

Factors associated with irritable bowel syndrome symptoms in hemodialysis patients

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Received: August 19, 2010 Revised: October 5, 2010

Accepted: October 12, 2010

Published online: April 21, 2011

METHODS: This was a cross-sectional study. A questionnaire based on the Bowel Disease Questionnaire that records gastrointestinal symptoms was given to 294 patients in 4 dialysis centers. A total of 196 (67%) subjects returned the survey. A multivariable logistic regression model was used to identify factors significantly associated with IBS symptoms.

RESULTS: Symptoms compatible with IBS were present in 27 (13.8%) subjects and independently associated with low post-dialysis serum potassium [OR = 0.258, 95% CI (0.075-0.891), $P = 0.032$], paracetamol use [OR = 3.159, 95% CI (1.214-8.220), $P = 0.018$], and Kidney Disease Quality of Life (KDQOL) cognitive function score [OR = 0.977, 95% CI (0.956-0.999), $P = 0.042$]. Univariate regressions were also performed and the reported significance is for multivariate analysis. No association was detected for age, gender, depressed mood, smoking (present or past), body mass index, albumin level, Kt/V, sodium pre- or post-dialysis level, change in potassium level during HD, proton pump inhibitor or H2 blocker use, aspirin use, residual diuresis, hepatitis B or C infection, diabetes mellitus, marital status and education level.

CONCLUSION: This study examined potential risk factors for symptoms compatible with IBS in HD patients and identified an association with paracetamol use, post-dialysis potassium level and KDQOL-cognitive function score.

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Key words: Hemodialysis; Irritable bowel syndrome; Risk factors

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Abstract

AIM: To investigate clinical characteristics associated with the presence of irritable bowel syndrome (IBS) symptoms in hemodialysis (HD) patients.

Fiderkiewicz B, Rydzewska-Rosołowska A, Myśliwiec M, Bi-recka M, Kaczanowska B, Rydzewska G, Rydzewski A. Factors associated with irritable bowel syndrome symptoms in hemodialysis patients. *World J Gastroenterol* 2011; 17(15): 1976-1981 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v17/i15/1976.htm> DOI: <http://dx.doi.org/10.3748/wjg.v17.i15.1976>

INTRODUCTION

Chronic gastrointestinal symptoms are common in patients with chronic kidney disease (CKD). The prevalence rate is reportedly as high as 70%^[1-4], and there is an association with impaired psychological well-being^[5]. Among these gastrointestinal symptoms, irritable bowel syndrome (IBS) is also more frequent than in the general population, and is present in 11%-44% of hemodialysis (HD) patients^[2-4]. Although the pathophysiology of IBS is uncertain, altered gut reactivity (motility, secretion), visceral hypersensitivity and dysregulation of the brain-gut axis are believed to play an important role^[6]. The risk factors associated with IBS in HD patients are not known. The aim of this study was to determine the possible relationship between IBS symptoms in HD patients and their clinical characteristics.

MATERIALS AND METHODS

Patients

This was a cross-sectional study. All patients in 4 HD centers (2 state financed and 2 privately owned) were asked to complete a questionnaire. The questionnaires were given to patients during a planned hemodialysis procedure. The study was approved by the local Ethics Committee.

All of the subjects were Caucasian. They were dialyzed 3 times a week for 180 to 300 min using either polysulfone or cellulose acetate dialyzers and bicarbonate dialysis fluid containing 2 mEq/L of potassium in 3 centers and 2 or 3 mEq/L (adjusted on the basis of the knowledge of prevailing pre-dialysis serum potassium levels in a given individual) in 1 center.

Causes of ESRD were as follows: glomerulonephritis, $n = 60$ (30.6%); diabetic nephropathy, $n = 32$ (16.3%); amyloidosis, $n = 11$ (5.6%); polycystic kidneys, $n = 22$ (11.2%); hypertension/atherosclerosis, $n = 16$ (8.2%); tubulointerstitial disease, $n = 39$ (19.9%); unknown/uncertain, $n = 15$ (7.7%); nephrectomy, $n = 1$ (0.5%).

Questionnaire

A questionnaire based on the Bowel Disease Questionnaire was used^[7]. It was translated to the Polish language by 2 of the authors (BF, AR). Translations were compared and discrepancies reconciled. The resulting translation was then tested in 20 randomly selected dialysis patients, and as a result some of the expressions in the translation were altered to make them easier to understand. The question-

naire was then checked by a person who was not involved in translation (ARR), and finally evaluated by a certified gastroenterologist (GR).

