The effects of Orem’s self-care model on the nutrition status and fatigue of colorectal cancer patients

Saba Karimi1, Zohreh Vanaki2*, Homayoon Bashiri3, Seyed Abdolmotalab Hassani4

Abstract

Background and Purpose: Colorectal cancer (CRC) is one of the most highly prevalent and life-threatening digestive tract cancers. CRC and its treatment are associated with numerous complications in the patients. Orem’s self-care model is a theory on clinical improvement and reducing fatigue in patients with CRC. This study aimed to investigate the effects of Orem’s self-care theory on the nutrition status and fatigue of CRC patients.

Methods: This quasi-experimental study was conducted on 70 patients diagnosed with CRC in the teaching hospital of Imam Reza in Kermanshah, Iran in 2014. Samples were randomly divided into two groups of experimental and control. Data were collected using the food frequency questionnaire (FFQ) and Brief Fatigue Inventory (BFI). After data collection, a self-care training program was implemented based on Orem’s self-care theory.

Results: Self-care training intervention in the experimental group improved the consumption patterns of fruits (P=0.002), vegetables (P=0.001), and dairy products (P=0.001). Moreover, general fatigue of CRC patients in the experimental group decreased after the intervention (P=0.0001).

Conclusion: According to the results of this study, Orem’s self-care model could reduce the clinical symptoms and fatigue of patients with CRC. Therefore, it is recommended that this model be applied to enhance the self-care behaviors and clinical conditions of CRC patients.

Keywords: Colorectal cancer, Fatigue, Nutrition, Orem’s model, Self-care

Introduction

Cancer is one of the leading causes of mortality in developed and developing countries, including Iran. Prevalence rate of cancer has been reported to be on the rise, and considerable healthcare resources are allocated to the management and treatment of this chronic disease (1).

In recent years, lifestyle changes and urbanism have resulted in the increased prevalence of different cancer types, especially digestive system cancers (2, 3). Colorectal cancer is the second most important cause of cancer deaths, as well as the third and second most prevalent cancer type among men and women, respectively (4, 5).

Considering that digestive system cancers account for 38% of all cancers and 44.4% of cancer deaths, they are reported as the most prevalent cancer types in Iran (2, 3). Consumption of foods rich in animal fat, insufficient dietary fiber intake (e.g., fruits,
vegetables, wheat husk), and inadequate physical activity contribute to the higher prevalence of cancer (6, 7).

Colorectal cancer (CRC) is among the most significant causes of cancer-related deaths across the world. According to statistics, 1.2 million patients are diagnosed with CRC, with the mortality rate estimated at 600,000 cases. Furthermore, CRC is the second most common cause of cancer deaths in the United States and other developed countries despite remarkable advancement in disease diagnosis, surgical procedures, and chemotherapy (8). CRC is a chronic disease associated with various symptoms, such as fatigue, lethargy, loss of appetite, anemia, and nutritional disorders.

Current treatments of CRC have been shown to induce complications such as nausea and vomiting, alopecia and stomatitis, which adversely affect the quality of life of the patients (9, 10). Fatigue is one of the most frequent and debilitating complications of CRC and its treatment, which is reported by 70-100% of the patients. Fatigue could be caused by the disease or its treatments. In many CRC patients, fatigue might be so intense that the patient would not be able to perform daily tasks without intervention (11).

Since CRC is a chronic disease associated with numerous treatment complications, self-care abilities play a pivotal role in enhancing the quality of life of the patients. Orem's theory is one of the key theories for the improvement of self-care abilities, which argues that health of an individual could be maintained through self-care. Evidently, self-care behaviors will ultimately bring about a sense of health in the individual (12, 13).

Similar to other nursing models, Orem’s theory emphasizes on facilitating the role of nurses as the major source of change in the care process (14). Considering the complications and problems of cancer patients, this self-care model is strongly recommended to lead the patient toward self-care behaviors through reinforcing their knowledge, attitudes, and skills, which are based on the medical needs of patients.

