ORIGINAL RESEARCH

Survival Benefit of Maintained or Increased Body Mass Index in Patients Undergoing Extended-Hours Hemodialysis Without Dietary Restrictions

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Objective: Low body mass index (BMI) is a potential risk factor for mortality in patients on maintenance hemodialysis. This suggests the usefulness of BMI as a prognostic factor and implies the importance of nutritional status, inflammation, and oxidative stress, all of which affect BMI. We aimed to evaluate BMI changes over time and the mortality risk in patients undergoing a novel combination therapy consisting of an extended-hours hemodialysis protocol without dietary restrictions, which enabled sufficient nutrition.

Design and Methods: This is a retrospective cohort study. Patients were divided into 2 groups based on BMI change (ΔBMI < 0, ΔBMI ≥ 0) between the 3rd and 12th month after transfer to the clinic. We studied the associations of BMI changes with all-cause mortality. Further subgroup analyses were performed using Cox models. We finally studied 187 patients who were receiving the combined therapy. The main outcome measure was all-cause mortality of the study group.

Results: The median (interquartile range) follow-up time was 4.9 (3.0-8.6) years. Overall, 138 patients were in the ΔBMI ≥ 0 group. As per unadjusted and adjusted Cox models, maintained or increased BMI during this period was associated with hazard ratios of 0.45 (confidence interval 0.23-0.87, $P < .05$) and 0.35 (confidence interval 0.17-0.75, $P < .01$) for all-cause mortality, respectively. In the same group, maintained or increased BMI was found to be significantly associated with decreased mortality in female, older, and nondiabetic patients. The data indicated that diabetic status could have a modifying effect on the association between variation in BMI and mortality ($P = .006$).

Conclusions: Extended-hours hemodialysis without dietary restrictions led to a beneficial effect of maintenance or increase in BMI, especially in females, patients aged ≥65 years, and those without diabetic nephropathy, which could lead to prolonged survival.

Introduction

THE OUTCOME IN patients on hemodialysis is poor.[1] Thus, predictive factors associated with a poor outcome need to be identified. Body mass index (BMI) is a noteworthy factor as its influence changes with chronic kidney disease severity. Many studies report an association between high BMI and incident chronic kidney disease or its progression to end-stage renal disease (ESRD),[2-4] whereas low BMI is associated with higher risk of both all-cause and cardiovascular mortality in patients on hemodialysis.[5-8] Association of a higher risk of mortality with a lower BMI in patients on hemodialysis may be due to malnutrition caused by adherence to strict dietary restrictions, designed to prevent occurrence of electrolyte abnormalities and excessive weight gain.[9,10] Additionally, inflammation and oxidative stress, causes of protein-energy wasting and cachexia, are pervasive in ESRD and can affect this association.

Several studies have shown an association between extended-hours hemodialysis and low mortality rates,[11] decreased left ventricular mass, and better regulation of both serum phosphorus and parathyroid hormone.[12] However, these studies focused on the removal of substances. In contrast, extended-hours hemodialysis with no dietary

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Setting: Kamome Hitachi Clinic in Ibaraki, Japan, from October 2002 to April 2016.

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restrictions is a novel treatment strategy, because it enables patients to eat sufficiently, leading to an increase in BMI, which can help improve the outcome in patients with ESRD. Using this approach, clinicians provide 6-8 hours of hemodialysis per session for 3-4 sessions per week, without any dietary restrictions imposed on the patients. The medical staff encourages patients to eat so that their body weight can increase. Despite the potential advantages of this approach, its efficacy is unclear. Therefore, we measured changes in BMI over time and examined the association between these variations and the mortality risk in patients receiving extended-hours hemodialysis without dietary restrictions. We also described the outcome in patients receiving this therapy.

Methods

Study Design and Participants

We conducted a retrospective cohort study, using data from 229 patients on maintenance dialysis, treated at our clinic. First, we consecutively identified patients on maintenance hemodialysis, who visited this clinic for ≥1 month between October 2002 and April 2016 (as some patients had visited the clinic only for a few days or weeks for temporary refuge following the 2011 East Japan great earthquake). Patients on hemodialysis, who had (1) incomplete or absent record of weight measurements over at least 12 months (n = 23), (2) unavailability of data on height or comorbidities (n = 14), and (3) undergone kidney transplantation during the observation period (n = 0), were excluded. Additionally, to ensure that the study patients were those who had received extended-hours hemodialysis, we also excluded (4) those who received <6 hours of dialysis in the 12th month period after being transferred to this clinic (n = 5). Therefore, we finally enrolled 187 patients (107 male, 80 female) in the study (Fig. S1).

