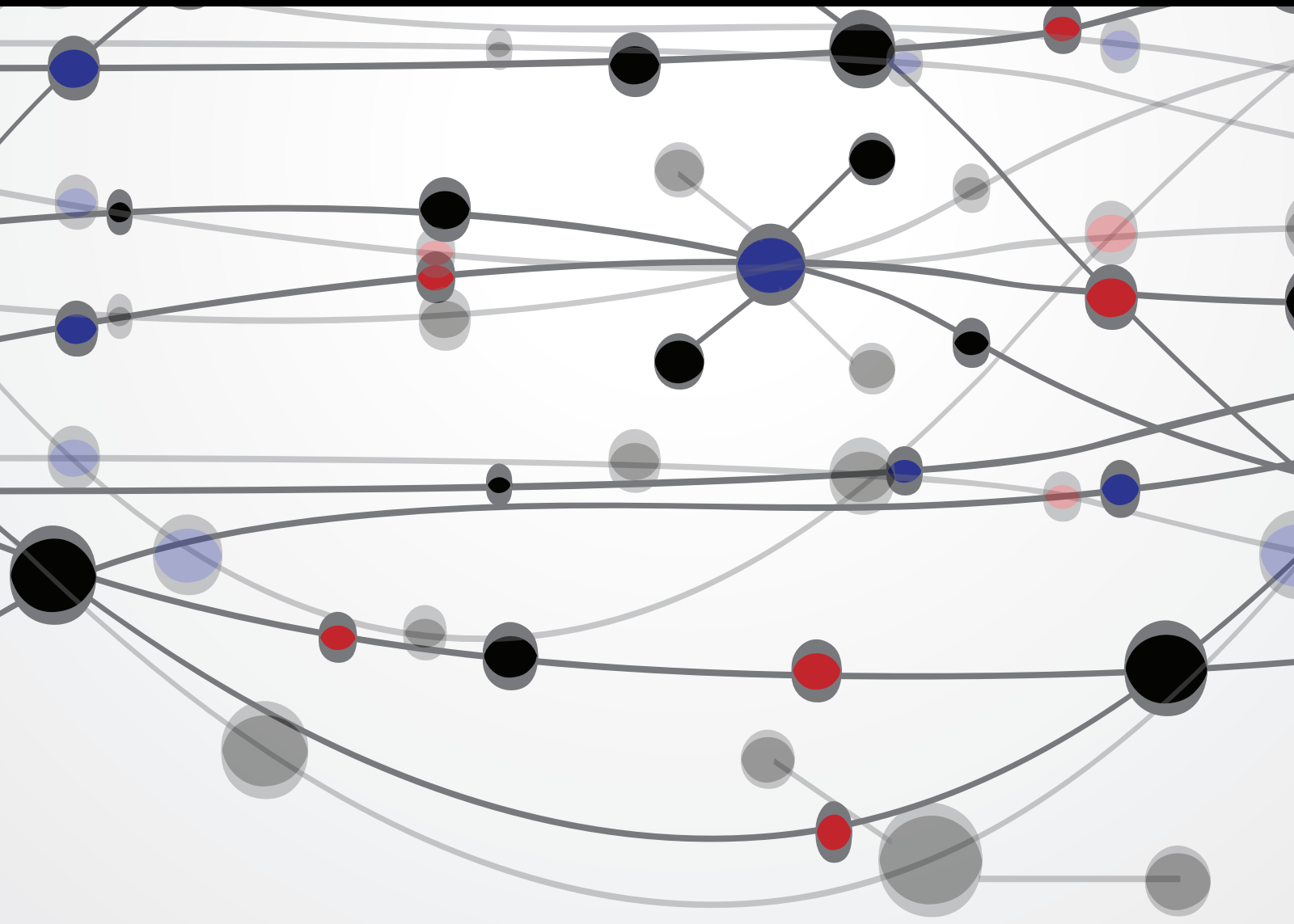
The Scientific World Journal

Hemodialysis-Associated Problems to Solve: Current and Future

Guest Editors: Fumihiko Hinoshita, Ryoichi Ando, Rumi Sakai, and Satoru Kuriyama



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Editorial

Hemodialysis-Associated Problems to Solve: Current and Future

Fumihiko Hinoshita,[1] Ryoichi Ando,[2] Rumi Sakai,[3] and Satoru Kuriyama[4]

[1] *Department of Nephrology, National Center for Global Health and Medicine, Tokyo 162-8655, Japan*
[2] *Department of Nephrology, Japanese Red Cross Musashino Hospital, Tokyo 180-8610, Japan*
[3] *Sakairumi Clinic, Kobe 658-0046, Japan*
[4] *Division of Kidney and Hypertension, Department of Internal Medicine, Jikei University School of Medicine, Tokyo 105-8461, Japan*

Correspondence should be addressed to Fumihiko Hinoshita; fhinoshi@hosp.ncgm.go.jp

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Hemodialysis (HD) is now an indispensable medical treatment for patients with end-stage renal disease (ESRD). The early establishment of this epoch-making treatment was very difficult. Based on the original concept of blood purification in the 19th century, many great scientists and physicians, such as John J. Abel, Georg Haas, Willem Kolff, Frederik Kiil, and Belding H. Scribner, made tremendous efforts to realize safe and efficient dialysis for patients in the 20th century. Thanks to Dr. Scribner and many other enthusiastic pioneers, the method of modern HD has been established and spread throughout the world in the 1960s. Since that time, HD-related technology and drugs have greatly evolved in many ways, and it may appear that HD is a completed medical technique which would hardly need any further innovation in the 21st century.

We must take a step back and ask ourselves if HD is truly an established treatment. Is there no need for further innovation? Are there no HD-associated clinical problems? We believe nearly all nephrologists and HD-devoted physicians and medical staff as well as clinical researchers would answer "no." Even though HD care has greatly progressed, more innovations and further modifications for HD are still necessary to improve the prognosis of HD patients and to prevent various types of complications. Moreover, some refined methods, techniques, and solutions to improve HD might be currently carried out only in limited or localized hospitals and HD facilities in particular areas. It is easy to imagine that most of these methods are not yet widely known, and they have not been introduced or tried in other hospitals or HD facilities in other countries, particularly in emerging and developing countries where HD was just introduced a mere 5 or 10 years ago and is not spread to every area of each country.

This special issue was planned and proposed to identify the current HD-associated problems which are not well known or not yet resolved. A number of researchers in clinical practice have indicated various HD-associated problems from diverse perspectives. Such problems include urogenital, cardiac, muscular, and gerontological problems as well as anemia, multiple myeloma, blood access, and also information related to erythropoietin and anticoagulant therapy. Treatment by exercises, a new hemodiafiltration (HDF) method, and so on are further included. All of these newly published findings would not necessarily ensure a perfect resolution for the problems in the HD area or nephrology; however, we hope that such contributions will lead to useful solutions and novel developments to overcome various insuperable HD-associated problems in the future. We also expected some innovative reports on CKD-mineral bone disease (MBD), HD session frequency and length, and the use of herbal or alternative medicines, all of which have been very important and still are a matter of controversy.

Unfortunately, however, the important findings on these problems could not be published in the current special issue. We earnestly hope that these problems will be covered and actively discussed in a near future issue of this journal.

Acknowledgment

The chief guest editor thanks Petr Boucek, M.D., Ph.D., for his assistance.

Fumihiko Hinoshita
Ryoichi Ando
Rumi Sakai
Satoru Kuriyama

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Review Article

Modification of the HeRO Graft Allowing Earlier Cannulation and Reduction in Catheter Dependent Days in Patients with End Stage Renal Disease: A Single Center Retrospective Review

Deirdre Hart,[1] Christie Gooden,[1,2] L. S. Cummings,[1,2] Brandt C. Wible,[3] John Borsa,[4] and Henry Randall[1,2]

[1] *General Surgery Department, University of Missouri-Kansas City School of Medicine, Kansas City, MO 64108, USA*
[2] *Saint Luke's Hospital Transplant Specialists, Kansas City, MO 64111, USA*
[3] *Section of Interventional Radiology, UMKC-SOM, Saint Luke's Hospital of Kansas City, 4401 Wornall Road, Kansas City, MO 64111, USA*
[4] *Saint Luke's Hospital Interventional Radiology Department, Kansas City, MO 64111, USA*

Correspondence should be addressed to Christie Gooden; cgooden@saint-lukes.org

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After creation of an arteriovenous fistula or placement of an arteriovenous graft, several weeks are required for maturation prior to first cannulation. Patients need an alternative way to receive hemodialysis during this time, frequently a catheter. After multiple failed access attempts, patients can run out of options and become catheter dependent. At our institution, we place HeRO grafts in eligible patients who have otherwise been told they would be catheter dependent for life. By combining the HeRO graft system with a Flixene graft, patients are able to remove catheters sooner or avoid placement as they can undergo cannulation for hemodialysis the next day. Utilizing this novel technique, twenty-one patients over a two-year period with various forms of central venous stenosis, catheter dependence, or failing existing arteriovenous access have been successfully converted to stable long term noncatheter based upper extremity access.

1. Introduction

According to the National Kidney and Urologic Diseases Information Clearinghouse; there were 398, 861 patients with end stage renal disease (ESRD) being treated with dialysis in 2009, and about 18% used a catheter for hemodialysis [1]. Once a patient is found to have central venous stenosis or occlusion, attempts at upper extremity long term hemodialysis access are often abandoned if it cannot be corrected [2]. As a result, these patients are relegated to lower extremity arteriovenous grafts or tunneled catheters for hemodialysis access. The HeRO graft was developed as an option for patients who are in this predicament.

A HeRO (Hemodialysis Reliable Outflow) graft is made of a venous outflow component and an arterial graft component (Figure 1). It is FDA approved as a hemodialysis graft and is located completely subcutaneously. The 19F outflow component has a radiopaque tip to assist with placement. There is a titanium connector to connect the venous outflow to the arterial ePTFE graft in the deltopectoral groove (Figure 2).

2. Materials and Methods

In 2011, the Saint Luke's Hospital Transplant Specialists started the Dialysis Access Center consisting of two surgeons and four interventional radiologists. Several patients considered catheter dependent were referred to the Dialysis Access Center and the HeRO graft was offered as an option for this subset of patients. Since that time we have placed twenty-one HeRO grafts in twenty-one patients. Patients range in age from twenty-five to eighty-nine and have been on hemodialysis from two to twenty years, with a mean of 7.5 years on hemodialysis. Fifteen patients had HeRO grafts

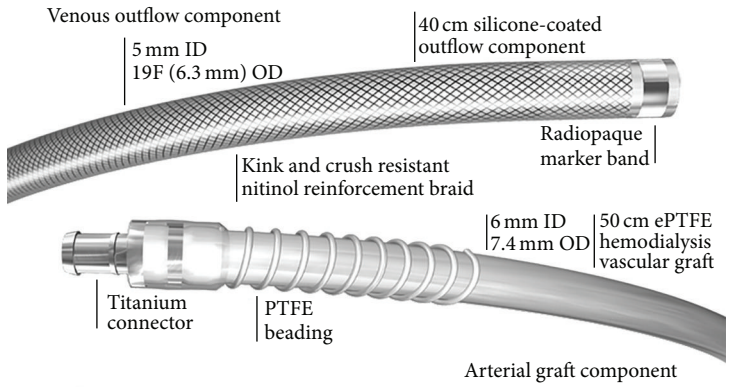

Figure 1: Used with the permission of CryoLife, Inc.

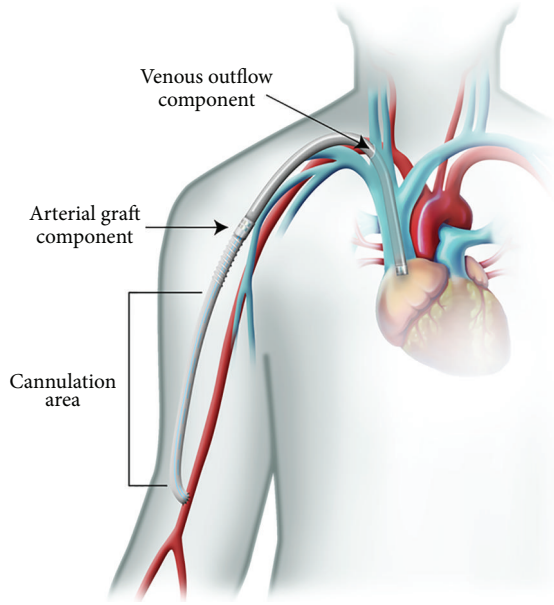

Figure 2: Used with the permission of CryoLife, Inc.

Table 1

Pertinent patient comorbidities	Number of patients
Hypertension	18
Diabetes mellitus	12
Cardiac disease	11
Anemia	9
Dyslipidemia	9
Cerebrovascular accident	6
Thyroid disease	6
Obstructive sleep apnea	5
Asthma	4
Deep vein thrombosis	3
Gastroparesis	3
Hyperparathyroidism	3
Morbid obesity	3
Chronic obstructive pulmonary disease	2
Seizures	2
HIV/AIDS	1
Paraplegia	1
Parkinson's disease	1
Pulmonary hypertension	1

placed secondary to multiple failed access attempts secondary to central venous stenosis. Two were placed secondary to superior vena cava occlusion requiring recanalization. Two were used to rescue existing fistulas that were failing due to ipsilateral central stenosis by connecting the fistula to the HeRO outflow component. In addition, two had central stenosis with poor peripheral arterial systems requiring proximalization of arterial inflow during graft placement. The first four procedures were performed as per the FDA approved method. Subsequently two modifications were made to the originally prescribed procedure to make it better suited to our complex patient population (Table 1).

It was noted that the approved method required a two-week waiting period before cannulation of the ePTFE component. This method still required the use of a tunneled catheter in the interim period. In patients who have limited access or in whom infection is a concern, obtaining or having an additional catheter is often problematic. In an attempt to obviate the need for this two-week waiting period, a portion of the ePTFE arterial component was replaced with a Flixene graft. The APHECS II trial showed no complications cannulating the Flixene graft within 72 hours of placement for hemodialysis access [3]. At our institution, Flixene grafts are routinely used for standard AV graft formation and success has been had with cannulation as early as postoperative day one. Using this experience, the decision was made to transect the ePTFE just proximal to the titanium connector. The Flixene graft is then anastomosed to the remaining ePTFE in an end-to-end fashion with 5-O prolene suture. The Flixene graft is then anastomosed to the inflow artery (Figure 3).

This modification has allowed temporary catheters to be removed sooner, or in some cases, to be completely replaced by the HeRO; thereby negating the need for an accessory catheter.

Table 2

Complication	Intervention	Patients
Perioperative myocardial infarction	Cardiac catheterization	1
Infection	Excision of graft	4
Dialysis-associated steal syndrome	Graft ligation	1

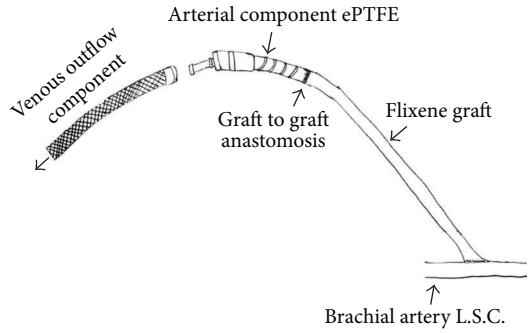

Figure 3

The second modification involves protecting the hybrid anastomosis. The Flixene to ePTFE connection is often immersed in the tunnel. To prevent bleeding, BioGlue is used to seal the anastomosis. The remaining seventeen patients received a HeRO graft using this technique.

Given the complexity of these patients, selection and work-up is of utmost importance. The majority of our referrals come with no available previous work-up and are often from a distance away. Therefore, patients are often admitted to the hospital the day prior to surgery to complete this work-up. The work-up includes bilateral upper extremity central venograms to assess patency of the venous system. Patients with known or suspected peripheral arterial disease also undergo bilateral upper extremity arteriograms. These studies are performed by our interventional radiology colleagues. As the patients often have a complex medical history with multiple medical comorbidities, a cardiopulmonary work-up can also be completed during this preoperative admission.

After review of the venogram and/or arteriogram the upper extremity for implantation is chosen. If venoplasty with or without stenting of the central venous system, including recanalization of central vessels, is required, it is performed at this time. In order to facilitate access to stenosed or previously occluded central veins intraoperatively, a temporary dialysis catheter is often also placed during this time. This allows the venous outflow component of the HeRO graft to be placed over a guidewire without difficulty. During the operative placement of the venous outflow component of the HeRO graft the following day, a guidewire can be placed through the temporary catheter, which is then subsequently removed. The tract is serially dilated and the venous component is positioned using fluoroscopic guidance. Having these interventions performed prior to proceeding to the operating room allows delineation of venous anatomy, identification of trouble areas, and pretreatment of stenosis. This has translated into assurance that the HeRO graft could be placed prior to proceeding to the operating room and undertaking the additional risks of general anesthesia.

3. Results and Discussion

We have placed twenty-one HeRO grafts in twenty-one patients over two years. Complications have included one perioperative myocardial infarction, four infections that required excision (one primary HeRO graft infection and three secondary infections from other primary sites), and one dialysis-associated steal syndrome that required ligation (in a patient without known peripheral arterial disease) (Table 2). At the time of this paper, five HeRO grafts have been removed for the above mentioned causes, two have failed due to poor inflow, 4 patients have died of other causes with functioning HeRO grafts, and ten HeRO grafts continue to function for hemodialysis.

HeRO grafts patency rates are comparable to standard arteriovenous grafts [4], but in our experience they respond well to thrombectomy. To that end, patients need enough of an ejection fraction to maintain flow throughout the length of the access. When considering HeRO graft placement, the company recommends an ejection fraction over 20% [5].

Catheter dependence places patients at high risk for infections and potentially subsequent hospitalization [6]. Centers for Medicare and Medicaid Services recognizes this and has encouraged the reduction of the number of catheter dependent patients in order to save valuable healthcare dollars. To this end dialysis centers are now held accountable for their catheter rates and can be penalized monetarily [7]. HeRO grafts are a viable option for hemodialysis patients who are running out of access or who are already catheter dependent secondary to central venous stenosis or occlusion. By using a combined approach with interventional radiology, one can gain valuable information about a patient's vasculature prior to proceeding to the operating room. This allows maximal chances of success in placement of hemodialysis graft access and reduced catheter dependence.

4. Conclusion

Central venous stenosis, often from the over use of catheters, is a serious problem in the ESRD population leading to loss of access and catheter dependence. The HeRO graft represents an advance that can obviate the need for long term tunneled catheters. Our method allows for more expedited use of this system, reducing catheter dependent days and thus decreasing risk for infections and death. This is achieved by allowing cannulation on postoperative day one and using BioGlue to reduce bleeding at the hybrid anastomosis.

Conflict of Interests

The authors of this paper declare that there is no direct financial relationship that might lead to a conflict of interests regarding the publication of this paper.

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Clinical Study

Association of Habitual Physical Activity Measured by an Accelerometer with High-Density Lipoprotein Cholesterol Levels in Maintenance Hemodialysis Patients

Ryota Matsuzawa,[1,2] Atsuhiko Matsunaga,[1] Toshiki Kutsuna,[3] Akira Ishii,[2,4] Yoshifumi Abe,[1] Kei Yoneki,[1] Manae Harada,[1] Mio Ishibashi,[2] Yasuo Takeuchi,[5] Atsushi Yoshida,[2] and Naonobu Takahira[1]

[1] *Department of Rehabilitation Sciences, Graduate School of Medical Sciences, Kitasato University, 1-15-1 Kitasato, Sagamihara, Kanagawa 252-0373, Japan*
[2] *Hemodialysis Center, Sagami Junkanki Clinic, Sagamihara, Japan*
[3] *Rehabilitation Center, Kitasato University East Hospital, Sagamihara, Japan*
[4] *Department of Cardioangiology, Graduate School of Medical Sciences, Kitasato University, 1-15-1 Kitasato, Sagamihara, Kanagawa 252-0373, Japan*
[5] *Division of Nephrology, Department of Internal Medicine, Kitasato University School of Medicine, Sagamihara, Japan*

Correspondence should be addressed to Atsuhiko Matsunaga; atsuhikonet@gmail.com

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After confirming the relationship between high-density lipoprotein cholesterol (HDL-C) levels and mortality in hemodialysis patients for study 1, we investigated the effect of physical activity on their HDL-C levels for study 2. In study 1, 266 hemodialysis patients were monitored prospectively for five years, and Cox proportional hazard regression confirmed the contribution of HDL-C to mortality. In study 2, 116 patients were recruited after excluding those with severe comorbidities or requiring assistance from another person to walk. Baseline characteristics, such as demographic factors, physical constitution, primary kidney disease, comorbid conditions, smoking habits, drug use, and laboratory parameters, were collected from patient hospital records. An accelerometer measured physical activity as the number of steps per day over five consecutive days, and multiple regression evaluated the association between physical activity and HDL-C levels. Seventy-seven patients died during the follow-up period. In study 1, we confirmed that HDL-C level was a significant predictor of mortality ($P = 0.03$). After adjusting for patient characteristics in study 2, physical activity was independently associated with HDL-C levels (adjusted $R^2 = 0.255$; $P = 0.005$). In conclusion, physical inactivity was strongly associated with decreased HDL-C levels in hemodialysis patients.

1. Introduction

The mortality rate of hemodialysis patients remains high despite continued improvements in dialysis technology. Cardiac disease is the leading cause of death among maintenance hemodialysis patients, accounting for approximately 38.1% of reported deaths in the United States [1] and 35% of deaths in Japan [2]. The relative risk of death from cardiovascular disease is reportedly 10 to 20 times greater in these patients than the general population [3]. Individuals with only low kidney function tend to have a high risk of developing generalized atherosclerosis and cardiovascular disease [4], while hemodialysis patients carry several additional risk factors. Although the underlying mechanisms for increased cardiovascular risk in dialysis patients are not completely understood, lipid disorder is one of the more well-known risk factors.

Shoji et al. examined the relationship between lipid parameters, cardiovascular events, and all-cause mortality in patients from a large cohort run by the Japanese Society for

Dialysis Therapy [5]. After adjusting for clinical variables, high-density lipoprotein cholesterol (HDL-C) levels were significantly and inversely associated with risks of incident myocardial infarction, cerebral infarction, and all-cause mortality in hemodialysis patients. Keeping HDL-C levels within a normal range may thus be important for disease management.

The best approach to modify HDL-C levels in dialysis patients is uncertain, although some studies found that physical activity increased HDL-C levels in general populations [6–9]. In a previous meta-analysis, Kodama et al. examined the relationship between physical activity, represented as walking or jogging, and HDL-C levels in the general population. Their findings showed that exercise resulted in a 2.53 mg/dL increase in HDL-C levels [10]. Physical activity could be similarly effective on HDL-C levels in dialysis populations.

The present study includes both confirmation and evaluation aspects. After first confirming the relationship between HDL-C levels and all-cause mortality in hemodialysis patients for study 1, we then investigated the effect of habitual physical activity on HDL-C levels in a cohort of clinically stable and adequately dialyzed patients for study 2.

2. Materials and Methods

2.1. Study Population. In study 1, 266 patients at the Hemodialysis Center at Sagami Junkanki Clinic in July 2008 were included in a prospective study and monitored for five years. In study 2, 116 patients were recruited from the same pool for a cross-sectional study with the following exclusion criteria: hospitalization within three months prior to the study; recent myocardial infarction or angina pectoris; uncontrolled cardiac arrhythmias, hemodynamic instabilities, uncontrolled hypertension, or renal osteodystrophy with severe arthralgia; or assistance by another person to walk.

The studies were approved by the Kitasato University Allied Health Sciences Research Ethics Committee. Physicians obtained informed consent from all patients.

2.2. Demographic and Clinical Factors. In study 1, demographic factors (age, sex, and time on hemodialysis) and lipid parameters (serum HDL-C, serum low-density lipoprotein cholesterol (LDL-C), and serum triglycerides (TG)) were collected at the time of patient entry.

In study 2, demographic factors (age, sex, and time on hemodialysis), physical constitution (body mass index), primary kidney disease, comorbid condition (cardiac disease, diabetes mellitus), smoking habits (Brinkman index), cardiovascular medications (antilipemics, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker, and beta blocker), laboratory parameters (serum albumin, serum creatinine, serum hemoglobin, hematocrit, serum phosphorus, serum calcium, intact parathyroid hormone (intact PTH), serum HDL-C, serum LDL-C, and serum TG), and habitual physical activity were collected from patient hospital charts. To quantify comorbid illnesses, a comorbidity index was developed for dialysis patients. The score was calculated with a method previously used to analyze survival in hemodialysis patients [11].

Table 1: Baseline patient characteristics.

	$N = 266$
Age, years	65 (57, 72)
Gender, women	103 (38.7%)
Time on hemodialysis, months	80.0 (26.0, 172.3)
Laboratory parameters	
HDL-C, mg/dL	41.0 (34.0, 53.0)
LDL-C, mg/dL	83.5 (65.8, 99.0)
Triglycerides, mg/dL	106.5 (83.0, 151.3)

Values are expressed as median (25th, 75th percentiles) or number (percentage of total).
HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

2.3. Habitual Physical Activity. An accelerometer pedometer (Lifecorder; Suzuken Co., Ltd., Nagoya, Japan) was used to measure the habitual physical activity of patients in study 2. The device obtains objective information on physical activity patterns because it continuously measures the intensity, duration, and frequency of activities. The accuracy and reliability of this instrument have been reported in previous studies [12, 13]. Because the monitor does not capture activities such as use of a stationary cycle, those activities were confirmed via interview at each patient's followup.

The accelerometer for this study was worn around the waist, where it translated acceleration of the body as motion that was recorded as number of steps taken. Patients were instructed to wear the device continuously during waking hours for seven days and avoid getting it wet. Patients were also asked to maintain their typical weekly schedules. To ensure that measurement periods were typical of their weekly activity patterns, data were excluded when patients traveled or manifested an acute illness.

Prior to analysis, accelerometer data were inspected to ensure that there were no obvious errors, such as failure to acquire data or wear the device. Measurements from a consecutive 5-day period were analyzed.

2.4. Statistical Analysis. Data are presented as medians (25th, 75th percentile) or number (%) and tested by the Mann-Whitney U test or chi-square test. In study 1, patients were categorized into four groups by quartile, and survival rate differences between groups were tested using the log-rank test. Multivariate analysis was performed with the Cox proportional hazards regression model to confirm the contribution of HDL-C levels to survival after adjusting for confounders. In study 2, physical activity was evaluated with an accelerometer as the number of steps per day for a consecutive 5-day period. Number of steps was used as the index of habitual physical activity because it was generalizable to daily practice. Patients were categorized into two groups by a physical activity median value, and the difference between groups was tested using the Mann-Whitney U test or chi-square test. Multiple linear regression analysis was used to evaluate the

Table 2: Univariate and multivariate analysis for associations with all-cause mortality.

Factors	Units of increase	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P	HR (95% CI)	P
Age, years	1 year	1.07 (1.05–1.09)	<0.001	1.07 (1.04–1.10)	<0.001
Women versus men	—	0.57 (0.35–0.93)	0.03	0.64 (0.39–1.07)	0.09
Time on hemodialysis, months	1 month	0.99 (0.99–1.00)	0.03	1.00 (0.99–1.00)	0.9
HDL-C, mg/dL	1 mg/dL	0.97 (0.96–0.99)	0.005	0.98 (0.95–0.99)	0.03
LDL-C, mg/dL	1 mg/dL	1.00 (0.99–1.01)	0.9	0.99 (0.99–1.01)	0.4
Triglycerides, mg/dL	1 mg/dL	0.99 (0.99–1.00)	0.2	0.99 (0.99–1.00)	0.3

Analyses were performed using a Cox proportional hazards regression model.
HR: hazard ratio; CI: confidence interval; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

relationship between physical activity and HDL-C levels. $P < 0.05$ was considered statistically significant. Analyses were performed using SPSS version 12.0 software (IBM Corporation, Armonk, NY, USA).

3. Results

3.1. Study 1: Lipid Parameters and Survival. Baseline demographic and clinical factors for the patients in study 1 are summarized in Table 1. The 266 patients (163 men, 103 women) ranged in age from 28 to 93 years (median, 65 years). Time on hemodialysis ranged from 3.0 to 404.0 months (median, 80.0 months). The median values of HDL-C, LDL-C, and TG were 41.0 mg/dL, 83.5 mg/dL, and 106.5 mg/dL, respectively.

Patients were followed for five years, with 77 deceased at the end of the follow-up period. The 5-year cumulative survival rates in quartiles 1, 2, 3, and 4 were more than half at 64.1%, 69.0%, 68.8%, and 82.1%, respectively. A total of 25% of the patients in quartiles 1, 2, and 3 died after 31, 48, and 42 months, respectively. This statistic was not applicable for patients in quartile 4, indicating greater survival in patients with the highest HDL-C levels (Figure 1).

Using the Cox proportional hazards model, the crude hazard ratio of HDL-C increased per mg/dL was 0.97 (95% confidence interval (CI), 0.96–0.99; $P = 0.005$), which indicated that maintenance of high HDL-C levels was associated with a reduction in all-cause mortality. After adjusting for age, sex, time on hemodialysis, LDL-C levels, and TG levels, the hazard ratio was 0.98 (95% CI, 0.95–0.99; $P = 0.03$) (Table 2).

3.2. Study 2: Effect of Physical Activity on HDL-C Levels. Table 3 shows baseline characteristics and results for the 116 patients in study 2, with physical activity < median value and ≥ median value. The most common underlying kidney diseases were diabetic nephropathy (35.3%) and glomerulonephritis (34.5%), and the median comorbidity score was 6.0 (3.3, 8.0). The median number of steps taken was 3208 (1828, 4481). Only one patient participated in the activity of cycling or swimming. Patients in the group of ≥ median value were significantly younger than the group of < median value ($P = 0.04$). HDL-C levels in patients with physical activity ≥ median value were significantly higher than the < median value group ($P = 0.001$), and intact PTH and TG levels were significantly lower ($P = 0.04$). There were no significant differences in other characteristics between groups.

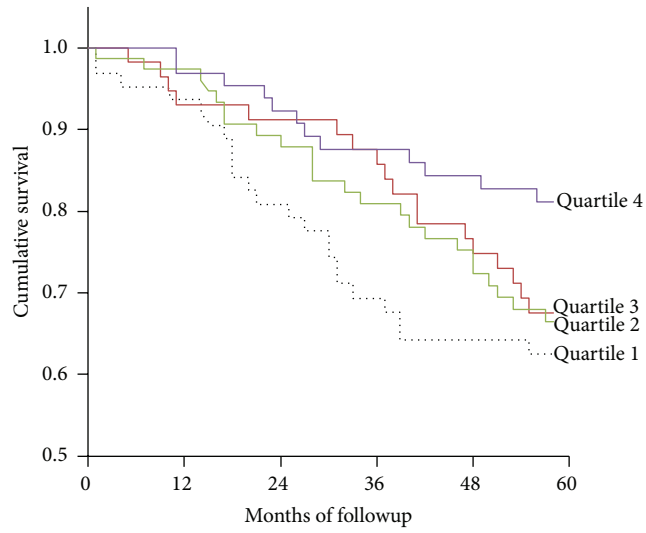

Figure 1: Kaplan-Meier analysis of survival for 266 hemodialysis patients. The survival rate of patients in the highest quartile (quartile 4) of HDL-C was significantly higher than that of patients in the lowest quartile (quartile 1) ($P = 0.02$ by log-rank test).

Parameters such as age, sex, body mass index, time on hemodialysis, presence of diabetes mellitus, albumin, creatinine, intact PTH, LDL-C, TG, treatment of lipid-modifying medication, Brinkman index, and physical activity were used as explanatory variables in the multiple linear regression analysis for HDL-C levels. As a result, only TG, age, body mass index, and physical activity were selected stepwise in multivariate analysis as significant ($R^2 = 0.40$) (Table 4). After adjustments, greater physical activity was significantly associated with increased HDL-C levels.

4. Discussion

In the present study, we reported the significant effect of physical activity on HDL-C levels, which was confirmed to be a risk factor for mortality in hemodialysis patients, independent of age, sex, body mass index, time on hemodialysis, presence of diabetes mellitus, albumin, creatinine, intact PTH,

Table 3: Baseline characteristics in patients with < median physical activity and ≥ median physical activity.

	All patients (n = 116)	Physical activity (steps/day)		P
		< Median value (n = 58)	≥ Median value (n = 58)	
Age, years	68 (62, 74)	70 (64, 75)	66 (61, 71)	0.04
Gender, women	58 (50.0%)	26 (44.8%)	32 (55.2%)	0.3
Body mass index, kg/m^2	20.9 (19.1, 23.3)	20.3 (18.9, 24.2)	21.1 (19.5, 22.8)	0.7
Time on hemodialysis, months	66.5 (34.3, 150.8)	73.0 (34.3,147.0)	65.5 (33.5, 164.8)	0.9
Primary kidney disease, %				0.6
Diabetic nephropathy	41 (35.3%)	20 (34.5%)	21 (36.2%)	
Glomerulonephritis	40 (34.5%)	19 (32.8%)	21 (36.2%)	
Hypertension	6 (5.2%)	2 (3.4%)	4 (6.9%)	
Polycystic renal disease	5 (4.3%)	4 (6.9%)	1 (1.7%)	
Other nephropathies	11 (9.5%)	7 (12.1%)	4 (6.9%)	
Unknown	13 (11.2%)	6 (10.3%)	7 (12.1%)	
Comorbid condition, %				
Presence of cardiac disease	31 (26.7%)	16 (27.6%)	15 (25.9%)	0.8
Presence of diabetes mellitus	57 (49.1%)	32 (55.2%)	25 (43.1%)	0.2
Comorbidity score	6.0 (3.3, 8.0)	6.0 (4.0, 8.0)	6.0 (3.0, 7.0)	0.5
Laboratory parameters				
Albumin, g/dL	3.8 (3.6, 3.9)	3.8 (3.6, 3.9)	3.8 (3.6, 4.0)	0.8
Creatinine, mg/dL	10.2 (8.9, 11.4)	10.3 (8.7, 11.2)	10.2 (9.0, 11.6)	0.7
Hemoglobin, g/dL	11.1 (10.7, 11.9)	11.1 (10.7, 11.7)	11.2 (10.7, 11.9)	0.7
Hematocrit, %	33.2 (31.9, 34.9)	33.2 (31.5, 34.6)	33.3 (32.0, 35.4)	0.3
Phosphorus, mg/dL	5.0 (4.2, 5.7)	5.1 (4.3, 5.7)	5.0 (4.2, 5.6)	0.4
Calcium, mg/dL	8.7 (8.4, 9.2)	8.8 (8.5, 9.1)	8.6 (8.4, 9.2)	0.2
Intact PTH, pg/mL	104.0 (57.5, 184.0)	127.0 (69.5, 208.5)	85.5 (40.0, 165.8)	0.04
HDL-C, mg/dL	41.0 (32.0, 52.5)	37.0 (30.0, 47.0)	47.0 (38.0, 57.0)	0.001
LDL-C, mg/dL	88.0 (70.0, 108.5)	84.0 (65.5, 103.5)	91.5 (71.5, 115.0)	0.1
Triglycerides, mg/dL	119.0 (82.0, 159.5)	136.0 (92.5, 179.5)	112.5 (69.0, 143.3)	0.04
Medications, %				
ACEI	6 (5.2%)	3 (5.2%)	3 (5.2%)	1.0
ARB	58 (50.0%)	34 (58.6%)	24 (41.4%)	0.06
CCB	52 (44.8)	26 (44.8%)	26 (44.8%)	1.0
Beta-blocker	32 (27.6%)	20 (34.5%)	12 (20.7%)	0.1
Lipid-modifier	12 (10.3%)	6 (10.3%)	6 (10.3%)	1.0
Smoking, %				0.7
Current	12 (10.3%)	7 (12.1%)	5 (8.6%)	
Past	56 (48.3%)	27 (46.6%)	29 (50.0%)	
Brinkman index	60.0 (0.0, 600.0)	225.0 (0.0, 787.5)	40.0 (0.0, 600)	0.5
Physical activity				
Number of steps	3208 (1828, 4481)	1833 (1185, 2382)	4478 (3726, 6242)	<0.001

Values are expressed as median (25th, 75th percentiles) or number (percentage) of patients.
Intact PTH: intact parathyroid hormone; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium channel blocker.

