

BEHAVIORAL MEDICINE SOLUTIONS FOR OVERWEIGHT AND OBESE BREAST CANCER PATIENTS WITH SLEEP DISTURBANCES

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ABSTRACT

Sleep disturbances overthrow breast cancer patients' eating behavior, aggravating sarcopenic obesity causes like insulin, leptin and dopamine resistance, thus increasing recurrence and mortality risks.

Seeking fat loss solutions for sarcopenic obesity in ER+ breast cancer patients with sleep disturbances, we randomized 50 – of which 16 were depressive – to follow a high protein diet (D) or the diet and sleep journal interventions (D+SJ). Patients ate only when hungry foods naturally high in protein, calcium, omega-3, pre- and probiotics, and were asked to write a daily food journal. Half of the patients were asked to write a 7-day Kalionka Institute type sleep journal – containing questions about the time it took them to fall asleep, number of awakenings during the night, how much they slept, how much they stayed in bed, and self-perceived sleep quality. After writing the sleep journal, we asked patients to follow set sleeping and wake up hours calculated based on their SJ answers, and to not sleep during the day. After 8 weeks we remeasured body composition with a multi-frequency bioelectrical impedance scale.

8 patients from the D+SJ group asked to leave the study, 5 being depressive.

D group lost $2.31 \pm 2.86\%$ body fat ($p=0.001$), and $0.76 \pm 1.16\%$ visceral fat ($p=0.001$); with no fat loss difference between patients with or without depression. Depressive patients did not obtain statistical significance for weight loss.

D+SJ group improved sleep quality and lost $2.16 \pm 2.35\%$ body fat ($p=0.002$), and $0.86 \pm 1.24\%$ visceral fat ($p=0.005$). Depressive patients didn't obtain statistically significant results neither for fat, nor for weight loss – maybe because of the overruling effect of the SJ intervention.

So, both D and D+SJ interventions improve breast cancer patients' body composition despite sleep disturbances, but only non-depressive patients also lose weight. And SJ intervention improves sleep quality in patients without depression, decreasing weight regain risk.

Keywords: breast cancer, sleep disturbances, sarcopenic obesity, body composition, Kalionska Sleep Journal

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The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and it is approved by the Ethical Committee of Alexandru Trestioreanu Oncology Institute, Bucharest. All patients expressed their free-given written consent to participate in this behavioral study. We declare no conflict of interest.

INTRODUCTION

Breast cancer patients who gain weight during treatment have higher risks of all causes mortality, oncology specific mortality and recurrence (1). Counteracting sarcopenic obesity causes can be hard in overweight or obese patients with sleep dis-

turbances, because they instinctively move less, eat more and crave more fattening foods (2).

Sleep disturbances are one of the first behavioral expressions of fight or flight reactions (through the adrenaline reactions commanded by the sympathetic autonomic nervous system), or freeze reactions (through the acetylcholine reactions com-

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manded by the parasympathetic autonomic nervous system) to stress. Because sleep is coordinated by the suprachiasmatic nucleus of the hypothalamus in conjunction with amygdala nuclei (3), falling asleep when over-stressed feels as dangerous as falling asleep in a life threatening situation. Thus, in a fight or flight stress reaction, the patient experiences various degrees of insomnia: having trouble falling asleep, waking up during the night, and then having trouble falling back asleep, or waking up too early in the morning (4). On the other hand, for some patients, breast cancer diagnosis represent an insurmountable stress trigger, thus they experience the hypersomnia side effect of the freeze reaction to stress (5). They can sleep for hours and hours and still wake up tired.

During over-tiring days following sleepless or overslept nights, the metabolic adaptation to stress is done by the same hormone: the cortisol (6). Chronic stress associated with breast cancer treatment lowers sleep quality and flattens diurnal cortisol rhythmicity – predicting a shorter survival for women with metastatic breast cancer (7) and de-regulating eating behavior through:

- insulin resistance – manifested by increased hunger and cravings (8);
- leptin resistance – caused by hyperinsulinemia, dyslipidemia and hyperleptinemia – manifested by lowered ability to perceive physical hunger when blood sugar is low, decreased ability to perceive satiety, and feeling like eating soon after taking a meal (9);
- dopamine resistance – manifested by decreased ability to perceive pleasure, be it eating pleasure or any other type of pleasure (10).

The main eating behaviors that increase insulin sensitivity are eating when physically hungry, respecting satiety (11).

Physical hunger is perceived by neurons inside our hunger center, because these neurons are sensitive to the blood sugar level. When our blood sugar level drops under 70-80 mg/dl, these neurons secrete neuropeptide Y (NPY) and agouty related peptide (AgRP) – substances that generate through the vagus nerve the hollow sensation in the middle upper abdominal area (12).