According to the literature, Orem’s self-care theory has the potential to be used for other chronic diseases, such as peritoneal hemodialysis and heart failure (15, 16). In a study entitled “Effects of exercise on the improvement of performance, fatigue, and quality of sleep in patients with colorectal cancer”, Chevilan et al. (2013) applying this model to reduce fatigue in CRC patients and concluded that the level of fatigue decreased in patients of the experimental group (17).

In another study, Zarief Yegane et al. (2009) assessed the nutritional status of cancer patients during chemotherapy. The results of this study showed that patients with gastrointestinal cancer and lungs are in an advanced stage more than any other cancer are malnourished (18).

Extensive research has been conducted regarding the promotion of self-care behaviors and nutrition status, as well as the improvement of fatigue, in CRC patients. In this context, nurses play a critical role in instructing cancer patients on self-care behaviors. Sufficient self-care abilities could reduce the costs of healthcare services and repeated hospitalization.

This study aimed to evaluate the effects of Orem’s self-care model on the nutrition status and fatigue of CRC patients.

Materials and Methods

This quasi-experimental study was conducted on 70 patients diagnosed with CRC, who were hospitalized in Imam Reza Hospital of Kermanshah, Iran in 2014. Participants were selected via random sampling and divided into two groups of experimental and control.

Inclusion criteria of the study were as follows: 1) age range of 40-70 years (male and female); 2) medical record of at least one surgery; 3) disease diagnosis within the past year and 4) ability of at least one family member to participate in the educational intervention and accompany the patient throughout healthcare stages. The only exclusion criterion was attending other educational courses held by Imam Reza Medical Educational Center. Sample size of the study was determined using the sample size formula, as obtained through literature review (19), and Altman’s nomogram ($\alpha = 0.05, \beta = 0.1, \text{test power}=0.90\%)$. 


**Applied questionnaires**

Data collection tools included the food frequency questionnaire (FFQ) and Brief Fatigue Inventory (BFI). FFQ is the most reliable instrument to evaluate dietary patterns and classify individuals based on nutrition status to determine the amount of nutrient intake. FFQ consists of 147 items on different food groups, including bread and cereals, proteins, fruits and vegetables, and dairy products. Reliability and validity of this questionnaire have been confirmed in previous studies (19, 20). In addition, internal consistency of FFQ has been determined at Cronbach’s alpha of 89%.

BFI consists of 10 items, and the first question determines whether the respondent has experienced unusual fatigue over the past week. Within a score range of 0-10, other items in BFI measure the level of current fatigue, general fatigue over the past 24 hours, highest level of fatigue over the past 24 hours, effects of fatigue on general activities over the past 24 hours, mood, ability to walk, communication with others, and enjoying life.

Scores in BFI are as follows: No fatigue=zero, mild fatigue=0-3, average fatigue=4-6, severe fatigue=7-9, and very severe fatigue=10. Reliability and validity of this questionnaire have been confirmed in previous studies, with Cronbach’s alpha estimated at 93% (21-24).

**Data collection**

After the approval of the study protocol by the Ethics Committee of Tarbiat Modares University, the researcher referred to the oncology and radiotherapy/chemotherapy departments of Imam Reza Hospital of Kermanshah and selected the candidates. Participants of the experimental and control groups completed a demographic questionnaire, BFI, and FFQ. In addition, participants of the experimental group completed Orem’s self-care form designed for CRC patients. Based on the collected data, self-care capabilities and needs of CRC patients, including self-care desire, awareness, and skills, were measured, and limitations of each patient were determined as well.

Afterward, the researcher listed the diagnosis results, determined the objectives of the study, and designed the healthcare intervention based on the study objectives. Intervention for the experimental group encompassed training, supporting, and coaching, which consisted of three stages based on Orem’s self-care model (five training sessions). The training sessions were focused on different aspects, including nutrition, fatigue reduction techniques, sleep quality improvement, phone/face-to-face follow-up, and checklist evaluation of available CRC patients in the clinic.

