \\ 0 & no\ diabetes \end{cases} + \begin{cases} -0.11 & heart\ failure \\ 0 & no\ heart\ failure \end{cases} \\ & + \begin{cases} -0.28 & PAD \\ 0 & no\ PAD \end{cases} + \begin{cases} -2.98 + 0.0008 \times time & low\ LTI \\ 3.18 - 0.0019 \times time & high\ LTI \\ 0 & normal\ LTI \end{cases} \\ & + \begin{cases} 0.61 - 0.0006 \times time & low\ FTI \\ -0.32 + 0.0003 \times time & high\ FTI \\ 0 & normal\ FTI \end{cases} \end{aligned} \quad [5]$$

For example, the LTI for a female, aged between 57 and 66 years old, no diabetes, without heart failure, without PAD, with low LTI and high FTI is given by Formula 6.

$$\begin{aligned} LTI(time) = {} & 13.91 - 0.0002 * time - 1.22 - 0.0002 \times time \\ & - 0.11 - 2.98 + 0.0008 \times time - 0.32 + 0.0003 \\ & \times time = 9.28 + 0.0007 \times time \end{aligned} \quad [6]$$

Table 2. Estimations of the Mixed Model for the Outcome BMI

Variable	Reference Group	Estimate	Standard Error	*P* Value
Intercept		25.7846	0.0938	<.001
Time (d)		0.0028	0.0003	<.001
Gender: male	Female	−0.2657	0.0815	.001
Age: (57; 67)	Age < 57	1.0163	0.1001	<.001
Age: ≥67	Age < 57	0.2179	0.0918	.018
Diabetes: yes	No	0.8555	0.0696	<.001
LTI-ref: low	Normal	−2.0646	0.0821	<.001
LTI-ref: high	Normal	2.7639	0.2308	<.001
FTI-ref: low	Normal	−4.9664	0.1488	<.001
FTI-ref: high	Normal	8.6878	0.0995	<.001
Ischemic heart disease: yes	No	0.3452	0.0927	<.001
Time × gender: male	**Female**	**−0.0013**	**0.0002**	**<.001**
Time × age: (57;67)	**Age < 57**	**−0.0004**	**0.0003**	**.167**
Time × age: ≥67	**Age < 57**	**−0.0009**	**0.0003**	**.001**
Time × LTI-ref: Low	**Normal**	**0.0002**	**0.0003**	**.519**
Time × LTI-ref: High	**Normal**	**−0.0015**	**0.0007**	**.031**
Time × FTI-ref: Low	**Normal**	**0.0005**	**0.0005**	**.288**
Time × FTI-ref: High	**Normal**	**−0.0015**	**0.0003**	**<.001**

BMI, body mass index; FTI, fat tissue index; LTI, lean tissue index.
The result of the time interactions are highlighted in bold.

After 2 years of follow-up: $LTI(730) = 9.28 + 0.0007 \times 730 = 9.79$

Discussion

This study, based on a large international cohort of incident hemodialysis patients, reports a mean BMI increase of ∼0.6 kg/m^2 over 24 months from baseline. Patient nutritional status was monitored by bioimpedance spectroscopy and revealed that changes in BMI were associated with an increase of 0.95 kg/m^2 in FTI and a decrease of 0.40 kg/m^2 in LTI. These latter results confirm trends reported by previous small-sized studies,[3,4,7] albeit the increase in fat body mass reported by Pupim et al.[3] during the first year on hemodialysis was not associated with significant changes in weight and BMI. This is the opposite of what was reported by Mathew et al.,[8] but it should be stressed that anthropometry measurements are not only operator-dependent but also subject to artifacts from fluid accumulation. Therefore, it cannot be excluded that previous

