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Impact of hypokalemia on peritonitis in peritoneal dialysis patients: a systematic review

Kentaro Nakai[1,2], Kei Saito[1,2], Hideki Fujii[1] and Shinichi Nishi[1*]

Abstracts

Background: Hypokalemia is a common electrolyte disorder in peritoneal dialysis patients. Some studies showed the association of serum potassium levels with all-cause and cardiovascular mortality and infection. This review aims to clarify the relationship of hypokalemia and peritonitis in peritoneal dialysis.

Methods: The MEDLINE and Cochrane Library databases were searched for articles published from 1990 to May 2016. The following search terms were used: hypokal(a)emia, potassium, peritoneal dialysis, peritonitis, and infection. Additional studies were identified by hand searching through references and using the MEDLINE-related articles option. Two investigators independently selected studies using predefined criteria and assessed each study's quality using the Newcastle-Ottawa Quality Assessment Scale.

Results: A total of 159 abstracts were identified and 6 trials were included in the systematic review (n = 3613). One national prospective study and two retrospective single-center studies indicated that hypokalemia increases the risk of peritonitis, whether two single-center studies indicated otherwise. One case-control study indicated that lower potassium level was associated with a poor therapeutic outcome in peritonitis.

Conclusion: Convincing clinical trial data are unavailable to show the association of hypokalemia with peritonitis in peritoneal dialysis patients, and we need to clarify whether the therapeutic intervention to normalize serum potassium levels decreases the risk of peritonitis and infection-related mortality in peritoneal dialysis patients.

Keywords: Hypokalemia, Infection, Peritoneal dialysis, Peritonitis, Potassium

Background

Peritonitis is one of the specific and major complications in peritoneal dialysis, which does not occur in hemodialysis. It is well known that peritonitis is the major reason for withdrawal of peritoneal dialysis [1, 2]. Candidates for renal replacement therapy often hesitate to select peritoneal dialysis due to fear of the possibility of peritonitis.

For reducing the risk of peritonitis, various strategies are indicated in position statement of the international society for peritoneal dialysis, such as prophylactic antibiotics at catheter insertion and before invasive gastrointestinal procedures, patient training program, and avoidance of constipation [3]. In spite of those efforts of prevention of peritonitis, peritoneal dialysis-associated peritonitis rates have not been reduced sufficiently [1, 4]. Even the introduction of disconnect systems has not been dramatically improved the risk of peritonitis [5, 6].

How can we reduce the risk of peritonitis more? Although strong evidence does not exist yet, hypoalbuminemia, vitamin D insufficiency, depression, and hypokalemia are reported as the residual modifiable risk factors for peritonitis [3, 7]. Hypokalemia is common, but insufficiently studied, electrolyte disorder that occurs in patients undergoing peritoneal dialysis. This review aims to clarify the relationship between hypokalemia and peritonitis in peritoneal dialysis.

* Correspondence: snishi@med.kobe-u.ac.jp
[1]Division of Nephrology and Kidney Center, Kobe University Graduate School of Medicine, 7-5-2, Kusunoki-cho, Chuo-ku, Kobe, Hyogo 650-0017, Japan
Full list of author information is available at the end of the article

Methods

The review protocol has been registered in PROSPERO International Prospective Register of Systematic Reviews (CRD42016039950).

Search strategy and selection criteria

The MEDLINE and Cochrane Library databases were searched for articles published from 1990 to May 2016. The following search terms were used: hypokal(a)emia, potassium, peritoneal dialysis, peritonitis, and infection. Additional studies were identified by manually searching through references and using the "related articles" option in MEDLINE. Eligible studies or studies in which eligibility criteria were unclear after the title and abstract screening underwent full-text review. A study that met the following criteria was included: (1) the study compared the clinical outcomes of peritoneal dialysis patients with or without hypokalemia and (2) the study reported the incidence of peritonitis. Two reviewers (K.N. and K.S.) assessed the criteria for all studies identified for full-text review.

Data extraction and quality assessment

We extracted characteristics of the study populations (sample size, age, sex, prevalence of diabetes mellitus, and other clinical information), characteristics of the studies (study design, source of cohort, and follow-up periods), and outcome characteristics. According to the Newcastle-Ottawa scale [8, 9], the quality of the included studies was scored independently by two investigators (K.N. and K.S.), with disagreements resolved by consensus. The systematic review of the literature was performed according to PRISMA guidelines [10].

Results

Figure 1 showed the steps in study selection for this review. A total of 159 abstracts were identified, and six trials were included in the systematic review (n = 3613). Table 1 shows details of the five cohort studies that were included in the qualitative review. One study, not listed in Table 1, included 60 patients with 120 episodes of peritonitis and compared persistent episodes with usual episodes responding to antibiotic therapy within 96 h [11].

