

# Men with idiopathic oligoasthenoteratozoospermia exhibit lower serum and seminal plasma melatonin levels: Comparative effect of night-light exposure with fertile males

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**Abstract.** Melatonin is a darkness hormone secreted by the pineal gland, which serves a role in idiopathic oligoasthenoteratozoospermia (iOAT). The present study aimed to evaluate the seminal plasma and serum melatonin levels of 50 patients with iOAT and 50 normal fertile controls and the effects of exposure to light at night on semen parameters. Semen analyses were performed according to the World Health Organization 2010 guidelines. Measurements of serum and seminal plasma melatonin, serum TSH, FT3, FT4, free testosterone, prolactin, FSH and LH were performed using ELISA. The overall results revealed that the serum and seminal plasma levels of melatonin were lower in patients with iOAT compared with the control subjects ( $P=0.0004$  and  $0.01$ , respectively). Patients with iOAT who were exposed to light at night exhibited lower serum and seminal plasma melatonin levels compared with those who were not exposed to light at night ( $P<0.0001$  and  $0.02$ , respectively). Additionally, similar significant differences were identified in control subjects exposed to light at night when compared to non-exposed controls. There was a significantly positive correlation between serum melatonin levels and sperm motility in the entire iOAT patient cohort ( $r=0.614$ ;  $P<0.0001$ ) and a significantly positive correlation between the serum and seminal plasma melatonin levels in the non-exposed iOAT patient subgroup ( $r=0.753$ ;  $P<0.001$ ). Thus, darkness and sleep at night may improve the semen parameters of patients with iOAT, as evidenced by the effects of light exposure at night on the serum and seminal

plasma levels of melatonin and, consequently, on semen parameters.

## Introduction

Infertility is defined as the inability of a sexually active couple to achieve pregnancy within one year of unprotected regular sexual intercourse (1). Worldwide, ~15% of couples experience infertility, with ~50% of cases attributed to male factor infertility (2). The aetiology of male infertility can be known or undetermined, with 30-50% of cases being idiopathic (3). Idiopathic oligoasthenoteratozoospermia (iOAT) is defined as an unexplained decrease in the semen parameters of a male; such as a sperm count of  $<15 \times 10^6$  cells/ml, abnormal sperm morphology  $>4\%$  and motility  $<40\%$ , with no possible cause found upon physical and endocrine examinations (4). Oxidative stress is one of the main factors implicated in the pathogenesis of iOAT and in most patients with iOAT, oxidative stress manifests as an increase in reactive oxygen species (ROS) with a reduction in the total antioxidant capacity in seminal plasma (5,6).

The pineal gland secretes melatonin (N-acetyl-5-methoxytryptamine), an antioxidant sleep-inducing hormone, in a cyclical rhythm that is affected by the light/dark cycle (7). Melatonin release is inhibited by bright light and stimulated by darkness and sleep (8). Additionally, the brain, ovaries, spinal cord, skin, gastrointestinal tract, testis, retina and lymphocytes produce melatonin (9).

Melatonin exerts its antioxidant mechanism by scavenging free radicals, thus decreasing levels of ROS and preventing the depletion of antioxidant enzymes (10). Melatonin improves the motility of human spermatozoa via protection from apoptosis and DNA fragmentation induced by ROS, thus maintaining sperm viability in the reproductive tract during transit (11,12). The present study aimed to evaluate serum and seminal plasma melatonin levels in patients with iOAT compared with those in normal fertile males and to assess the effects of light exposure at night on semen parameters.

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## Materials and methods

**Study design and participants.** The present cross-sectional, case-controlled study included 50 iOAT infertile laboratory workers who were classified into a group of 34 males (exposed to light at night; night working hours) and a second group of 16 males (not exposed to light at night; day working hours). The shift rotation schedule system was a 7-day cycle composed of daytime, evening and night shifts. There were 2 days off for every 5 days of work. The working times for the day, evening and night shifts were 8:00 a.m.-4:00 p.m., 4:00 p.m.-12:00 a.m. and 12:00 a.m.-8:00 a.m., respectively. The overall duration of exposure for patients was 6 working nights daily for 5 days/week over the course of 1 year and 4 months.