In this study, Orem’s nursing process was described in three steps. Initially, we determined the nursing care needs of the subjects, and following that, a system was designed for the standard process of nursing care accordingly. In the third step, nursing activities that were implemented by nurses were evaluated. Nurses assessment Self care in the field of nutrition and Fatigue. Orem’s self-care model, nurses with nursing history form using information from patients (25). Nursing history contributes to determining patient needs in terms of self-management and self-care abilities. In addition, in addition, this causes the patient care program to be developed based on the patient’s treatment needs. The main self-care needs in this regard include taking care of all the needs of patients, care needs in terms of self-development, In case of deviation of Health (25-27).

For the intervention, the designed self-care program was implemented based on self-care training and objectives, focusing on aspects such as proper nutrition, physical activities, and muscle relaxation techniques.

In the experimental group, training intervention consisted of three stages and was implemented in five sessions based on Orem’s self-care model. Intervention stages included patient training on CRC and its treatments, proper nutrition status, fatigue reduction methods, and techniques to improve sleep quality. The first session of self-care education was focused on self-care training, and the educational content included an introduction to the physiology of digestion system and causes of CRC, available treatments, and the associated complications of CRC treatments.

The first session was held for five groups of
patients (seven subjects in each group) through group discussion for 60 minutes. At the end of the first session, participants were asked different questions in order to evaluate and record the results. The second session was focused on proper nutrition and cooking techniques suitable for CRC patients. Due to the variable dietary habits of the subjects, this session was held privately for each subject in the presence of a family member.

The third session was focused on information about fatigue, causes of fatigue, and exercise techniques (warming up, walking, and cool-down activities), which was held for 20 minutes three times a week. Considering that pain and low quality of life are among the main causes of fatigue, participants were informed on non-medicinal methods of pain relief during the fourth session of intervention (e.g., music therapy and distraction). This session was held for five CRC patient groups (seven subjects in each group) through lectures and displaying therapeutic techniques and educational films.

The last session of the intervention was focused on the methods of fatigue reduction, improvement of sleep quality, and progressive muscle relaxation techniques (45-60 minutes). This session was held privately for each patient in the presence of a family member through lectures and displaying educational films in order to facilitate learning. At the end of each session, self-care checklists of the educational content were collected and evaluated.

After the intervention, participants were followed-up via phone contact, face-to-face meetings, contact with family members, and review of the checklists that were completed by the patients at the clinic.

Along with the training sessions, the researcher applied supportive techniques, such as motivating the patients to adhere to their diet, reasoning with the patients, and offering mental support. To this end, contact information of the researcher was provided for the patients and their family members in case of enquiries. All the training sessions were held in the presence of one family member to assure mental support and that the patient would fully comply with the self-care program.

Two months after the intervention, patients were asked to complete the self-care questionnaire for CRC patients. In this study, subjects of the control group received routine care.

**Statistical analysis**

Data analysis was performed in SPSS version 16 using descriptive (mean, frequency, and frequency percentage) and inferential statistics (Chi-square for qualitative variables and independent T-test for quantitative variables). To verify the normal distribution of data, we used the Kolmogorov-Smirnov test. In addition, Mann-Whitney U test and Wilcoxon test were used to assess and compare the quantitative variables between the two groups. In this study, P value of less than 0.05 was considered statistically significant.

**Results**

Participants of this study were within the age range of 40-70 years, and mean age of the subjects in the experimental and control groups was 54±7.61 and 54±7.89 years, respectively. In terms of marital status, the majority of participants in the experimental group (65.7%; n=23) and control group (62.9%; n=22) were married. Results of Chi-square and independent T-test showed no significant differences between the two groups in terms of demographic characteristics (Table 1).

Our findings were indicative of no significant differences between the experimental and control groups in terms of nutrition status before the intervention, including bread and cereals ($P=0.381$), proteins ($P=0.446$), dairy products ($P=0.85$), fruits ($P=0.777$), and vegetables ($P=0.459$). However, results of Wilcoxon test after the intervention were suggestive of changes in the nutritional behaviors of the experimental group, which was attributed to the implementation of Orem’s self-care model.

In this regard, results of Mann-Whitney U test were indicative of significant differences between the nutrition status of the experimental and control groups after the intervention, including bread and cereals ($P=0.253$), proteins ($P=0.07$), dairy products ($P=0.001$), fruits ($P=0.002$), and vegetables ($P=0.001$).

