RESEARCH ARTICLE

LEPTIN AND GHRELIN RESPONSE TO AEROBIC EXERCISES IN POST-COLECTOMY PATIENTS

Walaa Ibrahim A. Faris[1]; Haidy Nady Ashem[2]; Salah El DeinAbd El Ghany M. [3] and Eman M. Othman[4]

[1]Departmentof Physical Therapy for surgery, Faculty of Physical Therapy, Cairo University
[2] Professor of Physical Therapy for surgery, Faculty Physical Therapy, Cairo University
[3]Professor of General and Plastic Surgery, Faculty of Medicine, El Kasr El Einey, Cairo University
[4]Assistant professor of Physical Therapy Department for Surgery, Faculty of Physical Therapy, Cairo University

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ABSTRACT

*Background:*Patients post colectomy experience a substantial decline fitness level and quality of life. As obesity is one of the most important risk factors for colorectal cancer, studies show that aerobic exercises and weight loss program will result in reduction of leptin and increase of ghrelin in patients with colorectal cancer. *Objectives:* was to investigate plasma leptin and ghrelin concentrations in male patients with colorectal cancer post colectomy after 8 weeks of aerobic exercise and a week of detraining. *Materials and Methods:* A cross-sectional observational study was conducted on thirty men selected from surgery department at Minia University Hospital (Egypt). They were assigned randomly into two equal groups each group was 15 patients, their age ranged from 50-60 years. Patients were evaluated by rockportwalking test using (treadmill), Fazzini weight scale and fasting blood plasma test using (ELISA kit) before and after the study. The study group (A) received aerobic training for 8 weeks as 3 sessions /week each session last for 45 minutes and control group (B) were only advised about healthy lifestyle. *Results:* The results showed that heart rate was decreased and VO2peak was increased in the training group compared to the control group (P < 0.05). Ghrelin concentration was increased significantly in the training group compared to the control group (P < 0.05), while plasma leptin hormone did not change significantly after training for both groups. *Conclusion:* The study concluded that aerobic training increases ghrelin hormone levels VO2peak after 8 weeks of aerobic exerciseand a week of detraining however, plasma leptindose not affected by this protocol in male patients with colorectal cancer.

INTRODUCTION

Colorectal cancer is the 7th commonest cancer in Egypt, representing 3.47% of male cancers and 3% of female cancers. The estimated number of colon cancer patients (excluding rectal cancer) in 2015 was slightly more than three thousands(A.S. Ibrahim *et al*., 2014). Globally, colorectal cancer is the third most common type of cancer making up about 10% of all cancer. In 2012, there were 1.4 million new cases and 694,000 deaths from the disease. It is more common in developed countries, where more than 65% of cases are found (World Cancer Report, 2014). Treatments used for colorectal cancer may include some combination of surgery, radiation therapy, chemotherapy, and targeted therapy (NCI,2014).Research has shown that physical and mental quality of life for colorectal cancer survivors was inferior when compared with age-matched individuals without cancer. Long-term effects of treatment include fatigue, sleep difficulty, fear of recurrence, anxiety, depression, negative body image,

sensory neuropathy, gastrointestinal problems, urinary incontinence, and sexual dysfunction (Baker F. *et al*., 2005). Physical activity provides benefits to people with non-advanced colorectal cancer. Improvements in aerobic fitness, cancer-related fatigue and health-related quality of life have been reported in the short term. However, these improvements were not observed at the level of disease-related mental health, such as anxiety and depression. (McGettigan M. *et al*., 2020. Leptin is a hormone known as structure regulator for the amount of consumption of energy and weight control. It is highly correlated with body mass index (BMI) in humans, and also plays a role in regulation of appetite, and metabolism and in cell proliferation and angiogenesis as well as in apoptotic inhibition (Giovannucci *et al*.,1995). Although the data about role of leptin in colorectal cancer is limited, some studies have indicated that there is an increase in chance of colorectal cancer with increase of leptin. Also, there are observations which show that leptin receptors are stimulated in cancer cells (Jeon, 2012). Ghrelin is a peptide hormone produced by ghrelinergic cells in the gastrointestinal tract (Sakata *et al*., 2010) which functions as a neuropeptide in the central nervous system. Ghrelin regulates appetite and plays a role in regulating the distribution and rate of use of energy. Ghrelin is primarily produced by gastrointestinal tract (Berner, 2014).

