Exploring the Relationship between Diarrhea and Fatigue that can occur during Cancer Treatment: Using Structural Equation Modeling

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Objective: To examine the relationship of the symptoms of diarrhea and fatigue by testing a model that included multiple dimensions of the cancer-related-symptom experience.

Methods: A secondary data analysis was conducted on data from the self-reports of 102 cancer patients co-experiencing diarrhea and fatigue during treatment at a comprehensive cancer center in the Southeastern United States. Structural equational modeling was employed to examine the relationship between the 2variables. Fatigue and diarrhea were assessed using items from the Cancer Symptom Scale.

Results: The structural model results showed that (a) the model fit was adequate (b) diarrhea explained 7% of the variance in fatigue, and (c) the structural or path coefficient between diarrhea and fatigue was significant (0.267; p<0.05). Diarrhea had the strongest effect on fatigue interference (0.251).

Conclusion: Diarrhea is a potential contributing factor to the symptom of fatigue and a potential target for interventions to prevent and ameliorate fatigue. [*P R Health Sci J 2019;38:81-86*]

Key words: Cancer Symptom Scale, Diarrhea, Fatigue, Structural equational modeling, Cancer therapy–related symptoms

There were more than 15 million cancer survivors in the US in 2016, and this number is expected to increase in the coming years (1). The use of cancer treatment, which has improved the local control of cancer and survival, often produces disruptive side effects and behavioral symptoms that have a negative impact on the health-related quality of life of the patient (2). Contemporary researchers have acknowledged that the symptom experience is a multidimensional construct (e.g. intensity, distress, interference, and frequency)(3,4,5,6). It has also been proposed that symptoms could be experienced singly or in combinations of 2 or more (7), according to the individual, and may change over time (8). Nonetheless, symptom research has most often focused on only one symptom or one dimension at a time, perhaps missing important information that could be obtained from exploring the interactions of the multiple dimensions of the symptom experience (9).

Cancer patients undergoing treatments may experience a variety of co-existent symptoms, including diarrhea and fatigue. Further, these cancer therapy–related side effects are associated with disability and healthcare overuse, becoming a source of considerable financial burden to the patient, to the family, and to the healthcare system(9). Adding to the complexity of the multidimensionality of the symptom experience, there is also a need to understand the relationships among cancer-related symptoms, as such symptoms may interact with and exacerbate each other (10). For example, although it may seem intuitive that chronic diarrhea may lead to an increased perception of fatigue, the relationships of the multiple dimensions of the symptom experiences of cancer patients undergoing treatments and who have diarrhea and fatigue has not been well described. Therefore, the purpose of this secondary data analysis (SDA) was to examine the relationship of the symptoms of diarrhea and fatigue by testing a model that included the multiple dimensions (intensity, distress, interference, and frequency) of the symptom experience. We hypothesized that diarrhea would have a positive influence on fatigue and that the 4 dimensions may differ in terms of their impact on fatigue.

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Methods

Sample and Setting

This SDA used data from a longitudinal study (N= 534) evaluating the effectiveness of the COPE (creativity, optimism, planning, and expert information) intervention at ameliorating the intensity, frequency, distress, and interference of cancer-treatment-related symptoms in adults undergoing cancer treatments(11). Baseline data (before the COPE intervention) from the parent study was used to examine the relationship of the symptoms of diarrhea and fatigue. The setting for the parent study was a National Cancer Institute–designated comprehensive cancer center in the Southeastern United States. To be eligible for and participate in the parent study, men and women with a cancer diagnosis had to (a) be aged 18 or older; (b) be undergoing chemotherapy, radiotherapy (RT), or concurrent chemoradiotherapy, regardless of the time point of the initiation of treatment; (c) have (before the COPE intervention) intensity, distress, and/or interference scores of less than 4 for at least 2symptoms; (d) be able to read and understand English; and, (e) have signed the informed consent.