LDL-C, TG, lipid-modifying medications, and the Brinkman index. This report is the first to show a correlation between physical activity measured by accelerometer and HDL-C levels in hemodialysis patients. Based on our findings, greater amounts of physical activity are associated with a reduced risk for death in dialysis populations and could even improve prognosis.

Our study reconfirmed that low HDL-C blood levels were a strong risk factor for death in hemodialysis patients, as previously reported [5]. However, Briel et al. systematically reviewed the association of HDL-C change induced by medication with outcomes in nondialysis patients and reported that the risks of coronary heart disease events, coronary heart disease deaths, and total deaths were not reduced [14]. There are two possible reasons for this observation. First, the mean baseline value of HDL-C in patients was 47.3 mg/dL, meeting the concentration recommended as a lipid management goal by the 2007 Japan Atherosclerosis Society Guideline for

Table 4: Prediction models for level of high-density lipoprotein cholesterol.

Model	Standardized coefficients (β)	P value	R^2	R^2 change
High-density lipoprotein cholesterol			0.40	
Triglycerides, mg/dL	−0.39	<0.001		0.24
Age, years	−0.28	<0.001		0.08
Body mass index, kg/m^2	−0.26	0.003		0.05
Physical activity, steps/day	0.18	0.02		0.03

Analyses were performed using multiple linear regression analysis.

Diagnosis and Prevention of Atherosclerotic Cardiovascular Disease for Japanese (≥40 mg/dL) [15]. The median value of HDL-C in our study population was 41.0 mg/dL, which was below the recommended levels for approximately half of the patients. Second, the weighted mean change of HDL-C in the report was only 1.7 mg/dL, which indicates that cardiovascular medications may not be very effective in significantly increasing HDL-C levels. Other published data, however, indicate that physical activity can modify HDL-C levels.

Goldberg et al. examined the metabolic effects of exercise training in hemodialysis patients and reported an increase in HDL-C levels [16, 17]. The high intensity habitual exercise of that study does not appear realistic, however, because of the adverse symptoms related to hemodialysis, low physical function or general poor adherence to regular exercise programs [18–22]. Yano et al. instead studied the relationship between HDL-C levels and physical activity as measured by steps per day, which hemodialysis patients could participate in reasonably and comfortably [23]. Unfortunately, the small sample size of 35 patients and lack of confounding factors gave the study less reliability. We therefore evaluated habitual physical activity using an accelerometer and reexamined the effect of physical activity on HDL-C levels in 116 hemodialysis patients. The median number of steps our patients walked was approximately 3000 steps/day, a number markedly lower than for healthy controls [24, 25] and more similar to patients with chronic disease [26]. Our results showed that physical activity was significantly and positively associated with HDL-C levels after adjusting for the effects of confounders. We had previously showed the correlation between physical inactivity and higher mortality in a cohort of patients on maintenance hemodialysis [27]. Physical activity was evaluated using an accelerometer and this method was the same method as in the present study. In the study, the underlying mechanisms remained to be elucidated. However, the present study results may determine a part of the potential mechanisms. It might be that physical inactivity in patients on maintenance hemodialysis decreased their HDL-C levels and potentially worsened their prognosis.

Two possible reasons can explain the results of the present study. First, physical activity may increase HDL-C levels in hemodialysis patients partly by increasing insulin sensitivity. Insulin resistance tends to gain TG levels and reduce lipoprotein lipase activity, which boost HDL-C levels. In a previous study, exercise interventions improved the insulin sensitivity of patients afflicted with lifestyle-related diseases such as type 2 diabetes and hypertension [28]. Goldberg et al. also examined the association between physical activity and insulin sensitivity, reporting that improvements in insulin sensitivity could affect lipid abnormalities observed in dialysis patients [17]. Second, patients with adequate physical activity often have good nutrition. Malnutrition is a predictor of mortality in dialysis patients [29] and strongly associated with decreased HDL-C levels. Patients in this study with decreased physical activity may suffer from malnutrition as well as low HDL-C.

There are some limitations to this study. First, residual confounders remain possible because the study was observational. To our knowledge, this is the first study to identify physical activity as a strong predictor of HDL-C levels by using multivariate analysis adjusted for confounding factors. However, further randomized, controlled studies are still needed. Second, we excluded patients who needed assistance with walking. As a result, the severity of comorbidities in participants seemed mild. This should be considered when generalizing our results to more severely limited patients. Third, alcohol intake can influence HDL-C levels but was not included in our study. This was because there were no patients who consumed excessive alcohol in our study, as most hemodialysis patients are conscious about becoming overhydrated. Finally, although we reported lower HDL-C levels in hemodialysis patients with lower physical activity, the underlying mechanisms have yet to be elucidated.

5. Conclusion

Physical activity is strongly associated with increased HDL-C levels in hemodialysis patients. Although we believe it is important for these patients to engage in physical activities, further studies are needed to determine the possible mechanisms.

Conflict of Interests

There are no conflicts of interest to disclose regarding the publication of this paper.

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Review Article

Muscle Wasting in Hemodialysis Patients: New Therapeutic Strategies for Resolving an Old Problem

Chun-Ting Chen, Shih-Hua Lin, Jin-Shuen Chen, and Yu-Juei Hsu

Division of Nephrology, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, No. 325, Section 2, Cheng-Gong Road, Neihu, Taipei 114, Taiwan

Correspondence should be addressed to Yu-Juei Hsu; yujuei@mail2000.com.tw

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Muscle wasting has long been recognized as a major clinical problem in hemodialysis (HD) patients. In addition to its impact on quality of life, muscle wasting has been proven to be associated with increased mortality rates. Identification of the molecular mechanisms underlying muscle wasting in HD patients provides opportunities to resolve this clinical problem. Several signaling pathways and humeral factors have been reported to be involved in the pathogenic mechanisms of muscle wasting in HD patients, including ubiquitin-proteasome system, caspase-3, insulin/insulin-like growth factor-1 (IGF-1) signaling, endogenous glucocorticoids, metabolic acidosis, inflammation, and sex hormones. Targeting the aforementioned crucial signaling and molecules to suppress protein degradation and augment muscle strength has been extensively investigated in HD patients. In addition to exercise training, administration of megestrol acetate has been proven to be effective in improving anorexia and muscle wasting in HD patients. Correction of metabolic acidosis through sodium bicarbonate supplements can decrease muscle protein degradation and hormone therapy with nandrolone decanoate has been reported to increase muscle mass. Although thiazolidinedione has been shown to improve insulin sensitivity, its role in the treatment of muscle wasting remains unclear. This review paper focuses on the molecular pathways and potential new therapeutic approaches to muscle wasting in HD patients.

1. Introduction

Hemodialysis (HD) is a life-saving replacement therapy for patients with end-stage renal disease (ESRD). Although HD can maintain and even extend an acceptable quality of life for patients diagnosed with ESRD, long-term HD contributes to a number of serious complications, including cardiovascular disease, bleeding tendencies, renal osteodystrophy, gonadal dysfunction, protein malnutrition, insulin resistance, immunodeficiency, anemia, and muscle wasting [1]. Despite great advances in managing HD-related complications, muscle wasting is still an unresolved concern. Muscle wasting is defined as unintentional body weight loss, which can be divided into loss of lean body mass and fat mass, and has been recognized as a common and major problem of chronic kidney disease (CKD) that affects patient mortality rates, daily activity, quality of life, immunity function, and numbers of days of hospitalization [2]. In the general population, high body mass has been demonstrated as a conventional risk factor for cardiovascular events and all-cause mortality [3]. By contrast, previous studies have revealed a survival benefit in HD patients possessing high body mass, and patients on maintenance HD have been reported to suffer more severe muscle wasting than predialysis CKD patients [4]. Therefore, early recognition and treatment of muscle wasting are crucial for CKD patients to improve their quality of life and prognosis.

Muscle wasting in HD patients has been said to occur through either accelerated protein degradation or decreased protein synthesis. Protein homeostasis between synthesis and degradation depends on protein intake and utilization. Approximately 4 g of protein/kg of body weight is synthesized and degraded per day in a normal adult [5]. Skeletal muscle is a dynamic organ and is the largest reservoir of protein, which consists of amino acids and carbon chains. Muscle mass represents the most reliable indicator of protein homeostasis

and is affected by a variety of clinical catabolic illnesses such as stress, liver failure, cancer, sepsis, diabetes, and CKD [6]. Accelerated protein degradation without a sufficient protein supply may lead to skeletal muscle atrophy resulting in muscle wasting. It has been shown that by measuring the turnover of labeled amino acids, the rate of protein degradation exceeds synthesis during and after HD in ESRD patients [7]. Recent advances in research on molecular mechanisms involved in the development of muscle wasting in HD patients have provided opportunities to resolve this old problem. In this review paper, we focus on recent advances in research on molecular mechanisms and the development of new therapeutic strategies for muscle wasting in HD patients.

2. Mechanisms of Muscle Wasting in Hemodialysis Patients

Muscle wasting is determined by complex mechanisms and several of these have been documented to explain muscle wasting in CKD patients with and without HD (Figure 1).

2.1. Ubiquitin-Proteasome System. Ubiquitin-proteasome system (UPS), the major mechanism of proteolysis, is activated in skeletal muscle in CKD patients, as well as in patients with other chronic diseases. Protein degradation is increased mainly through activation and upregulation of the UPS [8]. Ubiquitin is a small protein, which becomes covalent by attaching to the ε-amino group of lysine residues in the substrate proteins. The first step of ubiquitin conjugation is activation of ubiquitin by the E1 enzyme. Activated ubiquitin is subsequently transferred to the E2 enzyme, which is the ubiquitin carrier protein. When activated ubiquitin is conjugated with the E2 enzyme, it can be recognized by the E3 enzyme, which is ubiquitin protein ligase. The E3 enzyme catalyzes ubiquitin ligation to the substrate protein. The process is repeated to form a polyubiquitin chain, which is recognized and degraded by proteasome. In the system, proteasome is the major proteolytic enzyme that converts proteins to small peptides and amino acids. However, only polyubiquitinated proteins can be recognized and degraded by the proteasome. Proteins containing mono- or diubiquitin chains on sequential lysine residues are not recognized by the proteasome [9, 10]. When muscle protein degradation is initiated, the expression and activity of two muscle-specific E3 ligases, atrogin-1 (known as muscle atrophy F-box, MAFbx), and muscle-specific ring finger-1 (MuRF-1) are upregulated. The increase of activation of these ligases correlates with the acceleration of protein degradation. The forkhead transcription factors (FoxO) and the transcription factor nuclear factor kappa B (NF-κB) have been identified as the regulatory factors of activation of E3 conjugating enzymes. The promoters for MAFbx and MuRF-1 are activated by FoxO and NF-κB, respectively, leading to muscle protein degradation in the UPS [11, 12].

2.2. Caspase-3 Proteolytic Pathway. Caspase-3 is a protease that participates in cell apoptosis. It cleaves actomyosin in myofibrillar complexes and generates the 14 kDa actin fragment. Caspase-3 activation accelerates protein degradation in muscles. Elevated levels of 14 kDa actin fragment were revealed in muscle biopsies obtained from patients diagnosed with ESRD on maintenance HD or from those who had suffered a burn injury. The higher levels of 14 kDa actin fragment revealed active muscle wasting in patients with catabolic conditions and suggested that levels of the 14 kDa actin fragment can be used as a biomarker of muscle protein degradation [13, 14].

2.3. Insulin, Insulin-Like Growth Factor-1, and Insulin Resistance. Insulin is a major regulator in the modulation of protein synthesis and degradation in skeletal muscle. The metabolic effect of insulin on muscle protein turnover is characterized by suppression of protein degradation in a phosphatidylinositol 3-kinase (PI3K)/Akt-dependent pathway. Insulin binds to the insulin receptor (IR) on the cell membrane and activates the internal tyrosine kinase activity in cytosol. The insulin receptor substrate (IRS) proteins in cytosol are phosphorylated by activated IR. PI3K consists of p85 regulatory and p110 catalytic subunits and becomes an activated enzyme after binding to the phosphorylated IRS proteins. The activated PI3K catalyzes the production of phosphatidylinositol (3,4,5) triphosphate, which activates the serine kinase Akt by phosphorylation. Phosphorylated-Akt (p-Akt) affects a variety of regulators involved in metabolic processes in skeletal muscle. Decreased p-Akt activity stimulates the expression of E3 conjugating enzymes, atrogin-1/MAFbx, and MuRF1 in muscles. Activated IRS also activates the MEK/ERK mitogen-activated protein (MAP) kinase pathway, which is involved in the regulation of many critical biological processes, including cell proliferation, differentiation, and death [12, 15].

Insulin resistance leads to impaired insulin/IGF-1 signaling in skeletal muscle. Impaired insulin/IGF-1 signaling results in a decreased level of p-Akt in the muscle, which causes suppression of the PI3K/Akt pathway and muscle protein degradation. Accumulating evidence has demonstrated accelerated activation of the caspase-3 proteolytic pathway and a decreased level of p-Akt in the skeletal muscle in patients exhibiting insulin resistance, excess angiotensin II, inflammation, acidosis, and CKD [16, 17]. It has been well established that patients diagnosed with CKD suffer increased insulin resistance, which may contribute to muscle wasting [18].

Inflammation is also a major consequence of both CKD and HD, and numerous inflammatory mediators have been proven to modulate insulin-related signaling pathways in skeletal muscle. Inflammatory factors such as tumor necrosis factor-α (TNF-α) suppress insulin receptor signaling through the inhibition and degradation of IRS in skeletal muscle [19]. In addition, TNF-α activates caspase-3 and NF-κB, which stimulates UPS activation, leading to muscle wasting [14, 20].

2.4. Glucocorticoids. The kidney normally excretes cortisol and its water soluble metabolites, and elevated serum cortisol levels have been reported in CKD patients because of the prolonged serum half-life of cortisol in advanced renal failure [21]. Glucocorticoids activate the glucocorticoid receptors, which can directly bind to the p85 subunit of PI3K, leading to muscle wasting by suppression of p-Akt. In addition,

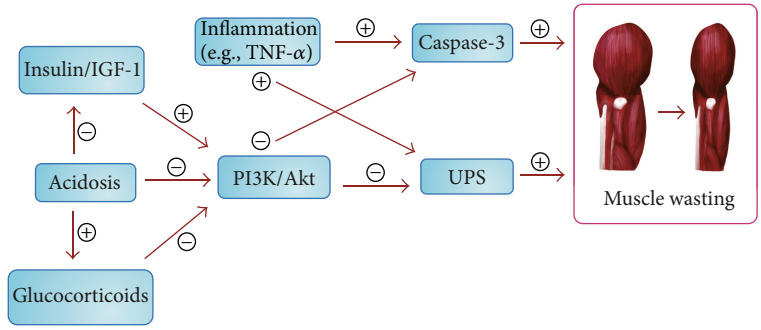

Figure 1: Molecular mechanisms and signaling pathways of muscle wasting in hemodialysis patients. UPS, ubiquitin-proteasome system; IGF-1, insulin-like growth factor-1; PI3K, phosphoinositide 3-kinase; TNF-α, tumor necrosis factor-α.

increased levels of the p85 subunit have been reported in CKD patients [22, 23]. Glucocorticoids also induce upregulation of UPS, atrogin-1, and MuRF1, which may lead to muscle protein degradation [24].

2.5. Metabolic Acidosis. Metabolic acidosis is a universal feature in the majority of patients diagnosed with CKD who have a glomerular filtration rate (GFR) that has decreased to less than 20% to 25% of the normal rate. Metabolic acidosis has been shown to cause negative nitrogen balance and decrease albumin synthesis, leading to muscle wasting. In addition, metabolic acidosis causes muscle protein degradation by activation of the UPS and caspase-3, and reduced intracellular pH in muscle cells impairs PI3K and p-Akt signaling [14, 25–27]. Moreover, decreased growth hormone concentration, low IGF-1 level, and increased glucocorticoids production have been reported in individuals with metabolic acidosis, which may partly explain the high prevalence of muscle wasting in CKD patients [28, 29].

2.6. Sex Hormones. It is well known that both estrogen and testosterone affect protein synthesis and degradation and that testosterone produces a more prominent effect on muscle protein turnover than does estrogen. A low testosterone level can induce muscle protein degradation by impaired IGF-1 signaling and promote muscle catabolism by upregulation of myostatin expression [30]. Evidence shows that low-testosterone concentrations are highly prevalent in elderly people and CKD patients and that low-testosterone levels closely correlate with muscle wasting and mortality in HD patients [31, 32]. Thus, androgen deficiency may be involved in the complex mechanisms that underlie muscle wasting in CKD patients.

3. Therapeutic Frontiers of Muscle Wasting in Hemodialysis Patients

To improve the quality of life and the long-term prognosis of patients, development of effective therapeutic strategies for muscle wasting is necessary in HD patients. Recent advances in understanding of the molecular mechanisms involved in CKD-related muscle wasting provide new hope for the development of a set of new therapies. The following therapeutic interventions have been reported to be effective in the improvement of muscle strength in CKD patients (Table 1).

Table 1: Therapeutic interventions for muscle wasting in hemodialysis patients.

Therapeutic targets	Therapeutic interventions
Muscle strength	Endurance exercise and resistance exercise
Insulin resistance	Endurance exercise, insulin sensitizers (e.g., Thiazolidinediones)
Metabolic acidosis	$NaHCO_3$ supplement
Hypogonadism	Testosterone supplement (e.g., Nandrolone decanoate)
Malnutrition	Endurance exercise, nutritional supplements, megestrol acetate (for adult) cyprohetadine (for children)

3.1. Endurance and Resistance Exercise. Endurance (aerobic) and resistance (anaerobic or strength training) exercise have been reported to reduce muscle wasting in HD patients. Resistance exercise induces muscular contraction, which may increase the strength, anaerobic endurance, and the size of skeletal muscles. Resistance exercise may be divided into traditional power lifting and Olympic lifting. Both endurance exercise and resistance exercise can lead to increased skeletal muscle strength and power [33].

In a typical endurance exercise program, at least 30 minutes per day of moderate intensity exercise must be performed 5 days per week. In patients who perform poorly, such as HD patients, it is necessary to initiate exercise training with a lower intensity, shorter duration, and fewer days per week [34, 35]. In patients on maintenance HD, a considerable improvement of aerobic exercise capacity and muscle strength has been demonstrated after endurance training [36]. It has been shown that after 6 months of supervised endurance exercise, an increase in ejection fraction, cardiac output index, and systolic volume index occurs [37]. An intradialytic aerobic exercise program with exercise bicycles in HD patients correlated with a considerable reduction in intra- and interdialytic systolic and diastolic blood pressure. In addition, 4 months of aerobic training in predialysis patients

also leads to a major reduction of systolic and diastolic blood pressure, accompanied by a considerable reduction in the number of prescribed antihypertensive drugs [38, 39]. Moreover, improvement of insulin resistance and anorexia have been reported in HD patients who have undergone endurance exercise training. It is noteworthy that the positive effects yielded from these exercise programs were completely reversed 2 months after training ceased [40, 41].

A resistance exercise program should be performed gradually and at least twice a week and should include training for all the major muscle groups. In HD patients with impaired exercise capacity and marked muscular atrophy, resistance exercise reduces muscle wasting and increases muscle fibers, based on histological examinations [42]. The serum levels of inflammatory factors, such as C-reactive protein and interleukin-6, are reported to decrease after 12 weeks of resistance exercise [43].

3.2. Treatment of Insulin Resistance. Insulin resistance induces muscle wasting through complex mechanisms, including insulin/IGF-1 and PI3K/Akt signaling pathways. Improving insulin resistance is crucial to prevent muscle wasting in patients diagnosed with HD. Aerobic exercise in HD patients is effective in improving insulin resistance [40]. Thiazolidinediones, which are insulin sensitizers, are widely used in the treatment of type 2 diabetes and have been shown to improve insulin resistance through activation of the PI3K/Akt pathway by initiating IRS signaling. Because the catabolism of thiazolidinediones mainly occurs in the liver, it is a potential drug for improving insulin resistance in HD patients [44–46]. Thiazolidinedione should be administered with caution because of increased risks of cardiovascular events and bladder cancer [47]. However, limited human data supports the major role of insulin sensitizers on muscle wasting in HD patients.

3.3. Correction of Metabolic Acidosis. Metabolic acidosis is an inevitable condition in patients with CKD, particularly those with HD [48–50]. A sodium bicarbonate ($NaHCO_3$) supplement has been demonstrated to improve growth in infants and children with acidosis [51]. In addition, protein loss in the muscle is approximately 2-fold higher in patients with serum $NaHCO_3$ levels <16 mM as compared to those with levels >22.6 mM [52]. These data suggest that maintenance of the serum $NaHCO_3$ level >22.6 mM may be a therapeutic goal for reducing muscle wasting in HD patients with metabolic acidosis.

3.4. Hormone Therapy. A decreased serum testosterone level has been frequently encountered in patients diagnosed with advanced CKD and on maintenance HD, and impaired IGF-1 signaling may participate in the mechanism of androgen-deficiency-mediated muscle wasting. In men with hypogonadism, testosterone supplements for 12 weeks improve muscle mass and strength [53, 54]. In HD patients, body composition and physical function improve considerably after treatment with an anabolic steroid, 19-nortestosterone (nandrolone decanoate) [55]. Administration of 100 mg nandrolone per week for 24 weeks increases lean body mass approximately 2-fold. Although nandrolone decanoate is effective in improving muscle wasting, its side effects, including gynecomastia, erectile dysfunction, and increased cardiovascular risks, should be cause for caution [56].

3.5. Nutrition. In HD patients, malnutrition is a major problem caused by anorexia and hypercatabolism through complex mechanisms including inflammation, metabolic acidosis, insulin resistance, and uremic toxins [57]. Anorexia is a common manifestation of uremic syndrome and is associated with increased risks of mortality and hospitalization in HD patients [58]. Appetite stimulants, such as megestrol acetate, melatonin, thalidomide, ghrelin, and cyproheptadine, are potential therapeutic agents for resolving anorexia in HD patients. Cyproheptadine is a first-generation antihistamine that generates additional anticholinergic and antiserotonergic effects. Although cyprohetadine is used as an appetite stimulant in children diagnosed with HD [59], its role in adult HD patients is not well established. Megestrol acetate is a steroidal progestin and progesterone derivative exhibiting antiandrogenic and antiestrogenic effects and has been proven to be an effective appetite stimulant in patients with advanced cancers. In patients on maintenance HD, megestrol acetate has also been reported to be useful to improve anorexia and muscle wasting. Oral administration of 160 mg megestrol acetate daily for 2 months considerably increases body mass index and serum albumin levels [60, 61]. The side effects of megestrol acetate, including impotence, hypogonadism, and increased risk of thromboembolism, should be monitored closely. No large scale clinical trials have been conducted to define the therapeutic effects of these agents in HD patients.

In addition to appetite stimulants, direct nutritional supplements are essential to reduce muscle wasting. Oral, enteral, or parenteral nutritional supplements should be considered if unresolved anorexia occurs. A systematic review and meta-analysis of 18 studies indicated that enteral nutritional supplements in HD patients resulted in increased total energy and protein intake and elevated serum albumin levels by 0.23 g/dL [62]. Oral nutrition alone and combined with intradialytic parenteral nutrition in patients diagnosed with HD revealed similar results, including improvement in body mass index, elevated serum albumin and prealbumin levels, decreased 2-year mortality, and reduced hospitalizations [63–65].

4. Conclusion

Muscle wasting in HD patients is caused by complex mechanisms and agents, including UPS, caspase-3, insulin/IGF-1, glucocorticoid, metabolic acidosis, and sex hormone-related signaling pathways. Development of new drugs targeting UPS, caspase-3, and insulin/IGF-1 offers new hope for the treatment of muscle wasting. Correction of metabolic acidosis with sodium bicarbonate reduces muscle protein degradation. Megestrol acetate and nandrolone decanoate are clinically available and could be applied to reduce muscle wasting. Adequate nutritional supplements are vital because they may improve muscle mass and reduce mortality. Endurance exercise not only reduces muscle wasting, but also improves

cardiac ejection fraction, blood pressure, and insulin resistance. Recent advances in understanding the molecular mechanisms of muscle wasting provide opportunities to resolve this clinical problem.

Conflict of Interests

The authors declare that they have no conflict of interests.

Acknowledgments

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Clinical Study

Post-Dilution on Line Haemodiafiltration with Citrate Dialysate: First Clinical Experience in Chronic Dialysis Patients

Vincenzo Panichi,[1] Enrico Fiaccadori,[2] Alberto Rosati,[3] Roberto Fanelli,[4] Giada Bernabini,[1] Alessia Scatena,[1] and Francesco Pizzarelli[4]

[1] *Nephrology and Dialysis Unit, Versilia Hospital, 55034 Lido Camaiore (Lucca), Italy*
[2] *Nephrology and Dialysis Unit, Parma Hospital, 43100 Parma, Italy*
[3] *Nephrology and Dialysis Unit, Lucca Hospital, 55100 Lucca, Italy*
[4] *Nephrology and Dialysis Unit, SM Annunziata Hospital, 50012 Florence, Italy*

Correspondence should be addressed to Vincenzo Panichi; vpanichi@usl12.toscana.it

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Background. Citrate has anticoagulative properties and favorable effects on inflammation, but it has the potential hazards of inducing hypocalcemia. Bicarbonate dialysate (BHD) replacing citrate for acetate is now used in chronic haemodialysis but has never been tested in postdilution online haemodiafiltration (OL-HDF). *Methods*. Thirteen chronic stable dialysis patients were enrolled in a pilot, short-term study. Patients underwent one week (3 dialysis sessions) of BHD with 0.8 mmol/L citrate dialysate, followed by one week of postdilution high volume OL-HDF with standard bicarbonate dialysate, and one week of high volume OL-HDF with 0.8 mmol/L citrate dialysate. *Results*. In citrate OL-HDF pretreatment plasma levels of C-reactive protein and β2-microglobulin were significantly reduced; intra-treatment plasma acetate levels increased in the former technique and decreased in the latter. During both citrate techniques (OL-HDF and HD) ionized calcium levels remained stable within the normal range. *Conclusions*. Should our promising results be confirmed in a long-term study on a wider population, then OL-HDF with citrate dialysate may represent a further step in improving dialysis biocompatibility.

1. Introduction

There is evidence that in chronic dialysis patients haemodiafiltration (HDF) induces better control of phosphatemia [1, 2] and lower β2-microglobulin (β2-m) blood levels [2, 3] with observed better clinical outcomes [4, 5]. The effect on β2-m has been related not only to HDF efficiency in toxin removal [6] but also to the potentials of convective treatments in slowing down inflammation. As a matter of fact, HDF has been associated with reduction of proinflammatory cytokines [7, 8] and circulating proinflammatory cells [9].

However, in online HDF (OL-HDF) the small amount of acetate of standard bicarbonate dialysate may itself induce inflammation due to the large amount of fluids infused into the patient blood stream [10]. Hence, search for optimal biocompatible dialysis treatments is still an unsolved goal.

Ahmad et al. were the first to use in bicarbonate dialysate an acid concentrate made by replacing citric acid for acetic acid [11]. The final dialysate had a citrate level of 2.4 mEq/L (0.8 mmol/L). This citrate-enriched "acid concentrate" is commercially available and is now widely used in haemodialysis in different countries, particularly USA [12–16].

The citrate in the dialysate crosses the dialyser membrane to chelate calcium in the blood flowing within the dialyser and the venous tubing, thus impairing the clotting process to bring about regional anticoagulation. By doing so, however, citrate has the potential drawback of inducing hypocalcemia, and this side effect may be amplified in OL-HDF, due to large amounts of dialysate infused. The rationale for citrate relies not only on anticoagulative properties [17] but also on its possible favorable effect on dialysis-induced inflammation [18–22]. Thus, OL-HDF with citrate dialysate may represent a further step in improving dialysis biocompatibility, providing that it does not induce clinically relevant hypocalcemia.

With this background, in this small, pilot study we wanted to evaluate safety, feasibility, and anti-inflammatory

Table 1: Dialysis prescription.

	Citrate HD-phase A	Standard OL-HDF-phase B	Citrate OL-HDF-phase C
Membrane	Low flux α polysulfone 2.0 m^2	High flux α polysulfone 2.3 m^2	High flux α polysulfone 2.3 m^2
Qb	≥300 mL/min	≥300 mL/min	≥300 mL/min
Qd	500 mL/min	500 mL/min	500 mL/min
Qinf*		6 L/h in function of MIDP	6 L/h in function of MIDP
Treatment time	240 ± 15 min	240 ± 15 min	240 ± 15 min

*Modulated according to the maximum inlet dialyzer pressure [MIDP] set at 650 mmHg according to manufacturer.
Qb: blood flow.
Qd: dialysate flow.
Qinf: infusion flow.

capability of high volume postdilution OL-HDF performed with citrate-enriched dialysate infusate.

2. Materials and Methods

2.1. Study Design. This is a pilot, short-term study. Patients underwent one week (3 dialysis sessions) of bicarbonate dialysis with 0.8 mmol/L citrate-enriched dialysate (citrate HD, phase A), sequentially followed by one week of OL-HDF with standard bicarbonate dialysate (standard OL-HDF, phase B), and then one week of OL-HDF with citrate-enriched dialysate (citrate OL-HDF, phase C).

2.2. Patients. Thirteen chronic dialysis patients of Florence and Versilia Nephrology Units were enrolled.

Inclusion criteria were AS follows: age >18 years and <80 years and a vascular access suitable for easily obtaining a blood flow >300 mL/min; patients affected by chronic liver disease, active neoplastic or inflammatory disease were excluded as well as patients receiving immunosuppressive or anti-inflammatory drugs.

The study was approved by the Local Ethical Committee of the two hospitals, and all patients signed a written consent form.

2.3. Dialysis Parameters. Citrate dialysate (Citrasate, Advanced Renal Technologies Inc., Washington, USA) contained 0.8 mmol/L of citric acid. Acetate concentration was 0.3 mmol/L in citrate dialysate and 2.5 mmol/L in standard bicarbonate dialysate. Ca dialysate concentration was always 1.5 mmol/L. Sodium and potassium were, respectively, 137 mmo/L and 2.0 mmo/L. Ultrapure dialysate was used in all the dialysis sessions.

Anticoagulation was performed as LMWH in all patients; dalteparin was administered starting dialysis at the dose of 60.4 ± 11.2 IU/kg, and the dose was not changed during the study period.

Patient-related (body weight, blood Pressure, BP, and heart rate, HR) and monitor-related parameters were collected during each session of all treatments. Dialysis prescription is reported in Table 1. Kt/V, as a proxy of treatment efficacy, was continuously monitored by a biosensor based on UV mass spectrometry (ADIMEA, B Braun Avitum, Melsungen Germany). This biosensor is integrated in the dialysis monitor utilized in this study, and it has been validated for use both in HD and in HDF [23, 24].

2.4. Laboratory. Serum total calcium, ionized calcium (Ca^{++}), and bicarbonate were determined at baseline (T0), one hour (T1), 2 hours (T2), and at the end (T4) of each treatment, while plasma samples for citrate and acetate measurements were drawn at T0-T2-T4. Activated partial thromboplastin time (aPTT), β2-m and CRP were checked at T0-T4. End-treatment β2-m, values were normalized for haematocrit according to the Bergstrom formula [25]. Commercially available UV test kits for enzymatic spectrophotometric analysis were used for citrate (Enzyplus EZA-785+, Biocontrol, Italy) and acetate (Enzyplus EZA811+, Biocontrol, Italy) measurements on serum and ultrafiltrate/dialysate samples. Citrate and acetate determinations were centrally performed in Nephrology laboratory of Parma University. Other routine parameters were analyzed by standard methods.

2.5. Statistics. Continuous data are presented as mean ± standard deviation (SD). Differences between mean values were evaluated by paired-samples t-Test or by Wilcoxon signed ranks test for not normally distributed data. Analysis of variance (ANOVA) for multiple comparisons was used to analyse differences between groups. Spearman correlation coefficient was calculated for correlation assessments between variables. A P value less than 0.05 was considered statistically significant.

3. Results

Parameters of dialysis prescription (Table 1) were satisfied during the three experimental procedures. Relevant hydraulic pressures achieved in the three phases of the study are reported in Table 2.

3.1. Safety. No adverse effect was observed. Hypotensive episodes were globally very low and similar over the three study phases. Average BP values were almost superimposable among various treatments, being systolic/diastolic figures 128 ± 22/73 ± 13 mmHg, 129 ± 25/74 ± 14 mmHg, and 130 ± 21/72 ± 16 mmHg in HD, standard HDF, and citrate HDF, respectively (P = NS), the same for HR, which was 77 ± 12 beats/min, 77 ± 14 beats/min, and 77 ± 13 beats/min in the 3 study phases, respectively [P = NS].

At the beginning of treatments plasma Ca^{++} was identical in the three phases (Table 3). At variance with standard OL-HDF, plasma Ca^{++} did not increase during both citrate

Table 2: Achieved operating dialysis monitor pressures.

	Citrate HD-phase A		Standard OL-HDF-phase B		Citrate OL-HDF-phase C	
	T0	T4	T0	T4	T0	T4
TMP (mmHg)	78.5 ± 31.4	56.9 ± 37.7	97.4 ± 26.18	127.2 ± 35.5	103.9 ± 43.5	157.5 ± 75.2
MDIP (mmHg)	276.9 ± 24.5	310 ± 51.8	333 ± 44.3	426.2 ± 103	337.4 ± 56.6	429.4 ± 131.5

TMP: 3 point trans membrane pressure; MDIP: Maximum dialyzer inlet pressure.
No statistically significant differences between phase B and C.
T0 starting dialysis.
T4 ending dialysis.

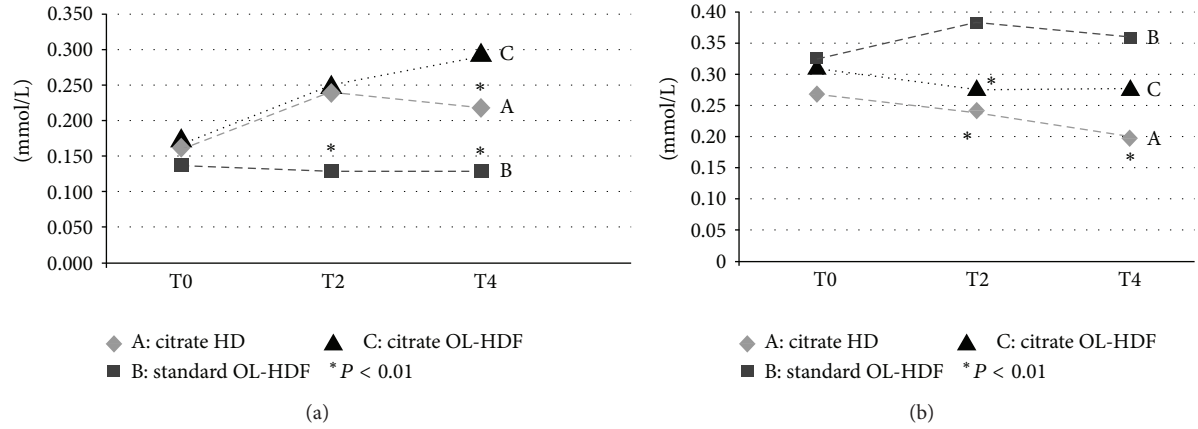

Figure 1: (a) Plasma levels of citrate during treatments. (b) Plasma levels of acetate during treatments.

treatments with values remaining always within the normal range; accordingly, Ca^{++} values were significantly higher at the end of standard OL-HDF with respect to citrate OL-HDF. Total calcium values (Table 3) progressively increased during all treatments but with different slope, such as absolute values of total calcium that were significantly higher at the end of standard OL-HDF in comparison to citrate OL-HDF. As for coagulation (Table 3), aPTT values were longer at the end of citrate OL-HDF than in standard OL-HDF, the difference being highly statistically significant although of minor clinical relevance.

