Effect of aerobic exercise on leptin and ghrelin in patients with colorectal cancer

ABSTRACT

Objectives: Aerobic exercise can improve the levels of leptin and ghrelin in healthy people, but the effect of aerobic exercise on these proteins in colorectal cancer patients is not well known. The purpose of this study was to investigate plasma leptin and ghrelin concentrations in male colorectal cancer after 8 weeks aerobic exercise and after a week of detraining.

Materials and Methods: Thirty men with colorectal cancer (aged: 51.56 ± 11.28 years; ± standard deviation (SD)) were randomly assigned to training group (n = 15) or control group (n = 15). Before the experiment, Rockport walking test was conducted in order to measure peak aerobic capacity (VO2peak) of all subjects. Exercise training program consisted of 8 weeks walking and three 45-min sessions in each week with 50–60% of target heart rate. After 8 weeks of training, subjects underwent a week of detraining. A repeated measure analysis of variance (ANOVA) was used to evaluate time-course change in variables.

Results: The results showed that body fat percentage 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 concentration and insulin resistance did not change significantly. After a week of detraining, the variables did not change significantly in the training group.

Conclusion: VO2peak and ghrelin levels increased after 8 weeks aerobic exercise; however, plasma leptin and insulin resistance were not affected by this protocol in male patients with colorectal cancer.

KEY WORDS: Aerobic exercise, colorectal cancer, hormone, insulin resistance

INTRODUCTION

Colorectal cancer is one of the most prevalent gastrointestinal cancers, which is considered as the second cause of death in the world. The new style of sedentary life and overweight is the reasons of 25% of all new cancers in the world.[1] Leptin is generated by rat genes which exist in white fat, pair, etc.[2] This hormone is known as structure regulator for the amount of input and consumption of energy and weight control; and its function depends on its receptor in hypothalamus.[3] 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 receptor is stimulated in cancer cells.[4] These leptin receptors have been found in both cancer tumor and HT29 colorectal cancer cells.[5] Therefore, it seems that there is relationship between high level of leptin and chance of colorectal cancer and its metastasis. On the other hand, it has been recently found that ghrelin increases the malignant and attacking cancer cells in colorectal cancer through autocrine and endocrine system.[6] Ghrelin is a 28-amino acid hunger-stimulating peptide that regulates food receiving behavior,[7] energy homeostasis, and body mass regulation through mechanisms independent from growth hormones.[8] Epithelial cells of large intestine, differently with ghrelin receptors, start to abnormally produce ghrelin in comparison with intestine cells; and this will cause the attacking behavior in tumor.[9] Some studies demonstrated that colorectal cancer affect the production of ghrelin, and cachexia from this cancer is related to lack of ghrelin and external injection of ghrelin is recommended.[10] 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.[11] Current studies show that exercise at workplace or home can reduce the chance of colorectal cancer between 20 and 60%.[12] 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.[13] Obesity is one of the most important risk factors for colorectal cancer[14] and studies show that aerobic exercises and weight loss program will result in reduction of leptin and increase of ghrelin.[15,16] 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\(^\text{[17]}\). Although previous researchers showed that leptin decreases and ghrelin increases in healthy subjects in response to aerobic exercise\(^\text{[15,16]}\) but there are few studies on the effect of exercise training on leptin and ghrelin in patients with colorectal cancer. 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; therefore, we investigated the effects of 8 weeks aerobic exercise on leptin and ghrelin in male patients with colorectal cancer. On the other hand, according to our knowledge there are no studies that have determined detraining effects on leptin and ghrelin in colorectal cancer patients. Therefore, we also examined the effects of 1 week detraining after the intervention on plasma leptin and ghrelin levels.

**MATERIALS AND METHODS**

**Subjects**

Thirty patients with colorectal cancer who were in 2nd–3rd month after their surgery and completed the informed consent and PAR-Q, were divided into training (n = 15) and control group (n = 15).

**Exercise training**

Subjects of training group had two 15-min aerobic exercise trainings with 50–60% of target heart rate 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 (Polar, FS3c, Finland) to ensure accuracy of the exercise level. Control group was equipped with a heart rate monitor (Polar, FS3c, Finland) to ensure accuracy of the exercise level. Control group was instructed to maintain their normal physical activity and dietary habits throughout the study. The nutrient composition was determined by a computer nutritional analysis program (COMP-EAT 4.0 National Analysis System, London, UK) using the Mc Cance and Widdowson food composition tables\(^\text{[21]}\).

