Tohoku J. Exp. Med., 2023, **260**, 135-140

Extended-Hours Hemodialysis without Dietary Restrictions Increases Body Mass Index and Normalizes Hypertension: A Case Report

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Dialysis technology has made remarkable progress. However, many patients still suffer from malnutrition and hypertension. They cause many complications and significantly impact patients' quality of life and prognosis. To solve these problems, we developed a new dialysis modality, extended-hours hemodialysis without dietary restrictions. Here we report a case of a man who has received this treatment for 18 years. He had been on conventional hemodialysis (three times a week for 4 hours) since his dialysis initiation. He suffered from hypertension and was on five antihypertensive drugs to control his blood pressure. In addition, dietary restrictions were strict, and the nutritional status was somewhat poor. After being transferred to our clinic, the dialysis time was gradually extended to 8 hours, and dietary restrictions were greatly relaxed. Interestingly, his body mass index (BMI) increased, and his hypertension was controlled. After 3 years, he stopped all antihypertensive drugs. This result suggests that improving nutritional status may control hypertension. However, salt intake was substantially increased. Serum phosphorus and serum potassium levels were at a slightly higher level but were controlled by medications. At the time of transfer, anemia was treated with erythropoiesis-stimulating agents and glycated iron oxide, but these drugs were gradually reduced and discontinued. However, he maintained high average erythrocyte counts and normal hemoglobin levels. Dialysis conditions were wholly slow dialysis, lower than conventional dialysis methods, but the dialysis efficiency was satisfactory. In conclusion, we speculate that extended-hours hemodialysis without dietary restrictions reduces the risk of malnutrition and hypertension.

Keywords: BMI; extended-hours hemodialysis without dietary restrictions; glycosaminoglycans; hypertension; malnutrition
Tohoku J. Exp. Med., 2023 June, **260** (2), 135-140.
doi: 10.1620/tjem.2023.J025

Introduction

More than half a century has passed since maintenance dialysis is first started in the world (Scribner et al. 1960). Since then, dialysis technology has made remarkable progress. However, current dialysis treatments are still inadequate because the majority of dialysis patients suffer from malnutrition and hypertension. Hypertension is associated with an increased risk of left ventricular hypertrophy, coronary artery disease, congestive heart failure, cerebrovascular complications, and death. Antihypertensive drugs alone cannot adequately control blood pressure in dialysis patients (Salem 1995; Mittal et al. 1999). Scribner and Oreopoulos (2002) reported that three times weekly 8-hour dialysis schedules, which had already performed by Charra et al. (1999), provided adequate dialysis. Furthermore, they showed the 30-year survival experience, which was the best in the world. Charra et al. (1992, 1998) emphasize that prolonged hemodialysis provides excellent blood pressure control in hypertensive patients.

Received December 22, 2022; revised and accepted March 15, 2023; J-STAGE Advance online publication March 30, 2023
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Controlling hypertension improves patients' survival. Conventional dialysis with strict dietary restrictions on salt and protein (phosphorus) results in nutritional deficiency and excessive amino acid loss. These may be one of the causes of malnutrition (Kirschbaum 1994; Murtas et al. 2019). Malnutrition increases the risk of infection and inflammation. Kalantar-Zadeh et al. (2003a) suggested that malnutrition-inflammatory complex syndrome (MICS) was common in dialysis patients and that malnutrition and inflammation interacted. They said that MICS was the main cause of decreased erythropoietin response, increased incidence of cardiovascular disease, atherosclerosis, decreased patients' quality of life, increased mortality, and hospitalization.

Since 1998, we have developed and started a unique new dialysis modality called "extended-hours hemodialysis without dietary restrictions." We had two strategies. First, extended-hours hemodialysis (at least 6 hours per session), dialysis time of up to 8 hours is recommended unless contraindicated by severe back pain or severe tremor. Second, rather than imposing dietary restrictions, patients are advised to eat the same diet as their healthy family members. We advise additional dialysis if the patient has excessive body fluid or electrolyte imbalance. To our knowledge, this strategy has no case reports of long-term treatment. Here, we report a case in which hypertension and nutrition improved and maintained during 18 years of extended-hours hemodialysis without dietary restrictions.