Combined Therapy

The clinic described in this study is an outpatient dialysis facility in Japan with 2 principal treatment policies. First, the clinic specializes in the provision of extended-hours hemodialysis. Except for the first few months after its opening, this clinic has consistently provided long duration hemodialysis, to those who require it. Patients receive at least 6 hours of hemodialysis therapy per session. The care providers recommend that patients receive longer hemodialysis (≤8 hours/session), as long as they do not have any contraindications for the extension of therapy. The clinic also provides a weekly fourth session for those who could benefit from it. Second, care providers ensure the maintenance of good nutritional status among the dialyzed patients. Rather than imposing dietary restrictions, patients are encouraged to consume normal meals with their families. When patients experience excessive fluid-related weight gain or electrolyte abnormalities, they receive extra hemodialysis therapy.

Dialysate flow is fixed at 300 mL/minute. Patients start an extended-hours hemodialysis session with a blood flow of 80-100 mL/minute. Following the blood examination, blood pressure recording, and considering the patients' reported fatigue levels, the blood flow is increased to 200 mL/minute, though increasing the blood flow is not the top priority in this clinic. The clinic monitors the microbiological quality of the dialysate. The levels of colony forming units and endotoxin units in the dialysate are maintained at <0.1 CFU/mL and <0.001 EU/mL, respectively.

Definitions

Dialysis vintage in each patient was defined as the duration between hemodialysis initiation and transfer to our clinic. BMI was calculated from the post-hemodialysis weight (kg) divided by the square of the patient's height (m^2). To evaluate the long-term predictive ability of variations in BMI in the early phase of dialysis, we focused on and assessed the difference in BMI (ΔBMI) values recorded at the 3rd and the 12th month after transfer to our clinic, assuming that a few initial months were needed for the body weight to adjust to the change in the dialysis protocol.[13] ΔBMI was calculated using the following formula: ΔBMI = (BMI at 12 months) − (BMI at 3 months). The baseline for survival analysis was set at the 12-month mark to find any association between ΔBMI and outcomes. We divided ΔBMI into 2 categories (ΔBMI < 0, ΔBMI ≥ 0) to assess its correlation with mortality risk. A history of cardiovascular disease (CVD) was defined as pre-existing coronary artery disease, heart failure, peripheral arterial disease, or cerebrovascular disease. The hemodialysis product (HDP), one of the indices of dialysis adequacy, was calculated using the following formula: HDP = hemodialysis hours × (hemodialysis sessions/week)^2.[14]

The presence of diabetes mellitus was defined if the diagnosis (made by a physician earlier) was self-reported, glycosylated hemoglobin (HbA1c) level was ≥6.5%, or if the patient was receiving oral hypoglycemics or insulin. Hypertension was defined according to the 2014 guidelines of the Japanese Society of Hypertension.[15]

Data Extraction

All data were retrospectively collated. We collected baseline information including the cause of renal disease, dialysis vintage before transfer to the clinic, and comorbidities, from the medical records. Of all available blood analysis results from the first year of dialysis at this clinic, the values closest to the baseline were adopted. Hemodialysis hours, sessions/week, and dialysis dose (Kt/V) in each patient were determined using the hemodialysis management system (Step II; NHOSA Corporation, Tokyo, Japan). BMI

data were extracted every month for the first 3 months, and thereafter at 3 monthly intervals, till the 12th month.

