RESEARCH ARTICLE

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Targeting Side Effects Associated with Androgen Deprivation Therapy Using Melatonin: A Randomized Trial on Hot Flashes and Sexual Health in Prostate Cancer Patients

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Abstract

Objective: The aim of this study was to examine melatonin as a potential adjunct therapy for managing treatment-related symptoms in prostate cancer patients, particularly those undergoing androgen deprivation therapy (ADT). **Methods:** In light of the increasing incidence of prostate cancer among younger males, this randomized, double-blind, placebo-controlled clinical trial was conducted at the Hematology-Oncology Center of Omid Hospital in Isfahan, Iran, between October 2019 and October 2020. Forty-one prostate cancer patients experiencing hot flashes or sexual dysfunction due to ADT were randomly assigned to receive either melatonin (3 mg twice daily) or a placebo for four weeks. Symptom assessment was performed using the Hot Flash Diary, the International Index of Erectile Function (IIEF), and the Functional Assessment of Cancer Therapy–Prostate (FACT-P) questionnaire. **Result:** The results showed a statistically significant improvement in FACT-P scores within the melatonin group ($P < 0.05$), while erectile function scores increased modestly in both groups without reaching statistical significance ($P > 0.05$). The most pronounced effect was observed in the reduction of the frequency of mild hot flashes in the melatonin group, with significant improvements noted by week four ($P < 0.05$). Melatonin was well tolerated, with no clinically significant adverse events reported. These findings suggest that melatonin may effectively alleviate vasomotor symptoms and enhance the quality of life in prostate cancer patients undergoing ADT. However, its impact on sexual function remains inconclusive. **Conclusion:** Further large-scale, long-term studies incorporating mechanistic endpoints are needed to validate these findings and inform clinical guidelines for melatonin use in supportive prostate cancer care.

Keywords: Melatonin- Prostate Cancer- Oncology- Androgen deprivation therapy- Sexual dysfunction

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Introduction

Prostate cancer is the second most commonly diagnosed malignancy among men worldwide and ranks fifth in cancer-related mortality [1]. Its global burden has risen sharply over the past three decades, with over 10 million cases reported in 2021 an increase of 188% since 1990 [1]. Traditionally considered a disease of aging, prostate cancer has been predominantly associated with men over 65. However, recent epidemiological trends reveal a concerning rise in incidence among younger men, including those under 55, with distant-stage diagnoses increasing by up to 6% annually in this group [2]. This shift challenges long-standing assumptions about age-related risk and underscores the need for earlier and more inclusive screening strategies.

The proliferation and survival of prostate cancer cells are strongly influenced by androgens, particularly testosterone, due to the intrinsic androgen sensitivity of these malignant cells. Central to this process is the androgen receptor (AR) signaling pathway, which, upon activation by testosterone or dihydrotestosterone, regulates gene transcription and drives disease progression. This reliance on androgen signaling forms the basis for androgen deprivation therapy (ADT), a cornerstone in the management of advanced prostate cancer. ADT aims to suppress circulating testosterone levels through either surgical orchiectomy or chemical castration using gonadotropin-releasing hormone (GnRH) agonists or antagonists [3, 4].

While effective in slowing tumor progression, ADT disrupts the hypothalamic-pituitary-gonadal axis, leading to hypogonadism and a range of side effects including hot flashes, reduced libido, erectile dysfunction, and

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gynecomastia. These symptoms often emerge early in treatment and can significantly impair quality of life. Moreover, testosterone deficiency adversely affects metabolic health, increasing the risk of cardiometabolic complications. Sexual dysfunction is particularly pronounced in younger patients, although recovery tends to be more rapid following cessation of therapy [5, 6].

Various pharmacologic agents have been explored to manage ADT-induced vasomotor symptoms, particularly hot flashes. Non-hormonal treatments such as neurokinin-3 receptor antagonists (e.g., fezolinetant), antidepressants (e.g., venlafaxine, paroxetine), gabapentin, and clonidine have shown variable efficacy and are often used off-label. Given the limitations of these therapies, alternative agents such as melatonin warrant investigation [7, 8].

Melatonin, a hormone produced by the pineal gland, is widely recognized for its role in regulating circadian rhythms and sleep. As a dietary supplement, it has demonstrated benefits in managing sleep disturbances, mood disorders, and treatment-related side effects in cancer patients. Beyond its chronobiotic effects, melatonin exhibits antioxidant and anti-inflammatory properties and may enhance aspects of sexual performance [9- 10]. It has also been proposed as a non-hormonal adjunct for managing menopausal symptoms and erectile dysfunction in men undergoing ADT [10- 13].

A randomized, double-blind, placebo-controlled trial previously demonstrated that melatonin supplementation (6 mg daily for four weeks) significantly improved sleep quality in men receiving ADT. Although the primary focus was on mood and sleep disturbances, these improvements may indirectly alleviate vasomotor symptoms such as night sweats and hot flashes [13]. Additionally, a study by Ghoniem et al. [12] found that low serum melatonin levels were significantly associated with the presence and severity of erectile dysfunction, suggesting a potential protective role mediated by its antioxidant and anti-inflammatory effects.