Table 3. Estimations of the Linear Mixed Model for the Outcome LTI

Variable	Reference Group	Estimate	Standard Error	*P* Value
Intercept		13.9088	0.0419	<.001
Time (d)		−0.0002	0.0001	.114
Gender: male	Female	2.8320	0.0362	<.001
Age: (57; 67)	Age < 57	−1.2249	0.0446	<.001
Age: ≥67	Age < 57	−2.6932	0.0409	<.001
Diabetes: yes	No	−0.1644	0.0378	<.001
LTI-ref: low	Normal	−2.9756	0.0366	<.001
LTI-ref: high	Normal	3.1785	0.1033	<.001
FTI-ref: low	Normal	0.6126	0.0668	<.001
FTI-ref: high	Normal	−0.3244	0.0443	<.001
Heart failure: yes	No	−0.1139	0.0424	.007
PAD: yes	No	−0.2830	0.0336	<.001
Time × gender: male	**Female**	**−0.0002**	**0.0001**	**.046**
Time × age: (57;67)	**Age < 57**	**−0.0002**	**0.0002**	**.277**
Time × age: ≥67	**Age < 57**	**−0.0003**	**0.0001**	**.017**
Time × diabetes: yes	**No**	**−0.0007**	**0.0001**	**<.001**
Time × LTI-ref: low	**Normal**	**0.0008**	**0.0001**	**<.001**
Time × LTI-ref: high	**Normal**	**−0.0019**	**0.0003**	**<.001**
Time × FTI-ref: low	**Normal**	**−0.0006**	**0.0002**	**.007**
Time × FTI-ref: high	**Normal**	**0.0003**	**0.0002**	**.034**

FTI, fat tissue index; LTI, lean tissue index; PAD, peripheral artery disease.
The result of the time interactions are highlighted in bold.

Table 4. Estimations of the Linear Mixed Model for the Outcome FTI

Variable	Reference Group	Estimate	Standard Error	*P* Value
Intercept		11.5251	0.0896	<.001
Time (d)		0.0030	0.0003	<.001
Gender: male	Female	−3.2891	0.0835	<.001
Age: (57; 67)	Age < 57	1.9908	0.0776	<.001
Age: ≥67	Age < 57	2.4403	0.0718	<.001
Diabetes: yes	No	0.7201	0.0865	<.001
LTI-ref: low	Normal	0.8755	0.0841	<.001
LTI-ref: high	Normal	−0.5028	0.2367	.034
FTI-ref: low	Normal	−5.8035	0.1528	<.001
FTI-ref: high	Normal	9.2372	0.1022	<.001
Ischemic heart disease: yes	No	0.2506	0.0887	.005
PAD: yes	No	0.1486	0.0879	.091
Time × gender: male	**Female**	**−0.0011**	**0.0003**	**<.001**
Time × diabetes: yes	**No**	**0.0009**	**0.0003**	**.001**
Time × LTI-ref: low	**Normal**	**−0.0006**	**0.0003**	**.020**
Time × LTI-ref: high	**Normal**	**0.0001**	**0.0008**	**.938**
Time × FTI-ref: Low	**Normal**	**0.0013**	**0.0005**	**.009**
Time × FTI-ref: High	**Normal**	**−0.0020**	**0.0003**	**<.001**

FTI, fat tissue index; LTI, lean tissue index; PAD, peripheral artery disease.
The result of the time interactions are highlighted in bold.

results can be distorted by the hydration status, especially considering that also DXA cannot provide diagnostic separation of muscle mass and fluid overload. In the present study, the increase of fat and the decrease in lean body mass was associated with an increased BMI already after 1 year (Fig. 3). This observation supports the theory[3] that fat mass may increase quickly during the first year of hemodialysis and continue to increase slowly thereafter for approximately 7 years.

An additional analysis was conducted to analyze whether changes in the nutritional parameters differ in different regions (West Europe [reference category], East Europe and Latin America and South Africa). Here, geographical area was included in the linear mixed models as main effect and interaction with the time. Significantly higher increases in BMI (0.0008 kg/m^2 per day; *P* value = .002) and FTI (0.0011 kg/m^2 per day; *P* value < .001) were found for patients from East Europe compared with patients from West Europe. All other comparisons between the areas regarding the development of BMI, LTI, and FTI were not significant.

Regarding the development of fat mass (Table 3), FTI increase was significantly lower for males compared with females, whereas the presence of diabetes was associated with a significantly higher increase of FTI over time. In agreement with the study of Pupim et al.,[3] patients with the lowest baseline FTI showed the highest increase over time. In addition, patients with high baseline LTI showed the greater increase of fat tissue.

Regarding the loss of lean mass (Table 4), LTI decreased more in elderly patients (age ≥67 years) and males than in younger patients and females. It is known from previous studies assessing total body potassium in normal subjects that lean body mass peaks in the third and fourth decade of life, followed by a steady decline with advancing age.[15,16] A more recent study[17] in older adults based on hydrodensitometry evaluations showed a 2% decrease in fat-free mass per decade in men but not in women, whereas fat mass increased similarly in both genders (7.5% per decade). It is known that the uremic state is associated with several endocrine abnormalities including the axis hypothalamus–pituitary gland–gonads regulation, growth hormone and insulin growth factor regulation, and hormone receptor interaction.[18] The consequent hormonal derangement is known as uremic hypogonadism,[18] possibly affects the accelerated loss of muscle mass in men.[17,19]

In our study, diabetes was also significantly associated with a greater decrease in LTI, confirming previous reports for older adults with type 2 diabetes not on renal replacement treatment.[5,20] Loss of lean tissue was higher in patients with lower baseline FTI and higher baseline LTI. One can speculate that if the energy reserve of fat is low, lean tissue (muscle mass essentially) catabolism is then facilitated. On the other hand, when the level of muscle mass is already low, the option to have further loss is quite limited.