With respect to the variable of fatigue in CRC
Table 1. Demographic characteristics of participants in experimental and control groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Groups</th>
<th>Experiment group</th>
<th>Control group</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=35 %</td>
<td>N=35 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education</td>
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<td></td>
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<tr>
<td>Below high school diploma</td>
<td>22 62.9</td>
<td>20 57.1</td>
<td>χ²=0.49</td>
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<tr>
<td>High school diploma</td>
<td>9 25.7</td>
<td>10 28.6</td>
<td></td>
<td></td>
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<tr>
<td>Above high school diploma</td>
<td>4 11.4</td>
<td>5 14.3</td>
<td></td>
<td></td>
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<tr>
<td>Income</td>
<td></td>
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</tr>
<tr>
<td>Low</td>
<td>23 65.7</td>
<td>24 68.57</td>
<td>χ²=0.79</td>
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<tr>
<td>Average</td>
<td>12 34.3</td>
<td>11 31.43</td>
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<tr>
<td>Disease record in the family</td>
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<tr>
<td>Yes</td>
<td>14 40</td>
<td>16 45.72</td>
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<tr>
<td>No</td>
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<td>19 54.28</td>
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<tr>
<td>Record of intestine polyp</td>
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<tr>
<td>Yes</td>
<td>6 17.1</td>
<td>8 22.9</td>
<td>χ²=0.55</td>
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<tr>
<td>No</td>
<td>29 82.9</td>
<td>27 77.1</td>
<td></td>
<td></td>
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<tr>
<td>Diagnosed for</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1 year</td>
<td>18 51.43</td>
<td>18 51.43</td>
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<tr>
<td>2 years</td>
<td>12 34.28</td>
<td>10 28.57</td>
<td>χ²=0.53</td>
<td>t=-0.6</td>
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<tr>
<td>3 years</td>
<td>5 14.29</td>
<td>7 20</td>
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<td>Smoking record</td>
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<tr>
<td>Yes</td>
<td>17 48.6</td>
<td>15 42.9</td>
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<td>No</td>
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<td>20 57.1</td>
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<td>Diet</td>
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<tr>
<td>Yes</td>
<td>8 22.85</td>
<td>7 20</td>
<td>χ²=0.77</td>
<td>t=0.085</td>
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<tr>
<td>No</td>
<td>27 77.15</td>
<td>28 80</td>
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<td>Physical activities</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8 22.85</td>
<td>5 14.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>27 77.15</td>
<td>30 85.71</td>
<td></td>
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<tr>
<td>Cancer</td>
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<td></td>
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<td></td>
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<tr>
<td>Colon</td>
<td>26 74.3</td>
<td>27 77.1</td>
<td>χ²=0.92</td>
<td>t=0.16</td>
</tr>
<tr>
<td>Rectum</td>
<td>5 14.3</td>
<td>5 14.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>4 11.4</td>
<td>3 8.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
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<td></td>
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<tr>
<td>Chemothepapy</td>
<td>23 65.7</td>
<td>22 62.9</td>
<td>χ²=0.8</td>
<td>t=0.062</td>
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<tr>
<td>Radiotherapy</td>
<td>12 34.3</td>
<td>13 37.1</td>
<td></td>
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</tbody>
</table>

Table 2. Average portion of bread and cereals, proteins, dairy products, and fruits and vegetables in diet of experimental and control groups before intervention and two months after intervention