*Corresponding author: *Walaa Ibrahim A. Faris,*
Departmentof Physical Therapy for surgery, Faculty of Physical Therapy, Cairo University.

Obesity is one of the most important risk factors for colorectal cancer and studies show that aerobic exercises and weight loss program will result in reduction of leptin and increase of ghrelin (Foster, 2005). A study reported that as a result of increased adipose tissue, level of ghrelin was reduced and the chance of colorectal cancer increased. Probably, increased physical activity level can play an important role in presentational care of colorectal cancer (Sobhani, 2010). Researchers showed that leptin decreases and ghrelin increases in healthy subjects in response to aerobic exercise. Regarding the role of leptin and ghrelin in colorectal cancer and as the aerobic exercise can affect the level of them in healthy people, we hypothesized that exercise training would reduce the fat mass and increase ghrelin and decrease leptin in male patients with colorectal cancer (Pérusse *et al*., 1997). In previous studies, a dose-dependent effect of exercise has been physical activity decreases the risk of developing comorbid diseases in patients with CRCand improves the disease outcomes in patients with comorbid diseases. Several studies have been conducted regarding the effects of aerobic exercise on cancer prevention and the outcome in patients with cancer.Despite advances in the diagnosis and treatment, the rate of recurrence for locally advanced colon cancer is 40% (Friedenreich CM *et al*., 2017). In addition to the risk of recurrence, CRC survivors experience the late and long-term effects of cancer treatment. Lifestyle interventions such as an improved diet and aerobic exercise are recommended to improve the side effects of cancer and cancer treatment. Aerobic exercises improve clinical conditions, such as weakness, quality of life, muscle strength, lymphedema, depression, functional status, and decrease the risk of recurrence of cancer before and after the diagnosis of CRC and also after colectomy (Ballard-Barbash R *et al*., 2012). Therefor the need of this study was developed from the lack in the quantitative knowledge and information in the published studies about the effect of aerobic exercises on leptin and ghrelin hormones with patients after colectomy surgery.

MATERIALS AND METHODS

A prospective, parallel groups, randomized controlled trial with a 1:1 allocation ratio was conducted from July 2021 to October 2021. Thirty male patients aged from 50 to 60 years old underwent colectomy and were in 2nd–3rd month after their surgery they were randomly selected from surgery department at El Minia University Hospital and were distributed into two equal groups (n)= 15 patients for each group.Group (A)received an aerobic training program of walking on a treadmill consisting of 24 sessions over 8 weeks as 3 sessions /week and one week of detraining. Training was carried out with 50–60% of target heart rate for 15 min and 5 min rest between them. Before and after the aerobic exercise training, all subjects had 5 min warm up and cool down, respectively (45 minutes totally). Each participant was equipped with a heart rate monitor, and group (B) who were advised with healthy life style after the operation and left to do their normal ADL. The patients participated in this study after signing an informed consent form before data collection. Recruitment began after approval was obtained from the Ethical committee of the Faculty of Physical Therapy, Cairo University. At this study only male patients were included if their age was between 50 and 60 years old , and at their 2nd to 3rd months having any type of colectomy, and were excluded if they were receiving chemotherapy or radiation ,there was any clinical evidence of pre-existing cardiac or pulmonary disease,

Patients who have ostomy, hypotension or hypertension, thrombosis of lower extremities, any acute disorders affected or aggravated by exercise (e.g. common cold), mental or orthopedic impairment that compromises exercise performance and evidence of anemia. All patients were evaluated before and after the treatment application which was 8 weeks of training and one week of detraining. All patients underwent complete history taking include: Name, Age, Address,Occupation, in addition they were asked about their past history like if there was any childhood illness,allergies, immunizations, past surgical history,prior accidents or hospitalizations,other cancer type or even recurrent colon cancer, or other colon diseases. Detailed analysis of the present complication post colectomy (present history)was evaluated and their medical history which include bleeding, DVT, infection, pulmonary embolism bowel, drugs and also health habits and exercise if there were any complications post-surgery. Evaluation was done using Fazzini weight scale for calculating BMI, it's calculated by dividing weight in (kg) kilograms by height in (m2) meter square.Rockport One-Mile Fitness Walking Test for calculating Vo2max. In this test, the patient walked 1 mile as fast as possible on a treadmill, the standard order that was given to the patients was: "walk as fast as possible, but don't run or jog", then total time was recorded and heart ratewasobtained in the final minute then using the following equation to calculate fitness level:

VO2peak=139.68-(0.388×age)-(0.077×bodymass(pound))-(3.265×time(min))-(0.156×heartrate(bpm)) (Robert, 2000).

