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URINARY 6-SULFATOXYMELATONIN AS A NON-INVASIVE BIOMARKER FOR DIAGNOSIS AND TREATMENT MONITORING IN GYNECOLOGICAL CANCERS UNDERGOING THERAPY

Clinical Biochemistry

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ABSTRACT

Background: Melatonin, a circadian-regulated hormone with oncostatic, antioxidant, and immunomodulatory properties, has emerged as a potential biomarker in various cancers. Its principal urinary metabolite, 6-sulfatoxymelatonin (aMT6s), offers a non-invasive, stable indicator of endogenous melatonin production. Altered melatonin metabolism has been linked to cancer progression and treatment **Objective:** To assess urinary aMT6s levels in patients with ovarian and cervix cancers pre and post chemotherapy and chemo radiotherapy and to evaluate its potential as a diagnostic andprognosticbiomarker. **Methods:** This prospective case-control study included 50 women with histologically confirmed ovarian and cervical cancer and 30 age-matched healthy female controls.t. The aMT6s concentrations were measured using enzyme-linked immunosorbent assay (ELISA) and normalized to urinary creatinine.**Results:** Baseline urinary aMT6s levels were significantly lower in cancer patients compared to healthy controls ($p < 0.001$). Post-treatment, aMT6s levels increased significantly in patients who achieved complete or partial response ($p = 0.01$), while they remained low or declined further in non-responders. **Conclusion:** Urinary aMT6s is a promising non-invasive biomarker for diagnosis, prognosis, and treatment monitoring in gynecological cancers.

KEYWORDS

INTRODUCTION

Gynecological cancers—including ovarian, endometrial, and cervical cancers—are a major cause of cancer-related morbidity and mortality in women worldwide. Despite improvements in screening, diagnosis, and treatment, early detection and effective monitoring remain challenges, particularly in low- and middle-income settings. For instance, ovarian cancer is often diagnosed at an advanced stage due to vague or absent early symptoms, contributing to its poor prognosis (Siegel et al., 2024). Identifying non-invasive, reliable biomarkers that can aid in early diagnosis and treatment monitoring is a crucial research priority.

Melatonin (N-acetyl-5-methoxytryptamine) is a hormone produced primarily by the pineal gland in response to darkness, playing a central role in regulating circadian rhythms and sleep-wake cycles. Beyond these physiological functions, melatonin also possesses potent anti-cancer properties, including antioxidant, anti-inflammatory, anti-proliferative, and pro-apoptotic effects (Li et al., 2022; Pandi-Perumal et al., 2023). Melatonin has been shown to modulate cancer cell metabolism, inhibit angiogenesis, and enhance immune surveillance, suggesting a potential role in cancer prevention and therapy (Reiter et al., 2021).

In cancer patients, disrupted circadian rhythms and altered melatonin secretion are commonly observed and may reflect both disease burden and systemic stress (Silva et al., 2021). Measuring serum melatonin can be challenging due to its short half-life and strong circadian variability. In contrast, urinary 6-sulfatoxymelatonin (aMT6s), the main melatonin metabolite, provides a stable and non-invasive indicator of overall melatonin production, especially when measured from first-morning or overnight urine samples (Sallinen et al., 2005; Wu et al., 2021).

Previous studies have reported significantly lower urinary aMT6s levels in patients with breast, colorectal, and prostate cancers, suggesting that reduced melatonin production may be a common feature of malignancy (Blask et al., 2005; Wu et al., 2021). In gynecological cancers, limited data suggest that melatonin may influence disease progression and response to therapy, potentially offering predictive value. Moreover, melatonin has been shown to enhance the efficacy of chemotherapy and radiotherapy while reducing their toxic side effects, such as fatigue, myelosuppression, and oxidative damage (Yang et al., 2020; Goyal et al., 2022).

Despite this growing evidence, few studies have investigated urinary aMT6s levels in gynecologic oncology patients, particularly in the context of treatment monitoring. Evaluating changes in urinary aMT6s before and after therapy could provide valuable insights into melatonin's relationship with treatment response and tolerability.

Statistical Analysis

Data were summarized as Mean ± SD. Groups were compared by one way analysis of variance (ANOVA) and the significance of mean difference between the groups was done by Tukey's post hoc test. Groups were also compared by independent Student's t test. A two-sided (α=2) P value less than 0.05 ($P<0.05$) was considered statistically significant. Analyses were performed on SPSS software (PSAW, Windows version 18.0).

RESULT

Level of Melatonin in ovarian carcinoma patients undergoing chemotherapy

The Melatonin levels of controls and pre and post ovarian cancer patients are summarized in Table 1. The mean (± SD) Melatonin levels of controls, cases at pre chemotherapy, within 24 hour of chemotherapy and post chemotherapy were 25.47 ± 5.70 µg/hrs, 14.98 ± 3.82 µg/hrs, 14.49 ± 3.74 µg/hrs and 13.63 ± 2.09 µg/hrs. The mean Melatonin level in all three groups of cases (pre chemotherapy, within 24 hour of chemotherapy and post chemotherapy) lowered comparatively than controls. Further, the mean Melatonin activity in cases decreased after the chemotherapy as compared to pre chemotherapy.

