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Smoking is a Risk Factor for Endogenous Peritonitis in Patients Undergoing Peritoneal Dialysis

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Background: Peritonitis is one of the most common complications in patients undergoing peritoneal dialysis, (PD) but it is difficult to predict or prevent. In this study, we analyzed the risk of endogenous peritonitis in patients receiving PD.

Methods: We included all patients who underwent PD at our hospital from April 2015 to March 2020. There were 22 cases of peritonitis, including 18 cases of endogenous peritonitis without evidence of exit-site infection or technical failure. We evaluated older age, female sex, obesity, diabetes, diverticulosis, and constipation as potential important risk factors for endogenous peritonitis and included these as confounding factors, along with a current or previous history of smoking, in univariate logistic regression models.

Results: A previous or current history of smoking ($p = 0.0065$) was the most significant risk factor for endogenous peritonitis in the univariate logistic regression model. In addition, smoking was the most significant independent risk factor for endogenous peritonitis ($p = 0.0034$) in multivariate logistic regression models. Diabetes was also significant in univariate and multivariate logistic regression analysis.

Conclusions: Smoking is a significant independent risk factor for endogenous peritonitis in patients undergoing PD. Cessation of smoking may lower the risk of endogenous peritonitis in this patient group. (J Nippon Med Sch 2021; 88: 461–466)

Key words: endogenous peritonitis, smoking, diabetes, peritoneal dialysis

Introduction

Peritonitis is one of the most common complications in patients receiving peritoneal dialysis (PD). PD-related peritonitis is associated with mortality and transfer from PD to hemodialysis[1–4]. Moreover, peritonitis is associated with higher risks of cardiovascular mortality and infection-related mortality in patients undergoing PD[2]. Therefore, prediction and prevention of peritonitis are important in these patients.

The International Society for Peritoneal Dialysis published the ISPD Peritonitis Recommendations: 2016 Update on Prevention and Treatment for patients undergoing PD. Many risk factors for PD-related peritonitis were highlighted in the guidelines and in other reports[1,3–8]. Specifically, exit-site infection (ESI) is a risk factor for peritonitis, and reducing the incidence of ESI is important for preventing PD-related peritonitis[3,9]. However, endogenous peritonitis may develop in patients receiving PD without evidence of ESI or technical failure[10]. Consequently, prevention and prediction of endogenous peritonitis is important. Although research has identified smoking as a risk factor for PD-related peritonitis[1,3–8], it is unclear if it is a risk factor for endogenous peritonitis. In our hospital, we identified all cases of endogenous peritonitis in current and former smokers undergoing PD and analyzed their risk of developing endogenous peritonitis.

Methods

We investigated all patients who underwent PD at our hospital from April 2015 through March 2020. We treated

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https://doi.org/10.1272/jnms.JNMS.2021_88-604
Journal Website (https://www.nms.ac.jp/sh/jnms/)

Table 1 Risk factors for PD-related peritonitis

Characteristics of patients
Older age
Female sex
Lower socioeconomic status
Smoking
Obesity
Pets
Living further from PD unit
Comorbidities
Diabetes
Depression
Clinical status
Hypoalbuminemia
Hypokalemia
Absence of vitamin D supplementation
Others
Nasal *Staphylococcus aureus* carrier status
Previous exit-site infection
Invasive medical interventions (e.g. colonoscopy)
Patient training

PD, peritoneal dialysis.

22 patients with peritonitis, including 18 with endogenous peritonitis without evidence of ESI or technical failure. Some factors, such as those shown in **Table 1**, have been reported as risk factors for peritonitis[1,3–8,11–16]. We evaluated older age, female sex, obesity, diabetes, diverticulosis, and constipation as potential important risk factors for endogenous peritonitis in patients undergoing PD and added these six factors as confounding factors, along with a current or previous history of smoking, to univariate logistic regression models.

Statistical Analyses

Statistical analyses were performed with Prism software version 8 (GraphPad Software, La Jolla, CA, USA). Multiple linear and logistic regression analyses were performed using JMP software version 12 (SAS Institute, Cary, NC, USA). Laboratory values are presented as mean ± SD, and a p value of <0.05 was considered to indicate statistical significance.

Results

This study included 17 men and 5 women; mean age was 64.6 ± 12.3 years. The most frequent primary condition (n = 17) was type 2 diabetes (77.3%). **Table 2** shows the baseline characteristics of all patients.

