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ORIGINAL RESEARCH

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Relationship between physical activity, objective sleep parameters, and circadian rhythm in patients with head and neck cancer receiving chemoradiotherapy: A longitudinal study

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Abstract

Objectives: This study was developed to assess the relationship between physical activity, sleep and circadian rhythm using accelerometer and urine melatonin levels in patients with head and neck cancer (HNC). Also, this study evaluated the changes in physical activity, sleep, and circadian rhythm during the seven-week course of chemoradiotherapy.

Methods: This longitudinal study recruited 27 participants diagnosed with HNC who were planning to undergo chemoradiotherapy. Accelerometers worn for 3 days during the 1st, 3rd, and 7th weeks of chemoradiotherapy were used to assess physical activity levels (step count and metabolic equivalents [METs]) and sleep quality (total sleep time [TST], sleep onset latency [SOL], and sleep efficiency [SE]). Urine melatonin analysis was conducted using the morning void urine sample on 1st, 3rd, and 7th weeks. The change in variables during the seven weeks and the correlation between them were analyzed.

Results: During the seven weeks, trends of reduction in variables of physical activity, sleep and circadian rhythm were observed with significant decrease in step count, TST and melatonin levels. SE was found to have strong negative correlation with physical activity. TST was found to have moderate correlation with SE and step count. The variables of physical activity also showed moderate correlation among them.

Conclusion: This study concludes that higher physical activity is associated with poor SE due to increased night-time activity. There was a significant reduction in physical activity and sleep observed during seven weeks with moderate association between them. The significant circadian rhythm deregulation however showed poor association with the other variables.

Level of Evidence: 2b

KEYWORDS
chemoradiotherapy, circadian rhythm, head and neck cancer, physical activity, sleep quality

1 | INTRODUCTION

Head and neck cancer (HNC) is one of the 10 most common cancers in the world with increased burden in low and middle income countries.[1] In India, HNC is the third most prevalent cancer and accounts for 30% of the total cancer incidence.[2] Patients with HNC are known to have a sedentary behaviour.[3] Reduced physical activity which is one of the major burdens faced by patients with HNC is associated with survival and recovery from cancer.[4,5] Physical activity assessed in patients with cancer undergoing treatment has shown that patients receiving chemoradiotherapy have a higher chance of physical activity reduction when compared to radiation alone, surgery or other forms of treatment.[6] According to the American College of Sports Medicine (ACSM) Guidelines, a minimum of 150 min of moderate or 75 min of vigorous intensity physical activity is necessary in a week, along with 2 days of weight training. The same guidelines have been adopted by the American Cancer Society's Head and Neck Cancer Survivorship Guidelines.[7] Physical activity levels when assessed in patients with HNC and compared to patients with other cancers have shown to be lower than the recommended values and there is a decline noted during the treatment for primary tumor.[8] Also, low physical activity status is shown to be associated with stage 2 to stage 4 of HNC.[9] Physical activity has shown to be directly proportional to the subjective sleep scores in patients with HNC.[10,11]

Patients with HNC during the course of primary treatment experience a spectrum of symptoms which include fatigue, sleep disturbances, pain, xerostomia, oral mucositis, sarcopenia, and emotional disturbances which reduce the quality of life. Sleep disturbance is one of the common devastating symptoms in patients with HNC having a prevalence of 45% during the course of treatment.[12] In patients with cancer, sleep disturbance is influenced by factors such as age, recent cancer surgery, obstructive sleep apnea, leg restlessness, fatigue, use of sedatives and mood fluctuations, among other things.[13]

Sleep being a physiological function, is also controlled by the internal body clock or the circadian rhythm. A molecular level study reports dysregulation noted in the regulatory genes of the circadian rhythm in patients with HNC.[14] Since melatonin is synthesized by pineal glands when there is no exposure to light,[15] first morning void urine sample analysis can be a noninvasive and a convenient way to measure melatonin levels in the body without hampering the sleep cycles of the patients. A number of factors including physical activity is known to have an influence on circadian rhythm. However, there is lack of evidence evaluating the relationship between physical activity and objectively measured sleep parameters.