Measures

Diarrhea and fatigue were assessed using items from the Cancer Symptom Scale (CSS). Participants also recorded demographic and health information on the demographic and clinical-data form.

Cancer symptom scale

The CSS measures the presence, intensity, distress, frequency, and interference of 35 symptoms (5). The presence of symptoms was defined as a "yes" or "no" foreach item. For each symptom, patients were asked 4 questions, regarding their symptom experience including: intensity, distress, frequency, and interference during the past week. Typical questions for the CSS are "Did you experience 'fatigue; no energy' in the past week?" and "How severe or intense has the 'fatigue; no energy' been this week?" Intensity/severity was rated on a numeric scale of 1 to 10, from least intense/severe(1; 0 was not used because failing to endorse the symptom was considered to be equivalent to a zero score) to most intense/severe(10); distress, frequency, and interference were also rated on a numeric scale of 0 to 10,from least (intense, distressing, frequent, or interfering) to most. In addition, the scoring for each subscale (intensity, distress, frequency, and interference) was computed by adding the individual item scores and dividing by the number of items answered. Higher scores represent worse symptoms. In the original study using the English version of the CSS, the reliability and validity were evaluated in a sample of 234 cancer patients(5).Construct validity was examined by correlating the CSS subscales with the Multidimensional Quality of Life-Cancer scale scores. Correlations ranged from r = -0.34 to -0.56; p<0.001 (at the hypothesized levels), thus supporting construct validity. In addition, test-retest reliability coefficients for the CSS subscales ranged from r = 0.74 to 0.81, in a subset of 15 patients, and Cronbach's alphas above 0.70 were reported (N=234) (5).

Demographic data and Health form

Information on age, gender, ethnicity, and years of education was gathered as well as information on diagnosis and treatment modality. The research assistant obtained this demographic and clinical information from each participant's self-report, on the demographic form.

Procedures for secondary analysis

The study was approved by the Scientific Review Committee of the Cancer Center and approved by the Institutional Review Board of the University of South Florida. De-identified data were collected and organized by removing outliers and missing data.

Data analysis

Descriptive statistics, such as frequency, percentages, and means, were used to characterize the demographics and disease characteristics of the sample population, and the same descriptive statistics were computed on the responses to the diarrhea and fatigue items from the CSS. A bivariate correlation analysis was performed to examine the associations among the study variables. A demographic data analysis was conducted using the Statistical Package for the Social Sciences (IBM Corp. Released 2013. IBM SPSS, Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.).

The most complex analysis conducted in the present study was structural equation modeling (SEM) to determine the direct and indirect influences of the dimensions of diarrhea on the fatigue dimensions. One of the main reasons for using SEM was the benefit of the ability to conduct hypothesis testing by being able to examine multiple relationships simultaneously while still accounting for measurement error (12). More specifically, SEM is a type of multivariate analysis in which an assessment of overall model fit is obtained, as well as the direct and indirect influences among latent variables (13). In the analysis, diarrhea and fatigue were treated as latent variables; each of the different symptoms' dimensions (e.g. intensity, distress, interference, and frequency) was treated as a measurable variable. The model was examined with LISREL MPlus using the maximum likelihood estimator to determine the fit of the model (14). In the analysis process, the fit indices evaluated included the maximum likelihood ratio $\chi 2$, the goodness of fit index (GFI), the comparative fit index (CFI), and the standardized root mean square residual (SRMR). All of these indices have standard cut-offs that indicate a good fit: $p<0.05$ for the $\chi 2$, GFI>0.90 (12), CFI>0.90 (11), and the SMSR < 0.10 (15).The good fit was further explored by observing the value obtained for the squared multiple correlation (R2), as well as whether the computed beta path coefficient was statistically significant and in the expected direction each statistical test had an alpha level set at 0.05 or lower.