3.2. Dialysis Efficiency. Kt/V was 1.35 ± 0.27, 1.68 ± 0.31, and 1.69 ± 0.28 in citrate HD, standard OL-HDF, and citrate OL-HDF, respectively, with highly significant ($P < 0.001$) differences among HD and OL-HDF treatments. The average infusion volumes obtained were very high, for example, 21.5± 2.2 liters in standard OL-HDF and 21.9 ± 1.9 liters in citrate OL-HDF (P = NS). Dialyzer hydraulic pressure profiles were similar in both OL-HDF treatments (Table 2). As expected, HDF treatments consistently reduced plasma β2m values, while HD did not (Table 3). β2m clearance was quite similar in both HDFs, being 83.8 ± 6.3 mL/min in standard OL-HDF and 83.0 ± 6.8 mL/min in citrate OL-HDF (P = NS). Plasma levels of phosphate, bicarbonate, Na, and K did not differ either at the beginning or at the end of treatments.

3.3. Biocompatibility. At the beginning of treatments, β2m plasma values were significantly higher in HD than in both OL-HDF treatments. What matters more here is the finding that β2m plasma values were highly significantly lower at the beginning of citrate OL-HDF with respect to standard OL-HDF. This datum is confirmed by the significantly lower levels of CRP at the beginning of citrate OL-HDF versus standard OL-HDF (Table 3). These analyses were made keeping into account that baseline values of the first treatment of the week actually belonged to the treatment performed in the previous week.

3.4. Citrate and Acetate Handling. As expected, plasma levels of citrate varied according to the presence or not of citrate in the dialysate. Citrate plasma levels reached zenith at T2 in HD to become then stable, while they progressively increased during citrate OL-HDF with values at T4 significantly higher than in citrate HD (Table 3 and Figure 1(a)). Zenith citrate plasma levels were much lower than the threshold values considered as potentially toxic [26]. Citrate was rapidly metabolized in the intertreatment period, and all subjects had baseline plasma values superimposable, irrespective of treatments.

Also plasma acetate levels reflect the amount of this buffer contained in the dialysate. Only in standard OL-HDF plasma acetate levels significantly progressed throughout treatment, while figures remained stable, or even reduced, in the other two procedures (Table 3 and Figure 1(b)). Since in our study patients were observed in clinical routine, thus with no control on diet nor advice to fast, baseline plasma acetate levels, proxy of acetate body production, were higher

Table 3: Laboratory data analysis.

	Citrate HD-phase A				Standard OL-HDF-phase B				Citrate OL-HDF-phase C			
	T0	T1	T2	T4	T0	T1	T2	T4	T0	T1	T2	T4
Ca^{++} (mmol/L)	1.07 ± 0.06	1.05 ± 0.04**	1.05 ± 0.04**	1.05 ± 0.03**	1.08 ± 0.05	1.16 ± 0.05	1.17 ± 0.05	1.21 ± 0.008	1.08 ± 0.06	1.07 ± 0.04**	1.07 ± 0.03**	1.06 ± 0.06**
Ca tot (mmol/L)	8.7 ± 0.5	9.0 ± 0.3	9.1 ± 0.3	9.5 ± 0.4	8.9 ± 0.4	9.5 ± 0.3	9.6 ± 0.4	10.2 ± 0.6	8.6 ± 0.6	9.1 ± 0.4	9.3 ± 0.5	9.4 ± 0.4**
Citratemia (mmol/L)	0.15 ± 0.03		0.22 ± 0.05	0.22 ± 0.05§§	0.13 ± 0.02		0.13 ± 0.02	0.13 ± 0.02	0.17 ± 0.07		0.24 ± 0.07**	0.28 ± 0.06**
Acetatemia (mmol/L)	0.25 ± 0.13**		0.26 ± 0.11**	0.20 ± 0.06**	0.32 ± 0.13		0.38 ± 0.08	0.35 ± 0.09	0.31 ± 0.18		0.27 ± 0.12**	0.28 ± 0.15**
$\beta 2$ (mg/L)	36.3 ± 8.0**§§			40.2 ± 14**§§	28 ± 5.5			6.5 ± 2.7	25.7 ± 4.7**			5.7 ± 2.1
CRP (mg/L)	8.0 ± 9.5				7.7 ± 5.9				5.9 ± 5**			
Aptt (sec)	31.6 ± 8.2			41.9 ± 9.7	31.1 ± 3.6			39.0 ± 6.5	34.92 ± 11.6			42.2 ± 10.7**

**$P < 0.01$ versus phase B; §§$P < 0.01$ versus phase C.

T0 starting dialysis.

T1 after one hour of dialysis.

T2 after two hours of dialysis.

T4 ending dialysis.

than figures observed in other studies where fasting was mandatory [10].

4. Discussion

In this small, pilot study we have observed that, in comparison with standard OL-HDF, OL-HDF performed with a new dialysate substituting citrate for acetate may bring about a lower inflammation, as heralded by the lower pretreatment β2m and CRP serum levels for the same treatment efficiency, and a light "anticoagulant" effect. As for safety, during both citrate techniques, for example, HD and OL-HDF, plasma calcium levels were stable within normal range. However, this is an acute study while safety ought to be challenged against time. It remains that, to the best of our knowledge, this is the first study performed in chronic dialysis subjects aimed at exploiting advantages and hazards of citrate dialysate in high-volume convective therapies.

Even if the two OL-HDF treatments challenged in this study showed similar urea and β2-m removal and no difference in hydraulic pressures inside the dialyzer, pretreatment plasma levels of β2-m and CRP were significantly lower with citrate OL-HDF. Since treatments were performed one week apart on the same patients utilizing the same dialyzer and the same amount of liters infused, we deem that the result may be explained by a direct anti-inflammatory action of citrate at low doses. In addition to this, citrate concentrate has lower levels of acetate than standard bicarbonate concentrates and it has demonstrated lower inflammatory effects linked to acetate-free dialysate [10].

In our study the anti-inflammatory effect of HDFs was achieved within few days, while in other studies pretreatment β2-m plasma levels were reduced, if any, only after several months of convective treatments [3, 4]. The difference might be due to the much higher volumes exchanged in our study. Aside from the volume effect, the anti-inflammatory effect of citrate is elicited *in vitro* within 48 hours of incubation [27] while favorable effects of acetate-free dialysate are achieved within few hours in both *in vitro* [28, 29] and *in vivo* studies [10].

The anticoagulant effect of citrate is due to the low-calcium environment in the blood; many important enzymatic steps of the coagulation cascade are in fact calcium dependent and citrate acts by chelating ionized calcium with the formation of Ca-citrate complexes [30]. To obtain regional anticoagulation, citrate is added in predilution either directly [31] or in the reinfusion fluid in continuous renal replacement therapies [32]. Otherwise, as in our study, citrate can be added to dialysate by utilizing a concentrate acidified with citric acid [11]. In this latter case, citrate crosses the dialyzer membrane to reach the blood, thus impairing coagulation in blood extracorporeal circuit. Different mechanisms contribute to keep low systemic citrate levels during regional anticoagulation. First of all, citrate has a short half-life, for example, 49 min, being rapidly metabolized to CO_2 and water when it enters the tricarboxylic-acid cycle in the liver, and to a lesser extent in the renal cortex and skeletal muscle [33]. Since citrate is metabolized as citric acid, its metabolism consumes hydrogen ions, produces bicarbonate, and may lead to an increase in blood pH [34]. Total metabolic body clearance of citrate in healthy subjects receiving short-term loads (0.5 mmol/Kg/hour) is about 700 mL/min. Although systemic metabolic clearance is reduced by at least 50% in patients with liver failure, safety of regional citrate anticoagulation has been recently demonstrated also in liver transplant patients and in liver failure [32, 35]. Secondly, calcium-citrate complexes are efficiently removed during renal replacement therapy. In fact, both diffusive and convective clearance markedly reduce the citrate load to the patients (up to 75% reduction), thus increasing the feasibility and tolerance of citrate-based protocols [33, 34]. In our patients citrate plasma levels at the end of treatments were lower than 0.29 mmol/L, well below the values of 0.85 mmol/L, considered the upper limit of safety even for critically ill patients [26].

With systemic citrate levels being exquisitely low in our patients, it comes as no surprise that their plasma calcium values (total and ionized) did not decrease during citrate dialysis sessions and instead remained stable within the normal range. Moreover, many protocols for citrate hemodialysis utilize calcium-free dialysate to prevent precipitation of calcium-citrate complexes with its attendant reduction of the anticoagulant effect of citrate. This was not the case in our protocol, being dialysate Ca concentration 1.5 mmol/L, thus preventing the negative effects on serum calcium levels of Ca-free dialysate.

We acknowledge several limitations of this study. Dialysis sequences were not randomized; thus we cannot exclude with certainty the bias of carry over effect.

Second, but not less relevant, our study was too short to affirm safety of citrate OL-HDF. We can only say that from the stand point of plasma calcium fluctuations, citrate OL-HDF was as safe as citrate HD being the latter an available option extensively implemented in several countries [12–16].

In conclusion, in this small, acute study we challenged for the first time a new acid concentrate containing citrate in OL-HDF with an average postdilution exchange of 21 liters per treatment.

This new dialysis technique did not generate hypocalcemia and was associated with lesser dialysis-induced inflammation. Randomized, prospective, long-term studies on a wider population are decisively necessary to confirm the encouraging results of this pilot study.

Conflict of Interests

All authors declare no conflict of interests with this study.

Acknowledgments

This paper has been read and approved by all authors, and it is not under consideration for publication elsewhere in any language, except in abstract form. Citrate and acetate determinations were performed in Nephrology laboratory of Parma University, partially making allowance of anunrestrictedgrant from B-Braun Avitum, the Citrasate distributor for Italy.

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Research Article

Renal Anemia Control in Lithuania: Influence of Local Conditions and Local Guidelines

Edita Ziginskiene,[1,2] Vytautas Kuzminskis,[1,2] Kristina Petruliene,[1,2] Ruta Vaiciuniene,[1,2] Asta Stankuviene,[1,2] and Inga Arune Bumblyte[1,2]

[1] *Department of Nephrology, Medical Academy, Lithuanian University of Health Sciences, Mickeviciaus str. 9, LT-44307 Kaunas, Lithuania*
[2] *Nephrological Clinic, Hospital of Lithuanian University of Health Sciences Kaunas Clinics, Eiveniu str. 2, LT-50009 Kaunas, Lithuania*

Correspondence should be addressed to Edita Ziginskiene; edita.ziginskiene@gmail.com

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Erythropoietin stimulating agents had a long haul in Lithuania—we had no epoetin till 1994 and there was no intravenous iron in 2001–2004. The aim of this study was to assess the changes of renal anemia control in hemodialysis patients from early independence of Lithuania till nowadays and to evaluate the link of anemia with hospitalization rates and survival and hemoglobin variability in association with mortality. In December of each year since 1996 all hemodialysis centers have been visited and data has been collected using special questionnaires. The history of renal anemia control in Lithuania was complicated; however, a significant improvement was achieved: 54.7% of hemodialysis patients reached the target hemoglobin; all patients have a possibility of treatment with epoetin and intravenous iron. The involuntary experiment with an intravenous iron occurred in Lithuania because of economic reasons and confirmed the significant role of intravenous iron in the management of renal anemia. Hemoglobin below 100 g/L was associated with a 2.5-fold increase in relative risk of death and 1.7-fold increase in relative risk of hospitalization in Lithuanian hemodialysis patients. Although hemoglobin variability was common in Lithuanian hemodialysis patients, we did not find the association between hemoglobin variability and all-cause mortality in our study.

1. Introduction

Lithuania is a country in Northern Europe, the largest of the three Baltic States. It is situated along the southeastern shore of the Baltic Sea with a territory of 65 200 km^2 and a population of 3 million inhabitants. Starting in 1940, Lithuania was occupied by the Soviet Union. On March 11, 1990, the year before the breakup of the Soviet Union, Lithuania became the first Soviet republic to declare independence. In the early period of independence (1991–1993) hemodialysis (HD) was only acetate and available only for recipients waiting for transplantation. There were old HD machines, no water treatment, lack of nephrology literature in English and no competent training in nephrology. This was followed by tremendous progress in renal replacement therapy later on: full renovation and expansion of HD service, start of peritoneal dialysis, establishment of a second center of kidney transplantation, development of a Western model of nephrology with the help of European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) and International Society of Nephrology (ISN).

The introduction of erythropoiesis stimulating agents (ESAs) has changed the management of renal anemia, leading to substantial reduction in the blood transfusion requirements, improvement in energy and physical function and improvement in health-related quality of life. However introduction of ESAs had a long haul in Lithuania: we did not have epoetin until 1994 and there were no intravenous iron in the period of 2001–2004 and very strict limitations by Lithuanian Ministry of Health for the prescription of epoetin. The Lithuanian anemia management guidelines were revised only in August 2011 and correspond to European

Renal Best Practice (ERBP) statements today, but, until then, hemoglobin (Hb) target range of 100–105 g/L was recommended. Maintaining Hb levels within such a narrow target range was a challenge in our clinical practice, so Hb variability was highly prevalent in our dialysis patients.

First data about control of renal anemia in HD patients in Lithuania were published in 2003 [1]. Authors presented relationship between lethality of HD patients and renal anemia control. They concluded that adequate HD procedures and a good management of HD patients decreased requirement of erythropoietin doses for renal anemia treatment. The aim of this study is

(1) to analyse the changes of renal anemia control in HD patients depending on local protocols from early independence of Lithuania till nowadays;

(2) to evaluate the link of anemia with hospitalization rate and survival;

(3) to evaluate Hb variability in association with mortality.

2. Materials and Methods

In the absence of official Renal Registry in Lithuania, in December of each year starting from 1996, all HD centers of the country have been visited and data has been collected using special paper questionnaires. Information about the number of patients and HD stations, demographic characteristics, etiology of end stage renal disease (ESRD), data about dialysis quality, blood tests, and the medicines used have been obtained. Changes of renal anemia control in HD patients depending on local protocols were evaluated from early independence of Lithuania till nowadays.

Influence of anemia on hospitalization rate was evaluated in a prospective study performed in 2002–2006. We investigated 559 patients from Kaunas region of Lithuania. The Kaunas region accounts for 12% of the Lithuanian territory and for 20% of the population. During the study 27% of all Lithuanian ESRD patients were hemodialysed in Kaunas region. Kaunas HD patients were representative of overall Lithuanian HD population: a comparative analysis using all Lithuanian data showed no statistically significant differences in age, gender, primary cause of ESRD, and hospitalization rate. Patients were followed prospectively 12 month for hospitalization rate, length of hospital stay, and causes of hospitalization.

Using data, collected at annual visits to HD centres, study on mortality of HD patients was performed. All patients who started chronic HD due to ESRD in Lithuania, between January 1, 1998 and December 31, 2005, were enrolled in our study. Outcomes and mortality and survival rates were analysed in the study.

Hb variability in HD patients was evaluated in another single-center, retrospective study ($n = 100$). This study was conducted in Lithuanian University of Health Sciences, Department of Nephrology. The study started on January 1, 2011 and the follow-up included 12 months till December 31, 2011. Serum Hb concentrations and ESA doses were measured each month for each patient. Monthly Hb values were categorized as low (L; <100 g/L), intermediate (I; 100–105 g/L), and high (H; >105 g/L), according to our local renal anemia management algorithm at that time, which defined a target range of Hb 100–105 g/L. Then a six-group classification system (according to [20]) was used based on the lowest and highest Hb categories seen during the six-month observation period (01/2011–06/2011): low-low (LL)—consistently low; intermediate-intermediate (II)—consistently within the target range; high-high (HH)—consistently high; low-intermediate (LI)—all six months with low or target range Hb values; intermediate-high (IH)—all six months with high or target range Hb values, and low-high (LH)—fluctuation of low, high, and target range Hb values within six-month period. The association of Hb levels and Hb variability with mortality was evaluated.

2.1. Statistical Analysis. For the statistical analysis we used Statistical Package for Social Science, version 20.0. Variables included in the study were expressed as percentages or position (mean, median) and dispersion parameters as appropriate for the type of variable. For evaluation of continuous variables the statistical mean and standard deviation were used. Kolmogorov-Smirnov statistics were used to evaluate sample normality distribution. Comparison between groups was performed using the Student's t test, chi-square test, and Mann-Whitney U test. Spearman's rank correlation coefficient was used to evaluate relationship between sets of data. The cumulative survival rate was estimated using the Kaplan-Meier method. The event of interest was death. Univariate Cox proportional hazards analysis was used to select variables significantly associated with the risk of death; then these variables were included in multivariate Cox proportional hazards models. Relative risk of hospitalization according to laboratory tests was estimated using Cox regression analysis model. Significant values were considered when $P < 0.05$.

3. Results and Discussion

3.1. Development of HD Service and Control of Anemia in Lithuania during 1996–2010 Period. Tremendous changes were observed in HD service of Lithuania during this period. There was an increase in number of HD centres (from 17 to 61) and HD stations (from 25 p.m.p. to 201 p.m.p.) in 1996–2010. The prevalence of HD patients increased from 60 p.m.p. in 1996 to 467 p.m.p. in 2010 and the incidence rate of HD patients increased from 54.3 p.m.p. in 1997 to 115 p.m.p. in 2010. The mean age of the prevalent HD patients increased from 47.2 ± 16.1 to 61.1 ± 15.4 (minimum 13, maximum 96, median 64) years. 84.7% of HD patients was dialysed 12 and more hours per week in 2010, versus 30.8% in 1996, $P < 0.001$. Mean Kt/V was 1.34 ± 0.25 in 2010 versus 0.81 ± 0.53 in 1999, $P < 0.001$. Improvement of the quality of HD was associated with improvement of anemia control during the period of 1997–2010. The mean Hb concentration increased from 92 ± 15.4 g/L to 107 ± 13.6 g/L, and the percentage of patients with Hb >100 g/L increased from 27.5% in 1997 to 68.2% in 2010 (Table 1). These changes were statistically significant during

Table 1: Changes of treatment and control of renal anemia in hemodialysed patients in Lithuania.

Year	The mean Hb concentration (g/L ± SD)	Percentage of HD patients with Hb > 100 g/L	Percentage of HD patients receiving epoetin	The mean dosage of epoetin (U/week ± SD)	Percentage of HD patients receiving i/v iron
1997	92 ± 15.4	27.5	78	6071 ± 2924	7.5
1998	99 ± 15.3*	44.1*	89.5*	6537 ± 3209*	27.6*
1999	101 ± 16	52.9	92.4	7058 ± 3732	35.1
2000	**104 ± 15**#	62.9	96.1	7092 ± 3424	70.8#
2001	105 ± 14.7	64	94.6	**9336 ± 3571**~	**20.9**~
2002	**101 ± 14.0**~°	**51.8**~°	**88.8**~°	**7145 ± 3882**°	Only single patient
2003	100 ± 14.5	49.7	91.1	8166 ± 5525	Only single patient
2004	101 ± 13	53.6	89	8121 ± 6243	Only single patient
2005	**105 ± 13.8**^	**65.1**^	**84**^	**6768 ± 4372**^	**86.9**^
2006	104 ± 13	62.4	78.8	7230 ± 4295	70.8
2007	105 ± 12.8	66.6	81.4	6716 ± 4417	85.1
2008	105 ± 13.6	66.3	76.6	6014 ± 4932	80.3
2009	105 ± 14.6	64.4	75.9	6196 ± 4414	78.2
2010	107 ± 13.6	67.8	76.6	6623 ± 4812	69.9

*$P < 0.05$ as compared to 1997, #$P < 0.05$ as compared to 1999, ~$P < 0.05$ as compared to 2000, °$P < 0.05$ as compared to 2001, and ^$P < 0.05$ as compared to 2004.

the first years of observation (Table 1). The target Hb level in patients on chronic HD was between 100 g/L and 105 g/L during the study according to our national algorithm for the management of anemia in Lithuania (it was introduced on 2000). The target of Hb is debated to this day. K/DOQI guidelines [2] and European Best Practice Guidelines [3] have recommended Hb target of 110 to 120 g/L and >110 g/L, respectively. 2012 KDIGO guidelines suggested limitation of the upper Hb level to ≤115 g/L [4]. So Hb 107 g/L was sufficient according to national and KDIGO guidelines in 2010, but it was too low as compared with other recommendations. According to results of The dialysis outcomes and practice patterns study (DOPPS), the same mean Hb of prevalent HD patients as in Lithuania was observed only in Japan (104 g/L in DOPPS III) [5]. Japanese Society for Dialysis Therapy recommended that a Hb level of 110–120 g/L at the first dialysis session in week is desirable in relatively young patients [6]. While it holds that the Hb level of the Japanese population seemed to be low when compared with that of the European and American populations, the mean Hb of other countries in DOPPS III was 115–120 g/L [5].

In 2010 76.6% of patients received epoetin in Lithuania. This percentage was low as compared to results of DOPPS study in 2010: lowest percentage was observed in Japan (87.3%) and Austria (87.7%) and ranged from 89.2% (France) till 96% (Belgium) in other countries [7]. In Lithuania 51.5% of HD patients was treated with epoetin beta, and 43.3% with epoetin alfa in 2005. Treatment with darbepoetin alfa was started in 2005 in Lithuania, so only 5.2% of patients received this medication. Increase of long-acting ESA usage was observed during 2005–2010. Percentage of patients treated with darbepoetin increased till 48.4% in 2010 in Lithuania as compared to 45.8% of patients in UK, 50.7% in Japan, and only 6.1% in USA [7]. Mircera is registered but not reimbursed in Lithuania so our HD patients have a possibility of this treatment only in frames of ongoing clinical trial. 25% of HD patients in France and 15.5% in Belgium were receiving Mircera in DOPPS study in 2010 [7].

3.2. The Role of Intravenous Iron (Experience of Lithuania). The oral route of iron administration was popular in Lithuania before 1997. Only 7.5% of patients received intravenous iron. After the increased use of intravenous iron in the year 2000 the mean Hb concentration increased significantly without serious changes in the doses of epoetin (Hb 104 ± 15 g/L in 2000 versus 101 ± 16 g/L in 1999, $P < 0.05$, Table 1). However in the period of 2001–2005 intravenous iron was poorly available in Lithuania. The percentage of patients receiving intravenous iron sharply decreased till 20.9% in 2001, and the Hb concentrations did not change at the expense of significant increase of the epoetin dose in this year (9336 ± 3571 U/week versus 7092 ± 3424 U/week in 2000, $P < 0.001$). Our results coincided with the data of other studies confirming importance of the intravenous route of iron administration in CKD HD patients as compared to oral administration [8, 9]. Intravenous iron administration led to a greater increase in Hb concentration, a lower ESA dose, or both in most studies [4]. Limitations to the prescription of epoetin were introduced by Lithuanian Ministry of Health at the same time with unavailable intravenous iron. This was followed by worsening of the control of renal anemia in 2002. According to this new algorithm target Hb was 100–105 g/L for HD patients and maximum weekly dose of epoetin was 20000 IU. The mean Hb concentration decreased to 101 ± 14 g/L, the percentage of patients with Hb >100 g/L decreased to 51.8%, the percentage of HD patients receiving epoetin decreased to 88.8%, and the mean weekly dose of epoetin decreased to 7145 ± 3882 U, $P < 0.001$ (Table 1). The rules

Table 2: Relationship between iron deficiency and dose of erythropoietin in the treatment of renal anemia of hemodialysed patients in 2002–2005.

Year	The mean Hb concentration (g/L ± SD)	Percentage of HD patients with ferritin <100 mcg/L	Percentage of HD patients receiving epoetin	The mean dosage of epoetin (U/week ± SD)
2002	101 ± 14.0	30.5	88.8	7145 ± 3882
2003	100 ± 14.5	49.5^	91.1	8166 ± 5525^
2004	101 ± 13	60.9^	89	8121 ± 6243
2005	105 ± 13.8^	18.5^	84^	6768 ± 4372^

^$P < 0.05$, as compared to previous year.

Table 3: Relative risk of death for hemoglobin categories.

Mean hemoglobin concentration (g/L)	Relative risk	P	95% CI	
			Lower limit	Upper limit
100–105	1.0			
<100	**2.472**	**<0.001**	1.923	3.177
106–109	1.076	0.687	0.754	1.534
110–120	1.058	0.731	0.767	1.459
121–130	1.031	0.915	0.593	1.791
>130	2.356	0.063	0.953	5.822

of renal anemia treatment were very strict in Lithuania, so it was difficult to keep higher Hb concentration. Fortunately usage of intravenous iron (iron dextran and iron sucrose) was restarted in 2005 and situation of anemia control improved. Hb concentration increased to 105 ± 13.8 g/L ($P < 0.001$), the percentage of patients with Hb >100 g/L increased to 65.1%, the percentage of HD patients receiving epoetin decreased to 84%, and the mean weekly dose of epoetin decreased from 8121 ± 6243 U in 2004 to 6768 ± 4372 U in 2005 (Table 2). All these changes were statistically significant. The changes of mean Hb due to influence of national algorithm and deficiency of iron are presented in Figure 1. Insufficiency of iron increased between 2002 and 2004, and percentage of patients with ferritin <100 mcg/L decreased till 18.5% in 2005 ($P < 0.001$, Table 2). It is true to say that Lithuania had involuntary experiment to show influence of intravenous iron for the treatment of renal anemia. It is a pity that this experiment was very expensive as it lasted four years and all patients were involved.

3.3. Influence of Anemia on Hospitalization Rate in HD Patients from Kaunas Region of Lithuania. There is no unified opinion about the influence of anemia to hospitalization rate of HD patients. Big retrospective study of dialysis patients showed that higher concentration of Hb associated with lower rate of hospitalization [10]. DOPPS study (data from 5 European countries) showed that higher Hb concentrations were associated with decreased relative risk of hospitalization: patients with Hb <100 g/L were 29% more likely to be hospitalized than patients with Hb 110–120 g/L [11]. But in prospective randomized trials hospitalization rate did not differ between groups of lower and higher Hb [12]. There were no Lithuanian data about relationship between hospitalization of HD patients and anemia till our study. Relative risk of hospitalization was estimated using Cox regression evaluating time to first hospitalization. Multivariate Cox regression model revealed that relative risk for hospitalization decreased by 0.98 for every 1 g/L rise of Hb (adjusted to age, sex, comorbid conditions, albumin, urea and phosphorus concentrations interdialytic weight gain, nonadherence to medications, systolic blood pressure before and dialysis, disability status). Cutoff value for Hb was <100 g/L: relative hospitalization risk increased by 1.7 (95% CI 1.4–1.95, $P < 0.001$) in patients with Hb <100 g/L (Figure 2).

3.4. Association of Anemia with Mortality in HD Patients in Lithuania. Annual data collection allows us to analyse associations between anemia and mortality in incident HD patients in Lithuania in 1998–2005. Analysis revealed that the mean Hb value of all these patients was 101.28 ± 12.59 g/L; in males it was higher than in females (102.34 ± 12.52 g/L versus 100.01 ± 12.56 g/L, $P < 0.001$) and did not differ comparing different age groups and primary renal disease groups.

Multivariate Cox proportional hazards analysis revealed that anemia was an independent risk factor of death (RR = 0.952, 95% CI 0.945–0.959, $P < 0.001$). Relative risk of mortality was 5% lower for every 1 g/L greater Hb concentration used as continuous variable and adjusted for age, sex, and primary kidney disease.

As shown in Table 3, the relationship of Hb level with mortality varied across different categories of Hb concentrations.

Patients with Hb level of 100 to 105 g/L were selected as the reference group, according to national algorithm for the management of anemia in Lithuania from 2002 (the target Hb level in patients on chronic HD was between 100 g/L and 105 g/L). The Hb concentration below 100 g/L was associated with a 2.5-fold increased relative risk of death. Hb levels

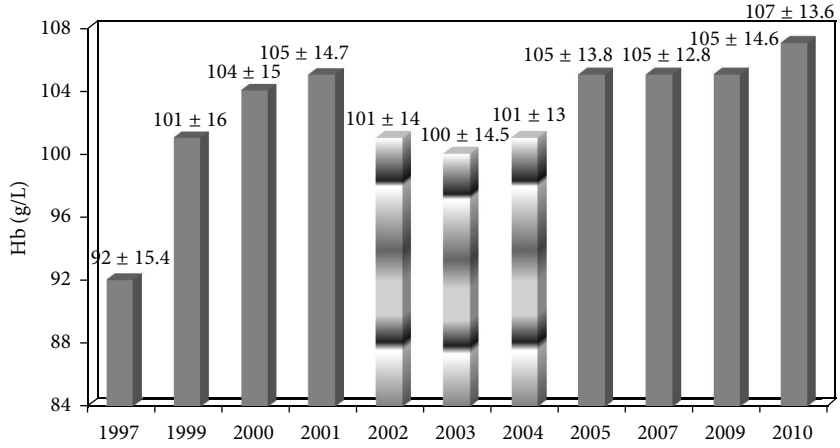

Figure 1: Changes of mean hemoglobin concentration of hemodialysis patients due to influence of national algorithm and deficiency of iron in 1997–2010.

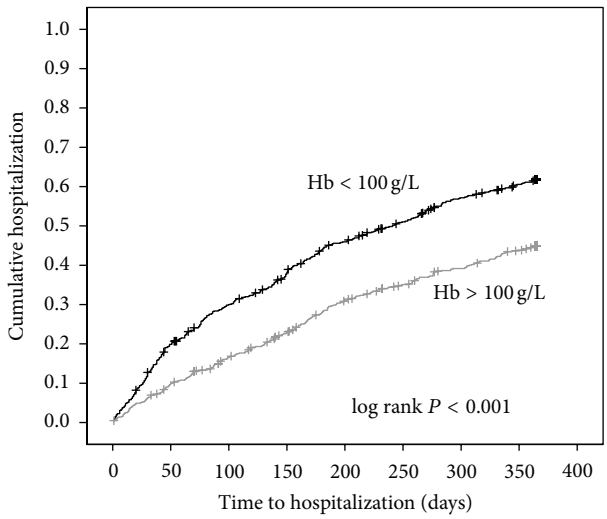

Figure 2: Relation between hemoglobin level and hospitalization in Lithuanian hemodialysis patients.

of >106 g/L were not associated with a lower risk of death. For Hb concentrations ≥130 g/L, a trend towards higher mortality risk was observed (RR = 2.356, 95% CI 0.953–5.822, $P = 0.063$), but it did not reach statistical significance. Anemia is associated with an increased risk of morbidity and mortality principally due to cardiac disease and stroke [13, 14]. Hb concentration <100 g/L is independent risk factor of cardiovascular diseases for dialysis patients [15]. DOPPS study showed that higher Hb concentrations were associated with decreased relative risk for mortality [11]. On the other hand, clinical trials showed that maintenance of Hb levels above 130 g/L may be associated with increased morbidity and mortality in dialysis. A recent meta-analysis indicated increased mortality at higher Hb target [12]. A trend towards a higher mortality risk was observed for patients with Hb concentrations >130 g/L in our study.

3.5. Hemoglobin Variability in Lithuanian HD Patients. Since the introduction of ESA, most of the clinical trials with ESA therapy have focused on Hb targets in CKD patients; however, there is a shortage of clinical trials studying the optimal strategy for Hb monitoring in patients treated with ESA and interventions to reduce Hb variability. Several factors affect Hb variability, including those that are drug related, such as pharmacokinetic parameters, clinical practice guidelines, treatment protocols, and reimbursement policies. Strategies that consider each of these factors and reduce Hb variability may be associated with improved clinical outcomes [16]. There is conflicting evidence on the effect of Hb variability on mortality with some studies demonstrating a strong association and others showing no association with mortality.

We evaluated Hb concentrations and ESA doses in 100 patients—56 (56%) men and 44 (44%) women. The mean age of patients was 61.88 ± 14.8 years (31–84). Mean time from the start of dialysis until inclusion into the study was 4.75 ± 4.33 years. The new anemia management algorithm in Lithuania (August 2011) gave a clear rise in the Hb concentrations during the second half-year of 2011 (Figure 3). We found that Hb concentrations increased significantly with a new algorithm, though mean doses of ESA remained unchanged (11073.17 U/week versus 11425 U/week; $P = 0.491$).

We looked in detail to each month (01/2011–06/2011) Hb concentrations and found that only 17.1% of patients during this period had Hb in the target range according to local algorithm (100–105 g/L), 50.2% of patients had Hb <100 g/L, and 32.7% had Hb >105 g/L. A big part of our patients exhibited fluctuations in the Hb levels corresponding to literature data where we found that 80–90% of ESRD patients on dialysis exhibit fluctuations in the Hb levels, known as Hb variability [16–19]. We used the six groups classification system (Ebben's principle) based on the lowest and the highest Hb categories seen during the 6-month observation period in our study and found: LL 10.9%; II 0%, HH 2.2%, LI 8.7%, IH 4.3%, and LH 73.9% of patients (Figure 4).

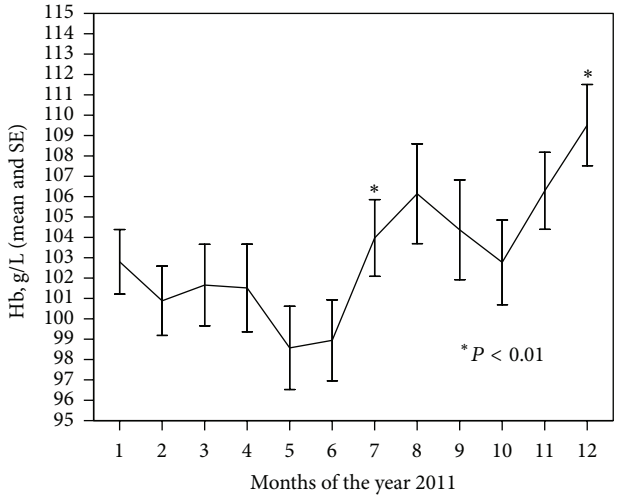

Figure 3: Mean hemoglobin concentrations during 2011 year. Influence of a new anemia management algorithm, certified in Lithuania August 2011.

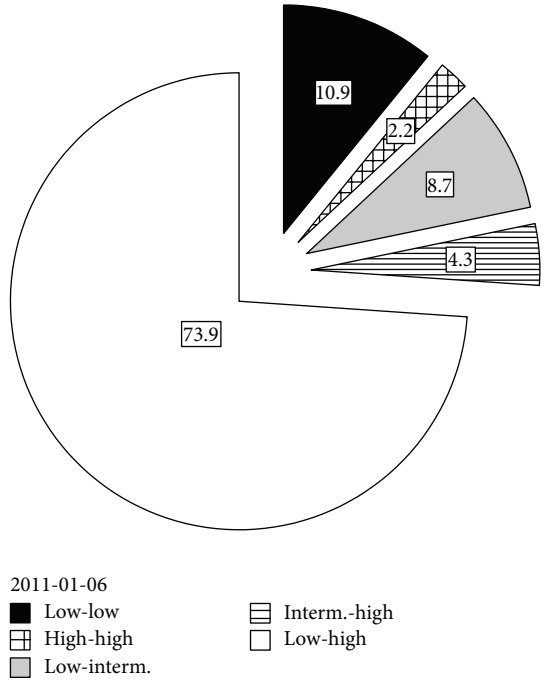

Figure 4: Pattern of fluctuations in hemoglobin levels during a six-month period (01/2011–06/2011) in Lithuanian hemodialysis patients, classified according to Ebben's principle ($n = 100$).

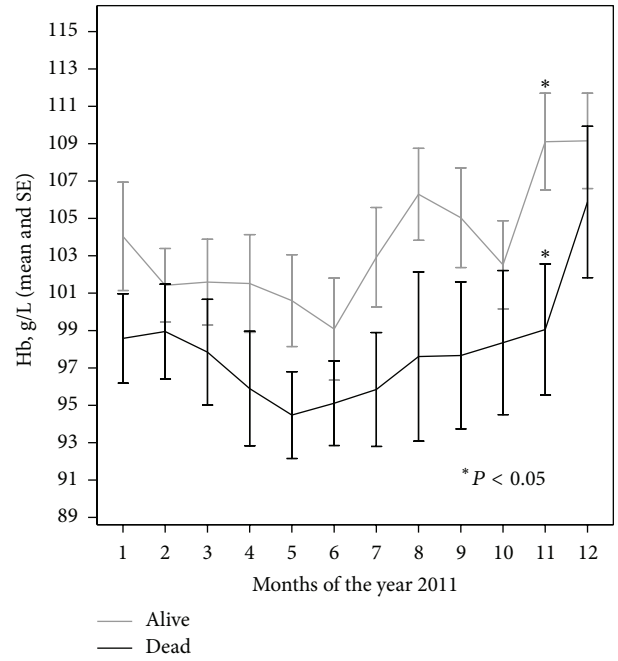

Figure 5: Comparison of mean hemoglobin concentrations during the year 2011 in dead and alive hemodialysis patients.

