Renal Replacement Therapy

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Prevalence of diarrhea in end-stage renal disease patients initiating hemodialysis

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Abstract

Background: Diarrhea is one of the symptoms occasionally seen in patients initiating hemodialysis. When they have diarrhea, they need several additional cares for defecation during the hemodialysis sessions and for infection control at dialysis facilities.

Methods: We retrospectively examined the prevalence and the characteristics of the patients with diarrhea initiating hemodialysis. Data were collected from medical records.

Results: Of 243 patients who initiated hemodialysis therapy, 46 patients (19%) had diarrhea. The age, gender, and etiology of end-stage renal disease did not differ between the patients with diarrhea and those without diarrhea. Body weight in the patients with diarrhea was lighter than those without diarrhea. The prevalence of concomitant diseases, such as cardiovascular diseases, malignancies, and diabetes, was not different between the groups, whereas the patients with diarrhea were complicated more frequently with infectious diseases. Antibiotics and steroids had been used more frequently in the patients with diarrhea (59% and 26%, respectively) than those without diarrhea (10% and 10%, respectively). Inflammatory markers, such as white blood cell numbers, C-reactive protein levels, and body temperature, were significantly higher in the patients with diarrhea. Serum levels of total protein, albumin, and creatinine were significantly lower in the patients with diarrhea, while urea nitrogen levels did not differ between the groups.

Conclusion: Results of the present study showed, for the first time, that 19% of the patients initiating hemodialysis had diarrhea and suggest that incident hemodialysis patients with infectious diseases and those under treatment with antibiotics and/or steroids are high-risk for diarrhea.

Keywords: Hemodialysis, Diarrhea, Uremia, Antibiotics, Steroids

Background

Diarrhea occurs occasionally in hemodialysis patients. When they have diarrhea, they need several additional cares for defecation during the hemodialysis sessions. Moreover, if diarrhea is the one caused by the infection of bacteria and/or viruses, infection control is intensively required at dialysis facilities [1, 2]. Because most patients undergo the hemodialysis therapy in a single room at the same time, infectious diarrhea easily transmits to many hemodialysis patients.

Classically, diarrhea is known as one of the symptoms for uremia [3–5]. Results of the previous studies have reported that the prevalence of diarrhea ranges from 3.5 to 17% in maintenance hemodialysis patients [6–8]. However, the prevalence of diarrhea in patients initiating hemodialysis due to end-stage renal disease (ESRD) remains unknown.

Moreover, it is considered that diarrhea occurs as a result of the combination of multiple factors, including retained molecules, deficiencies of important hormones, and metabolic factors rather than the effect of a single

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uremic toxin [5]. However, precise mechanisms remain unknown, and it is of interest to determine whether the symptom of diarrhea is related with the increased levels of uremic toxins, such as urea nitrogen and creatinine.

To address these questions, we sought to determine (1) the prevalence of diarrhea, (2) the characteristics of the patients with diarrhea, and (3) the relationship between the presence of diarrhea and the levels of uremic toxins, in ESRD patients initiating hemodialysis therapy.

Methods

Study subjects

This retrospective study was conducted at a single institution in Japan. The study protocol was approved by the Ethics Committee of Keio University School of Medicine (IRB Approval Number: 20180224). Written informed consent from the participants was waved, but the opportunity to opt out of the study was provided to the participants. Two hundred and forty-three ESRD patients who were admitted to our hospital and initiated maintenance hemodialysis therapy between January 1st, 2013, and December 31st, 2017, were recruited to the study.

Data

Data regarding sex, age, height, weight, ESRD etiology, concomitant diseases, medications, and the presence or absence of diarrhea were obtained from medical records. Laboratory data, including the levels of hemoglobin, total protein, albumin, urea nitrogen, creatinine, potassium, phosphorus, C-reactive protein, white blood cell count, and body temperature, were collected. Data regarding the stool culture were also collected. In the present study, diarrhea was defined as watery stools according to Bristol stool form scale type 6 or type 7 lasting for more than 2 days [9, 10]. The conditions of defecation from 7 days before hemodialysis initiation to 7 days after hemodialysis initiation were investigated.

Statistical analyses

Normally distributed continuous variables were expressed as the mean ± standard deviation (SD), non-normal variables as the median and interquartile range (IQR), and categorized data as the percentage frequency. To test the difference between groups, Student's unpaired *t*-test was used for normally distributed variables, Mann-Whitney test for non-normal variables, and χ^2 test for categorical data. All statistical analyses were performed using SigmaPlot/SigmaStat 9 (Systat Software Inc, San Jose, CA). $P<0.05$ was considered significant.