Given its favorable safety profile and multifaceted therapeutic potential, melatonin may offer a safe and cost-effective strategy to improve quality of life in men undergoing ADT. This study aims to evaluate the efficacy of melatonin in mitigating ADT-induced side effects specifically hot flashes and sexual dysfunction through a randomized, double-blind, placebo-controlled clinical trial.

To assess the therapeutic potential of melatonin in mitigating ADT-induced side effects specifically hot flashes and sexual dysfunction in prostate cancer patients, through a randomized, double-blind, placebo-controlled clinical trial. The study aims to determine whether melatonin, as a non-hormonal adjunct, can improve vasomotor symptoms and sexual health outcomes, thereby enhancing overall quality of life in men undergoing ADT.

Materials and Methods

This placebo-controlled, double-blind, randomized clinical trial was conducted over a one-year period, from October 2019 to October 2020, at the Hematology-Oncology Center of Omid Hospital in Isfahan, Iran. Omid Hospital is a renowned tertiary care institution affiliated with Isfahan University of Medical Sciences, specializing in the treatment of cancer and its associated complications. The trial was conducted in accordance with the principles of Good Clinical Practice (GCP) guidelines and adhered to all applicable ethical standards and regulatory requirements.

Study Participants

The study enrolled individuals aged 18 years and older who had been diagnosed with advanced metastatic or non-metastatic prostate cancer and were undergoing ADT. Inclusion criteria required participants to self-report sexual dysfunction or to have experienced a minimum of four episodes of hot flashes per week during the past month.

Exclusion criteria included any of the following conditions: history of liver, heart, or kidney failure of any grade; uncontrolled hypertension; history of other malignancies; current or planned chemotherapy, radiation therapy, or surgery for prostate cancer within the next month; known allergy to melatonin; prior treatment with medications such as propranolol (due to its partial central nervous system effects), warfarin (due to high interaction potential), recent use of selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), anticonvulsants, or monoamine oxidase inhibitors (MAOIs); consistent use of benzodiazepines or non-benzodiazepine sleep aids; use of phosphodiesterase inhibitors such as sildenafil or tadalafil for sexual dysfunction; use of yohimbine, dapoxetine (SSRI), or other herbal and non-herbal supplements affecting sexual performance; and use of progesterone-containing drugs or other medications for hot flashes.

Ethical Considerations

This clinical study received ethical approval from the Medical Research Ethics Committee of Isfahan Medical University (Approval Code: IR.MUI.RESEARCH.REC.1399.143) and was officially registered on the Iranian Clinical Trial Registry (ID: IRCT20180722040556N5). All participants were provided with a comprehensive informed consent form detailing the study's aims, procedures, potential benefits, and risks. Any uncertainties were clarified, and participants were assured of confidentiality and data protection. Those who agreed to take part signed the consent form after having sufficient time to review and ask questions.

Concealing and Randomization

To minimize bias, this clinical trial utilized a double-blind design with block randomization. Allocation codes were generated using specialized software [14] based on key statistical parameters, including sample size, group assignment (intervention vs. placebo), and block size (four participants per block). These codes were sealed in opaque envelopes to maintain allocation concealment.

The study medication 3 mg melatonin tablets and identical placebo tablets were manufactured and supplied by Razak® Pharmaceutical Company in Tehran, Iran. The placebo matched the melatonin tablets in size, shape, color, and packaging, differing only in the absence of the active

ingredient. Both formulations shared the same excipients, such as microcrystalline cellulose, calcium phosphate dibasic dihydrate, and magnesium stearate.

Each tablet pack contained 60 units and was labeled with a unique code series generated by the principal investigator. Throughout the trial, neither participants nor clinical staff including investigators, supervising physicians, and statistical analysts were aware of group assignments, ensuring full blinding across all levels of the study.

Intervention and Data Collection

Participants who voluntarily agreed to participate in our clinical study underwent a one-week monitoring period. During this time, we collected baseline clinical and demographic data, assessed participants' adherence to the study protocol, and familiarized them with the questionnaires to be used. Baseline data were included information such as age, family history of cancer, medical history, protocol of treatment and the type of androgen deprivation therapy (ADT) being received.

participants were asked to complete the International Index of Erectile Function (IIEF) [15] and the Functional Assessment of Cancer Therapy-Prostate (FACT-P) [16] questionnaires before starting any medication. Then, patients were randomly assigned to receive either melatonin (3 mg twice daily) or a matching placebo for a duration of four weeks. To assess the frequency and severity of daily hot flashes, patients were instructed to use a daily Hot Flash Diary [17] during four-week intervention. This instrument enabled participants to record the number of hot flash episodes occurring within a 24-hour period, as well as their intensity, based on the classification system provided in the diary. At the end of the 4-week follow-up, again patients filled the all-aforementioned questionnaires [15, 16] to be evaluated in reference to baseline data. (See Figure 1 and 2) Participants attended three scheduled clinic visits: the first at baseline during initial sampling, the second immediately prior to intervention one week after sampling, and the third at the end of the four-week follow-up period.