In the United States Renal Data System analysed by Ebben et al. [20], only 10% of patients maintained Hb levels within a single Hb category during the entire 6-month period. 29% of patients experienced Hb fluctuations between the high and target Hb groups, and 21% experienced fluctuations between the low and target Hb groups. Fluctuation across all three Hb categories during the 6-month period was observed in nearly 40% of patients [20]. We noted that none of our ESA-treated patients had Hb levels stable within the target range (100–105 g/L) over a 6-month period; 10.9% of patients had constantly low Hb concentration; 13% strayed outside their initial Hb group into the next closest group, 73.9% of the patients showed a high amplitude swing. However it is difficult to compare our data with data of other studies because a different target range of Hb concentration was used; beside, there is no single and uniformly accepted method to measure Hb variability.

The data on the effect of Hb variability on mortality are conflicting. In our study we did not find the association between Hb variability and all-cause mortality using an adjusted Cox regression model, although the Hb concentrations of dead patients had a tendency to be lower (Figure 5) and the mean ESA doses had a tendency to be higher.

The study of Ebben et al. suggested that variability itself may not have a strong association with mortality. The key factors seem to be the number and timing of Hb values <110 g/L. Patients whose Hb levels were consistently within the target range of 110 to 125 g/L experienced the lowest mortality in their study. The longer the amount of time with Hb level <110 g/L was the greater the risk of death was noted [19]. In a study involving 34 963 HD patients Yang and colleagues reported that the risk of all-cause mortality increased proportionately with Hb variability [21]. The HR and 95% CI per 0.5 g/dL, 0.75 g/dL, 1.00 g/dL, and 1.5 g/dL increases in Hb variability were 1.15 (1.10 to 1.2), 1.24 (1.16 to 1.32), 1.33 (1.22 to 1.45), and 1.53 (1.35 to 1.75), respectively. Not all studies have demonstrated a positive association between Hb variability and death in CKD. In the study of Eckardt and colleagues [17] Hb variability was not a statistically significant factor for mortality, except in the group of patients with low

amplitude fluctuations and with low Hb levels (HR 1.74, 95% CI 1.00 to 3.04) that correspond to our study data.

Our study has limitations that should be considered. The sample size was small and the data were collected retrospectively in only one dialysis center. The obtained database therefore reflects only a small sample of entire Lithuanian dialysis population. Further studies are needed to clarify the relationship between provided practices, Hb variability, and mortality.

3.6. Current Situation and Problems Remained. As it was mentioned before Lithuanian anemia management guidelines were revised in August 2011 and correspond to ERBP position (target Hb 100–120 g/L). The mean Hb of our HD patients was 109 ± 12.8 g/L at the end of 2011 ($P < 0.05$ as compared to 2009). 54.7% of all HD patients had Hb between 100–120 g/L, but 26.6% of them still had Hb <100 g/L. According to K/DOQI guidelines [2] target of ferritin must be 200–500 mcg/L. There were 46.4% of patients with ferritin in the target range in 2011 although the mean ferritin concentration was 375 ± 255.7 mcg/L. This percentage was similar to that in UK (45.5% in range of 200–499 mcg/L) or in Spain (45.9%) [7]. According to KDIGO [4] and K/DOQI [2] Guidelines additional intravenous iron should not routinely be administered in patients with serum ferritin levels that are consistently >500 mcg/L. According to local Lithuanian algorithm administration of iron must be interrupted when ferritin concentration exceeds 500 mcg/L; however transferrin saturation is not routinely performed in all Lithuanian HD patients. We determine a dose of iron according to ferritin concentration only, so we cannot accurately evaluate iron stores and prescribe appropriate iron dose. We are planning to continue the study of observation of renal anemia control in Lithuania, the study of Hb variability involving a larger number of patients hoping for more precise results. It is important to assess the percentage of hyporesponsiveness to ESAs in HD patients in Lithuania and to evaluate the reasons.

4. Conclusions

(1) The history of renal anemia control in Lithuania was complicated; however, a significant improvement was achieved and 54.7% of HD patients reached the target hemoglobin.

(2) The involuntary experiment with an intravenous iron occurred in Lithuania because of the economic reasons and confirmed the significant role of intravenous iron in the management of renal anemia.

(3) Hemoglobin concentration below 100 g/L increased relative hospitalization risk by 1.7-fold and it was one of the most important factors influencing hospitalization rate.

(4) Hemoglobin concentration below 100 g/L was associated with a 2.5-fold increased relative risk of death in Lithuanian hemodialysis patients.

(5) Although hemoglobin variability was common in Lithuanian hemodialysis patients, it did not independently predict mortality.

Conflict of Interests

The authors declare that there is no conflict of interests.

Acknowledgment

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Research Article

Urogenital Mycoplasmas and Human Papilloma Virus in Hemodialysed Women

Alicja Ekiel,[1] Bronisława Pietrzak,[2] Barbara Wiechuła,[1] Małgorzata Aptekorz,[1] Natalia Mazanowska,[2] Dominika Rady,[1] Paweł Kamiński,[1] and Gayane Martirosian[1,3]

[1] *Department of Medical Microbiology, Medical University of Silesia, Medyków 18, 40-752 Katowice, Poland*
[2] *Department of Obstetrics and Gynecology, Medical University of Warsaw, Starynkiewicza 1/3, 02-015 Warsaw, Poland*
[3] *Department of Histology and Embryology, Medical University of Warsaw, Chalubińskiego 5, 02-004 Warszawa, Poland*

Correspondence should be addressed to Gayane Martirosian; gmartir@sum.edu.pl

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Bacterial infections, especially endogenous, are the frequent complications among hemodialyzed and renal transplant patients. In this study we assumed the prevalence of urogenital mycoplasmas and HPV among hemodialysed women. We examined 32 hemodialysed women aged 20–48 (mean 35.6 ± 8.23) and 100 healthy controls of the same ages. Two swabs were collected for detection of mycoplasmas and HPV. Culture of *Ureaplasma* spp. and *M. hominis* was performed using Mycoplasma IST2 (bioMérieux, France), Identificaton of *U. parvum* and *U. urealyticum* was performed by Kong. Primers described by Jensen were used for *M. genitalium*. For detection of high-risk HPV types Amplicor HPV (Roche Molecular System, CA) was used. Prevalence of urogenital mycoplasmas in the hemodialysed women (53.1%) was significantly higher ($P = 0.0059$), compared with controls (25%). In both groups, *U. parvum* was the most frequently isolated. Cooccurrence of urogenital mycoplasmas was shown in 75% of the HPV-positive hemodialysed women and in 30.4% of HPV-positive controls ($P = 0.0461$). Cooccurrence of urogenital mycoplasmas with HPV was significantly higher in hemodialysed women. The need to take into account these microorganisms in routine diagnostic, especially for hemodialysed patients, was demonstrated. Further studies to demonstrate the role of this cooccurrence in etiopathogenesis of infection in hemodialysed patients are required.

1. Introduction

Bacterial infections are the frequent complications observed in hemodialyzed and renal transplant patients, a significant risk factor for transplant rejection and an essential mainspring of mortality in this population. Increased susceptibility to disease and severe infections are due to impairment of the immune system caused by primary diseases and immunosuppressive therapy. Common problems are endogenous infections caused by own microflora. Urogenital mycoplasmas occur in 20–50% of sexually active women. Molecular biology techniques allowed detection of *M. genitalium*, *U. parvum* and *U. urealyticum*. Thanks to this, studies on the epidemiology and etiopathogenesis of urogenital mycoplasmas in human diseases were intensified [1]. Recently in medical literature were published case reports of severe infections caused by urogenital mycoplasmas, very often at atypical localization, especially in patients in risk group for development of opportunistic infections. Furthermore, an important risk factor is also human papillomavirus (HPV). HPV infections can lead to serious consequences and are accepted as an important cause of invasive cervical carcinoma.

In the current study, we assumed the prevalence of urogenital mycoplasmas and HPV among hemodialysed and healthy asymptomatic women.

2. Material and Methods

Examination included 132 sexually active women. The study group consisted of 32 hemodialysed women aged 20–48 (mean age 35.6 ± 8.23 yr) under care of Clinic of Obstetrics and Gynecology, Medical University of Warsaw. The control

group included 100 women without diseases and subjectively experienced symptoms from the urogenital tract. The age of the control group was in the range of 20 to 48 years (mean age 33.5 ± 7.49 yr). This study was approved by Bioethical Committee of Medical University of Silesia (KNW/0022/KB1/88/09) and Medical University of Warsaw (KB/117/2007). Exclusion criteria of patients were based on lack of consent, antibiotic therapy and/or chemotherapy and antifungals (at least 4 weeks before examination), pregnancy, diagnosed STI, and vaginal discharge.

First swab from posterior vaginal fornix was taken in order to make a Gram-stained direct smear and evaluated vaginal biocenosis according to the 10-point Nugent score [2].

Second endocervical swab immediately after collection was cultured on Columbia agar with 5% defibrinated sheep blood (for aerobic and anaerobic incubation), Chapman, MacConkey, Sabouraud, de Man, Rogosa, and Sharpe agars. Identification of isolated strains was performed using microbiological analyzer Vitek Compact 2 (bioMérieux, France). Next two endocervical swabs were collected aseptically for determination of urogenital mycoplasmas and HPV, respectively. Culture of *Ureaplasma* spp. and *M. hominis* was performed using Mycoplasma IST2 test (bioMérieux, France), according to manufacturer's instructions.

Isolation of mycoplasmal DNA was performed from pellet of cells obtained from centrifuged (15 000 g, 30 min, at 4°C) mycoplasmal culture using DNeasy Tissue Kit (Qiagen Inc.). Identification of *U. parvum* and *U. urealyticum* was conducted in accordance with Kong et al. [3]. For detection of *M. genitalium* primers for adhesin genes MgPa-1, MgPa-3 and for 16S rRNA gene MG16-45F, MG16-447R, MG16-1204F, and MG16-1301R by Jensen et al. were used [4, 5]. The rule that a double-positive amplicon for adhesin gene with primers MgPa-1/MgPa-3 and double-positive for one of the primers for 16S rRNA gene could be considered as positive was used during interpretation of obtained results. Amplifications were performed using *Taq* PCR Core Kit (Qiagen Inc.) in thermocycler Mastecycler (Eppendorf AG). Negative samples were checked for presence of amplification inhibitors. The reference strains *Ureaplasma urealyticum* ATCC 27618, *Ureaplasma parvum* ATCC 27815 and genomic DNA of *Mycoplasma genitalium* ATCC 33530 were used as positive controls.

Detection of high-risk human papilloma virus (HPV) types 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82, and 83 was conducted using Amplicor HPV Test (Roche Molecular System, CA), according to manufacture's instruction.

Obtained results were subjected to statistical analysis in the STATISTICA programme, 9.1.210.0 version (StatSoft Poland, Sp. z o.o.).

3. Results

Prevalence of urogenital mycoplasmas in group of hemodialysed women was significantly higher ($P = 0.0059$), compared with the control group, 53.1% and 25%, respectively (Table 1). Furthermore, individual mycoplasmal species were also frequently reported, but these differences were not significant (Table 2).

Taking into consideration the 10-point Nugent score, the majority of the women demonstrated normal vaginal flora. In 18.8% of hemodialysed women versus 4% control group

Table 1: Occurrence of urogenital mycoplasmas in hemodialysed women and the controls (the number and percentage of positive cases).

	Hemodialysed women $n = 32$	Control group $n = 100$
U. parvum	6 (18.8%)	16 (16%)
U. parvum + *M. hominis*	2 (6.3%)	1 (1%)
U. parvum + *M. genitalium*	1 (3.1%)	0
U. urealyticum	4 (12.5%)	3 (3%)
U. urealyticum + *M. hominis*	1 (3.1%)	0
M. genitalium	2 (6.3%)	3 (3%)
M. hominis	1 (3.1%)	0
U. parvum + *M. hominis* + *U. urealyticum*	0	2 (2%)
Total	17 (53.1%)	25 (25%)

Table 2: Frequency of individual urogenital mycoplasmas in the group of hemodialysed women and in controls.

	Study group $n = 32$	Control group $n = 100$	P
	Number (%)		
U. parvum	9 (28.1)	19 (19)	0.3950
U. urealyticum	5 (15.6)	5 (5)	0.0619
M. genitalium	3 (9.4)	3 (3)	0.1529
M. hominis	4 (12.5)	3 (3)	0.0586

In both groups, *U. parvum* was the most frequent isolate. In the control group this species occurred significantly more often compared with *U. urealyticum* ($P = 0.0023$), *M. genitalium* ($P = 0.0003$), and *M. hominis* ($P = 0.003$). In the group of hemodialysed women *U. parvum* was also the most often detected, however, without statistical significance.

Table 3: Cooccurrence of mycoplasmal species in HPV-positive hemodialysed women and control group.

Cooccurrence	HPV-positive hemodialysed women $n = 8$	HPV-positive control group $n = 23$
HPV + *U. parvum*	1	3
HPV + *U. parvum* + *M. hominis*	2	1
HPV + *U. urealyticum*	2	2
HPV + *U. urealyticum* + *M. hominis*	1	0
HPV + *M. genitalium*	0	1
HPV individually	2	16

Table 4: Frequency of selected microorganisms in the group of hemodialysed women and controls (the number and percentage of positive cases).

	HPV	*Lactobacillus* spp.	GBS*	*Candida* spp.*	Gram-negative rods*
Hemodialysed women ($n = 32$)	8 (25%)	25 (78.1%)	2 (6.3%)	4 (12.5%)	13 (40.6%)
Control group ($n = 100$)	23 (23%)	87 (87%)	10 (10%)	10 (10%)	23 (23%)

*Single colonies.

the middle Nugent score was confirmed (4–6). Presence of HPV was detected in 8 women of the study group (25%) and in 23 of the control group (23%) (Tables 3 and 4). Cooccurrence of urogenital mycoplasmas was shown in 6/8 (75%) HPV-positive hemodialysed women and in 7/23 (30.4%) of HPV-positive women in the control group. Among various combinations the most frequent cooccurrence was of HPV and *U. parvum* in the control group and two cases equally in hemodialysed women: HPV + *U. parvum* + *M. hominis* and HPV + *U. urealyticum* (Table 3).

Significant cooccurrence of HPV and mycoplasmas was demonstrated in the control group, in contrast to individual presence of HPV ($P = 0.0461$).

Occurrence of *Lactobacillus* spp., group B *Streptococci* (GBS), Gram-negative rods, and *Candida* spp. was similar in both groups (Table 4). There was no meaningful effect of urogenital mycoplasmas on the prevalence of these microorganisms (data not included). We did not observe any specific symptoms in urogenital tract of women in study and control groups besides presence of urogenital mycoplasmas, HPV, or other potentially pathogenic microorganisms.

4. Discussion

Bacterial infections are the second most common cause of death in group of hemodialysed patients [6]. In conducted studies in 27 hemodialysis centres in France, 23% of infections were associated with urinary tract [6, 7]. Among infections with unknown etiology supposed to be also those caused by mycoplasmas. Colonization may constitute a source of dangerous endogenous infections; therefore, occurrence of pathogens in the risk group patients should be monitored. The decrease in the frequency of colonization reduces symptomatic infection rate. In Spanish studies, among a numerous group of renal donors, infections were the direct reason of death in 29% of patients, mainly due to sepsis, pneumonia, and systemic fungal and viral infections [8]. Urogenital mycoplasmas are frequently isolated from clinical materials. Despite the fact that in genitourinary tract they can cause rare infections in immunocompetent patients, but mycoplasmas are an important threat to patients with immunosuppression [9–11]. Yager et al. described a case of peritonitis caused by mycoplasmas in patient with peritoneal dialysis [12].

Majority of positive outcomes in our study concerned *U. parvum* detected in 28% hemodialysed women and in 19% controls and *U. urealyticum* in 15.6% and 5%, respectively. Significant higher percentage of *U. urealyticum* in hemodialyzed women may suggest future possible infections. The absolute domination of *U. parvum* strains (our results) was also shown by other authors [13–19].

After the division of *Ureaplasmas* into two new species *U. parvum* and *U. urealyticum* and demonstration of differences in the frequency of individual species detection, studies were undertaken to determine pathogenicity of these microorganisms. *U. urealyticum* is the commonest etiologic agent of infections, including severe infections in renal transplant patients. *U. urealyticum* detection in patients without infections and subjectively experienced symptoms from the urogenital tract is low (1.2%) [20, 21] and significantly increases in men with NGU [20–22] and women with PID and cervicitis [23]. Besides the fact that we did not note any specific symptoms of cervicitis in hemodialysed women, we speculate that presence of HPV in cervical epithelium may support colonization with *U. urealyticum*. *M. genitalium* DNA detection in our study was 3% in control group and 9.4% in hemodialysed women. Although it is a high percentage, our study was limited by small number of patients in study group. Many studies confirm low percentage of *M. genitalium* in healthy women without symptoms: 4.5% of positive cases were described by English authors [24]. In Denmark, among 731 men and 921 women aged 21–23 without any symptoms in the urogenital tract, *M. genitalium* DNA was demonstrated in 2.3% women and in 1.1% men [25]. *M. genitalium* is clearly defined as an etiologic agent of STI. Clinical indications for next studies of this species are urethritis, epididymitis, and prostatitis in men and cervicitis, urethritis, and PID in women [26]. More than 9% of positive *M. genitalium* cases among studied hemodialysed women suggest importance of this microorganism as an etiological agent of possible complications.

Fairley et al. demonstrated 20% HPV positive cases in hemodialysed women versus 4.5% cases in control group [27]. This suggests that hemodialysed women belong to higher risk group for abnormal Pap and/or development of cervical cancer. In our study we demonstrated equal detection of HPV in hemodialysed and healthy women (25% versus 23%). However, different primers for HPV detection were used by Fairley et al. and in our study (Amplicor detects 13 different genotypes of HPV). We demonstrated cooccurrence of HPV and urogenital mycoplasmas in 75% of hemodialysed women, suggesting importance of this cooccurrence and necessity of further studies.

We summarize that because of demonstrated significant differences in occurrence of urogenital mycoplasmas in hemodialysed women and controls these microorganisms can cause future complications especially in patients preparing for renal transplantation and receiving immunosuppressive therapy.

5. Conclusion

Significantly higher incidence of urogenital mycoplasmas and cooccurrence with HPV was demonstrated in hemodialysed women. The need to take into account these microorganisms in routine diagnostics, especially for hemodialysed patient, was demonstrated. Further studies to demonstrate the role of this cooccurrence in etiopathogenesis of infection in hemodialysed patients are required.

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Research Article

Usefulness of Multidetector Row Computed Tomography for Predicting Cardiac Events in Asymptomatic Chronic Kidney Disease Patients at the Initiation of Renal Replacement Therapy

Jung Eun Lee,[1] Yong Kyu Lee,[2] Eun Jeong Choi,[3] Ji Sun Nam,[1] Byoung Wook Choi,[3] and Beom Seok Kim[1,4]

[1] *Department of Internal Medicine, Yonsei University, College of Medicine, Seoul 120-752, Republic of Korea*
[2] *Nephrology Division, Department of Internal Medicine, NHIC, Ilsan Hospital, Goyang 410-719, Republic of Korea*
[3] *Department of Radiology, Yonsei University, College of Medicine, Seoul 120-752, Republic of Korea*
[4] *The Research Institute for Transplantation, Yonsei University, College of Medicine, Seoul 120-752, Republic of Korea*

Correspondence should be addressed to Beom Seok Kim; docbsk@yuhs.ac

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Background. The prevalence of coronary artery stenosis (CAS) at the initiation of renal replacement therapy (RRT) in chronic kidney disease (CKD) patients has not been fully elucidated. Although coronary angiography is the gold standard in diagnosing CAS its invasiveness and economic burden lead to searching for a noninvasive alternative method. In this study, we evaluated the prevalence of CAS by multidetector row computed tomography (MDCT) and related risk factor to articulate the usefulness of MDCT. *Method*. Seventy-four asymptomatic CKD patients who began dialysis were evaluated with echocardiography and MDCT. The patients were stratified into two groups according to CAS and coronary artery calcification score (CACS) by MDCT to detect silent CAS and evaluate its predictability for cardiac events. *Results*. CAS was seen in 24 (32.4%) of 74 asymptomatic CKD patients on MDCT. Both groups showed increasing frequencies of CAS with age ($P < 0.01$), presence of diabetes ($P < 0.05$), uric acid level ($P < 0.01$), and calcium score ($P < 0.01$). Multiple regression analysis revealed that age and uric acid level were independent risk factors for CAS and high CACS in asymptomatic CKD patients at the initiation of dialysis. Patients with both CAS and high CACS were presented with higher cardiac events rates compared to those without any of them. In Cox regression model, age and the presence of CAS and high CACS on MDCT were an independent risk factor for cardiac events in these patients. *Conclusion*. We showed that CAS was highly seen in asymptomatic CKD patients starting dialysis. Moreover, both high CACS and CAS on MDCT might predict cardiac events in these patients and MDCT can be a useful screening tool for evaluating coronary artery disease and predicting cardiovascular mortality noninvasively.

1. Introduction

Cardiovascular disease is the most common cause of death in patients with end-stage renal disease (ESRD) [1]. Coronary artery calcification is observed in chronic kidney disease (CKD) patients without undergoing dialysis and is progressed throughout dialysis [2, 3]. Consequently, stage 5 CKD patients at the initiation of renal replacement therapy (RRT) may already be a high-risk group for coronary artery disease (CAD) and the cardiac risk of these patients needs to be assessed accordingly. Despite a couple of reports on the high prevalence of coronary artery stenosis (CAS) in such patients with coronary angiography [4, 5], it is not generally accepted to perform invasive diagnostic procedure routinely in asymptomatic patients. Evaluation of CAD in CKD patients has been generally taken by noninvasive imaging techniques such as stress echocardiography [6] and single-photon emission computed tomography (SPECT) [7]. However, these examinations have certain limitations including high false-positive rate, misinterpretation of a hidden myocardial ischemia and/or infarction, and high prevalence of electrolyte disorders. Accordingly, more noninvasive

and available tools are introduced to evaluate CAD in CKD patients and new methods such as electron beam computed tomography (EBCT) and multidetector computed tomography (MDCT) are being raised as a modality for noninvasive coronary imaging. However, EBCT is not widely used due to its costs and MDCT is more widely accepted due to its high accuracy. The purpose of this study is to evaluate the prevalence of CAS by MDCT and the usefulness of MDCT in predicting cardiac disease in asymptomatic stage 5 CKD patients at initiation of RRT.

2. Materials and Methods

2.1. Subjects and Study Design. We enrolled 74 consecutive patients (46 male, 28 female; mean age 56.5 ± 13.8 years; range 24–80 years) who started RRT in the dialysis unit of Severance Hospital, College of Medicine. Exclusion criteria included a history of angina or acute myocardial infarction, a history of malignancy, previous allergic reactions to iodine contrast media, previous percutaneous transluminal coronary stent placement, and previous bypass surgery. The study protocol was approved by the Institutional Review Board of Yonsei University Hospital, and all patients gave written informed consent.

Medical charts were reviewed for clinical history and medications. MDCT and echocardiography were performed on all patients within 7 days after the initiation of RRT, and coronary angiography was recommended for those who showed luminal diameter narrowing of >50% of any major coronary arteries. Fasting blood samples were analyzed for total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, plasma homocysteine, plasma fibrinogen, free fatty acid, high sensitivity C-reactive protein (hsCRP), and lipoprotein (a).

Cardiac events were defined as nonfatal angina pectoris or myocardial infarction, heart failure requiring hospitalization, and cardiac death. Unstable angina and acute myocardial infarction were diagnosed by the presence of typical angina symptoms, ischemic change or QRS change on ECG, and elevated serum cardiac enzyme levels. Heart failure was diagnosed with typical symptoms such as dyspnea, shortness of breath, or raised jugular venous pressure with systolic or diastolic dysfunction by echocardiography which is in accordance with guideline from European Society of Cardiology [8]. Cerebrovascular disease (transient ischemic attack, cerebral infarction, or cerebral hemorrhage) was confirmed both by typical symptoms with physical findings and by computed tomography (CT) or magnetic resonance imaging (MRI). Peripheral vascular disease was diagnosed when the patient had typical symptoms, abnormal ankle brachial pressure index (ABPI), positive CT or CT angiography findings, or peripheral artery stenosis confirmed by catheterization. Cardiac death was defined as death with documentation of a significant arrhythmia, cardiac arrest, or death attributable to congestive heart failure or myocardial infarction and sudden death. Elective follow-up revascularization procedures were not considered to be cardiac events.

2.2. MDCT Protocol. All computed tomography angiographies (CTAs) were taken by 64-MDCT (Somatom Sensation 64, Siemens, Germany). Heart rate of each patient was checked before CT scan and in patients with more than 65 beat per minute (bpm), 100 mg of Metoprolol (Selokeen, AstraZeneca Pharmaceutics, UK) was administered. After 1-hour administration of Metoprolol, heart rate was rechecked. Images for coronary calcium score were taken before contrast media injection, and scan range was from tracheobronchial bifurcation to diaphragm. Parameters of coronary calcium scan were 120 Kvp, 33 mAs, slice thickness 0.6 mm, and feed 18 mm. The protocol of CTA had scan parameters as follows: 120 Kvp, 500 mA, pitch 0.2, slice thickness 0.75 mm, collimation 0.6 mm, and gantry rotation time 0.33 sec. All CTAs were taken with a single-breath hold (10–13 s), 20 G needle through right antecubital or right wrist venous route, two kinds of nonionic water-soluble tri-iodinated contrast media (Ultravist 300 mg I/mL, Shering, Germany, and Omnipaque 300 mg I/mL, Amersham Health, Norway), and test bolus method. At first, test bolus images were taken using contrast media 10 cc with 4 cc/sec injection flow rate. Housefield unit (HU) of ascending aorta was analyzed by time-density calculation program (DynEva, Siemens, Germany). The amount of contrast media and normal saline was calculated according to cardiac scan time of each CTA with injection flow rate 4 cc/sec (contrast media) and 5 cc/sec (normal saline).

Every coronary artery was analyzed by two methods, segment and diameter. Segmental analysis was according to the 15-segment American Heart Association model of the coronary tree. In addition to the segmental analysis, if the artery showed diameter less than 1.5 mm, it was grouped as difficult to assessment.

Coronary calcium score and coronary stenosis were analyzed in all CTA. Calcium score was estimated using CAC-analysis software (Cascore, Siemens, Germany) by the Agatston score system [9] with minimal level of 130 HU and every lesion was sorted out according to its score as up to 100, 101 to 400, 401 to 999, and 1000 or more.

Degree of coronary stenosis was divided as insignificant or significant stenosis. Criterion for significant luminal narrowing was defined as over 50% of luminal narrowing by diameter compared to those of normal portions of stenotic coronary arteries, and criteria of normal portions were proximal or distal part of stenotic lesions. All radiologic studies were interpreted independently by 2 experienced radiologists without knowledge of alternate result or clinical parameter.

2.3. Statistical Analysis. All values are expressed as the means ± standard deviation (SD). To compare differences between the significant coronary stenosis group and nonsignificant stenosis group, independent t-test was applied. Multiple linear regression analysis was used to evaluate independent predictors of coronary artery stenosis (CAS) and coronary artery calcification score (CACS). To evaluate independent predictors for adverse cardiac outcomes, multivariate Cox proportional hazard model was used. Hazard ratios (HR) are presented with 95% confidence intervals in

parentheses. Values of $P < 0.05$ were considered to indicate statistical significance. Statistical analysis was performed using SPSS for Windows Ver. 19.0 (SPSS, Inc., Chicago, IL, USA).

3. Results

3.1. Baseline Characteristics and Biochemical Data. The baseline characteristics of patients in present study are summarized in Table 1. Sixty-two percent of the study subjects were males. Their ages ranged from 24 to 80 years (mean age 56.5 ± 13.8 years). Thirty-eight (51.4%) patients had diabetes. Thirty-eight patients (51.4%) were started on HD, and 36 patients (48.6%) received CAPD. Twenty patients (27.0%) were smokers. Sixty-two (83.8%) patients received angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers. Thirty-three (44.6%) patients received statin treatment and 25 (33.8%) patients took calcium-based phosphate-binding agents. The mean CACS was 144.1 ± 286.5 mm^3, ranging from 0 to 1644 mm^3. Twenty-nine patients of 74 patients (39.1%) had no calcium deposition in their coronary arteries.

Patients were stratified into two groups according to CACS and CAS, no CACS and no CAS (CACS < 21.4 and CAS < 50%) versus CACS or CAS (≥21.4 or CAS ≥ 50%). The group with CACS or CAS showed statistically higher age ($P < 0.01$), the prevalence of diabetes ($P < 0.05$), and serum uric acid level ($P < 0.01$). No significant differences were observed in any other variables across the two groups (Table 2). A total of 24 of the 74 patients (32.4%) showed coronary artery stenosis. Seventeen of the 24 patients (70.8%) with CAS had diabetes. In the group with diabetes, the prevalence of CAS was 44.7%, while that in the group without diabetes was 19.4%. The prevalence of CAS in patients with diabetes was significantly higher than that in patients without diabetes ($P < 0.05$). Thirteen out of the 24 patients (54.1%) with severe stenosis of coronary artery (>50%) agreed to undergo coronary angiography. Eleven out of thirteen patients were the patients with diabetes and two patients were the patients without diabetes. Of these 13 patients, 6 (46.2%) had single-vessel disease, two (15.4%) had two-vessel disease, and five (38.4%) had triple-vessel disease on MDCT (Table 3).

3.2. Independent Predictors of Coronary Artery Stenosis and Coronary Artery Calcium Score in Asymptomatic Patients Starting Dialysis. In univariate analysis, age (hazard ratio (HR) 1.092; 95% confidence interval CI 1.043–1.144; $P < 0.01$), the presence of diabetes (HR 0.330; 95% CI 0.128–0.854; $P < 0.05$), CACS (HR 1.281; 95% CI 1.085–1.514; $P < 0.01$), uric acid levels (HR 2.090; 95% CI 1.359–3.215; $P < 0.01$), and LDL ($\beta = 0.259$, $P < 0.05$) were associated with CACS and CAS. Among these variables, age ($\beta = 0.483$, $P < 0.01$) and uric acid levels ($\beta = 0.357$, $P < 0.01$) were independently associated with CACS and CAS in a multivariate linear regression model (Table 4).

3.3. Prediction of Cardiac Events. In the univariate Cox analysis, age, the presence of diabetes, serum uric acid levels, serum LDL level, and the presence of CAS and CACS predicted cardiac events. Age (HR 1.064; 95% CI 1.018–1.112; $P < 0.01$) and the presence of CAS and CACS (HR 0.216; 95% CI 0.051–0.916) were independent risk factors in the multivariate Cox analysis (Table 5).

Table 1: Baseline characteristics and biochemical data.

	All patients ($n = 74$)
Age (years)	56.5 ± 13.8 (24–80)
Sex (male : female)	46 : 28
Diabetes mellitus, *n* (%)	38 (51.4)
SBP (mmHg)	140.6 ± 19.5 (100–195)
DBP (mmHg)	78.1 ± 12.0 (50–120)
Hb (g/dL)	8.6 ± 1.5 (4.0–13.1)
Calcium (mg/dL)	8.3 ± 1.1 (5.5–12.3)
Phosphate (mg/dL)	5.3 ± 1.5 (1.8–11.2)
iPTH (pg/mL)	163.2 ± 124.4 (5.7–534.9)
hsCRP (mg/L)	10.1 ± 19.0 (0.15–130.0)
Albumin (g/dL)	3.4 ± 0.6 (2.2–4.6)
Total cholesterol (mg/dL)	174.3 ± 48.6 (77–439)
HDL-C (mg/dL)	39.2 ± 10.7 (20.0–71.0)
LDL-C (mg/dL)	109.6 ± 43.7 (35.8–314.8)
Triglyceride (mg/dL)	130.2 ± 55.7 (39–351)
Free fatty acid (uEq/L)	297.2 ± 199.3 (22–971)
Lipoprotein(a) (mg/dL)	51.4 ± 50.6 (0.7–299)
Fibrinogen (mg/dL)	474.3 ± 133.8 (264–958)
PAI-1	16.7 ± 10.0 (6.7–51.3)
Homocysteine (umol/L)	20.5 ± 14.5 (5.4–124.4)
EF (%)	61.3 ± 10.0 (28–78)
LVMI	35.5 ± 13.5 (13.7–78.1)
CACS	144.1 ± 286.5 (0–1644)
Cause of ESRD, *n* (%)	
DM nephropathy	41 (55.4%)
Hypertensive nephropathy	19 (25.6%)
Chronic Glomerulonephritis	8 (10.8%)
Etc	4
unknown	2

All values are expressed as mean ± SD; SBP: systolic blood pressure; DBP: diastolic blood pressure; Hb: hemoglobin; iPTH: intact parathyroid intact hormone; hsCRP: high sensitivity C-reactive protein; HDL: high density lipoprotein; LDL: low density lipoprotein; PAI-1: plasminogen activator inhibitor-1; EF: ejection fraction; LVMI: left ventricular mass index; CACS: coronary artery calcium score.

4. Discussion

Due to several limitation of coronary angiography (CAG), there has been a constant effort to replace coronary angiography with noninvasive apparatus. Single-photon emission computed tomography (SPECT) is a noninvasive pharmacologic stress test which is useful in debilitated patients, such as dialysis patients [10]. However, SPECT overlooks patients with single vessel disease, balanced multivessel disease with global ischemia, and collaterals that prevent detection of different flow [11]. Electron beam computed tomography (EBCT) was considered as a potential screening method

Table 2: Basic characteristics of the two groups according to CACS and CAS by MDCT.

	No CACS/CAS (n = 33)	CACS or CAS (n = 41)	P value
Age (years)	49.0 ± 14.2	62.5 ± 10.2	<0.01
Sex (male : female)	20 : 13	26 : 15	NS
Diabetes mellitus, n (%)	12 (36.3%)	26 (63.4%)	<0.05
SBP (mmHg)	140.3 ± 21.9	140.8 ± 17.6	NS
DBP (mmHg)	79.7 ± 12.8	76.6 ± 11.4	NS
Hb (g/dL)	8.5 ± 1.8	8.8 ± 1.3	NS
Calcium (mg/dL)	8.2 ± 1.1	8.3 ± 1.2	NS
Phosphate (mg/dL)	5.6 ± 1.8	5.0 ± 1.2	NS
iPTH (pg/mL)	184.0 ± 137.9	145.9 ± 110.9	NS
Uric acid	6.2 ± 1.4	7.5 ± 1.2	<0.01
hsCRP (mg/L)	10.5 ± 25.0	9.6 ± 13.4	NS
Albumin (g/dL)	3.4 ± 0.7	3.4 ± 0.5	NS
TC (mg/dL)	167.5 ± 34.9	179.7 ± 57.0	NS
HDL-C (mg/dL)	42.0 ± 12.3	37.2 ± 8.9	NS
LDL-C (mg/dL)	99.0 ± 31.6	117.4 ± 49.6	NS
Triglyceride (mg/dL)	124.3 ± 48.7	134.8 ± 60.9	NS
Free fatty acid (uEq/L)	299.3 ± 234.5	295.5 ± 169.9	NS
Lipoprotein(a) (mg/dL)	55.4 ± 47.3	48.3 ± 53.3	NS
Fibrinogen (mg/dL)	481.7 ± 130.5	468.4 ± 138.0	NS
PAI-1	15.8 ± 7.6	17.2 ± 11.4	NS
Homocysteine (umol/L)	22.1 ± 20.9	19.2 ± 6.6	NS
EF (%)	61.3 ± 12.7	61.4 ± 7.8	NS
LVMI	33.1 ± 9.0	36.9 ± 15.7	NS

All values are expressed as mean ± SD; SBP: systolic blood pressure; DBP: diastolic blood pressure; Hb: hemoglobin; iPTH: intact parathyroid intact hormone; hsCRP: high sensitivity C-reactive protein; HDL: high density lipoprotein; LDL: low density lipoprotein; PAI-1: plasminogen activator inhibitor-1; EF: ejection fraction; LVMI: left ventricular mass index; CACS: coronary artery calcium score; NS: not significant.

by several groups [12, 13]. But, due to its slow scanning rate, EBCT has led to frequent artifact and low resolution, which led to inaccurate assessment of CAS [14]. Recently, 64-channel MDCT has emerged as a strong potential screening method. MDCT is superior to other apparatus, because MDCT shows reduced cardiac motion artifact and higher resolution and needs less amount of dye infusion which is crucial in CKD patients.

