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A RANDOMIZED CONTROLLED TRIAL OF ORAL MELATONIN SUPPLEMENTATION AND BREAST CANCER BIOMARKERS

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Abstract

We examined compliance with and the effects of melatonin supplementation on breast cancer biomarkers (estradiol, insulin-like growth factor I (IGF-1), insulin-like growth factor binding protein 3 (IGFBP-3), and the IGF-1/IGFBP-3 ratio) in postmenopausal breast cancer survivors. In a double-blind, placebo-controlled study, postmenopausal women with a prior history of stage 0–III breast cancer who had completed active cancer treatment (including hormonal therapy) were randomly assigned to either 3 mg oral melatonin (n=48) or placebo daily for 4 months. Plasma samples were collected at baseline and after completion of the intervention. The primary endpoints were compliance and change in estradiol and IGF-1/IGFBP-3 levels. 95 women were randomized (48 to melatonin and 47 to placebo). 86 women (91%) completed the study and provided pre and post intervention bloods. Melatonin was well-tolerated without any grade 3/4 toxicity and compliance was high (89.5%). Overall, among postmenopausal women with a prior history of breast cancer, a 4 month course of 3 mg melatonin daily did not influence circulating estradiol, IGF-1, or IGFBP-3 levels. Compliance was comparable between the two groups. Short-term melatonin treatment did not influence estradiol and IGF-1/IGFBP-3 levels. Effects of longer courses of melatonin and among premenopausal women are unknown. The particularly low baseline estradiol levels in our study population may have hindered the ability to detect any further estradiol lowering effects of melatonin.

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AUTHOR CONTRIBUTION

None of the authors has a conflict of interest to report.

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Keywords

melatonin; aMT6s; estradiol; IGF; postmenopausal; breast cancer

INTRODUCTION

Breast cancer is the most common cancer diagnosed in women in the U.S., with modestly declining mortality rates over the past decade [1]. Both early detection and improvements in breast cancer therapy have been linked with this decline in mortality [2, 3]. However, comparatively little progress has been made in the prevention of breast cancer. Although tamoxifen and raloxifene have been approved by the FDA to reduce breast cancer risk, concern remains regarding its widespread use among healthy women because of tamoxifen's associations with endometrial cancer and with thromboembolic events [4]. No other drugs are currently known to effectively prevent breast cancer.

Epidemiologic and laboratory data suggest that melatonin may influence cancer risk, and in particular that of breast cancer [5, 6]. The safety of melatonin supplementation in humans has been extensively documented with no significant adverse effects reported at a wide range of doses [7]. Because melatonin's effect on breast cancer risk is thought to work through several different mechanisms, it would make for a particularly attractive target drug for chemoprevention. The two primary mechanisms of melatonin in relation to breast cancer are its apparent influence on estrogens through down-regulation of the hypothalamic-pituitary reproductive axis including a reduction of circulating estrogen levels [8] and through direct actions of melatonin at the tumor cell level, thus behaving both as a selective estrogen-receptor modulator (SERM) as well as an aromatase inhibitor [9, 10]. Secondly, melatonin blocks linoleic acid uptake and metabolism to 13-hydroxyoctadecadienoic acid (13-HODE), which, via down-regulation of the mitogen-activated protein/extracellular signal-regulated kinase (ERK) kinase (MEK) MEK/ERK1/2 growth signaling pathway, is directly related to the insulin-like growth factor (IGF) system [11]. Higher levels of circulating estradiol levels [12], and to a lesser degree insulin-like growth factor [13], are widely viewed as risk factors for postmenopausal breast cancer risk.

While several previous studies have suggested an association between melatonin and estradiol [14–17] as well as IGF levels [15, 18–24], none of these were randomized placebo-controlled trials. However one small (n=14) open-label study observed a significant decrease in circulating estradiol and IGF levels among postmenopausal women after 6 months of 2mg melatonin daily [25]. To confirm this relationship, we conducted a double-blind randomized, placebo-controlled trial of oral melatonin supplementation over four months in postmenopausal healthy survivors of early stage breast cancer without current hormonal therapy use. We hypothesized that melatonin would lower estradiol and IGF levels, and that compliance would be satisfactory. Because in the US melatonin is sold as a dietary supplement and not as a drug and the endpoints were biomarkers, no trial registration number was assigned to this NIH funded study.