The Assessed Questionnaires

The frequency and intensity of hot flashes were measured using the Hot Flash Diary. Patients were instructed to document three aspects of each hot flash episode: the date and time of occurrence, severity rated on a scale from 0 to 10 (where 0 signifies no symptoms and 10 indicates severe symptoms), and duration in minutes [17].

Sexual dysfunction, the secondary endpoint of the study, was assessed with the International Index of Erectile Function (IIEF) questionnaire. This instrument

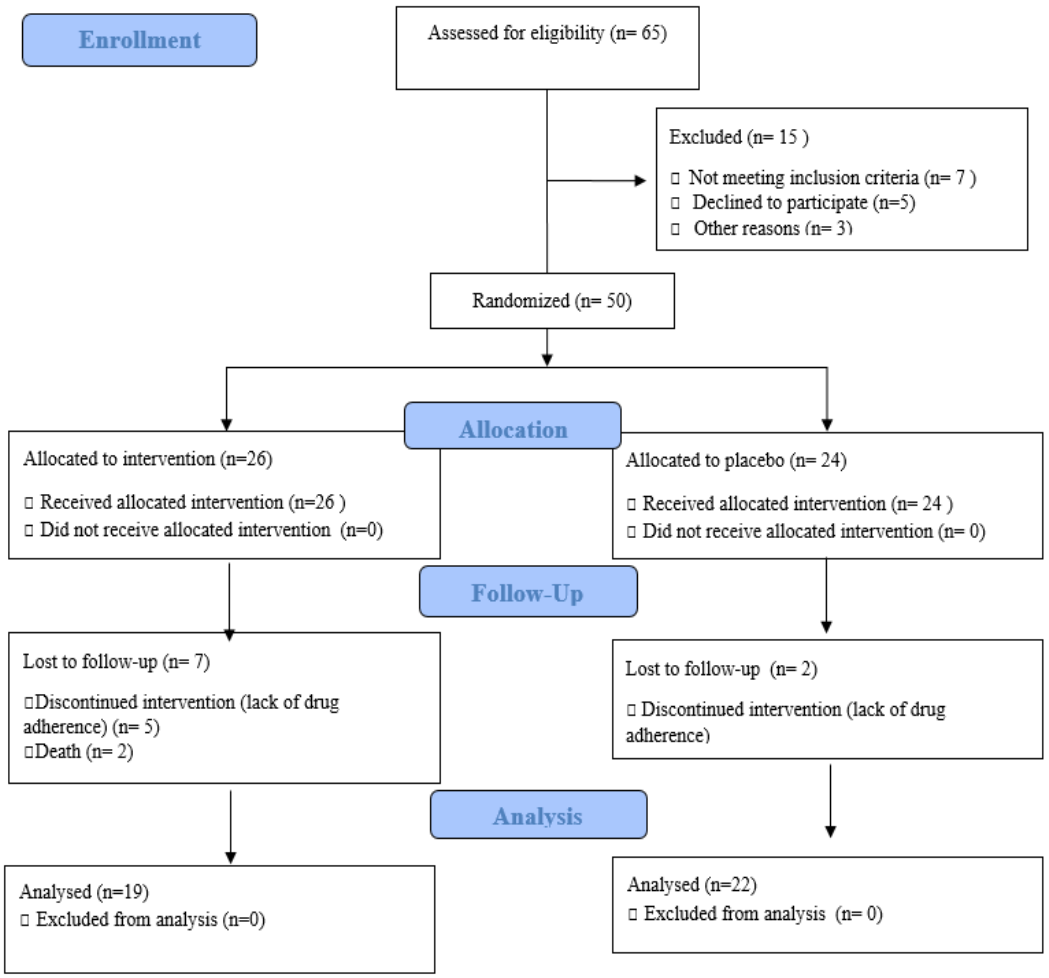

Figure 1. CONSORT Flow Diagram of Study

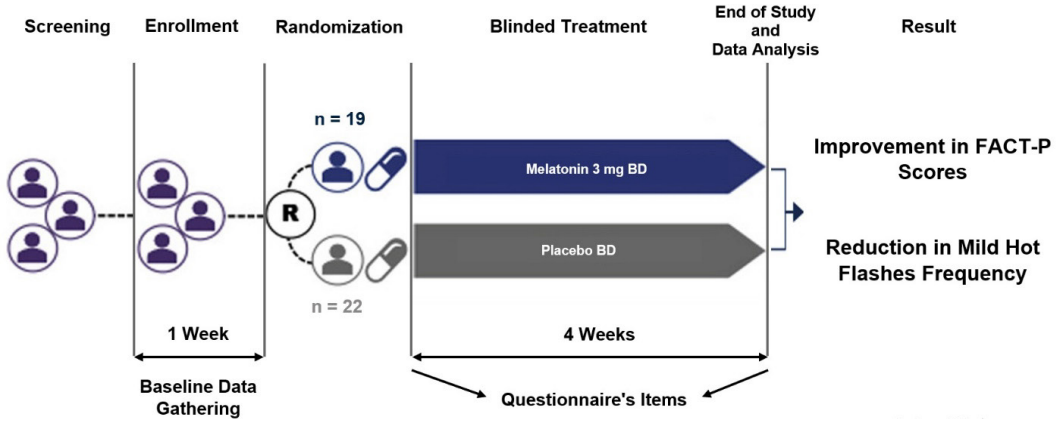

Figure 2. Overview of Study Design and Follow-Up Timeline

comprised fifteen items that evaluated five domains of sexual function: erectile function (six items), orgasmic function (two items), sexual desire (two items), intercourse satisfaction (three items), and overall satisfaction (two items). Specifically, questions 3 and 4 targeted erectile function by assessing the ability to achieve penetration and maintain an erection, respectively. A higher score reflected a lower degree of sexual dysfunction [15].

Changes in quality of life were evaluated using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire. The FACT-P includes two sections: FACT-G (general) and the prostate cancer subscale (PCS). The FACT-G section measures health-related quality of life through a 27-item questionnaire, with scores ranging from 0 to 180. The PCS, comprising 12 items, specifically assesses the quality of life for men diagnosed with prostate cancer, with scores ranging from 0 to 48 [16].

The English versions of the IIEF and FACT-P questionnaires, previously validated in earlier studies [18, 19], served as the foundational instruments for developing their Persian counterparts. To ensure linguistic and conceptual fidelity, two independent bilingual translators initially translated the English questionnaires into Persian. Subsequently, two additional bilingual translators blinded to the underlying constructs performed back-translations into English to verify accuracy and neutrality.

An expert panel comprising specialists with expertise in the study's methodology and relevant clinical domains was convened to oversee the translation process. This panel meticulously reviewed all translation iterations to ensure semantic, idiomatic, experiential, and conceptual equivalence between the original and translated versions. Any discrepancies identified during the review were resolved through structured discussions, culminating in a consensus-based pre-final version of each questionnaire.

To assess face and content validity, a second multidisciplinary panel was assembled. This panel included two pharmacists, two general practitioners, one Persian literature expert, ten oncologists, and two psychologists. Their task was to evaluate the relevance, clarity, and cultural appropriateness of each item in relation to the theoretical constructs being measured. The panel employed both qualitative feedback and quantitative metrics such as the Content Validity Index (CVI) to refine the items.