Outcomes

In the observation period of this study from October 2002 to April 2016, the crude mortality rate was calculated by dividing the number of deaths by total person-years. The main outcome measure was all-cause mortality. Survival time was defined as the time from baseline to death, with censoring of included patients performed for reasons including transfer to other hemodialysis clinics, loss to follow-up, undergoing renal transplantation, or reaching the end of the observation period (i.e., administrative censoring) in April 2016.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation or median (interquartile range); categorical variables are expressed as numbers and percentages. Differences in demographic and clinical characteristics among the ΔBMI categories were evaluated using chi-squared test and *t*-test, as appropriate. The differences in BMI between the 2 ΔBMI categories were evaluated over time, using analysis of variance with continuous covariates. Survival curves were prepared using the Kaplan-Meier method and differences were assessed via the log-rank test. Cox models were used to estimate hazard ratios (HRs) of all-cause mortality associated with $\Delta\text{BMI} \geq 0$, after performing adjustment for potential confounders, such as age, sex, BMI at baseline, dialysis vintage, history of diabetic nephropathy (DN), history of CVD, and serum ferritin level. The proportional hazards assumption for covariates was tested using scaled Schoenfeld residuals. Association between ΔBMI and the HRs for all-cause mortality was assessed using restricted cubic spline (RCS) regression to ascertain the validity of a specific cutoff point of BMI change. In the RCS, the nonlinear association was analyzed as a spline curve combining cubic polynomials and linear terms. In this study, we set 3 knots to analyze the associations between the predictor and outcome, placed on the 10th, 50th, and 90th percentiles of the predictor value range. Additionally, we explored determinants of maintained or increased BMI using logistic regression analysis. In the subgroup analyses, interactions between $\Delta\text{BMI} \geq 0$ and each factor were evaluated using likelihood-ratio tests. All statistical analyses were performed using the Stata software for Windows, version 14.0 IC (STATA Corporation, College Station, TX). In all tests, a *P*-value $<.05$ was considered statistically significant.

Ethics Statement

The study conformed to the Japanese Ministry of Health, Labor, and Welfare's "ethical guidelines for clinical research" (created July 30, 2003; full revision December 28, 2004; full revision July 31, 2008) and the Helsinki Declaration (revised 2013). The study protocol was approved by the Institutional Review Boards of both Nagoya University and Kamome Clinic. As this is a retrospective study, the need for informed consent was waived.

Results

Patient Characteristics

Median age at baseline was 61.0 (interquartile range 53.4-69.6) years and the median follow-up duration was 4.9 (3.0-8.6) years. The RCS analysis showed a nonlinear association between BMI change and HRs of all-cause mortality. HRs were significantly higher in patients with a BMI change <0, which indicated the validity of dividing the cohort into 2 categories ($\Delta\text{BMI} < 0$ and $\Delta\text{BMI} \geq 0$) (Fig. S2). Table 1 shows the characteristics of the study population at baseline according to the ΔBMI categories. Overall, 49 and 138 patients were categorized into the $\Delta\text{BMI} < 0$ and $\Delta\text{BMI} \geq 0$ subgroups, respectively. The mean (standard deviation) of ΔBMI was estimated at -0.77 (0.62) versus 0.78 (0.72) in those with $\Delta\text{BMI} < 0$ and $\Delta\text{BMI} \geq 0$, respectively. Patients in the $\Delta\text{BMI} \geq 0$ subgroup were likelier to be female, have DN, and have a longer dialysis vintage. Although the dialysis vintage before transfer to our clinic was <6 months in half of the population in both categories, it was ≥ 5 years in 30.5% of patients. Hemodialysis duration (hours) and number of sessions per week were similar between the 2 categories. The changes in mean BMI over the observation period, in each category, are plotted in Figure 1. The mean BMI of both groups increased for ~2 years after transfer to our clinic. Those patients who experienced BMI increase between the 3- and the 12-month intervals showed constantly higher BMI throughout the extended observation period, as compared to those with $\Delta\text{BMI} < 0$ ($P < .001$). The crude mortality rate in the clinic from 2002 to 2016 was 3.5 per 100 person-years.

ΔBMI and All-Cause Mortality

The clinical outcomes in these 2 subgroups are shown in Table S1. The mean follow-up durations for the $\Delta\text{BMI} < 0$ and $\Delta\text{BMI} \geq 0$ subgroups were 4.6 (1.8-6.7) and 5.3 (3.1-9.0) years, respectively. Fourteen (29%) patients died in the $\Delta\text{BMI} < 0$ subgroup, compared to 23 (17%) in the $\Delta\text{BMI} \geq 0$ subgroup. The Kaplan-Meier survival curve analysis demonstrated that a maintained or increased BMI was associated with lower all-cause mortality (Fig. 2, Y-label: Survival estimate). Table 2 shows the HR for all-cause mortality. $\Delta\text{BMI} \geq 0$ was associated with HRs of 0.45 (0.23-0.87) ($P < .05$) and 0.35 (0.17-0.75) ($P < .01$) in the unadjusted and fully adjusted models, respectively.

