A moderately high protein diet and 4' isometric exercises efficacy in breast cancer patients treated with antiestrogenic medication

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ABSTRACT

Many breast cancer patients gain weight during treatment increasing recurrence, oncology specific mortality and general mortality risks. Breast cancer diagnosis and treatment overthrow patients' lifestyle aggravating sedentariness and any preexisting weight gain causes like insulin and leptin resistance, dysbiosys and dyslipidemia.

The aim of this study is to evaluate the efficiency of a moderately high protein diet – based on foods naturally high in proteins, omega-3 fatty acids, calcium, probiotics and prebiotics – and of an isometric exercise protocol to generate fat loss without muscle loss in ER+ breast cancer patients taking antiestrogenic treatment.

We randomized 50 ER+ breast cancer patients – taking either Tamoxifen or Aromatase Inhibitors (AI) after surgery and chemotherapy – to follow a high protein diet, or a high protein diet and 4' isometric exercises for 12 weeks. Patients were instructed to eat only when hungry and to keep a food journal. We measured weight and body composition with a bioelectrical impedance scale after checking for hydration status.

The diet group lost 2.17 ± 2.42% subcutaneus fat (p = 0,000) with no muscle loss, and there was no statistical difference between patients taking Tamoxifen or AI regarding body composition evolution.

The diet + isometric exercise group lost 2.2 more pounds than the diet group and 0.66 ± 0.91% visceral fat (p = 0,001) also with no muscle loss. AI patients from the diet and exercise grup did not improve muscle mass – maybe because of the musculoskeletal impact of AI medication.

In conclusion, a moderately high protein diet can decrease body fat in ER+ breast cancer patients on antiestrogenic medication. Adding a daily minimal exercise protocol to a high protein diet decreases visceral fat – which is more hormonally active. And resistance-training exercises are more appropriate than isometric exercises for patients on AI.

Keywords: oncology nutrition, breast cancer, weight gain in breast cancer patients, antiestrogenic treatment, isometric exercises

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INTRODUCTION

Breast cancer patients that gain weight during treatment have higher risks of all causes mortality, oncology specific mortality and recurrence (Chlebowski et al., 2002). Besides overeating or eating regardless of physical hunger, the main weight gain causes – insulin and leptin resistance, dysbiosis and dyslipidemia – are potentially aggravated during breast cancer chemotherapy by sarcopenia (Messier et al., 2011).

Sarcopenia is not the main cause of weight gain during breast cancer chemotherapy, but it is aggravated by the other weight gain main causes:

- induced menopause – accentuates muscle protein catabolism, generating the decrease in active motor units and type II muscle fibres atrophy (Winkels et al., 2014),
- insulin resistance – generated by sedentariness or by overeating – causes triglycerides accumulation in miocytes and decreased sarcolemma GLUT4 expression (Stenholm et al., 2008),
- dyslipidemia – either caused by the eating behaviour or by chemotherapy per se – generates leptin resistance manifested by a decreased ability to perceive satiety (Baek et al., 2014),
- intestinal dysbiosis – directly generated as a chemotherapy side effect – cause modified intestinal permeability (increased for improper digested proteins and decreased for disaccharides) causing bloating, cramps, constipation or diarrhea which disturb the eating behaviour and eventually lead to/or insulin resistance and weight gain (Teixeira et al., 2012).

Then these main weight gain causes are worsened by sarcopenia through basal metabolic rate decrease (Denmark-Wahnfried et al., 2001) and sustained by the eating behaviour and sedentariness of the patient.

Compensating these etiologycal weight loss factors can be hard during chemotherapy, because many patients feel ill, but during antiestrogenic medication treatment they can be compensated through nutritional and kinetic interventions.

Nutritionally, both sarcopenia and overeating can be decreased by a high protein diet through improvement of the muscle protein synthesis/degradation ratio, and through an improved insulin sensitivity and satiety by influencing the postprandial secretion of insulin (McAuley et al., 2005), ghrelin (Bloom et al., 2006), and of the main satiety hormones: GLP-1, cholecystokinin and peptide Y (Batterham et al., 2006).