Risk-of-bias and quality assessment

All of the cohort studies defined hypokalemia as serum potassium levels below 3.5 mEq/L and controls as normokalemic subjects in the same population. The study by Ribeiro et al. [12] was well designed for our purposes and performed a propensity score analysis to account for any underlying differences between patients with a time-averaged potassium under 3.5 mEq/L and others. Although the study with the lowest risk of bias by Su et al. [13] excluded cases with acute complication including peritonitis occurred in the previous month, Su et al. [13] and Chuang et al. [14] had no description about the history of peritonitis. Peritonitis was not present at the start of the other three studies [12, 15, 16], which included only incident cases of peritoneal dialysis (Table 2). Ribeiro et al. [12] performed a national prospective cohort study with complete follow-up, whereas lost follow-up rate was not described in two retrospective studies [15, 16]. One case-control study defined controls as responding episodes from partially duplicated subjects with persistent cases [11]. In this study, the relationship between therapeutic response and serum potassium levels was adjusted by age and serum albumin levels, but specified cutoff level of potassium levels was not described.

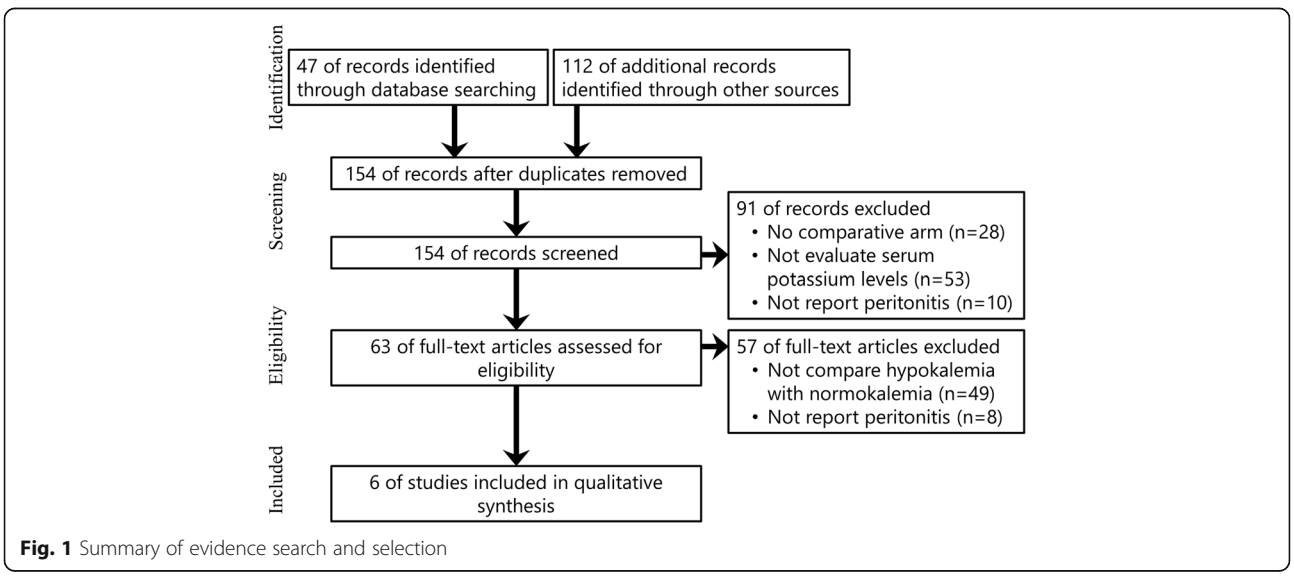

Fig. 1 Summary of evidence search and selection

Table 1 Details of cohort studies included in this analysis

Study and year (reference)	Design	Sample size	Population	Age (y.o)	Men (%)	DM (%)	Follow-up period	Peritonitis rate (patient-month per episode)
Ribeiro, 2015 [12]	Prospective cohort	1817	National wide	62.7	37.0	45.2	Not described	Not described
Fan, 2014 [16]	Retrospective cohort	1117	Single center	48.3	58.7	22.6	26.1 months	60.0
Liawnoraset, 2011 [15]	Retrospective cohort	318	Single center	49.9	50.9	34.9	3262.2 patient-months	25.5
Su, 2012 [13]	Prospective cohort	158	Single center	62.46	51.3	29.7	22.09 months	75.87
Chuang, 2009 [14]	Retrospective cohort	140	Single center	47.8	39.3	18.4	1961 patient-months	30.6