The plasma ghrelin and leptin levels were measured using an enzyme-linked immunosorbent assay (ELISA) kit.Fasting blood sample test was collected at rest (before training) and after ending the one week of detraining. All the subjects fasted at least for 12 hours and a fasting blood sample was obtained by venipuncture. Blood samples were kept at a temperature of−20°C in order to separate the plasma. The plasma ghrelin and leptin levels were measured using an enzyme-linked immunosorbent assay (ELISA) kit.

Training program: An aerobic training (AT) program included a 45 minutes session three times a week (135 min/week) was carried out for eight weeks followed by one week of detraining. Aerobic exercises consisted of three phases: warm-up, training and cool down.At the beginning of exercise session, subjects had a five minutes warm-up. The warm-up protocol was slowly walking on treadmill followed by the training phase. At baseline, the training phase was be commenced with two 15 minutes walking on treadmill at 50-60% of the subject's maximal heart rate (MHR) and 5 minutes rest between them.

To assure that the desired heart rate (exercise intensity) was achieved and maintained for 30 minutes, during the aerobic sessions, each participant underwent heart-rate monitoring with heart rate monitor to ensure accuracy of the exercise level (Lequin, 2005). To calculate target heart rate 60%, first calculate maximum heart rate using the formula: (HRMax = age−220) then multiply it by 0.6. and find the accurate speed to that heart rate on the treadmill. (Chaudhary *et al*., 2010).

Detraining: After completion of the 8 weeks' intervention, the subjects were instructed to resume their normal lifestyles and avoid any type of high intensity physical activity for a week.

RESULTS

In control group the weight, heart rate, VO2 peak, BMI, and leptin and ghrelin hormones shows slightly decrease in their values after the testing period. On other hand, in training group the weight, heart rate, BMI, and leptin hormone values are showing a markedly decrease in their values after the testing period. In contrast VO2 peak, and ghrelin hormone values are showing a markedly increase after the testing period. Figure (1) shows the difference between pre- and post- training with VO2 peak variable that in control group the result is not change greatly after the period ends but it shows broad in result that means some change present in limit number of participants as a slightly decrease, but a clear increase in VO2 peak among training group are notice after the training period according to our finding.
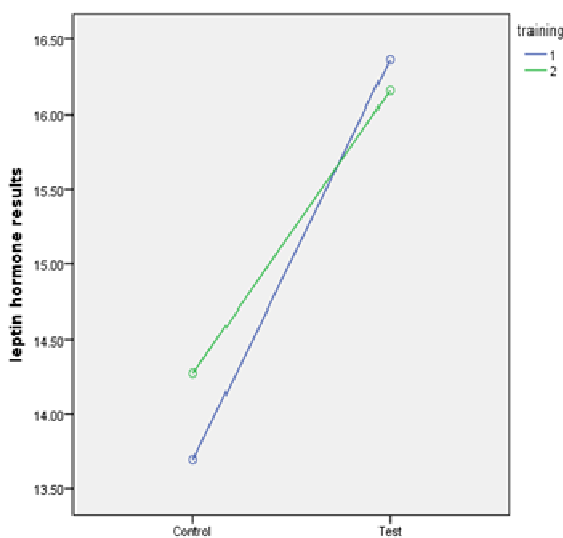
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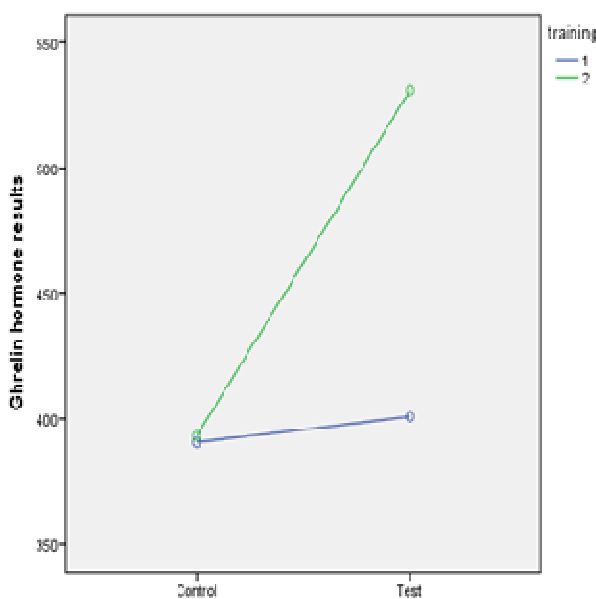**Figure 1 to 2 missing**
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Physical characteristics of participants with VO^2 peak: After applying a suitable test to assess the significant of the used variables weight, heart rate, VO2 peak, BMI, and leptin and ghrelin hormones on fitness status and oxygen capacity/ uptake among colorectal cancer patients. To the control group weight and leptin are having a statistically significant relation with the VO^2 peak, but BMI and ghrelin don't show any statistically significant with the oxygen capacity among pre-training control group. In post training status no statistically significant present in control group except for weight variable. In pre-training period for training group only heart rate is show statistically significant association, the other variables show no statistically significant. In post-training period among training group heart rate and ghrelin hormone show statistically association with the VO^2 peak.

