RESEARCH ARTICLE

Change in Adiponectin and Oxidative Stress after Modifiable Lifestyle Interventions in Breast Cancer Cases

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Abstract

Background: Breast cancer is one of the most frequent diseases in women today. Little information exists on modifiable lifestyle factors including effects of ginger supplements (as an anti-oxidant and anti-inflammatory herbal) and water-based exercise on biomarkers related to oxidative stress such as malondialdehyde (MDA), nitric oxide (NO) and glutathione peroxidase (GPx) and adiponectin in obese women with breast cancer. The aim of this study was to determine the single and concomitant effect of 6-wks water-based exercise and oral ginger supplement on the aforesaid markers in obese women with breast cancer. Materials and Methods: Forty women diagnosed with breast cancer (48±5.4 years, 76±9 kg, fat mass 41.8±4%), volunteered to participate in the study. Subjects were randomly assigned into four groups; placebo, water-based exercise, ginger supplement and water-based exercise+ginger supplement groups. Subjects in the ginger supplement group and the water-based exercise+ginger supplement group orally received 4 capsules (each capsule contained 750 mg), 7 days a week for 6 weeks. The water-based exercise program featured progressive increase in intensity and time, ranging from 50% to 75% of heart rate reserve, in a pool with 15 meters width, 4 times a week for 6 weeks. Fasting blood samples were collected at pre-test and post-test time points. Results: The ginger supplementation and or the water-base exercise resulted in an increase of adiponectin, NO and GPx and reduction MDA, as compared to pre-test values. However, the combined intervention (water-base exercise and ginger supplement) group showed significantly a far better effect on the biomarkers related to oxidative stress and adiponectin levels, as compared to the water-base exercise or ginger supplement alone groups and the age-matched placebo group. Conclusions: Our results revealed that water-base exercise is a non-drug therapeutic strategy to reduce systemic stress in obese women suffering from breast cancer. Further, ginger supplementation alone or in combination with training, also play an important role in the pathogenesis of oxidative stress in obese women diagnosed with breast cancer.

Keywords: Mortality - breast cancer - oxidative stress - aerobic exercise - adipokine

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Introduction

Cancer is a major public health problem worldwide with millions of new cancer patients diagnosed each year and many deaths resulting from this disease (Barbaric et al., 2010; Yaacob et al., 2010). Breast cancer is the second most diagnosed cancer worldwide with a total of 1.38 million cases (Cleary et al., 2010). The etiology of breast cancer is multifactorial. Significant breast cancer risk factors include age, diet, obesity, lack of physical activity, hormone replacement therapy, family history and etc (Rajneesh et al., 2008). Epidemiological studies indicate that overweight and/or obesity, usually reflected by body mass index (BMI), is a risk factor for the development of postmenopausal breast cancer (Margot et al., 2009). Adipocyte dysfunction plays an important role in the development of chronic disease include cancer. Adipocyte synthesizes and secretes biologically active molecules called adipocytokines. Adiponectin is one of the most important adipocytokines, and is specifically and highly expressed in adipocytes (Yasuka et al., 2008). Obesity has been associated with increased risk of breast cancer in postmenopausal women, with increased risk of triple negative breast cancer in both pre- and postmenopausal women, and with poor breast cancer outcomes (Goodwin et al., 2011). In cross-sectional studies, obese subjects have higher levels of oxidative stress biomarkers compared with their leaner counterparts. Also, overweight significantly increases the concentration of these biomarkers. There are multiple sources for oxidative stress in relation to obesity. Researchers reported increased adipose tissue and, in particular, visceral adiposity is significantly correlated with systemic levels of oxidative stress biomarkers (Fujita et al., 2006; Michael et al., 2010). Oxidative stress occurs when there is an imbalance between reactive oxygen species (ROS) and antioxidants reaction capacity which stimulate the development of a disease such as breast cancer (Suzana et al., 2008).