The relationship between physical activity, objective sleep parameters, and circadian rhythm previously studied in lung cancer survivors showed that robust values of circadian rhythm and light intensity physical activity has found to have a positive effect on sleep parameters.[16] However, there is lack of evidence regarding this relationship specifically during the course of treatment in the HNC population. This study was initiated with the objective of assessing the relationship between the physical activity levels, sleep parameters and circadian rhythm obtained objectively using a tri-axial accelerometer and urine melatonin levels. This study also evaluated the changes in the physical activity, sleep parameters, and circadian rhythm levels longitudinally during the course of chemoradiotherapy.

2 | MATERIALS AND METHODS

2.1 | Participants and setting

This study followed a longitudinal design and was conducted in a tertiary care university hospital. The study began after obtaining the ethical clearance from the Institutional Ethics Committee (IEC KMC MLR 11-19/569). The patients referred by the radiation oncologist were screened for the following inclusion for recruitment through convenient sampling—patients diagnosed with HNC stage 3, 4A, and 4B, patients planning to undergo chemoradiotherapy irrespective of their operative status and having an Eastern Cooperative Oncology Group (ECOG) score of <2. Whereas patients with prior diagnosed sleep disorders and undergoing treatment for the same, reduced alertness and non-ambulatory status were excluded from the study. A total of 27 patients were screened and included in the study; 21 participants completed the study. Six participants could not be followed up for 7 weeks due to death ($n = 4$) or discontinuation of the chemoradiotherapy due to personal reasons ($n = 2$). Participants provided informed consent and were assessed in the 1st, 3rd and 7th weeks of chemoradiotherapy.

2.2 | Study materials

Actigraph accelerometers are noninvasive, light weight devices which can be worn for long periods which detect physical activity and sleep parameters objectively. Measurement of physical activity in this study was determined using the step count and METs assessed by accelerometers. Objective sleep parameters like total sleep time (TST), sleep efficiency (SE), and sleep-onset latency (SOL) were assessed to determine the quality of sleep of the participants.

Urine melatonin analysis was performed using Elabscience ELISA kit. In urine samples, 6-hydroxymelatonin sulfate, a primary metabolite of melatonin is an indicator of melatonin concentration.[17]

2.3 | Procedure

Physical activity was objectively measured using Actigraph accelerometers worn on the right anterior superior iliac spine (ASIS) by the participants for the initial 3 days of the 1st week and last 3 days of the 3rd and 7th week. The parameters assessed for indicating physical activity included average step count and metabolic equivalents (METs).

Sleep quality was objectively assessed by Actigraph accelerometer worn on the right ASIS by the participants for the initial 3 days of the 1st week and last 3 days of the 3rd and 7th weeks. The parameters assessed were—sleep efficiency (SE), total sleep time (TST), and sleep onset latency (SOL). TST is the total duration of sleep during the 24 h, measured in minutes. SE is the percentage of total sleep time to the total time spent in bed. SOL is the time taken to fall asleep once in bed and is measured in minutes. Along with the objective values, subjective bedtime and wake up time were obtained from the participants on the days of accelerometer analysis.

Circadian rhythm was assessed by melatonin levels in the first morning void urine samples collected in the 1st, 3rd, and 7th week of chemoradiotherapy. The samples were stored at a temperature of -20°C and the analysis was performed using Elabscience ELISA kit.

2.4 | Data analysis

The accelerometer data was obtained using Actilife6 software. The data of all the variables were entered on SPSS software for analysis and checked for normal distribution. The demographic data of the participants was summarized as percentage (except age and BMI reported as mean and SD). Repeated measures ANOVA was performed for variables which followed normal distribution and Friedman test was performed for variables which did not follow normal distribution. Spearman's rank correlation was performed to determine the correlation between the variables. The correlation value of 0.01 to 0.19 was considered as negligible correlation, 0.2 to 0.29 as weak, 0.3 to 0.39 as moderate, 0.40 to 0.69 as strong correlation, and >0.7 as very strong correlation.