Dyslipidemia and leptin resistance can be improved by a daily intake of foods high in omega-3 fatty acids (fish, cold pressed extra virgin olive oil, rapeseed oil or canola oil, avocado and various raw seeds, almonds and nuts) and by avoiding soft drinks (high in colorants and high fructose corn syrup), fried food and any food with hydrogenated fats on the ingredients list.

The most important role omega-3 fatty acids have in oncology nutrition is decreased biosynthesis of arachidonic acid's eicosanoids. Eicosanoids play a critical role in cells proliferation and differentiation, and the polyunsaturated fat proportion in cell membranes is the decisive factor by which different eicosanoids are synthesized.

Eicosanoids synthesized from arachidonic acid are involved in breast cancer initiation, proliferation, avoiding apoptosis and metastasis phases (Liu and Ma, 2014). But a high intake of omega-3 fatty acids increases their incorporation in cells membranes, partially replacing arachidonic acid, thus decreasing its availability for inflammatory and carcinogenic eicosanoids synthesis. Moreover, unlike AA synthesized PGE2, which stimulates aromatase, EPA synthesized PGE3 inhibits this breast cancer prognostic essential enzyme (Meyer et al., 2003).

And dysbiosis can be compensated by a daily intake of foods high in prebiotics (like whole grain cereals, beans, lentils and fresh fruits and vegetables) and probiotics (yoghurt, kephir and sour milk). Studies prove that probiotics have antiproliferative effects in tissues with non-intestinal localization like breast and prostate by improving estrogenic metabolism and by inactivating carcinogenic substances (Aragón et al., 2014).

Comparative studies between probiotics supplements and fermented dairy foods prove that dairies have higher anticarcinogenic effects because they also contain beneficial metabolites produced by probiotics during milk fermentation (Commane et al., 2005).

Fermented dairies also ensure a highly bioavailable calcium intake, important for the protective impact of calcium and vitamin D sensing receptors. Yet some patients have the assumption that milk intake is contraindicated in patients with breast cancer either because of the fact that one of the defining characteristics of

breast cancer are micro calcifications, either because of the potential estrogenic impact.

But vitamin D and calcium are key regulators of cells proliferation, differentiation and apoptosis. Studies prove that a high calcium intake associates with a better breast cancer prognostic (Lin et al., 2007). Also, a meta-analysis of 11 studies demonstrates that a high calcium intake decreases breast cancer risk by 19% (Chen et al., 2010).

Of course calcium can also be found in plants, but – because of their phytic and oxalic acids content – calcium from foods high in calcium like spinach, grains, sesame seeds, nuts and almonds has a lower bioavailability than the one of the calcium in fermented dairy.

Also plants contain phytoestrogens, which have an agonist estrogenic activity during menopause be it induced or natural (Kang et al., 2010). Thus if we would accept that breast cancer patients should avoid dairies due to the estrogenic impact, then we should also accept that breast cancer patients should also avoid broccoli due to its glucobrascin content, beans, lentils and whole grains due to their flavones content, and raisins, walnuts, almonds, blueberries or tea due to their genistein and daidzein content – all substances with estrogenic impact (Ross and Kasum, 2002).

And unlike dairies intake proved beneficial for breast cancer patients by most studies, there are studies proving phytoestrogens intake causative for endometrial hyperplasia (Unfer et al., 2004), and studies proving that genistein inhibits Tamoxifen's actions – thus increasing the recurrence and metastasis risks in ER+ breast cancer patients either through phytoestrogens supplements intake, either in the vegans' exclusive plant food intake (Ju et al., 2002).

Also, although eating a high plant diet is healthy for breast cancer patients, excluding dairies and foods can supply the malign cell with the much needed energy and proliferation source: glucose (Greiner et al., 1994).

Because cells' membranes are not permeable for glucose and because glucose is osmotic, cells use GLUT transmembrane transporters to introduce glucose into their cytoplasm. Most healthy cells have only one GLUT type, but malign cells have four GLUT types GLUT 1, GLUT 3, GLUT 4 and GLUT 12 *(*Barron et al., 2012*)* – being an actual glucose black whole. And not only that is absorbs more glucose from the blood than any healthy cell could ever do (Calvo et al., 2010), but it also use it in a energetically inefficient way, continuingly depriving healthy cells of this essential nutrient (Schwartzenberg-Bar-Yoseph et al., 2004). This way of using glucose is aerobic conditions as a healthy cell would do in anaerobic ones is called the Warburg effect and it can be objectively demonstrated by the lactate dehydrogenase increase associated with carcinogenesis (Feron, 2009).