Case Presentation

A 60-year-old man was found to have proteinuria at the age of 26 and was diagnosed with chronic glomerulonephritis by renal biopsy. Since then, he has been taking antihypertensive medications to treat his high blood pressure. The disease worsened to end-stage at the age of 41, and was placed on hemodialysis at a general hospital. He was on regular dialysis for 4 hours three times a week. He suffered from hypertension and found that extended-hours hemodialysis provided excellent blood pressure control. Then, at the age of 42, he transferred to our clinic. He underwent a total parathyroidectomy (PTX) with forearm autotransplantation because of secondary hyperparathyroidism two weeks before transfer. Also, after about 13 years (age 55), he began to experience significant psychological stress due to family health issues.

His body mass index (BMI) was 26.7 kg/m^2 in his thirties. It was declined to 20.9 kg/m^2 at the start of hemodialysis and 20.2 kg/m^2 when transferred to our clinic half a year after starting regular dialysis because he wanted extended-hours hemodialysis without dietary restrictions. Then, mean arterial pressure (MAP) before dialysis was about 110 mmHg despite taking many antihypertensive drugs. Because of his high blood pressure, he was on a strict diet with restricted salt intake. His BMI was 20.2 kg/m^2. It was in the normal range but below the optimal 23.0 kg/m^2 (Fouque et al. 2007).

Fig. 1 shows changes in dialysis time, antihypertensive medications, MAP, BMI, and interdialytic weight gain (IDWG). Data extracted from recordings of all dialysis sessions during the observation period are presented as mean values for 1-year intervals. The dialysis time was extended from three times a week for 4 hours to three times a week for 6 hours after obtaining the patient's consent from the start of treatment at our clinic. After 1.3 years, it was extended to 7 hours, and 2.8 years later to 8 hours. He then underwent extended-hours hemodialysis for 8 hours until 18 years later. It is twice as long as conventional dialysis time. At the time of transfer, five antihypertensive drugs were administered daily: angiotensin-converting enzyme (ACE) inhibitor (temocapril hydrochloride, 2 mg/day), angiotensin II receptor blocker (ARB) (valsartan, 40 mg/day; candesartan cilexetil, 8 mg/day), and calcium channel blocker (CCB) (nifedipine L, 20 mg/day; nifedipine CR, 40 mg/day). Two years later, during 7-hour dialysis period, the dose of antihypertensive drugs was gradually reduced, and hypertension was controlled with a combination of two or three antihypertensive drugs: ARB (valsartan, 40-160 mg/day), CCB (nifedipine CR, 10-40 mg/day), α2-agonists (clonidine hydrochloride, 0.15 mg/day), and α-blockers (doxazosin mesylate, 1-8 mg/day). After 3 years, the antihypertensive drugs could be stopped completely because the predialysis MAP had been normalized. During the period of antihypertensive drugs (3 years from the time of transfer), MAP was 110.6-115.3mmHg. Then MAP gradually decreased to 96.5-106.6 mmHg without antihypertensives. It increased slightly after 13-14 years but remained between 109.6-114.4 mmHg until 18 years later. The mean MAP during the whole period was 109.3 ± 5.5 mmHg (mean ± standard deviation, SD). The mean MAP during no hypertensives (4-18 years) was 108.6 ± 5.7 mmHg. BMI, an index of nutritional state, was 20.2 kg/m^2 at the time of transfer but increased to 21.2 kg/m^2 one year after starting 6-hour dialysis. Furthermore, when the dialysis time was extended to 7 hours, BMI increased to 23.2 kg/m^2. After the extension to 8 hours, it increased further and remained around 26.0 kg/m^2 for 12 years thereafter. Although it gradually decreased after 13 years, it remained between 23.6 and 25.7 kg/m^2 until 18 years later. The average BMI during the entire observation period was 24.7 ± 1.4 kg/m^2. The IDWG one month after the transfer was 1.9 kg, and the same dietary restrictions as conventional dialysis were imposed. IDWG gradually increased to 2.6 kg one year after starting 6-hour dialysis and 2.8 kg after 3 years with 7-hour dialysis. Furthermore, 4 years later, the IDWG significantly increased to 4.2 kg when he switched to 8-hour dialysis. By extending the dialysis time to 8 hours, he seems to not need dietary restrictions. IDWG peaked at 7 years and maintained 4.5-5.0 kg until 11 years later. IDWG was maintained 3.5-4.4 kg for 18 years thereafter. We observed that increasing IDWG had only a small effect on blood pressure instability during dialysis. The mean MAP before and after hemodialysis was 110.0 ± 5.3 mmHg and