Risk Factors for Endogenous Peritonitis

We used univariate logistic regression models for smoking, older age, female sex, obesity, diabetes, diverticulosis, and constipation. Older age was defined as an age > 65 years and obesity as a body mass index >25. We defined laxative use at onset of PD as having constipation.

A previous or current history of smoking (p = 0.0065) was the most significant risk factor for endogenous peritonitis in univariate logistic regression models. Although not a primary focus of this study, diabetes was a significant risk factor (p = 0.0106) for endogenous peritonitis in univariate logistic regression models.

For multivariate logistic regression models for risk of endogenous peritonitis, we selected smoking and diabetes as significant factors. In our multivariate logistic regression model, smoking was the most significant independent risk factor for endogenous peritonitis (p = 0.0034); diabetes was also a significant independent risk factor (p = 0.0055). The results are shown in **Table 3**.

Discussion

PD-related Peritonitis and Risk Factors

Peritonitis is one of the most common complications in patients undergoing PD and leads to discontinuation of PD and potential fatality[1–4]. Peritonitis is associated with morbidity and mortality caused independently by cardiovascular events and infection[2]. Therefore, correct management of peritonitis in patients receiving PD is crucial. Our hospital manages patients undergoing PD in accordance with the International Society for Peritoneal Dialysis Practice Recommendations of 2016, which describes the risk factors for developing PD-related peritonitis[3]. Although many putative risk factors for PD-related peritonitis have been reported, evidence for a benefit in reducing rates of peritonitis is sufficient only for topical exit-site antimicrobial prophylaxis and nasal eradication of *Staphylococcus aureus*[4]. Moreover, because risk factors for endogenous peritonitis in this patient group are unclear, it is important to predict and prevent endogenous peritonitis, as it may present without evidence of ESI or technical failure.

PD-related Peritonitis and Smoking

Smoking is a modifiable cardiovascular risk factor and is significantly associated with mortality in patients receiving PD [17–19,20]. However, smoking is not associated with cardiovascular events in patients receiving PD or hemodialysis, despite a reduction in all-cause mortality[18]. The guidelines published by the International Society for Peritoneal Dialysis describe smoking as a risk factor for peritonitis, and additional studies have confirmed this[1,3–8]. However, to our knowledge, no report has clearly de-

Table 2 Patients' baseline characteristics and variables

total, n	22
Female, n (%)	5 (22.7)
Age (years)	66.6 ± 12.3
BMI (kg/m^2)	23.7 ± 4.0
Smoking , n (%)	13 (59.1)
Diabetes, n (%)	17 (77.3)
RASi, n (%)	12 (54.5)
Diuretic-use (%)	11 (50.0)
Vit D supplementation at onset of PD, n (%)	7 (31.8)
Malignant tumor, n (%)	9 (40.9)
CVA, n (%)	4 (18.2)
Hepatitis, n (%)	4 (18.2)
History of abdominal operation, n (%)	9 (40.9)
Diverticulosis, n (%)	11 (50.0)
Pancreatic cyst, n (%)	6 (27.3)
Gallstone, n (%)	8 (36.4)
Laxative at onset of PD, n (%)	4 (18.2)
Laxative at onset of peritonitis, n (%)	12 (54.5)
Phosphate binder at onset of PD, n (%)	5 (22.7)
Phosphate binder at onset of peritonitis, n (%)	13 (59.1)
eGFR at start of PD (mL/ min/1.73m^2)	7.57 ± 5.48
Serum K (mEq/L)	4.64 ± 0.61
Serum Alb (g/dL)	3.18 ± 0.70
CRP (mg/dL)	0.47 ± 1.22
D/P ratio	0.71 ± 0.15
D/D0 ratio	0.37 ± 0.10

BMI, body mass index; RASi, renin angiotensin system inhibiter; Vit D, vitamin D; PD, peritoneal dialysis; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; Alb, serum albumin; CRP, C-reactive protein.

Table 3 Logistic regression analysis for endogenous peritonitis

Variables	Univariate analysis		Multivariate analysis	
	Odds ratio (95%CI)	*p* value	Odds ratio (95%CI)	*p* value
Older age	0.5238095(0.0232836-5.0904939)	0.5931		
Female	0.2(0.0168925-2.1865373)	0.1777		
Obesity	1.4999998(0.1514566-33.961144)	0.7419		
Diabetes	23.999996(2.0503527-658.36579)	0.0106	75,847,820(1.83e+126-4.88e+140)	0.0055
Smoking	92,131,825(2.7235235-ND)	0.0065	1.135e+14(5.9276547-ND)	0.0034
Diverticulosis	3.75(0.3924605-84.23298)	0.2599		
Constipation	0.6(0.0508106-14.409328)	0.7051		

scribed the mechanisms underlying the association of smoking and PD-related peritonitis. In one study, the major cause of peritonitis in current and former smokers was gram-positive cocci[8]. The authors state that this might be attributable to management of hygiene and/or care with sterile, no-touch disconnection techniques for patients.