**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.

**Anthropometric and body composition measurements**

Height and body mass were measured, and body mass index (BMI) was calculated by dividing body mass (kg) by height (m\(^2\)). Waist circumference was determined by obtaining the minimum circumference (narrowest part of the torso, above the umbilicus) and the maximum hip circumference while standing with their heels together. The waist to hip ratio (WHR) was calculated by dividing waist by hip circumference (cm)\(^\text{[18]}\). Fat mass and lean body mass were assessed by bioelectrical impedance analysis using a Body Composition Analyzer (Boca XI, Johannesburg, South Africa).

**Measurement of peak aerobic capacity**

VO\(_{2\text{peak}}\) was determined by Rockport One-Mile Fitness Walking Test. In this test, an individual walked 1 mile as fast as possible on a track surface. Total time was recorded and HR was obtained in the final minute. VO\(_{2\text{peak}}\) was calculated using the below formula\(^\text{[19]}\):

\[
VO_{2\text{peak}} = 139.68 - (0.388 \times \text{age}) - (0.077 \times \text{body mass (pound)}) - (3.265 \times \text{time (min)}) - (0.156 \times \text{heart rate (bpm)})
\]

Rockport walking test was conducted 48 h before taking blood sample and 48 h after last session of aerobic training.

**Blood samples and laboratory analysis**

Fasting blood samples were collected at rest (before training) and 48h after last session of training. All the subjects fasted at least for 12 h 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, samples were centrifuged at the rate of 2,000 rpm for 10 min. The plasma leptin level was measured in duplicate using an enzyme-linked immunosorbent assay (ELISA) kit (Biovendor, Czech Republic). Leptin level was determined in duplicate via an ELISA kit (Mediagnost, Germany). Plasma glucose was determined by photometric method and the serum insulin level was measured in duplicate using an ELISA kit (DAKO, Denmark). The insulin resistance index was calculated according to the homeostasis model assessment (HOMA-IR), which correlates well with the euglycemic hyperinsulinemic clamp in people with diabetes\(^\text{[20]}\).

**Energy intake controls**

All the subjects completed the 3-day diet recall forms and were instructed to maintain their normal physical activity and dietary habits throughout the study. The nutrient composition was determined by a computer nutritional analysis program (COMP-EAT 4.0 National Analysis System, London, UK) using the Mc Cance and Widdowson food composition tables\(^\text{[21]}\).

**Statistical analysis**

Results were expressed as the mean ± standard deviation (SD) and distributions of all variables were assessed for normality. 2 × 3 repeated measures analysis of variance (ANOVA) was used to evaluate time-course change in variables. Independent t-test was used to compute differences in the variables. Pearson’s a correlation between leptin and ghrelin with fat percentage and HOMA-IR. The level of significance in all statistical analyses was set at P < 0.05. Data analyses were performed using Statistical Package for Social Sciences (SPSS) software for windows (version 17, SPSS Inc, Chicago, IL).
RESULTS

Changes in diet composition and calorie intake
All data were not significant for normality check. Data of carbohydrate, fat, and protein consumption and calorie intake of subjects during 8 weeks is given in Table 1. Result showed that the subjects maintained their dietary habits throughout the study.

Changes in anthropometric and body composition variables
Anthropometric and body composition characteristics of the subjects at baseline and after training and detraining are presented in Table 2. Before the intervention, there were no significant differences in any of the variables among the two groups. Body fat percentage decreased (P < 0.05, 14.45%) after 8 weeks aerobic exercise training compared to the control group, while no significant changes in the body mass and BMI were found after training. After 8 weeks intervention, peak aerobic capacity increased (P < 0.05, 25.8%) in the training group, while no significant change in the control group was found. All these differences were maintained after a week's detraining (P < 0.05) [Table 2].

Changes in biochemical variables
Our results showed that plasma ghrelin increased in training group compared with the control group (P < 0.05, 25.4%) [Figure 1]. After detraining, ghrelin levels remained higher than baseline values (P < 0.05, 15.6%) in the training group [Figure 1]. Pearson’s correlation demonstrated a significant negative relationship between plasma ghrelin levels and body fat percentage (r = −0.55, P = 0.004) and a significant positive relationship between plasma ghrelin levels with body peak aerobic capacity (r = 0.67, P = 0.001).

For leptin; fasting glucose and insulin and insulin resistance determined by HOMA-IR, there were no significant differences between the training and control group [Figure 1 and Table 2]. Pearson’s correlation demonstrated a significant positive relationship between plasma leptin levels with body fat percentage (r = 0.67, P = 0.001) and HOMA-IR (r = 0.65, P = 0.001).