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stage</th>
<th>Experimental group (Mean±SD)</th>
<th>Control group (Mean±SD)</th>
<th>Mann-Whitney U test</th>
<th>Wilcoxon test Experimental group Before and after test</th>
<th>Wilcoxon test control group Before and after test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bread and cereals</td>
<td>Before intervention</td>
<td>0.79±6±2.11</td>
<td>0.71±8±2.11</td>
<td>P=0.38</td>
<td>Z=2.45</td>
<td>P=0.002</td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>0.80±8±2.37</td>
<td>0.80±9±2.06</td>
<td>P=0.253</td>
<td>Z=1.43</td>
<td></td>
</tr>
<tr>
<td>Proteins</td>
<td>Before intervention</td>
<td>1.89±0.867</td>
<td>1.89±0.932</td>
<td>P=0.446</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>2.34±0.873</td>
<td>1.86±0.912</td>
<td>P=0.07</td>
<td>Z=1.65</td>
<td>P=0.024</td>
</tr>
<tr>
<td>Dairy products</td>
<td>Before intervention</td>
<td>1.77±0.902</td>
<td>1.89±0.900</td>
<td>P=0.85</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>After intervention</td>
<td>2.87±0.877</td>
<td>1.83±0.923</td>
<td>P=0.001</td>
<td>Z=3.37</td>
<td>P=0.001</td>
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<tr>
<td>Fruits</td>
<td>Before intervention</td>
<td>1.60±0.881</td>
<td>1.46±0.870</td>
<td>P=0.777</td>
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<tr>
<td></td>
<td>After intervention</td>
<td>2.17±0.923</td>
<td>1.51±0.818</td>
<td>P=0.002</td>
<td>Z=3.13</td>
<td>P=0.001</td>
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<tr>
<td>Vegetables</td>
<td>Before intervention</td>
<td>1.63±0.843</td>
<td>1.46±0.780</td>
<td>P=0.459</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>After intervention</td>
<td>2.14±0.944</td>
<td>1.60±0.847</td>
<td>P=0.001</td>
<td>Z=4.26</td>
<td>P=0.001</td>
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</table>
patients, our findings were indicative of significant differences between the experimental and control groups after the intervention in terms of current fatigue, highest level of fatigue over the past 24 hours, and communication with others. In addition, the same results revealed significant changes in the general fatigue of participants after the intervention in the experimental group (P=0.0001) (Table 3).

Discussion

The present study aimed to investigate the effects of Orem’s self-care model on the fatigue and nutrition status of patients diagnosed with CRC. According to the findings, Orem’s self-care model improved the nutrition status of CRC patients in food groups of dairy products and fruits and vegetables, and it reduced the fatigue of these patients as well.

Furthermore, results of the current study were indicative of increased intake of bread and cereals in the daily diet of the subjects in the experimental group, so that bread and cereals model approached the standard level. This finding is in congruence with the studies by Pasdar (28) and Pourfarzi (29), while inconsistent with the findings of Aysha. This discrepancy could be due to the variations in the nutritional culture of different regions in Iran and other countries (30).

As for the category of proteins, dietary habits of the majority of CRC patients in the present study was lacking in proteins, and despite emphasis on the necessity of adequate protein intake for these patients, no significant difference was observed between the control and experimental groups before
and after the intervention in this regard. This is consistent with the findings of Lopes (31) and Dehghanzadeh (32), which could be due to the fact that high-protein foods are relatively expensive, and the majority of CRC patients in our study were coming from low-income families. Our findings showed a significant difference between dietary protein intake and income status of the participants in both study groups before and after the intervention.

Considering the effect of calcium on tumor control, milk and other dairy products are inherent to the diet of patients with digestive cancers. In the current study, consumption of milk and other dairy products was below the standard level in the control and experimental groups before the intervention, which is in line with the studies by Aysha and Pasdar et al. (28, 30). However, subjects of the experimental group reported increased intake of milk and other dairy products in their diet after the intervention, which was mainly attributed to the implemented training and self-care capacity of the patients.

With regard to the category of fruits and vegetables, our participants in both study groups had inadequate dietary intake of fruits and vegetables before the intervention, which is consistent with the results obtained by Aysha and Lopes (30, 31). For many reasons, fruits and vegetables are important dietary ingredients for CRC patients since these nutrients are abundant sources of antioxidants and different vitamins, which are essential to preventing tumor recurrence.

Furthermore, specific medicines used in chemotherapy protocols might lead to complications such as flatulence, constipation and dehydration, and consumption of fruits and vegetables largely contributes to the reduction of constipation and flatulence. In the present study, patients of the experimental group reported increased intake of fruits and vegetables in their diet after the training intervention (28).

With respect to fat consumption, the majority of our patients used 8-11 units of fat in their diet before the intervention. To reduce fat consumption, participants of the experimental group received training on the reduction of fat intake, as well as the advantages of herbal oils, and after the implementation of the self-care program, they reported reduced fat consumption in their diet.