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Physical activity is a low-cost, safe, and effective strategy to complement current adjuvant therapies, and possibly aid in the primary prevention of breast cancer (Sheri et al., 2011; Loprinzi et al., 2012). While moderate-vigorous intensity physical activities confer the greatest health benefits, evidence suggests that light-intensity activities are also beneficial, particularly for older adults and individuals with moderate-severe comorbidities (Blair et al., 2013). It can reduce visceral adiposity (Donnelly et al., 2009), which is associated with increased risk of breast cancer in postmenopausal women (Goodwin et al., 2011). Although, various researchers reported exercise interventions implemented concurrent with breast cancer treatment can cause increase in cardiovascular fitness, muscular strength, and body composition and decrease in cancer-related fatigue (Löf et al., 2012), water-based exercise is an ideal form of exercise for obese patients and may provide an attractive alternative to land-based exercise for achieving improved health and fitness in these populations (Takeshima et al., 2002; Meredith-Jones et al., 2011).

Ginger (Zingiber officinale Roscoe) has been widely used as a condiment throughout the world for centuries. In Asian countries, ginger has also been used as an herbal medicine to treat a wide range of disorders such as inflammation, dyspepsia, nausea, vomiting, pain, the common cold and diarrhoea (Ling et al., 2010). Ginger extract has antioxidant properties and scavenges superoxide anion and hydroxyl radicals (Afshari et al., 2007). Furthermore, earlier studies have indicated that ginger possess anticancer and anti-inflammatory effects. Atashak et al. (2011) investigated the effects of ginger supplementation and progressive resistance training on some cardiovascular risk factors in obese men. Results revealed that resistance training is an effective therapeutic strategy to reduce cardiovascular risk in obese Iranian men (Atashak et al., 2011). Michael et al. (2010), reported Obesity plays a complex role in breast cancer and is associated with increased inflammation and alterations in serum levels of potential growth regulators such as adiponectin (Michael et al., 2010). In contrast, anti-inflammatory compounds such as ginger may ameliorate the adipocyte dysfunction associated with metabolic syndrome by inhibiting the downregulation of the adiponectin expression (Yasuka et al., 2008). In addition, ginger has been shown to be effective at inhibiting the expression of inflammatory mediators, inducible nitric oxide synthase (Afshari et al., 2007). However, little research is available to our understanding about the efficacy of oral ginger on adiponectin/and biomarkers related to oxidative stress (malondialdehyde, nitric oxide, glutathione peroxidase) in obese women with breast cancer.

To date, there are few data available with respect to effects of water-based exercise and or/ginger antioxidant/anti-inflammatory supplementation, particularly concomitant interventions in obese women suffering from breast cancer. Therefore, the purpose of this study was to determine the individual and concomitant effects of 6 weeks water-based exercise and herbal supplementation on adiponectin and biomarkers related to oxidative stress including malondialdehyde (MDA), nitric oxide (NO) and glutathione peroxidase (GPx). It was hypothesized that these results would provide novel insights into the ameliorative potential of herbal use and regular exercise training during chronic exposure to breast cancer.

Materials and Methods

Subjects and selection procedure

The current study included 40 women, mean fat mass 42±4 %, weight 76±9 kg, height 156±5 cm age 48±6 years, BMI 32±4 kg/m^2, diagnosed with breast cancer. All participants had completed radiation and/or chemotherapy treatments. After expressing an initial interest in the study protocol, each potential participant met with the study coordinator, was screened for inclusion criteria using a brief eligibility checklist, and learned about the details of the study including assessment and training program. Participants were informed of the voluntary and confidential nature of the study and were free to discontinue at any time. Informed consent was obtained before participation in the study. Participants received comprehensive screening followed by an initial medical examination before they were included in the study.

Inclusion and exclusion criteria

Eligibility criteria included; a primary diagnosis of breast cancer during stage I–II, no distant metastases, ≥40 years old, completed radiation and/or chemotherapy treatments. Furthermore, women were excluded if they had evidence of recurrent disease, had previously engaged in any formal exercise programs for at least six months prior to participation in this study. Also, according to medical examinations, the subjects don't have any cardiovascular and diabetic diseases. In addition, they did not smoke at least six months before the study began.