Table 3: Prevalence of CAS by MDCT among 74 asymptomatic CKD patients.

		DM (n = 38)	Non-DM (n = 36)	PCI (n = 13)
CAS positive, n (%)	24 (32.1)	17	7	13
One vessel, n (%)	15 (62.5)	9	6	6
Two vessels, n (%)	3 (12.5)	1	2	2
Three vessels, n (%)	6 (25.0)	5	1	5

Table 4: Multiple linear regressions of factors associated with CAS and CACS in CKD patients at the start of dialysis.

Variables	Univariate analysis		Multivariate analysis	
	β	P value	β	P value
Age	0.488	<0.01	0.401	<0.01
diabetes	0.269	<0.05	0.153	NS
CACS	0.452	<0.01	0.152	NS
Uric acid	0.436	<0.01	3.071	<0.05
LDL	0.209	NS	—	—
EF	0.007	NS	—	—
SBP	0.012	NS	—	—
hsCRP	0.025	NS	—	—

CACS: coronary artery calcium score; LDL: low density lipoprotein; EF: ejection fraction; SBP: systolic blood pressure; hsCRP: high sensitivity C-reactive protein; NS: not significant.

Table 5: Cox regression models in CKD patients at the start of dialysis.

	HR (95% CI)	P value
Age	1.064 (1.018~1.112)	<0.01
The presence of diabetes	0.469 (0.184~1.196)	NS
SBP	1.009 (0.981~1.038)	NS
Uric acid	0.726 (0.515~1.023)	NS
LDL	0.987 (0.972~1.001)	NS
CACS + CAS	0.216 (0.051~0.916)	<0.05

SBP: systolic blood pressure; LDL: low density lipoprotein; CACS: coronary artery calcium score; CAS: coronary artery stenosis; NS: not significant.

In this study, we have demonstrated that (1) coronary artery stenosis (CAS) is highly prevalent in asymptomatic CKD patients at the start of renal replacement therapy, (2) age and serum uric acid level are independent risk factors for CAS and CACS in MDCT, and (3) CACS and CAS on MDCT are useful in predicting cardiac events in these patients.

Generally, the prevalence of significant CAS (10%) among dialysis patients was believed not to be different from that in the general population (5~10%) [8, 15]. However, many other recent reports have contradicted this theory and have shown a high prevalence of CAS in patients who were receiving dialysis treatment [16]. Additionally, there have been a few reports about the prevalence of CAS at the initiation of dialysis therapy [4, 5, 16]. Ohtake et al. reported that 53.3% patients of asymptomatic CKD patients who underwent

coronary angiography showed significant CAS [5]. In this study, the prevalence of CAS was as high as 32% but relatively low compared to a previous study by Ohtake et al. The discrepancy might be due to several reasons. Selection bias from a small sample size and a difference in ethnicity may have been attributed to such a difference. And MDCT is a less sensitive method compared to coronary angiography. However the strict exclusion criteria should have excluded possible subclinical ischemic heart disease.

Interestingly, CAS was not affected by serum Ca, P, and PTH levels which have been believed to have grave influences on calcification pathophysiology in ESRD patients. Thus, we can assume that unknown underlying risks other than Ca or P levels seem to be responsible, and certain inflammatory process may be involved. Further research is needed regarding this aspect. Our study also shows that conventional risk factors for atherosclerosis such as hypertension or hyperlipidemia did not differ between the two groups. As seen in several recent studies, our study shows that coronary artery calcification in ESRD patients can be affected by uric acid level. Elevated serum uric acid level can result in coronary calcification and eventually coronary artery stenosis through inflammatory activation, metabolic disorders, and calcium deposition [17–21].

The patients with both CACS and CAS were at higher risk for cardiovascular complication compared to those without any of them. Thus, MDCT, which can assess both parameters simultaneous, is a very useful, noninvasive tool in predicting cardiac disease in CKD patients.

However, this study has several limitations. First, this study is a single-center study with a small number of patients. Larger multicenter studies will be essential in examining MDCT for the diagnosis of coronary artery stenosis. Second, no head-to-head comparison was done with functional tests such as SPECT. Third, coronary angiography was not performed on patients whose MDCT results were negative because it was considered unethical. Therefore false-negative MDCT results were not evaluated.

In conclusion, nearly 30% of asymptomatic ESRD patients who start RRT have significant CAS. Thus, MDCT of the coronary arteries can be a useful screening method in predicting cardiovascular events in ESRD patients.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Jung Eun Lee and Yong Kyu Lee have equally contributed to this study.

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Review Article

Oral Anticoagulant Therapy in Patients Receiving Haemodialysis: Is It Time to Abandon It?

Marek Saracyn, Dorota Brodowska-Kania, and Stanisław Niemczyk

Department of Internal Diseases, Nephrology and Dialysis, Military Institute of Medicine, Szaserów Street 128, 04-141 Warsaw, Poland

Correspondence should be addressed to Marek Saracyn; msaracyn@interia.pl

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Oral anticoagulant (OAC) therapy in haemodialysis patients causes a great deal of controversy. This is because a number of pro- and anticoagulant factors play an important role in end-stage renal failure due to the nature of the disease itself. In these conditions, the pharmacokinetic and pharmacodynamic properties of the OACs used change as well. In the case of the treatment of venous thromboembolism, the only remaining option is OAC treatment according to regimens used for the general population. Prevention of HD vascular access thrombosis with the use of OACs is not very effective and can be dangerous. However, OAC treatment in patients with atrial fibrillation in dialysis population may be associated with an increase in the incidence of stroke and mortality. Doubts should be dispelled by prospective, randomised studies; at the moment, there is no justification for routine use of OACs in the above-mentioned indications. In selected cases of OAC therapy in this group of patients, it is absolutely necessary to control and monitor the applied treatment thoroughly. Indications for the use of OACs in patients with end-stage renal disease, including haemodialysis patients, should be currently limited.

1. Introduction

Chronic kidney disease (CKD) constitutes an increasingly serious challenge for modern medicine, both in its strictly clinical aspect and in the epidemiological one. According to different but essentially consistent estimates, it is assumed that its various stages currently affect more than 600 million people worldwide, including 10 million patients with its end stage, and 2 million patients undergoing various forms of renal replacement therapy. The high incidence and morbidity in the terminal stages of CKD are also associated with a high mortality rate, which is almost 19% of all patients undergoing different forms of dialysis treatment [1]. The most common causes of death in this population of patients include cardiovascular diseases (CVDs) (39%), infections (12%), stroke (10.3%), and neoplastic diseases (10%) [2]. The high epidemiological indices result from both the aging of the population and other concomitant diseases (such as cardiovascular diseases, diabetes, and arterial hypertension) increasingly and commonly occurring also in this group of patients. Epidemiological data fully justify the statement that CKD has become a serious social issue and, like the above-mentioned conditions, another lifestyle disease.

As the incidence and prevalence of CKD, and its end stages in particular, increase, the number of patients undergoing various forms of renal replacement therapy also constantly increases. Of the three basic treatment methods, haemodialysis (HD) therapy is the one that is most commonly applied. This is because, according to global data, more than 68% of patients requiring renal replacement therapy undergo haemodialysis; patients after renal transplant account for approximately 23% of the discussed population, while patients treated with peritoneal dialysis constitute less than 9% [3]. Prognoses for the next few years suggest a further increase in the number of patients requiring different forms of renal replacement therapy, including patients receiving haemodialysis, especially among patients with diabetes, arterial hypertension as well as the elderly ones [4].

In recent years, the indications for treatment with oral anticoagulants (OACs) as well as their use have increased significantly [5]. This phenomenon included both the entire population of patients with CKD and patients receiving

Table 1: Factors conducive to coagulation disorders in patients with end-stage renal disease and receiving haemodialysis [8–13].

Factors conducive to bleeding events	Factors conducive to thrombosis
Directly	
Platelet adhesion disorders—decreased activity of von Willebrand factor and receptor GPIb, increased release of PGI_2, NO Platelet aggregation disorders—decreased activity of GPIIb/IIIa receptor, impaired binding of fibrinogen to platelets Platelet secretion disorders—decreased production of thromboxane A_2, serotonin and ADP, decreased release of β-thromboglobulin, and impaired Ca^{++} mobilization Reduced number and volume of platelets	Accelerated atherosclerotic processes, damaged endothelium Defective GPIb expression on the surface of platelets Disorders of protein C metabolism, decreased concentration of protein C and antithrombin III Elevated concentrations of plasminogen activator inhibitor-1 (PAI-1)
Indirectly	
Anaemia—altered rheological features of blood, impaired platelet aggregation Uraemic toxins—for example, PTH Medications—antiplatelet, anticoagulant, cephalosporins, antitubercular, inhibitors of lipid absorption, NSAIDs Concomitant diseases—for example, affecting the gastrointestinal tract Invasive procedures—cannulations, biopsies, vascular access	

GP: glycoprotein, PGI_2: prostacyclin, NO: nitric oxide, ADP: adenosine diphosphate, Ca: calcium ions, PTH: parathormone, NSAIDs: non-steroidal anti-inflammatory drugs.

haemodialysis [6]. The continuously growing population of patients receiving haemodialysis as a result of the increasing prevalence of the aforementioned lifestyle diseases or social and demographic factors associated with them has an undoubted impact on this fact. Attempts to find new applications for OACs in this group of patients are, however, not less important. Although they are based on a number of prospective, randomised studies in the general population, there are no such studies in the group of patients receiving haemodialysis [7]. Attempts to apply the results of studies carried out in the general population, from which patients with end-stage renal failure are usually excluded to begin with, to patients receiving haemodialysis are not only unjustified but sometimes have downright negative influence on the effectiveness of treatment and patients' safety.

2. Chronic Kidney Disease and Haemostasis Disorders

As renal failure progresses, increasingly significant disturbances occur in the process of blood coagulation. At the initial stages of CKD, mostly as a result of disorders of the plasma coagulation system and fibrinolysis (e.g., decreased levels of protein C and antithrombin III, elevated concentrations of fibrinogen, von Willebrand factor, factor VIII, elevated concentration of plasminogen activator inhibitor-1 (PAI-1), decreased concentration of tissue plasminogen activator (t-PA)), prothrombotic processes, clinically expressed as hypercoagulation, dominate [8, 9]. As glomerular filtration rate (GFR) decreases and renal failure progresses, uraemic bleeding diathesis, characteristic of end-stage renal failure and patients during dialysis therapy, worsens. At the end stages of CKD, the accumulating uraemic toxins, both low-molecular-weight (e.g., urea, phenol and guanidinosuccinic acid) and medium-molecular-weight ones (e.g., RGD polypeptides), affect mostly platelet function, inhibiting their adhesion and aggregation and releasing platelet factors, such as serotonin or thromboxane A_2 [10, 11]. These phenomena mostly lead to platelet haemostasis disorders. Uraemic toxins and proinflammatory cytokines, frequently co-occurring lipid disorders or arterial hypertension damage endothelium and in this way disrupt also vascular haemostasis. As a result of their stimulation, endothelial cells produce large amounts of prostacyclin (PGI_2) and nitric oxide (NO) [12]. The former is a strong inhibitor of platelet aggregation and the latter of platelet adhesion. Their elevated concentrations, therefore, increase the existing haemorrhagic diathesis.

A clear bleeding tendency does not exclude, of course, a simultaneous state of increased prothrombotic susceptibility even in the same patient. The peculiar competition between these two antagonistic systems is presented in Table 1, which includes factors that occur as renal failure progresses, predisposing the patient to bleeding events and, on the other hand, to the formation of thrombi [13]. The factors conducive to bleeding mentioned in the table, as we can see, mostly disrupt platelet haemostasis; they disrupt vascular haemostasis to a lesser extent, mainly those that do not take part in the process of coagulation directly. On the other hand, prothrombotic factors include, apart from those affecting plasma haemostasis, first and foremost, the state of endothelium and accelerated atherosclerotic processes inextricably linked with end-stage renal failure [14]. Most frequently, this dynamic equilibrium is slightly shifted towards haemorrhagic diathesis, which is suggested by the clinical characteristics of the haemodialysed patient; the results of his or her additional tests usually increased bleeding time with usually normal APTT and INR. This state of equilibrium is, however, extremely unstable and the slightest additional factor affecting the processes of blood coagulation/fibrinolysis shifts it to either of the sides.

3. Chronic Kidney Disease and Oral Anticoagulant Treatment

The applied medications are a factor which frequently and significantly disturbs the above-described equilibrium. Vitamin K antagonists are still the most commonly used oral anticoagulant medications (incidentally, the erroneous name "antagonists" has been adopted, though they do not have antagonist effects on vitamin K, only inhibitory ones, so, to be precise, they are its inhibitors). The first medicine from this group was dicoumarol, isolated by Karl Link at the University of Wisconsin in 1941 [15]. However, they really started to be commonly used in 1950, when a more effective and bioavailable medicine was introduced—warfarin [16]. Their mechanism of action consists in inhibiting the activity of the vitamin K reductase complex, which makes the carboxylation of the residues of glutamic acid in the N-terminal fragments of different proteins impossible. This way, the activity of four key factors of the blood coagulation system, factors II, VII, IX, X, is inhibited [17]. It is a strong anticoagulant activity, because key factors both to the auxiliary endogenous pathway and, first and foremost, to the exogenous pathway, fundamental to the coagulation system, are inhibited. At therapeutic doses, the inhibition of the aforementioned coagulation factors should range from 30 to 50% [18]. This very narrow therapeutic window can, on the one hand, result in the ineffectiveness of treatment, and, on the other, in frequent serious adverse reactions, mostly severe bleeding events. OACs in the blood strongly bind to albumins, but the active free fraction fluctuates in a fairly wide range (from 0.5 to 3%) [19]. Elimination occurs via hepatic metabolism by various cytochromes for each of the isomers of the active ingredient of the medicine; its inactive metabolites are excreted by the kidneys [20]. The half-life is from 18 to 70 hours [21]. It would seem that the hepatic metabolism of coumarin derivatives justifies the use of these medications in patients with end-stage renal failure and receiving haemodialysis following the same rules and at the same doses as in the general population. However, the above-described pharmacodynamic and pharmacokinetic properties make treatment with OACs in patients receiving haemodialysis extremely difficult. The therapeutic window becomes even narrower, the concentrations of the free fraction of the medicine fluctuate even more, depending on changes in peridialytic volaemia, and the amount of fraction bound to albumins decreases as a result of malnutrition or patient cachexia [22]. Moreover, there are a number of known nutritional limitations associated with using OACs, restrictions in the treatment of elderly individuals (slower hepatic metabolism) or their numerous interactions with other medicines (especially antiplatelet ones) [23]. In the conditions of advanced CKD, the impact of all these factors is much greater [24].

Maruyama et al. [25], evaluating INR and albumin values before and after HD procedures, demonstrated a significant decrease in the value of INR following HD in comparison with its levels determined prior to HD, while albumin concentrations increased significantly following the procedure in relation to values prior to dialysis. What is more, the authors also showed a significant, negative correlation between both of the above-described parameters during haemodialysis. Abe et al. [26], apart from similar changes regarding INR and proteins during HD, demonstrated a significant rise in warfarin concentrations post-HD versus pre-HD, both with respect to the more potent S-isomer, and the weaker R-isomer. Interestingly, multifactorial analysis revealed the strongest links between peridialytic values of INR and albumin concentrations. The ability of blood proteins, especially albumin, to bind warfarin is very strong, and therefore changes in their concentration during HD result in significant changes in the concentrations of the active ingredient of the medicine, INR, and, consequently, treatment complications. In a retrospective study of 142 haemodialysed patients who received acenocoumarol for typical indications at a dose of 1 mg a day for a year, Gompou et al. [27] demonstrated that 30% of the INR values determined at this time were below target values, 37% were in the therapeutic range, and nearly 33% exceeded therapeutic values. Admittedly, there is no information regarding the severe complications of such treatment in the report, but the fact that OACs were overdosed in 1/3 of the cases seems alarming.

So far, among patients with end-stage renal failure and patients receiving haemodialysis, no prospective, randomised studies evaluating the effectiveness and safety of OACs have been conducted. In spite of that, in this group of patients, these medications are attempted to be used according to their typical indications, taking, however, special precautions in using them due to the considerably increased risk of adverse reactions [28]. Indeed, the literature includes a number of reports of such reactions, including very severe and fatal ones [29–31]. It is also interesting to read the official contraindications for the use of OACs approved in registration documents by regulatory bodies authorised to do that [32] (e.g., the FDA) (Table 2). On the list presented in Table 2, almost every other item (e.g., 1, 3, 5, 7, and the last one) refers to patients with end-stage renal failure, including patients receiving haemodialysis. Admittedly, chronic renal failure is not explicitly listed, but the items enumerated above refer directly to it. In any case, most of them overlap with factors predisposing to bleeding events in patients with end-stage renal failure and receiving haemodialysis as described earlier (Table 1). As we can see, platelet function disorders, other thrombocytopathies, the risk of gastrointestinal bleeding, urinary tract bleeding, falls, or lack of adequate collaboration in this specific treatment are especially significant in this respect. After all, it is a picture of patients that we see in nephrology units or at dialysis centres on a daily basis. Is, therefore, OAC treatment according to its typical indications in patients with end-stage CKD or in those receiving haemodialysis an off-label use? an experimental one? and therefore, is it justified? these questions remain open.

4. OACs in Patients with End-Stage Renal Disease in Clinical Practice

Attempts to use OACs in patients at the end stages of CKD and receiving haemodialysis encounter a number of difficulties. Practically all prospective, controlled, randomised

Table 2: Contraindications for the use of oral anticoagulants [32].

(i) **Increased risk of bleeding events—platelet function disorders, thrombocytopenia, von Willebrand disease, and haemophilia**
(ii) Recent intracranial bleeding. Conditions predisposing to intracranial bleeding—cerebral artery aneurysms
(iii) **Conditions predisposing to gastrointestinal, urinary, and respiratory tract bleeding**
(iv) Surgical procedures within the central nervous system or the eye
(v) **Increased risk of frequent falls—caused by a neurological or another condition**
(vi) Severe liver failure, cirrhosis
(vii) **Untreated or poorly controlled arterial hypertension**
(viii) Pregnancy
(ix) Infective endocarditis or pericardial effusion
(x) Hypersensitivity to the active substance or any of the excipients
(xi) **Dementia, psychoses, alcoholism, and other conditions in which compliance may not be satisfactory and when anticoagulant treatment cannot be safely administered**

End-stage renal-disease-associated items are bold.

studies, which evaluated the effectiveness and safety of OACs in the general population, carried out so far excluded patients with creatinine clearance <30 mL/min. Applying the results of these studies to the population with advanced renal failure should not therefore be automatic, because their simple use not only may prove to be ineffective in this group of patients, but, what is worse, may be dangerous to them as well.

4.1. OACs in the Treatment of Venous Thromboembolism in Patients with CKD. The prevalence of pulmonary embolism in the population of patients receiving haemodialysis is several times higher than its prevalence in the general population. The annual incidence of pulmonary embolism in this group of patients is approximately 15/100,000 versus 25/100,000 patients in the general population [33]. However, there are no evidence-based studies evaluating the use of OACs in this disease and in this population. The remaining option, therefore, is beginning treatment with unfractionated heparin, usually on an inpatient basis, then changing it over the next several days and continuing the OAC treatment while monitoring INR, which is the treatment accepted generally for the population without renal failure [34]. Due to the lack of relevant research, the length of therapy depending on the aetiology of the disease, the individual risk of thrombosis/bleeding events for a given patient and often the decision of the patient him- or herself regarding the applied OAC treatment remain to be evaluated. In the case of absolute contraindications for OACs, implantation of a filter in the inferior vena cava could be an alternative therapy, but there are no such studies for patients receiving haemodialysis in the available literature, and they are inconclusive even in the general population [35].

4.2. OACs in Preventing Thrombosis of Vascular Access for Haemodialysis. It is estimated that the causes of almost 1/3 of cases requiring hospitalisation among patients receiving haemodialysis are associated with vascular access failure [40]. The likelihood of the occurrence of vascular access failure due to thrombosis in over a year-long observation of patients receiving haemodialysis is approximately 15% in the case of autologous arteriovenous fistulae and two times higher in the case of vascular grafts [41]. It would therefore seem that OACs can be an effective treatment option in reducing this risk.

Several such prospective, controlled studies (some of which were even randomised) have been conducted, though on small groups of patients. Their results, however, proved to not be very encouraging. In a group of 75 patients receiving haemodialysis, OAC treatment, whose therapeutic target was INR 1.5–2.0, was found to be only slightly more effective in the prevention of thrombotic complications in comparison with the control group, in which OAC treatment was not initiated (66% versus 57%), but the recorded difference was not statistically significant [42]. What is more, in spite of the unchanging study protocol, the target INR values were achieved in only a half of the subjects. While serious bleeding events were not recorded, the target INR range was not high. In another randomised study on a group of 144 patients receiving haemodialysis, Colì et al. [43] used OACs with a little higher therapeutic range of INR (1.8–2.5). Statistically significant differences between the study group and the control group not treated with OACs were observed only after taking the time at which OAC treatment was initiated into consideration. In the group in which this treatment was initiated in the first 24 hours after the implantation of a vascular catheter, vascular complications were found in a little more than 10% of patients, in comparison with patients who received OACs after their first thrombotic event, where the proportion of complications was a little over 50%. In another study, carried out on a group of 63 patients receiving haemodialysis, the use of OACs, whose therapeutic aim was INR of 2.0-3.0, was proved to be significantly more effective in preventing thrombosis than in the group of patients not receiving such treatment [44]. However, when the results of the group treated with OACs were compared with the group in which acetylsalicylic acid at a dose of 325 mg/day was used, differences in the effectiveness regarding vascular access thrombosis were not observed. Serious bleeding events, which significantly more frequently occurred in the group receiving OACs, were the only significant difference between these groups.

Table 3: Mortality risk in haemodialysis patients with atrial fibrillation treated with warfarin.

Study	Population (n)	Period (y)	Mortality (HR)
Knoll et al. [36]	n—235 pts	3 years	HR—0.80 (95% CI 0.28–2.29, $P < 0.67$)
Chan et al. [37]	n—1671 pts	1 year	HR—1.10 (0.94–1.30)
Wizemann et al. [38]	n—17513 pts (AF—12.5%)	7 years	All ages: HR—1.16 (95% CI 1.08–1.25, $P < 0.001$) Age < 65: HR—1.29 (95% CI 0.45–3.68, $P < 0.63$) Age 65–75: HR—1.35 (95% CI 0.69–2.63, $P < 0.39$) Age > 75: HR—2.17 (95% CI 1.04–4.53, $P < 0.04$)
Chan et al. [39]	n—41425 pts	11 years	
	Warfarin—8.3%		HR—1.73 (95% CI 1.62–1.85)
	Clopidogrel—10%		HR—1.50 (95% CI 1.39–1.62)
	Acetylsalicylic acid—30.4%		HR—1.17 (95% CI 1.12–1.22)
	Acetylsalicylic acid and warfarin—8%		HR—1.11 (95% CI 1.03–1.86)

HR: hazard ratio, CI: confidence interval, n: number of patients.

How effective is, therefore, the application of OACs in this group of patients? As the few, not very reliable studies suggest, it, admittedly, increases with the increase in the target INR but at the price of significant adverse reactions in the form of serious bleeding events. Moreover, in the last of the cited studies, which confirmed such effectiveness, similar effectiveness was recorded with the use of acetylsalicylic acid, without severe complications. The results of the above studies and the opinions of experts in the area do not allow, therefore, a routine use of OACs due to the discussed indications [45]. This is because a target, safe INR range for this group of patients has not been established, the effectiveness of the medications is doubtful and the risk for the patient is high; furthermore, there are alternative methods that are no less effective and, as it appears, are safer [44].

4.3. OACs in the Prevention of Thromboembolic Complications Associated with Atrial Fibrillation. Atrial fibrillation (AF) is the most common cardiac dysrhythmia. It is estimated that it affects several percent of the population over the age of 65 and the proportion increases with age [46]. However, in the group of patients with end-stage renal failure, this proportion is much higher and reaches, according to various studies, from 10 to as high as 30% [47]. The annual mortality rate among these patients is approximately 25% in the general population and almost 30% in patients receiving haemodialysis [48]. The prevalence of stroke in patients with atrial fibrillation without renal failure is, on the other hand, close to that in patients receiving haemodialysis (17% versus 15%, resp.) [49, 50]. Similarly, studies evaluating the risk of stroke among patients receiving haemodialysis depending on the presence of AF or sinus rhythm are inconclusive. Some of them show a several-fold increase in the incidence of stroke in the group with AF, while others do not record such a correlation [50, 51]. These two factors, among other things, are probably responsible for the inconclusive results of studies evaluating the effectiveness and safety of OAC treatment due to AF in the group of patients with end-stage renal failure and patients receiving haemodialysis. The confusion in the literature regarding the plausibility and significance of the discussed issue is increased, however, mostly by the fact that there are simply no prospective, controlled, randomised studies in this group.

First, let us look at the impact of the use of OACs in this group of patients on the hard end-point, which is patient mortality (Table 3). Knoll et al. [36], carrying out a study on a group of 235 haemodialysed patients with AF receiving OACs, recorded a slightly lower mortality rate than that which characterised the control group, not receiving OACs, although not significant. Chan et al. [37], in a retrospective study conducted on more than 1,600 patients with AF receiving haemodialysis, showed that the use of warfarin in the prevention of thromboembolic events is not associated with all-cause mortality or an increase in the number of hospitalisations. In turn, Wizemann et al. [38] observed a clear increase in mortality rate in patients receiving warfarin for the same reasons as in haemodialysed ones, which was especially apparent in the older population (>75 years old). Another study confirmed the negative impact of OACs used for the same indications on the mortality rate in patients with end-stage renal failure in comparison with the control group, which did not receive such treatment [39].

Data regarding effectiveness in decreasing the risk of stroke in patients with AF receiving haemodialysis are also inconclusive. In one of the latest of such studies, Olesen et al. [52], in a group of more than 900 patients in whom warfarin was used in fewer than 20% of cases, observed for a period of 11 years and found a statistically significant decrease in the risk of the occurrence of stroke or another systemic thromboembolic event. However, in several other studies, such an effect was not observed; what is more, the effect of using OACs was decidedly negative. In the study cited above, Chan et al. [37] recorded a two times higher risk of stroke in the group treated with warfarin than in the control group not receiving OACs. Furthermore, there was an increase in the risk of both haemorrhagic and ischaemic stroke (HR 2.2 and 1.8, resp.). Similar results were presented by Wizemann

et al. [38] in a group of 3,245 patients participating in DOPPS I and DOPPS II (Dialysis Outcomes and Practice Patterns Study). In this study, the patients' age was the factor differentiating the risk. In the oldest group (>75 years old), warfarin treatment was associated with a significant, more than twofold, increase in the risk of stroke; in younger groups (65–75 and <65), the increase in the risk of stroke was evident but statistically insignificant. In another study, which covered 2,313 haemodialysed patients with newly diagnosed AF and treated with warfarin for the first time, Winkelmayer et al. [53] observed an over twofold increase in the risk of haemorrhagic stroke; such a relationship was not found in the case of ischaemic stroke.

The risk of adverse reactions, including severe bleeding events, during OAC treatment in patients receiving haemodialysis rises considerably. Previous studies, in which OACs were used for different indications, had already reported that [54]. In the case of the treatment of AF, the situation looks similar; most reports suggest a several-fold increase in this risk. The results of the study by Chan et al. [39] suggest a significant, almost threefold increase in the risk of severe bleeding events during OAC treatment in haemodialysed patients due to AF. In the same study, clopidogrel was associated with a more than 2.5-fold (higher) risk of significant haemorrhagic complications; what is interesting is that the use of acetylsalicylic acid also increased this risk, but not significantly. Holden et al. [55], in turn, observed an increase in such risk, which was more than threefold in the case of warfarin and over fourfold in the case of acetylsalicylic acid; the use of these medications in combination was associated with more than a sixfold increase in this risk. Other studies also suggested a significant risk of severe bleeding events associated with the use of OACs in the prevention of thromboembolic complications due to AF [52, 56].

Is, therefore, OAC treatment for the above indications in patients receiving haemodialysis effective and safe? Do the benefits of using OACs outweigh the risk of severe bleeding events in patients with end-stage renal failure?

All of the above study results should be treated cautiously. As we have mentioned, there are no large-scale, controlled, prospective, randomised studies here. Only on the basis of such studies would it be possible to present guidelines or recommendations regarding OAC treatment in this group of patients. Most of them are studies conducted on small groups, observational, retrospective groups; only a few of them were prospective, but not randomised. It is also difficult to perform a reliable meta-analysis, because the individual studies sometimes differ in their design, specific assumptions, methods of collecting data, or methods of analysis [37, 38, 53]. Decisions regarding the initiation of OAC treatment and the time when it occurred depended mostly on the patient's clinical data and the physician's experience. Some studies also excluded patients taking OACs or patients with AF that had developed before renal failure. All these circumstances make it necessary to evaluate these studies cautiously.

Moreover, let us look at two epidemiological issues [49–51]. The prevalence of stroke in patients with atrial fibrillation without renal failure, in comparison with that in patients receiving haemodialysis, turned out to be comparable in the above-cited studies. However, the evaluation of the risk of stroke in patients receiving haemodialysis depending on the presence of AF or sinus rhythm proved to be inconclusive. If, therefore, there is no such risk, what role are OACs supposed to play? Perhaps a significant portion of the causes of stroke in the group with end-stage renal failure are vascular ones and atherosclerosis, considerably accelerated in this group of patients? In this situation, OACs would not change such risk significantly.

In turn, the increase in the risk of death and the increase in the incidence of stroke in haemodialysed patients treated with OACs may be explained by two things. The first one is, of course, inappropriate management of anticoagulation, or rather the time during which the patient remains in the desired INR range. After all, its deviation towards higher or lower values is associated with an increase in morbidity or adverse reactions. On a daily basis, in nephrology units or dialysis centres, we can see how difficult it is to keep INR in such a therapeutic range in patients receiving haemodialysis. It is associated with the fact that chronic renal failure, and haemodialysis therapy to an even larger extent, are a significant and independent factors that may decrease the period in which the desired value of INR is maintained [57]. Anyway, the above-cited data regarding the increase in the risk of bleeding events during OAC treatment in patients receiving haemodialysis most likely result from the same cause. The described impact of vitamin K antagonists on the processes of vascular calcification and calciphylaxis is another noteworthy, potential factor. As a number of studies, both experimental and clinical, show, vitamin K inhibition, for example, by OACs, inhibits the activity of matrix Gla protein (MGP), an important protein, playing a preventive role in vascular calcification [58, 59]. OACs can therefore directly interfere and accelerate the process of vascular calcification, already increased in end-stage renal failure. Is it a causative factor, significantly raising the incidence of ischaemic stroke and mortality among haemodialysed patients receiving OACs? This question must be answered by future studies.

Patients with end-stage renal failure, including, above all, those who receive haemodialysis, are a group of patients with exceptionally many concomitant diseases [60]. Considerably accelerated atherosclerotic processes, vascular calcification, chronic inflammation, lipid disorders, and malnutrition are inherent characteristics of this population of patients. Can OACs have an impact on the risk of stroke in haemodialysed patients with AF in these conditions and with the existing vascular changes also within the central nervous system?—this Question remains open. However, the results of the cited studies do not allow us to use OACs routinely for these indications in this group of patients.

5. Conclusions

The population of patients with CKD, including patients receiving haemodialysis, keeps growing all over the world.

Table 4: Potential indications for oral anticoagulants in patients with end-stage renal disease and receiving haemodialysis.

(i) Status after prosthetic heart valve implantation
(ii) Antiphospholipid syndrome
(iii) Secondary prevention of severe thromboembolic events (for example, pulmonary embolism)
(iv) Atrial fibrillation with a high risk of stroke

However, OAC treatment in this group of patients, irrespective of its indications, causes a great deal of controversy. This is because a number of pro- and anticoagulant factors play an important role in end-stage renal failure due to the nature of the disease itself. In these conditions, the pharmacokinetic and, especially, pharmacodynamic properties of the OACs used change as well. All these factors make proper anticoagulation in these patients more difficult, and, most importantly, they decrease the time during which patients remain in the therapeutic range of INR. In the case of the treatment of venous thromboembolism, the only remaining option is OAC treatment according to regimens used for the general population, as there are no relevant studies concerning the group of patients receiving haemodialysis. Prevention of HD vascular access thrombosis with the use of OACs, according to the presented studies and experts' opinions, is not very effective and can additionally be very dangerous. However, OAC treatment in haemodialysed patients with AF in order to prevent thromboembolic events, according to some authors, is associated with an increase in the incidence of stroke and mortality.

Is the provocative question included in the title justified? Doubts should be dispelled by prospective, controlled, randomised studies; at the moment, there is no justification for routine use of OACs in the above-mentioned indications. In selected cases of OAC treatment in this group of patients, it is absolutely necessary to control and monitor the applied treatment thoroughly. According to the authors and the opinions already partially reported in the literature [45], indications for the use of OACs in patients with end-stage renal failure, including patients receiving haemodialysis, should be limited to those included in Table 4.

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Research Article

Aerobic Exercise Improves Signs of Restless Leg Syndrome in End Stage Renal Disease Patients Suffering Chronic Hemodialysis

Mojgan Mortazavi,[1] Babak Vahdatpour,[2] Aida Ghasempour,[3] Diana Taheri,[4] Shahrzad Shahidi,[1] Firouzeh Moeinzadeh,[5] Bahareh Dolatkhah,[6] and Shahaboddin Dolatkhah[3]

[1] *Isfahan Kidney Disease Research Center, Department of Nephrology, Isfahan University of Medical Sciences, Isfahan, Iran*
[2] *Department of Physical Medicine and Rehabilitation, Isfahan University of Medical Sciences, Isfahan, Iran*
[3] *Isfahan University of Medical Sciences, Isfahan, Iran*
[4] *Isfahan Kidney Disease Research Center, Department of Pathology, Isfahan University of Medical Sciences, Isfahan, Iran*
[5] *Department of Internal Medicine, Alzahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran*
[6] *Department of Animal Science, Isfahan University of Technology, Isfahan, Iran*

Correspondence should be addressed to Shahaboddin Dolatkhah; shahab_dolatkhah@yahoo.com

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Background. Restless leg syndrome (RLS) is one of the prevalent complaints of patients with end stage renal diseases suffering chronic hemodialysis. Although there are some known pharmacological managements for this syndrome, the adverse effect of drugs causes a limitation for using them. In this randomized clinical trial we aimed to find a nonpharmacological way to improve signs of restless leg syndrome and patients' quality of life. *Material and Methods*. Twenty-six patients were included in the study and divided into 2 groups of control and exercise. The exercise group used aerobic exercise during their hemodialysis for 16 weeks. The quality of life and severity of restless leg syndrome were assessed at the first week of study and final week. Data were analyzed using SPSS software. *Results*. The difference of means of RLS signs at the first week of study and final week was -5.5 ± 4.96 in exercise group and -0.53 ± 2.3 in control group. There was not any statistical difference between control group and exercise group in quality of life at the first week of study and final week. *Conclusions*. We suggest using aerobic exercise for improving signs of restless leg syndrome, but no evidence was found for its efficacy on patient's quality of life.