Predictive Factors of Maintained or Increased BMI

We examined the ability of certain variables to predict $\Delta\text{BMI} \geq 0$ (Table 3). Longer dialysis vintage was associated with $\Delta\text{BMI} \geq 0$ with an odds ratio of 1.09 (1.01-1.18).

Table 1. Characteristics of the Study Population at the 12th month Correlated With Changes in Body Mass Index

Characteristics	ΔBMI < 0 (n = 49)	ΔBMI ≥ 0 (n = 138)	*P*-Value
Age (y)	61.6 ± 14.8	60.7 ± 11.8	.69
≥65	24 (49%)	53 (38%)	.22
Sex (female)	15 (31%)	65 (47%)	.05
Dialysis vintage (y)	2.6 ± 3.6	4.9 ± 7.3	.03
<6 mo	27 (55%)	70 (51%)	.6
6-24 mo	4 (8%)	9 (7%)	.7
2-5 y	6 (12%)	14 (10%)	.68
≥5 y	12 (24%)	45 (33%)	.29
Cause of renal disease			
Diabetic nephropathy	18 (37%)	65 (47%)	.21
Vascular nephropathy	10 (20%)	18 (13%)	.21
Chronic glomerulonephritis	16 (33%)	43 (31%)	.85
Polycystic kidney disease	2 (4%)	2 (1%)	.27
Others	3 (6%)	10 (7%)	.79
Comorbidities			
Hypertension	27 (55%)	63 (46%)	.32
Cardiovascular disease	8 (16%)	31 (22%)	.13
Laboratory data			
Ferritin (ng/mL)	198.2 ± 317.6	182.6 ± 322.7	.77
Hemoglobin (g/dL)	10.6 ± 1.3	10.4 ± 1.2	.43
HbA1c (%)	6.6 ± 0.8	6.5 ± 1.1	.67
Calcium (mg/dL)	9.1 ± 0.6	9.2 ± 0.8	.37
Phosphate (mg/dL)	4.8 ± 1.3	5.3 ± 1.3	.05
Hemodialysis procedure data			
Hemodialysis duration/session (h)	6.7 ± 0.7	6.6 ± 0.7	.53
Hemodialysis sessions/week	3.1 ± 0.2	3.1 ± 0.2	.86
HDP	62.8 ± 10.9	61.8 ± 10.5	.62
Kt/V	1.5 ± 0.4	1.6 ± 0.4	.62
BMI values (kg/m^2)			
3rd month	23.1 ± 4.5	22.3 ± 3.4	.22
12th month	22.3 ± 4.4	23.1 ± 3.5	.21

BMI, body mass index; HbA1c, hemoglobin A1c; HDP, hemodialysis product: hemodialysis hours × (hemodialysis sessions/week)^2.
Data are expressed as number (percentage) or mean ± standard deviation.

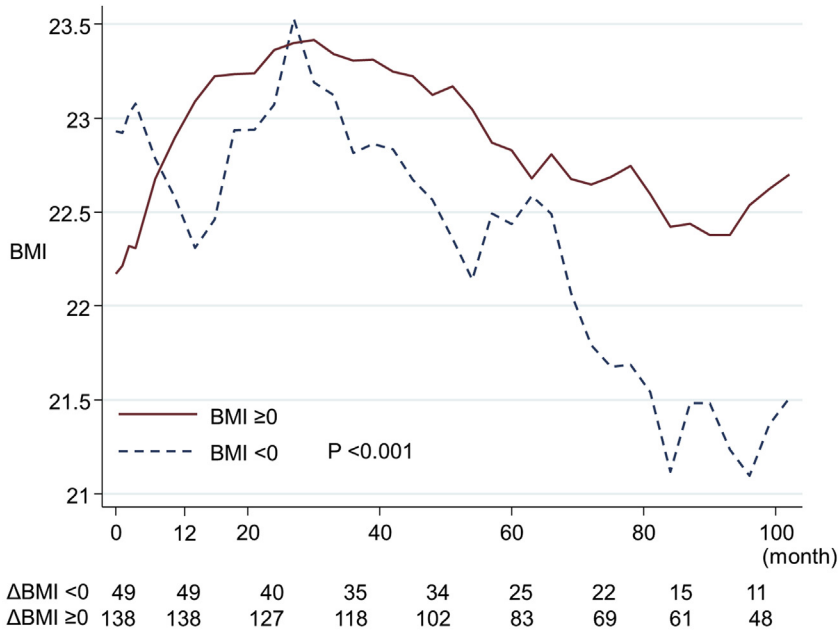

Figure 1. Mean body mass index changes in the 2 study groups over the study period. BMI, body mass index.

