The Effects of Chronic Dialysis on Physical Status, Quality of Life, and Arterial Stiffness: A Longitudinal Study in Prevalent Dialysis Patients

Rens J.R. Gadaen\textsuperscript{a} Jeroen P. Kooman\textsuperscript{a, b} Tom Cornelis\textsuperscript{c}
Frank M. van der Sande\textsuperscript{a} Bjorn J. Winkens\textsuperscript{d} Natascha J.H. Broers\textsuperscript{a, b}

\textsuperscript{a}Department of Internal Medicine, Division of Nephrology, Maastricht University Medical Center+, Maastricht, The Netherlands; \textsuperscript{b}NUTRIM school of Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, The Netherlands; \textsuperscript{c}Jessa Hospital, Hasselt, Belgium; \textsuperscript{d}Department of Methodology and Statistics, Care and Primary Health Research Institute (CAPHRI), Maastricht University, Maastricht, The Netherlands

\textbf{Abstract}

\textbf{Introduction:} It is widely known that dialysis patients have significantly impaired functional outcomes and arterial stiffness, but still few studies have investigated the effects of dialysis longitudinally by a multidimensional approach. We aimed to assess longitudinal patterns of physical activity (PA), physical functioning (PF), health-related quality of life (HrQoL), body composition (BC), and arterial stiffness in prevalent dialysis patients. \textbf{Materials and Methods:} Thirty-nine prevalent dialysis patients (23 conventional hemodialysis [CHD] and 16 peritoneal dialysis) with a mean vintage of 25.7 (±22.1) months were included in this observational prospective study with a 2-year follow-up, and at baseline 20 healthy controls were included. Measurements were performed every 6 months. HrQoL was assessed using the Short Form-36 (SF-36) questionnaire. PA was assessed using the SenseWear™ Pro3 accelerometer. PF was assessed by walking speed, the PF subscale of the SF-36, and handgrip strength (HGS). BC was assessed using the Body Composition Monitor\textsuperscript{®} and arterial stiffness by measuring carotid-femoral pulse wave velocity (PWV). The longitudinal trend was assessed using linear mixed models, correcting for sex, age, and dialysis vintage. For PWV, the trend was additionally corrected for diabetes and systolic blood pressure. \textbf{Results:} After correction, no statistically significant changes over time were observed for the parameters of PA, PF, HrQoL, and BC. In the combined group and in the group of CHD patients only, a significant change was observed for PWV (overall trend: $p = 0.007$ and $p = 0.008$, respectively). A statistically significant difference at baseline was observed between dialysis patients and healthy controls in all parameters, except for HGS and PWV. \textbf{Discussion/Conclusion:} We observed no statistically significant changes in functional outcomes during a 2-year follow-up period, but a significant increase was observed for arterial stiffness. These results might suggest that after a certain period in time, a relatively stable course is present in functional outcomes, but an ongoing deterioration in arterial stiffness occurs, which might increase the risk of cardiovascular disease and all-cause mortality in these patients.

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Rens J.R. Gadaen
Division of Nephrology, Department of Internal Medicine
Maastricht University Medical Center+, Postbus 5800
NL–6202AZ Maastricht (The Netherlands)
Rensgadaen@gmail.com
Introduction

The number of incident dialysis patients increases each year, for instance, due to the growing proportion of elderly patients and improved dialysis techniques [1], and it is estimated that these numbers will continue to rise each year with approximately 6% [2]. Although health-related quality of life (HrQoL) has overall improved in dialysis patients in the last decades [3], it is widely known that this patient group still has diminished HrQoL, lower levels of physical activity (PA), and decreased physical functioning (PF), as compared with the general population [4, 5]. Moreover, a decline in HrQoL and PA is associated with an increased risk of mortality and hospitalization [6, 7]. Therefore, it is important to monitor and correctly identify these parameters in this patient group. Especially since patients with end-stage renal disease (ESRD) have a 10–20 times higher risk of death due to cardiovascular disease (CVD) as compared with the general population [8].

Despite these potential modifiable parameters, studies have shown that self-management programs and stimulation of PA by nephrologists and dialysis staff remain underexposed [6, 9, 10] and are not gaining more popularity over time [11–13]. It is widely recognized that in dialysis patients, adverse outcomes are not solely associated with one single risk factor. Therefore, a multidimensional assessment of dialysis patients using simple and noninvasive tests such as measuring handgrip strength (HGS), walking speed (WS), administering of Short Form-36 (SF-36) questionnaires, body composition (BC) measurements, and measurement of pulse wave velocity (PWV), to determine arterial stiffness, could contribute to better insights of mortality risk, risk of hospitalization, and CVD risk in this patient group.