3 | RESULTS

3.1 | Participant characteristics

The demographics of the participants with the details of the disease stage presented in Table 1. The age of the included 27 participants ranged from 37 to 70 years with mean age of 54.7 years. Amongst the participants 85.2% were males and 14.8% were females. Buccal mucosa was the site of involvement in significant minority (40%) of the participants. Other cancer sites included tongue, salivary gland, oral cavity, tonsil, pharynx and epiglottis. Of the included participants, 40.8% were diagnosed with stage 3 and 50.2% had stage 4 of HNC. The mean BMI of the participants at baseline was 21.01. However, over the 7 weeks of chemoradiotherapy, significant reduction of BMI to 18.3 was noted ($p = 0.07$). Out of the 27 participants, 21 completed the 7 weeks follow up.

TABLE 1 Characteristics of participants

Variables	Mean	SD	Percentage (*n*)
Age	54.7	10.3	
BMI	21	3.5	
Gender (M/F)			85.2(23)/14.8(4)
Cancer stage			
3			40.8 (11)
4			59.2 (16)
Cancer site			
Buccal mucosa			40 (11)
Tongue			18.5(5)
Pharynx			18.5 (5)
Tonsil			11.1 (3)
Oral cavity			3.7 (1)
Epiglottis			3.7 (1)
Salivary gland			3.7 (1)

3.2 | Change in physical activity, objective sleep parameters, and circadian rhythm

The changes in physical activity, sleep parameters, and circadian rhythm is presented in Table 2. Physical activity was assessed by the step count indicated that average step count reduced statistically over a period of 7 weeks from 3883 steps/day to 2300 steps/day in the participants, indicating reduction in physical activity levels during the course of treatment ($p = 0.001$). There was a reduction in the METs recorded over the 7-week duration from 1.02 to 1 which however failed to show statistical significance ($p = 0.38$).

The SOL, SE, and TST were calculated using the accelerometer data and the self-reported sleep time during the 3 days of the 1st, 3rd, and 7th weeks of chemoradiotherapy. The SOL calculated over the period of 7 weeks showed no significant change with median of 0 min indicating that the participants had no difficulty in initiation of sleep. There was a mild reduction in the SE noted from week 1 to 7 (97.2-97%), but however this change was not statistically significant ($p > 0.5$). TST was found to reduce significantly over the period of 7 weeks from 459.8 to 381.1 min ($p < 0.001$). The sleep parameters hence showed that there is reduction in the total sleep duration, with mild reduction in the efficiency of sleep. However, there is no change in the time taken for initiation of sleep.

Circadian rhythm assessed by the melatonin analysis of the first morning void urine samples during the 1st, 3rd, and 7th weeks revealed reduction of urine melatonin to 76.35 pg/ml by the end of 7 weeks when compared to baseline (103.67 pg/ml). However, the change was marginally significant ($p = 0.05$). Further analysis from week 1 to 3 showed a significant reduction in urine melatonin value indicating a marked deregulated circadian rhythm in the initial 3 weeks of chemoradiotherapy ($p = 0.004$).

TABLE 2 Change in the physical activity, circadian rhythm, and sleep parameters during 1st, 3rd, and 7th weeks

			Week 1		Week 3		Week 7		
Variable	Outcome measure	*N*	Mean	SD	Mean	SD	Mean	SD	*p* value
Physical activity	METs	21	1.022	0.07	1.02	0.053	1.0	0.012	0.39
Sleep parameters	TST (min)	21	459.84	62.47	421.06	32.44	381.14	32.04	<0.001[a]
Variable	Outcome measure	*N*	Median	IQR	Median	IQR	Median	IQR	*p* value
Physical activity	Step count (steps/day)	21	3883.0	(2609, 6015)	3308.0	(2040, 4162)	2300.0	(1630, 2979)	0.001[a]
Sleep parameters	SE (%)	21	97.2	(95.85, 98.85)	97.4	(95.13, 98.74)	97.0	(94.95, 98.16)	0.5
	SOL (min)	21	0.0	(0.0,0.15)	0.0	(0.0,0.16)	0.0	(0.0-0.00)	0.000
Circadian rhythm	Melatonin (pg/ml)	21	103.31	(57.48, 188.31)	49.4	(40.67, 119.32)	76.35	(34.85, 116.94)	0.05[b]