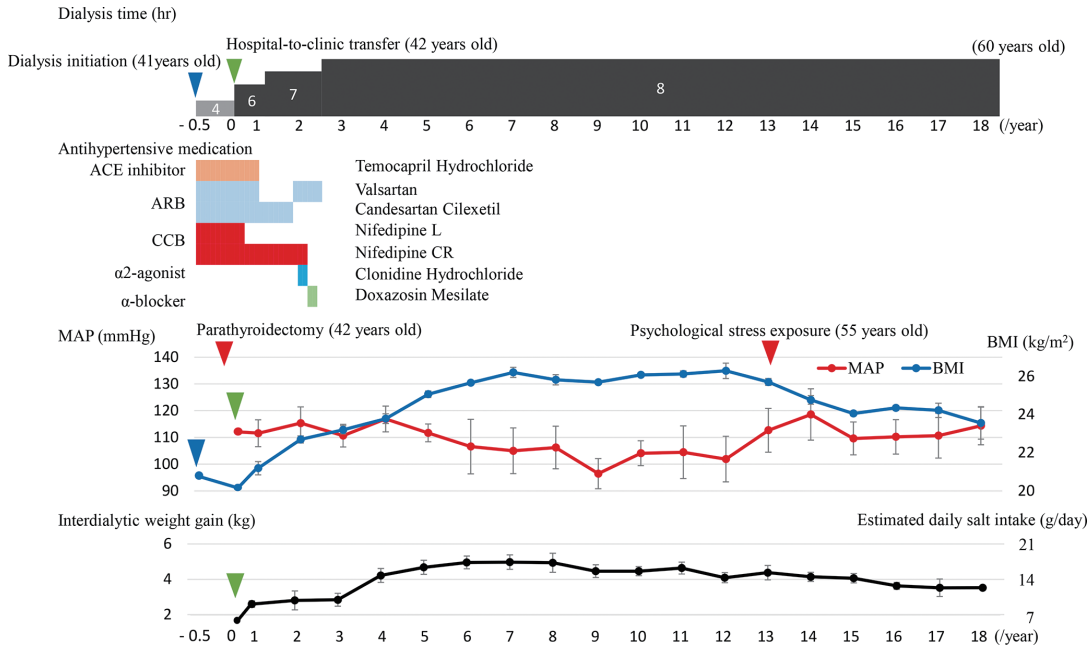

Fig. 1. Clinical course for 18 years (42-60 years old) after the transfer.
After starting extended-hours hemodialysis without dietary restrictions treatment, the dialysis time gradually extended to 8 hours. Then BMI increased, and MAP decreased, despite increased interdialytic weight gain (estimated daily salt intake) and discontinuation of antihypertensive medication. The blue arrow indicates the dialysis initiation, and the green arrow indicates hospital-to-clinic transfer. Data are expressed as mean ± standard deviation. ACE inhibitor, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; MAP, mean arterial pressure; BMI, body mass index.