In addition, early detection of changes in these parameters could guide clinicians to optimize treatment and motivate patients to participate in exercise programs, thereby optimizing HrQoL and possibly decrease their risk of mortality and hospitalization. Several studies have investigated changes in PA, PF, HrQoL, BC, and PWV in dialysis patients treated with different dialysis modalities [14–17]. However, to the best of our knowledge, these studies did not combine the parameters and were often cross-sectional in nature.

In this longitudinal prospective study, it is hypothesized that chronic dialysis, when performed over prolonged periods of time, leads to further deterioration of PA, PF, HrQoL, alterations in BC, and arterial stiffness. The aims of this study were to assess (1) patterns of change in parameters of PA, PF, HrQoL, BC, and arterial stiffness in prevalent chronic dialysis patients during a 2-year follow-up and (2) possible correlations between these parameters.

Materials and Methods

Study Design

This study included participants from 2 separate observational studies. The measurements as described below have been discussed previously by our group [17–21].

Patients were included from a study which was conducted between June 2012 and December 2017. Data from 39 prevalent dialysis patients that were recruited in the study "Uremic Toxins, Cardiovascular Effect, and Physical Activity in Intensive Hemodialysis (INTHEMO)," were included in the analyses. In these analyses, only data from conventional hemodialysis (CHD) and peritoneal dialysis (PD) patients were used. Outcomes of the intensive hemodialysis group have been previously published [20, 22] and were therefore excluded for the analyses. At baseline, 20 healthy age- and sex-matched controls were included as a control group, who were included from a study which was conducted between February 2012 and July 2017.

Patients were eligible for inclusion if they were incident or prevalent hemodialysis or PD patients, 18 years of age or older, and able to provide informed consent. Patients who had strict medical indication for CHD (>12-h hemodialysis a week), anticipating renal transplantation or switching dialysis modality within 12 months, had a Charlson Comorbidity Index of 5 or higher, had a colectomy or used antibiotics chronically, or had a pacemaker or implantable cardioverter defibrillator were excluded from participation.

Office blood pressure was measured with an electronic sphygmomanometer (Omron M4-I; Omron, Japan). Data were collected by trained researchers before each patients’ midweek dialysis over a follow-up period of 2 years, with each data collection visit approximately 6 months apart, yielding a total of 5 visits.

Physical Activity

PA was measured as total steps taken per 24h, total energy expenditure (kcal/kg/day), and activity-related energy expenditure (kcal/kg/day). Participants were asked to wear a SenseWear™ Pro3 armband (BodyMedia®, Pittsburgh, PA, USA) for 2 consecutive weekdays. Participants were asked to wear a SenseWear™ Pro3 armband (BodyMedia®, Pittsburgh, PA, USA) for 2 consecutive days. There was no distinction made between measurements of weekdays and weekends. The mean of the total on-body time was calculated to compromise both dialysis and nondialysis days. The SenseWear™ armband has been validated for obtaining adequate data on daily PA [23, 24].

Physical Functioning

The parameters that were defined within PF were WS, HGS, and the PF subscale of the SF-36 (SF-36 PF) questionnaire.

Four-Meter Walking Test

The 4-m walking test was used to assess WS (meters per second). The validity and sensitivity of this test were proven by several studies [25–28] and were also confirmed for use in PF in ESRD patients [29].
Muscle Strength
Muscle strength, as a parameter of PF, was assessed by determining HGS (in kilograms [kg]) with a handheld dynamometer (Jamar®; Sammons Preston Inc., Bolingbrook, IL, USA). Assessment of HGS was performed in a standing position with the arm in a flexed position of 90°, contralateral to the shunt arm (CHD patients) or in PD patients in the dominant hand. This procedure was performed twice during each visit, and the mean of both measurements was used for analysis.

Health-Related Quality of Life
The widely used SF-36 survey was used to assess HrQoL scores. The SF-36 is validated for use in ESRD patients [30, 31] and consists of 36 items with scores ranging from zero (worst possible health) to 100 (best possible health). These items can be converted into 8 subscales (PF, role-physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health). The subscales can be converted into a physical component summary (PCS) score and a mental component summary (MCS) score. Questionnaires were scored using the algorithm by Ware et al. [32, 33]. To normalize scores, t-score transformation was used to make them comparable to the general population and other patients with specific diseases [34]. Self-reported PF was measured using the SF subscale of the SF-36. PA-related quality of life was defined using the PCS score from the SF-36.