1. Introduction

Restless leg syndrome (RLS) is one of the most common complaints among end stage renal disease (ESRD) patients [1]. This syndrome is characterized by a strong urge in the legs and other extremities which force the patient to move during rest [2]. Previous studies estimated the prevalence of RLS between ESRD patients to be 20% to 57% [3–5]. Multiparity, older age, sedentary life style, obesity, and positive family history are factors associated with RLS outbreak [6, 7]. In about 40% of patients presenting with RLS, a family history of this syndrome could be seen, and a dominant pattern of inheritance is known about its heritage [8]. RLS may occur idiopathic or secondary to conditions such as iron deficiency, pregnancy, peripheral neuropathy, rheumatoid arthritis, intake of psychopharmacological drugs, diabetes, or chronic kidney disease [9–13]. RLS has also substantial influence on quality of life of patients. Anxiety and depressed feelings are mental problems affecting patients with RLS that are specially seen in men [2]; however, neurological examination of patients suffering from RLS may be normal, but abnormalities on polysomnographic studies containing periodic limb movement might be seen in about 80% of patients [8, 14]. There are some diagnostic features which suggest RLS

according to the international RLS study group (IRLSSG): (1) desire to move the extremities that is usually associated with paresthesias and/or dysesthesias, (2) motor restlessness, (3) worsening of symptoms particularly at rest, and (4) worsening of symptoms in the evening or night [15, 16].

Although there are not any known pathophysiological mechanisms to explain RLS, alleviation of symptoms with dopamine agonists (such as L-dopa) and worsening of symptoms with dopamine antagonists (such as metoclopramide) suggest that dopaminergic dysfunction in central nervous system may play an important role in the presence of symptoms [17, 18]. Secondary RLS in ESRD patients might be correlated with iron deficiency which has concurrence with anemia (due to lack of erythropoietin) [19] also in the absence of anemia in these patients [20, 21] and so iron treatment is an option to manage ESRD patients presenting RLS with anemia [22].

Although data suggesting effectiveness and safety of drugs for management of RLS are very limited [23]; the following drugs are assumed effective to decrease symptoms of RLS: levodopa, ropinirole, pramipexole, cabergoline, pergolide, and gabapentin [24, 25].

Lithium, selective serotonin reuptake inhibitors, and tricyclic antidepressant play a deteriorative role in RLS symptoms (related to their dopamine antagonists activity) [26].

Home short daily hemodialysis, as a nonpharmacological choice of therapy, is also associated with long-term improvement of RLS severity [27].

However, Aukerman et al. demonstrated the beneficial impact of exercise on the improvement of RLS severity and symptoms as a whole [28], but to the best of our knowledge there is only one published article on the effect of aerobic exercise on RLS symptoms between ESRD patients suffering chronic hemodialysis [29].

In this randomized clinical trial study we aimed to assess the effect of aerobic exercise on RLS severity and patients' quality of life during chronic hemodialysis.

2. Materials and Methods

Out of all patients undergone hemodialysis in Alzahra and Noor hospitals (two referral hospitals in Isfahan-center of Iran) with any etiology of renal failure, all patients were evaluated for RLS and according to inclusion criteria, 26 patients were enrolled in this randomized clinical trial. Inclusion criteria were hemodialysis for at least 3 months, sufficient dialysis for at least 3 times weekly, presence of RLS, ferritin (Fr) >100 ng/mL, and transferrin saturation rate (TSAT) >20%. Patients with the following disorders were excluded: musculoskeletal disorders which incapacitated them from physical activity, history of ischemic heart disease (recent myocardial infarction or unstable angina), any catabolic process such as malignancies, opportunistic infections, and infections needing antibiotic therapy during the last 3 months.

All of the participants (26 patients) were informed about the details of the experiment and then were randomly divided into control group (13 patients) and exercise group (13 patients). Patients in the exercise group pedaled the bicycle (Medi-bike made in Switzerland) 3 times a week for 16 weeks. Each time for exercise consisted of 30 minutes of continuous pedaling between hour 2 and 3 during dialysis. For prevention of cardiovascular disorders, the first 5 minutes was spent for warm-up by slow heartbeat which made the body ready for main exercise. After that the main exercise started and participants pedaled for 20 minutes, and finally 5 minutes of cool-down was performed to lower heartbeat. Exercise intensity was evaluated using Borg scale [30] and Borg scale of 10–12 applied to it.

Patients' blood pressure and heart rate were determined before and after dialysis and at hour 2 and 3 during dialysis. Systolic blood pressure more than 160 mmHg or diastolic blood pressure more than 110, chest pain, dyspnea, body temperature more than 37.8°C, cardiac arrhythmias, signs of insufficient tissue perfusion, and neurological signs such as vertigo or imbalance were criteria for interrupting exercise. These complications did not occur to any of the participants during the test.

Severity of RLS was evaluated using RLSQ questionnaire [31] at the beginning of the study and week 16. Quality of life was evaluated by using SF-63 [32] questionnaire at the beginning of the study and week 16. Finally, gathered data analyzed by SPSS-16 software (Chicago, IL, USA), dependent t-test, and independent t-test were used for comparing intragroup and intergroup data.

Table 1: Mean of restless leg syndrome scoring in both groups.

Group	Timing	
	Start of the experiment	At the end of experiment
Exercise	19.3 ± 3.8	13.9 ± 5.9
Control	22.8 ± 5.5	22.3 ± 4.6

3. Results

Out of all patients, 18 patients (69%) were males and 8 patients (31%) were females. Mean age of patients was 41.5 ± 12.1 as a whole, 32.3 ± 6.7 in exercise group and 47.1 ± 13.1 in control group.

Considering Table 1, scores of restless leg syndrome showed a descending pattern in exercise group during weeks of experiment, but no significant difference in control group was seen.

Difference of means between the first week of experiment and the final week was −5.5 ± 4.96 in exercise group and −0.53 ± 2.3 in control group. Comparing groups by using independent t-test showed significant statistical difference between them (P value = 0.003).

Assessment of quality of life indicated mean number of 118 ± 8.4 in control group and 141 ± 5.7 in exercise group at the first week of study. The final assessment of quality of life at the end of study showed mean number of 116 ± 8.32 in control group and 142 ± 6.1 in exercise group. The independent t-test did not show any statistical difference between groups (P value = 0.61).

4. Discussion

The goal of this study was to find a suitable non-pharmacological interaction for decreasing the severity of restless leg syndrome's signs in patients suffering chronic hemodialysis. However, prevalence of this syndrome is not rare in hemodialysis patients, but only 26 patients met our criteria to participate in the study and this issue was assumed as a limitation in our study. By our data, signs of restless leg syndrome significantly improved during aerobic exercise. Sakkas et al. had also suggested aerobic exercise as an appropriate management for restless leg syndrome in patients suffering chronic hemodialysis [29]. Although Sakkas et al. found an improving pattern for quality of life during weeks of exercise in patients with RLS [29], we did not find a significant impact of aerobic exercise on quality of life between patients with RLS using aerobic exercise and those in control group; perhaps with prolongation of study, the quality of life may improve. This discrepancy of findings may also come from other aspects of life influencing quality of life between our patients and patients in previous studies. Because of adverse effects of RLS on patients' life, it is really important to find suitable ways for alleviating their symptoms and improving quality of life between them. Future studies with more patients could clarify whether aerobic exercise has an improving effect on patients' quality of life.

We suggest doing aerobic exercise for improving signs of restless leg syndrome for patients suffering chronic hemodialysis, but more studies are recommended for evaluating the role of aerobic exercise to improve quality of life.

Conflict of Interests

The authors have no conflict of interests.

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Clinical Study

Carpal Tunnel Release Surgery and Venous Hypertension in Early Hemodialysis Patients without Amyloid Deposits

Ismail Kocyigit,[1] Aydin Unal,[1] Ahmet Guney,[2] Ertugrul Mavili,[3] Kemal Deniz,[4] Merva Kocyigit,[5] Murat Sipahioglu,[1] Eray Eroglu,[6] Bulent Tokgoz,[1] Ali Ihsan Gunal,[7] and Oktay Oymak[1]

[1] *Department of Nephrology, Erciyes University Medical Faculty, 38039 Kayseri, Turkey*
[2] *Department of Orthopedics and Traumatology, Erciyes University Medical Faculty, 38039 Kayseri, Turkey*
[3] *Department of Radiology, Erciyes University Medical Faculty, 38039 Kayseri, Turkey*
[4] *Department of Pathology, Erciyes University Medical Faculty, 38039 Kayseri, Turkey*
[5] *Department of Neurology, Erciyes University Medical Faculty, 38039 Kayseri, Turkey*
[6] *Department of Internal Medicine, Erciyes University Medical Faculty, 38039 Kayseri, Turkey*
[7] *Department of Nephrology, Kayseri Training and Research Hospital, 38010 Kayseri, Turkey*

Correspondence should be addressed to Ismail Kocyigit; iikocyigit@gmail.com

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Aim. Carpal tunnel syndrome (CTS) is one of the frequent problems of the patients who underwent hemodialysis (HD). The role of venous hypertension due to arteriovenous fistula (AVF) has not been clarified completely; therefore, we aimed to investigate the role of venous hypertension due to AVF in hemodialysis patients who had CTS. *Patients and Methods*. We included 12 patients who had been receiving HD treatment for less than 8 years and the newly diagnosed CTS patients with the same arm of AVF. All patients were diagnosed clinically and the results were confirmed by both nerve conduction studies and electromyography. Open carpal tunnel release surgery was performed on all of them. Venous pressure was measured in all patients before and after two weeks of surgery. *Results*. There were significant differences before and after the surgery with regard to pressures ($P > 0.05$). After the surgery, all carpal ligament specimens of the patients were not stained with Congo red for the presence of amyloid deposition. *Conclusion*. Increased venous pressure on the same arm with AVF could be responsible for CTS in hemodialysis patients. Carpal tunnel release surgery is the main treatment of this disease by reducing the compression on the nerve.

1. Introduction

Peripheral nerve entrapment is one of the common problems in patients with end stage renal disease, especially in those receiving hemodialysis. The most encountered form is median nerve entrapment entitled carpal tunnel syndrome that is seen between the rates of 9% and 32% in HD population [1–6]. The syndrome has been increasingly reported in HD patients over the years, since its first description in 1975 [1]. Many authors focused on the underlying etiology and pathogenesis of this syndrome. Although there is no precise cause defined this syndrome, it has been demonstrated that many factors are attributed to developing this syndrome in HD patients. These factors are often related to vascular access [2], fluid overload [3], duration of hemodialysis [6, 7], accumulation of β-2 microglobulin amyloid fibrils [8, 9], and arterial calcifications [10]. Recently, investigators have emphasized the role of amyloid accumulation based on the cases with long hemodialysis duration and presence of β-2 microglobulin associated amyloid fibrils in biopsy specimens after surgery for CTS [8, 9].

However, early developed and amyloid negative CTS cases had been declared by many authors, and the role of amyloid accumulation became suspicious to elucidate the etiology. Conformably, predilection of CTS on the same arm

with fistula was taken into consideration in the role of vascular access. Based upon these findings, another important hypothesis was unveiled that consists of the compression of arteriovenous fistula, vascular steal syndrome edema due to venous outlet obstruction and also venous hypertension. Especially, increased symptoms during dialysis sessions promoted this hypothesis to be more accountable [1–4].

Although the role of venous hypertension has been demonstrated in earlier reports, the underlying mechanism remained unclear. Therefore, we aimed to clarify the role of the venous hypertension for the etiology of the hemodialysis patients with CTS. In this study, we reported our experience in 12 HD patients with unilateral CTS on the fistula arm and its close relation to venous hypertension.

2. Patients and Method

2.1. Study Population. The study included patients referred to our university hospital with signs and symptoms of the CTS confirmed by electrodiagnostic tests including nerve conduction studies and electromyography. We excluded patients aged less than 18 years or patients who had already been treated for CTS. In addition patients, who underwent hemodialysis for more than 8 years were excluded because CTS has the average time to onset being approximately 8–10 years after the initiation after dialysis [8]. The study was approved by the local ethics committee. Patients gave written informed consent.

2.2. Measurement of Venous Pressure. First, a Doppler ultrasound was performed and the outflow vein was identified. Then, a tourniquet was applied for passive vein congestion. Thereafter; the outflow vein was punctured with a 16-gauge sheath needle (Abbott) in a retrograde fashion against the flow direction under local anesthesia. Then, a 5-F introducer sheath (Terumo, Tokyo, Japan) was placed into the vein. And images were obtained to identify the fistula. After that a 5-F multipurpose catheter (William Cook Euro pe ApS, Bjaeverskov, Denmark) and a hydrophilic-coated and steerable 0.035-inch guidewire (Terumo) were passed across the fistula and placed into the artery. The guidewire was withdrawn and a transducer (Pressure Monitoring Set, Bicakcilar, Istanbul, Turkey) was attached to the catheter. All pressures were measured using a multipurpose monitor (KMA 900, PETAs, Turkey). The pressures were measured at the venous, fistula, and arterial parts. Calculations were repeated three times at each level and the mean values were recorded. At each level the systolic, diastolic, and mean pressures were measured. This procedure was repeated one week after operation.

The reduction in pressure (i.e., venous pressure (ΔVP)) was calculated following the next formula

$$\begin{aligned}\Delta P = {} & [(\text{pressure before the operation}) \\ & - (\text{pressure after the operation})] \\ & \times ((\text{pressure before the operation}) \times 100)^{-1}.\end{aligned} \quad (1)$$

2.3. Open Carpal Tunnel Release Surgery. Using the described techniques below the full release of the median nerve has been performed.

Open carpal tunnel release is technically straightforward and this technique does not required additional instruments. The procedure is performed with the patient supine and the extremity on a hand table. A general anesthesia is performed. The extremity is exsanguinated and the tourniquet is not used because of the AV fistula. We can use S-shaped incision which extended from the distal palm to the proximal forearm allowing full exposure of the median nerve at the wrist and forearm. In an effort to decrease the risk for injury to the palmar cutaneous branches of the median and ulnar nerves, the incision for the open carpal tunnel release is made along the ring finger axis. Although there is not a true internervous zone between the palmar cutaneous branch of the median nerve and the palmar cutaneous branch of the ulnar nerve, an incision in the ring finger axis should result in the injury of fewer nerve fibers [11, 12].

We can expect good relief of neurologic symptoms, although grip-strength weakness and pillar pain have led to a search for alternative procedures.

2.4. Histopathological Examination. Materials were available for histopathologic examination for each of them. All specimens were fixed in 4% buffered formaldehyde, decalcified in 5% formic acid for one to two weeks, embedded in paraffin, and cut into serial slides. The slides were stained by hematoxylin eosin and alkaline Congo red [13]. When detected, amyloid was typed by an avidin-biotin-peroxidase complex and anti-b2m (dilution 1/100; Dako, Copenhagen, Denmark), anti-P component (dilution 1/500; Dako), anti-amyloid protein A (dilution 1/500; Dako), antiprealbumin (dilution 1/200; Dako), anti-kappa (dilution 1/10,000; Bio-Yeda Ltd, Rehovot, Israel), and antilambda (dilution 1/10,000; Bio-yeda, Rehovot, Israel) antibodies.

2.5. Electrodiagnostic Tests. Nerve conduction studies were performed using a Counterpoint MK2 (Dantec, Copenhagen, Denmark). The median, ulnar, peroneal, and tibial motor nerves and median, ulnar, and sural sensory nerves were evaluated using standard conduction techniques. The distance between the recording electrode and stimulation was 8 cm in all of the compound muscle action potential (CMAP) recordings and was 14 cm for the sensory nerve action potential (SNAP) recordings. The F waves of all the motor nerves and the H reflex were also evaluated. Skin temperature was maintained at 32°C or above in the upper extremity nerves and 30°C or above in the lower extremity nerves. PN was diagnosed and graded from I to IV based on the criteria of our laboratory, a modification of the diabetes control and complication trial (DCCT) research group [14]. CTS was diagnosed when the findings met at least one of the following items regardless of the presence or absence of a PN: (1) ratio of median sensory latency of a 7 cm wrist segment to a 7 cm palm segment > 2.0, (2) ratio of distal latency of a median SNAP to that of an ulnar SNAP > 1.2, (3) ratio of the amplitude of a median sensory SNAP with wrist stimulation

Table 1: Characteristics of 12 patients.

Age, years	63 ± 7
Gender, female/male	7/5
Dialysis duration, years	3.5 ± 1.3
Serum beta 2-microglobulin, mg/dL	21.0 ± 10.0
High sensitive C-reactive protein, mg/dL	7.8 (3.4–21.0)
Intact parathormone, pg/mL	247 (189–2484)
Hemoglobin, g/dL	12.5 ± 1.7
Systemic systolic blood pressure, mmHg	118 ± 16
Systemic diastolic blood pressure, mmHg	76 ± 12
Location of arteriovenous fistula	
Radial	10 (83.3%)
Brachial	2 (16.7%)
Cause of end stage renal disease	
Diabetes mellitus	4 (33.3%)
Hypertension	4 (33.3%)
Polycystic kidney disease	1 (8.3%)
Obstructive uropathy	1 (8.3%)
Unknown	2 (16.7%)

to that with palm stimulation < 0.5, (4) ratio of the distal latency of a median CMAP to that of an ulnar CMAP > 1.5, and (5) ratio of the amplitude of a median CMAP to that of an ulnar CMAP < 0.6. These cut off values are obtained from the 50 healthy volunteers aging from 26 to 75 (mean age, 55.2 ± 12.0 yr).

2.6. Statistical Analysis. SPSS 16.0 software was used for the statistical analysis. Kolmogorov-Smirnov test was used for normality analysis of quantitative variables. Continuous variables with normal distribution were presented as mean ± standard deviation. Statistical analysis for the parametric variables was performed by the paired t-test. Median value was used where normal distribution is absent. The Wilcoxon signed-rank test was used to compare nonparametric variables. The correlation analysis was evaluated by the Pearson's correlation test. A P value <0.05 was considered statistically significant.

3. Results

Characteristics of patients are seen in Table 1.

Consider

$$\Delta P = \Big|\Big[(\text{pressure before the operation}) - (\text{pressure after the operation}) \times (\text{pressure before the operation})^{-1}\Big] \times 100\Big|. \quad (2)$$

None of the biopsy specimens, which were obtained from 12 patients, was stained with Congo red for the presence of amyloid deposition.

Table 2 shows comparison of the pressures in different localizations before and after the operation. There were significant differences between the 2 time periods with regard to pressures ($P < 0.05$). Pressures in all localizations were significantly lower after the operation than those before the operation (Figure 1).

ΔP in all localizations was not correlated with levels of serum β-2 microglobulin level, high sensitive C-reactive protein, intact parathormone, dialysis duration, BMI, and systemic systolic and diastolic blood pressures ($P > 0.05$). Similarly, serum β-2 microglobulin levels were not correlated with dialysis duration ($P > 0.05$).

4. Discussion

In terms of CTS, risk was shown to be increased in HD patients compared to the general population [15]. In addition to the burden of chronic kidney disease and hemodialysis, impaired health-related quality of life and socioeconomic deprivation due to CTS have been well established [16, 17]. Moreover, surgical treatment is widely accepted in HD patients with CTS; thus, authors have focused on the underlying mechanism to prevent CTS in HD patients before its occurrence [1, 4, 18–22].

CTS was first described in the HD population in 1975 by Warren and Otieno. It has been reported that increased venous pressure due to vascular access could be responsible for CTS in HD patients [1]. Since then, many factors have been proposed for the development of CTS, particularly β2 microglobulin amyloid accumulation in long term dialysis patients independently from vascular shunt. However, the early development of CTS in HD patients could not be explained by amyloid accumulation [8, 9]. Therefore, we aimed to investigate venous hypertension and its close relation with CTS in HD patients. Based on previous studies, we hypothesized that increased venous hypertension contributes to the extravasation of fluid and leads to extrinsic compression of the median nerve that results in CTS. We reviewed 12 patients with CTS in the same arm as the fistula who were treated with open surgery. Additionally, pathologic examination did not reveal β-2 microglobulin amyloid accumulation in the surgical specimens. After surgery, decreased venous pressure on the affected limb was demonstrated for the first time in this study setting.

The carpal tunnel is a narrow area circumscribed by the carpal ligament superiorly and by the carpal bones inferiorly. The median nerve that is located in this tunnel may be affected by increased pressure throughout the passage or compressed by surrounding structures. After the observation of CTS in HD patients in the same arm as the AVF, researchers addressed the role of vascular shunt and its complications [19]. There are two main hypotheses on the development of CTS : (I) venous hypertension and congestion of the distal limb result in compression on the median nerve inside the carpal tunnel [1, 4] and (II) a vascular steal phenomenon resulted in ischemic neural injury and nerve dysfunction [4, 20]. The occurrence of CTS symptoms during hemodialysis sessions and early development of CTS after fistula creation support these vascular hypotheses [1, 4, 16, 18]. We hypothesized that increased venous hypertension due to fistula results in congestion and leakage of fluid throughout the carpal

Table 2: Comparison of pressures in different localizations before and after operation.

Parameters	Before operation	After operation	ΔP (%)	P value
Arterial systolic pressure, mmHg	127 ± 48	106 ± 26	13.5	0.027
Arterial diastolic pressure, mmHg	64 ± 19	53 ± 20	17.1	0.027
Arterial mean pressure, mmHg	90 ± 22	74 ± 17	15.6	0.006
Fistula systolic pressure, mmHg	103 ± 35	92 ± 32	10.6	0.009
Fistula diastolic pressure, mmHg	58 ± 20	48 ± 22	17.6	0.027
Fistula mean pressure, mmHg	77 ± 23	66 ± 23	14.7	<0.001
Venous systolic pressure, mmHg	76 ± 41	65 ± 42	17.5	0.011
Venous diastolic pressure, mmHg	42 ± 28	33 ± 27	23.1	0.004
Venous mean pressure, mmHg	57 ± 35	46 ± 33	21.9	0.002

ΔP = |[(pressure before the operation) − (pressure after the operation)/pressure before the operation] × 100|.

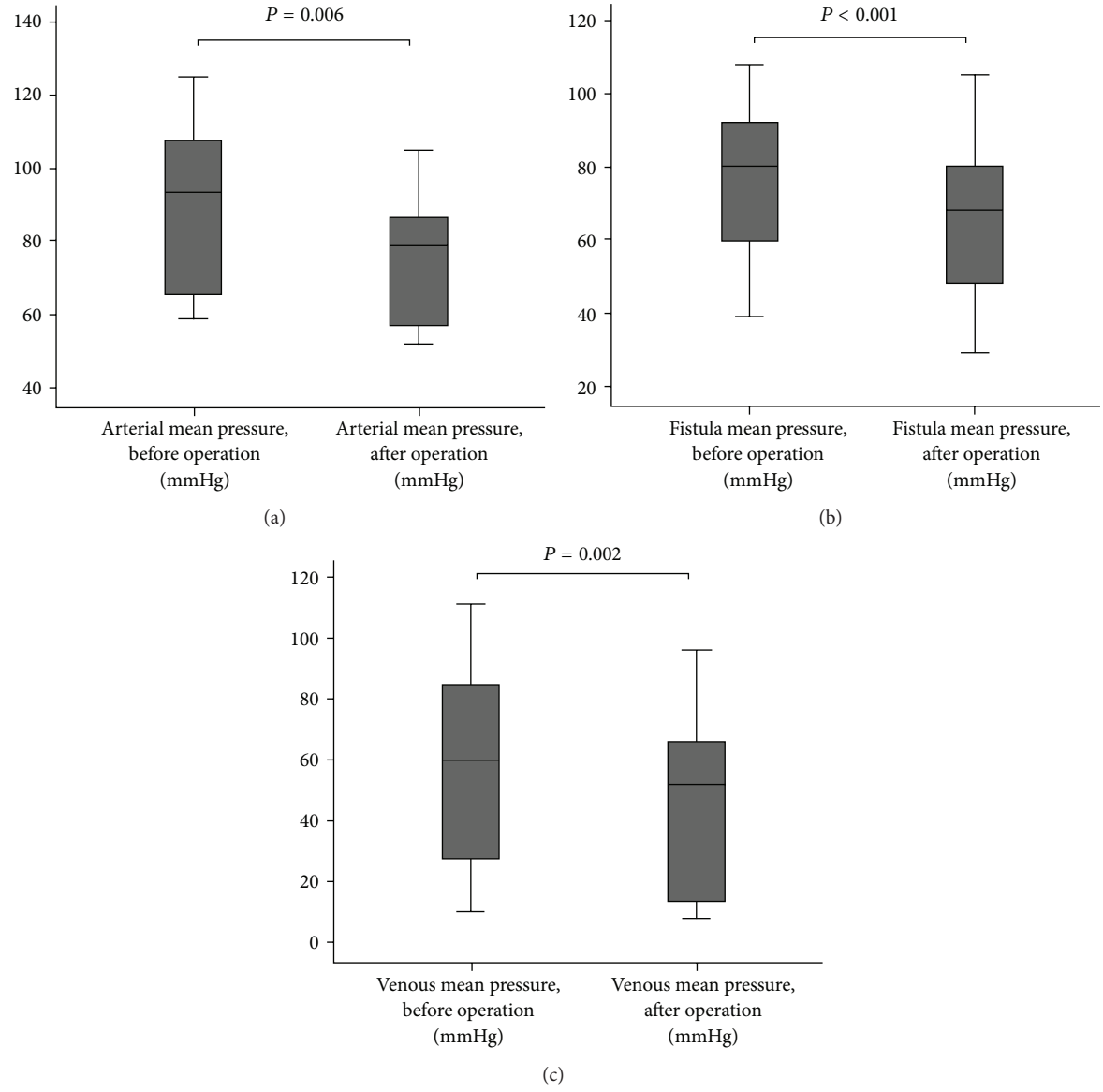

Figure 1: Comparison of arterial mean pressure, venous mean pressure, and fistula mean pressure before and after release surgery.

tunnel and this could be responsible for increased pressure on the median nerve. Therefore, chronic irritation of the ligament might induce thickening of the carpal ligament as a consequence. In a vicious cycle, narrowing of the carpal canal might contribute to an increased in venous tension. Despite our results, our hypothesis may be insufficient to explain the previously reported CTS cases associated with β-2 microglobulin composed amyloid fibrils [8, 9]. Otherwise, the role of time-dependent β-2 microglobulin accumulation and its relation to CTS patients with long term dialysis duration are still under debate, due to the gradual occurrence of vascular complications that was exposed by researchers [1, 4, 19–21].

One early study on CTS in HD patients [1] suggested that side-to-side type anastomosis could be responsible for venous hypertension and hand edema; conversely, we did not observe hand edema on the fistula hand affected with CTS and all of our patients had end-to-side type anastomosis. Recent studies showed that the type of anastomosis was not associated with the development of CTS [23, 24].

In contrast to studies on vascular phenomenon, Charra et al. reported that the limb affected by CTS was not related to the location of the arteriovenous fistula and amyloid positive CTS cases were also noticed predominantly to have shoulder pain; these relations were confirmed in many studies [8, 23, 24]. Interestingly, no complaints of shoulder pain were made by our patients and the pathologic examination of surgery specimens was negative for amyloid fibrils. Therefore, shoulder pain might be a clue in amyloid related arthropathy [24, 25]. The amyloid theory on CTS has been supported by consecutive reports of contralateral and bilateral cases independent of fistula creation [9, 20, 26]. On the other hand, McClure et al. stated that CTS is one of the clinical entities in patients receiving long term hemodialysis that is associated with amyloid deposition in the perineural and periarticular structures [27]. Moreover, the prevalence of CTS correlates with the duration of hemodialysis since it is thought that the accumulation of β-2 microglobulin amyloid fibrils is time dependent [8, 28]. β-2 microglobulin levels were reported to be increased in chronic renal failure, significantly in HD patients compared to peritoneal dialysis patients [29]. Nomoto et al. reported only 7 CTS cases in 5050 peritoneal dialysis patients and only 2 biopsies of the patients were positive for amyloid accumulation so they concluded that PD minimizes the emergence of CTS [30]. However, in a recent study, it was demonstrated that there was no correlation with β-2 microglobulin levels and CTS [22]. In contrast, Chanard et al. demonstrated that CTS cases were lowered in HD patients using β-2 microglobulin permeable membranes compared to less permeable ones [31]. According to these studies, β-2 microglobulin amyloid fibril deposition alone could not explain the pathogenesis of CTS in HD patients, but it may be a contributing factor, especially in late cases of CTS. Possibly, CTS might be triggered exclusively by β-2 microglobulin amyloidosis due to increased venous pressure near the AVF in late cases. Obviously, further studies with a larger number of patients and a longer observation period are needed to clarify the temporal realtionship with increased venous pressure and accumulation of amyloid fibrils near the fistula.

In addition to CTS symptoms, the diagnosis of CTS in HD patients requires electrodiagnostic tests to exclude both uremic and diabetic neuropathies. Since diabetic nephropathy is the most common cause of end stage renal disease, diabetic neuropathy is a frequently encountered problem in this population. However, uremic and diabetic neuropathies are generally distal and symmetric; mononeuropathic types should be kept in mind as they could cause similar symptoms to CTS. In this regard, we used such electro diagnostic tests to exclude other neuropathy types and to diagnose CTS clearly in our HD patients [22, 32, 33].

There are possible limitations of this study. One of the limitations is the small number of patients included in the study. Larger studies should be conducted to clarify our findings. Another possible limitation could be the lack of bilateral CTS cases.

In conclusion, we demonstrated the role of venous hypertension in early CTS in HD patients in the absence of β-2 microglobulin amyloid fibrils. Increased venous pressure on the fistula hand might be a clue for CTS development in HD patients. Decreased venous pressure after open carpal tunnel release surgery was associated with the relief of CTS symptoms. As a result, increased venous hypertension due to vascular shunt might be an important reason for early CTS in HD patients.

Conflict of Interests

The authors declare that they have no conflict of interests.

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Review Article

Multiple Myeloma and Kidney Disease

Daisuke Katagiri,[1] Eisei Noiri,[1] and Fumihiko Hinoshita[2]

[1] *Department of Nephrology and Endocrinology, University Hospital, University of Tokyo, 7-3-1 Hongo, Bunkyo, Tokyo 113-8655, Japan*
[2] *Department of Nephrology, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjyuku, Tokyo 162-8655, Japan*

Correspondence should be addressed to Daisuke Katagiri; dkatagiri-tky@umin.ac.jp

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Multiple myeloma (MM) has a high incidence rate in the elderly. Responsiveness to treatments differs considerably among patients because of high heterogeneity of MM. Chronic kidney disease (CKD) is a common clinical feature in MM patients, and treatment-related mortality and morbidity are higher in MM patients with CKD than in patients with normal renal function. Recent advances in diagnostic tests, chemotherapy agents, and dialysis techniques are providing clinicians with novel approaches for the management of MM patients with CKD. Once reversible factors, such as hypercalcemia, have been corrected, the most common cause of severe acute kidney injury (AKI) in MM patients is tubulointerstitial nephropathy, which results from very high circulating concentrations of monoclonal immunoglobulin free light chains (FLC). In the setting of AKI, an early reduction of serum FLC concentration is related to kidney function recovery. The combination of extended high cutoff hemodialysis and chemotherapy results in sustained reductions in serum FLC concentration in the majority of patients and a high rate of independence from dialysis.

1. Introduction

Kidney dysfunction is a worldwide public health problem with an increasing incidence and prevalence, and it is associated with high costs and relatively poor outcomes [1]. Multiple myeloma (MM) is a clonal B-cell disease of proliferating plasma cells that mainly affects elderly and accounts for almost 10% of all hematologic malignancies [2]. High dose chemotherapy with autologous stem-cell transplantation (ACST) has become the standard strategy for newly young MM patients. However, the median duration of response after this procedure does not exceed 3 years, and few patients remain free of the disease for more than 10 years [3]. Relative survival rate is approximately 40% for 5 years and 20% for 10 years [4]. Kidney disease is a common and a potentially serious complication of MM that occurs in 20%–25% patients [5] and in up to 50% patients [6] during the course of their disease. It is possible to reverse kidney dysfunction in approximately 50% patients, but the remaining patients will have some degree of persistent chronic kidney disease (CKD); and of these, 2%–12% will require renal replacement therapy (RRT) [7]. Kidney dysfunction in MM may result from various factors, and in most cases it is minor and recovered easily with infusion solution and correction of serum calcium levels [5, 6], though occasionally the condition may become exacerbated. Both acute kidney injury (AKI) and progressive CKD can result in end-stage renal disease (ESRD). Persistent kidney dysfunction in MM is most commonly caused by tubular nephropathy due to monoclonal Ig secreted by the plasma cell clone, or a fragment thereof, most frequently a monoclonal light chain (LC) [8]. In this paper, we focus on the clinical management of the kidney dysfunction associated with MM.

2. Clinical Impact of Kidney Dysfunction in Multiple Myeloma

Along with other clinical features including hypercalcemia, anemia, and lytic bone lesions, kidney dysfunction is a common complication in active MM (Figure 1) [9, 11]. Among newly diagnosed MM patients, 25%–50% present with kidney dysfunction, and approximately 9% require hemodialysis (HD) [5, 6]. Patients with AKI are more likely to experience early mortality and have worse overall survival [12, 13]. Before the introduction of the International Staging System

Table 1: The Durie-Salmon and International Staging systems criteria.

Stage	Durie-Salmon criteria	International Staging system criteria
I	All of the following: hemoglobin value > 10 g/dL, serum calcium value normal or ≤3 mmol/L bone X-ray, normal bone structure (scale 0), or solitary bone plasmacytoma only Low M-component production rate (IgG value < 5 g/dL; IgA value < 3 g/dL; Bence-Jones protein < 4 g/24 h)	Beta-2 microglobulin < 3.5 mmol/L and albumin ≥ 3.5 g/dL
II	Neither stage I nor stage III	Neither stage I nor stage III
III	One or more of the following: hemoglobin value < 8.5 g/dL serum calcium value > 3 mmol/L, advanced lytic bone lesions (scale 3) High M-component production rate (IgG value > 7 g/dL; IgA value > 5 g/dL; Bence-Jones protein > 12 g/24 h)	Beta-2 microglobulin > 5.5 mmol/L

Durie-Salmon subclassifications: relatively normal renal function (serum creatinine level < 177 mmol/L [<2 mg/dL]). Abnormal renal function (serum creatinine level ≥ 177 mmol/L [≥2 mg/dL]).

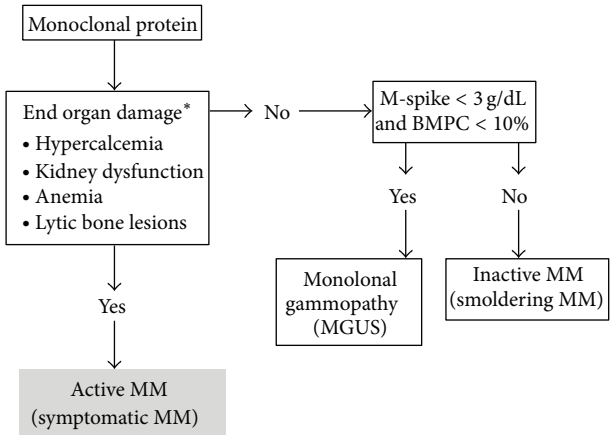

Figure 1: International Myeloma Working Group definition of multiple myeloma [9]. *MM-related organ damage includes the following: hypercalcemia [serum calcium > 0.25 mmol/L (1 mg/dL) above normal]; renal insufficiency (serum creatinine > 1.0 mg/dL above base line); anemia (hemoglobin > 2 g/dL below baseline); bone, lytic lesions, or osteoporosis with compression fracture; and symptomatic hyperviscosity, amyloidosis, or recurrent bacterial infections (>2 in 12 months). BMPC = bone marrow plasma cells.

Table 2: Associations between clinical manifestations and types of kidney injury in MM [10].