Trial characteristics and outcome

A summary of study characteristics is shown in Table 1. A Brazilian national cohort study [12] enrolled older subjects and higher prevalence of diabetes than the other single-center cohort studies. In this study, hypokalemia based on time-average potassium levels, measured monthly in all patients throughout the whole observational period, had a higher risk for time to first peritonitis episode compared to propensity-matched patients (Fig. 2). Chuang et al. [14] showed that the prevalence of peritonitis was significantly higher in patients with at least one episode of hypokalemia than those with normokalemia (6.9 vs. 2.1%, respectively, $p < 0.001$). Although the association was not adjusted for any confounders, there was no correlation between peritonitis and age, body mass index, and gender, with or without diabetes mellitus, as well as comorbidity. Liawnoraset [15] showed that patients with hypokalemia had a lower mean peritonitis-free survival time than those without hypokalemia in subgroup univariate analysis (16.2 vs. 28.1 months, $p < 0.05$). Similarly, patients > 60 years old with hypoalbuminemia had a lower mean peritonitis-free survival time. However, the association of hypokalemia and peritonitis was not adjusted for any confounders, including age and serum albumin levels. Fan et al. [16] reported that hypokalemia based on the potassium levels, measured within 1 to 3 months of the start of peritoneal dialysis therapy, was not associated with the risk for the first episode of peritonitis. Su et al. [13] also showed that hypokalemia based on the potassium levels, measured only at the time of symptoms survey, was not associated with a first peritonitis episode during the follow-up period. Murata et al. [11] indicated that lower potassium level, based on the four-month mean immediately before the episode of peritonitis, was associated with a poor therapeutic response of peritonitis in case-control study.

Discussion

The association between hypokalemia and peritonitis in patients undergoing peritoneal dialysis is feasible but currently inconclusive. Because common effect indicators could not be derived from the information described in the papers, some studies were excluded from Fig. 2. The results were controversial and insufficiently adjusted for confounding factors contributing to the association between peritonitis and hypokalemia. Occasionally, hypokalemia has close links with poor dietary intake, malnutrition, and poor general condition (Fig. 3), so that the association with peritonitis also may depend on such status. Ultimately, we must determine whether the therapeutic interventions used to normalize serum potassium levels, such as the administration of potassium chloride and adjustment of food or dialysate, decrease the risk of peritonitis and infection-related mortality in patients undergoing peritoneal dialysis. In fact, hypokalemia is so common in peritoneal dialysis that several attempt to adjust serum potassium levels in such patients [17, 18]. The effectiveness of spironolactone for peritoneal dialysis patients was evaluated in

Table 2 Risk of bias in included cohort studies

Study and year (reference)	Representativeness	Selection of controls	Exposure ascertained	Not present at outset	Comparability	Outcome assessment	Duration of follow-up	Adequacy of follow-up
Ribeiro, 2015 [12]	1	1	1	1	2	1	0	1
Fan, 2014 [16]	1	1	1	1	2	1	1	0
Liawnoraset, 2011 [15]	1	1	1	1	0	1	1	0
Su, 2012 [13]	1	1	1	1	2	1	1	1
Chuang, 2009 [14]	1	1	1	0	0	1	1	1

The Newcastle-Otawa Scales were used to assess risk of bias for the cohort studies. Each domain was rated on a maximum of one star, except comparability, which can be given up to two stars. 0, high risk of bias or no description; 1 or 2, low risk of bias