Body Composition
Bioimpedance spectroscopy was used to assess BC. This was achieved with the Body Composition Monitor (BCM®, Fresenius Medical Care, Bad Homburg, Germany), which uses a 3-compartment model in which adipose tissue mass, lean tissue mass, and a separate fluid overload (FO) compartment can be determined [35]. Lean tissue index (LTI) and fat tissue index (FTI) are calculated as lean tissue mass and adipose tissue mass, respectively, corrected for height.

PD patients were visited in the outpatient clinic. For practical reasons, PD patients were measured with a full abdomen. Furthermore, sequestered fluid in the trunk has only a minor influence on whole-body bioimpedance measurements [36–38]. Per manufacturers’ instructions, body weight was corrected for PD fluid, and measurements were performed with participants lying in bed or sitting reclined in a dialysis chair prior to the dialysis treatment [39].

Pulse Wave Velocity
As a parameter of arterial stiffness, PWV was assessed. Increased arterial stiffness as measured by PWV is considered to be an independent predictor for all-cause mortality and CVD in ESRD patients [40]. PWV was assessed with the SphygmoCor system (AtCor Medical, Sydney, Australia) using application tonometry by means of the carotid and femoral artery.

Biochemical Parameters
Laboratory parameters such as dialysis adequacy (Kt/V), β2-microglobulin, and routine laboratory measurements were determined during routine patient laboratory measurements.

Dialysis Therapy Modalities
Detailed data on renal replacement therapy modalities were collected retrospectively and could be retrieved for 20 CHD patients and 16 PD patients. In prevalent CHD patients, dialysis was performed 3 times per week for about 4 h, using ultrapure dialysates and mostly high-flux dialyzers with synthetic membranes. In addition, 4 CHD patients were on low-flux dialyzers with synthetic membranes. Four patients were treated with hemodiafiltration. Vascular access was via an arteriovenous shunt in all CHD patients.

Twenty-two CHD patients were prescribed a dialysate with 1.50 mmol/L calcium, and 1 CHD patient was prescribed a dialysate with 1.25 mmol/L calcium. In PD patients, a calcium concentration of 1.25 mmol/L was used.

In PD patients, only PD fluids with low glucose-derived degradation product content were used (Physioneal®, Extraneal®, and Nutrineal® from Baxter, Castlebar, Ireland). The glucose concentration was prescribed at the discretion of the treating physician.

Other Clinical Characteristics
Electronical medical files from participants were used to retrieve data such as renal diagnosis, dialysis vintage, comorbidity (diabetes, hypertension, obesity, and cardiovascular history), and medication use. These were utilized to retrospectively derive the Davies’s comorbidity score [41] that divides participants into 3 mortality risk groups: low, medium, and high. The Davies comorbidity score has been validated in ESRD patients [42] and significantly correlates with hospitalization and mortality [41, 43].

Statistical Analysis
Numerical data are presented as mean ± SD and categorical data as % or median (25th–75th percentile). Analysis at baseline, between dialysis patients and healthy controls, was assessed using the independent-samples t tests or Mann-Whitney U tests, as appropriate. The longitudinal trend over time (0, 6, 12, 18, and 24 months) was assessed using linear mixed model analysis to incorporate all available data and account for correlation between repeated measurements within the same patient. Several covariance structures for repeated measures were considered, such as unstructured, autoregressive moving average (1,1), (heterogeneous) first-order autoregressive, and (heterogenous) compound symmetric, where the best fitting according to the Bayesian information criterion was selected and reported, with time as a categorical fixed effect and no random effects. All time trends were adjusted for age, sex, and dialysis vintage. For PWV, results were additionally adjusted for diabetes and systolic blood pressure as is common for this parameter. In addition, variables related to missing outcome values were included as a fixed effect to satisfy the assumption of missing at random. As subgroup analysis, trends over time within the CHD group were analyzed for those parameters which turned out to be significant in the combined group. For the PD group, only descriptive statistics, that is, observed means ± SD per time point, were computed as the number of patients within this group was limited.

Correlations between baseline values and between change scores (24 months vs. baseline) of PA, PF, HrQoL, BC, and PWV were assessed with Pearson’s correlation coefficient or Spearman’s rho, where appropriate. Statistical analyses were performed using IBM SPSS Statistics for Mac version 24 (IBM Corp., Armonk, NY, USA). Two-sided p values ≤0.05 were considered to be statistically significant.
Table 1. Baseline patient characteristics (N = 59)