IBS was defined using Manning criteria^[8] as described by Talley *et al.*^[9], as an ache or pain that occurred more than 6 times per year which was either often made better by a bowel movement or often associated with more frequent or looser bowel movements when the pain began. In addition, 2 or more of the following symptoms had to be present: fewer than 3 bowel movements per week or more than 3 bowel movements per day; loose, watery stools or hard stools; straining to have bowel movements; feelings of incomplete rectal evacuation; urgency; mucus; or bloating with distention.

Additionally, we included questions taken from the validated Polish translation of Kidney Disease Quality of Life (KDQOL) questionnaire, related to depressed mood and cognitive function^[10]. Depressed mood was measured by the following KDQOL items: How much of the time during the last 30 d have you felt so down in the dumps that nothing could cheer you up? and How much of the time during the last 30 d have you felt downhearted and blue? The six possible responses to these questions were (1) none of the time; (2) a little of the time; (3) some of the time; (4) a good bit of the time; (5) most of the time; and (6) all of the time. Patients were classified as reporting depressed mood when they indicated that they had felt down in the dumps or felt downhearted and blue a good bit of the time or more often^[11].

Cognitive function was measured by the KDQOL-CF score. Patients had to answer the following questions: During the past 4 wk, did you react slowly to things that were said or done? Did you have difficulty concentrating or thinking? Did you become confused? Responses on a six-point scale were weighted and transformed to a score ranging from 0 to 100, with higher scores indicating better self-assessed cognitive function^[12].

Relevant laboratory and clinical data were extracted from medical records. Data corresponding closest to the date of the HD session during which the questionnaire was distributed, were used. We allowed for a time span of 14 d before and after HD.

Statistical analysis

Results are expressed as means \pm SD or frequency. Variables were tested for normality of distribution using the Wilk-Shapiro test. The Fisher's exact test and χ^2 test were used for comparing categorical variables, as appropriate.

Univariate and multivariable logistic regression was used to identify patient characteristics associated with IBS compatible symptoms. Risk factors considered in this analysis included age, sex, education level, marital status, presence of diabetes mellitus, procedure, hemoglobin level, pre- and post-HD potassium level, change in potassium level during HD, use of paracetamol in the last year, KDQOL-CF score, depressed mood, smoking

Table 1 Patients' demographic and clinical data expressed as (mean \pm SD) *n* (%)

Group	IBS symptoms		All	P value
	(+)	(-)		
<i>n</i>	27	169	196	
Gender (M/F)	13/14	105/64	118 / 78	0.168
Age (yr)	68.1 \pm 11.5	63.2 \pm 13.4	63.9 \pm 13.2	0.073
Dialysis duration (min)	40.1 \pm 36.9	38.6 \pm 45.8	38.8 \pm 44.6	0.874
BMI (kg/m ²)	25.0 \pm 3.7	24.9 \pm 4.9	24.9 \pm 4.7	0.897
Residual diuresis (mL/24 h)	301 \pm 559	401 \pm 592	388 \pm 42	0.411
Kt/V	1.26 \pm 0.31	1.21 \pm 0.27	1.22 \pm 0.28	0.355
Hepatitis C or B infection (<i>n</i>)	7 (25.9%)	31 (18.3%)	38 (19.4%)	0.430
Hemoglobin (g/dL)	11.4 \pm 1.4	10.7 \pm 1.5	10.8 \pm 1.5	0.026 ^a
Albumin (g/dL)	3.72 \pm 0.40	3.71 \pm 0.44	3.71 \pm 0.44	0.857
Smoking (<i>n</i>)	7 (25.9%)	23 (13.6%)	30 (15.3%)	0.144

IBS: Irritable bowel syndrome; BMI: Body mass index. ^a*P* < 0.05.

(present or past), body mass index (BMI), albumin level, Kt/V, sodium pre- and post-dialysis level, proton pump inhibitor (PPI) or H2 blocker use, aspirin and paracetamol use, residual diuresis, hepatitis B or C infection. Variables were included in the multivariable logistic model if *P* < 0.10 in the univariate analysis. A *P* value less than 0.05 was considered statistically significant. The software, used for statistical computations was Stata 9.2 (StataCorp, College Station, TX, USA).

RESULTS

Patients

A total of 294 HD patients were asked to complete the questionnaire, of which 196 were returned giving a 67% response rate. All the responders completed the questionnaires by themselves. Their clinical characteristics are given in Table 1.