Abbreviations: METs, metabolic equivalents; SE, sleep efficiency; TST, total sleep time.
[a]Statistically significant.
[b]Marginally significant.

TABLE 3 Correlation (*r*) between physical activity and sleep quality, circadian rhythm

	TST			SE			Melatonin		
	Week 1	Week 3	Week 7	Week 1	Week 3	Week 7	Week 1	Week 3	Week 7
Step count	−0.24	0.02	0.35	−0.65[a]	−0.31	−0.02	0.26	0.03	−0.17
METs	−0.31	0.24	0.13	−0.24	0.04	0.06	−0.15	−0.02	−0.08

Abbreviations: METs, metabolic equivalents; SE, sleep efficiency; TST, total sleep time.
[a]Statistically significant.

TABLE 4 Correlation (*r*) between sleep quality and circadian rhythm, physical activity

	Melatonin			Step count			METs		
	Week 1	Week 3	Week 7	Week 1	Week 3	Week 7	Week 1	Week 3	Week 7
TST	−0.02	−0.21	−0.12	−0.24	0.02	0.35	−0.31	0.24	.13
SE	−0.01	0.23	0.04	−0.65	−0.31	−0.02	−0.24	0.04	0.06

Abbreviations: METs, metabolic equivalents; SE, sleep efficiency; TST, total sleep time.

TABLE 5 Correlation (*r*) between circadian rhythm and physical activity, sleep

	Step count			METs			TST			SE		
	Week 1	Week 3	Week 7	Week 1	Week 3	Week 7	Week 1	Week 3	Week 7	Week 1	Week 3	Week 7
Melatonin	0.26	0.03	−0.17	−0.15	−0.02	−0.08	−0.02	−0.21	−0.12	−0.01	0.23	0.04

Abbreviations: METs, metabolic equivalents; SE, sleep efficiency; TST, total sleep time.

3.3 | Relationship between physical activity, objective sleep parameters, and circadian rhythm

Correlation between physical activity, sleep parameters, and circadian rhythm during the 1st, 3rd, and 7th weeks is denoted in the Tables 3–5. The correlation between the two physical activity and two sleep quality variables are presented in Table 6.

At baseline, SE was found to have strong negative correlation with step count ($r = -0.65$, $p < 0.0001$), indicating that participants with efficient sleep had less physical activity levels. At the end of 3 weeks, there was still a moderate negative correlation observed between SE and step count ($r = -0.31$, $p = 0.15$). There was a moderate correlation noted between METs and physical activity levels ($r = 0.39$, $p = 0.06$). At the end of 7 weeks, TST was found to be moderately correlated to step count ($r = 0.35$, $p = 0.12$) and SE ($r = 0.31$, $p = 0.17$).

4 | DISCUSSION

This study was conducted with an aim to determine the relationship between physical activity, sleep quality and circadian rhythm in patients

TABLE 6 Correlation (*r*) between the variables of sleep and physical activity

	Week 1	Week 3	Week 7
TST and SE	0.08	0.01	0.31
Step count and METs	0.23	0.39	−0.03

Abbreviations: METs, metabolic equivalents; SE, sleep efficiency; TST, total sleep time.

with HNC, and to check their change during chemoradiotherapy. To the best of our knowledge this is the first study to evaluate this relationship and change in the individual variables in HNC population during chemoradiotherapy objectively. With a high incidence and long-term prevalence of sedentary behavior and sleep disturbances in HNC population, it is important to analyze the factors affecting and influencing them. Although, there is evidence regarding the relationship in lung cancer survivors, due to lower physical activity levels in patients with HNC and sleep disturbances being associated to region specific factors such as Obstructive Sleep Analysis (OSA) and disturbance due to the presence of tracheostomy there is a need to assess this relationship in HNC population.[18]