Another objective of the present study was to evaluate the fatigue of CRC patients and reduce this variable in the experimental group. According to our findings, participants in the experimental and control groups had a significant difference in this regard before the intervention. However, fatigue level reduced in patients of the experimental group after the intervention, which confirms the effectiveness of Orem’s self-care model in controlling fatigue.

Our findings were suggestive of a significant association between the level of fatigue and lack of sufficient sleep in CRC patients. To reduce fatigue and compensate for sleep deprivation, we implemented routine exercise programs and progressive muscle relaxation techniques, while balancing rest and activity in the patients. Fatigue and sleep deprivation were observed to decrease in CRC patients through improving self-care awareness, skills, and capabilities. Moreover, use of muscle relaxation techniques proved to be effective in relieving mental and physical pressure through alleviating muscle tension, weariness and fatigue.

In a study, Pizarro et al. reported that progressive muscle relaxation improved sleep quality and reduced fatigue in patients (33). In the present study, development of self-care program of progressive muscle relaxation was used to reduce fatigue and improve sleep quality in patients in the experimental group. Furthermore, our findings denoted an association between routine physical exercise, fatigue, and quality of sleep in CRC patients of the experimental group. In other words, routine exercise was found to reduce the fatigue of CRC patients in the experimental group.

In another research, Mock et al. reported that fatigue of patients in the experimental group reduced after the implementation of an exercise program, so that there was a significant difference between the level of fatigue before and after the intervention (34).

Consistent with our findings, Rad et al. stated that fatigue of the majority of patients in the experimental group (56%) was at an average level before the intervention and it decreased significantly after the
implementation of a physical exercise program. This confirms the positive effects of physical exercise planning on the reduction of fatigue in chronic patients (35).

Similarly, the results obtained by Cheville et al. showed that after eight weeks of physical exercise plan, fatigue of the patients decreased and sleep quality enhanced in the subjects (17). It could be inferred that in the mentioned study, application of Orem’s self-care model could effectively improve the awareness of patients, resulting in increased sleep quality and decreased fatigue.

Consistent with the study by Hoseini (36), other findings were suggestive of the difference between the severity of nausea and vomiting before and after the intervention. In this regard, Piamjariyakul et al. reported that 73% and 61% of the patients had self-care disorders in the areas of nutrition and oral health, respectively. Among these patients, 5% had nausea and vomiting, 58% suffered from fatigue, and 50% had constipation. Findings of the mentioned study revealed a direct correlation between nutritional disorders, nausea and vomiting, and lack of oral hygiene (37), so that patients undergoing chemotherapy and radiotherapy required self-care training on nutrition, nausea and vomiting, and fatigue.

According to the results of the current study, self-care awareness of CRC patients in the experimental group was relatively low before the intervention, and a significant improvement was observed in this variable after the implementation of Orem’s self-care model. Similarly, Oshvandi and Taghdisi reported increased scores of self-care awareness, desire, skills, and capabilities among the studied patients (38, 39).

Some of the limitations of the present study were the psychological characteristics of CRC patients, economic problems of the patients, and differences in the motivation and interests of the participants.

In the current study, we aimed to clarify whether the application of Orem’s self-care theory could influence the nutrition status and severity of fatigue in patients diagnosed with CRC. According to the results, this behavioral model could improve nutrition status and reduce fatigue in CRC patients.

Conclusion

According to the results of this study, implementation of a training program based on Orem’s self-care theory could enhance the clinical condition of patients diagnosed with CRC. Furthermore, a significant improvement was observed in the self-care capabilities of the participants after the training intervention. Owing to the fact that the main purpose of clinical nursing is to provide care services for patients to improve their conditions, proper patient education is of paramount importance. Therefore, it is recommended that oncology nurses adhere to Orem’s self-care model in order to raise the quality of nutrition and diminish the level of fatigue in cancer patients.

Conflicts of interest

None declared.

Authors’ contributions

All authors contributed equally to the writing of the scientific proposal, data collection, and manuscript drafting. The final manuscript was reviewed and approved by all the authors.

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