IBS symptoms

Symptoms compatible with IBS were present in 27 (13.8%) subjects. They were more common in women (18.0%) than in men (11.0%), but the difference was not statistically significant (*P* = 0.168). Symptoms of IBS were more frequent in patients with a post-hemodialysis potassium level \leq 3.5 mEq/L than in subjects with potassium > 3.5 mEq/L. Also pre-dialysis potassium level was related to the frequency of IBS symptoms (Figure 1).

In univariate logistic regression, pre-dialysis serum potassium [OR = 0.462, 95% CI (0.222-0.965), *P* = 0.040], post-dialysis serum potassium [OR = 0.237, 95% CI (0.084-0.666), *P* = 0.006], hemoglobin level [OR = 1.403, 95% CI (1.038-1.897), *P* = 0.028], use of paracetamol in the last year [OR = 3.541, 95% CI (1.499-8.364), *P* = 0.004], and KDQOL-CF score [OR = 0.972, 95% CI (0.954-0.991), *P* = 0.004] were associated with IBS symptoms. Age (*P* = 0.076), gender (*P* = 0.172), depressed mood (*P* = 0.118), smoking (present or past) (*P* = 0.105), BMI (*P* = 0.896),

Table 2 Multiple logistic regression analysis to identify independent predictors of irritable bowel syndrome symptoms in hemodialysis patients

Variable	<i>b</i> coefficient (SE)	<i>P</i> value	OR (95% CI)
Potassium level pre-HD	-0.325 \pm 0.437	0.457	0.723 (0.307-1.703)
Potassium level post-HD	-1.356 \pm 0.633	0.032 ^a	0.258 (0.075-0.891)
Paracetamol use	1.150 \pm 0.488	0.018 ^a	3.159 (1.214-8.220)
Cognitive function	-0.023 \pm 0.011	0.042 ^a	0.977 (0.956-0.999)
Hemoglobin	0.327 \pm 0.168	0.052	1.387 (0.998-1.928)
Age	0.026 \pm 0.021	0.213	1.027 (0.985-1.070)

HD: Hemodialysis; OR : Odds ratio. ^a*P* < 0.05.

albumin level (*P* = 0.856), Kt/V (*P* = 0.353), sodium pre- (*P* = 0.961) or post-dialysis level (*P* = 0.176), change in potassium level during HD (*P* = 0.556), PPI or H2 blocker use (*P* = 0.857), aspirin use (*P* = 0.172), residual diuresis (*P* = 0.411), hepatitis B or C infection (*P* = 0.358), diabetes mellitus (*P* = 0.822), marital status (*P* = 0.941) and education level (*P* = 0.377) were not associated with IBS symptoms.

When the risk factors for symptoms of IBS were assessed by multiple logistic regression analysis, independent predictors of IBS symptoms included: paracetamol use, post-dialysis serum potassium and KDQOL-CF score (Table 2).

DISCUSSION

The frequency of symptoms compatible with IBS in our study is somewhat higher than that reported (11%) among 105 Austrian HD patients^[3] using similar criteria, and lower than that among 148 English HD patients (21%) using Rome II criteria^[2]. In the latter study, IBS was significantly more common in HD subjects than in both hospital outpatients and community controls^[2]. In a study from Turkey, the prevalence of IBS, using Rome II criteria, was 44% among 93 HD patients, significantly more common than in healthy volunteers (21%)^[4].

The overall IBS prevalence in Europe is 11.5%^[13]. It varies, however, widely among countries, being highest in the UK and Italy^[13], depending to a large extent on the diagnostic criteria used^[14]. There is even more variability between continents^[13]. Unfortunately, there is no data on IBS prevalence in the general population in Poland.

As there is no biologic marker of the disease, the diagnosis of IBS relies heavily on symptom-based criteria. The most widely used is a consensus definition called the Rome criteria^[16,17], where IBS is defined chiefly by abdominal pain associated with defecation or a change in bowel habit and with features of disordered defecation. Some researchers have suggested that these criteria over-emphasize abdominal pain and fail to emphasize post-prandial urgency, abdominal pain, and/or diarrhea^[18,19]. We thought that for the HD population, with frequent comorbidities, the use of supportive symptoms that are not part of the Rome criteria would be more appropriate. The Kruis scoring system^[20], which in addition to self-reported symptoms includes: erythrocyte sedimentation

