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Cancer Epidemiology, Biomarkers & Prevention

Null Results in Brief

Effects of Physical Activity on Melatonin Levels in Previously Sedentary Men and Women

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Abstract

Background: The inverse association between physical activity and cancer risk may be mediated by higher melatonin levels. However, few studies have examined the effect of increased physical activity on melatonin levels.

Methods: The parent study was a randomized controlled trial that randomized 51 men and 49 women to a 12-month moderate-to-vigorous aerobic exercise intervention ("exercisers") and 51 men and 51 women to a stretching control ("controls"). Participants were of ages 40 to 75 years, and previously sedentary. Levels of the principal urinary metabolite of melatonin, 6-sulfatoxymelatonin (aMT6s), corrected for creatinine levels, were measured in spot morning urine samples by immunoassay at baseline and 12 months. Changes in levels between exercisers and controls were compared using generalized estimating equations for linear regression.

Results: We observed no statistically significant difference in the change in aMT6s levels from baseline to 12 months in exercisers compared with controls (change in aMT6s levels: exercisers, +6.5%; controls, +13%; $P = 0.66$). There was no evidence of effect modification by age, sex, or body mass index.

Conclusions: A 12-month moderate-intensity exercise intervention did not affect levels of aMT6s.

Impact: Further research needs to focus on other potential mechanisms through which physical activity may reduce the risk of cancer. *Cancer Epidemiol Biomarkers Prev; 23(8); 1696–9. ©2014 AACR.*

Introduction

Regular moderate-to-vigorous intensity physical activity lowers cancer risk (1). Possible mechanisms include decreasing sex hormones, metabolic hormones, and inflammation levels (1). Largely unexplored mechanisms include effects of melatonin (5-methoxytryptamine), a hormone secreted primarily by the pineal gland during the dark phase of the light–dark cycle (2). Physical activity may increase melatonin levels, resulting in decreased estrogen production, improved fat metabolism, and reduced cancer risk (3). Few studies have examined the effects of physical activity on melatonin (4). In the only randomized controlled trial (RCT) to date, a 16-week exercise intervention in healthy women (18–30 years) had no effect (5). To our knowledge, no studies have examined the effect of a long-term physical activity intervention. The primary aim was to determine the effect of a 12-month exercise intervention versus control on levels of the principal urinary metabolite of melatonin, 6-sulfatoxymelatonin (aMT6s), in sedentary men and women. We also investigated associations between aMT6s and changes in markers of cell proliferation (Ki67) in colon biopsies obtained at baseline and 12 months (6), and cross-sectional associations between aMT6s and levels of previously measured biomarkers, anthropometric measurements, and self-reported measures of sleep quality and duration.

Materials and Methods

This study is ancillary to the A Program Promoting Exercise and an Active Lifestyle study (http://clinicaltrials.gov/show/NCT00668161; ref. 6). Briefly, 102 men and 100 women, 40 to 75 years of age, sedentary (<90 min/wk of moderate-to-vigorous exercise in past 3 months), no history of cancer or serious illness, and <2 alcoholic beverages/day, were randomized into an exercise (*exercisers*) or control (*controls*) group. Randomization was stratified by sex, use of non-steroidal anti-inflammatory drugs, smoking status, and, among women, menopausal status and current use of

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Table 1. Correlations with baseline urinary aMT6s (ng/mg creatinine)