But malign cells are not entering aerobic glycolysis to starve healthy cells by depriving them of vital food (or not only for that), but because from aerobic glycolysis chains of reactions it obtains the biomass needed for accelerate proliferation (Walenta and Mueller-Klieser, 2004). Moreover, when in need, malign cells can stop aerobic glycolysis and survive by using glucose in the Krebs cycle exactly as a healthy cell would – effect named Crabtree (Diaz-Ruiz et al., 2011).

This ability to proliferate through the Warburg effect and to survive through the Crabtree effect makes cancer treatment very difficult due to the high adaptability of the malign cells (Jones and Thompson, 2009). And strictly from an oncology nutrition point of view, going vegan can generate both a high glucose and phytoestrogen intake directly usable by malign cells and a diminished ability to perceive satiety due to the lower protein content plant foods have (Ernst and Cassileth, 1996). And of course this does not mean excluding plant foods for their glucose content, but consuming them in moderation.

Kinetically, the regular practice of physical exercise during breast cancer treatment sustains a better prognostic (Knols et al., 2005). Resistance exercises are the most effcient type of exercise for treating both sarcopenia (Schmitz et al., 2005) and the other weight gain causes (Denmark-Wahnefried și Rock, 2003), but are difficult to do after breast cancer surgery without a physical therapyst supervision.

Whole body balance isometric exercises are not as effective as resistance exercises because they cannot counteract insulin resistance, leptin resistance, dyslipidemia or dysbiosis (De Rezende și colab., 2006). But they can prevent skeletal muscle loss (Bamman și colab., 1998), they can be practiced even during days when the patient feels ill, after learning the proper way to do them they can be safely done without monitoring, and they take very little time – argument that make most patients to easily accept to do them.

Isometric exercises have an anaerobic-like effect – their effect is not purely anaerobic because the patients can voluntarily stop the exercise before entering anaerobic condition, shifting piruvate back from Cori cycle towards Krebs

cycle – improving muscle protein turn-over towards maintaining active skeletal muscle mass (Schulte and Yarasheski, 2001). And if we add these muscle protective effects to a high protein diet meant to counteract insulin and leptin resistance, dyslipdemia and dysbiosis we can obtain fat loss without muscle loss despite antiestrogenic medication administration.

As for the safety of practicing physical exercises by breast cancer patients, one meta-analysis of 51 studies performed in the last 25 years proves that low and moderate intensity physical exercise is safe and beneficial (Battaglini et al., 2014).

METHOD

Purpose: This study aimes to answer three questions:

1. Is a high protein diet effective for fat loss in ER+ breast cancer patients on antiestrogenic medication?
2. Is the addition of only 4 minutes of daily isometric exercises to this high protein diet more effective to improve their body composition?
3. And how does the antiestrogenic treatment type influences the effects of these interventions?

Study design

- duration: 12 weeks
- interventions:
  - moderately high protein diet;
  - moderately high protein diet + 4 minutes isometric exercises per day.
- number of patients: 50
- inclusion criteria:
  - ER+ breast cancer patients after surgery and chemoterapy, on antiestrogenic medication (25 on Tamoxifen and 25 on Aromatase Inhibitors).
- exclusion criteria:
  - Her2+ and Triple – breast cancers, diabetes, kidney disease, osteoporosis, depression.
- monitoring:
  - body measurements: height, total body weight (W), body fat percentage (%BF), skeletal muscle percentage (%SkM) and visceral fat percentage (% VF);
  - food journal: patients were instructed to keep a daily food log where to write the time they took each meal, exactly what it contained and in what quantity and if they were hungry or not when they ate.

Interventions

A high protein diet based on foods naturally high in proteins, omega-3 fatty acids, calcium, pro- and prebiotics can improve body composition by increasing insulin and leptin sensitivity, by ameliorating dysbiosis and by counteracting skeletal muscle protein catabolism, and it can assist in recurrence prevention through a moderate intake of glucose.