Experimental design

The experimental protocol of current study was approved by Department of Physiology, University of Mazandaran. Subjects were randomly divided into four groups consist; i) placebo, ii) water-based exercise, iii) ginger and iv) water-based exercise+ginger groups (10 cases in each group). Patients in the placebo group were instructed not to begin any new formal physical exercise program during the study intervention period. All patients underwent a series of baseline assessments. The subjects' anthropometric variables included height, age, body mass, percent of body fat, lean body mass, and body mass index (BMI) were assessed. After completing all baseline assessments, patients were performed individually prescribed exercise with and without oral ginger interventions.

Water-based exercise program

Subjects in the placebo and ginger groups did not participate in any exercise program. However, each subject in the exercise training groups (water-based exercise group and water-based exercise+ginger group) participated in four familiarization sessions. For the subjects in the aforesaid training groups, a pool exercise training program

was implemented and subjects were instructed to begin with an individually determined number of training sets and repetitions at a determined intensity during first week. Each exercise session was individualized for the cancer survivor but generally included a 10 minute warm up, 20-60 minutes of aerobic exercise in water and concluded with a 10-minute cool down.

Deep-water exercise protocol was defined as those in which participants had no foot contact with the bottom of the pool. The upright water-based exercise training program was performed in a pool with 15 meters width and 4 meter depth, as was described by Meredith-Jones et al. (2011). This exercise program was implemented for 6 weeks and 4 sessions at a week. The training groups were divided to the various subgroups and in each subgroup, those who had similar cardiorespiratory fitness, swimming in the water with equal intensity and rhythm. The distance of exercise was increased gradually with regard to overload principle, the training sets and training cycle. Exercise intensity was based on the cancer survivors' treadmill assessment results, and ranged from 50% to 75% of heart rate reserve (HRR). The Karvonen method or percentage of HRR was used to determine exercise heart rate intensity by using the formula (exercise target heart rate=[max HR-rest HR]×% exercise intensity+rest HR (Carole et al., 2007).

After every set, the exercise intensity was controlled with pulse rate. On the average, the subjects swimming every 30-meter distances with aforesaid intensity in 50 to 60 seconds. The recovery time between every walking was 30 to 40 seconds. The rests time between the sets was 5 to 6 minutes in order to allow heart rate to return to primary situation. Generally, the participants exercised two sets daily during the first week, but for the next weeks, they exercised three sets daily. In addition, the number of repeats of swimming in the pool with 30-meter length from the first week until the 6th week was 34, 75, 24, 92, 112 and 131, respectively. The subjects in the training groups swimming a total of 14,850 meters during 24 sessions of pool swimming.

Ginger supplementation

Subjects in the ginger officinale group and the water-based exercise+ginger group orally received 3 capsules (Each capsule contained 750 mg) of ginger rhizome powder (Goldaroo. Company, Tehran, Iran), 7 days a week and for 6 weeks, consistent with previous studies (Christopher et al., 2010). The subjects consumed the powder in approximately 250 ml of water. The supplement was ingested 4 times a day, with breakfast, lunch, dinner and afternoon. The placebo group received capsules contained 1 gr starch (placebo), in the same manner and for the same duration of time as the experimental groups. Subjects during the supplementation period, maintain their normal food program and recommended them to refrain from consuming any antioxidants and multivitamins-containing substances, with the exception of tamoxifen drug.

Blood sampling and biochemical analysis

Blood samples were collected from each subject at pretest and at the end of 6 weeks of water-based exercise with and without ginger in an overnight 10 to12-h fasting state. A 5mL blood sample was collected via venipuncture of an antecubital vein. The blood samples were allowed to clot at room temperature for 10 min and then centrifuged (10 min at 5°C, 3,000 g).The serum was then pipette into polystyrene tubes. The aliquots were frozen at −80°C for subsequent assays. Adiponectin concentration and biomarkers related to oxidative stress were assessed by commercially available enzyme immunesorbent assay (ELISA) kit (R and D Systems) according to the instructions of the manufacturer.