| Variable                          | Patients (n = 39) | Healthy controls (n = 20) |
|----------------------------------|-------------------|---------------------------|
| Male, %                          | 74.4              | 65                        |
| CHD/PD, %                        | 59.0/41.0         |                           |
| Age, years                       | 62.5±13.2         | 59.7±14.1                 |
| Dialysis vintage, months         | 22.0 (IQR: 12.0–31.0) |                        |
| Height, cm                       | 171.9±8.6         | 174.8±11.4                |
| Weight, kg                       | 81.0±16.1         | 76.7±15.8                 |
| BMI, kg/m²                       | 27.3±4.7          | 24.9±3.4                  |
| FO, L                            | 1.4 (0.4–2.6)     | 0.1±0.8                   |
| Residual urine output, mL/24 h (n = 30) | 1,137.0±812.3     |                           |
| eGFR<sub>residual</sub>, mL/min 1.73 m (n = 39) | 4.8±3.1          | 77.9±13.5                 |
| Origin of ESRD, %                |                   |                           |
| Diabetic nephropathy             | 20.5              |                           |
| Polycystic kidney disease        | 20.5              |                           |
| Renovascular disease             | 5.1               |                           |
| Hypertensive nephropathy         | 28.2              |                           |
| Glomerulonephritis               | 15.4              |                           |
| Unknown cause                    | 2.6               |                           |
| Others                           | 7.7               |                           |
| Afro-American ethnicity, %       | 7.7               | 0                         |
| Diabetes mellitus, %             | 35.9              | 0                         |
| CVD, %                           | 28.2              | 0                         |
| Smoker, %                        | 25.6              |                           |
| Davies comorbidity group, %      |                   |                           |
| Low risk                         | 35.9              |                           |
| Medium risk                      | 46.2              |                           |
| High risk                        | 17.9              |                           |
| Previous transplant, %           | 17.9              |                           |
| SBP, mm Hg                       | 148.2±25.0        | 138.0±13.4                |
| DBP, mm Hg                       | 80.4±12.0         | 82.3±6.9                  |
| HsCRP, mg/L                      | 2.8 (IQR: 0.9–8.2) | 1.82±2.9                  |

Data are given in mean ± SD, median (IQR), or percentages. CHD, conventional hemodialysis; PD, peritoneal dialysis; BMI, body mass index; FO, fluid overload; eGFR<sub>residual</sub>, estimated residual glomerular filtration rate according to CKD-EPI; ESRD, end-stage renal disease; CVD, cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; HsCRP, high-sensitive C-reactive protein.

Results

Baseline Characteristics
In total, 39 patients (23 CHD and 16 PD) from 1 center were included. The mean (±SD) age was 62.5 ± 13.2 years, and 74.4% were male. Baseline characteristics are presented in Table 1. During follow-up, a total of 11 (28.2%) participants underwent a kidney transplant, 2 (5.1%) participants died, 1 (2.6%) participant was excluded due to malignancy, and 1 (2.6%) participant was excluded due to cessation of dialysis. Between PD and CHD patients, no statistically significant differences in residual kidney function according to CKD-EPI were observed at baseline (p = 0.288).

At baseline, statistically significant differences were observed in all parameters between dialysis patients and healthy controls, except for PWV and HGS. A trend toward significance was observed with HGS. Results are presented in Table 2.

Longitudinal Analysis
The longitudinal findings for indicators of dialysis efficiency are reported in online suppl. Table 1 (see www.karger.com/doi/10.1159/000510624 for all online suppl. material). For PA measurements, mean on body time for the SenseWear™ Pro3 armband was >95% for all visits. The average monitoring period in days was 2.18.
± 0.70, 1.97 ± 0.23, 1.81 ± 0.29, 1.81 ± 0.37, and 1.73 ± 0.34 for visits 1–5, respectively.

During 2-year follow-up, no significant changes were observed in parameters of PA, that is, the number of steps, total energy expenditure, and activity-related energy expenditure (overall \( p \) values ≥0.387, Table 3). For both objectively measured PF through WS and HGS and subjectively measured PF by SF-36 PF, no significant changes were observed over time (overall \( p \) values ≥0.292, Table 4).

Concomitant, for HrQoL parameters, no significant longitudinal changes were observed in the summary scores of the SF-36, that is, PCS (overall \( p = 0.236 \)) and MCS (overall \( p = 0.587 \), Table 3). With regard to BC parameters, LTI, FTI, and FO did not change significantly over time (overall \( p \) values ≥0.351, Table 5). Nevertheless, our study showed that 60.7% of the male patients and 30.0% of the female patients had an LTI below the 10th percentile.

However, for PWV, a significant increase was observed during the 2-year follow-up period. An increase in PWV was observed from 11.93 m/s (95% CI: 10.56–13.30) at baseline to 14.41 m/s (95% CI: 12.90–15.93) after 24 months of follow-up (Table 6; Fig. 1). In an additional analysis within CHD patients only, PWV significantly increased from 12.31 m/s (95% CI: 10.85–13.78) at baseline to 15.34 m/s (95% CI: 13.68–17.00) after 24 months of follow-up (overall \( p = 0.008 \)), adjusting for age, sex, and systolic blood pressure.