A total of 50 normal male subjects served as the control fertile group. Each patient of this group exhibited normozoospermia and had fathered at least one child with no history of infertility. Controls worked the same job as patients with iOAT and were thus exposed to the same type of light with the same intensity and wavelength for the same duration to avoid any confounding factors that could affect serum and seminal plasma melatonin levels. Controls were categorized into 19 males (night light-exposed subgroup) and 31 males (non-exposed subgroup).

The control subjects were recruited from a population of men accustomed to going to bed early (10:00 p.m.) and not exposed to light at night. All subjects were randomly selected from the outpatient clinic of Dermatology, Venereology and Andrology, Qena University Hospitals, Egypt, between December 2015 and March 2016. The subjects were selected during winter to avoid seasonal variations in melatonin secretion as a confounding factor. The exclusion criteria were as follows: i) History of epididymo-orchitis, prostatitis, urinary tract infection or varicocele; ii) Abnormal hormonal profiles of thyroid stimulating hormone (normal range, 0.30-6.00 mIU/ml), free triiodothyronine (normal range, 1.80-4.60 pg/ml) and thyroxine (normal range, 0.93-1.70 ng/ml), follicle stimulating hormone (normal range, 1.5-12.4  $\mu$ IU/ml), leuteinizing hormone (normal range, 1.70-8.60 mIU/ml), prolactin (normal range, 2.5-21.5 ng/ml) and free testosterone (normal range, 2.0-95.0 pg/ml); iii) presence of any endocrine disorders; iv) use of cytotoxic drugs, immune suppressants or anti androgens; v) leukocytospermia ( $>1 \times 10^6$  white blood cells/ml); vi) smoking; vii) chronic alcohol intake and viii) hepatobiliary or renal disorders.

All subjects were informed of the study procedures and signed written informed consent prior to the start of the study. The current study was approved by the Local Scientific and Ethical Committee of Qena University Hospitals, Egypt (approval no. 09/2015).

Cases and controls were matched in terms of age and body mass index (BMI). The study included 50 infertile patients with iOAT [age range, 23-44 years; mean  $\pm$  standard deviation (SD) age, 31.56 $\pm$ 5.36 years; BMI range, 19-29.6 kg/m<sup>2</sup>; mean  $\pm$  SD BMI, 24.69 $\pm$ 3.59 kg/m<sup>2</sup>). The parameters of patients with iOAT were comparable to those of the 50 age-matched healthy fertile subjects who were included in the control group (age range, 23-49 years;

mean  $\pm$  SD age, 31.94 $\pm$ 5.19 years; BMI range, 18-28.7 kg/m<sup>2</sup>; mean  $\pm$  SD BMI, 24.38 $\pm$ 2.93 kg/m<sup>2</sup>).

**Semen analysis.** Once patient history was recorded and general/genital examinations were performed, all semen samples were collected by masturbation at 9:00 p.m. after 3-5 days of abstinence from sexual activity, and kept at 37°C for 30 min for liquefaction, followed by semen analysis. The criteria for oligozoospermia, asthenozoospermia and teratozoospermia were based on the World Health Organization 2010 guidelines (13). Samples were observed via light microscopic examination (magnification, x100) of sperm motility (%), count ( $1 \times 10^6$  cells/ml) and abnormal head or tail forms of sperms (%) using a haemocytometer. The remaining semen samples were washed with nutrient mixture F-10 Ham medium (Sigma-Aldrich; Merck KGaA) and centrifuged at 12,000 x g for 5 min at 4°C. The upper layer of the seminal plasma was collected and stored at -80°C until sample collection was complete. A peroxidase test (Leucoscreen test kit; FertiPro N.V.) was used to exclude leukocytospermia.