On the other hand, appetite is triggered by ghrelin acting on the same NPY and AgRP secreting neurons within hypothalamic arcuate nucleus, but ghrelin is mainly secreted by oxyntic gastric cells when the stomach is empty, which may or may not coincide with the blood sugar being low enough to generate physical hunger. When they don't coincide, and patients decide to eat in response to ghre-

lin instead of to a blood sugar level lowered enough to generate physical hunger, muscle's insulin sensitivity decreases (13).

Respecting satiety is also essential for increasing back the insulin sensitivity, but insulin resistant overweight and obese patients with sleep disturbances have a lowered ability to perceive it due to leptin resistance (because insulin stimulates leptin secretion by the already higher body fat percentage), and dopamine resistance (because they use eating to feel better emotionally).

Leptin inhibits the hunger NPY and AgRP secreting neurons, being the main satiety hormone even it is mainly secreted by the white fat tissue. Overweight and obese patients have less ghrelin and more leptin than normal weight patients, but their hypothalamus' satiety POMC and CART secreting neurons become leptin-resistant which practically means that their hunger neurons function continuously, with no inhibitions whatsoever (14). So, the very fact that their body fat percentage is increased over the healthy range creates and increases the mental need to eat (15).

Moreover, besides inducing leptin resistance, hyperinsulinemia can induce dopaminergic dysfunction leading to depressive-like behaviors (16).

Moreover, under stress POMC stops being just a satiety neurotransmitter, being transformed into CRH, aMSH and β endorphins. CRH further commands the pituitary gland to secrete ACTH which stimulates corticosuprarenal glands' cortisol secretion. aMSH grays the hair and potentially depigment areas of the skin. And β -endorphins are responsible feeling numb enough to get out of the danger zone (17).

Many patients actually look for β endorphins' created numbness, and try to self-medicate their feelins and pains with food. For instance they report eating in order to get to sleep at night or to fall back asleep if they wake up during the night. But β -endorphins' anesthesia is followed by cortisol induced hyperglycemia, which represents a metabolic stress per se which decreases insulin sensitivity, putting these patients into a worse position than before they ate for emotional comfort (18).

Chronic stress is part of breast cancer patients lives and β -endorphins are part of their unconscious relationship with food. When stress becomes chronic and feel they can't fight it anymore, they re-enter into the β -endorphins/cortisol loop – loop that can lead to not only emotional eating, but also to depression.

METHOD

Purpose

This study is part of a series of studies aimed to find a preventive solution for sarcopenic obesity during breast cancer treatment. The current study is meant to answer three questions:

1. Is a high protein diet effective in generating fat loss in breast cancer patients with sleep disturbances?
2. Is adding a sleep journal intervention to this diet more effective than the diet alone intervention?
3. Are there any metabolic evolutive differences between patients with or without depression subject to these interventions?

Study design

- study duration: 8 weeks
- number of patients: 50, 16 of them being depressive
- inclusion criteria:
 - ER+ breast cancers;
 - During antihormonal treatment, after chemotherapy, radiotherapy and surgical treatment.
- exclusion criteria:
 - Her2+ and Triple – breast cancers;
 - patients without sleep disorders;
 - patients with eating disorders, diabetes, renal disease, thyroid disease.
- interventions – patients were randomly assigned to one of the two interventions below:
 - diet group (referred to as the “D” group);
 - diet + sleep journal (referred to as the “D+SJ” group).
- monitoring:
 - multi-frequency bioelectrical impedance scale 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;
 - sleep journal: patients were instructed to keep a 7-day sleep log before and after the 8 week intervention.

Detailed 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, and it can assist in breast cancer recurrence prevention through a moderate intake of glucose.

1. 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.

2. To increase satiety and to counteract the Warburg effect 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 weight, which practically meant for most of our patients a 25-30 g protein intake per meal.

3. To increase hypothalamic leptin sensitivity we asked patients to not eat between meals, to have not have meals based only on fruits (patients were given a table where foods were classified as proteins and healthy fats, carbohydrates or fibres supplying sources and they were taught to consume mixed meals).

4. To counteract depressive-like behaviors we asked patients to have a daily intake of foods high in omega-3 fatty acids (high fat fish, cold pressed extra virgin olive oil, rapeseed oil or canola oil, avocado, and various raw seeds, almonds and nuts), and to avoid soft drinks, fried food and any food with hydrogenated fats on the ingredients list.

5. To counteract dysbiosis, we asked them to have 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).

6. 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).

7. 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.

8. To ensure a proper gastric emptying time, an interval of 2 hours minimum was recommended between taking any meal and sleeping.

9. And finally, 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.

Patients were instructed to keep a 7-day sleep log before and after the intervention where to write each morning the time they went to bed at night, how long it took them to fall asleep, how many times they woke up during the night, how much time it took them to fall back asleep, at what time they woke up in the morning, at what time they got off bed in the morning, and the self-perceived sleep quality based on how tired they woke up (on a scale from 1 to 10, 1 being very tired and 10 being completely refreshed).