**Table 2.** Baseline results between dialysis and healthy controls

| Parameter          | Dialysis (\( n = 39 \))               | Healthy controls (\( n = 20 \)) | \( p \) value |
|--------------------|---------------------------------------|---------------------------------|--------------|
| Mean steps, per 24 h | 3,888 [2,219.5–7,276.25]              | 11,062 [7,687.0–13,839]         | <0.001       |
| TEE, kcal/kg/day   | 26.78 [24.67–30.78]                   | 36.20 [32.91–39.68]             | <0.001       |
| AEE, kcal/kg/day   | 2.14 [0.77–4.41]                      | 8.34 [6.24–12.35]               | <0.001       |
| WS, m/s            | 1.49 [1.18–1.71]                      | 1.75 [1.66–1.99]                | 0.002        |
| HGS, kg            | 28.0 [20.0–35.1]                      | 32.25 [24.75–39.75]             | 0.155        |
| SF-36 PF           | 41.76 [31.03–48.20]                   | 56.78 [54.64–56.78]             | <0.001       |
| PCS                | 40.73 [32.67–47.44]                   | 54.75 [52.20–56.78]             | <0.001       |
| MCS                | 52.84 [42.38–57.60]                   | 56.92 [53.82–59.94]             | 0.015        |
| LTI, kg/m²         | 13.0 [11.08–13.83]                    | 10.0 [7.75–11.23]               | 0.001        |
| FTI, kg/m²         | 13.70 [10.0–18.1]                     | 14.6 [13.8–16.0]                | 0.003        |
| FO, L              | 1.4 [0.4–2.6]                         | 0.25 [−0.55 to 0.48]            | 0.001        |
| PWV, m/s           | 10.8 [9.1–13.2]                       | 10.74 [9.7–13.95]               | 0.861        |

Data are given as median with interquartile range. TEE, total energy expenditure; AEE, activity-related energy expenditure; WS, walking speed; HGS, handgrip strength; SF-36 PF, Short Form-36 physical functioning; PCS, physical component summary; MCS, mental component summary; LTI, lean tissue index; FTI, fat tissue index; FO, fluid overload; PWV, pulse wave velocity.

**Fig. 1.** Longitudinal analyses of PWV. Data are given as mean with 95% confidence intervals. PWV, pulse wave velocity.
Correlations between PA, PF, HRQoL, PWV, and BC

Figure 2 shows that significant correlations were observed at baseline for SF-36 PF with objectively measured parameters of PF and PA: HGS ($r = 0.394$, $p = 0.014$), number of steps ($r = 0.380$, $p = 0.019$), and WS ($r = 0.458$, $p = 0.004$). Furthermore, number of steps correlated significantly with WS ($r = 0.523$, $p = 0.001$), and HGS correlated significantly with LTI ($r = 0.654$, $p < 0.001$).

Correlations in change scores were observed for WS with PCS ($r_s = -0.498$, $p = 0.016$) and FTI with PCS and SF-36 PF scores ($r_s = -0.550$, $p = 0.007$ and $r_s = -0.420$, $p = 0.046$, respectively). For PWV, correlations were found with PCS ($r_s = -0.441$, $p = 0.031$) and HGS ($r_s = -0.459$, $p = 0.028$). No correlation was observed between PWV and FO. Also, no correlations between SF-36 PF and LTI were observed.

Data are given in estimated marginal means with 95% confidence intervals, correcting for age, sex, and dialysis vintage. Overall $p$ value was obtained from the overall $F$ test for the categorical variable time, assessing the longitudinal trend over the whole time period. PA, physical activity; CI, confidence interval; TEE, total energy expenditure; AEE, activity-related energy expenditure.

**Table 3. Longitudinal outcomes of parameters of PA**

| Parameter Estimated marginal means with 95% CI |
|------------------------------------------------|
| Mean steps, per 24 h |
| Baseline ($n = 38$) | 4,383.80 [3,317.81–5,449.79] |
| 6 months ($n = 34$) | 4,055.75 [2,968.51–5,142.99] |
| 12 months ($n = 29$) | 4,691.60 [3,580.66–5,802.55] |
| 18 months ($n = 26$) | 4,453.91 [3,326.14–5,581.69] |
| 24 months ($n = 23$) | 4,018.02 [2,866.61–5,169.42] |
| Overall $p$ value | 0.447 |
| TEE, kcal/kg/day |
| Baseline ($n = 37$) | 33.35 [24.30–42.41] |
| 6 months ($n = 32$) | 30.70 [24.85–36.54] |
| 12 months ($n = 29$) | 31.62 [25.16–38.08] |
| 18 months ($n = 26$) | 32.69 [23.28–42.14] |
| 24 months ($n = 22$) | 40.79 [3.07–78.51] |
| Overall $p$ value | 0.414 |
| AEE, kcal/kg/day |
| Baseline ($n = 37$) | 3.00 [0.620–5.37] |
| 6 months ($n = 32$) | 2.61 [1.28–3.94] |
| 12 months ($n = 29$) | 2.75 [1.42–4.08] |
| 18 months ($n = 26$) | 2.09 [0.9–3.27] |
| 24 months ($n = 22$) | 2.70 [1.33–4.08] |
| Overall $p$ value | 0.387 |