MATERIALS AND METHODS

Eligibility criteria

To be eligible for enrollment, women had to have had a history of ductal carcinoma in situ (DCIS), lobular carcinoma in situ (LCIS), or stage I-III breast cancer, not be currently receiving chemotherapy or hormonal therapy; be postmenopausal, understand written or spoken English, signed an informed consent, and have a normal liver and kidney function and complete blood count. Exclusion criteria were stage IV breast cancer or systemic recurrence; prior malignancies, other than breast, basal or squamous cell carcinoma of skin, or carcinoma in situ of the cervix; use of adjuvant hormonal therapy within 60 days; concomitant use of beta-blockers; concomitant, nightly use of sleep aids; working more than one overnight shift per month on a regular basis; concomitant use of post menopausal hormone therapy, black cohosh, flaxseed, or soy in pill supplement; use of melatonin supplement within 30 days prior to enrollment; use of warfarin during the 30 days prior to enrollment; and active seizure disorder requiring daily anti-epileptic medication. The study was approved by the Internal Review Board of the Dana-Farber Cancer Institute and Brigham and Women's Hospital and written informed consent was obtained from each participant.

Randomization and Masking

All women were recruited through the Breast Oncology Center at the Dana-Farber Cancer Institute (Boston, MA), and were randomly assigned by central pharmacy to receive in a double-blind fashion either 3 mg melatonin or placebo. Melatonin supplements were purchased from a single supplier (Rugby Laboratories, a subsidiary of Watson Laboratories, Duluth, GA, USA) by the DFCI Investigational Drug (ID) pharmacy. For each lot of melatonin, Rugby Laboratories issued a certificate of analysis guaranteeing the composition and purity. The DFCI ID pharmacy placed melatonin in blue gelatin capsules with methylcellulose filler and used identical blue capsules filled with methylcellulose filler alone as placebo. Distribution of medication and randomization were performed by the DFCI pharmacy. Subjects received a 4-months supply at the time of the baseline visit. Women who participated in the trial were instructed to take the assigned pill (melatonin or placebo) daily at 9pm or 30 minutes before bedtime, whichever occurred earlier, for four months. Each subject was instructed to note any missed doses in her medication diary; missed doses were not replaced. The study team contacted each participant once monthly to follow-up on medication use, compliance, and side effects. All adverse-event reporting in this trial used the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events Version 3. Per protocol, the trial was to be suspended for any grade-3 or grade-4 adverse event that could possibly be related to the study intervention.

Outcome Measurements

Prior to the beginning of the intervention and immediately after completion of the 4 month intervention, subjects had their blood drawn to assess levels of circulating estradiol, IGF-1, and IGFBP-3. All blood samples were processed and stored at the DFCI. In addition, at both visits, assessments of sleep quality were performed and medication use was assessed.

Blood Samples

Blood samples were drawn, then immediately processed and stored at -80°F . A woman's initial and follow-up blood samples were assayed in the same batch, and we included masked quality control samples for analysis. Estradiol was measured in plasma by liquid chromatography tandem mass spectrometry (LC-MS/MS) at ARUP Laboratories (Salt Lake City, UT, USA). IGF-1 and IGFBP-3 levels were assayed by ELISA in Michael Pollak's laboratory (McGill University, Montreal, Canada), using reagents from Diagnostics Systems Laboratories (Webster, TX, USA). Laboratory data for IGF-1 and IGFBP-3 were reported with two replicated values at baseline and follow-up; these were averaged for each patient at each time point for the analysis. Data reported for estradiol did not include replicates. Twelve baseline and two follow-up estradiol measurements were reported as " <1.0 " indicating that the level was below the lower limit of detection of the assay. For statistical analyses, the levels of these women were imputed at the lowest detectable level (1.0). None of the women who had " <1.0 " reported at baseline also had " <1.0 " reported at follow-up. The number of substitutions was identical between treatments (baseline: 6 melatonin, 6 placebo; 4-months: 1 melatonin, 1 placebo). We included masked split specimens to calculate the coefficient of variation. Mean intra-assay coefficients of variation were 18.9% for estradiol, 2.7% for IGF-1, and 2.7% for IGFBP-3.