	Men ($n = 100$)				Women ($n = 95$)			
	Pearson correlation		Partial Pearson correlation[a]		Pearson correlation		Partial Pearson correlation[a]	
	ρ	*P*	ρ	*P*	ρ	*P*	ρ	*P*
Age, y	−0.01	0.94			−0.04	0.73		
BMI, kg/m^2	0.01	0.94	0.03	0.80	0.14	0.18	0.12	0.24
Waist circumference, cm	0.06	0.53	0.09	0.39	0.07	0.52	0.05	0.62
Hip circumference, cm	0.02	0.81	0.03	0.81	0.14	0.19	0.12	0.25
Waist-to-hip ratio	0.09	0.37	0.14	0.18	−0.07	0.53	−0.07	0.52
Total fat mass, kg[b]	0.06	0.57	0.09	0.42	0.10	0.34	0.09	0.39
Dexa% body fat[b]	0.10	0.33	0.14	0.19	0.18	0.08	0.18	0.08
Total abdominal fat, cm^2	0.05	0.64	0.10	0.34	0.15	0.13	0.14	0.17
Intra-abdominal fat, cm^2	−0.07	0.46	−0.03	0.81	0.07	0.50	0.06	0.60
Subcutaneous fat, cm^2	0.13	0.21	0.20	0.07	0.15	0.14	0.14	0.19
VO_2 maximum, mL/kg/min	0.09	0.36	0.02	0.89	−0.09	0.44	−0.10	0.33
Moderate-to-vigorous Met, min/wk	0.14	0.18	0.08	0.45	−0.10	0.33	−0.10	0.35
Steps per day	0.03	0.75	0.08	0.47	−0.04	0.69	−0.05	0.67
Energy intake, kcal[c]	0.01	0.85	0.04	0.70	−0.01	0.91	−0.01	0.92
3-A-G, ng/mL[d]	−0.09	0.36	−0.10	0.35	—	—	—	—
DHT, pg/mL[d]	−0.04	0.71	−0.04	0.71	—	—	—	—
Estradiol, pg/mL[d]	−0.06	0.53	−0.06	0.53	—	—	—	—
Free estradiol, pg/mL[d]	−0.04	0.71	−0.04	0.68	—	—	—	—
Bioavailable estradiol, pg/mL[d]	−0.04	0.71	−0.04	0.68	—	—	—	—
Testosterone, ng/dL[d]	−0.01	0.94	0.00	0.96	0.13	0.20	0.11	0.31
Free testosterone, ng/dL[d]	0.06	0.58	0.06	0.55	0.11	0.27	0.06	0.57
Bioavailable testosterone, ng/dL[d]	0.06	0.57	0.06	0.55	—	—	—	—
Prolactin, ng/mL[d]	—	—	—	—	−0.12	0.23	−0.13	0.20
Androstenedione, pg/mL[d]	—	—	—	—	0.24	0.02	0.27	0.01
DHEAS, μg/dL[d]	—	—	—	—	0.26	0.01	0.24	0.02
Insulin[d]	0.01	0.95	−0.01	0.95	0.17	0.10	0.13	0.24
Glucose, mg/dL[d]	0.02	0.81	0.02	0.85	0.03	0.79	0.04	0.69
HOMA score[d]	0.01	0.95	−0.01	0.93	0.15	0.14	0.11	0.30
SHBG, ng/mL[d]	−0.10	0.32	−0.11	0.27	−0.06	0.54	−0.02	0.88
IGFI, ng/mL[d]	0.21	0.03	0.23	0.03	0.05	0.65	0.07	0.49
IGFBP-3, ng/mL[d]	0.03	0.74	0.06	0.56	−0.01	0.91	0.00	0.98
Ratio IGFI:IGFBP-3[d]	0.22	0.03	0.22	0.03	0.05	0.66	0.06	0.55
CRP, mg/L[d,e]	−0.11	0.29	−0.13	0.21	0.13	0.23	0.08	0.53

Abbreviations: CRP, C-reactive protein; DHT, dihydrotestosterone; SHBG, sex hormone–binding globulin.

[a]Partial Pearson correlation, adjusted for age.

[b]Men, $n = 97$; women, $n = 94$.

[c]Men, $n = 95$; women, $n = 94$.

[d]Partial Pearson correlation adjusted for age and BMI.

[e]Men, $n = 96$; women, $n = 93$.

postmenopausal hormone therapy. The intervention was a 12-month program, with a goal of 60 min/d, 6 d/wk of moderate-to-vigorous aerobic exercise at 60% to 85% of maximal heart rate (determined by baseline VO_{2max}). Fasting blood and spot urine samples, colon biopsies, anthropometrics, and questionnaire data were collected at baseline and 12 months. The study was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center (Seattle, WA), and all participants signed informed consent.

aMT6s and creatinine levels were assayed from the same spot urine samples at the Biomarker Core Laboratory (Yerkes National Primate Research Center, Emory University, Atlanta, GA), using commercially available competitive ELISA kits (aMT6s: ALPCO Diagnostics; sensitivity 0.14 ng/mL, inter- and intra-batch coefficients

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variation <15%; creatinine: Sigma Diagnostics Creatinine reagents).

Statistical analysis

aMT6s was not normally distributed and was log-transformed. We assessed baseline associations with aMT6s using analysis of variance (ANOVA) to compare means between groups and Spearman partial correlation coefficient ρ, adjusted for age and body mass index (BMI), to assess baseline correlations. We compared percentage change in mean aMT6s levels from baseline to 12 months in exercisers and controls by generalized estimating equations for linear regression. Secondary analyses examined associations between adherence to the intervention and change in aMT6s adjusted for age, sex, and BMI. We assessed statistical significance at $P < 0.05$. Statistical tests were two-sided and analyses were conducted in SAS 9.1 (SAS Institute).