**Table 4. Longitudinal outcomes of parameters of PF and HRQoL**

| Parameter Estimated marginal means with 95% CI |
|------------------------------------------------|
| WS, m/s |
| Baseline ($n = 37$) | 1.41 [1.26–1.56] |
| 6 months ($n = 34$) | 1.45 [1.29–1.60] |
| 12 months ($n = 28$) | 1.43 [1.27–1.59] |
| 18 months ($n = 25$) | 1.50 [1.33–1.66] |
| 24 months ($n = 24$) | 1.35 [1.18–1.51] |
| Overall $p$ value | 0.292 |
| HGS, kg |
| Baseline ($n = 38$) | 23.79 [20.00–27.58] |
| 6 months ($n = 36$) | 22.53 [18.72–26.33] |
| 12 months ($n = 29$) | 22.54 [18.69–26.38] |
| 18 months ($n = 27$) | 22.70 [18.85–26.56] |
| 24 months ($n = 25$) | 22.24 [18.37–26.11] |
| Overall $p$ value | 0.293 |
| SF-36 PF |
| Baseline ($n = 39$) | 39.89 [35.83–43.96] |
| 6 months ($n = 36$) | 37.95 [33.82–42.07] |
| 12 months ($n = 30$) | 39.48 [35.24–43.72] |
| 18 months ($n = 27$) | 37.15 [32.84–41.46] |
| 24 months ($n = 25$) | 37.38 [32.99–41.73] |
| Overall $p$ value | 0.302 |
| PCS |
| Baseline ($n = 39$) | 38.75 [34.96–42.54] |
| 6 months ($n = 36$) | 37.75 [33.91–41.59] |
| 12 months ($n = 30$) | 38.10 [34.16–42.05] |
| 18 months ($n = 27$) | 36.15 [32.14–40.16] |
| 24 months ($n = 25$) | 35.84 [31.78–40.00] |
| Overall $p$ value | 0.236 |
| MCS |
| Baseline ($n = 39$) | 51.73 [47.96–55.50] |
| 6 months ($n = 36$) | 51.45 [47.60–55.29] |
| 12 months ($n = 30$) | 49.31 [45.31–53.31] |
| 18 months ($n = 27$) | 50.14 [46.05–54.23] |
| 24 months ($n = 25$) | 51.50 [47.33–55.66] |
| Overall $p$ value | 0.587 |

Data are given in estimated marginal means with 95% confidence intervals, correcting for age, sex, and dialysis vintage. Overall $p$ value was obtained from the overall $F$ test for the categorical variable time, assessing the longitudinal trend over the whole time period. PF, physical functioning; HRQoL, health-related quality of life; CI, confidence interval; WS, walking speed; HGS, handgrip strength; SF-36 PF, Short Form-36 physical functioning; PCS, physical component summary; MCS, mental component summary.

**Discussion**

The current study focused on longitudinal patterns in various domains in prevalent dialysis patients, over a 2-year follow-up period. No statistically significant
changes were observed in the studied parameters of PA, PF, HrQoL, and BC. However, a statistically significant increase in PWV was observed in the overall group and the subgroup of CHD patients.

At baseline, a statistically significant difference between CHD patients and healthy controls was observed for all parameters, except for HGS and PWV. This is in line with previous findings where it is widely known that dialysis patients have diminished HrQoL, lower levels of PA, and increased PF, as compared with the general population [4, 5].

While dialysis is an intensive treatment with often restrictions in diet and fluid intake, dialysis patients have a considerable higher risk of cardiovascular events than nondialysis patients and often have concomitant severe limitations in activities of daily living. These findings might suggest that, in stable chronic dialysis patients, no further deterioration in parameters of physical status, HrQoL, or BC necessarily occur beyond the already substantially decreased levels which are already present at the start of dialysis. Moreover, in a previous longitudinal study of our group [19], no significant changes were observed in parameters of HrQoL in a group of CKD-5 nondialysis patients in the first year after the transition period from CKD-5 nondialysis to dialysis. Furthermore, no significant changes in PA in the first 6 months after initiation of dialysis were observed in that study as well [19].