DISCUSSION
From our literature review, we found that the present study is the first research considering the effect of exercise on leptin and ghrelin level in colorectal cancer patients. In the present study, plasma ghrelin levels were significantly increased in patients with colorectal cancer after 8 weeks aerobic exercise and ghrelin levels remained higher than baseline values after detraining (P < 0.05). Many researchers suggested that improving body fat mass and body fat percentage as a result of endurance training are the main mechanisms for increase circulating levels of ghrelin.[22,23] Our results showed that body fat percentage decreased by 14.45% in response to endurance training.

Table 1: Composition of the subjects’ diets (carbohydrate, fat, and protein) and calorie intake during 8 weeks (mean±SD)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Training</th>
</tr>
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<tbody>
<tr>
<td>Carbohydrate (g)</td>
<td>467.5±45.7</td>
<td>499.4±47.8</td>
</tr>
<tr>
<td>Fat (g)</td>
<td>77.9±15.7</td>
<td>78.9±12.1</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>112.5±9.7</td>
<td>114.2±9.4</td>
</tr>
<tr>
<td>Energy intake (kcal)</td>
<td>3121.1±29.7</td>
<td>3173.5±22.1</td>
</tr>
</tbody>
</table>

Data are the mean±SD of carbohydrate, fat, and protein consumption and calorie intake of subjects in each group. Result showed that the subjects maintained their dietary habits throughout the study. SD=Standard deviation

Table 2: Anthropometric and metabolic characteristics (mean±SD) of the subjects before and after training and detraining

<table>
<thead>
<tr>
<th></th>
<th>Control (mean±SD)</th>
<th>Training (mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass (kg)</td>
<td>69.0±11.7</td>
<td>68.0±12.9</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>23.3±3.1</td>
<td>22.9±3.5</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>18.5±8.7</td>
<td>18.4±9.07</td>
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<tr>
<td>VO2peak (ml/kg/min)</td>
<td>22.08±12.6</td>
<td>21.7±15.5</td>
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<tr>
<td>Fasting glucose (mg/dl)</td>
<td>92.2±6.6</td>
<td>91.1±7.1</td>
</tr>
<tr>
<td>Fasting insulin (µU/ml)</td>
<td>6.9±1.5</td>
<td>6.7±1.5</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.59±0.4</td>
<td>1.53±0.4</td>
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<tr>
<td>Pretraining</td>
<td></td>
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<td>Post-training</td>
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<td>Detraining</td>
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<td>Pretraining</td>
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<td>Post-training</td>
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<td>Detraining</td>
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Data are the mean±SD of baseline and after training and detraining values and of the anthropometric, body composition and metabolic change on each variable in each group. 2×3 repeated measures ANOVA was used to evaluate time-course change in variables. *P<0.05 for between-group differences; †P<0.05, pretraining vs post-training values; ††P<0.05, pretraining vs detraining values. ANOVA=Analysis of variance, BMI=body mass index, HOMA-IR=Homeostasis model assessment-insulin resistance, SD=Standard deviation

Figure 1: Changes in plasma ghrelin and leptin levels at baseline, after training, and detraining. Repeated measures ANOVA demonstrated that plasma ghrelin increased in training group compared with the control group after 8 weeks training (P < 0.05). After detraining, ghrelin levels remained higher than baseline values in the training group (P < 0.05). However, plasma leptin levels were not affected by the 8 weeks aerobic exercise as compared with the control group. (a) P < 0.05 for between-group differences; (b) P < 0.05, pretraining vs post-training values; and (c) P < 0.05, pretraining vs detraining values.
8 weeks aerobic exercise and there was a significant negative relationship between plasma ghrelin levels and body fat percentage. It was revealed that ghrelin affects the appetite, metabolism, body mass, and body composition; all of which help the body to balance the energy. On the other hand, it has been reported that changes in plasma level of ghrelin occur for liver cells and skeletal muscle during exercise training. Recent studies show that overweight and metabolic disorders have a direct relationship with colorectal cancer; and as exercise training affect the level of ghrelin directly, it seems that increased aerobics has resulted in elevated levels of ghrelin. In the present study, also a significant positive relationship was observed between plasma ghrelin levels with peak aerobic capacity. On the other hand, although previous studies demonstrated that low plasma ghrelin is associated with insulin resistance, in our study there was virtually no change in fasting glucose and insulin and insulin resistance after 8 weeks training and no significant relationships were observed between ghrelin levels and fasting glucose and insulin and insulin resistance. Thus, it seems that improving body fat percentage and aerobic capacity as a result of 8 weeks aerobic exercise are the main mechanisms for increased plasma ghrelin levels in male patients with colorectal cancer.