Patients were given a table were foods were classified as proteins, carbohydrates or fibres supplying sources and were taught to eat proteins, carbohydrates and fibres at each meal. To prevent sarcopenia and to counteract the Warburg effect (especially in patients during neoadjuvant chemotherapy) we decreased the recommended percentage of carbohydrate intake from the common 55-60% to only 30%. Protein intake was calculated to reach 1.5 g/kg body, which practically meant for most patients a 25-30 g protein intake per meal.

To prevent anaemia, we instructed them to eat foods high in proteins and calcium (yoghurt, sour milk and kephir, raw seeds and nuts) at different meals than foods high in iron (fish, chicken, eggs, beans, chickpeas and other lentils). To prevent gastro-intestinal infections potentially associated with dysbiosis we instructed them to wash raw fruits and vegetables very well, to avoid eating foods containing raw animal ingredients (like unpasteurized ice cream or mayonnaise, sauces, deli meats or cheese, smoked raw fish, canned fish or roe), and to eat at least two fermented dairies portions per day.

To improve eating behaviour, we explained the metabolic differences between eating when not hungry and eating when physically hungry (Ciampolini, Lovell-Smith, and Sifone, 2010) and we asked patients to learn to recognize gastric hunger and to respect it by not eating when not hungry and also by eating within a maximum of 1 hour after feeling it. To sustain an effective lipolysis, beta-oxidation and complete fatty acids catabolism for energy, when not hungry patients were allowed to only drink plain water, no snacks, and no other drinks than water. One coffee was allowed at the first meal of the day, and tea with other meals, but no in between meals due to caffeine and theine impact on insulin secretion and no soft drinks due to their impact on presynaptic dopamine re-transporters and on hypothalamic leptin sensitivity. Also to ensure a

proper gastric emptying time, an interval of 2 hours minimum was recommended between taking any meal and sleeping. And, to avoid phytoestrogen interaction with antiestrogenic treatments, we recommended the complete avoidance of plant supplements and we asked patients to only take vitamins and minerals at their oncologists' recommendation.

As exercises, patients were taught how to perform 7 isometric exercises, one for each day of the week. All 7 exercises involved maintaining whole body balance for 1 minute, four times per day.

RESULTS AND DISCUSSIONS

The diet group lost 2.17 ± 2.42% body fat (p = 0,000) with no muscle loss.

TABLE 1. *Evolution of patients from the diet group*

	ME	SD	95% CI		p
			Min.	Max.	
W (kg)	-0.86	± 1.94	-0.03	-1.70	*0.043*
BF%	-2.17	± 2.42	-1.12	-3.22	*0.000*
SkM%	+1.73	± 3.66	-0.15	+3.32	*0.033*
VF%	-0.34	± 0.83	+0.01	-0.70	0.057
BMI	-0.30	± 0.72	+0.00	-0.62	0.054

ME = mean evolution, SD = standard deviation, 95% CI = 95% confidence interval, W = total body weight, % BF = body fat percentage, % SkM = skeletal muscle percentage and %VF = visceral fat percentage, BMI = body mass index

There was no statistical difference between diet group patients taking Tamoxifen or AI regarding body composition evolution.

TABEL 2. *Comparative evolution of patients from the diet group on Tamoxifen (n=12) vs. on IA (n=11)*

	Group	ME	SD	95% CI		p
				minim	maxim	
W (kg)	T	-0.80	± 1.78	+0.32	-1.94	0.146
	IA	-0.93	± 2.18	+0.53	-2.40	0.185
BF%	T	-2.18	± 2.34	-0.69	-3.67	*0.008*
	IA	-2.17	± 2.62	-0.40	-3.93	*0.021*
SkM%	T	*+2.85*	± 4.56	-0.03	+5.75	0.053
	IA	*+0.51*	± 1.85	-0.72	+1.76	0.377
VF%	T	-0.41	± 0.99	+0.21	-1.04	0.175
	IA	-0.27	± 0.64	+0.16	-0.70	0.192
BMI	T	-0.33	± 0.70	+0.10	-0.78	0.124
	IA	-0.27	± 0.77	+0.24	-0.79	0.269

ME = mean evolution, SD = standard deviation, 95% CI = 95% confidence interval, W = total body weight, % BF = body fat percentage, % SkM = skeletal muscle percentage and %VF = visceral fat percentage, BMI = body mass index

The diet + isometric exercise group lost 2.2 more pounds than the diet only group and 0.66 ± 0.91% visceral fat (p = 0,001) also with no muscle loss.