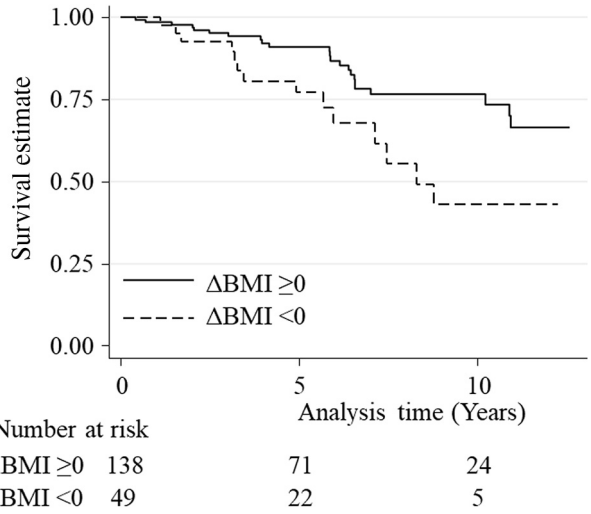

Figure 2. Comparison of all-cause mortality rates between the 2 study groups. BMI, body mass index.

There was a tendency for a drop in BMI on transfer, in those patients with a longer dialysis vintage (Fig. S3).

Sensitivity Analysis

Stratified Analysis

In this study, there were 77 patients aged ≥65 years, 80 female patients, 83 patients with DN, and 39 patients with a history of CVD. Figure 3 shows the HRs for all-cause mortality in patients, according to these factors. The HRs, obtained through stratified analyses, indicated correlations between all-cause mortality and the groups divided on the basis of factors including age, sex, presence of DN, history of CVD, and changes in BMI.

Association of ΔBMI With Sex of the Patient

ΔBMI between the 3rd and the 12th month was 0.25 kg/m^2 in male patients and 0.54 kg/m^2 in female patients. Although ΔBMI ≥ 0 was significantly associated with a low HR of 0.13 (0.03-0.56) in female patients (vs. 0.43 [0.16-1.11] in male patients), no significant association was observed between sex of the patient and the predictive value of ΔBMI ($P = .21$).

Association of ΔBMI With Different Age Groups

ΔBMI between the 3rd and 12th month was 0.41 kg/m^2 and 0.33 kg/m^2 in patients aged <65 years and in those aged ≥65 years, respectively. Although ΔBMI ≥ 0 was found to be significantly associated with a low HR of 0.28 (0.10-0.78) only in patients aged ≥65 years, the association between the predictive value of ΔBMI and age was insignificant ($P = .90$).

Association of ΔBMI With Diabetic Nephropathy

ΔBMI ≥ 0 was associated with HRs of 0.75 (0.23-2.43) and 0.11 (0.03-0.45) in patients with and without DN, respectively. Although the survival benefit of ΔBMI ≥ 0 in the DN group was unclear, the positive effect of ΔBMI ≥ 0 in the non-DN group was found to be statistically significant. The tests of interactions between the predictive value of ΔBMI and presence of DN demonstrated statistical significant ($P = .007$).

Association of ΔBMI With History of Cardiovascular Disease

ΔBMI ≥ 0 was associated with HRs of 0.50 (0.10-2.65) and 0.33 (0.13-0.83) in patients with and without CVD, respectively. Although ΔBMI ≥ 0 was found to be beneficial in patients without a history of CVD (but not in those with a positive history), this association between the predictive value of ΔBMI and a history of CVD was not statistically significant ($P = .61$).

Association Between Dialysis Vintage and BMI

When categorized into quartiles according to dialysis vintage, BMI at transfer was found to be lower in patients with a longer vintage (Table S2). The HR for mortality, associated with ΔBMI ≥ 0, was significantly lower in patients with a longer dialysis vintage (Fig. S4).