Results

Sample demographic and Clinical characteristics

The sample consisted of 102 patients who reported having both diarrhea and fatigue. The participants' average age was 56.8 years (SD = 10.5; range, 28 to 78 years). Most of the participants were female (72.5%) and white/non-Hispanic (82.4%). The participants were, for the most part, well-educated, with an average of 15.2 years of education (SD = 2.8). Most of the participants' cancer diagnoses were breast (30.3%), colon (8.8%), and lung (7.8%). A summary of the sample cancer diagnoses is provided in Table 1. Approximately two thirds of the sample (70.6%) were treated with chemotherapy, alone, while 21 (20.6%) received combined chemo-radiation therapy and 7 (6.9%) had RT.

Table 1. Participants' Cancer diagnoses (N = 102)

Characteristic	N (%)
Cancer diagnosis	
Breast	31 (30.3)
Colon	9 (8.8)
Lung	8 (7.8)
Ovarian	7 (6.9)
Pancreatic	6 (5.9)
Lymphocytic	5 (4.9)
Prostate	4 (3.9)
Brain	3 (2.9)
Cervical	3 (2.9)
Leukemia	3 (2.9)
Lip & oral cavity	3 (2.9)
Nasal cavity & sinus	3 (2.9)
Esophageal	2 (2.0)
Multiple myeloma	2 (2.0)
Sarcoma	2 (2.0)
Bladder	1 (1.0)
Endometrial	1 (1.0)
Kidney	1 (1.0)
Laryngeal	1 (1.0)
Merkle cell	1 (1.0)
Rectal	1 (1.0)
Squamous cell	1 (1.0)
Uterine	1 (1.0)
Vaginal	1 (1.0)
Unknown primary	1 (1.0)
Other	1 (1.0)

Symptoms of diarrhea and fatigue

The means and SDs of each dimension of diarrhea and fatigue are shown in Table 2.

Table 2. Diarrhea and fatigue: symptom occurrence with means and SDs of symptom scores for intensity, distress, frequency, and interference

	Intensity		Distress		Interference		Frequency	
Symptom	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Fatigue	6.34	2.02	6.10	2.62	6.11	2.64	6.55	2.43
Diarrhea	5.83	2.76	5.75	3.08	5.79	3.23	5.63	2.88

Relationships among diarrhea and fatigue variables

Table 3 shows the Pearson correlation coefficients among all the measured variables. The correlations between the diarrhea variables with the fatigue variables ranged from small (0.13; diarrhea intensity and fatigue distress) to moderate (0.33; diarrhea distress and fatigue frequency).The strongest significant correlation between the diarrhea variables with the fatigue variables was found between the diarrhea distress, and fatigue frequency ($r = 0.33$; $p = 0.001$). Table 3 also shows that age had very weak (and no significant) correlations with the symptom variables. It is apparent from Table 3 that there is high co-linearity among the dimensions (intensity, distress, frequency, and interference) of diarrhea and among the dimensions (same) of fatigue. Additionally, this issue of co-linearity is another reason for why SEM was used instead of traditional regression techniques.

Structural model

One structural model was run to examine the inter-relationships among diarrhea and fatigue and to determine the influence of diarrhea on fatigue during cancer treatments (Figure 1). The maximum likelihood method was employed after establishing that the data were normally distributed. The structural model results showed that the model fit was adequate. Specifically, the $\chi 2 = 38.45$;$df = 19$; $p<0.05$; GFI = 0.92; CFI = 0.98; SRMSR = 0.041.In addition, an inspection of the residuals showed that all the standardized residuals were normally distributed and ranged from -2.05 and 2.14.No pre-specified associations between the dimensions of diarrhea and fatigue were altered to achieve a good fit.

As illustrated in the path analysis model (Figure 1), the factor loadings for the dimensions of diarrhea ranged from 0.89 to 0.94 and were significantly greater than zero ($p<0.05$). Similarly, the factor loadings for the dimensions of fatigue ranged from 0.74 to 0.94, all high. High factor loadings suggest that each dimension measures the same construct. Further, the R2 value was 0.07, indicating a low explained variance. Nonetheless, Figure 1 also shows that the beta path coefficient was both positive in the expected direction and statistically significant (0.27; $p<0.05$). With respect to the total effect of diarrhea on fatigue, it was found that diarrhea had the strongest effect on fatigue interference (standardized total effect coefficient = 0.25; not shown in figure), followed by fatigue distress (0.23), fatigue severity (0.22), and, lastly, fatigue frequency (0.20).