Following expert review, a pilot study was conducted with a sample of ten patients to evaluate the clarity, feasibility, and acceptability of the Persian versions. Based on participant feedback, minor revisions were made to enhance comprehension and contextual relevance.

To establish reliability, external consistency was assessed using a test-retest method over a two-week interval with the same pilot group. Internal consistency was evaluated using Cronbach's alpha coefficient.

Safety and Adherence Assessment

Adverse events were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, [20] a standardized tool for grading the severity of side effects in clinical trials. This study specifically monitored the effects of melatonin and placebo on the central nervous system (CNS) and gastrointestinal system. Daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS) [21], a validated self-administered questionnaire consisting of eight items that measure the likelihood of dozing off in various situations, with total scores ranging from 0 to 24. Medication adherence was monitored using the pill count method. Participants were instructed to return all unused tablets at each follow-up visit. The number of tablets dispensed and returned was recorded, and adherence was calculated as the proportion of tablets consumed relative to the total number prescribed during the study period.

Data analysis

In alignment with the methodology employed by Chen et al. [22], where the treatment ratios for the intervention and control groups were reported as 7.2 ± 3.3 and 5.5 ± 4.0, respectively, the initial sample size was calculated to be 29 participants per group. To enhance statistical power and account for potential attrition, the minimum sample size was increased to 33 participants per group. This adjustment was based on a power of 80%, a 95% confidence interval, a significance level of 0.05, and an anticipated dropout rate of 10%.

To analyze outcomes among participants who completed the study protocol, a per-protocol analysis was conducted. The normality of demographic and clinical variables was assessed using the Kolmogorov–Smirnov

test. Between-group comparisons were performed using appropriate statistical tests, including the chi-squared test, independent samples t-test, and Fisher's exact test, depending on the nature and distribution of the data.

For within-group comparisons of pre- and post-intervention scores on questionnaires paired-sample t-tests were employed. The internal consistency of the IIEF and FACT-P questionnaires were evaluated using Cronbach's alpha coefficient, which demonstrated acceptable reliability.

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 20. A p-value of less than 0.05 was considered indicative of statistical significance.