100.9 ± 11.7 mmHg, respectively. The MAP change before and after dialysis was −9.1 ± 7.8 mmHg, and intradialysis hypotension was slight (K/DOQI Workgroup 2005). It has also been reported that the daily salt intake of dialysis patients can be estimated from IDWG (Watanabe et al. 2015). Estimated daily salt intake was calculated as follows: Estimated daily salt intake = total weight gain (kg) per week × 8.2/7 days. The vertical axis on the right side of the IDWG in Fig. 1 indicates the estimated daily salt intake. The estimated daily salt intake at the time of transfer was about 6.7 g, but the maximum was 17.6 g, about 2.6 times higher.

Laboratory data represent the mean (SD) of all data obtained during observation (Table 1). Electrolytes were nearly normal, and serum potassium and phosphorus levels were drug-controlled. Serum potassium levels were maintained at normal levels with a hyperkalemia-improving drug (calcium polystyrene sulfonate, 25-75 g/day). Serum phosphorus was treated with a phosphorus adsorbent alone or in combination with precipitated calcium carbonate (1.5-4.0 g/day) and sevelamer hydrochloride (1.5 g/day). Red blood cell count was 413.3 ± 26.8 × $10^4/\mu$L, and mean hemoglobin (Hb) was10.9 ± 0.6 g/dL. His anemia was treated with the erythropoiesis-stimulating agents (ESAs) (rHuEPO, 4,500 IU/wk) and glycated iron oxide (40 mg/wk) at the time of transfer. These drugs were gradually tapered, and all drugs for anemia were discontinued after 4.2 years. Thereafter, the Hb level was maintained above 10 g/dL without administration of ESAs or saccharified iron oxide.

The dialysis conditions were as follows: the blood flow rate (Qb) was 178.8 ± 9.7 mL/min, and the dialysate flow rate (Qd) was 300 mL/min. Both are lower than the conventional dialysis method (Qb > 200 mL/min, Qd = 500 mL/min). However, the dialysis efficiency index single pool Kt/V (1.8 ± 0.2), time-average urea concentration (TAC-urea) (34.2 ± 3.6 mg/dL), hemodialysis product (HDP) recommended by Scribner and Oreopoulos (2002) and HDP (69.8 ± 5.1) show sufficient values. The following formula calculated HDP; HDP = hours/dialysis session × (session/week)^2. The dialysate was Na^+ = 140 mEq/L, K^+ = 2.0 mEq/L, Ca^{++} = 3.0 mEq/L (Table 2).

Informed consent was obtained from the patient for this case report.

Discussion

We often experience well-controlled hypertension in patients undergoing extended-hours hemodialysis without dietary restrictions. In the case reported here, there was a close relationship between blood pressure control and nutritional status. Charra et al. (1992) reported that 8 hours hemodialysis with dietary restrictions provided adequate blood pressure control, allowing 98% of patients to discontinue antihypertensive drugs. They achieved control of hypertension with strict salt and IDWG restrictions. On the contrary, our extended-hours hemodialysis controlled hypertension without dietary restrictions, such as salt,

Table 1. Average of laboratory data for 18 years after transfer (April 2003-March 2021).

		n	(Reference values)
Sodium	139 ± 0.9 mEq/L	226	(136~147)
Potassium	5.0 ± 0.2 mEq/L	433	(3.6~5.0)
Calcium	9.3 ± 0.4 mg/dL	262	(8.4~10.0)
Phosphate	6.2 ± 0.7 mg/dL	262	(3.5~6.0)
UN	54.3 ± 5.4 mg/dL	46	
Creatinine	13.7 ± 1.1 mg/dL	46	(12.0~14.0)
β_2MG	28.6 ± 1.4 mg/L	37	(< 30)
intact-PTH	111.0 ± 108.6 pg/mL	136	(60~240)
Total protein	6.9 ± 0.2 g/dL	45	(6.5~8.3)
Albumin	3.9 ± 0.1 g/dL	126	(3.5~5.0)
Total cholesterol	159.4 ± 24.3 mg/dL	45	(< 180)
White blood cell	6,595.4 ± 530.4/μL	379	(4,000~8,500)
Red blood cell	413.3 ± 26.8 $\times 10^4/\mu$L	379	(330~390)
Hemoglobin	10.9 ± 0.6 g/dL	379	(10.0~12.0)
Ferritin	41.1 ± 80.2 ng/mL	53	(100~300)
h-ANP	40.8 ± 17.3 pg/mL	44	(< 43.0)