**Hormone assays.** A total of 5 ml of venous blood was collected in a plain vacutainer tube at 9:00 p.m. for all subjects following a 12 h fast. Blood was left to clot for 10-20 min at room temperature before centrifugation at a speed of 3,000 x g for 5 min at 4°C. Subsequently, the serum was removed, aliquoted and stored at -80°C for further biochemical analysis of melatonin, which was performed within 3 months of sample collection. Seminal plasma and serum samples were centrifuged after thawing as previously stated before melatonin analysis. Hormonal investigations were performed to exclude subjects according to the aforementioned exclusion criteria. Commercially available ELISA kits were used to measure levels of the following serum hormones according to the manufacturer's protocol: Free triiodothyronine (FT3; cat. no. F3106T; Calbiotech, Inc.), thyroxine (FT4; cat. no. F4107T; Calbiotech, Inc.), follicle stimulating hormone (FSH; cat. no. FS046F; Calbiotech, Inc.), leuteinizing hormone (LH; cat. no. 500720; Cayman Chemical Company), prolactin (cat. no. PR234F; Calbiotech, Inc.) and free testosterone (cat. no. 11-FTSHU-E01; ALPCO). Serum and seminal plasma melatonin levels were determined using a human melatonin ELISA kit (cat. no. SL1169Hu; Sunlong Biotech Co., Ltd) according to the manufacturer's protocol, using an assay range of 2-70 ng/l. ELISA was performed on the EMR-500 clinical microplate reader (Labomed, Inc.) The sensitivity and inter- and intra-assay coefficient of variations were 7.5 and 9.5%, respectively.

Radiological investigation was performed using scrotal color Doppler ultrasonography to confirm the presence or absence of varicoles or inflammatory conditions of testicles and/or epididymis.

**Statistical analysis.** SPSS (v20.0; IBM Corp.) was used for data analysis. The Shapiro-Wilk test was performed to assess whether the data were normally distributed (parametric vs. non-parametric, respectively). Parametric data are presented as the mean  $\pm$  SD and non-parametric data are presented as the median and inter-quartile range. The Mann-Whitney U test was used for comparison between two quantitative

Table I. Serum and seminal plasma melatonin levels in patients and controls.

Parameter	Oligoasthenoteratozoospermia (n=50)	Controls (n=50)	P-value
Serum melatonin (ng/l)			0.0004
Mean ± SD	11.01±10.99	19.51±16.82	
Median (range)	5.38 (2.62-42.11)	12.33 (2.52-63.78)	
Seminal plasma melatonin (ng/l)			0.01
Mean ± SD	4.84±4.06	6.96±6.35	
Median (range)	2.82 (0.90-9.02)	4.80 (1.83-24.66)	

SD, standard deviation.

variables. The correlation between melatonin levels in seminal plasma and serum with sperm parameters were assessed by Spearman's rank correlation coefficient to measure correlations between quantitative variables in non-parametric data.

**Results**

*Serum and seminal plasma melatonin levels.* In patients with iOAT, mean serum melatonin levels were 11.01±10.99 ng/l and seminal plasma levels were 4.84±4.06 ng/l. In the control group, mean serum melatonin levels were 19.51±16.82 ng/l, and mean seminal plasma levels were 6.96±6.35 ng/l. Serum melatonin levels (P=0.0004) and seminal plasma levels (P=0.01) of the iOAT group were significantly lower compared with the control group (Table I and Fig. 1).

*Effect of light exposure on serum and seminal plasma melatonin levels and semen parameters.* Patients with iOAT exposed to light at night presented with melatonin serum levels ranging from 1.6-7.57 ng/l (4.54±1.48 ng/l) and seminal plasma levels ranging from 0.90-9.02 ng/l (3.36±2.94 ng/l). Non-exposed patients with iOAT presented with serum melatonin levels ranging from 11.26-42.11 ng/l (mean ± SD, 24.77±9.65 ng/l) and seminal plasma melatonin levels ranging from 1.58-16.89 ng/l (7.34± 5.29 ng/l). Serum melatonin levels (P<0.0001) and seminal plasma levels (P=0.02) in patients with iOAT exposed to light at night were significantly lower compared with non-exposed cases (Table II and Fig. 2).