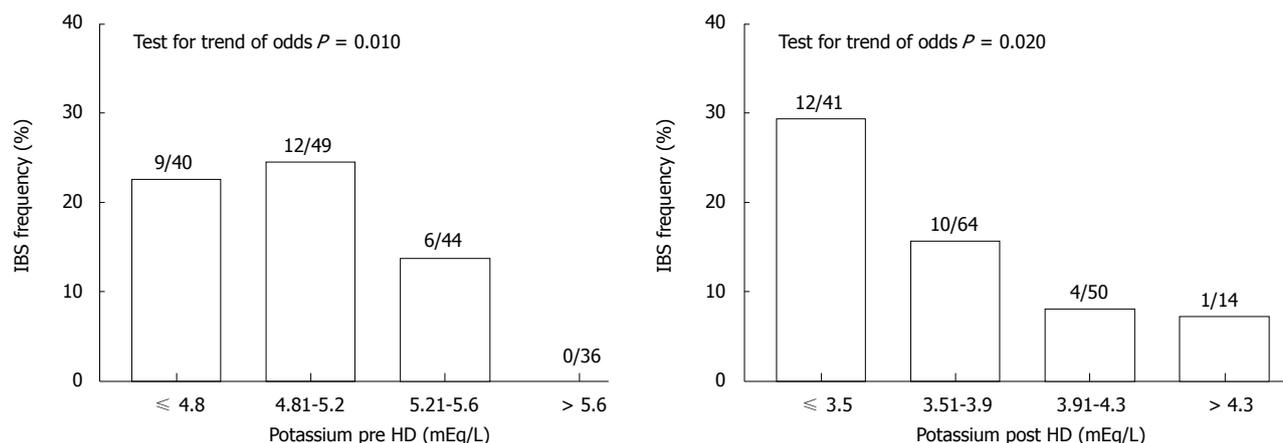


Figure 1 Frequency of irritable bowel syndrome symptoms in hemodialysis subjects stratified by pre- or post-hemodialysis potassium level. Numerator corresponds to number of irritable bowel syndrome (IBS) cases and denominator to number of all patients with given potassium level. HD: Hemodialysis.

rate, leukocytosis and anemia could not be used in HD patients for obvious reasons.

Fulfillment of IBS criteria is not unequivocally diagnostic of IBS, however, to make a positive diagnosis of IBS the use of diagnostic criteria is the recommended method, rather than exhaustive investigations to exclude an underlying organic cause^[21]. Surprisingly, however, very few studies have examined the utility of the various diagnostic criteria in differentiating IBS from organic disease. The authors of a recent systematic review were able to find only 4 studies that reported on the accuracy of the Manning criteria, 1 study that reported on the Rome I criteria, and no studies on the Rome II or Rome III criteria^[21].

In clinic-based studies, IBS has been associated with female gender, psychological distress, physical and sexual abuse, food allergies, enteric infections, and previous abdominal surgeries^[22]. In a community-based study Locke *et al*^[23] found associations with somatic symptoms, analgesic use, and food allergies and sensitivities^[23].

The association between acetaminophen use and IBS has been previously reported, and is difficult to explain^[23]. A possibility exists that most people take paracetamol for their IBS. It is interesting that there was no association between aspirin use and IBS symptoms, similar to Locke *et al*^[23] when the use of these drugs was reported independently. Additionally, in this country aspirin is most frequently used for cardiovascular prophylaxis.

Cognitive deficits often accompany chronic illnesses, although the underlying mechanisms are not fully understood and may differ between diseases. Cognitive impairment is common in HD patients^[24]. Risk factors include: age, race, stroke, diabetes, low education status, anemia, measures of malnutrition and an equilibrated Kt/V ≥ 1.2 ^[25,26]. Also, IBS in the general population is associated with cognitive impairment^[27,28]. An observed association between IBS symptoms and KDQOL-CF score might suggest that IBS worsens cognitive deficits in HD patients. We used the KDQOL-CF self reported score for the assessment of cognitive function. Although

the KDQOL-CF provides estimates rather than a definitive assessment of cognitive function, it was shown that the KDQOL-CF scale scores correlate with the Modified Mini-Mental State Examination, and are acceptable for estimating cognitive function in dialysis subjects^[12,29].

In the general population, IBS is associated with stress^[6]. In our study, the presence of IBS compatible symptoms was not related to the presence or absence of anxiety or depression. This is similar to the findings by Cano and colleagues^[2]. They, therefore, concluded that IBS in HD patients might be related to either the “uremic” state or the treatment method. This is in contrast to Kahvecioglu *et al*^[4] who found that IBS in dialyzed patients was associated with depression and anxiety. In the general population, IBS seems to be more common in younger people. Our population was mostly over 50 years, and that might explain the lack of an age effect on the frequency of IBS symptoms.