1. Based on their sleep journals, we calculated – using the Kalionska Institute's behavioral medicine method for increasing sleep quality – the sleeping and wake up time needed by each patient for sleep quality increase.

2. The wake up time was initially calculated as a mean between the patient's wake up hours, then we asked each patient if that wake up hour suits its lifestyle and working ours. Based on the answer we established the wake up time.

3. Then we calculated the mean time slept during the 7 nights and we subtracted it from the wake up time to get to going to sleep at night time

4. Then we asked them to:

- respect these set sleeping and wake up time each day during the whole 8 weeks, and
- refrain from sleeping during the day.

RESULTS AND DISCUSSIONS

Study completion

8 patients from the D+SJ group asked to leave the study, 5 being depressive.

Results

As whole groups, there were no difference between the weight and fat loss evolution in patients with D versus patients with D+SJ interventions (Table 1).

But when we took depression into account, all patients in group D improved their body composition, but those with depression did not obtain statistically significant weight loss.

On the other hand, in group D+SJ only patients without depression obtained statistically significant weight and fat loss, improving body composition on all parameters tested (Fig 1). They also improved self-perceived sleep quality, reported as into falling asleep faster at night, decreased number of waking ups during the night and waking up less tired.

Study limitations

Although all body composition measurement devices are indirect and subjected to biased results even in the same person using consecutive measurements, the gold standard in sarcopenia diagnosis and body composition measurements remains DEXA and we suggest study replication with such measurements. Yet BIA measurements can also be used in scientific research when trying to limit 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).

TABLE 1. Comparative evolution of D patients vs. D + SJ patients

	Depression	No.	ME	SD	95% CI		p
					minim	maxim	
W (kg)	D	25	-2.16	± 2.51	-1.21	-3.2	0.001
	D+SJ	17	-2.21	± 2.93	-0.7	-3.72	0.007
BF %	D	25	-2.31	± 2.86	-1.13	-3.49	0.001
	D+SJ	17	-2.16	± 2.35	-0.95	-3.37	0.002
SkM%	D	25	1.2	± 1.50	0.58	1.83	0.001
	D+SJ	17	0.86	± 1.24	-0.3	1.5	0.011
VF%	D	25	-0.76	± 1.16	-0.27	-1.24	0.003
	D+SJ	17	-0.76	± 0.97	-0.26	-1.26	0.005
BMI	D	25	-1.09	± 1.47	-0.48	-1.7	0.001
	D+SJ	17	-1.13	± 1.51	-0.35	-1.91	0.007

Paired Samples Correlations						
Depression	Intervention			N	Correlation	Sig.
No	diet+sleep journal	Pair 1	Weight bf & Weight aft	19	.969	.000
		Pair 2	Body fat bf & Body fat aft	19	.805	.000
		Pair 3	Skeletal mass bf & skeletal mass aft	19	.781	.000
		Pair 4	Visceral fat bf & Visceral fat aft	19	.640	.003
		Pair 5	Body mass index & Body mass index	19	.857	.000
	diet	Pair 1	Weight bf & Weight aft	12	.970	.000
		Pair 2	Body fat bf & Body fat aft	12	.957	.000
		Pair 3	Skeletal mass bf & skeletal mass aft	12	.948	.000
		Pair 4	Visceral fat bf & Visceral fat aft	12	.858	.000
		Pair 5	Body mass index & Body mass index	12	.861	.000
Yes	diet+sleep journal	Pair 1	Weight bf & Weight aft	6	.981	.001
		Pair 2	Body fat bf & Body fat aft	6	.937	.006
		Pair 3	Skeletal mass bf & skeletal mass aft	6	.932	.007
		Pair 4	Visceral fat bf & Visceral fat aft	6	.954	.003
		Pair 5	Body mass index & Body mass index	6	.974	.001
	diet	Pair 1	Weight bf & Weight aft	5	.877	.051
		Pair 2	Body fat bf & Body fat aft	5	.771	.127
		Pair 3	Skeletal mass bf & skeletal mass aft	5	.780	.120
		Pair 4	Visceral fat bf & Visceral fat aft	5	.990	.001
		Pair 5	Body mass index & Body mass index	5	.920	.027

FIGURE 1. Comparative evolution of D and D + SJ groups of patients

This was a home based intervention, so we could only monitor if patients complied with our recommendations or not on their self-reported food and sleep journals and on their weight and body composition evolution.

CONCLUSIONS

In conclusion, a high protein diet is effective in generating fat loss in overweight and obese breast

cancer patients with sleep disturbances with or without depression. And adding a sleep journal intervention improves sleep quality in patients without depression, decreasing weight regain risk. Still, the sleep journal intervention is overtiring for depressive patients diminishing the overall effectiveness of the proposed oncology nutrition intervention.

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