Fertile controls exposed to light at night presented with melatonin serum levels ranging between 2.52-8.88 ng/l (5.83±1.76 ng/l) and seminal plasma levels ranging between 1.83-6.60 ng/l (3.85±1.45 ng/l). In non-exposed controls, serum melatonin levels ranged from 7.96-63.78 ng/l (27.89±16.40 ng/l) and seminal plasma melatonin levels ranged from 1.95-24.66 ng/l, (8.86±7.40 ng/l). Serum melatonin levels (P<0.0001) and seminal plasma levels (P=0.0006) of fertile controls exposed to light at night were significantly compared with non-exposed controls (Table III and Fig. 3).

Sperm parameters of patients with iOAT exposed to light at night exhibited sperm concentrations ranging between 0.5-7x10<sup>6</sup> cells/ml (3.30±1.87x10<sup>6</sup> cells/ml). Non-exposed patients with iOAT exhibited sperm concentrations ranging

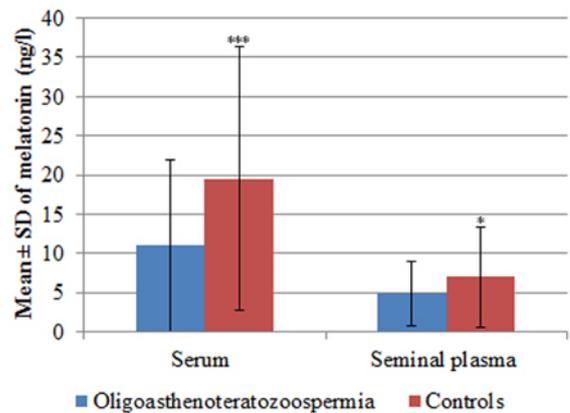


Figure 1. Serum and seminal plasma melatonin levels in patients with oligoasthenoteratozoospermia and the control group. \*P<0.05 and \*\*\*P<0.001. SD, standard deviation.

between 10-14x10<sup>6</sup> cells/ml (11.97±1.25x10<sup>6</sup> cells/ml). The percentage of sperm motility in exposed cases ranged from 0-50% (18.29±13.09%). In non-exposed cases, the percentage of sperm motility ranged from 0-50% (27.81±16.43%). The percentage of abnormal sperm forms in exposed cases ranged from 30-80% (59.26±17.97%). In non-exposed cases, the percentage of abnormal sperm forms ranged from 20-85% (46.62±32.45%).

A significant difference in sperm concentration (P<0.0001), sperm motility (P=0.04) and abnormal sperm form percentage (P=0.04) was found between exposed and non-exposed groups (Table IV).

*Correlation between serum and seminal plasma melatonin levels and semen parameters.* Spearman's correlation revealed a significantly positive correlation between serum melatonin and sperm motility (r=0.614; P<0.0001) among all patients with iOAT. Additionally, there was a significant positive correlation between the serum melatonin and seminal plasma melatonin levels in non-exposed patients with iOAT (r=0.753; P=0.0008). No other significant correlations were identified between seminal plasma or serum melatonin levels and semen parameters (Table V). Additionally, no significant correlations were identified between seminal plasma or serum melatonin levels with semen analysis parameters among controls (Table VI).

Table II. Serum and seminal plasma melatonin levels in night light-exposed and non-exposed oligoasthenoteratozoospermia cases.

Parameter	Night light-exposed (n=34)	Non-exposed (n=16)	P-value
Serum melatonin (ng/l)			<0.0001
Mean $\pm$ SD	4.54 $\pm$ 1.48	24.77 $\pm$ 9.65	
Median (range)	4.11 (1.62-7.57)	25.60 (11.26-42.11)	
Seminal plasma melatonin (ng/l)			0.02
Mean $\pm$ SD	3.36 $\pm$ 2.94	7.34 $\pm$ 5.29	
Median (range)	2.31 (0.90-9.02)	5.94 (1.58-16.89)	

SD, standard deviation.