Results

Internal Consistency of IIEF and FACT-P Questionnaires

The Persian version of the IIEF demonstrated excellent internal reliability with a Cronbach's alpha of 0.95, while the FACT-P questionnaire showed acceptable reliability with a coefficient of 0.76. These procedures collectively ensured that the Persian versions of the IIEF and FACT-P questionnaires were both psychometrically sound and culturally appropriate for use in clinical and research settings.

Clinical and Demographic Characteristics

In the initial phase of the study, 65 patients were screened for eligibility based on the predefined inclusion criteria, as illustrated in Figure 1. Of these, 15 individuals were excluded either for failing to meet the eligibility requirements or due to unwillingness to participate in the study. Consequently, 50 eligible patients remained and were randomly assigned to either the melatonin intervention group (n = 26) or the placebo group (n = 24).

During the follow-up period, nine participants were lost due to non-adherence to the medication regimen. The clinical and demographic characteristics of the remaining patients are presented in Table 1. Finally, 19 patients in the intervention group and 22 patients in the placebo group completed the 4-week follow-up period and were included in the statistical analyses.

As shown in Table 1, the mean age was 70.57±6.77 years in the intervention group and 68±17.44 years in the placebo group. No statistically significant differences were observed between the two groups at baseline with respect to age, prostate-specific antigen (PSA) levels, comorbid conditions, family history of cancer or prior treatment protocols.

FACT-P and IIEF questionnaires

All patients completed an initial assessment at baseline using the FACT-P and IIEF questionnaires, and the results showed no statistically significant differences between the groups at the study's outset (refer to Table 2).

Table 2 shows the mean FACT-P scores before and after the intervention for both groups. The post-intervention results indicated an increase in average FACT-P scores for both groups, with a statistically significant difference (p= 0.01) noted only in the intervention group. No significant differences were observed between the two groups either at baseline or post-intervention (P > 0.21), indicating that while melatonin may have had an effect within its group, it was not statistically superior to placebo in direct comparison.

Table 1. Baseline Clinical and Demographic Characteristics of Enrolled Patients (N= 41)

Variables	Intervention group (N=19)	Placebo group (N=22)	P-value
Age (mean ± SD)	70.57±6.77	68±17.44	0.53
Baseline PSA (mean ± SD)	30.55±15.24	29.54±14.25	0.45
Family history cancer N (%)	6 (31.6)	5 (22.7)	0.55
Type 2 diabetes	4 (21.1)	3 (13.6)	0.53
Dyslipidemia	4 (21.1)	6 (27.3)	0.64
Hypertension	4 (21.1)	2 (9.1)	0.28
Ischemic heart disease	2 (10.5)	1 (4.5)	0.46
Others*	5 (31.6)	9 (40.9)	0.33
ADT	7 (36.8)	6 (27.3)	0.24
ADT + Radiotherapy	7 (36.8)	8 (36.4)	
ADT + Surgery	4 (21.1)	2 (9.1)	
ADT + Radiotherapy + Surgery	1 (5.3)	6 (37.3)	
Goserelin	9 (47.4)	9 (40.9)	0.58
Triptorelin	4 (21.1)	10 (45.5)	
Triptorelin + Abiraterone Acetate	2 (10.5)	1 (4.5)	
Goserelin + Abiraterone Acetate	1 (5.3)	0 (0)	
Triptorelin + Bicalutamide	1 (5.3)	0 (0)	
Goserelin + Bicalutamide	1 (5.3)	1 (4.5)	
Triptorelin + Flutamide	1 (5.3)	1 (4.5)	

PSA, Prostate Specific Antigen; ADT, Androgen Deprivation Therapy; *Others included: Hypothyroidism, Osteoarthritis, Inflammatory bowel disease, Peptic ulcer and Asthma. SD: Standard Deviation

Table 2. FACT-P and IIEF Mean Score between Two Intervention and Placebo Groups during 4-Week Follow-up Period

IIEF Questionnaire	Study groups	Before intervention		After intervention		P-value*
		Mean	SD	Mean	SD	
	Melatonin (N=19)	7.53	15.66	7.76	16.01	0.15
	Placebo (N=22)	7.59	14.32	8	14.5	0.68
	P-value**	0.94		0.81		
	* Wilcoxon Signed Ranks test					
	** Mann-Whitney U test					
FACT-P Questionnaire	Study groups	Before intervention		After intervention		P-value*
		Mean	SD	Mean	SD	
	Melatonin (N=19)	131.65	13.19	132.94	13.21	0.01
	Placebo (N=22)	135.91	12.63	137.68	10.41	0.17
	P-value**	0.31		0.21		
	* Paired T test					
	** Independent T test					

As shown in Table 3 and Figure 3, the average IIEF scores increased slightly in both the intervention and placebo groups following the 4-week intervention. However, these changes were not statistically significant within either group (intervention: P = 0.15; placebo: P = 0.68), indicating that the intervention did not lead to meaningful improvements in erectile function. Furthermore, no significant differences were observed between the two groups at baseline (P = 0.94) or post-intervention (P = 0.81). Overall, Melatonin did not produce a statistically significant enhancement in erectile function compared to placebo over the 4-week period, as measured by IIEF scores.