For Control group before test, a multiple regression was run to predict VO2 peak from age, weight, leptin and ghrelin hormones and heart rate. These variables statistically significantly predicted VO2 peak, $F_{(5,9)} = 6.082$, $p < 0.010$, $R2 = 0.772$. For Control group after **test**, a multiple regression was run to predict VO2 peak from age, weight, leptin and ghrelin hormones and heart rate. These variables not statistically significantly predicted VO2 peak, $F_{(5,9)} = 3.233$, $p < 0.060$, $R2 = 0.642$. For training group before test, a multiple regression was run to predict VO2 peak from age, weight, leptin and ghrelin hormones and heart rate. These variables not statistically significantly predicted VO2 peak, $F_{(5.9)} = 2.550$, $p < 0.105$, $R2 = 0.586$. For training group after test, a multiple regression was run to predict VO^2 peak from age, weight, leptin and ghrelin hormones and heart rate. These variables not statistically significantly predicted VO2 peak, $F(5.9) = 3.736$, $p < 0.042$, $R2 = 0.675$.

Hormonal change between pre- and post- test period: The figure (3) shows that for leptin hormone there were no statistically significantly difference between pre and post applying the test through the participants ($p < 0.491$), accepted the null hypothesis that no association present between leptin levels and the training performed. For figure (4) that shows a statistically significantly difference between pre and post applying the test through the participants ($p < 0.000$), accepted the alternative hypothesis that the association present between ghrelin levels and the training performed.

DISCUSSION

Most colorectal cancers are due to old age and lifestyle factors with only a small number of cases is due to underlying genetics. Five years survival rates in the United States are around 65% (NCI, 2014). Globally, colorectal cancer is the third most common type of cancer making up about 10% of all cancer. In 2012, there were 1.4 million new cases and 694,000 deaths from the disease. It is more common in developed countries, where more than 65% of cases are found. It is less common in women than men (World Cancer Report, 2014). Leptin has been implicated in the pathogenesis of several types of obesity-related cancers, including colorectal cancer. It has been proven to be able to regulate cell proliferation in various normal and neoplastic cell types. In colorectal cancer leptin acts as a potent mitogen and promotes the invasiveness of familial adenomatous colonic cells (Somasundar *et al.*, 2003). Ghrelin is identified as a natural ligand of the growth hormone secretagogue receptor (GHS-R). It has various biological functions, including regulation of appetite and body weight, control of energy homeostasis, modulation of cardiovascular and gastrointestinal system and anti-inflammatory effect (Alnema *et al.*, 2010).