Data are expressed as mean ± standard deviation.
UN, urea nitrogen; β_2MG, β_2-microglobulin; intact-PTH, intact parathyroid hormone; h-ANP, human atrial natriuretic peptide.

Table 2. Average of hemodialysis procedure data for 18 years after transfer.

Blood flow rate (Q_B)	178.8 ± 9.7 mL/min
Dialysate flow rate (Q_D)	300 mL/min
Dialysate composition (mEq/L)	Na^+ = 140, K^+ = 2.0, Ca^{++} = 3.0
Dialysis membrane	PES and/or PS
Membrane area	2.1m^2
spKt/V	1.8 ± 0.2
TAC-urea	34.2 ± 3.6 mg/dL
HDP	69.8 ± 5.1
nPCR	0.86 ± 0.07 g/kg/day
CGR	131.7 ± 9.8 mg/kg/day

spKt/V, single-pool urea fractional clearance; TAC-urea, time-average concentration of urea; HDP, hemodialysis product; nPCR, normalized protein catabolic rate; CGR, creatinine generation rate.

IDWG, and protein. It resulted in significant increases in BMI and IDWG. Therefore, it is suggested that improvement in nutritional status may suppress hypertension. Conversely, malnutrition can cause hypertension.

Titze et al. (2002, 2004) argued that negatively charged glycosaminoglycans (GAGs) in the skin store cationic sodium (Na^+). They suggested that GAGs took up osmotically active Na^+ in the circulation. If salt intake is high, excessive sodium moves into skin GAGs as osmotically inactive Na^+, preventing fluid accumulation (extracellular volume). Olde Engberink et al. (2015) proposed that GAGs, abundant in the endothelial surface layers (ESLs) of blood vessels, functioned as an intravascular buffer that temporarily stored substantial amounts of sodium. Red blood cells (RBCs) were also covered by GAGs and function similarly to ESLs (Oberleithner 2015). They also reported that ESL and RBCs were in continuous contact with flowing blood and thus might act as an initial buffer for sodium. GAGs may lower blood pressure by storing osmotically active Na^+ and removing it from circulation. Becker et al. (2015) reported that ensuring sufficient albumin levels was the most obvious option for protecting the GAGs. GAGs are also decreased by long-term protein and calorie deficiencies (Kaggwa 1986; Oishi et al. 2003). Therefore, improving the nutritional state of maintenance long-term dialysis patients is considered essential for the synthesis, repair, and protection of damaged GAGs. Our patient, 5 years before starting dialysis, underwent strict salt

and protein restrictions to slow the progression of chronic kidney disease, causing a significant decrease in BMI and an increase in blood pressure. After extended-hours hemodialysis without dietary restrictions, BMI increased from 20.2 kg/m^2 to 26.3 kg/m^2, and blood pressure was normalized. The BMI approached 26.7 kg/m^2, the value before the dietary restrictions. Hypertension may have been caused by malnutrition. Many maintenance dialysis patients have lowered kidney function to excrete sodium. The authors speculate that GAGs may modulate extracellular volume in maintenance dialysis patients and consequently play a role in blood pressure regulation. Therefore, it is interesting to speculate that GAGs regulate sodium balance by improving nutritional status and play an essential role in controlling blood pressure.