Discussion

Symptoms of diarrhea and fatigue

It has been generally recognized that symptom experience is a multidimensional construct that includes at least the dimensions of intensity, distress, interference, and frequency (3,4,5). Interestingly, the participants in this SDA had mean scores for both diarrhea and fatigue (intensity, distress, frequency, and interference) that were near the midpoint

Table 3. Correlations between age and the intensity, distress, interference, and frequency of both fatigue and diarrhea

Variable	1	2	3	4	5	6	7	8	9
1. Age	1.00								
2. Diarrhea intensity	-.08	1.00							
3. Diarrhea distress	-.04	.90**	1.00						
4. Diarrhea interference	-.03	.82**	.84**	1.00					
5. Diarrhea frequency	-.13	.84**	.80**	.83**	1.00				
6. Fatigue intensity	-.12	.14	.20*	.22*	.21*	1.00			
7. Fatigue distress	-.11	.13	.22*	.27**	.16	.71**	1.00		
8. Fatigue interference	-.05	.17	.26**	.32**	.22*	.76**	.82**	1.00	
9. Fatigue frequency	-.13	.19	.33**	.24*	.21*	.61**	.63**	.70**	1.00

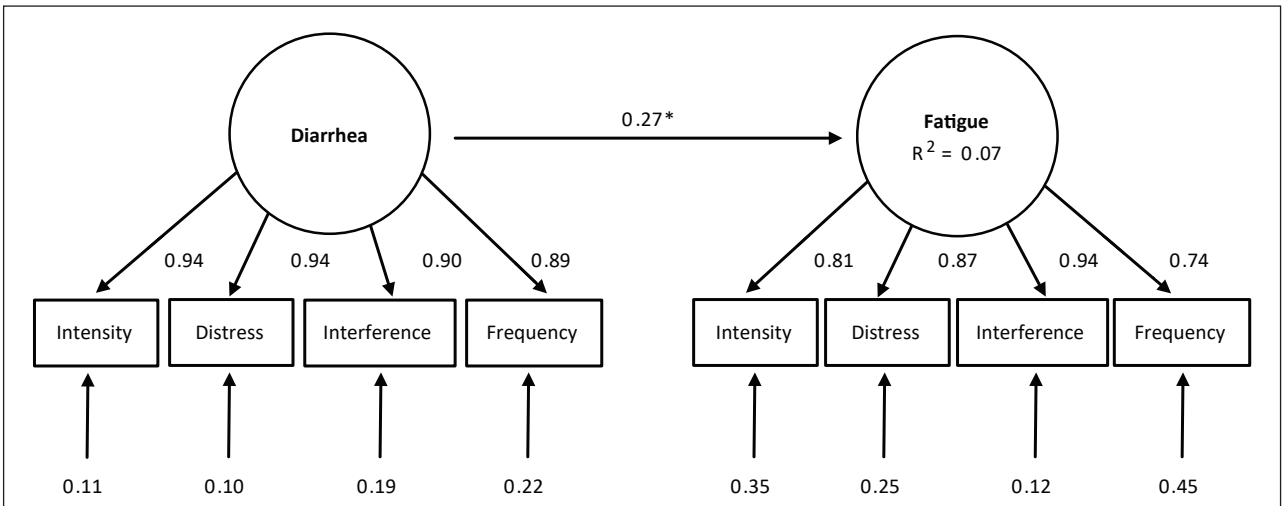
*p< .05; **p< .001

of the scale (greater than 5). An earlier study using the CSS had findings similar to those of the present SDA (5). The reported symptoms were consistent with the side effects and toxicities of radiotherapy and the chemotherapy drugs (e.g. leucovorin calcium, fluorouracil, oxaliplatin, capecitabine, and irinotecan) used in oncology (9,16). Notably, it is important for health professionals to examine the trajectory of a given patient's symptoms of diarrhea and fatigue and evaluate the need to include an ongoing individualized plan to manage those symptoms.