Results

Frequency and characteristics of the incident hemodialysis patients with diarrhea

Between January 1st, 2013, and December 31st, 2017, 243 ESRD patients initiated maintenance hemodialysis therapy at our hospital (Table 1). Their conditions regarding defecation from 7 days before hemodialysis initiation to 7 days after hemodialysis initiation were investigated. Of importance, 46 patients (19%) had diarrhea which continued over 2 days. To clarify the characteristics of the patients having diarrhea, multiple parameters were examined. The male/female ratio and the median age at the initiation of hemodialysis did not differ between the patients with diarrhea and those without diarrhea. The height of the patients with diarrhea [161 (IQR 155–166) cm] was shorter than the patients without diarrhea [165 (IQR 158–170) cm], and the weight of the patients with diarrhea [54.8 (IQR 47.9–63.2) kg] was lighter than the patients without diarrhea [61.2 (IQR 54.0–70.7) kg]. The body mass index did not differ between the two groups. The etiology of ESRD was not different between the groups. The prevalence of concomitant diseases, such as cardiovascular diseases, neurological disorders, malignancies, and diabetes, was not different between the groups, whereas the patients having diarrhea were complicated with infectious diseases more frequently (28%, 13 out of 46 cases) than those without diarrhea (9%, 18 out of 197 cases). Infectious diseases in the patients with diarrhea included pneumonia (8 cases), pyelonephritis (1 case), colitis (1 case), phlegmon (1 case), and catheter infection (2 cases). Inflammatory bowel disease was seen in only 1 patient with diarrhea, but not in the patients without diarrhea. The antibiotics and steroids had been used more frequently in the patients with diarrhea than those without diarrhea. Indeed, the antibiotics had been prescribed to 59% of the patients with diarrhea, whereas they had been prescribed to 10% of the patients without diarrhea. Steroids had been used in 26% of the patients with diarrhea, while 10% of the patients without diarrhea had taken steroids. On the other hand, the frequency of the use of immunosuppressive agents, chemotherapeutic agents, purgatives, proton pump inhibitors, and ferric citrate hydrate did not differ between the groups.

As shown in Table 2, inflammatory markers, such as white blood cell count, C-reactive protein level, and body temperature, were significantly higher in the patients with diarrhea than those without diarrhea. Serum levels of total protein and albumin were significantly lower in the patients with diarrhea than those without diarrhea. Serum levels of creatinine were significantly lower in the patients with diarrhea, although urea

Table 1 Characteristics of the patients

	All	Diarrhea (+)	Diarrhea (-)	
Patient number [n, (%)]	243 (100%)	46 (19%)	197 (81%)	
Male (%)	74	63	77	P=0.233[a]
Age (years)	67 (57–79)	63 (53–80)	69 (58–78)	P=0.320[b]
Height (cm)	164 (157–169)	161 (155–166)	165 (158–170)	P=0.049[b]
Weight (kg)	59.9 (52.2–69.8)	54.8 (47.9–63.2)	61.2 (54.0–70.7)	P=0.002[b]
Body mass index (kg/m^2)	23.0 (20.2–25.5)	21.4 (18.9–25.0)	23.0 (20.5–25.7)	P=0.065[b]
ESRD etiology (%)				P=0.198[a]
Primary glomerular diseases	24	30	23	
Diabetes	32	26	33	
Hypertension	19	11	21	
Others	25	33	23	
Complications (%)				
Cardiovascular diseases	31	30	31	P=0.968[a]
Neurological disorders	8	11	8	P=0.671[a]
Malignancies	10	17	9	P=0.136[a]
Infectious diseases	13	28	9	P=0.001[a]
Diabetes	38	37	38	P=0.997[a]
Medications (%)				
Steroids	13	26	10	P=0.006[a]
Immunosuppressive agents	9	15	8	P=0.230[a]
Chemotherapeutic agents	4	9	3	P=0.119[a]
Antibiotics	19	59	10	P<0.001[a]
Purgatives	21	24	20	P=0.734[a]
Proton pump inhibitors	44	50	43	P=0.459[a]
Ferric citrate hydrate	1	2	1	P=0.826[a]

Age, height, weight, and body mass index are expressed as the median values and IQR. χ^2 test (a) or Mann-Whitney test (b) was performed to test the differences between the patients with diarrhea and those without diarrhea