Discussion

In this study, the BMI of many patients increased or was successfully maintained after the initiation of extended-hours hemodialysis, without dietary restrictions. The mean BMI gradually decreased after attaining a peak, but the decrease was not as continuous as observed in patients on conventional hemodialysis.[16] The outcome in our patients was better than that reported in domestic data of patients undergoing conventional dialysis, and the maintained or increased BMI was found to be associated with a lower risk of mortality. Although the relationship between dialysis duration (hours) and outcome has been extensively studied, the additive treatment strategy based on active nutritional intake, reported in this study, is novel. Some reports have shown an increased risk of mortality associated with reduced BMI in patients on dialysis.[17–20] Based on this, our clinic launched a treatment protocol including extended-hours hemodialysis with no dietary restrictions. When a patient's weight or electrolyte levels increased, extra hemodialysis therapy was recommended instead of dietary restriction. Approximately 74% of patients at our clinic were found to have maintained or increased BMI by the 12th month of following this treatment protocol. The mean BMI of all patients increased to 22.9 ± 3.8 kg/m^2, which is greater than that reported in patients on hemodialysis nationwide (21.5 ± 3.9 kg/m^2).[21,22] In contrast to the national Japanese dialysis mortality rate (9.2%-10.2%),[21] the crude mortality rate at our clinic was estimated at 3.5 per 100 person-years.

Several possible mechanisms underlie the correlation between BMI changes and mortality. First, chronic inflammation increases the risk of mortality and protein-energy wasting, which is commonly observed in patients with ESRD.[23–25] Malnutrition may further exacerbate the effects of inflammation.[26–28] However, even after adjusting for

Table 2. Hazard Ratios (95% Confidence Intervals) for All-Cause Mortality

Variables	Univariable	Multivariable
⊿BMI ≥ 0	0.45 (0.23-0.87)*	0.35 (0.17-0.75)†
Sex (female)	1.08 (0.56-2.07)	1.35 (0.63-2.89)
Age at 12th mo, per 10 y	1.73 (1.25-2.38)†	1.74 (1.19-2.52)†
BMI at 12th mo (kg/m^2)	0.93 (0.84-1.03)	0.99 (0.88-1.11)
Dialysis protocol		
Kt/V at 12th mo	0.79 (0.21-2.90)	
Duration/session at the 12th mo (h)	0.96 (0.46-1.98)	
Sessions/week at the 12th mo (vs. ≤3)	0.81 (0.42-1.58)	
HDP at the 12th mo	1.02 (0.97-1.07)	
Dialysis vintage (y)	1.00 (0.95-1.04)	1.06 (1.00-1.12)*
Cause of renal disease		
Diabetic nephropathy	1.70 (0.89-3.25)	1.76 (0.73-4.20)
Nephrosclerosis	1.24 (0.52-2.99)	
Chronic glomerulonephritis	0.48 (0.22-1.06)	
Polycystic kidney disease	0.83 (0.11-6.10)	
Comorbidities		
Hypertension	0.99 (0.52-1.90)	
Diabetes mellitus	1.42 (0.74-2.71)	
Cardiovascular disease	3.04 (1.53-6.03)†	3.68 (1.52-8.92)†
Laboratory data		
Ferritin ≥200 (ng/mL)	1.22 (0.63-2.35)	1.42 (0.66-3.11)
Hemoglobin (g/dL)	0.76 (0.56-1.03)	
HbA1c (%)	1.21 (0.82-1.80)	
Calcium (mg/dL)	0.81 (0.51-1.29)	
Phosphate (mg/dL)	0.90 (0.71-1.14)	
Oral medications at transfer		
ACE inhibitor	1.39 (0.42-4.56)	
ARB	0.66 (0.31-1.39)	
CCB	0.60 (0.30-1.21)	
α-blocker	0.67 (0.24-1.92)	
β-blocker	0.39 (0.05-2.83)	
Statin	2.47 (0.73-8.35)	
Antiplatelet	1.15 (0.57-2.30)	
Warfarin	4.12 (0.54-31.30)	
Vitamin D	0.14 (0.02-1.00)*	
Diuretics	0.95 (0.45-2.00)	
Proton pump inhibitor	1.29 (0.39-4.23)	
H2 blockers	0.18 (0.02-1.29)	

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; BMI, body mass index; CCB, calcium channel blocker; HbA1c, hemoglobin A1c; HDP, hemodialysis product: hemodialysis hours × (hemodialysis sessions/week)^2.

Multivariable adjustment was performed for factors including age, sex, BMI at the 12th month, dialysis vintage, diabetic nephropathy, history of cardiovascular disease, and ferritin.

*$P < .05$.

†$P < .01$.