Relationships between diarrhea and fatigue

As expected, we observed that diarrhea had a significant direct influence on fatigue. Indeed, a study in adult patients receiving pelvic RT showed a positive correlation between diarrhea and fatigue intensity (17). Several studies have shown similar findings (18,19). However, the finding that diarrhea had a smaller effect on the dimension of fatigue frequency was unexpected. Although not evaluated, it is possible that since the majority of the participants were undergoing chemotherapy, alone, the prescribed drug regime did not produce intense diarrhea, compared to what may be expected from a larger representation of pelvic cancers undergoing chemo-radiation and its standardized treatments; as a result, patients may have not experienced frequent fatigue Nonetheless, the findings supported our hypothesis that the multiple dimensions of diarrhea had a significant direct influence on the multiple dimensions of fatigue, providing support to the notion that the symptom experience of patients with cancer is a multidimensional phenomenon.

The current SDA tested one structural model to examine how the dimensions of diarrhea are related to the dimensions of fatigue, in adults undergoing cancer treatments. Our findings/model supported our proposition that diarrhea precedes fatigue along the causal pathway. The etiology and associated mechanism of cancer-related fatigue are not comprehensively understood; however, it has been proposed that the perception of cancer-related fatigue may result from the dysregulation associated with the physiological symptom of diarrhea (17). Studies linking intestinal injury to the development of fatigue have found a significant worsening of fatigue in patients with diarrhea 3 to 5 weeks after pelvic RT; however, no significant increase in fatigue was observed in patients without diarrhea (8,17). Further, Wang et al. (18) found that fatigue positively correlated with diarrhea and the systemic markers of



*P<0.05. The values of the numbers to the right of the arrows pointing downwards from the above 2 latent variables are the standardized factor loading scores. The numerical value above the arrow pointing right from the latent variable (diarrhea) to the other latent variable (fatigue) is the structural "path" coefficient. The numerical values adjoining the arrows pointing upwards to each dimension of the latent variables are the estimated standard error.

Figure 1. Structural equation model: Measured variables are presented in rectangles; latent variables are presented in circles. All factor loadings relating measured and latent variables are significant.

inflammation (haptoglobin). Future research should focus on elucidating how cancer-related enteropathy can play a part in inducing the aberrant activation of an immune pathway, such as a cytokine-induced inflammatory reaction that could in turn lead to the worsening of fatigue, as suggested by Jakobsson et al. (17). A further comprehension of this pathway could broaden our understanding of the biological underpinnings of cancer-related fatigue.

The finding that diarrhea explained only a small portion of the variability of fatigue was unexpected. Future studies should explore the relationship between fatigue and psychological symptoms (e.g. anxiety, depression); it is possible that they may have had a stronger association with fatigue than does the physical symptom of diarrhea. Nonetheless, our findings have potential clinical implications.

Clinical implications

Based on our finding that diarrhea had a significant direct influence on fatigue, we encourage clinicians to conduct a routine assessment of disease-related and treatment-related diarrhea during the cancer trajectory. For example, we recommend that, in addition to the information obtained from the assessment of the diarrhea intensity, distress, interference, and frequency, a bowel assessment be complemented with a patient self-report (in the form of a diary), a nutritional evaluation, and/or a laboratory work-up (16,20). The information to record in the diary may include data related to episodes of diarrhea (e.g. number and consistency of stools per day) as well as daily weight, dietary intake, and any drugs that may be used to manage said diarrhea (21). Clinicians could also benefit from becoming familiar with and adopting into practice the available evidence-based guidelines for managing cancer-related diarrhea (20,21,22). In addition, patients and caregivers must be continuously educated about treatment-induced side effects and the life-threatening consequences of underreporting and/or undermanaging this symptom. Furthermore, they should also be educated that, when properly diagnosed, most symptoms can be managed with currently available medical, behavioral–cognitive (23) therapies, resulting in significant symptom reduction and improved treatment outcomes (24).