The findings in the current study are partially in line with an earlier study by Johansen et al. [44], where no significant changes in PF, measured by SF-36, were observed. However, in contrast to our findings, there was a significant change in PA measured by accelerometry, which could possibly be explained by differences in baseline characteristics between our study and the study by Johansen et al. [44] such as mean age, sex (ratio males to females), and differences in measurement units (number of steps in our study vs. arbitrary units).

Furthermore, with regard to parameters of HrQoL, our results showed no significant changes over time in the summary scores of the SF-36 (MCS and PCS), which is in line with the study by Johansen et al. [44], where HD patients who had a 1-year follow-up showed no significant changes in different domains of the SF-36 (MCS, PCS, and PF), and a study by Eneanya et al. [16], in which no significant changes over time in the MCS and PCS domains in a group of HD and PD patients were observed.

From the outcomes of the present study, together with those of previous studies, it might be hypothesized that deterioration with regard to PA, PF, and HrQoL might already occur in earlier stages of CKD, and only minor

### Table 5. Longitudinal outcomes of BC parameters

| Parameter     | Estimated marginal means [95% CI] |
|---------------|----------------------------------|
| LTI, kg/m²    |                                 |
| Baseline (n=38) | 11.97 [11.20–12.75]              |
| 6 months (n=33) | 12.35 [11.56–13.15]              |
| 12 months (n=28) | 12.18 [11.37–12.98]              |
| 18 months (n=27) | 11.98 [11.16–12.79]              |
| 24 months (n=24) | 12.12 [11.30–12.95]              |
| Overall p value | 0.567                             |
| FTI, kg/m²    |                                 |
| Baseline (n=38) | 14.91 [13.12–16.70]              |
| 6 months (n=33) | 14.65 [12.84–16.46]              |
| 12 months (n=28) | 14.54 [12.72–16.36]              |
| 18 months (n=27) | 14.79 [12.98–16.62]              |
| 24 months (n=24) | 14.41 [12.57–16.25]              |
| Overall p value | 0.777                             |
| FO, L         |                                 |
| Baseline (n=39) | 1.13 [0.57–1.68]                 |
| 6 months (n=36) | 0.88 [0.19–1.57]                 |
| 12 months (n=30) | 1.44 [0.74–2.13]                 |
| 18 months (n=27) | 1.12 [0.69–1.55]                 |
| 24 months (n=25) | 0.99 [0.47–1.50]                 |
| Overall p value | 0.351                             |

Data are given in estimated marginal means with 95% confidence intervals, correcting for age, sex, and dialysis vintage. Overall p value was obtained from the overall F test for the categorical variable time, assessing the longitudinal trend over the whole time period. BC, body composition; CI, confidence interval; LTI, lean tissue index; FTI, fat tissue index; FO, fluid overload.

### Table 6. Longitudinal outcomes of PWV

| PWV, m/s | Estimated marginal means [95% CI] |
|----------|----------------------------------|
| Baseline (n=37) | 11.93 [10.56–13.30]              |
| 6 months (n=35) | 12.55 [11.15–13.96]              |
| 12 months (n=30) | 13.23 [11.79–14.66]              |
| 18 months (n=26) | 12.93 [11.45–14.41]              |
| 24 months (n=25) | 14.41 [12.90–15.93]              |
| Overall p value | 0.007                             |

Data are given in estimated means with 95% confidence intervals, correcting for age, sex, dialysis vintage, diabetes, and systolic blood pressure. Overall p value was obtained from the overall F test for the categorical variable time, assessing the longitudinal trend over the whole time period. PWV, pulse wave velocity; CI, confidence interval.
changes occur during the dialysis process in outcomes of functional parameters in relatively stable patients.

Also, no significant changes over time were observed in the BC domain, as expressed by FTI, LTI, and FO, during follow-up. This might be explained by the stable disease setting as well, in combination with periodic dietician consultation.

Our results are in some contrast to a recent study by Marcelli et al. [45], in which significant changes in both LTI and FTI were found during a 2-year follow-up period in incident dialysis patients, where LTI decreased and FTI increased. However, in our study, the mean dialysis vintage was 25.7 months. This might suggest that after a finite period, a stable disease course is reached with regard to BC parameters. Nevertheless, our study showed that a large part of the patients had LTI below the 10th percentile, as was also observed in the study by Marcelli et al. [45]. This might be a sign of protein energy wasting, which is known to be an important risk factor in dialysis patients for survival and cardiovascular risk [46, 47]. This is probably part of the frail phenotype which is regularly observed in dialysis patients [48] but should be considered as hypothesis generating only.