Small and middle molecules are removed more adequately from the deeper compartments when performing extended-hours hemodialysis (Basile et al. 2011). Furthermore, it has been reported that this treatment may inhibit chronic inflammation (Nishiyama et al. 2021). Thus, adequate dietary intake, reduced uremic substance accumulation, and inhibition of chronic inflammation may have lowered the risk of protein energy wasting (Obi et al. 2015). In addition, we often experience improvement in appetite after extended-hours of hemodialysis. Extended-hours hemodialysis is excellent at removing middle molecules and may decrease leptin (Alix et al. 2014), that acts as an appetite suppressant. In addition, many oral medications may induce anorexia. The removal of these factors increased appetite, and one of our treatment strategies, "no dietary," may have improved nutritional status. MICS has also been implicated in anemia in dialysis patients (Kalantar-Zadeh et al. 2003b). The improving malnutrition and inflammation may explain why this patient can maintain high-normal red blood cell counts and normal hemoglobin levels without the use of ESAs or glycated iron oxide.

After extended-hours hemodialysis without dietary restrictions, patients with increased or maintained BMI had a lower risk of death (Hishida et al. 2020). In addition, Tabata et al. (2021) also reported a decreased risk of developing dialysis amyloidosis. Therefore, starting extended-hours hemodialysis early in the induction of dialysis (younger age) may reduce the risk of various complications. In Japan, hemodialysis patients are aging, especially those over 70. Frailty and sarcopenia in older dialysis patients are becoming an issue. Intensive reduction of uremic toxins by extended-hours hemodialysis or frequent dialysis may improve frailty (Chao and Lin 2021). Adequate energy, protein intake and exercise reduce the prevalence of sarcopenia (Sabatino et al. 2021). A decreased risk of death in patients over 70 who received extended-hours hemodialysis without dietary restrictions has been reported (Okazaki et al. 2020), suggesting that extended-hours hemodialysis without dietary restrictions may be an effective treatment option for elderly dialysis patients.

He underwent a total PTX two weeks before transfer. It has been reported that blood pressure decreased within a few months after total PTX (Goldsmith et al. 1996). In addition, recent studies have reported that elevated parathyroid hormone levels are associated with weight loss (Komaba et al. 2021). Total PTX may have affected blood pressure normalization and BMI increase. However, it took him three years after his total PTX to discontinue his antihypertensive medications. Furthermore, his MAP gradually declined over a long period, up to 12 years later. In addition, BMI continued to increase over time until 12 years later. Therefore, it is unclear whether total PTX played a long-term role in suppressing his hypertension and increasing his BMI.

BMI began to decrease 13 years after the start of treatment (55 years old), and MAP gradually increased. The gradual decrease in IDWG may have contributed to the reduction of BMI. However, BMI remained normal and required no antihypertensive medication, as the IDWG remained between 3.5 and 4.4 kg. He began to experience significant psychological stress from this period due to family health issues. These may have contributed to a decrease in the quantity and quality of his diet and an increase in his blood pressure.

One treatment strategy, "no dieting," increases IDWG. Increased IDWG is usually associated with increased blood pressure, but several studies have reported that increased IDWG is not associated with increased blood pressure (Testa and Plou 2001; Jalalzadeh et al. 2021). They also reported that higher IDWG was associated with better nutritional status (Testa and Beaud 1998).

The disadvantage of extended-hours hemodialysis is the length of the restraints. We offer the option of in-center long nocturnal hemodialysis for full reintegration for patients who work full time. We perform 8 hours of dialysis in the middle of the night during bedtime. Some of our clinics perform long nocturnal hemodialysis three times a week for about 50 patients.

In conclusion, patients undergoing extended-hours hemodialysis without dietary restrictions may have a reduced risk of malnutrition and hypertension. Dialysis patients may benefit greatly from extended and slow dialysis and adequate dietary intake.

Acknowledgments

We would like to thank Professor Emeritus Kaoru Yoshinaga and Professor Shoichi Maruyama for their kind assistance and cooperation.

Conflict of Interest

The authors declare no conflict of interest.

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