Predominant renal syndrome	Major types of renal lesions
Acute kidney injury (AKI)	Myeloma cast nephropathy
	Acute tubular necrosis
	Iatrogenic effects
	Direct infiltration of renal parenchyma
	Acute tubulointerstitial nephropathy
Proteinuria/nephrotic syndrome	Monoclonal Ig deposition disease (MIDD)
	Amyloidosis
	Rare types of glomerular involvement
Chronic kidney disease (CKD)	Amyloidosis
	Myeloma cast nephropathy
	Monoclonal Ig deposition disease (MIDD)
Fanconi syndrome	Proximal tubulopathy

(ISS) [14], the commonly used staging system for Durie and Salmon criteria [15], which was well known to be a good predictive indicator for prognosis in MM patients. Serum creatinine level was included in the staging system because it strongly predicted survival. However, as shown in Table 1, the estimated glomerular filtration rate (eGFR) was not accounted in ISS. In the 1980s, serum beta-2 microglobulin levels were identified as a strong prognostic factor in MM [15]. Recently, a risk score has been proposed that identified eGFR and beta-2 microglobulin levels as the capital predicting prognosis but did not include serum albumin levels because the unavailability of results for all patients [16]. The accumulation of the evidence suggests that kidney function is closely correlated with myeloma cell mass; that is, patients with a large tumor burden are more likely to have CKD. In the ISS cohort, 82% patients with levels ≥177 mmol/L were in stage III disease [14]. Cast nephropathy, also called myeloma kidney, is the most common cause of CKD, followed by amyloid light chain (AL)-type amyloidosis and monoclonal Ig deposition disease (MIDD) [17, 18]. Table 2 summarizes the association between clinical manifestations and various types of kidney injury in MM patients [10].

3. Acute Kidney Injury in Multiple Myeloma

AKI is defined as a sudden decrease in kidney function. AKI is one of the serious conditions that affect the structure and function of kidneys. It is a broad clinical syndrome, including specific diseases affecting the kidney such as MM. Even a minor acute reduction in kidney function correlates to an adverse prognosis. A schematic view of the conceivable course of AKI has been proposed (Figure 2) [19]. AKI could be an important cause of CKD or ESRD. Therefore, early detection and treatment of AKI would improve outcomes. Two criteria of AKI, which were based on sCr and urine

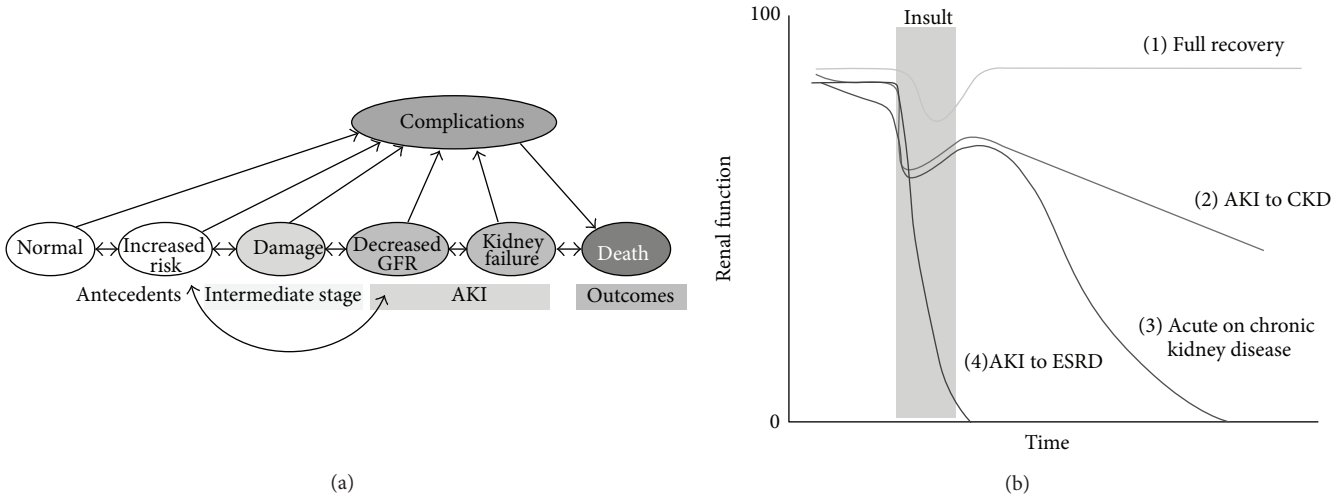

Figure 2: Acute kidney injury and progression to CKD [19]. (a) Conceptual model of acute kidney injury (AKI). (b) Natural history of AKI. Patients who develop AKI may experience (1) complete recovery of renal function, (2) development of progressive chronic kidney disease (CKD), (3) exacerbation of the rate of progression of preexisting CKD, or (4) irreversible loss of kidney function and evolve into ESRD.

output, the Risk, Injury, Failure, Loss, End-Stage Renal Disease (RIFLE) [21] and Acute Kidney Injury Network (AKIN) [22] have been proposed and validated. Recently, severity of AKI staged by RIFLE criteria (OR = 2.04 Failure stages versus Risk and Injury stage $P = 0.06$) has been reported as associated with marginally better long-term outcome in MM patients [23]. In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) AKI Guideline Work Group accepted the existing criteria for the diagnosis and staging of AKI and proposed a single definition of AKI that should be useful for practice, research, and public health (Table 3) [20]. It is widely accepted that GFR is the most useful kidney function index, and changes in sCr levels and urine output are surrogates marker for changes in GFR. In the clinical settings, an abrupt decline of GFR is detected as an increase in sCr levels. Although a small creatinine increase will predict adverse outcomes, the limitations of serum creatinine for early detection and accurate estimation of renal injury in AKI are well known [24]. Recently, AKI biomarkers have been developed to facilitate early detection, differential diagnosis, and prognosis. Among them, novel biomarkers such as urinary L-type fatty acid-binding protein (L-FABP) or neutrophil gelatinase-associated lipocalin (NGAL) are considered to reflect tubular epithelial cell injury [25, 26].

Table 3: Staging of acute kidney injury [20].

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ≥0.3 mg/dL (≥26.5 mmol/L) increase	<0.5 mL/kg/h for 6–12 h
2	2.0–2.9 times baseline	<0.5 mL/kg/h for ≥12 h
3	3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dL (≥353.6 mmol/L) OR Initiation of renal replacement therapy OR, in patients <18 years, decrease in eGFR to <35 mL/min per 1.73 m^2	<0.3 mL/kg/h for ≥24 h OR Anuria for ≥12 h

In patients with suspected MM, monoclonal heavy or light chains, known as Bence-Jones protein, should be analyzed in concentrated urine using electrophoresis with immunofixation of any identified protein bands in accordance with current myelomas guidelines [27]. Coincidence measurement of serum/urine albumin should be performed when the possibility of immunoglobulin light chain (AL) amyloid or monoclonal Ig deposition disease (MIDD) is suspected. The casts contain monoclonal free light chains (FLC) and Tamm-Horsfall glycoproteins and have been shown to acutely depress single nephron glomerular filtration rate [28]. The FLCs are freely filtered by the glomerulus and taken up by mesangial cells (toxicity to which may cause amyloidosis or light chain deposition disease) or tubular epithelial cells, where they can activate nuclear factor kappa beta (NF-kB) and cause apoptosis or epithelial-mesenchymal transition, leading to transcription of inflammatory cytokines. Recruitment of inflammatory cells to the interstitium ensues, promoting fibrosis [29].

Cast nephropathy is nearly always observed in advanced MM, when production of large amounts of LC overwhelms the capacity of catabolism in proximal tubules [8]. This nephropathy is usually triggered by several factors that increase urine FLC concentration. These factors include dehydration, hypercalcemia, infections, contrast medium

Table 4: Criteria for chronic kidney disease [33].

Markers of kidney damage (for >3 months)
Albuminuria (AER ≥ 30 mg/dL; ACR ≥ 30 mg/g)
Urinary sediment abnormalities
Electrolyte and other abnormalities due to tubular disorders
Abnormalities detected by histology
Structural abnormalities detected by imaging
History of kidney transplantation
Decreased GFR (for >3 months)
GFR < 60 mL/min per 1.73 m^2 (GFR categories G3a–G5)

ACR: albumin-creatinine ratio; AER: albumin excretion rate; GFR: glomerular filtration rate.

usage, or use of nephrotoxic medications, including NSAIDs, diuretics, angiotensin-conversing enzyme inhibitors (ACEI), and angiotensin II receptor blockers (ARB). Also, patients with high serum monoclonal FLC (>500 mg/L) have a risk of developing AKI [30]. Even in the setting of severe kidney dysfunction, the serum FLC assay is a sensitive and specific screening tool [31]. The lack of sensitivity of serum protein electrophoresis in the detection of monoclonal FLC [32], which causes cast nephropathy, makes this test inappropriate as a screening tool, particularly in the setting of AKI. Because cast nephropathy develops in MM, the diagnosis may be straightforward but can become a challenge when the underlying myeloma has not yet been identified.

4. Chronic Kidney Disease in Multiple Myeloma

There is an even higher prevalence of the earlier stages of CKD, with adverse outcomes, including loss of kidney function, cardiovascular disease (CVD), and premature death. The KDIGO organization developed clinical practice guidelines in 2012 to provide guidance on the evaluation, management, and treatment of CKD (Table 4) [33]. Diagnostic thresholds of GFR of less than 60 mL/min/1.73 m^2 and an albumin-creatinine ratio (ACR) of 30 mg/g or greater were retained. The exact frequency of GFR and ACR monitoring will depend on the severity of CKD Figure 3 [33] and the risk and rate of progression. The International Myeloma Working Group (IMWG) has recommended the use of the Modification of Diet in Renal Disease (MDRD) formula for the estimation of GFR in MM patients with stabilized sCr [34] as well as the KDIGO classification for the classification of CKD in MM [1, 35].

Factors associated with progression include cause of CKD, level of GFR, level of albuminuria, AKI, age, gender, race or ethnicity, elevated BP, hyperglycemia, dyslipidemia, smoking, obesity, history of cardiovascular disease, and ongoing exposure to nephrotoxic agents. The cause of CKD has been traditionally assigned based on presence or absence of underlying systemic diseases and location of known or presumed pathological abnormalities. The distinction between systemic diseases affecting the kidney and primary kidney diseases is based on the origin and locus of the disease process. In primary kidney disease the process arises and is confined to the kidney, whereas in systemic diseases the kidney is only one victim of a specific process, for example, diabetes. Certain genetic diseases cross this boundary by affecting different tissues, for example, adult polycystic kidney disease. The location of pathological and anatomical findings is based on the magnitude of proteinuria and findings from the urine sediment examination, imaging, and renal biopsy. In MM patients, CKD occurs mainly as a result of damage caused to renal tubules by FLCs (cast nephropathy). A variety of other nephrotoxic processes may also contribute to this damage including dehydration, hypercalcemia, nephrotoxic drugs, and infection. Table 5 represents an example of a classification of causes of kidney diseases based on these two domains. MM is classified as tubulointerstitial disease in systemic disease affecting the kidney.

5. Kidney Dysfunction, and Chemotherapy, and Stem-Cell Transplant

In the era of conventional chemotherapy, several studies have confirmed that CKD is associated with poor prognosis in MM, with a median survival of <2 years [36–38]. Effective treatment of MM is the best management strategy for complicating kidney dysfunction. Melphalan-prednisone (MP) was established as the standard treatment in a trial involving 183 patients, which demonstrated that it prolonged the survival by 6 months compared with the use of melphalan alone [39]. Because melphalan is more likely to cause hematological toxicity in CKD patients, dose modification is needed [34]. Autologous stem cell transplantation (ASCT) with high-dose chemotherapy has been shown to improve the overall survival [40]. However, ASCT has been considered as an option for selected CKD patients because kidney dysfunction was associated with a shorter overall survival [41].

Since 2005, the treatment strategy for MM has significantly changed because of the successful introduction of new therapeutic agents. Three drugs, a proteasome inhibitor (bortezomib) and two immunomodulatory drugs (IMiDs, lenalidomide, and thalidomide), are referred to as novel agents, and each drug has a characteristic efficacy. Notably, there are reports of hyperkalemia occurring with the use of thalidomide in patients with severe CKD (including those on RRT); thus, at present, its usage requires caution [42, 43]. Thalidomide is metabolized by hydrolysis in serum and can be used without dose modification in severe CKD. Lenalidomide is a 4-amino substituted analog of thalidomide, which was first shown to be useful in the treatment of relapsed MM, though patients with advanced CKD were more likely to become thrombocytopenic or require dose reduction or interruption of lenalidomide [3, 44].

While these agents can be expected to restore kidney function by improvement in the primary disease, bortezomib, with a strong antitumor effect, is reported to rapidly improve kidney function [45]. Bortezomib was first administered to treat relapsed or refractory MM but has also shown to be effective as front-line therapy [46]. Bortezomib is cleared via

				Albuminuria categories		
				A1	A2	A3
				Noral to mild	Moderate	Severe
				ACR < 30 mg/g	ACR of 30–300 mg/g	ACR > 30 mg/g
GFR categories (mL/min per 1.73 m^2)	G1	Normal	≥90	1 if CKD	1	2
	G2	Mild	60–89	1 if CKD	1	2
	G3a	Moderate	45–59	1	2	3
	G3b	Moderate	30–44	2	3	3
	G4	Severe	15–29	3	3	4+
	G5	ESRD	<15	4+	4+	4+

Figure 3: Guide to frequency of monitoring by GFR and albuminuria categories [33]. This GFR and albuminuria grid reflects the risk for progression by intensity. The numbers in the boxes are a guide to the frequency of monitoring (number of times per year). ACR = albumin – creatinine ratio; CKD = chronic kidney disease; GFR = glomerular filtration rate.

Table 5: Classification of CKD based on presence or absence of systemic disease and location within the kidney of pathologic-anatomic findings [33].

	Examples of systemic diseases affecting the kidney	Examples of primary kidney diseases
Glomerular diseases	Diabetes, systemic autoimmune diseases, systemic infections, drugs, and neoplasia (including amyloidosis)	Diffuse, focal, or crescentic proliferative GN, focal and segmental glomerulosclerosis, membranous nephropathy, and minimal change disease
Tubulointerstitial diseases	Systemic infections, autoimmune, sarcoidosis, drugs, urate, and environmental toxins, *Multiple myeloma*	Urinary-tract infections, stones, and obstruction
Vascular diseases	Atherosclerosis, hypertension, ischemia, cholesterol emboli, systemic vasculitis, thrombotic microangiopathy, and systemic sclerosis	ANCA-associated renal limited vasculitis and fibromuscular dysplasia
Cystic and congenital diseases	Polycystic kidney disease, Alport syndrome, and Fabry disease	Renal dysplasia, medullary cystic disease, and podocytopathies

hepatic oxidative deboronation [44], and so doses do not require adjustment in CKD [34]. The kidney response rate is based on improving creatinine clearance and response time, which were 59% and 1.8 months (traditional chemotherapy), 79% and 1.6 months (IMiDs), and 94% and 0.69 month (bortezomib), respectively [47]. The introduction of novel agents has led to an improved survival of patients with MM [48, 49], even in those with CKD.

6. Apheresis Therapy in Multiple Myeloma

There are several types of apheresis therapy that are applicable in MM patients. Plasma exchange (PE) or plasmapheresis involves the separation and removal of the blood cells and other substances from the plasma by centrifugation (based on cell density) or ultrafiltration using large-pore hemofilters (based on molecular size) [50]. This method is used to remove pathogenic substances, including autoreactive antibodies, immune complexes, paraproteins, lipoproteins, and inflammatory mediators such as cytokines. Fluid replacement after PE maintains normal plasma volume and electrolyte concentrations. Plasma filters have a pore size of approximately 0.3 μm and membrane area of 0.1–0.8 m [2]. Homogenization of pore size has been sought to decrease cell leakage and hemolysis. The PE circuit includes the plasma filter, circuits for blood cells and plasma, equipment for plasma exchange (blood pump, plasma pump, hemadynamometer, plasma filtration manometer, trans-membrane-pressure (TMP) manometer, and an anticoagulant pump). A circuit for fluid replacement should be prepared when HD or hemodiafiltration is combined with PE. The ideal replacement solution should maintain normovolemia and normal plasma electrolyte concentrations. The choice of replacement fluid includes crystalloids, semisynthetic colloids (hetastarch, gelatin, and dextrans), human albumin solutions, liquid stored plasma, fresh-frozen plasma (FFP), and cryoprecipitate. The replacement solutions most commonly used are

liquid stored plasma and human albumin solution for the removal of some pathogenic substances. FFP infusion can cause hypocalcemia as a result of calcium chelation by sodium citrate, and alkalosis and sodium overload can also occur. The hypotensive effects of citrate-induced hypocalcemia can be minimized by administering calcium gluconate as a continuous intravenous infusion and monitoring serum calcium levels. The treatment of choice for patients with AKI is combined plasmapheresis and HD to correct electrolyte abnormalities and provide renal support. A high flow volume may be needed when combining HD or hemodiafiltration with PE in patients undergoing long-term HD. When combining PE with HD in a serial circuit, a medical practitioner should monitor the procedure and stop it, if necessary, to prevent overfiltration at the HD side caused by decreased or obstructed blood flow at the PE side. Double-filtration plasmapheresis (DFPP) is a PE in which two filters with different pore sizes are used to separate toxic substances from plasma. The two-stage filtration allows the removal of albumin and its return into the blood circulation. This feature provides the advantage of decreasing the need for replacement fluid and its associated complications, including allergic reaction and infection, that can occur with PE. Using DFPP also decreases the high cost associated with the replacement fluid [51]. Cryofiltration is a modification of DFPP that involves cooling the separated plasma at the plasma separator (first membrane) to gelatinize the proteins in the plasma, which are then ablated at the large-pore plasma component separator (second membrane) [52]. The gelatinized and ablated proteins form cryoglobulin or cryogel. Cryoglobulin is the collective term for abnormal proteins, including single immunoglobulins and multiimmunoglobulins (mainly IgG or IgM) that clump into a gel at 39.2°F and dissolve at 98.6°F. Cryogel is a complex of heparin, fibronectin, and fibrinogen. Cryofiltration is used to treat patients with cryoglobulinemia, a medical condition in which the blood contains large amounts of cryoglobulins. Patients may have essential cryoglobulinemia or secondary cryoglobulinemia associated with various diseases, including macroglobulinemia, MM, connective tissue disease, and hepatitis C infection.

FLC removal by apheresis therapies has been investigated as a means of preserving kidney function. The initial treatment investigated was PE, which has been tested in three trials [53–55], and overall there is no evidence of benefit. Two early trials had methodological fallacy. The first compared PE and HD with peritoneal dialysis (PD) alone [54]; the second was small; and the two groups were significantly different in terms of baseline prognostic factors. The lack of efficacy of PE would not be surprising. Light chains are so small (κ, 25 kDa; λ, 50 kDa) that they equilibrate between the intravascular and extra vascular compartments; thus, the intravascular compartment may only contain 20% of the total capacity. Namely, a standard series of single PE session might remove only 65% of intravascular FLCs [56]. However, rapid removal of FLC with PE in combination with chemotherapy could prevent further kidney dysfunction. A previous trial failed to show evidence that PE improved the outcome in patients with MM and AKI [57]. In this randomized controlled study of 107 patients who developed AKI after the diagnosis of MM, PE (5–7 exchanges of 50 mL/kg body weight) coupled with a chemotherapy regimen based on VAD (vincristine, doxorubicin, and dexamethasone) or MP (described previously) did not show significant effect on a composite criterion defined by death, RRT-dependent ESRD, or ESRD with a GFR <30 mL/min/1.73 m^2, compared with chemotherapy alone. In this study, FLC levels were not measured, and histologic evidence of cast nephropathy was insufficient. Recently, Leung et al. have suggested that histological confirmation of cast nephropathy should be considered to analyze the effects of PE. In a retrospective series of 40 patients with MM-associated CKD, 18 cases had cast nephropathy that was biopsy proven. In their study including patients with cast nephropathy, the combination of PE with high-dose dexamethasone-based chemotherapy induced an attenuation of kidney dysfunction in 45% and in 75% of patients in whom serum FLC levels decreased by >50% with treatment. In contrast, no correlation between renal response and reduction in serum FLC levels was observed in another study including patients without biopsy-proven cast nephropathy [18], indicating that pathological confirmation might influence therapeutic strategy and prognosis in MM with CKD. A treatment strategy was recently designed combining bortezomib-based therapy and PE in patients with biopsy-proven cast nephropathy or a high probability of cast nephropathy (>200 mg/dL of FLC) [58]. The reported renal recovery rate of 86% will probably lead to improved patient survival. However, the relative contribution of PE prognosis improvement was not apparent. Therefore, these results should be interpreted with caution. The early decrease in FLC concentrations probably represents efficacy of the chemotherapy rather than that of PE [59, 60].

7. Dialysis Therapy in Multiple Myeloma

CKD is a common clinical feature of MM. Even with aggressive treatment, progression to ESRD occurs in up to 65% patients with cast nephropathy within 3 months of diagnosis [61]. Treatment-related mortality (29%) and morbidity (3.4%) are higher in patients with CKD than in patients with normal kidney function [15]. The unadjusted median overall survival (OS) on HD was 0.91 years in patients with MM and 4.46 years in non-MM patients [62]. With a review of the United States Renal Data System, MM-induced CKD is a considerable burden [63]. Of the 375 152 patients in the registry who initiated HD for ESRD, 3298 (0.88%) patients had MM. The 2-year all-cause mortality of patients with ESRD due to MM was 58% versus 31% in all other patients ($P < 0.01$) [63]. MM patients with progressive CKD have a tendency to die within 2–9 months after the diagnosis [64, 65]. If patients who die within 2 months of diagnosis are excluded, the median survival of patients with MM with ESRD is almost 2 years, and 30% survive for over 3 years [66, 67]. Similarly, another report showed that from 1985 to 2005, 1.5% (2453) of the 159 637 patients placed on RRT had MM [34]. The incidence of RRT for ESRD due to MM increased from 0.70 per million people (1986 to 1990)

to 2.52 per million people (2001 to 2005) [34]. Some studies have also indicated that reversibility of kidney dysfunction is associated with improved survival [12, 13, 68]. Even patients who have not been diagnosed with MM at the time HD was initiated for ESRD are at risk of MM for several years, with odds ratios of 3.7, 1.9, 0.9, and 0.8 for 0–12 months, 12–25 months, 25–44 months, and >44 months after starting HD, respectively [69]. According to the recent report, between 0.9 and 1.5% of patients initiating maintenance HD suffer from MM, which may reflect therapeutic success because patients in whom renal function is not completely recovered survive long enough to be chronically dialyzed [62]. Patients with MM and ESRD can be treated either with HD or PD, and both seem to be equally effective [7, 70]. Patients who recover their renal function and obtain independence from HD have the same good prognosis as those who never developed AKI. Blade et al. reported that hypercalcemia, degree of renal failure, and amount of proteinuria are factors associated with renal dysfunction in MM-associated CKD patients [12]. We previously showed that degree of serum beta-2 microglobulin and hypercalcemia in MM-associated HD patients were significant and independent prognostic factors for predicting the probability of recovery from severe renal failure and discontinuation of HD [71]. Erythropoiesis-stimulating agents (ESAs) are agents similar to the cytokine erythropoietin, which stimulates red blood cell production (erythropoiesis). They can be used in patients with MM on HD to decrease transfusion requirements, although some studies suggest that they may decrease the overall survival [44, 72].

Besides the theoretical limitations of PE [58–60], high cutoff dialyzers have been verified in patients with myeloma kidney. These dialyzers have membranes with very large pores, allowing the passage of molecules up to 60–65 kDa, through which light chains can pass. An early analysis of this method suggested that up to 90% of light chains can be removed with 3 weeks of extended daily HD, while PE might remove only 25% of the total amount during the same period [73]. However, this success rate is dependent on the plasma cell clone responding to chemotherapy. The combination of extended high cutoff hemodialysis (HCO-HD) and chemotherapy was recently shown to result in sustained decrease in serum FLC concentrations in the majority of patients and a high rate of dialysis independence [74, 75].

8. Conclusion

Kidney dysfunction is a common feature of symptomatic MM and may cause major problems in clinical management. Its management remains challenging. Cast nephropathy is the most common cause of severe kidney dysfunction in MM. Serum FLC concentrations should be considered in MM patients with AKI. The successful introduction of new therapeutic agents and novel techniques for serum FLC removal has profoundly altered the therapeutic approach toward patients with cast nephropathy. Long-term dialysis is an efficacious treatment for patients with MM and ESRD. FLC removal with a combination of HCO-HD and chemotherapy may lead to early decrease in serum FLC concentrations and ameliorate AKI complicating MM.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Prognosis of Elderly Japanese Patients Aged ≥80 Years Undergoing Hemodialysis

Shingo Hatakeyama,[1] Hiromi Murasawa,[1] Itsuto Hamano,[1] Ayumu Kusaka,[1] Takuma Narita,[1] Masaaki Oikawa,[1] Daisuke Noro,[1] Kazuhisa Hagiwara,[1] Hirofumi Ishimura,[2] Takahiro Yoneyama,[1] Yasuhiro Hashimoto,[3] Takuya Koie,[1] Hisao Saitoh,[2] Tomihisa Funyu,[2] and Chikara Ohyama[1,3]

[1] *Department of Urology, Hirosaki University Graduate School of Medicine, 5 Zaifu-chou, Hirosaki 036-8562, Japan*
[2] *Department of Urology, Oyokyo Kidney Research Institute, Hirosaki 036-8243, Japan*
[3] *Department of Advanced Transplant and Regenerative Medicine, Hirosaki University Graduate School of Medicine, Hirosaki 036-8562, Japan*

Correspondence should be addressed to Chikara Ohyama; coyama@cc.hirosaki-u.ac.jp

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Although the number of elderly patients requiring dialysis has increased, data regarding the prognosis of elderly patients undergoing hemodialysis are limited. In the present study, prognosis in Japanese hemodialysis patients aged ≥80 years was evaluated. From January 1988 to July 2013, 1144 consecutive patients with end-stage renal disease required renal replacement therapy at our institution; of these, 141 were aged ≥80 years. These patients' charts were retrospectively reviewed for relevant clinical variables and survival time. The life expectancies table from the National Vital Statistics database was used, and prognostic factors were assessed by multivariate analysis. In total, 107 deaths (76%) were recorded during the study period. The median survival time and estimated life-shortening period in the patients were 2.6 years and −5.3 years, respectively. Eastern Cooperative Oncology Group Performance Status and hemoglobin level were revealed as prognostic factors in the multivariate analysis. Estimates of prognosis and prognostic factors may provide useful information for physicians as well as elderly patients with end-stage kidney disease.

1. Introduction

As the Japanese population continues to age and the prevalence of chronic kidney disease increases [1, 2], clinicians are frequently faced with the decision of whether or not to initiate renal replacement therapy for their patients. According to the latest nationwide review conducted by the Japanese Society for Dialysis Therapy in 2012, 309,946 patients were on dialysis, and dialysis was initiated in 38,165 new patients that year [3]. Along with this increase in the number of dialysis patients, the number of older patients (≥80 years) undergoing hemodialysis treatment each year has also increased. In 2004, 14% of all dialysis patients in Japan were ≥80 years old. These figures were 16% in 2006, 18% in 2008, 19% in 2010, and 22% in 2012, whereas the number of Japanese patients aged 70–79 years receiving dialysis has remained unchanged in the last decade (Figure 1) [3].

Many clinicians believe that age is a barrier for initiation of renal replacement therapy because dialysis in elderly patients has been associated with an increased risk of mortality. However, data regarding the prognosis of elderly patients undergoing hemodialysis are limited. Thus, in the present study, the median survival time in hemodialysis patients aged ≥80 years was evaluated, and the period of time by which these patients' lives were shortened (life-shortening period) was estimated using a life expectancies table from the National Vital Statistics data for 2008 [4]. Prognostic factors were then assessed by multivariate analysis.

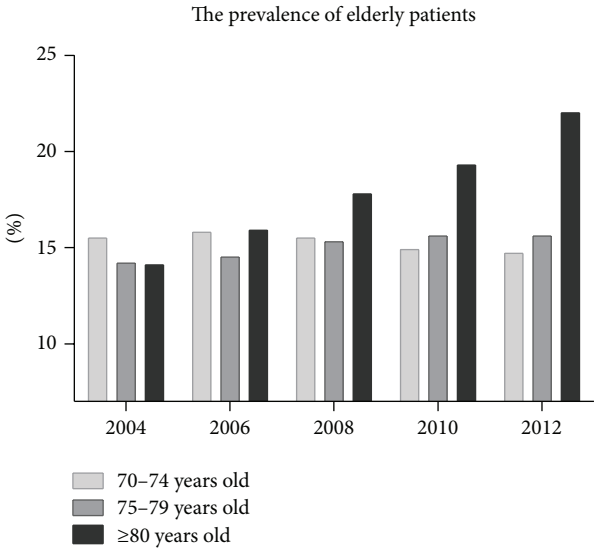


Figure 1: Prevalence of elderly patients receiving dialysis treatment in the overall Japanese population according to age.

2. Materials and Methods

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki and approved by the Institutional Ethics Committee. From January 1988 to July 2013, 1144 consecutive patients with end-stage renal disease required renal replacement therapy at the Oyokyo Kidney Research Institute, Hirosaki, Japan. Of these, 141 were aged ≥80 years. Patient charts were retrospectively reviewed for relevant clinical variables and survival time.

The following data were collected for use in the analyses: patient age, gender, body mass index, and blood pressure; hemoglobin, serum albumin, phosphorus, potassium, and corrected calcium levels; blood urea nitrogen level and estimated glomerular filtration rate (eGFR); concomitant use of antihypertensive drugs (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or calcium blockers); and presence or absence of diabetes mellitus or cerebral and cardiovascular disease (cerebral infarction, heart failure, myocardial infarction, and angina pectoris) at the initial visit. The eGFR was calculated using values for age, gender, and serum creatinine levels and the equation shown below [5]. This eGFR equation for Japanese patients is a modified version of the abbreviated Modification of Diet in Renal Disease Study formula: eGFR mL/min/1.73 m^2 = 194 × $sCr^{-1.094}$ × $age^{-0.287}$ (×0.739, if female) [6]. Patient general health status before dialysis initiation was evaluated on the Eastern Cooperative Oncology Group Performance Status scale (ECOG-PS) [7].

The life expectancy is calibrated using the life expectancies table [4] based on expected age of death on specific age at dialysis initiation. To evaluate differences in life expectancy between these patients and the general population, life-shortening periods were calculated according to the following formula: expected age of death on specific age at dialysis initiation—the actual age of death.

2.1. Basic Policies for Indication of Renal Replacement Therapy. Hemodialysis is the standard treatment strategy for renal replacement therapy in elderly patients (≥80 years) with end-stage renal disease at our institution. The purpose of this treatment is to minimize present suffering, gain time to consider continuation of renal replacement therapy and its alternatives, and ensure renal survival. Patients who refuse renal replacement therapy and those with systemic comorbidities, extremely advanced heart failure, or severe complications are designated as "not indicated for treatment."

2.2. Follow-Up Schedule. All patients were routinely followed up for thrice-weekly hemodialysis with standard care according to the guidelines of the Japanese Society for Dialysis Therapy for the management of patients on chronic hemodialysis [8, 9] and tracked until the occurrence of death, loss of follow-up, or end of study (July 31, 2013), whichever came first. Erythropoiesis-stimulating agents were used when hemoglobin level was lower than 10 g/L in all patients. The target hemoglobin level was 10-11 g/L.

2.3. Statistical Analysis. Patient survival was evaluated using the Kaplan-Meier method. Variables were compared among groups using Student's t-test or Mann-Whitney U test. Age, gender, body mass index, blood pressure, hemoglobin, serum albumin, phosphorus, potassium, and corrected calcium levels, blood urea nitrogen, estimated glomerular filtration rate (eGFR), concomitant use of antihypertensive drugs, presence or absence of diabetes mellitus, and cerebral and cardiovascular disease were analyzed using stepwise Cox regression multivariate analysis to determine independent predictors for overall survival. After these factors were identified, a receiver operating characteristic (ROC) curve was used to determine the optimal cut-off value for prognosis. This value was calculated using the following formula [10]: $(1-\text{sensitivity})^2 + (1-\text{specificity})^2$. Each patient was categorized according to the number of risk factors identified in the Cox regression multivariate analysis to evaluate the predictive potential of risk criteria for prognosis. Each positively identified risk factor was given a score of 1, and scores for all other risk factors were summed. Patients were classified into three groups according to the number of risk factors: the low-risk group (patients with no risk factors), the intermediate-risk group (one risk factor), and the high-risk group (two risk factors). The statistical significance of the differences between the three groups was evaluated by the log rank test.

All statistical analyses were performed using the SPSS software package version 19.0 (SPSS, Chicago, IL, USA) and GraphPad Prism version 5.03 (GraphPad Software, San Diego, CA, USA). A P value of <0.05 was considered statistically significant.

3. Results

Characteristics of all 1144 dialysis patients are summarized in Table 1. The age distribution of patients was as follows: 129 (11%), 202 (18%), 324 (28%), 348 (30%), and 141 (12%)

Table 1: Characteristics of 1144 dialysis patients included in this study.

	All	<50 years	50s	60s	70s	≥80s
Number of patients	1144	129	202	324	348	141
Male/female	714/430	78/51	137/65	209/115	217/131	73/68
Age at start dialysis (years)	65.8 ± 12.9	41.1 ± 7.2	55.8 ± 2.8	64.7 ± 2.9	74.5 ± 3.1	84.2 ± 3.1
Survival after dialysis initiation (years)	6.8	20	9.1	7.7	4.4	2.6
Life expectancy (years)	18.6	40.2	28.1	20.2	13.4	7.7
Life-shortening periods (years)	−11.6	−30.1	−22.5	−14.6	−9.4	−5.3
Deceased patients	667 (58%)	39 (30%)	108 (53%)	182 (56%)	230 (66%)	107 (76%)
Cause of death						
Cerebro-cardiovascular disease	235 (35%)	14 (36%)	41 (38%)	75 (41%)	76 (33%)	29 (27%)
Infections	167 (25%)	7 (18%)	27 (25%)	37 (20%)	61 (27%)	35 (33%)
Cancer	88 (13%)	5 (13%)	14 (13%)	25 (14%)	30 (13%)	14 (13%)
Others	132 (20%)	7 (18%)	17 (16%)	30 (16%)	22 (10%)	22 (21%)
Unknown	44 (7%)	6 (15%)	9 (8%)	15 (8%)	7 (3%)	7 (6.5%)

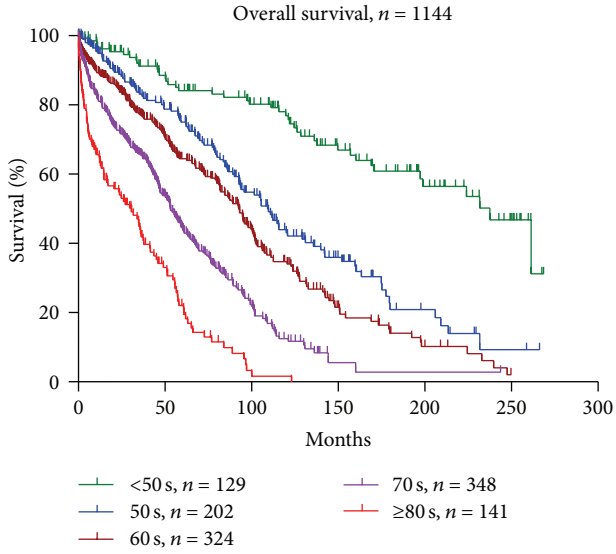
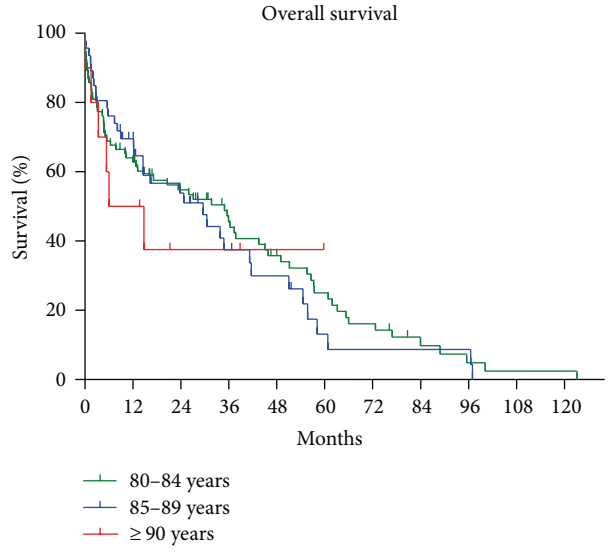


Figure 2: Overall survival in 1144 dialysis patients according to age.