Statistical Analysis

Assuming an attrition rate of 15%, the accrual goal in this study was 50 participants per study arm with usable biomarker data. Due to expiration of study funding, the trial was closed to accrual shortly before this goal was reached. Based upon the 47 (placebo) and 48 (melatonin) women in each treatment arm at the end of the trial, we calculated that we had 80% power to detect a decrease from baseline in estradiol of 41% in the melatonin arm compared to 0% in the control arm. For comparison, with 50 participants per arm we would have been able to detect a 38% decrease in estradiol. Because all hormones showed skewed distributions, log-transformed values were used for analyses. The primary trial analysis was performed according to the intent-to-treat principle. Wilcoxon rank-sum tests were used to compare the ratios (or, equivalently, the difference in the natural log) of follow-up to baseline levels (i.e., 4-month/baseline) of estradiol, IGF-1, and IGFBP-3 between melatonin and placebo arms, and Fisher's exact test was calculated to compare compliance.

RESULTS

Baseline Demographics and Tumor Stage

Ninety-five postmenopausal women aged 38 to 80 were enrolled between March 2007 and March 2009. Forty-seven women were randomized to receive placebo and 48 to receive melatonin. Baseline characteristics were well balanced at the time of study entry. Table 1 summarizes baseline demographics and disease characteristics overall and by treatment assignment for all 95 women enrolled in the trial. Median age at enrollment was 59 years (placebo: 60 years, melatonin: 58 years), with an overall range of 38 to 80 years. Median age at breast cancer diagnosis was 50 years (range: 32 to 69), with a median time of 8 years after diagnosis of breast cancer (range: 0.9 to 27.9 years). Median body mass index (BMI) at

enrollment was 25.6 (range: 19.1 to 44.9) overall, and 25.0 (range: 19.1 to 39.6) and 25.7 (range: 20.1 to 44.9) for those randomized to receive placebo and melatonin, respectively.

Attrition

Of 95 subjects enrolled, 86 (90.5%) completed the 4-month intervention and 9 subjects (9.5%) did not complete the intervention. Of these, one subject withdrew consent for continued participation after approximately 7 weeks of follow-up due to insomnia (she was randomized to placebo). As part of the study eligibility criteria, she was required to stop her regular sleep medication and suffered severe insomnia as a result. Four subjects (all four in the melatonin arm) withdrew due to toxicity (all grades 1 or 2): one withdrew from the study after 11 weeks due to dizziness, fatigue, and headaches; the second subject withdrew after 13 weeks due to headaches, trouble sleeping, and bad dreams; the third and fourth subjects withdrew at 5 and 9 weeks, respectively, due to insomnia and nightmares. Three subjects were lost to follow-up (two on placebo and one on melatonin) and another subject left the study after 10 weeks to begin radiotherapy for local breast cancer recurrence (placebo).

Thus, 43 women enrolled and randomized to receive placebo (91.5%) completed the study, and 43 women enrolled and randomized to receive melatonin (86.9%) completed the study. The study was designed to allow for a 15% drop-out rate. The observed rate of attrition is 9.5% (8.5% placebo, 10.4% melatonin). There was no difference in the rates of completion between the placebo and melatonin groups (Fisher's exact p-value = 0.75).

Circulating Estradiol and IGF

Eighty-six women had data assessable for changes in the primary biomarker endpoints (43 melatonin, 43 placebo). Table 2 summarizes each of the assays by time and treatment. Baseline levels of estradiol, IGF-1 and IGFBP-3 were not statistically significantly different between treatment groups [Wilcoxon rank-sum p-values: 0.22 (estradiol), 0.98 (IGF-1), 0.18 (IGFBP-3)]. For baseline estradiol, 90 percent of the serum levels were below 6.3 for women in the placebo arm, and below 8.1 for women in the melatonin arm. There was considerably more variability in the ratios of follow-up to baseline measures of estradiol compared with the ratios of IGF-1 and IGFBP-3 (Table 4). However, mean and median values were comparable between treatment groups for each of the markers. The 90th percentiles of the ratios for estradiol were 3.9 and 3.4 for placebo and melatonin, respectively. Wilcoxon rank-sum p-values for the comparisons of the ratios between melatonin and placebo were: 0.84 (estradiol), 0.36 (IGF-1), and 0.62 (IGFBP-3), suggesting that there is no difference between melatonin and placebo with respect to change in any of the three markers over the course of study follow-up.