Table III. Serum and seminal plasma melatonin levels in night light-exposed and non-exposed controls.

Parameter	Night light-exposed (n=19)	Non-exposed (n=31)	P-value
Serum melatonin (ng/l)			<0.0001
Mean $\pm$ SD	5.83 $\pm$ 1.76	27.89 $\pm$ 16.40	
Median (range)	5.68 (2.52-8.88)	24.49 (7.96-63.78)	
Seminal plasma melatonin (ng/l)			0.0006
Mean $\pm$ SD	3.85 $\pm$ 1.45	8.86 $\pm$ 7.40	
Median (range)	3.50 (1.83-6.60)	5.82 (1.95-24.66)	

SD, standard deviation.

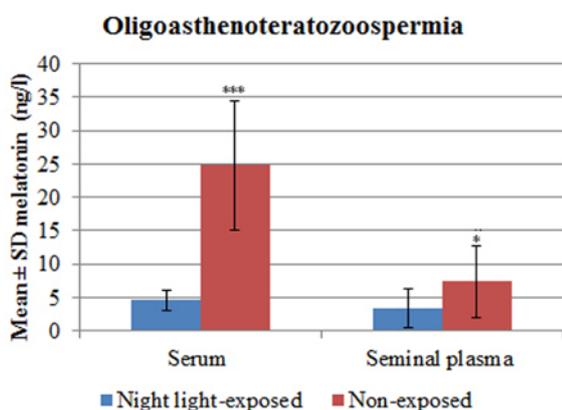


Figure 2. Serum and seminal plasma melatonin levels following night light exposure in patients with oligoasthenoteratozoospermia and the control group. \*P&lt;0.05 and \*\*\*P&lt;0.001. SD, standard deviation.

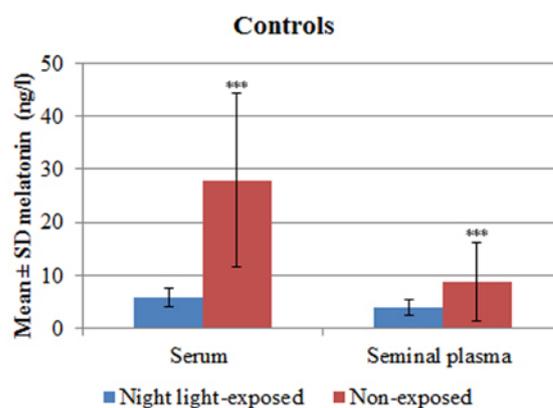


Figure 3. Serum and seminal plasma melatonin levels in light-exposed and non-exposed fertile controls. \*\*\*P&lt;0.001. SD, standard deviation.

## Discussion

Melatonin has important effects on testicular function and male reproduction, particularly in patients with idiopathic infertility, due to its anti-proliferative and anti-inflammatory effects on testicular macrophages and its protective effects against oxidative stress in testicular mast cells (14). Melatonin is involved in the modulation of inflammatory and oxidant/antioxidant states in testicular pathology (14). In the current study, significantly lower mean seminal plasma and serum melatonin

levels were measured in the iOAT group compared with the normal fertile control group. These results are consistent with a previous study by Awad *et al* (15), which demonstrated an association between a reduction in sperm motility and low melatonin levels.

The observed antioxidant scavenger effect of melatonin, which is important for the neutralization of ROS and reactive nitrogen species, has been revealed to improve semen quality in animal and human studies (16). Sharbatoghli *et al* (17) demonstrated that seminal plasma melatonin is positively correlated with sperm DNA damage in infertile patients but

Table IV. Semen parameters in night light-exposed and non-exposed oligoasthenoteratozoospermia.