Since our findings suggest that patients who experience diarrhea are more likely (than those who do not) to experience fatigue, the early and accurate management of diarrhea would be expected to alleviate fatigue. It is plausible that pharmacological and lifestyle interventions targeting an early and accurate management of diarrhea may provide insight into the prevention or amelioration of fatigue. The management of uncomplicated diarrhea includes dietary changes (e.g. the avoidance of high fat and spicy foods), nutritional management, and pharmacologic measures (antispasmodic and antidiarrheal drugs: e.g. loperamide, octreotide) (20,25). Additionally, research on how probiotic supplementation might help prevent or treat intestinal barrier injury is underway and seems promising (19,26). A recent review of the literature found evidence in experimental studies for the benefits of probiotics in the prevention and treatment of radiation-induced diarrhea and acknowledged the need for more randomized, placebo-controlled studies (26).

Limitations of this study include the relatively modest sample size and the heterogeneity of the cancer types and stages, types of treatment, and time points of treatment. There may be other variables (e.g. hemoglobin, weight, nutritional status, physical activity, sleep, and depressive symptoms) that account for variance in the symptom experiences of cancer patients with fatigue; however, data on those variables were not available for the current analysis. Another limitation was not including the variable of gender in the model, despite some evidence that gender contributes to symptom expression (27); much research exploring the clinical relevance of those promising variables is needed. One may also debate that the current study is based on an analysis of a single-item measure of fatigue and of diarrhea. However, it has been stated (28) that in the clinical setting, relevant single-item questions are generally understood and accepted by patients; the advantage of using such questions is that they often provide strong data that can be used in the design of behavioral interventions, particularly when items from instruments with good psychometric properties are used. Future researchers may consider using other validated multi-item measures of fatigue and diarrhea to expand on or replicate our findings. Finally, our sample was of a moderate size and limited to 1site; therefore, the findings are not representative of the entire cancer population in the US.

Conclusions

Our results suggest that, during cancer treatments, patients who have diarrhea should receive prompt attention, not only to prevent the symptom's well-known life-threatening consequences but also to relieve fatigue. Continuous symptom assessment and management can optimize medical care and improve the health-related quality of life of patients and families. Additional research into the biological linkages among the symptoms of diarrhea and fatigue and into, as well, probiotics-driven interventions that could alleviate both the diarrhea and the associated debilitating fatigue in the cancer population is needed.

Resumen

Objetivos: Examinar la relación de los síntomas de diarrea y fatiga probando un modelo que incluye múltiples dimensiones de la experiencia con síntomas relacionados al cáncer. Métodos: Se realizó un análisis de datos secundarios sobre los datos reportados por 102 pacientes con cáncer que experimentaron simultáneamente diarrea y fatiga durante el tratamiento en un centro integral de cáncer en el sureste de los Estados Unidos. Se empleó el modelo ecuacional estructural para explicar la relación entre las dos variables. Los síntomas de fatiga y diarrea se evaluaron usando premisas de la Escala de Síntomas del Cáncer. Resultados: Los resultados del modelo estructural mostraron

que: (a) el ajuste del modelo fue adecuado; (b) la diarrea explicó el 7% de la varianza en la fatiga, y (c) el coeficiente estructural "path" entre diarrea y fatiga fue significativo (0.267, p <0.05). La diarrea tiene el efecto más fuerte sobre la interferencia por fatiga (0.251). Conclusión: La diarrea es un posible factor que contribuye a la experiencia sintomática de la fatiga y un objetivo potencial para la intervención en la prevención y la mejora de la fatiga.

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