Compliance

A subject was considered compliant if at least 75% of the pills were taken at the time of the final study visit (90 or more of 120 pills). Subjects who withdrew from the study before completion are considered non-compliant. Of the 95 subjects enrolled in the study, 10 were considered non-compliant (9 non-completers and 1 who took less than 75% of the study medication). Therefore, compliance with the intervention occurred in 85 (42 in the placebo arm and 43 in the melatonin arm) of 95 subjects (89.5%). There was no difference in

compliance between subjects who received placebo and subjects who received melatonin (Fisher's exact p-value = 0.99).

Toxicity and Adverse Events

Adverse events are summarized in Table 4. For the melatonin arm, there were no grade 3/4 toxicities. The most common grade 1/2 toxicities for melatonin were headache, fatigue, and bad dreams.

DISCUSSION

In this double-blind randomized, placebo-controlled trial of oral melatonin supplementation over four months in 86 postmenopausal healthy survivors of early stage breast cancer without current hormonal therapy use, we found no significant differences in circulating estradiol, IGF-1, and IGFBP-3 levels, as well as compliance, in relation to melatonin use. Compliance was high with daily melatonin and well-tolerated.

Melatonin appears to both selectively neutralize the effects of estrogens on the breast and the local biosynthesis of estrogens from androgens, thus acting at different levels of the estrogen-signaling pathway. It is difficult to foresee whether the net effect of these actions would lead to a reduction or an increase of circulating estrogen levels in our trial. Our primary hypothesis was that it will decrease estrogen, although we recognize that estrogen blockage may occur at the tissue level without influencing circulating levels (e.g., tamoxifen).

Several studies lend direct [14, 15] and indirect [16, 17] support to an inverse association between melatonin and estrogen levels. To date, one small study by Siegrist et al did not find a significant association between 3 mg melatonin daily for 6 months and estrogen levels among 16 women, but this study did not take into account differences in hormone levels during the menstrual cycle [26]. Two other more carefully conducted studies suggest that both low dose (5 mg daily) [15] and high dose (300 mg daily) [14] melatonin supplementation may decrease estrogen levels in both post- [15] and premenopausal women [14]. Specifically, Pawlikowski et al. [15] administered 2 mg melatonin daily over 6 months in their small study of 14 women aged 64 to 80. They observed a significant decrease in estradiol levels after 6 months of melatonin in these postmenopausal women. Similarly, Voordouw et al. studied oral melatonin over 4 months, but chose to administer a much higher dose of 300 mg per day (8 received it daily and 4 on days 5–17 of their cycle) [14]. The daily melatonin administration caused a significant decrease in estrogen levels, but only after 4 months of treatment. No significant effect was seen after only one month of melatonin. In sum, several small pilot studies to date have provided some evidence for an effect of melatonin on estradiol levels, but ours is the first placebo-controlled, randomized study to evaluate these associations.

Although less data exist on the relationship between melatonin and the IGF axis, several studies have also evaluated the effects of oral melatonin administration on circulating IGF-1 levels [15] or provided indirect evidence for an association between melatonin and the IGF axis [18–23]. IGF remains an interesting outcome because of its possible association with a

breast cancer risk pathway separate from a sex steroid hormonal mechanism. Although one study among postmenopausal women did not observe a strong association between IGF-1 levels and low dose melatonin (2 mg daily), an inverse association between plasma melatonin and IGF-1 ($r=-.39$, $p=0.06$) was reported in a study of 24 premenopausal stage II breast cancer patients (compared to 16 healthy controls) [20]. Another trial among women with metastatic breast cancer also demonstrated a decrease in IGF-1 levels after melatonin supplementation. However, these women took melatonin and tamoxifen concurrently so it was impossible to differentiate the effects of melatonin from those of tamoxifen [24]. Our results do not support an effect of oral melatonin, at the dose we used in our trial, on circulating IGF levels.