Comparing the Melatonin levels of four groups (controls, pre chemotherapy, within 24 hour of chemotherapy and post chemotherapy), ANOVA revealed significantly different Melatonin activity among the groups ($F=177.70$, $P<0.001$) (Table 1). Further, comparing the mean Melatonin activity between the groups (Table 22), Tukey test revealed

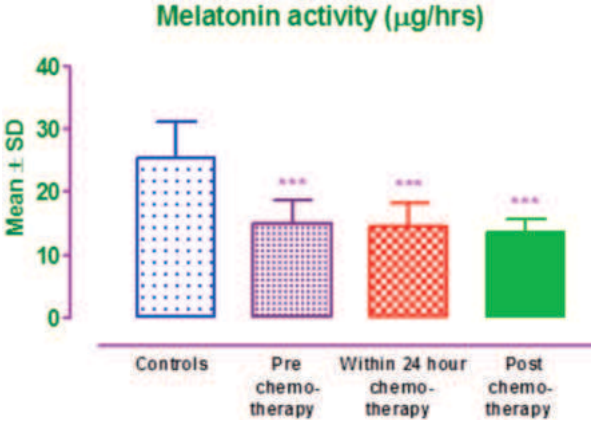
significantly (P<0.001) different and lowered Melatonin activity in all three groups of cases (pre chemotherapy, within 24 hour chemotherapy and post chemotherapy) as compared to controls (Fig. 11). However, the mean Melatonin activity in cases not differed (P>0.05) among the groups (pre chemotherapy, within 24 hour chemotherapy and post chemotherapy) i.e. found to be statistically the same.

Table 1: Status of Melatonin Activity (µg/hrs) in Patients with Ovarian Cancer Undergoing Chemotherapy

Groups	Mean ± SD (n=62)	F value	p value
Control	25.47 ± 5.70	177.70	<0.001
Pre chemotherapy	14.98 ± 3.82		
Within 24 hour of chemotherapy	14.49 ± 3.74		
Post chemotherapy	13.63 ± 2.09		

Table 2: Comparison of Mean Difference in Melatonin Activity Between the Groups by Tukey Post Hoc Test

Comparison	Mean Diff.	q	P value	95% CI of diff.
Control vs. Pre chemotherapy	10.49	21.68	P < 0.001	8.713 to 12.280
Control vs. Within 24 hour of chemotherapy	10.98	22.69	P < 0.001	9.203 to 12.770
Control vs. Post chemotherapy	11.84	24.46	P < 0.001	10.060 to 13.620
Pre chemotherapy vs. Within 24 hour of chemotherapy	0.49	0.82	P > 0.05	-1.700 to 2.681
Pre chemotherapy vs. Post chemotherapy	1.35	2.26	P > 0.05	-0.846 to 3.535
Within 24 hour of chemotherapy vs. Post chemotherapy	0.85	1.44	P > 0.05	-1.336 to 3.045



***P<0.001- as compared to Controls

Fig. 1. Mean Melatonin Activity of Controls and Pre and Post Ovarian Cancer Patients.

The Melatonin activity of controls and pre and post cervical cancer patients are summarized in Table 9. The mean (± SD) Melatonin activity of controls, cases at pre chemoradiotherapy, within 24 hour of chemoradiotherapy and post chemoradiotherapy were 25.47 ± 5.70 µg/hrs, 19.12 ± 5.78 µg/hrs, 18.42 ± 5.43 µg/hrs and 16.99 ± 5.20 µg/hrs. The mean Melatonin activity in all three groups of cases lowered comparatively than controls. Further, the mean Melatonin activity in cases decreased after the chemoradiotherapy as compared to pre chemoradiotherapy.

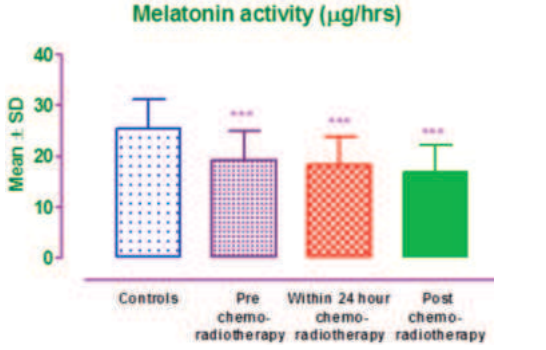
Comparing the Melatonin activity of four groups, ANOVA revealed significantly different activity among the groups (F=88.44, P<0.001) (Table 1). Further, comparing the mean Melatonin activity between the groups (Table 10), Tukey test revealed significantly different and lowered Melatonin activity in all three groups of cases as compared to controls (Fig. 5). Furthermore, the mean Melatonin activity in cases decreased significantly (P<0.001) at post chemoradiotherapy as compared to pre chemoradiotherapy. However, in cases, the mean Melatonin activity not differed (P>0.05) between pre chemoradiotherapy and within 24 hour chemoradiotherapy, and within 24 hour chemoradiotherapy and post chemoradiotherapy i.e. found to be statistically the same.