Statistical analysis

Statistical analysis was performed using a commercial software package (SPSS version 20.0 for Windows). Results are expressed as means±SE. Dependent t-test was used to determine the changes of the adiponectin and biomarkers related to oxidative stress between pre-test and post-test in experimental groups. In addition, one-way ANOVA was used to detect statistical differences between the four groups. Post-Hoc tests (Tukey) were performed to establish differences in the adiponectin and biomarkers related to oxidative stress between groups. Differences were considered significant at $p<0.05$.

Results

Changes in the adiponectin and biomarkers related to oxidative stress including malondialdehyde (MDA), nitric oxide (NO) and glutathione peroxidase (GPx) in women with breast cancer are shown in Table 1. Six weeks of the ginger supplementation resulted in an increase in adiponectin (6.31%, p=0.307), GPx (14.15%, p=0.002), NO (4.96%, p=0.406) and a decrease in MDA (0.41%, p=0.951) in comparison to before 6-wk of ginger supplementation. However, in the sedentary placebo (control) group, the aforesaid markers levels remained unchanged, as compared to pretest.

In contrast, 6-wk of the water-base exercise cause an increase in serum adiponectin levels (17.22%, p=0.004),

Table 1. The Biomarkers Related to Oxidative Stress and Adiponectin Levels in Before and After Treatment Interventions in Women with Breast Cancer

Markers & Groups	Adiponectin (μg/ml)	GPx (μmol/min/dl)	NO (μmol/l)	MDA (μmol/ml)
Placebo (control)				
Pre	8.43±0.86	25.1±5.47	36.23±5.96	25.39±5.12
Post	7.84±1.03	24.3±4.62	34.46±4.34	25.05±3.23
Water-base exercise				
Pre	8.65+1	25.9±2.51	35.26±5.51	25.55±4.83
Post	10.45±1.53*	36.9±2.42*	41.33±6.22*	21.62±3.2*
Ginger supplementation				
Pre	8.03+1.07	27.3±2.26	35.47±5.55	24.17±3.68
Post	8.56±1.07	31.8±3.61*	37.32±4.90	24.07±3.5
Water-base exercise+ginger				
Pre	8.18±0 .74	26.3±2	36.06±6.27	23.97±4.02
Post	11.86±0.74*	44.4±4.79*	45.45±7.01*	19.55±3.76*

*Significantly different from pretest phase ($p<0.05$). Data are presented as the mean±SD for 10 subjects. Abbreviations; glutathione peroxidase (GPx), nitric oxide (NO) and malondialdehyde (MDA)