Table 3. Determinants of Maintained or Increased Body Mass Index Between the 3rd and 12th month

Determinants	Univariable Analysis Result	Multivariable Analysis Result
Age at transfer, per 10 y	0.95 (0.73-1.23)	0.95 (0.72-1.26)
Sex (female)	2.02 (1.01-4.04)*	1.91 (0.92-4.00)
Dialysis vintage (y)	1.07 (1.00-1.15)*	1.09 (1.01-1.18)*
Diabetic nephropathy	1.53 (0.78-3.00)	2.19 (1.01-4.77)*
Cardiovascular disease	1.48 (0.63-3.50)	1.34 (0.52-3.42)
Baseline BMI (kg/m^2)	0.95 (0.88-1.03)	0.98 (0.89-1.08)
Ferritin ≥200 (ng/mL)	0.87 (0.43-1.76)	0.78 (0.36-1.62)

BMI, body mass index.

*$P < .05$.

ferritin (200≥ vs. <200)[29] as one of the markers of chronic inflammation, the association of low risk of mortality with maintained or increased BMI was found to be persistent.

The second potential mechanism is hemodynamic stability. Patients on hemodialysis with decreased cardiac function are likely to experience intradialytic hypotension. Even temporary hypotension and myocardial ischemia during hemodialysis are thought to potentially lead to mortality induced by cardiovascular events.[30,31] The extended-hours protocol helps maintain the systolic blood pressure during the hemodialysis[32] and might help reduce the risk of cardiovascular events such as hypotension, which might cause nausea. Consequently, this could lead to an improved appetite in the dialyzed patients.

The association of maintained or increased BMI with decreased mortality was largely similar across differing demographic and clinical subgroups. However, the effect of maintained or increased BMI on improvements in the survival outcome was more pronounced in patients without DN. A similar association was reported in patients even on conventional hemodialysis.[33] The mechanisms of these differences between patients with and without diabetes are unclear. One hypothesis is that the patients with no dietary restrictions might have higher blood glucose levels and suffer from its complications. However, HbA1c levels were not found to be significantly different between those patients with and without maintained or increased BMI (6.8% vs. 6.7%, $P = .80$) along with DN at baseline. Based on our findings, we hypothesized that the BMI increase in those without DN (22.2-22.6 kg/m^2) was more beneficial than in patients with DN (22.8-23.3 kg/m^2), because lower BMI was associated with a significantly elevated risk of mortality. Additionally, diabetes mellitus may decrease antioxidant defenses. Levels of plasma-free protein thiols, reported to be associated with antioxidant defense,[34] are generally low in patients with diabetes.[33] This deficiency in patients with diabetes can exaggerate oxidative stress related to obesity.[35] In contrast, patients without DN were considered unlikely to show maintenance or increase in BMI, but once successfully occurred, it suggested prognostic improvement. Further studies should help clarify the pathophysiology of this finding.

The BMI at the 3rd month was lower (21.9 vs. 22.9 kg/m^2 [men]) and the increase from the 3rd to 12th month was greater (0.54 vs. 0.25 kg/m^2 [men]) in women. This might lead to an improved prognosis in women