Hot Flash Diary

As shown in Table 4 and Figure 3, the repeated-measures ANOVA revealed a statistically significant reduction in the mean total frequency of hot flashes in the melatonin group over the 4-week follow-up period (P = 0.00). This reduction was particularly evident among patients reporting mild episodes of hot flashes, with significant within-group improvements across the first three weeks. In contrast, the frequency of moderate hot flashes remained statistically unchanged in both the intervention (P = 0.35) and placebo (P = 0.34) groups. Notably, while the intervention group demonstrated a consistent downward trend in total and mild hot flash episodes, the placebo group exhibited a slight increase in frequency over time. Independent t-test analyses further confirmed significant differences between the intervention and placebo groups at each weekly time point, favoring melatonin (P < 0.05). Moreover, patients receiving melatonin were more likely to experience a reduction or stabilization in hot flash frequency compared to baseline, indicating a higher likelihood of therapeutic response relative to placebo.

Table 3. The Mean of Hot Flases Frequency and Intensity between Two Intervention and Placebo Groups during 4-Week Follow-up Period.

	Total hot flashes frequency				
Time	1st week	2nd week	3rd week	4th week	P-value**
Melatonin mean±SD (N=19)	28.6±11.03	27± 11.01	26.06±11.07	24.24±9.38	0
Placebo mean±SD (N=22)	19.86±10.05	22.23±9.86	21.64±10.64	23.18±10.76	0.03
P-value*	0.02	0	0.02	0.03	
	Mild hot flashes frequency				
Time	1st week	2nd week	3rd week	4th week	P-value**
Melatonin mean±SD (N=19)	21.41±5.95	20.18±6.48	19.94±6.3	18.59±7.05	0
Placebo mean±SD (N=22)	14±7.37	14.91±7.21	15.05±7.04	15.82±8.23	0.19
P-value*	0	0.02	0.03	0.27	
	Moderate hot flashes frequency				
Time	1st week	2nd week	3rd week	4th week	P-value**
Melatonin mean±SD (N=19)	6.65±7.61	6.82±7.81	6.12±6.90	5.65±5.92	0.35
Placebo mean±SD (N=22)	6.32±7.17	7.73±9.16	7.64±9.34	7.36±9.12	0.34
P-value*	0.89	0.74	0.57	0.5	

* Independent T test; ** Repeated measures analysis test

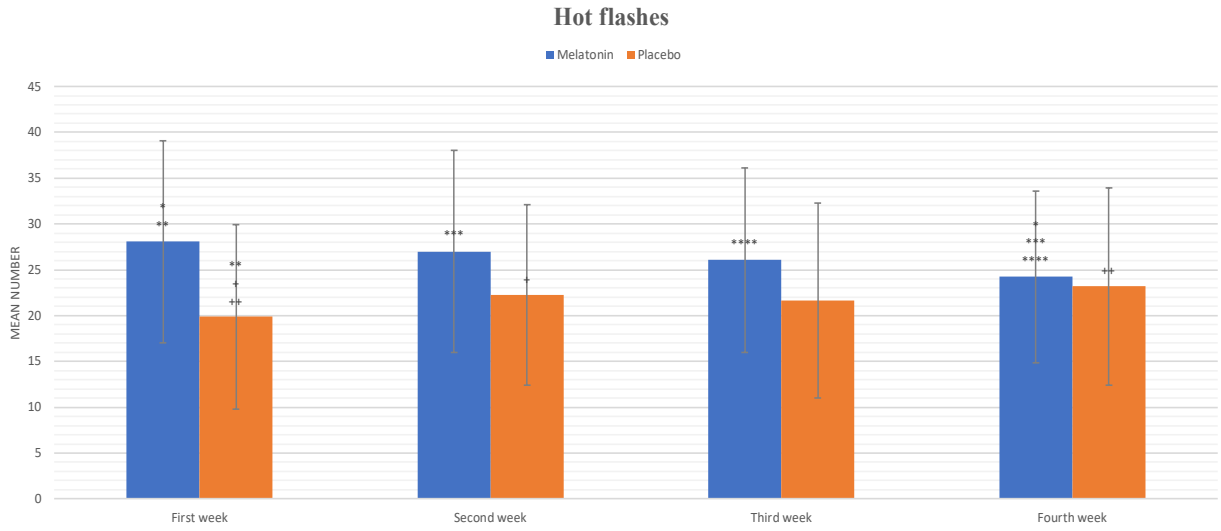

Figure 3. The Mean Number of Total Hot Flashes Frequency in Intervention and Placebo Group

Table 4. Adverse Drug Reactions in Enrolled Patients based on Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. During the study, grades 4 and 5 reactions were not reported.