One study reported that CT-detected silent diverticulosis is not a risk factor for enteric diverticulosis-related peritonitis[21]. However, another study found that diverticulosis might be a risk factor for peritonitis[12]. The association of diverticulosis with peritonitis risk in patients receiving PD remains controversial; however, smoking is a significant risk factor for colonic diverticulosis[22]. In addition, smoking is associated with complicated diverticulitis and worse prognosis, and smoking cessation decreases the rate of diverticulitis recurrence[23,24]. Moreover, smoking is an independent prognostic factor for colon

cancer[25], is associated with a failure of gas exchange in the lungs, and is linked to systemic and intestinal ischemia[26]. In addition, smoking causes angiogenesis and failure of the gastrointestinal tract epithelial barrier[26]. Smoking affects innate and adaptive immunity, thus worsening the pathogenic immune response or defensive immunity[27]. Some studies have shown that smoking affects the intestinal microbiome and may lead to development of intestinal and systemic diseases, such as inflammatory bowel disease[28]. Moreover, smoking affects the skin and delays cutaneous wound healing, because of dysfunction of the innate immune response in the skin[29].

In our hospital, there were 18 cases of endogenous peritonitis without evidence of ESI or technical failure. Smoking was a significant risk factor for endogenous peritonitis in both univariate and multivariate logistic regression models in this study. As previously stated, the harmful effects of smoking are associated with compromised peritoneal health, which might increase the risk of endogenous peritonitis. Moreover, the harmful effect of smoking on skin near the exit site is a consideration. Smoking may also cause ESI and ESI-related peritonitis in patients undergoing PD, although this association was unclear in our study. Further research in this patient group is warranted, to confirm this finding.

PD-related Peritonitis And Diabetes

Previous guidelines and studies indicate that diabetes is a risk factor for peritonitis in patients undergoing PD[1,3–6,11,30]. Although not a primary focus of our study, diabetes was the second most significant risk factor for endogenous peritonitis, after smoking and constipation, in univariate and multivariate logistic regression models. Patients with diabetes who receive PD are at risk of developing peritonitis, perhaps owing to dysfunction of the immune system and technical problems caused by visual impairment[31]. Diabetes is associated with carcinogenesis[32], and persons with diabetes may have cutaneous microbiome dysbiosis, a possible risk factor for cutaneous infection[33]. Although the mechanism underlying the association of diabetes and endogenous peritonitis is unclear, diabetes was a significant risk factor for endogenous peritonitis in this study. It is possible that diabetes is associated not only with peritonitis caused by ESI and technical failure, but also with endogenous peritonitis. Further research is necessary to confirm these findings.

In this study, smoking was the most significant independent risk factor for endogenous peritonitis in univariate and multivariate logistic regression models. In addition, diabetes was a significant independent risk factor for endogenous peritonitis. Current smoking in patients undergoing PD is treatable and modifiable, and management of smoking may prevent endogenous peritonitis. Prediction and prevention of endogenous peritonitis needs to be considered in addition to ESI in smokers undergoing PD.

Limitations

This study has limitations. First, it was conducted at a single center and the number of participants was insufficient for robust statistical analysis. Second, endogenous peritonitis was diagnosed clinically in some patients, without investigatory confirmation. These limitations may have biased our results.

Conclusions

In conclusion, smoking is a significant independent risk factor for endogenous peritonitis in patients receiving PD. Smoking cessation may lower the risk of endogenous peritonitis in such patients.

Data Availability

All data generated or analyzed during this study are available from the corresponding author upon reasonable request.

Ethics Statement

The study protocol was approved by the Ethical Committee of Nippon Medical School Hospital (B-2020-122) and designed in accordance with the principles of the Declaration of Helsinki. The study was registered to the University Hospital Medical Information Network (UMIN No.000041046).

Consent

All participants signed written informed consent forms, which included information about the research. Confidentiality of information and patient anonymity were safeguarded in this study.

Authors' Contributions: KT drafted the first manuscript. KT, YSu, SA, AH, TK, and YSa managed the patients. YSa coordinated the data analysis and helped write the manuscript. All authors participated in discussions and read and approved the final manuscript.