Melatonin has been used extensively in cancer patients, both alone and in combination with chemotherapy, with no significant adverse effects reported thus far, and they have been reviewed extensively elsewhere [27]. 20 mg daily was the most common dose of melatonin used in the clinical trials among cancer patients. Two of these studies showed a statistically significant improvement in clinical response rate and overall survival among people with metastatic solid tumors randomly assigned to chemotherapy and melatonin compared to chemotherapy alone, as well as a decrease in chemotherapy induced toxicity, such as neurotoxicity, thrombocytopenia, cachexia, and asthenia in the melatonin arm [28, 29]. The other two studies were single arm studies in which tamoxifen 20 mg daily was given in combination with melatonin 20 mg daily [24] [30]. Again, the treatments were well tolerated without any significant adverse effects. We, too, did not observe any noteworthy adverse events in our placebo-controlled trial of 3m melatonin daily.

Strengths of this study include its double-blind design, relatively large study population, and compliance rates comparable or better than observed in similar studies at the DFCI. That we fell slightly short of our accrual goal may have hampered our ability to detect differences in the biomarkers we chose to evaluate; however, updated power analyses suggest that we still had a sufficient number of participants to detect an intervention effect close to our initial estimates.

Our study may have been limited in detecting a potential lowering effect of melatonin on estradiol levels in that the majority of our postmenopausal participants were lean and with very low baseline estradiol to begin with (mean estradiol level at baseline = 3.97 pg/ml). Hence, we cannot rule out an effect of melatonin on estradiol levels in postmenopausal women with higher baseline estradiol levels (e.g. if their BMI, on average, is higher than in our study), or in premenopausal women.

In sum, this double-blind randomized, placebo-controlled trial of oral melatonin supplementation did not support an important effect of 3mg melatonin daily on circulating breast cancer biomarkers in postmenopausal women with a history of breast cancer, if given over four months. The effects of longer intake or different doses of melatonin, also in premenopausal women, need to be determined in future studies. Whether postmenopausal women with higher baseline estradiol levels than ours may have benefited from melatonin supplementation remains unclear.

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Research into Context

In this paper, we examined for the first time in a controlled fashion, the effects of melatonin supplementation on breast cancer biomarkers. Melatonin was well-tolerated without any grade 3/4 toxicity and compliance was high. Overall, among postmenopausal women with a prior history of breast cancer, a 4 month course of 3 mg melatonin daily did not influence circulating estradiol, IGF-1, or IGFBP-3 levels. We conclude that short-term melatonin treatment did not influence estradiol and IGF-1/IGBBP-3 levels. Effects of longer courses of melatonin and among premenopausal women are unknown. The particularly low baseline estradiol levels in our postmenopausal, lean study population may have hindered the ability to detect any further estradiol lowering effects of melatonin, and future studies should take this into consideration.

Table 1

Baseline Characteristics

	Treatment				Total	
	Placebo		Melatonin		N	%
	N	%	N	%		
Race						
Caucasian	45	95.7	46	95.8	91	95.8
African-American	1	2.1	1	2.1	2	2.1
Asian	1	2.1	-	-	1	1.1
Multi-racial	-	-	1	2.1	1	1.1
Ethnicity						
Hispanic/Latino	1	2.1	1	2.1	2	2.1
Non-Hispanic	46	97.9	47	97.9	93	97.9
Stage grouping						
0 (DCIS/LCIS)	6	12.8	6	12.6	12	12.7
1	15	31.9	20	41.7	35	36.8
1C	-	-	1	2.1	1	1.1
2	6	12.8	4	8.3	10	10.5
2A	11	23.4	7	14.6	18	18.9
2B	5	10.6	4	8.3	9	9.5
3A	4	8.5	4	8.3	8	8.4
3B	-	-	2	4.2	2	2.1
	Median	Range	Median	Range	Median	Range
Age at enrollment	60	38–71	58	48–70	59	38–71
Body mass index (BMI)	25.0	19.1–39.6	25.7	20.1–44.9	25.6	19.1–44.9

Table 2

Summary of estradiol (pg/ml) and IGF (ng/ml) values at baseline and at the end of the 4-month trial.