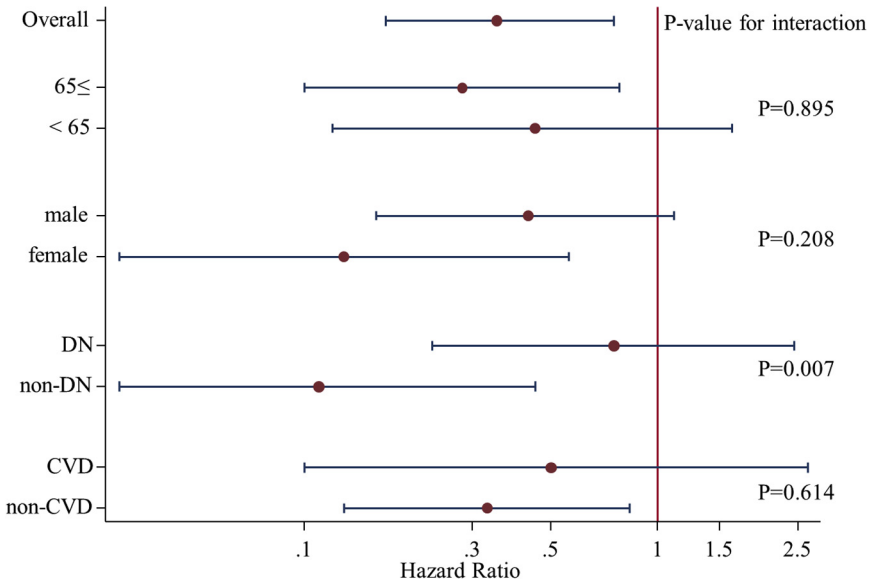

Figure 3. Hazard ratio (95% confidence interval) for all-cause mortality according to maintained or increased body mass index between the 3rd and 12th month in different subgroups. Results were obtained from Cox models, adjusted for age, sex, BMI at the 12th month, dialysis vintage, diabetic nephropathy, history of cardiovascular disease, and ferritin. *P*-values represent significance levels of each association. BMI, body mass index; CVD, cardiovascular disease; DN, diabetes nephropathy.

because lower BMI and an increase in BMI were found to be associated with a significantly elevated and reduced mortality risk, respectively, in our study. Nonetheless, there is a clinical need for further research to validate these findings.

There are several possible reasons for the BMI increase observed in this study population. Logistic regression analysis showed that a longer dialysis vintage before transfer to our clinic was associated with maintained or increased BMI. BMI can decrease during longer dialysis vintage with strict dietary restrictions. Our therapeutic concept may be more effective for increasing BMI in patients with low indices. Another possibility is that extended-hours hemodialysis is particularly effective in patients without residual kidney function. Patients with longer dialysis vintages tend to experience a decline in kidney function.[36] This could be why some studies including patients with a relatively short dialysis vintage have not demonstrated the usefulness of extended-hours hemodialysis.[37,38] Our observations suggest that even patients who have received conventional hemodialysis for a long time can benefit from maintained or increased BMI, as a result of extended-hours hemodialysis with no dietary restrictions.

There are some limitations to this study. First, our center is an outpatient dialysis clinic, and all included patients were able to attend the clinic independently; some moved closer to the clinic to receive this unique therapy. These factors may have introduced selection bias. However, most patients already resided close to the clinic, and there were no limits on patient enrollment. Thus, our study population may be representative of an average dialysis patient. Second, patients who dropped out of this treatment protocol due to declining physical strength may have been transferred to another hospital and died, introducing a misclassification bias. However, we followed up with patients for at least 1 year and accounted for any deaths in our analysis. Third, it is possible that the patients with a decrease in BMI might have severe forms of comorbidities. This indicates a need for more detailed data on the effects of various comorbidities depending on their severity. Fourth, survival bias may be present, which is why a longer dialysis vintage was associated with better survival in those with increasing BMI. However, generally those who undergo hemodialysis therapy for a long duration are unlikely to experience an increase in their BMI. We also adjusted for the vintage of conventional dialysis to minimize this influence. Thus, the combined therapy offered at our clinic (after transfer) is considered to have independently improved the prognosis of patients by increasing their BMI. Fifthly, we don't have precise information on the dietary habits of the patients, including whether the patients had self-imposed dietary restrictions. Systematic evaluation of the dietary intake will help further researches. Finally, this is a retrospective, nonrandomized study with a small sample size. We did not perform adjustments for some factors, which could have affected the prognosis of this population, including a poor control of hyperparathyroidism, presence of vascular calcifications and atrial fibrillation, because of the lack of information or the small population size. Future prospective studies with a larger cohort are required to validate our findings. Additional research is indicated to evaluate this protocol with respect to its effects on the quality of life, an objective and clearer evaluation of the nutritional status, and financial feasibility.

In conclusion, patients receiving extended-hours hemodialysis with no dietary restrictions had a low mortality rate. Maintained or increased BMI reduced the risk of mortality and was beneficial in female patients, those without DN, and those aged ≥65 years. In selected patients, extended-hours hemodialysis with no dietary restrictions improved outcome by maintaining or increasing BMI.

Practical Application

Malnutrition is a prognostic issue in patients undergoing maintenance hemodialysis therapy, and restricted diet is reportedly one of the reasons why malnutrition is common in this population. To address this issue, we implemented and studied a combined therapy consisting of an extended-hours hemodialysis protocol without any dietary restrictions. With extended-hours hemodialysis without dietary restrictions, patients who showed maintained or increased BMI were found to be associated with a decreased risk of mortality.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1053/j.jrn.2019.06.002.

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