Parameter	Night light-exposed (n=34)	Non-exposed (n=16)	P-value
Sperm concentration (1x10 <sup>6</sup> cells/ml)			<0.0001
Mean ± SD	3.30±1.87	11.97±1.25	
Median (range)	3 (0.5-7)	12 (0.50)	
Motility (%)			0.04
Mean ± SD	18.29±13.09	27.81±16.43	
Median (range)	18 (0-50)	30 (0-50)	
Abnormal form (%)			0.04
Mean ± SD	59.62±17.97	46.62±23.45	
Median (range)	65 (30-80)	39 (20-85)	

SD, standard deviation.

Table V. Correlation between serum and seminal melatonin levels with semen parameters in patients with iOAT.

A, Serum melatonin (ng/l)

Parameter	iOAT patients (n=50)		Night light-exposed iOAT patients (n=34)		Non-exposed iOAT patients (n=16)	
	r-value	P-value	r-value	P-value	r-value	P-value
Seminal melatonin (ng/l)	0.259	0.069	0.143	0.417	0.753	0.0008 <sup>a</sup>
Sperm concentration (1x10 <sup>6</sup> cells/ml)	0.191	0.183	0.096	0.590	0.324	0.221
Motility (%)	0.614	<0.0001 <sup>a</sup>	0.232	0.187	0.089	0.743
Abnormal form (%)	-0.021	0.887	-0.199	0.259	-0.215	0.424

B, Seminalmelatonin (ng/l)

Parameter	iOAT patients (n=50)		Night light-exposed iOAT patients (n=34)		Non-exposed iOATpatients (n=16)	
	r-value	P-value	r-value	P-value	r-value	P-value
Sperm concentration (1x10 <sup>6</sup> cells/ml)	0.250	0.080	0.121	0.497	0.112	0.680
Motility (%)	0.196	0.172	0.166	0.349	0.088	0.747
Abnormal form (%)	-0.168	0.244	-0.226	0.120	-0.052	0.848

<sup>a</sup>P<0.05. SD, standard deviation; iOAT, idiopathicoligoasthenoteratozoospermia.

is also not associated with certain sperm parameters such as concentration, motility and morphology. Bejarano *et al* (18) also determined that orally-administered melatonin improved sperm quality, which is important for successful natural and assisted pregnancy outcomes. Furthermore, Shang *et al* (19) demonstrated that melatonin protected sperm mitochondria from ROS-induced damage through its antioxidant effects. Lewis *et al* (20) also revealed that low antioxidant levels were observed in the seminal plasma of infertile men compared with fertile men, particularly in those with poor semen motility. These results might explain the decreased levels of melatonin in all infertile groups of the current study. In

contrast to previous results, Shang *et al* (21) did not identify any significant difference in the serum and seminal plasma levels of melatonin between fertile and infertile men, and the mean seminal plasma melatonin concentration was lower compared with serum melatonin. Yie *et al* (22) demonstrated that seminal plasma melatonin hormone levels were higher in oligozoospermic and azoospermic patients compared with normozoospermic men. A negative correlation between progressive sperm motility and seminal plasma melatonin hormone levels was also demonstrated. These differences in results may be attributed to different inclusion criteria of the studied subjects.

Table VI. Correlation between serum and seminal melatonin levels with semen parameters in control subjects.

A, Serum melatonin (ng/l)						
Parameter	Controls (n=50)		Night light-exposed patients (n=19)		Non-exposed patients (n=31)	
	r-value	P-value	r-value	P-value	r-value	P-value
Seminal melatonin (ng/l)	0.220	0.601	0.250	0.207	0.209	0.5128
Sperm concentration ( $1 \times 10^6$ cells/ml)	0.013	0.976	0.254	0.160	0.476	0.233
Motility (%)	0.048	0.060	0.245	0.558	0.527	0.180
Abnormal form (%)	-0.476	0.233	-0.095	0.823	-0.048	0.911

B, Seminal melatonin (ng/l)						
Parameter	Controls (n=50)		Night light-exposed patients (n=19)		Non-exposed patients (n=31)	
	r-value	P-value	r-value	P-value	r-value	P-value
Sperm concentration ( $1 \times 10^6$ cells/ml)	0.220	0.601	0.233	0.420	0.114	0.788
Motility (%)	0.071	0.867	0.024	0.955	0.323	0.435
Abnormal form (%)	-0.048	0.911	-0.235	0.394	-0.571	0.139

SD, standard deviation; iOAT, idiopathic oligoasthenoteratozoospermia.