Acknowledgments: The authors are grateful to all the participants and medical staff of Nippon Medical School Hospital

Blood Purification Center.

Conflict of Interest: The authors declare no conflicts of interest.

References

1. Mehrotra R, Devuyst O, Davies SJ, Johnson DW. The current state of peritoneal dialysis. J Am Soc Nephrol [Internet]. 2016 Nov;27(11):3238–52. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27339663
2. Ye H, Zhou Q, Fan L, et al. The impact of peritoneal dialysis-related peritonitis on mortality in peritoneal dialysis patients. BMC Nephrol [Internet]. 2017 Jun 5;18(1):186. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28583107
3. Li PK, Szeto CC, Piraino B, et al. ISPD Peritonitis Recommendations: 2016 Update on prevention and treatment. Perit Dial Int [Internet]. 2016 Sep 10;36(5):481–508. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27282851
4. Cho Y, Johnson DW. Peritoneal dialysis-related peritonitis: towards improving evidence, practices, and outcomes. Am J Kidney Dis [Internet]. 2014 Aug;64(2):278–89. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24751170
5. McDonald SP, Collins JF, Rumpsfeld M, Johnson DW. Obesity is a risk factor for peritonitis in the Australian and New Zealand peritoneal dialysis patient populations. Perit Dial Int [Internet]. 2004 Jul-Aug;24(4):340–6. Available from: https://www.ncbi.nlm.nih.gov/pubmed/15335147
6. See EJ, Johnson DW, Hawley CM, et al. Early peritonitis and its outcome in incident peritoneal dialysis patients. Perit Dial Int [Internet]. 2017 Sep 28;pdi. 2017. 00029. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28970365
7. Karagulle IV, Kaynar K, Ulusoy S, Ozkan G, Cansiz M. Risk factors for peritonitis related to peritoneal dialysis. Bratisl Lek Listy [Internet]. 2013;114(9):531–3. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24020711
8. Kotsanas D, Polkinghorne KR, Korman TM, Atkins RC, Brown F. Risk factors for peritoneal dialysis-related peritonitis: can we reduce the incidence and improve patient selection? Nephrology (Carlton) [Internet]. 2007 Jun;12(3):239–45. Available from: https://www.ncbi.nlm.nih.gov/pubmed/17498118
9. van Diepen AT, Tomlinson GA, Jassal SV. The association between exit site infection and subsequent peritonitis among peritoneal dialysis patients. Clin J Am Soc Nephrol [Internet]. 2012 Aug;7(8):1266–71. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22745277
10. Suh H, Wadhwa NK, Cabralda T, Sorrento J. Endogenous peritonitis and related outcome in peritoneal dialysis patients. Adv Perit Dial [Internet]. 1996;12:192–5. Available from: https://www.ncbi.nlm.nih.gov/pubmed/8865900
11. Bolton L. Preventing Peritoneal Dialysis Infections. Wounds [Internet]. 2019 Jun;31(6):163–5. Available from: https://www.ncbi.nlm.nih.gov/pubmed/31215869
12. Yip T, Tse KC, Lam MF, et al. Colonic diverticulosis as a risk factor for peritonitis in Chinese peritoneal dialysis patients. Perit Dial Int [Internet]. 2010 Mar-Apr;30(2):187–91. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20124196
13. Kosmadakis G, Albaret J, Da Costa, Correia E, Somda F, Aguilera D. Constipation in peritoneal dialysis patients. Perit Dial Int [Internet]. 2019 Sep-Oct;39(5):399–404. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30852519
14. Su CY, Pei J, Lu XH, Tang W, Wang T. Gastrointestinal symptoms predict peritonitis rates in CAPD patients. Clin Nephrol [Internet]. 2012 Apr;77(4):267–74. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22445469
15. Singharetnam W, Holley JL. Acute treatment of constipation may lead to transmural migration of bacteria resulting in gram-negative, polymicrobial, or fungal peritonitis. Perit Dial Int [Internet]. 1996 Jul-Aug;16(4):423–5. Available from: https://www.ncbi.nlm.nih.gov/pubmed/8863339
16. Afsar B, Elsurer R, Bilgic A, Sezer S, Ozdemir F. Regular lactulose use is associated with lower peritonitis rates: an observational study. Perit Dial Int [Internet]. 2010 Mar-Apr;30(2):243–6. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20200371
17. Zaza G, Rugiu C, Trubian A, Granata S, Poli A, Lupo A. How has peritoneal dialysis changed over the last 30 years: experience of the Verona dialysis center. BMC Nephrol [Internet]. 2015 Apr;14(16):53. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25885318
18. Liebman SE, Lamontagne SP, Huang LS, Messing S, Bushinsky DA. Smoking in dialysis patients: a systematic review and meta-analysis of mortality and cardiovascular morbidity. Am J Kidney Dis [Internet]. 2011 Aug;58(2):257–65. Available from: https://www.ncbi.nlm.nih.gov/pubmed/21664017
19. Braatvedt GD, Rosie B, Bagg W, Collins J. Current and former smoking increases mortality in patients on peritoneal dialysis. N Z Med J [Internet]. 2006 May 19;119(1234):U1977. Available from: https://www.ncbi.nlm.nih.gov/pubmed/16718288
20. Foley RN, Herzog CA, Collins AJ. Smoking and cardiovascular outcomes in dialysis patients: the United States Renal Data System Wave 2 study. Kidney Int [Internet]. 2003 Apr;63(4):1462–7. Available from: https://www.ncbi.nlm.nih.gov/pubmed/12631362
21. Toda S, Ito Y, Mizuno M, et al. Asymptomatic diverticulosis identified by computed tomography is not a risk factor for enteric peritonitis. Nephrol Dial Transplant [Internet]. 2012 Jun;27(6):2511–6. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22189207
22. Wijarnpreecha K, Boonpheng B, Thongprayoon C, Jaruvongvanich V, Ungprasert P. Smoking and risk of colonic diverticulosis: A meta-analysis. J Postgrad Med [Internet]. 2018 Jan-Mar;64(1):35–9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29067919
23. Wilkins T, Embry K, George R. Diagnosis and management of acute diverticulitis. Am Fam Physician [Internet]. 2013 May 1;87(9):612–20. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23668524
24. Turunen P, Wikstrom H, Carpelan-Holmstrom M, Kairaluoma P, Kruuna O, Scheinin T. Smoking increases the incidence of complicated diverticular disease of the sigmoid colon. Scand J Surg [Internet]. 2010;99(1):14–7. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20501352
25. Sharp L, McDevitt J, Brown C, Comber H. Smoking at diagnosis significantly decreases 5-year cancer-specific survival in a population-based cohort of 18 166 colon cancer patients. Aliment Pharmacol Ther [Internet]. 2017 Mar;45(6):788–800. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28176335