It was reported that ghrelin and the endocrine system led to the development of malignant cells and invasion of colorectal cancer. Malignant intestinal epithelial cells differentially overexpress ghrelin receptors and produce more ghrelin as compared to normal human colonocytes, leading to their enhanced proliferative and invasive behavior. Systemically available endocrine ghrelin levels in patients with colorectal cancer do not have significant correlation with any tumor stage. However, locally produced autocrine tissue ghrelin strongly correlates both with colorectal malignancy in a stage-dependent manner and body mass index and body fat percentage of the men with colorectal cancer. Ghrelin might play an important role in development of colorectal malignancy. On the other hand, low levels of ghrelin reported in a group of men with lung and prostate cancer and infusion of low level of ghrelin is important for elevated energy in patients with cancer.

The results showed that plasma leptin levels did not change in the training group after the intervention and a week of detraining compared to the control group. Elevated fat will increase the leptin secretion and gradually increase the leptin resistance. Previous studies also demonstrated that there is a positive relationship between insulin resistance and plasma leptin level. Although Pearson's correlation demonstrated a significant positive relationship between plasma leptin levels with body fat percentage and HOMA-IR in our study; there was virtually no change in plasma leptin levels and HOMA-IR after 8 weeks training. By general linear regression analysis, plasma leptin was related only to HOMA-IR (P = 0.005) and no significant relationship was found between plasma leptin and body fat percentage (P = 0.8). It means that changes in plasma leptin level independently correlated with changes in HOMA-IR. Thus, it seems that our protocol did not have sufficient stimuli to decrease plasma leptin and HOMA-IR in male patients with colorectal cancer. However, more studies are needed to establish the effects of exercise training on plasma leptin and insulin resistance in these patients.

Leptin sensitivity may increase with exercise training. Researchers believe that the connection between leptin and aerobic exercise is due to the hypothalamus. Leptin receptors are widely placed in brain telencephalic networks. Although other parts of brain participate in receiving leptin messages, but arcuate nucleus is the most important part in receiving the leptin messages during exercise training. This acute nucleus reduces the desire of food by receiving the messages from hypothalamus which result in the reduction of leptin secretion. Because leptin levels did not change significantly in the current study, it may be considered that defect of sending messages from telencephalic networks or sending the messages from hypothalamus has caused so, but this claim needs more study.

After 8 weeks aerobic exercise; VO\textsubscript{2peak} increased in male patients with colorectal cancer. Previous study showed that aerobic exercise can improve the consumption of oxygen in postmenopausal women with breast cancer. It seems that increased VO\textsubscript{2peak} can improve the oxygen uptake and treat cancer cachexia in patients with colorectal cancer. VO\textsubscript{2peak} decreased in patients with colorectal cancer and cause cancer cachexia. It may be that increased VO\textsubscript{2peak} in male patients with colorectal cancer can improve cancer cachexia and reduce the fatigue induced by treatment.

However, the current study has some strengths and limitations that need to be understood. To the best of our findings, present study was the first research about the effect of exercise training on leptin and ghrelin concentrations in male patients with colorectal cancer. A study demonstrated that some variables such as disease stage, cancer site, treatment type received (chemotherapy or radiation therapy), current disease status, treatment status, or even presence of an ostomy, may influence colorectal cancer patient's ability to engage in prolonged exercise. These variables were not considered in present study. Also, daily physical activities in our subjects were not measured. Therefore, it recommended that future studies will be conducted with control of daily physical activity and control of variables such as disease stage, cancer site, treatment type received (chemotherapy or radiation therapy), current disease status, treatment status, or even presence of an ostomy.

In summary, despite improvement in body fat percentage and plasma ghrelin level, 8 weeks aerobic exercise had no effect on plasma leptin and insulin resistance in male patients with colorectal cancer. Since aerobic exercise training in present study led to decrease in body fat percentage, it seems that...
decreased body fat percentage could be a strategy in decreasing colorectal cancer recurrence or its metastasis to other tissues. In fact, in colorectal cancer patients, increased body mass, body fat percent, and leptin levels resist to the chemical therapy; and therefore, as the aerobic exercise decreases the body fat percentage, it reduces the chance of colorectal cancer recurrence or its metastasis to other tissues. In conclusion, the present study suggests that 8 weeks aerobic exercise training improves the plasma ghrelin level, body fat percentage, and VO$_2$peak in patients with colorectal cancer.

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REFERENCES


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