The results of this study showed that patients with HNC receiving chemoradiotherapy had low physical activity levels not only during the course of treatment but even at baseline prior to initiation of chemoradiotherapy. Overall, there was a lower physical activity noted when compared to the physical activity guidelines by ACSM and ACS with 7.4% achieving 10 000 steps/day target at baseline and 3.7% by the end of 3 weeks. A low MET value observed with reduction during chemoradiotherapy shows that patients with HNC have a sedentary behavior which is line with the findings of a systematic review.[8] This could be due to fatigue, sarcopenia, reduced and difficulty in food intake and xerostomia observed in these patients during the course of treatment. Unlike expected, the average step count in this study was found to be negatively correlated to sleep efficiency. The possible explanation for this could be increased activity during the night which was associated with reduced SE. During the course of chemoradiotherapy reduced step count was found to be associated with reduced METs, showing overall reduction in the physical activity of the patients.

Results also showed that participants had reduction in the average duration of sleep to 381.1 min by the end of primary treatment which is comparable with the lung cancer survivors who had TST of 390 min.[16] This implies that patients undergoing chemoradiotherapy had drastic reduction in the total sleep time during treatment. A SOL of 13 min was reported in newly diagnosed patients with HNC as reported by subjective sleep scores.[11] However, this was not comparable with the low SOL observed in this study, as 48.1% of the study participants had undergone surgery prior to the chemoradiotherapy regime. A SOL of 0 min suggested that the participants had no difficulty in initiation of sleep. This could be related to the participants going to bed at their convenience and not having a set bedtime in the study protocol. This also could be attributed to the recording of no activity when lying down by the accelerometer or the recall bias of the participants regarding the bedtime. The downward trend in the SE observed in this study can be attributed to the increased wake time after sleep onset along with the sleep duration. In addition, this study also showed a trend of decrease in TST being associated with reduction in SE suggesting that patients with HNC have difficulty in maintenance of sleep as the chemoradiotherapy cycles progress.

The decrease in the urine melatonin values by the end of chemoradiotherapy as compared to the baseline indicates dysregulation of the circadian rhythm during the course of chemoradiotherapy in patients with HNC. Also, the trend highlights a rapid reduction in melatonin levels by the end of 3rd week. This indicates that circadian rhythm dysregulation can possibly be an early side effect experienced by patients with HNC during chemoradiotherapy. Though patients with prior diagnosed sleep disorders and undergoing treatment for the same were excluded in the study, the other factors which could affect the circadian rhythm include nutrition status and light exposure.[19,20]

Since reduced physical activity in patients with HNC is associated with prognosis and survival rate, it is essential for clinicians to undertake strategies to improve physical activity levels in this population. Studies have shown exercise interventions for maintaining physical activity to be safe, feasible, and effective in outcomes other than sleep and circadian rhythm.[21-23] Hence, there is need for future studies to evaluate the effect of physical activity intervention on circadian rhythm and sleep parameters.

The strength of this study includes the use of objective measures such as Actigraph accelerometer values and melatonin analysis for determining sleep, physical activity and circadian rhythm. This study also followed up the patients with HNC throughout the course of chemoradiotherapy and addressed the change at three time periods over seven weeks.

Future studies need to include higher sample size and subgroup analysis based on cancer site, stage, surgical status, and presence of tracheostomy.

5 | CONCLUSION

This study concludes that higher step count was associated with lower SE in patients with HNC receiving chemoradiotherapy possibly due to increased nighttime activity. Also, variables of sleep showed moderate association with physical activity. However, there is need for further studies with higher sample size to confirm these findings. In addition, there is reduction in physical activity, sleep quality, and circadian rhythm observed in patients with HNC during chemoradiotherapy with significant reduction in TST, melatonin levels, and step counts.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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