Table 2 Laboratory data at the initiation of hemodialysis

	All (n=243)	Diarrhea (+) (n=46)	Diarrhea (-) (n=197)	
Body temperature (°C)	36.7 (36.5–37.0)	36.8 (36.6–37.2)	36.7 (36.5–36.9)	P=0.014[a]
White blood cells (×1000/μl)	6.7 (4.7–8.3)	7.4 (5.6–9.5)	6.0 (4.6–8.0)	P=0.011[a]
Hemoglobin (g/dL)	9.1±1.6	8.8±2.1	9.2±1.5	P=0.173[b]
Total protein (g/dL)	5.9±0.8	5.5±1.0	6.0±0.8	P<0.001[b]
Albumin (g/dL)	3.0±0.6	2.6±0.6	3.1±0.6	P<0.001[b]
Urea nitrogen (mg/dL)	85 (69–105)	89 (70–108)	83 (69–104)	P=0.651[a]
Creatinine (mg/dL)	8.7 (7.0–11.0)	8.1 (4.5–10.7)	8.9 (7.2–11.4)	P=0.013[a]
Potassium (mEq/L)	4.4 (3.9–5.0)	4.4 (3.8–4.7)	4.5 (4.0–5.0)	P=0.263[a]
Phosphorus (mg/dL)	5.9 (5.0–7.3)	6.2 (4.9–7.9)	5.9 (5.0–7.2)	P=0.497[a]
C-reactive protein (mg/dL)	0.46 (0.09–2.48)	4.00 (1.34–7.72)	0.32 (0.06–1.54)	P<0.001[a]

Data are expressed as the mean ± SD for normally distributed continuous variables, or the median and IQR for non-normal variables. Mann-Whitney test (a) or Student's unpaired *t*-test (b) were performed to test the differences between the patients with diarrhea and those without diarrhea

nitrogen levels did not differ between the groups. The levels of hemoglobin, potassium, and phosphorus were not affected by the presence of diarrhea.

Relationship between diarrhea and uremic toxins

Serum levels of urea nitrogen and creatinine in the patients initiating hemodialysis were categorized and plotted in Fig. 1. Distribution of serum levels of urea nitrogen was similar between the patients with diarrhea and those without diarrhea (Fig. 1A). However, although not significant, the trend of the distribution of serum creatinine levels was different between the groups (Fig. 1B). That is, the most popular category was the range of creatinine < 6 mg/dL in the patients with diarrhea, whereas the range of creatinine >12 mg/dL was most popular in the patients without diarrhea.

Causes of diarrhea as determined by stool culture

Many patients who initiated hemodialysis therapy with diarrhea had received the examination of stool culture. The implementation rate of stool culture was 59% (27 out of 46 cases), and 48% (13 out of 27 cases) of stool cultures exhibited positive results. A variety of bacteria, such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Clostridium difficile*, were detected (Table 3). There was no tendency that a certain type of bacterial infection was dominant in the incident hemodialysis patients with diarrhea.

Table 3 Bacteria detected by the stool culture

Bacteria	n
Escherichia coli	1
Escherichia coli (ESBL-producing)	4
Escherichia coli O114&O025	1
Escherichia coli O018	1
Klebsiella pneumoniae	2
Klebsiella pneumoniae (ESBL-producing)	1
Staphylococcus aureus	1
Staphylococcus aureus (methicillin-resistant)	1
Pseudomonas aeruginosa	1
Pseudomonas aeruginosa (multi-drug resistant)	1
Clostridium difficile	3

Twenty-seven incident hemodialysis patients with diarrhea underwent the examination of stool culture. Of these, 13 patients exhibited the positive results. Some patients were positive for multiple bacteria
ESBL extended spectrum β-lactamase

Discussion

In the present study, we examined 243 ESRD patients who initiated hemodialysis therapy and showed that 19% of them had diarrhea lasting for over 2 days. The incident hemodialysis patients with diarrhea were complicated with infectious diseases more frequently than those without diarrhea, and they had been treated more frequently with antibiotics and/or steroids. We also showed that inflammatory markers, such as white blood cell count, C-reactive protein levels, and body temperature, were significantly higher in the patients with diarrhea than those without diarrhea, whereas serum levels of total protein, albumin, and creatinine were lower in the patients with diarrhea. Moreover, we demonstrated that there was no positive correlation between the presence of diarrhea and the levels of uremic toxins at the first hemodialysis session in ESRD patients. Finally, we showed that diarrhea was caused by various types of bacteria in these patients.