In the present study, significantly lower serum and seminal plasma levels of melatonin were revealed in cases exposed to light at night (night shift work) compared with non-exposed cases. There were also significantly higher sperm concentrations and motilities and a significantly lower abnormal sperm form percentage in non-exposed cases compared with cases exposed to light at night in the iOAT group. In humans, melatonin is secreted during the dark phase of the light/dark cycle (23,24). Daytime melatonin levels are much lower compared with night-time levels (23,24). There is a delay and a slowing of melatonin secretion, even with the low-intensity light emitted by recent technologies, such as LEDs, computer screens, televisions, mobile phones and tablets (25). Ortiz *et al* (26) demonstrated the positive effects of melatonin on sperm motility and attributed the antioxidant effects of melatonin, as it maintained the efficiency of oxidative phosphorylation and stimulated synthesis of ATP while protecting the mitochondria from oxidative damage. Additionally, Arendt (27) reported higher sperm concentration levels during winter compared with during the summer. The authors explained their results as being due to less exposure to light during winter and increased melatonin secretion, which confirmed the negative effect of light on melatonin. Sletten *et al* (28) demonstrated that the administration of 0.5 mg melatonin combined with behavioural factors involving sleep/wake scheduling improved sleep in patients with delayed sleep-wake phase disorder.

The pineal hormone, melatonin, participates in reproductive processes over the course of the day through its stimulation of gonadotropin-releasing hormone and the consequent secretion of follicle stimulating hormone and

luteinizing hormone (29). In addition, melatonin regulates testosterone secretion by Leydig cells and Sertoli cell function (29). However, other studies have reported differing results, suggesting that regulation by melatonin is not entirely light-dependent and concluding that exposure to light at night may have no effect on melatonin hormone secretion (29,30).

Correlations between serum or seminal melatonin levels and various semen parameters are still a matter of speculation. In the present study, significantly positive correlations were identified between serum melatonin levels and sperm motility in the entire iOAT patient cohort and between seminal plasma and serum melatonin levels in non-exposed iOAT patients, while no significant correlation was identified between seminal and serum melatonin levels and sperm count or abnormal form percentage in the entire patient cohort and in the exposed or non-exposed iOAT patient subgroups. These results are in agreement with those of Awad *et al* (15) and Pitout *et al* (31). Bornman *et al* (32) reported a positive correlation between plasma and seminal melatonin levels but did not identify any significant correlation between melatonin levels and various semen variables such as sperm concentration, motility percentage and percentage of abnormal sperm forms. Several mechanisms have been postulated regarding the effect of melatonin on sperm motility, including the influencing role of melatonin on the microtubular sliding mechanism of the sperm axoneme, the involvement of melatonin in the cAMP protein phosphorylation cascade that is involved in sperm motility and the presence of melatonin binding sites in spermatozoa that are regulated by sialic acid (31,33,34).

In conclusion, serum and seminal levels of melatonin are lower in patients with iOAT compared with normal controls and exposure to light at night can negatively affect these levels, consequently affecting semen parameters. Therefore, regular night-time darkness is important to improve semen quality in patients with iOAT.

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### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Authors' contributions

MHH, HMI and MAET conceived and designed the study. HMI and MAET clinically evaluated patients. NNF, MHH and HMF collected the samples. MHH and HMF performed laboratory assays. HMI, MAET, RT, MHH and HMF analysed the data. HMI, MAET, RT, MHH, NNF and HMF performed literature search. MHH drafted the manuscript. All authors read and approved the final version of the manuscript.

### Ethics approval and consent to participate

The current study was approved by the Ethics Committee of the Faculty of Medicine, South Valley University, Qena, Egypt and was performed in accordance with the Declaration of Helsinki. Informed written consent was obtained from each patient.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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