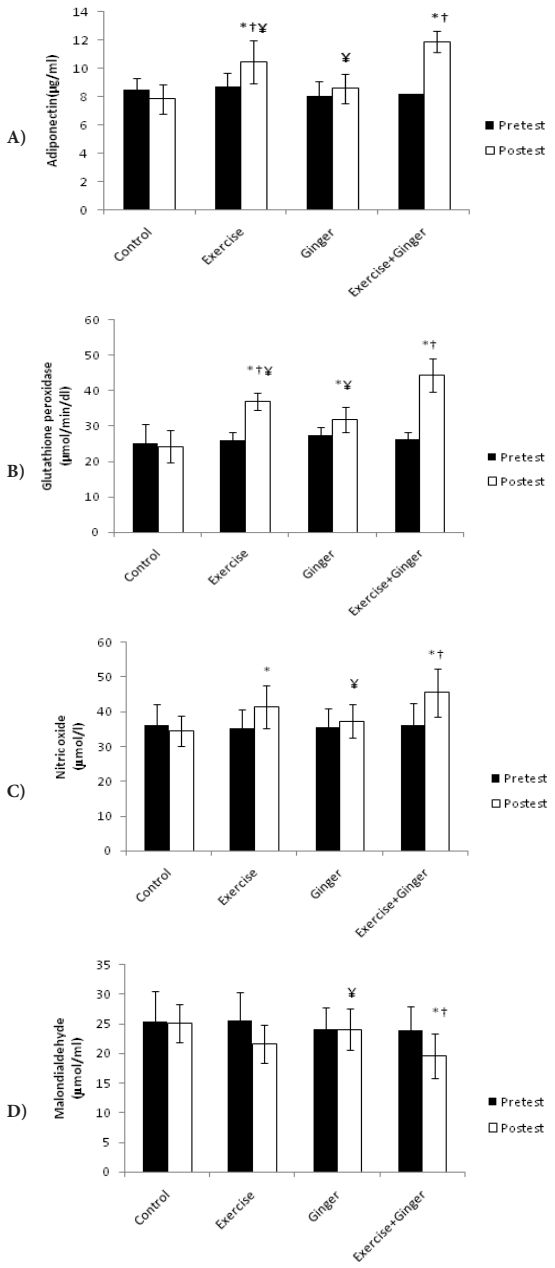

Figure 1. Level of A) Adiponectin, B) Glutathione Peroxidase (GPx), C) Nitric Oxide (NO) and D) Malondialdehyde (MDA) during Water-base Exercise with and without Ginger Supplement Interventions. *significantly different from placebo group (p<0.05), †significantly different from ginger group (p<0.05), ¥significantly different from combined (Ginger+exercise) group (p<0.05)

GPx (29/81%, p<0.001), NO (14.69%, p=0.032) and a decrease in MDA (18.18%, p=0.028). However, the water-base exercise+ginger treatment was more effective than the water-base exercise and the ginger supplement, alone treatment, so that, it led to an increase in adiponectin (31.03%, p<0.001), GPx (40.76%, p<0.001), NO (20.68%, p=0.032) and a reduce of MDA (22.56%, p=0.045), in comparison to before 6-wk of treatment (Table 1).

One-way analysis of variance (ANOVA), showed the ginger supplement resulted in a significant increase in GPx (p=0.001), as compared to the placebo group. Also, a significant increase in adiponectin (p<0.001), GPx (p<0.001), NO (p=0.05) levels were present not only in the water-base exercise group, but increase were also observed in the water-base exercise+ginger supplement group (p<0.001, p<0.001 and p=0.01, respectively), as compared to the placebo group (Figure 1, 2, 3). In addition, a significant decrease was detected in MDA levels (p=0.005), as compared to placebo group (Figure 4). However, after 6-wk of training, adiponectin (p=0.003) and GPx (p=0.033) levels increase significantly, as compared to ginger supplementation group. The combination of water-base exercise and ginger supplement has a far better effect on the adiponectin and biomarkers related to oxidative stress (Figure 1A-1D).

Discussion

There is growing evidence to support the negative prognosis role of obesity and/or overweight in female breast cancer (Margot et al., 2009; Goodwin et al., 2011). There exists a direct relationship between obesity and lipid peroxidation. Furthermore, obesity has been associated with elevated lipid peroxidation among human subjects, and the elevation seems to be removable by weight reduction (Gago-Dominguez et al., 2005). In addition, adiponectin secreted by adipose tissue and is associated with breast cancer that reduced levels of serum adiponectin have been reported in breast cancer patients compared to healthy controls, particularly in postmenopausal women (Mantzoros et al., 2004; Michael et al., 2010). However, lifestyle interventions, including exercise training and dietary components may eventually ameliorate their profile.

The present study was designed to determine the individual and concomitant effects of 6 weeks water-based exercise and herbal supplementation on adiponectin and biomarkers related to oxidative stress including malondialdehyde (MDA), nitric oxide (NO) and glutathione peroxidase (GPx) in women with breast cancer. Our findings demonstrate that 6 weeks of water-based exercise cause significant increase in adiponectin, glutathione peroxidase and nitric oxide and an insignificant decrease in malondialdehyde concentrations, as compared to control (placebo) group. However, water-based exercise with ginger supplementation significantly influenced adiponectin and biomarkers related to oxidative stress (malondialdehyde, nitric oxide, glutathione peroxidase) in obese women with breast cancer, as compared to the other groups. The available studies using upright water-based exercise interventions are limited and the methodological limitations of these studies should be considered when assessing their findings. our data are consistent with data from previous findings on the effects of aerobic exercise in walking versus running on land, so that some studies showed benefits on oxidative stress (Campbell et al., 2010), adiponectin levels (Sheri et al., 2011; Loprinzi et al., 2012) and improve in cardiovascular health (Meredith-Jones et al., 2011). Researchers suggest findings obtained in land-based exercise training studies cannot be simply extrapolated to aquatic activities (Meredith-Jones et al., 2011). Overall, non-weight bearing exercise is recommended by the American College of