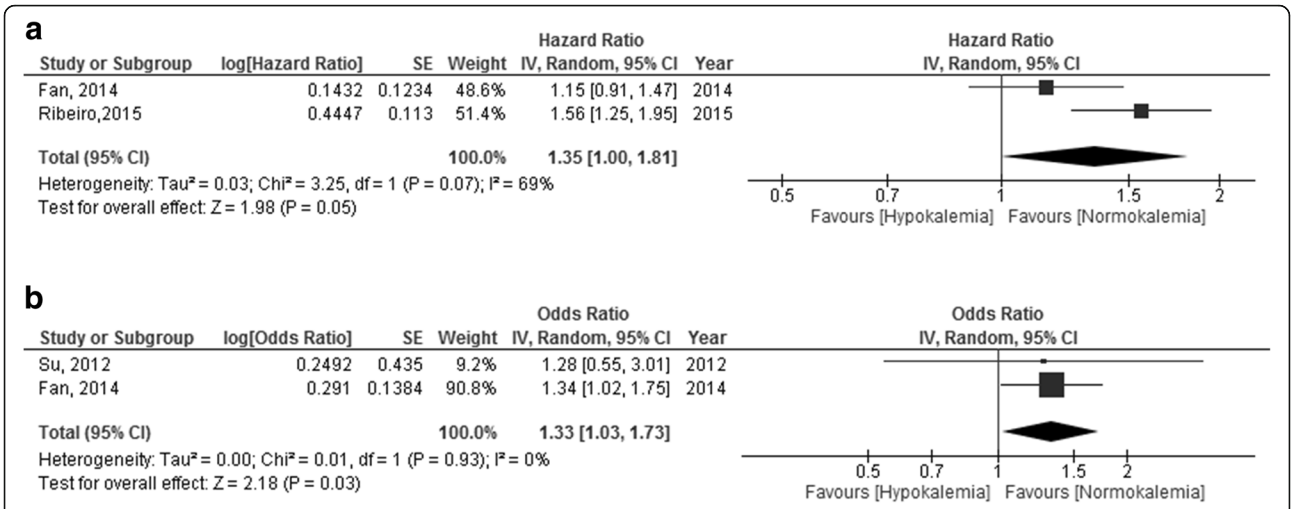

Fig. 2 Comparison of the time to first peritonitis episode (**a**) and the first peritonitis episode (**b**) with and without hypokalemia

several surveys [17, 19, 20]; however, serum potassium levels were not influenced by spironolactone in two studies [17, 19]. Ito, et al. [20] showed that serum potassium levels were increased in patients with spironolactone, but the prevalence of hypokalemia and peritonitis were comparable between patients with and without spironolactone. Yi et al. [21] showed the effect of glucose-free icodextrin on the improvement of hypokalemia compared with conventional glucose-containing dialysate, possibly through an enhanced nutritional status and an intracellular potassium shift. Spital et al. [18] reported the effectiveness of acute potassium loading via the dialysate in peritoneal dialysis patients; however, the influence to peritonitis was not studied. The risk of potassium supplements should also be considered. For example, in patients with chronic heart failure, potassium supplements could increase hospitalization because of worsening heart failure against all expectations [22].

Several mechanisms can be speculated for hypokalemia to promote peritonitis in peritoneal dialysis (Fig. 3). At first, hypokalemia may induce gastrointestinal dysmotility [23] and intestinal bacterial overgrowth [24]. As a result, the translocation of bacteria from the intestine to peritoneal cavity may cause peritonitis. Moreover, potassium chloride supplementation decreased pain intensity and erythrocyte sediment rate in patients with rheumatoid arthritis [25] and may have the protective effect on inflammatory response [26].

Conclusions

Our review could not find a consistent correlation between hypokalemia and peritonitis in patients with

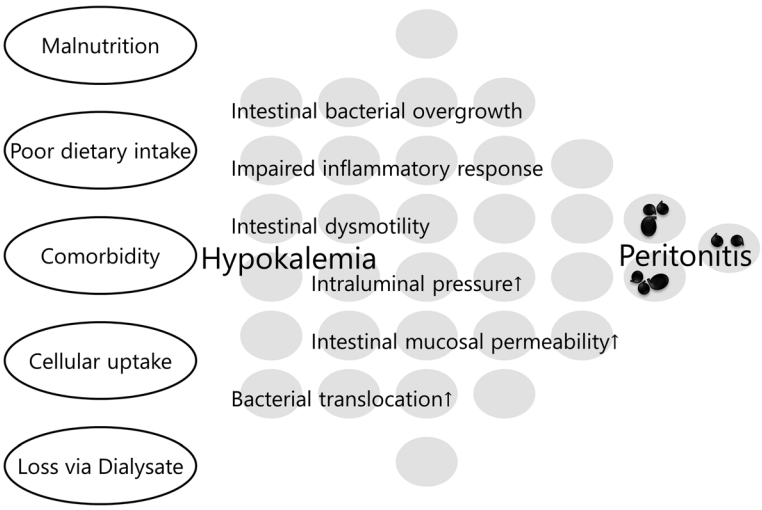

Fig. 3 Putative association of hypokalemia with peritonitis in peritoneal dialysis patients

peritoneal dialysis. We did not identify sufficient data and studies with low-risk bias to clarify the association. To confirm the causal connection, further well-designed studies are needed whether the adjustment of potassium levels can improve the risk of peritonitis in peritoneal dialysis patients with hypokalemia.

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Availability of data and materials
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Authors' contributions
KN contributed to the research idea and study design. KN and KS contributed to the data acquisition and data analysis/interpretation. HF and SN contributed to the supervision or mentorship. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. All authors approved the final version of the submitted manuscript.

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare that they have no competing interests.

Publisher's Note

Author details
[1]Division of Nephrology and Kidney Center, Kobe University Graduate School of Medicine, 7-5-2, Kusunoki-cho, Chuo-ku, Kobe, Hyogo 650-0017, Japan. [2]Department of Nephrology and Kidney Center, Kakogawa Central City Hospital, 439, Honmachi, Kakogawa-cho, Kakogawa, Hyogo 675-8611, Japan.

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