Inflammation and metabolic acidosis cause wasting of muscle mass through a ubiquitin-mediated process.[21] Patients treated with a catheter 6 months after initiation of RRT were excluded from the study to ensure a homogenous well-treated population, ruling out catheter as an inflammatory source. Recovery of visceral proteins (specifically albumin) after inflammatory events occurs fairly quickly, but regeneration of lost somatic proteins, specifically muscle, is less well assured. Although inflammation occurs in episodes in hemodialysis patients,[22] patients who have evidence of inflammation at 1 point in time are more likely to experience inflammation later. In an additional

analysis, we also considered the presence of a microinflammatory process by means of a C-reactive protein higher than 10 mg/dL, but we did not find any significant association, possibly due to the paucity of data points (data not shown).

Non-CKD patients with other chronic diseases (e.g., breast cancer) frequently gain weight after diagnosis that is accompanied by either no change in lean tissue or with a loss of lean tissue. This pattern is defined as sarcopenic obesity and, like the pattern in dialysis patients, is associated with a long history of corticosteroid use, hypopituitarism, hypogonadism, and prolonged physical inactivity.[23,24]

This study has limitations inherent in any observation study, particularly that causality cannot be assumed. It is well known that physical exercise facilitates development of muscle and may blunt the negative impact of inflammation on muscle, but a surrogate, such as muscle strength, was not evaluated in this study. Also, no direct comparison with a healthy population matched for age and gender was done. However, our previous study reported that as much as 47% of almost 38,000 prevalent hemodialysis patients studied had LTI lower than the 10th percentile of an age- and gender-matched healthy population.[25] Diet changes may also affect the course of LTI and FTI changes, but the network neither prescribes diets nor were there adequate nPNA data available to facilitate investigation of this aspect. Another limitation was our assumption that the decrease in LTI was due to loss of muscle mass. However, it is also possible that LTI loss may be affected by loss of bone, organ, or connective tissue mass. Unfortunately, reliable data for residual renal function and for eGFR at time of initiation were not available. However, as baseline was defined at 6 months after initiation of RRT, residual renal function can be assumed to be negligible. Strengths of the study lie in the prospective collection of data, the homogenous practice in all clinics, the reliability and frequency of BC measurements, the large international cohort of incident patients, and the statistical methodology applied versus previous studies. The level of homogeneity of hemodialysis practice in these clinics was high due to the clinics belonging to the same network and thus sharing a common set of medical and process targets, standard operating procedures, and identical hemodialysis equipment/disposables. This was verified by a quality control tool that detects deviations and benchmarks outcome.[26]

After admission to hemodialysis, patients generally experience an improvement in appetite and general well-being.[27] This study reports an increase in weight in incident hemodialysis patients during 2 years of follow-up that is mainly the result of a significant increase in FTI. This was accompanied by a parallel, albeit of small magnitude, decrease in LTI. A recent retrospective study of 37,345 prevalent hemodialysis patients addressing the association between BC and survival found mortality was lowest with both LTI and FTI in the 10th to 90th percentile (reference group) and significantly higher at the lower LTI and FTI extreme.[25] Interestingly, the results of our longitudinal study support the hypothesis generated in that cross-sectional study[25] of a possible protective effect of high FTI in patients with low LTI. Because malnutrition, LTI, and FTI are recognized important predictors of outcome in hemodialysis patients, incident patients should be closely monitored from the initiation of dialysis. Bioimpedance spectroscopy offers clinicians a convenient method to assess both fluid status and BC changes. The findings of this study deserve further investigation including aspects of physical exercise and muscle strength to address BC changes in incident dialysis patients in a more comprehensive manner.

Practical Application

In the months after start of dialysis therapy, BMI increased, FTI increased, and LTI decreased in this cohort of 8,227 incident hemodialysis patients. Some patient characteristics were associated with higher risk for having/developing malnutrition. The magnitude of the problem supports regular monitoring of all kidney disease patients in terms of BC, at least from time of admission to dialysis.

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