	Treatment											
	Placebo						Melatonin					
	N	Mean	S.D.	Median	Min	Max	N	Mean	S.D.	Median	Min	Max
Estradiol, pg/ml (baseline)	43	3.35	2.19	2.80	1.00	9.70	43	4.59	4.03	3.80	1.00	20.30
Estradiol, pg/ml (4-month)	43	3.39	2.25	2.80	1.00	9.50	43	4.59	3.42	3.50	1.00	15.60
IGF-1, ng/ml (baseline)	43	177.83	46.67	171.91	98.61	285.33	43	181.95	60.22	168.13	74.03	385.30
IGF-1, ng/ml (4-month)	43	173.97	44.81	169.81	99.57	270.23	43	171.83	54.30	166.36	72.50	329.87
IGFBP-3, ng/ml (baseline)	43	4232.34	753.22	4202.71	2298.82	5721.01	43	4487.67	891.07	4351.90	2086.29	6499.34
IGFBP-3, ng/ml (4-month)	43	4208.55	800.23	4250.50	2689.54	5995.15	43	4407.09	994.01	4330.23	1841.29	6875.48

	Overall					
	N	Mean	S.D.	Median	Min	Max
Estradiol, pg/ml (baseline)	86	3.97	3.29	3.20	1.00	20.30
Estradiol, pg/ml (4-month)	86	3.99	2.94	3.25	1.00	15.60
IGF-1, ng/ml (baseline)	86	179.89	53.60	169.30	74.03	385.30
IGF-1, ng/ml (4-month)	86	172.90	49.50	168.09	72.50	329.87
IGFBP-3, ng/ml (baseline)	86	4360.00	830.15	4281.68	2086.29	6499.34
IGFBP-3, ng/ml (4-month)	86	4307.82	902.55	4285.30	1841.29	6875.48

Table 3

Ratios of estradiol (pg/ml) and IGF (ng/ml) values (month-4/baseline).

Ratios (Month-4 / baseline)	Treatment												Overall					
	Placebo						Melatonin											
	N	Mean	S.D.	Median	Min	Max	N	Mean	S.D.	Median	Min	Max						
Estradiol	43	1.45	1.40	0.94	0.20	6.60	43	1.56	1.74	1.00	0.15	8.64	86	1.51	1.57	0.98	0.15	8.64
IGF-1	43	0.99	0.13	0.98	0.75	1.32	43	0.95	0.14	0.95	0.68	1.19	86	0.97	0.14	0.98	0.68	1.32
IGFBP-3	43	1.00	0.09	1.00	0.79	1.22	43	0.98	0.10	0.98	0.62	1.16	86	0.99	0.10	0.99	0.62	1.22

Table 4

Worst Grade of Toxicities / Adverse Events.

		Treatment		Total
		Placebo	Melatonin	
		N	N	N
Toxicity	Grade			
Hypertension	1 (Mild)	1	-	1
Fatigue	1 (Mild)	-	1	1
		2	1	3
		1	-	1
	2 (Moderate)	-	2	2
Insomnia	1 (Mild)	1	1	2
		1	-	1
	2 (Moderate)	-	1	1
	3 (Severe)	1	-	1
Bad dreams/nightmares	1 (Mild)	1	3	4
	2 (Moderate)	-	1	1
Chelitis	2 (Moderate)	1	-	1
Pruritus/itching	1 (Mild)	1	-	1
Hot flashes	1 (Mild)	1	-	1
	2 (Moderate)	-	1	1
	3 (Severe)	1	-	1
Dry mouth	1 (Mild)	1	-	1
Taste alteration	1 (Mild)	1	-	1
Bladder (urinary) infection	2 (Moderate)	1	-	1
Upper airway infection NOS	2 (Moderate)	1	-	1
Vaginal infection	2 (Moderate)	-	1	1
Edema: limb	1 (Mild)	1	-	1
Dizziness	1 (Mild)	-	1	1
Back pain	2 (Moderate)	1	-	1
Headache/Pain, Head	1 (Mild)	-	1	1
	2 (Moderate)	-	2	2
Pain, Middle ear	2 (Moderate)	1	-	1