Results

After excluding participants with missing or extreme aMT6s levels, the analyses included 95 women (33% premenopausal; 46 exercisers and 49 controls) and 100 men (49 exercisers and 51 controls). Baseline aMT6s levels were significantly higher among women compared with men (14.4 vs. 8.0 ng/mg creatinine; $P = 0.001$). In men, aMT6s levels were positively correlated with insulin-like growth factor (IGFI; $\rho = 0.23$; $P = 0.03$) and the IGFI/IGFBP (binding protein)-3 ratio ($\rho = 0.22$; $P = 0.03$), and negatively correlated with mean Ki67 staining in colon biopsies ($\rho = -0.28$; $P = 0.01$). For women, aMT6s levels were positively correlated with androstenedione ($\rho = 0.27$; $P = 0.01$) and dehydroepiandrosterone sulfate (DHEAS; $\rho = 0.24$; $P = 0.02$). aMT6s was not associated with other metabolic hormones (Table 1) or measures of sleep quality and duration (data not shown). The exercise intervention had no effect on aMT6s levels (change in aMT6s: exercisers, +6.5%; controls, +13%; $P = 0.66$). There was no evidence of effect modification by age, sex, or BMI (Table 2). Similarly, there was no effect on aMT6s levels within subgroups defined by adherence to the intervention (data not shown).

Discussion

Physical activity is associated with lower risk of cancer (1); however, the mechanisms remain largely unknown. The effect of physical activity may be mediated by higher melatonin levels but data are limited. Results from observational studies are conflicting (4), and a short-term exercise intervention had no effect on aMT6s (5). Results from our study add to these findings and, when taken together, provide evidence, suggesting that physical activity does not substantially influence melatonin levels in either the short or long term.

Table 2. Baseline and 12-month follow-up urinary aMT6s geometric means (ng/mg creatinine), overall and within subgroups

	Baseline		12-mo Follow-up				
	Exercisers	Controls	Exercisers		Controls		
	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)	Change (%)	Mean (95%CI)	Change (%)	P^a
Overall	6.0 (4.8–7.6) ($n = 95$)	6.7 (5.3–8.3) ($n = 100$)	6.4 (5.2–7.9) ($n = 95$)	0.4 (6.5)	7.5 (6.2–9.2) ($n = 99$)	0.9 (13.1)	0.66
Age, y							
<55	7.2 (5.4–9.7) ($n = 46$)	6.4 (4.7–8.7) ($n = 54$)	6.7 (5.0–9.0) ($n = 46$)	−0.5 (−7.1)	8.0 (6.1–10.4) ($n = 53$)	1.6 (24.8)	0.18
≥55	5.1 (3.6–7.1) ($n = 49$)	7.0 (5.0–9.7) ($n = 46$)	6.1 (4.6–8.3) ($n = 49$)	1.1 (20.6)	7.0 (5.2–9.5) ($n = 46$)	0.1 (0.7)	0.29
Sex							
Men	4.9 (3.7–6.6) ($n = 49$)	5.4 (4.0–7.3) ($n = 51$)	5.2 (3.9–7.0) ($n = 49$)	0.3 (6.7)	5.7 (4.3–7.6) ($n = 50$)	0.3 (5.8)	1.00
Women	7.5 (5.3–10.6) ($n = 46$)	8.3 (6.0–11.5) ($n = 49$)	7.9 (5.9–10.6) ($n = 46$)	0.4 (5.7)	10.0 (7.8–12.8) ($n = 49$)	1.7 (20.4)	0.55
BMI, kg/m^2							
<25	7.2 (4.5–11.4) ($n = 23$)	4.6 (2.6–8.2) ($n = 19$)	7.2 (4.3–12.0) ($n = 23$)	−0.0 (−0.3)	7.7 (5.0–11.9) ($n = 19$)	3.1 (67.1)	0.17
25–29	4.7 (3.3–6.6) ($n = 32$)	6.1 (4.1–9.0) ($n = 37$)	5.2 (3.9–7.0) ($n = 32$)	0.6 (12.0)	6.9 (4.7–10.1) ($n = 37$)	0.8 (13.4)	0.96
≥30	6.7 (4.6–9.8) ($n = 40$)	8.5 (6.4–11.3) ($n = 44$)	7.1 (5.1–9.8) ($n = 40$)	0.4 (5.7)	8.1 (6.3–10.4) ($n = 43$)	−0.4 (−4.6)	0.59

[a]*P* value comparing the changes from baseline to follow-up between exercisers and controls.

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Although our results suggest possible sex-related difference in associations between aMT6s levels and metabolic hormones, and Ki67 staining, they should be interpreted cautiously as correlations were modest. The strengths of this study include the RCT design, 12-month duration, excellent adherence and low drop-out rates, and adequate power (80% power to detect a 60% relative change in aMT6s between groups).

Other potential mechanisms through which physical activity may reduce the risk of cancer need to be examined.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: S.R. Patel, S.S. Tworoger, C. Duggan
Development of methodology: C. Duggan
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A. McTiernan
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.P. Thrift, L. Xiao, S.S. Tworoger, C. Duggan
Writing, review, and/or revision of the manuscript: A.P. Thrift, S.R. Patel, S.S. Tworoger, A. McTiernan, C. Duggan
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