Table 1. Title Missing

Variables	Control (mean±SD)		Training (mean±SD)	
	Pretraining	Post-training	Pretraining	Post-training
Weight (Kg)	76.20±8.86	75.40±8.58	79.07±6.34	73.87±6.23
Heart Rate	74.87±2.10	74.27±2.52	73.60±1.30	70.87±1.685
VO2 peak	26.66±10.33	26.28±8.62	31.39±6.10	40.10±5.00
BMI	25.08±1.05	24.82±1.23	25.80±2.44	24.09±2.08
Leptin	13.69±6.82	14.27±6.11	16.36±5.52	16.15±4.84
Ghrelin	390.73±115.56	393.27±115.80	400.87±73.34	530.80±75.936

Table 2. Significance of control and taining group pre-training and post-training

Variables	Control Group				Training Group			
	Pre-training (sig)		Post-training (sig)		Pre-training(sig)		Post-training (sig)	
	t- value	p-value	t- value	p-value	t- value	p-value	t- value	p-value
Weight	-4.923	0.001	-3.988	0.003	-0.479	0.643	-1.362	0.206
Heart Rate	-2.361	0.043*	-861	0.412	-2.664	0.026*	-3.339	0.009*
BMI	0.451	0.662	0.900	0.392	-0.287	0.781	-0.590	0.570
leptin	2.515	0.033*	1.623	0.139	1.179	0.268	-0.510	0.622
ghrelin	-1.856	0.096	-1.107	0.297	-0.587	0.572	2.506	0.034*

Multiple studies have demonstrated the role of ghrelin in cancer cells proliferation, differentiation, invasiveness and apoptosis inhibition (Arnaldi *et al*., 2003). Physical low-intensity exercise is a strategy used to improve body fitness especially with healthy overweight and obese people since it shares with applying a negative energy balance by increasing energy consumption. As a result, any energy used in exercise increases the intensity of hunger and drives food consumption (Bilski *et al*., 2009; Hopkins *et al*., 2010). Also, it affects cancer patients as one of several mechanisms used to control the disease. On other hand, mechanisms responsible for the regulation of food intake are still under investigation (Vatansever *et al*., 2011). Exercise training has effect on many biological mechanisms such as energy metabolism, hormone levels like leptin, insulin resistance, prostaglandins, C-reactive protein (CRP) and inflammatory indices (Kim *et al*., 2010). Current studies show that exercise at workplace or home can reduce the chance of colorectal cancer between 20 and 60% (McTiernan, 2003). In recent years, it has been found that exercise training not only prevents the cancer but also it has positive effect for both function and quality of life (Courneya *et al*., 2003).

During the past decade, our knowledge of such homeostatic system which regulates food intake and body weight has improved with the discovery of circulating peptide ghrelin that makes signals to the brain about the body's nutritional status (Vriese *et al*., 2008). Current evidence does not clarify which elements of exercise are most effective, including type (aerobic and/or resistance), mode, and dose,(frequency, intensity, length of sessions) and physical activity interventions need to be individualized based on the level of physical capacity and pre-existing conditions and should begin at low intensity levels with gradual progression. Most studies prescribed less than moderate intensity aerobic activity, as recommended for healthy adults, probably because participants were advised to start at a lower level and to progress according to their physical capacity(Ann *et al*., 2012). This study was designed to determine the effect of aerobic exercises on the Leptin and Ghrelin hormones in patients with colorectal cancer post colectomy using treadmill to improve fitness levels and an ELISA kit examination as a method of evaluation to blood hormones. Thirty men with colorectal cancer post their operation and at 2nd to 3rd months after the operation participated in this study.