Patients suffering from diabetes mellitus report a greater prevalence of gastrointestinal symptoms than controls, which is not related to glycemic control^[30]. We did not observe, however, any difference in the frequency of IBS symptoms between diabetic and non-diabetic HD patients. This is in agreement with Cano *et al*^[2].

It is difficult to offer an explanation for the unexpected univariate association between IBS symptoms and hemoglobin level. Patients dialyzed in central and eastern European dialysis centers have lower mean hemoglobin levels and are less likely to attain target levels than those treated in western European counterparts^[31]. HD patients with higher hemoglobin levels report higher quality of life, and IBS patients in the general population have lower health-related quality of life^[32]. Additionally, gastrointestinal symptoms in patients with chronic kidney disease are associated with impaired general psychological well-being^[5]. However, IBS patients have a propensity to report pain and label negatively expected adverse sensations, so it is conceivable that IBS specific symptoms are “unmasked” in patients who have an overall higher quality of life.

To our knowledge, the association between serum potassium level and the frequency of symptoms compatible with IBS has not been reported before. This finding, however, has to be treated with caution. Although gastrointestinal motility is impaired in chronic pre-dialysis kidney disease^[33], it is alleviated by hemodialysis^[34]. Thus, another mechanism may be responsible. Hypokalemia may cause decreased motility and propulsive activity of the intestine, and even lead to ileus. We recorded potassium levels before and after a single HD session, whereas a level prevailing over a specific time period might be more appropriate. It may be, however, that episodes of hypokalemia, which are likely just after hemodialysis, are responsible for the appearance of IBS symptoms. A consistent trend of a higher prevalence of IBS compatible symptoms with lower potassium concentration, also suggests a causative role for hypokalemia. During conventional HD, large amounts of potassium are removed, approximately 40% of which originates from the extra- and the remainder from the intracellular space^[35]. A change in the plasma potassium concentration during hemodialysis, however, is difficult to predict, due to the concomitant movement of the ion into cells due to correction of metabolic acidosis. After HD, plasma potassium concentration increases rapidly during the first hour and steadily thereafter. The post-dialysis rise in potassium concentration is not correlated with pre- or post-dialysis plasma K^[35].

In CAPD patients, it has been reported that episodes of hypokalemia are a risk factor for developing peritonitis and bacterial overgrowth, possibly due to altered intestinal motility^[36,37].

In our study, neither the dialysis session time nor the change in potassium level influenced the prevalence of IBS symptoms, what suggests that the between dialyses level rather than the intradialytic change is important. In line with this electrophysiological mechanism reasoning, is the observation that pre-dialysis potassium < 4.0 or > 5.6 mEq/L is associated with increased mortality in HD patients, most probably due to cardiac arrhythmias^[38]. Despite the plausible electrophysiological mechanism, the association between potassium level and IBS symptoms might be confounded by other factors. It has been suggested for both HD and PD patients, that hypokalemia could be a surrogate marker for poor nutrition and associated comorbidities^[38,39].

This study has a number of shortcomings: firstly the Bowel Disease Questionnaire was not formally validated. To that end we ensured that the Polish translation was faithful and easy to understand. Additionally, the number of subjects was rather low, the study was observational and could not prove causality in relationships. Finally, the study potentially lacked generalizability due to cross-cultural differences in the symptomatology of functional gastrointestinal disorders^[15].

In summary, this study examined potential risk factors for symptoms compatible with IBS in HD patients and identified an association with acetaminophen use, serum potassium level, and KDQOL-cognitive function score.

The role of hypokalemia requires further well designed and controlled clinical studies.

COMMENTS

Background

Chronic gastrointestinal symptoms are very common in patients with chronic kidney disease (CKD) treated by hemodialysis (HD) including irritable bowel syndrome (IBS). Risk factors associated with IBS in HD patients are not known.

Research frontiers

Risk factors that are associated with IBS in the general population include: somatic symptoms, female gender, psychological distress, physical and sexual abuse, food allergies, enteric infections, previous abdominal surgeries, analgesic use, and food allergies and sensitivities. Of the 196 HD patients included in this study, symptoms compatible with IBS were present in 27 (13.8%) subjects and were independently associated with low post-dialysis serum potassium, paracetamol use, and KDQOL cognitive function score.

Innovations and breakthroughs

This study showed that low post-dialysis serum potassium, paracetamol use, and KDQOL cognitive function score are independently associated with increased risk of IBS compatible symptoms.

Applications

This analysis of the risk factors for IBS may be helpful in reducing the risk of abdominal symptoms in HD patients.

Peer review

The authors report an observational study looking at various factors associated with IBS as defined by Manning criteria in haemodialysis patients.

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