In contrast to the other dimensions, a change was observed for PWV, as a parameter of arterial stiffness, in both the overall group and within the subgroup of CHD patients, whereas in PD patients, a numerical trend might be observed. However, no statistical analysis could be performed due to the small number of PD patients in the current study. This is in line with a previous study by Blacher et al. [40] that observed a significant increase in PWV over time in a group of CHD patients. The increase could be explained by ongoing damage of uremic toxins, abnormalities in mineral metabolism, low-grade inflammation from dialyzers, and FO [49, 50]. These factors, associated with ESRD, contribute to an environment which leads to arterial remodeling and calcification [50]. In addition, PWV is known to be an independent predictor for all-cause mortality and CVD in patients with ESRD [40, 51].

Furthermore, in this study, correlations were assessed between the different dimensions. The correlations within the PF domain and between the domains of PA and PF are in line with earlier studies correlating PA parameters to outcomes in the physical domains of HrQoL [19, 52]. These results are explainable since both PF and PA contribute to the overall physical status of patients.

Moreover, correlations for change scores in PWV correlated inversely with those in PCS and HGS. No significant correlations were found with FO.

Between the domains of BC and PF, longitudinal changes in FTI inversely correlated with those in SF-36 PF. A positive correlation at baseline was found between
LTI and HGS. Correlations between BC and PF were also observed in a study by Martinson et al. [53] where correlations between BC and PF were observed in HD patients although other parameters were used. Moreover, the observed correlation between LTI and HGS at baseline is in line with a cross-sectional study by Garagarza et al. [54] in HD patients. The correlations between BC and PF might be explained by the fact that the assessed parameters of PF are partly dependent on lean tissue such as in WS and HGS [55].

Few limitations deserve consideration in the current study. First to be considered is the relatively small study population in contrast to earlier follow-up studies. Nevertheless, we believe this study is relatively unique in providing a longitudinal multidimensional approach whereby both relevant risk factors as well as important factors affecting HrQoL of the patients were included. We acknowledge that the lack of statistically significant changes in all dimensions, except from arterial stiffness, might be due to selection bias, as healthier, more stable dialysis patients were included in comparison with the general dialysis population.

Second, PA was measured for a relatively short period of time with no differentiation made between weekdays and weekends, which could lead to over- or underestimation of the separate PA parameters. Nonetheless, although measured for a relatively short period, previous studies showed that this is considered sufficient to gather reliable data [23, 24]. Due to the measuring techniques used in this present study, we were able to obtain both subjectively measured and objectively measured data for PF.

Third, this study consisted of both PD and CHD patients. Since PD patients are generally considered to be in better health than CHD patients, this could have led to bias and difficulty in extrapolation of the results to specific dialysis modalities due to small sample sizes in both groups.

Conclusion

We found no significant changes over a 2-year follow-up period in dialysis patients with regard to parameters of PA, PF, HrQoL, and BC. These results together with the results of earlier studies might suggest that a large part of the deterioration of functional outcomes possibly occurs in earlier stages of CKD. Furthermore, it might be suggested that after a certain period in time, a stable disease course can be reached with regard to functional outcomes in dialysis patients who are in relatively good health. Nevertheless, a progressive increase in arterial stiffness was observed within continued dialysis patients, which might increase the risk of CVD and all-cause mortality in this patient group. These results might aid clinicians in interpreting changes in the different risk domains, as our study suggests that even prolonged dialysis treatment does not necessarily lead to a further deterioration of the studied parameters.

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Statement of Ethics

Written informed consent was obtained for each participant. Approval of the study was given by the ethical committee (NL35039.068.10 [patient group] and NL33129.068.10 [healthy controls]) and by the hospital board of the participating center, Maastricht University Medical Center+ (MUMC+).

Conflict of Interest Statement

N.J.H.B. and J.P.K. received lectures fees from Fresenius Medical Care. R.J.R.G., T.C., F.M.v.d.S., and B.J.W. have no conflicts of interest to declare.

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Author Contributions

Study design: T.C., J.P.K., and F.M.v.d.S.; data acquisition: N.J.H.B.; research hypothesis: T.C., J.P.K., F.M.v.d.S., and N.J.H.B.; data analysis/interpretation: R.J.R.G., N.J.H.B., and J.P.K.; statistical analysis: R.J.R.G. and B.J.W.; manuscript preparation: R.J.R.G., N.J.H.B., and J.P.K.; manuscript review: N.J.H.B., J.P.K., T.C., F.M.v.d.S., and B.J.W.; supervision and mentorship: N.J.H.B. and J.P.K.
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