They were assigned into two groups equal in number, each group had 15 patients. Physical characteristics: Our study shows that the mean of age for training group is 54.60±3.04 years, which near the mean of 54 ± 10 years in (Sperandio *et al*., 2015). On other hand, higher than other studies, such as 50±13 years in (Ma¨ntta¨ri *et al*., 2018), 39.3±17.8 years in (de Vries*et al*., 2021) and 22.0±1.4 years in(Liu *et al*., 2021), this variation in mean among various kind of studies indicate the importance of scanning the suitable results associated with fitness for healthy or patient's people. Our results showes that the mean of weight for training group is 79.07±6.34kg, which is higher than other studies, such as 64.9±8.6 Kg in (de Vries *et al*., 2021).The weight change among our life according to specific activities, nutritional habits and diseases. For our study the colorectal cancer may place the weight as a big indicator about their status because the affected organ is huge and make difference due to weight. The heart rate as shown in our study decrease significantly with training group from 73.60±1.30Bpm to 70.87±1.685Bpm because the aerobic exercises increase the fitness show the heart turn to control beating and become within normal range with low intensity activities, according to this finding heart rate play a vital role to improve the fitness and health status of patients. According to our finding the VO^2 peak show mean of 31.39±6.10 ml/kg/min with p<0.105and increase significantly after the training to reach 40.10±5.00 ml/kg/mi withp<0.042,the initial mean is lower than the mean of VO2 peak equal 37.1±11.8 ml/kg/min in (de Vries*et al*., 2021), 35 ± 11 ml/kg/min in (Sperandio *et al*., 2015), and 35.2±7.8 8 ml/kg/min in (Ma¨ntta¨ri *et al*., 2018). After eight weeks of doing aerobic exercise; VO2peak increased significantly in male patients with colorectal cancer. This is according to the ability of aerobic exercise which improves the consumption of oxygen in elderly men. It appears that the increase in VO2peak can improve the oxygen uptake and treat cancer in patients with colorectal cancer. Normally, VO2peak decreased, in contrast, when it is increased in male patients with colorectal cancer can improve cancer cachexia (remove of cancer mass) and reduce the fatigue caused by treatment (Nuri*et al*., 2016). Our study shows that the mean BMI for the training group is 25.80±2.44 Kg/m2, and 24.09±2.08 Kg/m2 after the training period that shows no statistical difference between pre-and post-training in colorectal cancer. BMI mean is 22.9±3.3 in (Liu *et al*., 2021) the BMI shows the state of obesity among the observed studies the mean for BMI falls into healthy and overweight categories.

Leptin and Ghrelin hormones: Our finding shows that the mean of ghrelin hormone is increased significantly with training group from 400.87±73.34 pg/ml to 530.80±75.936pg/ml when compared pre- to post- training period which indicates the physical changes through the colorectal disease, according to the explanation of ghrelin mechanisms of action via the human body that affects the appetite, metabolism, body mass, and body composition. All help the body to balance the energy (Kojima *et al.*, 2001), the changes of ghrelin hormone plasma for skeletal muscle during exercise training (Housa *et al.*, 2006, and Fairey *et al.*, 2002) increased aerobic exercises have resulted in elevated levels of ghrelin. (Chung *et al.*, 2009, and Fujisawa *et al.*, 2008). A significant positive relationship was presented between plasma ghrelin levels with VO2 peak (Nuri*et al.*, 2016). Malignant intestinal epithelial cells via colorectal cancer patients differentially overexpress ghrelin receptors, this results to produce more ghrelin compared with normal healthy humans, leading to stimulating proliferative and invasive behavior. The different types of the ghrelin hormone, the first is systemically available endocrine ghrelin levels in patients with colorectal cancer which do not have any significant relation with any tumor stage (Pöykkö*et al.*, 2003) The second is locally produced autocrine tissue ghrelin which is strongly related to colorectal malignancy in men with colorectal cancer (Waseem*et al.*, 2008 and Gil Campos *et al.*, 2006). On other hand, our finding shows no significant relation when compared pre- and post- training period which indicates that such low intensity training with such health status no effect on Leptin. But according to other studies when applying a high intensity training it increase more significantly.because sensitivity may increase with training. The connection between leptin and aerobic exercise is according to the hypothalamus (Nuri *et al.*, 2016). This study was limited by some factors as the cooperation and commitment of patients to the program of treatment and their familiarity with aerobic exercise training and walking on the treadmill device, also some patients were still suffering from operation complications with the stitches and tissue adhesions and scars that made them less interested in participation because of pain and limited movement. Our study has indicated a need to consider the following recommendations such as addingaerobic training with different levels not only low intensity to patients with colorectal cancer post colectomy, practicing those exercises for longer times and on both sexes not only male patients. Also it's recommended to take large samples of different ages of participants for better statistical design and analysis of data and finally to practice aerobic exercises on different types of cancers.

CONCLUSION

Improving the health status of colorectal patients by applying a program of low intensity training is vital as a modern strategies used during the treatment of cancer patients. Heart rate, VO2peak and ghrelin hormone levels improved after eight weeks of aerobic exercise and a week of detraining. In contrast, plasma leptin was not affected by this low intensity training in male patients with colorectal cancer.

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