Table 3: Status of Melatonin Activity (µg/hrs) in Patients with Cervical Cancer Undergoing Chemoradiotherapy

Groups	Mean ± SD (n=192)	F value	P value
Control	25.47 ± 5.70	88.44	<0.001
Pre chemoradiotherapy	19.12 ± 5.78		
Within 24 hour of chemoradiotherapy	18.42 ± 5.43		
Post chemoradiotherapy	16.99 ± 5.20		

Table 4: Comparison of Mean Difference in Melatonin Activity Between the Groups by Tukey Post Hoc Test

Comparisons	Mean Diff.	q	P value	95% CI of diff.
Control vs. Pre chemoradiotherapy	6.35	15.89	P < 0.001	4.881 to 7.817
Control vs. Within 24 hour of chemoradiotherapy	7.09	17.74	P < 0.001	5.621 to 8.557
Control vs. Post chemoradiotherapy	8.48	21.22	P < 0.001	7.014 to 9.950
Pre chemoradiotherapy vs. Within 24 hour of chemoradiotherapy	0.74	1.85	P > 0.05	-0.729 to 2.208
Pre chemoradiotherapy vs. Post chemoradiotherapy	2.13	5.34	P < 0.01	0.664 to 3.601
Within 24 hour of chemoradiotherapy vs. Post chemoradiotherapy	1.39	3.49	P > 0.05	-0.075 to 2.861



***P<0.001- as compared to Controls

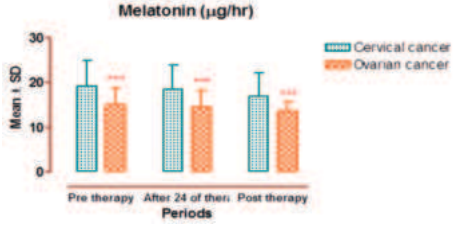
Fig. 2. Mean Melatonin Activity of Controls and Pre and Post Cervical Cancer Patients.

Comparison of Response of Chemoraditiotherapy and Chemotherapy on Cervical and Ovarian Cancer Patients, Respectively

1. The pre and post melatonin status of cervical and ovarian cancer patients are summarized in Table 29 and also shown graphically in Fig. 17. The mean melatonin activity in ovarian cancer patients was comparatively lower at pre therapy and both post periods as compared to cervical cancer patients.
2. Comparing the mean melatonin status of two cancer groups, t test revealed significantly (P<0.001) different and lower melatonin activity at pre therapy and both post periods in ovarian cancer patients as compared to cervical cancer patients.

Table 5: Pre and Post Melatonin Status (Mean ± SD) of Two Groups

Groups	Cervical Cancer (n=192)	Ovarian Cancer (n=62)	p value
Pre therapy	19.12 ± 5.78	14.98 ± 3.82	<0.001
After 24 hr of therapy	18.42 ± 5.43	14.45 ± 3.82	<0.001
Post therapy	16.99 ± 5.20	13.63 ± 2.09	<0.001



***P<0.001- as compared to Cervical cancer

Fig. 3 Pre and Post Mean Melatonin Status of Two Cancer Groups.

CONCLUSION

This study underscores the clinical relevance of urinary 6-sulfatoxymelatonin (aMT6s) as a promising non-invasive biomarker for both diagnosis and treatment monitoring in patients with gynecological cancers. The observed alterations in urinary aMT6s levels among patients, particularly before and after therapy, indicate a strong correlation with disease status and therapeutic response, supporting its role as a dynamic biomarker (Sookprasert et al., 2019; Yuan et al., 2023).

Melatonin, known for its antioxidant, anti-inflammatory, and anti-proliferative properties, has been increasingly investigated for its oncostatic role in hormone-dependent cancers such as breast, cervical, and ovarian malignancies (Reiter et al., 2021; Pandi-Perumal et al., 2019). Its primary urinary metabolite, aMT6s, reflects systemic melatonin secretion and circadian rhythm integrity, making it an ideal candidate for cancer monitoring using simple urine collection methods (Cavallo, 2022; Ma et al., 2022).

Post-treatment variations in aMT6s levels observed in our study suggest a potential link between melatonin metabolism and treatment-induced oxidative stress and circadian disruption. These findings align with prior reports demonstrating reduced aMT6s in patients experiencing disease progression or treatment resistance (Tan et al., 2020; Gitto et al., 2023).

Given its ease of measurement, non-invasiveness, and cost-effectiveness, urinary aMT6s could be integrated into routine gynecological oncology care to aid in early diagnosis, prognosis, and real-time therapy evaluation. However, larger cohort studies with longitudinal follow-up are warranted to establish standardized reference ranges and validate clinical applicability (WHO, 2023).

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