Adverse drug reactions	Intervention group (N = 19) N(%)	Placebo group (N = 22)N (%)	P-value
Nausea	5 (26.3%)	7 (31.8%)	0.37
Grade 1	3	5	
Grade 2	1	2	
Grade 3	1	-	
Vomiting	3 (15.8%)	5 (22.7%)	0.46
Grade 1	2	3	
Grade 2	1	2	
Grade 3	-	-	
Daytime drowsiness	4 (21%)	0	0.08
Grade 1	3	-	
Grade 2	1	-	

Adverse effects

According to the CTCAE version 5 [20], administration of melatonin at a daily dose of 6 mg over a 4-week period was not associated with any clinically significant adverse events or treatment discontinuation. Nonetheless, three cases of excessive daytime sleepiness characterized by Epworth Sleepiness Scale scores [21] ranging from 7 to 15 p;were observed in the intervention group; however, this finding did not reach statistical significance when compared to the placebo group.

Discussion

This study investigated the effects of melatonin on quality of life, erectile function, and hot flash frequency over a 4-week intervention period. The results suggest that melatonin may offer selective benefits, particularly in alleviating mild hot flashes, while its impact on other domains remains limited.

The improvement in FACT-P scores within the melatonin group indicates a potential enhancement in prostate cancer-related quality of life. Although both groups showed increased scores post-intervention, statistical significance was observed only in the intervention group ($p = 0.012$). However, the absence of significant between-group differences ($P > 0.21$) suggests that melatonin's effect, while notable within its group, was not superior to placebo when directly compared.

These findings are consistent with a systematic review by Fan et al. [23] which found that melatonin improved sleep quality, fatigue, and overall well-being in cancer patients. Beyond oncology, melatonin has also demonstrated quality-of-life benefits in non-cancer populations. For example, a randomized trial in men with opioid addiction showed that melatonin significantly improved mental health scores and overall satisfaction compared to placebo and zolpidem [24].

Further support for melatonin's therapeutic potential in prostate cancer patients comes from a randomized, double-blind, placebo-controlled trial conducted by Etedali et al. [13] which evaluated its effects on mood and sleep disturbances induced by ADT. In this study, patients receiving 6 mg of melatonin daily for four weeks showed

significant improvements in sleep quality, sleep latency, sleep efficiency, and daytime functioning, as measured by the Pittsburgh Sleep Quality Index (PSQI). Although reductions in depression and anxiety scores were observed, these changes did not reach statistical significance. These findings reinforce melatonin's role in ameliorating ADT-related sleep disturbances and suggest broader benefits for quality of life in prostate cancer populations.

In contrast, melatonin did not significantly improve erectile function, as measured by IIEF scores. Both groups experienced slight increases post-intervention, but these changes were not statistically significant (Melatonin: $P = 0.15$; Placebo: $P = 0.68$). The lack of between-group differences further supports the conclusion that melatonin does not exert a meaningful effect on erectile function over a short-term period. However, animal studies have suggested a potential role for melatonin in modulating sexual function. In rodent models, melatonin administration has been shown to influence testosterone levels, improve sperm parameters, and protect against testicular oxidative damage [25]. Additionally, in non-cancer human populations, such as those undergoing methadone maintenance therapy, melatonin improved sexual function scores modestly, particularly in domains of satisfaction and desire [24].

The most pronounced effect of melatonin was observed in the reduction of hot flash frequency. Repeated-measures ANOVA revealed a significant decrease in total and mild hot flash episodes within the melatonin group ($P = 0.00$), with consistent improvements across the first three weeks. Independent t-tests confirmed significant differences between groups at each weekly time point, favoring melatonin ($P < 0.05$). These results suggest that melatonin may be particularly effective in managing mild vasomotor symptoms, potentially due to its regulatory influence on circadian rhythms and thermoregulatory pathways.

Animal studies [25, 26] support this mechanism: melatonin has been shown to modulate hypothalamic thermoregulatory centers and reduce core body temperature fluctuations in rats. In menopausal women, melatonin has also been associated with improved sleep and reduced vasomotor symptoms, reinforcing its potential as a non-hormonal therapeutic option [27].

While animal studies have provided valuable mechanistic insights into melatonin's physiological effects—such as its influence on hormonal regulation, thermoregulation, and oxidative stress—their direct applicability to human prostate cancer patients remains limited. Rodent models often lack the complexity of human disease, particularly in the context of prostate cancer and its treatment-related side effects. Differences in metabolism, endocrine feedback loops, and disease progression between species necessitate caution when extrapolating findings. Translational research is therefore essential to bridge the gap between preclinical models and clinical applications. Integrating mechanistic insights from animal studies with rigorously designed clinical trials can help clarify melatonin's therapeutic potential, optimize dosing strategies, and identify biomarkers of response. Such efforts would ultimately guide its application as a supportive care agent in oncology and beyond.