Sports Medicine as a possible alternative to improve health and well-being for individuals who find weight bearing exercise difficult (Meredith-Jones et al., 2011).

Previous researchers reported participation in the regular physical activity improves rates of breast-cancer survival. Although the exact mechanism through which the regular physical activity may affect breast-cancer survival is unknown, a few possible hypotheses exist. The regular physical activity may influence prognosis by similar mechanisms to those thought to prevent the incidence of breast cancer, including decreased adipose tissue, lifetime estrogen exposure and improved oxidative stress (Michael et al., 2010). Increased physical activity can reduce oxidative stress, especially among overweight/obese persons who generally have high oxidative stress levels (Gago-Dominguez et al., 2005). Several reports present evidence that reactive oxygen species (ROS) are involved in the etiology and progression of breast cancer because certain markers of oxidative stress, including DNA adducts and lipid peroxidation products, such as malondialdehyde (Gago-Dominguez et al., 2005). The present study results indicate that 6-week of the water-base exercise cause decrease in serum MDA levels in women with breast cancer. However, the water-base exercise+ginger treatment was more effective than the water-base exercise and the ginger supplement, alone treatment. On the other hand, the antioxidant status in breast cancer patients demonstrated a decrease in antioxidant defenses (Panis et al., 2011). Studies shows regular exercise lead to increase in antioxidant activity including GPx, that in turn, are associated with decreased proliferative activity in breast tissue (Gago-Dominguez et al., 2005; Panis et al., 2011). Our study shows that adiponectin and biomarkers related to oxidative stress after 6 weeks of water-based exercise have beneficial changes, as compared to control group.

In the present study, we examined the protective effects of ginger supplementation following of 6 weeks in doses of 3 gr per day in obese women with breast cancer. The present study reveals that ginger supplementation cause improvement adiponectin and biomarkers related to oxidative stress, as compared to before the supplementation period and compared to placebo group. Zingiber officinale, commonly known as ginger, is traditionally used as a spice in various foods and beverages in a wide variety of ailments such as; asthma, diabetes, nausea and pain (Afshari et al., 2007). Also, Habib et al. (2008) reported that ginger might act as an anti-inflammatory and anti-cancer (Habib et al., 2008). The dried rhizomes of ginger (rich in pungent phenolic compounds: gingerols and shogaols) or extracts thereof are important ingredients of many traditional/ alternative medicines worldwide (Ling et al., 2010). Both of 6-shogaol and 6-gingerol can significantly inhibit the down-regulation of adiponectin expression (Yasuka et al., 2008). According to the Atashak et al. (2010) study, ginger supplementation seems to exert no effect on blood lipid profiles and insulin resistance in obese men (although the decrease in lipids and insulin resistance were not statistically significant, it did tend to decrease) and suggest that consumption of ginger could aid in the treatment of obesity and other diseases related to cardiovascular disease (Atashak et al., 2010). In Harliansyah et al. (2005) study suggests the possible chemoprotective role of ginger extract (Zingiber officinale) by eliminating superoxide radicals and hydrogen peroxide in the cancer cell (Harliansyah et al., 2005).

In summary, the present findings demonstrate that the nondrug strategies such as water-base exercise and ginger supplementation play important role in up-regulation of antioxidant system and adiponectin and down-regulation of oxidative peroxidant in obese women diagnosed with breast cancer. However, the combination of water-base exercise and ginger supplement has a far better effect on the aforesaid biomarkers rather than using each of them separately. These results suggest that water-based exercise with oral ginger supplementation may have a more anti-oxidant and anti-dysmetabolism effect.

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