The infection control is of particular importance at dialysis facilities [1, 2]. First, the hemodialysis therapy uses extracorporeal circulation of the blood, which is a risk for blood-borne infections, such as hepatitis B, hepatitis C, and human immunodeficiency virus. Second, since the hemodialysis therapy is normally performed for many patients together in a single room at the same

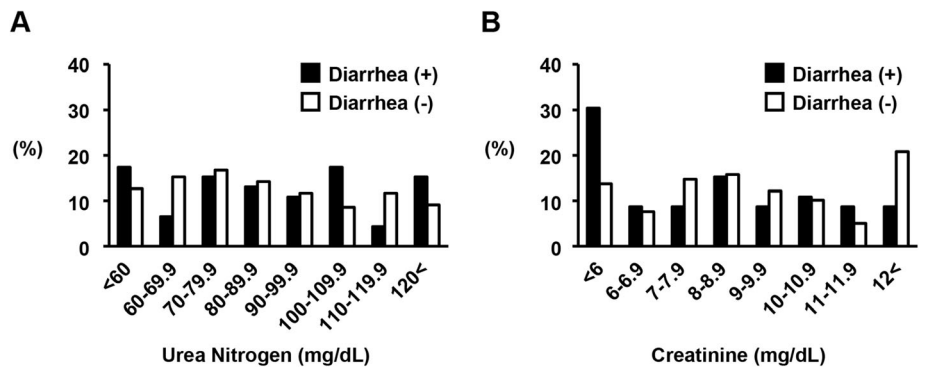

Fig. 1 Serum levels of urea nitrogen (**A**) and creatinine (**B**) before the first session of hemodialysis were categorized. The incident hemodialysis patients with diarrhea (black bars, n=46) and those without diarrhea (white bars, n=197) were analyzed. Although χ^2 test was performed, there were no differences among the groups

time, various infectious diseases, such as influenza, tuberculosis, norovirus gastroenteritis, and vancomycin-resistant enterococcal infections, rapidly and widely transmit to many hemodialysis patients. Third, hemodialysis patients themselves are in the immunocompromised state due to ESRD. Because of these situations and conditions, complete utilization of recommended infection control guidelines is essential to prevent infections in this vulnerable population. In addition to this, it is worth knowing the high-risk patients of infectious diseases for the practical infection control. In this regard, we showed that 19% of ESRD patients initiating hemodialysis exhibited diarrhea. This prevalence was higher than that of maintenance hemodialysis patients reported previously [6–8]. Moreover, we showed that the incident hemodialysis patients with infectious diseases and those being treated with antibiotics and/or steroids were high-risk for diarrhea. It is hoped that these data are useful for the infection control at dialysis facilities.

Results of the present study showed that serum levels of creatinine were significantly lower in the incident hemodialysis patients with diarrhea than those without diarrhea, whereas urea nitrogen levels did not differ between the groups. These results suggest that the ratio of urea nitrogen to creatinine was elevated in the incident hemodialysis patients with diarrhea in the present study. One of the pathophysiological conditions presenting the elevation in the urea nitrogen to creatinine ratio is dehydration. We consider that the incident hemodialysis patients with diarrhea were in the dehydrated state, thereby exhibiting the increase in the urea nitrogen to creatinine ratio. However, without the adjustment of the dehydrated state, the hemodialysis therapy was introduced because of the disproportional elevation of urea nitrogen. It is possible that the timing of the initiation of hemodialysis could have been delayed, if their dehydrated state had been treated sufficiently. Alternatively, malnutrition and/or smaller muscle volume may also contribute to the increase in the urea nitrogen to creatinine ratio. Indeed, serum levels of total protein and albumin were significantly lower in the patients with diarrhea, as compared to those without diarrhea, suggesting that the nutritional status was not good in the patients with diarrhea. Body weight in the patients with diarrhea was significantly lighter than those without diarrhea, suggesting that the muscle volume was smaller in the patients with diarrhea. These mechanisms are not mutually exclusive and may additively exacerbate the urea nitrogen to creatinine ratio.

There are multiple limitations in the present study. First, all of the 243 cases examined initiated hemodialysis at a single institution. The cases we analyzed might be unique and not to be generalized. Moreover, the retrospective nature of the analysis is also a limitation in the study. Further prospective studies are warranted to confirm and extend our findings.

Conclusion

In conclusion, the results of the present study showed, for the first time, that 19% of the patients initiating hemodialysis therapy had diarrhea, and suggest that incident hemodialysis patients with infectious diseases and those being treated with antibiotics and/or steroids are high-risk for diarrhea.

Abbreviations

ESRD: End-stage renal disease; SD: Standard deviation; IQR: Interquartile range

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Authors' contributions

MO: collected and analyzed the data, drafted manuscript, read and approved the final manuscript; HM: collected and analyzed the data, helped to draft manuscript, read and approved the final manuscript; TY: principal project leader, conceived study, participated in design and coordination, read and approved the final manuscript.

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Availability of data and materials

The dataset used during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Keio University School of Medicine (IRB Approval Number: 20180224). Written informed consent from the participants was waved, but the opportunity to opt out of the study was provided to the participants.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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