TABLE 3. *Comparative evolution between the diet (D) vs. the diet + exercises interventions (D+Ex)*

	Group	ME	SD	95% CI		p
				minim	maxim	
W (kg)	D	-0.86	± 1.94	-0.03	-1.70	*0.043*
	D+Ex	-1.84	± 3.09	-0.61	-3.06	*0.005*
BF%	D	-2.17	± 2.42	-1.12	-3.22	*0.000*
	D+Ex	-1.39	± 3.55	+0.01	-2.79	0.052
SkM%	D	+1.73	± 3.66	-0.15	+3.32	*0.033*
	D+Ex	+1.25	± 2.37	+0.31	+2.19	*0.011*
VF%	D	-0.34	± 0.83	+0.01	-0.70	0.057
	D+Ex	-0.66	± 0.91	-0.30	-1.03	*0.001*
BMI	D	-0.30	± 0.72	-0.00	-0.62	0.054
	D+Ex	-0.61	± 1.30	-0.09	-1.12	*0.022*

ME = mean evolution, SD = standard deviation, 95% CI = 95% confidence interval, W = total body weight, % BF = body fat percentage, % SkM = skeletal muscle percentage and %VF = visceral fat percentage, BMI = body mass index

AI patients from the diet and exercise grup did not improve muscle mass – maybe because of the detrimental musculoskeletal impact of AI medication.

TABEL 4. *Comparative evolution of patients on Tamoxifen (n=13) vs. patients on IA (n=14) from the diet + exercise intervention*

	Group	ME	SD	95% CI		p
				Min.	Max.	
W (kg)	T	-2.55	± 4.14	-0.04	-5.05	*.046*
	IA	-1.17	± 1.53	-0.29	-2.06	*.013*
BF%	T	-1.54	± 4.71	+1.30	-4.39	.260
	IA	-1.25	± 2.17	-0.00	-2.50	.051
SkM%	T	+1.89	± 3.11	+0.01	+3.77	*.049*
	IA	+0.65	± 1.24	-0,06	+1.37	.071
VF%	T	-0.69	± 1.03	-0.06	-1.31	*.032*
	IA	-0.64	± 0.84	-0.15	-1.12	*.013*
BMI	T	-0.99	± 1.71	-0.04	-2.02	.059
	IA	-0.25	± 0.64	-0.11	-0.63	.160

ME = mean evolution, SD = standard deviation, 95% CI = 95% confidence interval, W = total body weight, % BF = body fat percentage, % SkM = skeletal muscle percentage and %VF = visceral fat percentage, BMI = body mass index

Study limitations

Although the body composition measurement used in our study are indirect, BIA measurements can be used in scientific research by limiting biased results by the hydration and feeding status of the patient at the time of the measurement, and by doing measurements in the same standard conditions (Mialich, Sicchieri and Junior, 2014). Future studies are needed to replicate this study results with DEXA, the gold

standard in sarcopenia diagnosis and body composition measurements.

Also because the kinetic intervention was done at home without monitoring, we have no way to know if the patients actually did the exercises or not.

DISCUSSIONS

To our knowledge, this is the first study to evaluate body composition change in breast cancer patients on antiestrogenic medication using an whole body isometric exercise protocol. And although patients on AI might have lower active skeletal muscle mass – possibly due to the higher risks of AI medication of musculoskeletal side effects (Garreau et al.., 2006), osteoporosis (Smith and Dowsett, 2003), and a higher bone fractures (Jakesz et al., 2005) – our results might have been influenced by the fact that the group on Tamoxifen was in average 4 years younger and obese according to BMI than the older and overweight group on AI (despite existing no initial statistically significant difference between the two groups if measured by a two tail student T test).