26. Fricker M, Goggins BJ, Mateer S, et al. Chronic cigarette smoke exposure induces systemic hypoxia that drives intestinal dysfunction. JCI Insight [Internet]. 2018 Feb 8;3(3): e94040. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29415878
27. Qiu F, Liang CL, Liu H, et al. Impacts of cigarette smoking on immune responsiveness: Up and down or upside down? Oncotarget [Internet]. 2017 Jan 3;8(1):268–84. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27902485
28. Savin Z, Kivity S, Yonath H, Yehuda S. Smoking and the intestinal microbiome.. Arch Microbiol [Internet]. 2018 Jul; 200(5):677–84. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29626219
29. Maarouf M, Maarouf CL, Yosipovitch G, Shi VY. The impact of stress on epidermal barrier function: an evidence-based review. Br J Dermatol [Internet]. 2019 Dec;181(6): 1129–37. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30614527
30. Tsai CC, Lee JJ, Liu TP, et al. Effects of age and diabetes mellitus on clinical outcomes in patients with peritoneal dialysis-related peritonitis. Surg Infect (Larchmt) [Internet]. 2013 Dec;14(6):540–6. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24116738
31. Benabed A, Bechade C, Ficheux M, Verger C, Lobbedez T. Effect of assistance on peritonitis risk in diabetic patients treated by peritoneal dialysis: report from the French Language Peritoneal Dialysis Registry. Nephrol Dial Transplant [Internet]. 2016 Apr;31(4):656–62. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26932691
32. Wojciechowska J, Krajewski W, Bolanowski M, Krecicki T, Zatonski T. Diabetes and cancer: a Rrview of current knowledge. Exp Clin Endocrinol Diabetes [Internet]. 2016 May;124(5):263–75. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27219686
33. Thimmappaiah Jagadeesh A, Prakash PY, Karthik Rao N, Ramya V. Culture characterization of the skin microbiome in Type 2 diabetes mellitus: A focus on the role of innate immunity. Diabetes Res Clin Pract [Internet]. 2017 Dec; 134:1–7. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28951341

(Received, October 16, 2020)
(Accepted, December 23, 2020)
(J-STAGE Advance Publication, March 9, 2021)