Number at risk								
80–84 years	84	52	40	28	20	14	3	1
85–89 years	47	30	20	12	9	3	2	0
≥90 years	10	6	3	3	2	1		

Figure 3: Overall survival in 144 dialysis patients aged ≥80 years. The median survivals in the age groups of 80–84, 85–89, and >90 years were 3.0, 2.5, and 0.9 years, respectively. There were no significant differences in survival among the groups.

in the following age groups: <50 years (<50 s), 50–59 years (50 s), 60–69 years (60 s), 70–79 years (70 s), and ≥80 years (≥80 s), respectively. The median survival times were 20, 9.1, 7.7, 4.4, and 2.6 years in the same age groups (Figure 2). The most frequent and second most frequent causes of death were cerebro-cardiovascular disease and infectious diseases, respectively, except for patients in the ≥80s group. Mortality increased with age. The estimated mean life-shortening values were −30.1, −22.5, −14.6, −9.4, and −5.3 years, respectively, in deceased patients in the five age groups.

Characteristics of the 141 patients in the ≥80s group are summarized in Table 2. All patients were undergoing hemodialysis, and their median age was 83 years. The median survival times in patients aged 80–84, 85–89, and >90 years old were 3.0, 2.5, and 0.9 years, respectively (Figure 3). Among the 141 patients, 107 deaths (76%) were recorded as of July 31, 2013. The highest number of patients who died within 1 year was 49 (46%). The most frequent causes of death were infectious disease in 35 patients (33%), and the second most frequent causes of death were cerebro-cardiovascular disease in 29 patients (27%). The median estimated life-shortening period was −5.3 years in deceased patients aged ≥80 years.

Table 2: Characteristics of dialysis patients aged ≥80 years.

	All	Living	Deceased	*P* value
Number of patients	141	34	107	
Male/female	73/68	17/17	56/15	*0.0026*
Duration from first visit to dialysis initiation (months)	4.2 ± 13	8.3 ± 18	4.2 ± 11	*0.2154*
Age at start dialysis (years)	84 ± 3.1	84.5 ± 3.6	84.1 ± 3.0	*0.5540*
Deceased within 1 year			49 (46%)	
ECOG-PS at dialysis initiation	2.2 ± 1.3	1.2 ± 1.4	2.2 ± 1.2	*0.0004*
Cerebro-cardiovascular disease	88 (62%)	20 (59%)	68 (64%)	*0.6200*
Diabetes mellitus	49 (35%)	11 (32%)	38 (36%)	*0.7360*
Mean blood pressure (mmHg)	117 ± 21	114 ± 22	117 ± 22	*0.4817*
Systolic	156 ± 31.7	159 ± 34.1	156 ± 31.1	*0.7437*
Diastolic	78 ± 16	69.6 ± 15.6	77.6 ± 16.2	*0.0132*
Body mass index	22 ± 4.3	23.2 ± 4.0	22.2 ± 4.4	*0.2319*
Hemoglobin (g/L)	8.9 ± 1.9	9.2 ± 1.9	8.9 ± 1.9	*0.4054*
BUN (mg/dL)	84 ± 33	76.7 ± 33.7	83.5 ± 33.1	*0.3071*
eGFR	8.4 ± 4.5	7.9 ± 4.1	8.4 ± 4.7	*0.5604*
Albumin (mg/dL)	3.4 ± 0.6	3.5 ± 0.5	3.4 ± 0.7	*0.1813*
Phosphorus (mg/dL)	5.3 ± 1.6	5.0 ± 1.3	5.3 ± 1.7	*0.2801*
Potassium (mEq/L)	4.8 ± 1.0	5.0 ± 0.8	4.8 ± 1.0	*0.3065*
Calcium (mg/dL)	8.8 ± 0.7	8.4 ± 0.6	8.1 ± 0.8	*0.0110*

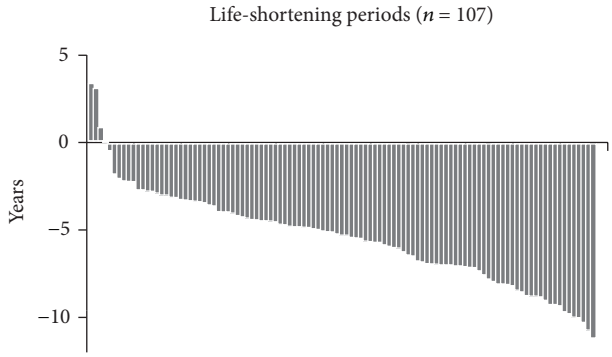


Figure 4: Life-shortening periods in dialysis patients aged ≥80 years. The median estimated life-shortening periods were −5.3 years in deceased patients aged ≥80 years.

Only three patients survived longer than the general life expectancy in the Japanese population (Figure 4).

Results of the multivariate analysis revealed ECOG-PS and hemoglobin levels as significant prognostic factors in elderly patients undergoing hemodialysis (Table 3). Risk criteria were constructed using these significant independent risk factors for stratification of patient survival. The optimal cut-off points calculated from ROC curves for ECOG-PS and hemoglobin level were >1 and <9.55 g/L, respectively. Patients were then categorized according to the number of independent risk factors for overall survival. This risk classification indicated significantly poor prognoses in the intermediate- and high-risk groups compared with those in the low-risk group ($P = 0.0059$) (Figure 5). The median survival time in the low-risk group was 63 months, whereas that in the other groups was 23-24 months.

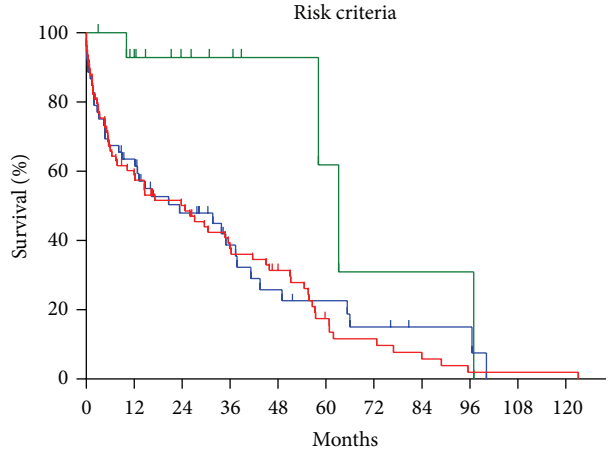
4. Discussion

In Japan, the number of elderly patients with end-stage renal disease requiring dialysis treatment continues to grow. Data from the latest Japanese Society for Dialysis Therapy database (2012) showed that the number of dialysis patients aged ≥80 years increased by more than 8% between 2005 and 2013 [3], and 22% of all dialysis patients were aged ≥80 years. Several studies have particularly evaluated the indications and outcomes of maintenance dialysis in elderly patients [11–18]; however, no reports have examined prognosis in these patients in Japan. In this study, survival outcome in elderly Japanese hemodialysis patients aged ≥80 years was compared with that in the general population. The median survival time of 2.6 years was comparable to that in previous reports of approximately 2.4–3.2 years [13, 16, 17, 19].

Japan is a country where life expectancy is high [4, 20]. Thus, in the general population, life expectancy among patients aged ≥80 years is 7.6 years. The estimated median life-shortening period calculated from the life expectancies table was −5.3 years in deceased patients. These data could not be compared with those from other industrialized countries; however, comparison using the estimated median life-shortening periods from various countries may reveal social differences, including those related to medical or insurance systems. Further studies are required on this issue. Because elderly patients on hemodialysis constitute a heterogeneous

Table 3: Results of univariate and multivariate Cox regression analyses for overall survival in dialysis patients aged ≥80 years.

	Univariate analysis				Multivariate analysis		
	P value	HR	95.0% CI		*P* value	HR	95.0% CI
Age (years)	*0.443*	1.024	0.96–1.09				
Cerebro-cardiovascular disease	*0.163*	1.327	0.89–1.98				
Diabetes mellitus	*0.976*	0.994	0.67–1.46				
ECOG-PS	*0.000*	1.327	1.15–1.54	ECOG-PS	*0.004*	1.27	1.08–1.49
Mean blood pressure (mmHg)	*0.164*	0.994	0.99–1.01				
Body mass index	*0.060*	0.961	0.92–1.01				
Hemoglobin (g/L)	*0.231*	1.070	0.96–1.20	Hemoglobin	*0.040*	1.13	1.01–1.28
BUN (mg/dL)	*0.177*	1.004	0.99–1.01				
eGFR (mL/min./1.73 m^2)	*0.782*	1.006	0.97–1.05				
Albumin (mg/dL)	*0.013*	0.652	0.47–0.91	Albumin	*0.067*	0.71	0.48–1.03
Phosphorus (mg/dL)	*0.068*	1.132	0.99–1.29				
Potassium (mEq/L)	*0.265*	1.133	0.91–1.41				
Calcium (mg/dL)	*0.861*	1.024	0.79–1.33				
Antihypertensive agents	*0.275*	1.324	0.80–2.19				



Number at risk

Low risk	15	12	8	6	4	3	2	2	2
Inter. risk	53	32	21	13	9	7	5	3	2
High risk	73	43	34	25	19	10	6	4	2

Figure 5: Risk classification for prognosis in dialysis patients aged ≥80 years. Each patient was categorized according to the number of selected risk factors using Cox regression multivariate analysis to evaluate the predictive potential of risk criteria for prognosis. Each existing risk factor was scored as 1, and scores for all the other risk factors were summated. Patients were classified into three groups according to the number of risk factors: the low-risk group (patients with no risk factor), the intermediate-risk group (1 risk factors), and the high-risk group (2 risk factors).

group of patients, their chronological age may not necessarily correlate with their biological age. Several risk factors pertain to elderly hemodialysis patients aged ≥80 years, including body mass index, late referral to a nephrologist, poor performance status, presence of peripheral vascular disease [17], older age, acute congestive heart failure, any walking impairment, and hemoglobin level (<10 g/L) [18]. Establishing a standard risk-associated classification system for planning dialysis initiation may help clinicians in treatment decision-making. In the multivariate Cox analysis, independent predictors for overall survival were ECOG-PS ≥1 and hemoglobin level was ≤9.55 g/L. Based on these risk criteria, survival rates were significantly lower in the intermediate- and high-risk groups.

Because of technological advancements in dialysis treatment, old age is no longer considered as a contraindication in

most industrialized countries [15–18, 21, 22]. Recent studies suggested that dialysis provides a survival benefit compared with conservative management for patients with stages 4-5 chronic kidney disease over the age of 75 years [23–25]. However, dialysis may or may not offer a substantial prolongation of life expectancy with an acceptable quality of life (QOL) among elderly patients. QOL is very important for older patients for whom renal transplantation is an unlikely option. However, very few studies have addressed QOL issues in elderly patients with end-stage renal disease because of the controversial nature of this decision [19, 21, 26]. Lamping et al. reported no significant differences in QOL scores between elderly dialysis patients and elderly individuals in the general population in the UK and USA [26]. In contrast, Tamura et al. reported an association between dialysis initiation and substantial and sustained decline in functional status among nursing home residents with end-stage renal disease [27]. Carson et al. demonstrated prolonged survival for elderly patients (≥70 years of age) on dialysis compared with those conservatively treated. However, survival time in patients who were conservatively treated may be substantial, considering that a similar number of hospital-free days was recorded for both groups of patients [19]. Benefits and disadvantages of dialysis in elderly patients and its effects on QOL continue to be debated. The particular needs and traditional customs of the populations in each individual country or region must be considered. In addition, because randomized controlled trials comparing outcomes and QOL in patients receiving renal replacement therapy compared with those conservatively treated are not feasible, observational studies remain the only means by which treatment methods can be compared.

The present study has several important limitations, including its retrospective nature, small sample size, and the inclusion of patients within a single institution. We could not address the total dose and its influences of erythropoiesis-stimulating agents. There might be association between the dose of erythropoiesis-stimulating agents and patients' death. Higher use of erythropoiesis-stimulating agents for poor responder or excessively higher hemoglobin levels may link to poor prognosis. Therefore, the results of this study cannot be generalized. In addition, the primary question as to who will receive survival and comprehensive benefits may remain unanswered. In elderly patients undergoing hemodialysis, details of patient characteristics such as late referral, presence of peripheral vascular disease, frailty, and information regarding QOL were lacking and must therefore be considered in future studies.

Despite these limitations, the present study provided some useful information. Shortening of life expectancy was investigated using the National Vital Statistics survey database for Japan in 2008. Because medical and insurance systems differ among countries, decision-making regarding dialysis initiation and its indications may also differ. Because Japan is a country with a high life expectancy rate [4, 20], life expectancy in elderly patients should be calculated using life expectancy tables in each individual country or region. The present study is the first to investigate the shortening of life expectancy in Japanese hemodialysis patients aged ≥80 years.

5. Conclusion

In conclusion, the results of this study shed light on the prognosis of elderly dialysis patients in Japan, whose number is increasing. Our observations suggest that old age is no longer considered as a contraindication, and hemodialysis initiation is acceptable for the rather elderly patients with end-stage renal disease in consideration of risk factors. Further clinical study is required to determine the most appropriate treatment for elderly patients with end-stage renal failure. A new evaluation system is required to aid decision-making between conservative or renal replacement therapy with consideration of comorbidities, health status, and patient preferences in the elderly Japanese population.

Conflict of Interests

All authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

rHuEPO Hyporesponsiveness and Related High Dosages Are Associated with Hyperviscosity in Maintenance Hemodialysis Patients

Mehtap Erkmen Uyar,[1] Selami Kocak Toprak,[2] Hatice Saglam,[3] Emre Tutal,[1] Meltem Bay,[4] Osman Ilhan,[4] Zeynep Bal,[1] and Siren Sezer[1]

[1] *Department of Nephrology, Baskent University Medical School, 06490 Ankara, Turkey*
[2] *Department of Hematology, Baskent University Medical School, 06490 Ankara, Turkey*
[3] *Department of Internal Medicine, Baskent University Medical School, 06490 Ankara, Turkey*
[4] *Department of Hematology, Ankara University Medical School, 06490 Ankara, Turkey*

Correspondence should be addressed to Mehtap Erkmen Uyar; mehtap94@yahoo.com

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Objective. Increased viscosity may increase the risk of thrombosis or thromboembolic events. Recombinant human erythropoietin (rHuEPO) is the key stone treatment in anemic ESRD patients with the thrombotic limiting side effect. We evaluated the influence of clinical and laboratory findings on plasma viscosity in MHD patients in the present study. *Method*. After applying exclusion criteria 84 eligible MHD patients were included (30 female, age: 54.7 ± 13.7 years). *Results*. Patients with high viscosity had longer MHD history, calcium × phosphorus product, and higher rHuEPO requirement (356.4 versus 204.2 U/kg/week, *P*: 0.006). rHuEPO hyporesponsiveness was also more common in hyperviscosity group. According to HD duration, no rHuEPO group had the longest and the low rHuEPO dosage group had the shortest duration. Despite similar Hb levels, 68% of patients in high rHuEPO dosage group; and 38.7% of patients in low rHuEPO dosage group had higher plasma viscosity (*P*: 0.001). Patients with hyperviscosity had higher rHuEPO/Hb levels (*P*: 0.021). Binary logistic regression analyses revealed that rHuEPO hyporesponsiveness was the major determinant of hyperviscosity. *Conclusion*. We suggest that the hyperviscous state of the hemodialysis patients may arise from the inflammatory situation of long term HD, the calcium-phosphorus mineral abnormalities, rHuEPO hyporesponsiveness, and related high dosage requirements.

1. Introduction

The resistance of blood against blood flow is called plasma viscosity. Blood is a complex body fluid, so not only body temperature but also components of blood like hematocrit and plasma and rheological characteristics like the deformability of erythrocytes all affect plasma viscosity [1]. Plasma viscosity is influenced by diseases with altered plasma protein composition, determined by various macromolecules, for example, fibrinogen, immunoglobulin, and lipoproteins [2, 3]. An elevated viscosity significantly increases the risk of inflammatory diseases; the strong positive correlation between plasma viscosity and fibrinogen has been reported in several studies [2, 3].

Chronic kidney disease (stages 4 and 5) (CKD) is also associated with alterations of coagulation that favor a hypercoagulable or prothrombotic state [4, 5] and thus an increased thrombotic risk that may contribute to an increase in cardiovascular morbidity and mortality [6]. In the uremic state, mechanisms including hypertension, hyperhomocysteinemia, dyslipidemia with high lipoprotein (a) (Lp(a)) levels, elevation of hemostatic derived cardiovascular risk factors (fibrinogen and proconvertin) [6], and amplification of the inflammatory cascade at the endothelial cell (growth factors,

cytokines, and adhesion molecules) [7] are activated [8]. The characteristic of blood flow is closely related to the blood flow circumstances with all the factors above as seen in atherosclerotic diseases [9].

Elevated plasma viscosity results in greater flow resistance and a high incidence of circulatory complications [10]. Increased blood and plasma viscosity has been described in patients with coronary and peripheral arterial disease. An increase in factor VII plasma levels, hematocrit, and platelet function [11–13] and a decrease in anticoagulant protein S, C, and antithrombin III [14, 15] have been described in ESRD. Increased viscosity may increase the risk of thrombosis or thromboembolic events [16].

In ESRD patients the limiting side effect of recombinant human erythropoietin (rHuEPO) is the thrombotic side effect. Several reports have associated long-term rHuEPO treatment with thrombotic complications of arteriovenous fistulae, convulsion and cerebrovascular disease, hyperviscosity, and hypertension [17–21]. In patients undergoing dialysis, the risk of death has been shown to be inversely associated with a good hematopoietic response to rHuEPO [22]. It has specifically been shown in the TREAT cohort that poor hemoglobin response to ESA treatment is associated with poor outcomes [23]. The patients with the poorest initial response received the highest average doses of ESAs and had the highest event rates [24]. Also the weak association between a poor initial response and the C-reactive protein level also suggests that inflammatory factors may contribute to a poor initial response [25]. Normal hemoglobin levels in patients without rHuEPO usage had no influence on mortality [25].

In the light of all these data, we planned to evaluate the influence of clinical and laboratory findings including iron parameters, hemoglobin, albumin, CRP, parathyroid hormone, and monthly rHuEPO requirements on plasma viscosity in maintenance hemodialysis (MHD) patients in this present study.

2. Patients and Methods

258 ESRD patients receiving MHD in our hemodialysis unit for at least 12 months were prospectively analyzed for 12 months. Patients who had active infection, iron deficiency (ferritin levels < 200 mg/dL or transferrin saturation < 20%), malignancy, severe clinical malnutrition, receiving antiaggregant, or anticoagulant therapy (except intradialytic heparinization) were excluded. After applying exclusion criteria 84 eligible patients were included (30 female, age: 54.7 ± 13.7 years). Informed consent was obtained in each patient. Plasma viscosity was studied in a fasting blood sample which was sampled just before a clinically stable HD session. Plasma viscosities of all subjects were measured at 37°C in a Brookfield DV-II + Clone Plate Viscometer [Brookfield, Stoughton, MA, USA]. Data including iron parameters and treatment dosage, hemoglobin, albumin, CRP, calcium, phosphorus, parathyroid hormone, and monthly rHuEPO requirement were collected from patient charts and a mean value of the 12 months follow-up period was recorded as the final data. Patients' thromboembolic events like myocardial infarction, cerebrovascular disease, deep venous thrombosis and pulmonary thromboembolism, and arteriovenous fistula complications (like thrombus, emboli, or clotting) were analyzed and recorded in the one-year followup.

Study group was divided into two equal sized groups as high (n: 42) and low viscosity groups (n: 42) for statistical analysis. Then these two groups were compared with each other in means of demographical and biochemical characteristics. rHuEPO hyporesponsiveness was defined as rHuEPO requirements >150 U/kg/week to achieve a target hemoglobin level of 11-12 g/dL. We classified patients receiving rHuEPO (>150 U/kg/week) as hyporesponsive (n: 40), low dose rHuEPO (75–300 U/kg/week) (n: 23), and no rHuEPO (n: 21) groups.

2.1. Statistical Analysis. Statistical analyses were performed by using SPSS software (Statistical Package for the Social Sciences, version 11.0, SSPS Inc., Chicago, IL, USA). Normality of data was analyzed by using a Kolmogorov-Smirnov test. All numerical variables with normal distribution were expressed as the means ± standard deviations (SD), while variables with skew distribution were expressed as medians and interquartile range (IR). Categorical variables were expressed as percentages and compared by chi-square test. Normally distributed numeric variables were analyzed by independent samples t- or one-way ANOVA (post hoc Tukey) tests according to distribution normality. Skew distributed numeric variables were compared using the Mann-Whitney U and Kruskal-Wallis tests according to distribution normality. Spearman and Pearson Correlation tests were used for correlation analyses. A P value <0.05 was considered as statistically significant.

3. Results

Demographic and biochemical characteristics of study groups are summarized in Table 1. Plasma viscosity of whole study group was 2.52 ± 0.65 (range 1.6–3.9) mPas. Plasma viscosity was positively correlated with duration of MHD (r: 0.287, P: 0.008, Figure 1). Comparison of high and low viscosity groups revealed that patients with high viscosity had longer MHD history (133.2 ± 77.1 versus 97.5 ± 83.1 months, P: 0.044), higher calcium (9.51±0.61 versus 9.13±0.65 mg/dL, P: 0.009), phosphorus (5.18 ± 0.8 versus 4.71 ± 1.09 mg/dL, P: 0.035), calcium × phosphorus product (49.37 ± 9.39 versus 43.45 ± 11.4, P: 0.011), and higher rHuEPO requirement (356.4 (295.7) versus 204.2 (350.8) U/kg/week, P: 0.006, Table 2). rHuEPO hyporesponsiveness was also more common in hyperviscosity group (28/42, 66.7% versus 13/42, 31%, P: 0.004). those of Patients with hyperviscosity had higher rHuEPO/Hb levels (P: 0.021). In hyperviscosity group the rHuEPO requirements of patients were higher (28/42, 66.7% versus 13/42, 31%, P: 0.004) than patients having lower viscosity.

According to the one-year follow-up data of the patients, thromboembolic complications of arteriovenous fistula were significantly higher in patients with hyperviscosity in than

Table 1: Demographic and biochemical characteristics of the whole study group.

	Study group (n = 84)
Age (years)	54.88 ± 13.7
Gender (F/M)	30/54
Mean plasma viscosity (mPas)	2.52 ± 0.65
MHD duration (months)	115.41 ± 81.72
Mean serum Hb level (g/dL)	11.28 ± 1.53
Mean serum WBC count (/μL)	7.40 ± 1.84
Mean serum Plt count (/μL)	215.89 ± 64.35
Median serum PTH level (pg/mL)	397.85 (498.30)
Mean serum Ca level (mg/dL)	9.31 ± 0.65
Mean serum P level (mg/dL)	4.95 ± 1.00
Mean Ca × P product	46.41 ± 10.80
Mean serum CRP level (mg/L)	16.28 ± 11.28
Mean serum albumin level (g/dL)	3.64 ± 0.35
Median serum ferritin level (ng/mL)	531.00 (331.50)
Total parenteral iron therapy (U/12 months)	20000 (3000)
Total rHuEPO usage (U/kg/week)	295.00 (422.35)
rHuEPO/Hb	25.49 ± 20.48

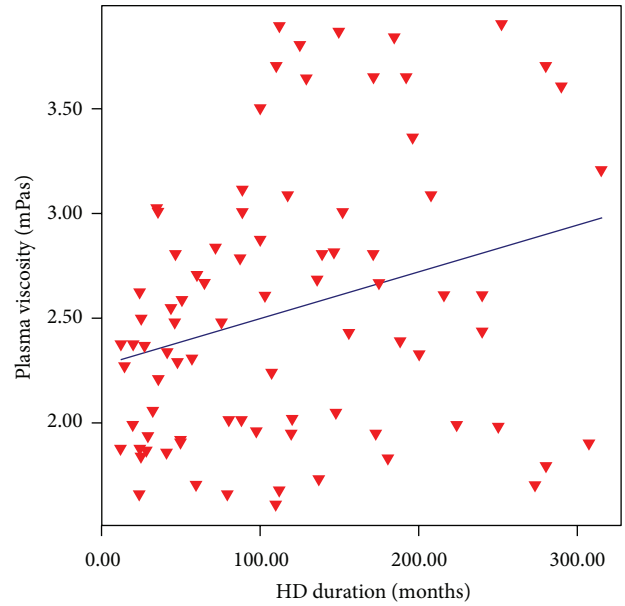

Figure 1: Plasma viscosity was positively correlated with patients' hemodialysis duration (r: 0.287, P: 0.008).

patients with lower viscosity (54.8% versus 36.3%, P: 0.023). Other thromboembolic events like myocardial infarction, cerebrovascular disease, deep venous thrombosis, pulmonary thromboembolism, and mortality rates were similar between the two groups (Table 3). Acute myocardial infarction, pulmonary thromboembolism, and mortality rates were also not significant but higher in hyperviscosity group (Table 3).

Plasma viscosity of patients with no rHuEPO group (n = 21), low rHuEPO dosage group (n = 31), and high rHuEPO dosage group (n = 32), was 2.5 ± 0.6, 2.4 ± 0.7 and 2.6 ± 0.5, respectively (P > 0.05). The clinical and biochemical characteristics of rHuEPO user and nonuser patients are summarized in Table 4. In the three groups, there was no statistically significant difference in plasma viscosity of patients between different Hb levels (P > 0.05). Despite similar Hb levels (11-12 g/dL), 68% of patients in high rHuEPO dosage group and 38.7% of patients in low rHuEPO dosage group had higher plasma viscosity (P: 0.001). According to HD duration, no rHuEPO group had the longest and the low rHuEPO dosage group had the shortest HD duration.

Binary logistic regression analyses revealed that rHuEPO hyporesponsiveness was the major determinant of hyperviscosity (P: 0.001).

4. Discussion

Hyperviscosity has effects leading to atherosclerosis, and its negative impact on atherosclerosis was found to be more intense than that of the traditional risk factors [26, 27]. Increased viscosity also has negative impact on vascular structure. Yarnell et al. found that in a population of 4860 men, death, acute myocardial infraction, and urgent cardiovascular surgery requirement were significantly higher in hyperviscosity group than in patients with lower blood viscosity [28]. On the other hand traditional cardiovascular risk factors like hypertension, obesity, smoking, high LDL-cholesterol levels and diabetes are also known to cause hyperviscosity [29–31]. Therefore, the interaction between blood viscosity and cardiovascular risk factors is complex but undeniable [32].

Survival of ESRD patients is significantly lower than that of normal population. Factors associated with increased mortality in ESRD were extensively studied and some significant factors like chronic inflammation, malnutrition, hyperphosphatemia, increased calcium × phosphorus product levels, and severe anemia are already defined as factors associated with all-cause and atherosclerosis related mortality [33–38]. In a study by Suzuki et al., the severity of atherosclerosis in maintenance hemodialysis patients was dependent on age and HD, gender, dyslipidemia, smoking, HD therapy, and HD duration [39].

In this study, we found higher plasma viscosity levels in ESRD patients undergoing MHD than that in normal population. We also found longer MHD duration, higher calcium, phosphorus, calcium × phosphorus product values, and higher dose rHuEPO requirement in patients with high viscosity. rHuEPO hyporesponsiveness was also more common in hyperviscosity group as for similar Hb levels higher dosage rHuEPO were required in this group. Longer HD duration and high dosage rHuEPO usage due to rHuEPO hyporesponsiveness were the major determinants of hyperviscosity.

In chronic kidney disease, serum calcium and especially phosphorus levels have been associated with vascular calcification and atherosclerosis [40]. Studies have shown a correlation between elevated phosphorus levels in dialysis and mortality [41]. Phosphorus has been shown to be an independent risk factor for cardiovascular disease

Table 2: Demographic and biochemical characteristics of the study groups.

	Group 1 ($n = 42$) (lower viscosity)	Group 2 ($n = 42$) (hyperviscosity)	P value
Age	55.4 ± 14.8	54.3 ± 12.5	0.728
HD duration (months)	97.5 ± 83.1	133.2 ± 77.1	0.044
PTH (pg/mL)	492.3 ± 500.3	562 ± 436	0.498
Calcium (Ca) (mg/dL)	9.1 ± 0.6	9.5 ± 0.6	0.009
Phosphor (P) (mg/dL)	4.7 ± 1	5.1 ± 0.8	0.035
Ca × P	43.4 ± 11.4	49.3 ± 9.3	0.011
Albumin (g/dL)	3.7 ± 0.3	3.5 ± 0.3	0.171
URR (%)	69.4 ± 5.8	71.7 ± 6.1	0.079
Hb (g/dL)	11.4 ± 1.7	11.1 ± 1.3	0.439
Platelet (/μL)	221.8 ± 66.4	209.7 ± 62.3	0.396
CRP (mg/L)	16.7 ± 11.4	15.8 ± 11.2	0.735
Gender (F/M)	12/32	18/24	0.255
Need of rHuEPO usage for Hb 11-12 g/dL (%)	31	66.7	0.004
rHuEPO dosage (U/kg/week)	204.2 (350.8)	356.4 (295.7)	0.006
rHuEPO/Hb	20.39 ± 19.83	30.71 ± 20.04	0.021

Table 3: Thrombotic complications and mortality of the study groups.

	Group 1 ($n = 42$) (lower viscosity)	Group 2 ($n = 42$) (hyperviscosity)	P value
Thrombotic AVF complications (n, %)	13, 30.9%	23, 54.7%	0.023
Acute myocardial infarction (n, %)	8, 19%	13, 30.9%	0.208
Deep venous thrombosis (n, %)	2, 4.7%	0	0.152
Pulmonary thromboembolism (n, %)	0	1, 2.38%	0.314
Cerebrovascular disease (n, %)	2, 4.7%	1, 2.38%	0.557
Mortality (n, %)	3, 7.1%	5, 11.9%	0.457

[42], including increased intima media thickness [43–45], vessel stiffness [46, 47], and left ventricular hypertrophy [44]; PTH per se may contribute to vascular injury via mechanisms other than its effect on calcium-phosphorus homeostasis [48]. In previous studies, a strong correlation between higher rates of vascular calcification, cardiovascular mortality, and malnutrition and endothelial dysfunction and inflammation states were found in dialysis patients [49–51]. Serum fetuin-A levels, as both a calcification inhibitor protein and a negative acute-phase reactant, are significantly lower in dialysis patients and results of these studies suggest a link between inflammation and atherosclerosis in these patients [49–51]. In this present study, patients with high viscosity levels were found to have higher calcium, phosphorus, and calcium × phosphorus product values but similar CRP levels (mean 16.28 ± 11.28 mg/dL) when compared to low viscosity group. We suggest that long HD duration and high calcium and phosphorus levels leading endothelial dysfunction and microinflammation may cause hyperviscosity, thus increased thrombogenicity and atherosclerotic lesions.

Iron deficiency can increase the number of platelets in blood, which is linked with a hypercoagulable state [52]. As serum iron is an important regulator of thrombopoiesis and normal iron levels are required to prevent thrombocytosis by acting as an inhibitor [53], we selected patients with normal iron parameters.

Although anemia has been associated with increased rates of death and complications in patients with chronic or end stage kidney disease [54, 55] a reduced hematopoietic response to ESAs has also been associated with an increased risk of an adverse outcome [56–60]. It has been shown in the TREAT cohort that the patients with the poorest initial response to ESA treatment received the highest average doses of ESAs and had the highest event rates and the poor outcome [23]. Of note, a higher rate of increase in the hemoglobin level was not associated with greater risk. Indeed, patients with the greatest increase in hemoglobin level during the initial month of therapy had the lowest risk of clinical events [24]. In our study, higher dosage of rHuEPO was required for similar Hb levels in hyperviscosity group without iron deficiency.

Higher ESA requirements may lead to an increased risk for adverse outcomes due to the underlying factors affecting rHuEPO response, such as inflammation, and the potential nonerythropoietic effects of greater administered ESA doses [23, 61, 62]. However, the pathway inducing inflammation-mediated EPO resistance has not been determined [63]. The inflammatory cytokines are in turn thought to directly inhibit erythropoiesis and promote apoptosis of erythroid precursors [64, 65]. In our study, the serum CRP levels of both groups with high and low viscosity were similar and slightly

Table 4: Demographic and biochemical characteristics of the study groups.

	Patients with no rHuEPO ($n = 21$)	Patients with low dose rHuEPO ($n = 31$)	Patients with high dose rHuEPO ($n = 32$)
Age (years)	54.3 ± 8.9	57.6 ± 17.4	53.5 ± 13.4
Mean plasma viscosity (mPas)	2.5 ± 0.6	2.4 ± 0.7	2.6 ± 0.5
MHD duration (months)	141.3 ± 87.6	83.7 ± 79.8	120.0 ± 75.5
Mean serum Hb level (g/dL)	13.1 ± 1.1	10.7 ± 1.06	10.5 ± 1.02
Mean serum Plt count (/μL)	216.4 ± 60.4	209.7 ± 59.5	219.2 ± 70.1
Median serum PTH level (pg/mL)	409.5 ± 372.07	422.4 ± 359.8	649.2 ± 540.7
Mean serum Ca level (mg/dL)	9.3 ± 0.4	9.1 ± 0.7	9.4 ± 0.6
Mean serum P level (mg/dL)	4.8 ± 0.8	4.6 ± 1.03	5.1 ± 1.02
Mean serum CRP level	12.4 ± 11.6	18.08 ± 10.03	17.2 ± 11.5
Mean serum albumin level (g/dL)	3.7 ± 0.2	3.6 ± 0.3	3.6 ± 0.4
Total parenteral iron therapy (U/12 months)	2523.8 ± 1141.4	2231.3 ± 1079.2	2278.3 ± 1644.5
Mean URR (%)	68.5 ± 5.6	70.1 ± 6.6	71.9 ± 5.8

increased; the rHuEPO hyporesponsiveness in high viscosity group was not associated with clinically evident inflammation. We suggest microinflammation due to increased cytokine production as a result of comorbidity [such as heart failure, atherosclerosis, and volume overload], accumulation of advanced glycation end products, carbonyl stress, and oxidative stress could influence both viscosity and rHuEPO resistance.

In this present study, the frequency of thromboembolic complications of arteriovenous fistula [AVF] was significantly higher in patients with hyperviscosity. Vascular access failure is a major contributor to the morbidity and mortality of hemodialysis patients [66, 67]. AVF prevention and management of its complications remain the safest and most comfortable solution to ensure AVF survival and thus a satisfying survival and quality of life in MHD patients [68]. Regression analyses of our study revealed that rHuEPO hyporesponsiveness was the major determinant of hyperviscosity; therefore we strongly suggest that higher EPO dosage need in MHD may predispose thromboembolic events of AVF. Hyperviscosity seems to play a key role for thromboembolic AVF complications of rHuEPO hyporesponsiveness.

5. Conclusion

In conclusion, according to our findings we suggest that the hyperviscous state of the hemodialysis patients may arise mostly from the inflammatory situation of long-term HD, the calcium-phoshorus mineral abnormalities and rHuEPO hyporesponsiveness and related high dosage requirements. Hyperviscosity seems to play a critical role for the thrombotic side effects of rHuEPO and not hemoglobin levels but high serum viscosity level is probably associated with high serum calcium-phosphorus levels, endothelial dysfunction, and vascular calcification. Therapies targeting hyperviscosity may reduce cardiovascular complications of the hemodialysis patients. Further prospective studies with long-term followup are needed to show the exact mechanisms of hyperviscosity in hemodialysis patients.

Conflict of Interests

The authors declare that there is no conflict of interests.

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