TABLE 5. *Comparative initial distribution of patients by weight and body composition*

	Group	Age (years)	W (kg)	% BF	%SkM	%VF	BMI
Mean initial values	T	51	83.8	41.4	24.6	9.7	31.4
	AI	55	74.3	38.5	26.6	8.7	27.6

T = patients taking Tamoxifen, AI = patients taking aromatase inhibitors, W = total body weight, % BF = body fat percentage, % SkM = skeletal muscle percentage and %VF = visceral fat percentage, BMI = body mass index

Many studies prove high protein diets effective in counteracting sarcopenia.

Campbell et al. questioned the recommended 0.8 g/kg per day dietary allowance for protein as inadequate for older people to maintain skeletal muscle (Campbell et al., 2001). Then, in 2007, he coauthored Leidy's study proving that higher protein intake preserves lean mass and satiety during weight loss interventions in 28-30 BMI women (Leidy et al., 2007). The chemotherapy patients in our study were also 28-30 BMI and at risk for sarcopenia, thus we used a 1.5g protein intake/kg body weight per day.

Paddon-Jones et al. proved that high protein diets may represent a viable intervention for individuals at risk of sarcopenia in their 2004 study, when they managed to maintain lean leg mass in patients during 28 days bed rest. But they offset the catabolic response to prolonged inactivity with essential amino acids and carbohydrates supplemented to mixed meals offered every 5 h (Paddon-Jones et al., 2004). Then in a further study he proved that amino acid supplementation acutely stimulated muscle protein synthesis in both young and elderly individuals (Paddon-Jones et al., 2004).

We only used foods and we instructed patients to eat only when hungry. Thomson et. al. proved in 2010 when comparing low-fat vs. reduced carbohydrate diets that overeating is not the main cause of weight gain among breast cancer patients who receive chemotherapy, suggesting that CT-induced weight gain is distinctive and indicative of sarcopenic obesity (weight gain in the presence of lean tissue loss).

Thus, to improve eating behaviour, we explained the metabolic differences between eating when not hungry and eating when physically hungry (Ciampolini, Lovell-Smith and Sifone, 2010) and we asked patients to learn to recognize gastric hunger and to respect it by not eating when not hungry and also by eating within a maximum of 1 hour after feeling it.

Then, in 2009, Paddon-Jones et al. proposed a novel and specific dietary approach to prevent or sarcopenia, recommending clinicians to stress the importance of ingesting 25-30g of protein with each meal – recommendation we also used in our study (Paddon-Jones, Douglas and Blake, 2009).

To our knowledge, other studies using high protein diets in breast cancer patients during chemotherapy found them effective but most also used resistance exercise to counteract chemotherapy side effects.

A 2002 study authored by Demark-Wahnefried et al. yield promising results in preventing chemotherapy-induced weight and body composition changes among young women who received adjuvant chemotherapy for breast cancer. They used a specialized program of strength training, aerobic activity and a healthful diet (≤20% fat; fruit, vegetable and calcium-rich). Demark-Wahnefried's study more than half of the patients approached for the intervention refused to participate because the exercises where performed in hospital settings, which raised the recommendation that weight gain preventing interventions would be more effective with a home-based approach.

Other studies also proved that a high calcium intake associates with a better breast cancer

prognostic (Lin et al., 2007). Thus we recommended fermented dairies as one of the main protein sources (besides raw nuts, seeds and fish) both for the calcium and vitamin D and for the probiotics.

To determine the effectiveness of weight loss intervention for breast cancer survivors, Playdon et al. performed in 2013 a systematic review of 15 weight loss studies in breast cancer survivors. Successful interventions used dietary, physical activity and behavior modification components, yet there was insufficient evidence to identify the interventions that led to successful weight loss, or to determine the weight loss necessary to affect biomarkers linked to breast cancer prognosis. The main drawbacks of these studies were short duration, the small study sample sizes and lack of follow-up beyond 6 months. We also have a short duration and small sample size study.

And as the results of these studies, ours are also encouraging, but more research on fat loss impact on breast cancer recurrence and mortality risks is needed.

CONCLUSIONS

A high protein diet can decrease body fat in ER+ breast cancer patients on antiestrogenic medivation. Adding a daily minimal exercise protocol to a high protein diet decreases visceral fat – which is more hormonally active. And resistance-training exercises are more appropriate for patients on AI.

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