In addition, an evaluation of preclinical studies examining the impact of melatonin on chemotherapy-induced reproductive toxicity suggests that melatonin may confer dual benefits: safeguarding the integrity of the reproductive system during cytotoxic treatment while concurrently enhancing the therapeutic efficacy against cancer cells. Several mechanistic pathways have been proposed to account for these protective effects. These include receptor-mediated stabilization of Leydig cell function, direct stimulation of steroidogenic activity resulting in elevated testosterone production, and modulation of gonadotropin-releasing hormone (GnRH) secretion through its influence on the hypothalamic–pituitary–gonadal (HPG) axis. Furthermore, melatonin has demonstrated the capacity to potentiate the cytotoxicity of specific chemotherapeutic agents, thereby amplifying their antitumor activity [28]. The findings from animal studies exploring melatonin's protective effects during chemotherapy are highly relevant to our study, as they provide mechanistic context for the observed improvements in quality of life and vasomotor symptoms among prostate cancer patients.

Insights from animal and clinical research on melatonin's protective effects against sexual dysfunction suggest that melatonin can inhibit detrimental signaling pathways, thereby reducing the side effects of chemotherapy on healthy cells by reducing oxidative stress, apoptosis, inflammation, and preserving mitochondrial function [29]. Furthermore, melatonin may enhance pathways that promote chemotherapy-induced cancer cell death while safeguarding the reproductive system from chemotherapy's adverse effects [30-32].

Investigating the impact of melatonin administration on the quality of life of prostate cancer patients is crucial, yet there is limited data available on this subject. Sookprasert et al. [33] conducted a randomized placebo-controlled trial on patients with advanced non-small cell lung cancer, evaluating health-related quality of life (HRQoL) using the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire at baseline, 2 months, 3 months, and 7 months after melatonin administration. The findings showed that HRQoL declined over time with cancer progression, and melatonin administration could counteract the deterioration in HRQoL across all assessed domains. In our study, we observed an increase in FACT-P scores in both groups after one month, with a significant increase only observed in the intervention group. However, there was no significant difference between the intervention and placebo groups at the end of the study, possibly due to limitations in sample size and the duration of follow-up.

Importantly, melatonin was well tolerated, with no clinically significant adverse events reported. Although three cases of excessive daytime sleepiness were noted in the intervention group, this did not reach statistical significance compared to placebo. These findings support the safety profile of melatonin at a 6 mg daily dose, consistent with prior studies in both clinical and non-clinical populations. Animal toxicology studies have confirmed melatonin's high safety margin, and human trials have reported minimal side effects even at doses

exceeding 10 mg/day [34].

Overall, while melatonin demonstrated promising effects in reducing mild hot flashes and improving quality of life within its group, its impact on erectile function was negligible. Future studies with larger sample sizes, longer follow-up periods, and mechanistic endpoints may help clarify the scope of melatonin's therapeutic potential and explore its biological pathways in greater detail.

This study offers valuable insights into the potential benefits of melatonin in improving quality of life and reducing vasomotor symptoms in prostate cancer patients; however, several limitations should be acknowledged. Notably, the absence of mechanistic assessments such as hormonal profiling, circadian biomarkers, or inflammatory markers limits our ability to elucidate the biological pathways underlying the observed effects. Additionally, potential confounding factors, including comorbid conditions and concomitant medications, were not fully controlled, which may have influenced treatment responses and symptom variability. Despite these limitations, the study's randomized, double-blind, placebo-controlled design enhances its internal validity, and the use of validated instruments (FACT-P, IIEF, and hot flash diaries) strengthens the reliability of outcome measures. Future research should focus on dose-ranging studies to determine optimal melatonin regimens, explore combination therapies with other supportive agents, and incorporate mechanistic investigations to clarify melatonin's physiological effects. Longer treatment durations and stratified analyses based on patient characteristics may also help refine its role in personalized supportive care for prostate cancer patients.

In conclusion, this study highlights melatonin's potential as an adjunct therapy to improve quality of life in prostate cancer patients undergoing androgen deprivation therapy (ADT), particularly through its effects on mild hot flashes and sleep-related symptoms. While the intervention group showed significant within-group improvements in FACT-P scores, the lack of between-group differences and negligible impact on erectile function underscore the need for cautious interpretation. Melatonin was well tolerated, reinforcing its safety profile at a 6 mg daily dose. Supporting evidence from clinical and animal studies suggests broader benefits through circadian regulation, thermoregulatory modulation, and oxidative stress reduction. However, limitations such as short follow-up, modest sample size, and absence of mechanistic assessments constrain the generalizability of these findings. Therefore, further research is essential to confirm melatonin's therapeutic effects, clarify its biological pathways, and establish evidence-based clinical guidelines for its use in supportive prostate cancer care.

Author Contribution Statement

All authors contributed equally in this study.

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Declarations

Ethics approval and consent to participate

The Medical Research Ethics Committee of Isfahan Medical University has approved this clinical research (Approval code: IR.MUI.RESEARCH.REC.1399.143). We registered the protocol of study in Iranian registry website for clinical trial (ID: IRCT20180722040556N5). Informed consent was obtained from all participants included in the study.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

All data of the current study are available from the corresponding author on reasonable request.

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