Melatonin as a Biomarker of Circadian Dysregulation

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Abstract

It would be most useful to identify a biomarker of circadian dysregulation that could be used in epidemiologic studies of the effects of circadian disruption in humans. An indicator of circulating melatonin level has been shown to be a good biomarker of circadian dysregulation and has been associated with nightshift work and exposure to light-at-night in both laboratory-based and field studies. Among other circadian markers (such as core body temperature), it remains comparatively robust in the presence of various external influences. It can be reliably measured directly and indirectly through its metabolites in urine, blood, and saliva. Urinary melatonin has been shown to be stable over time, making it useful in epidemiologic studies in which laboratory processing is not immediately available, as well as studies of cancer with long latency periods. Several studies have shown melatonin to be useful in measuring diurnal type, which is of increasing interest as it becomes more apparent that successful adaptation to shift work may be dependent on diurnal preference.

Introduction

The production and release of nearly all hormones exhibits a diurnal timing patterned on approximately a 24-h cycle. Lifestyle factors (e.g., nightshift work and sleep disruption) or exposures to particular agents [e.g., light-at-night (LAN)] that disrupt circadian rhythm may therefore also alter endocrine function and possibly the regulation of reproductive hormones that are relevant to the etiology of hormone-related diseases, such as breast or prostate cancer (1). Given the importance of normal circadian rhythm in regulating reproductive hormone levels, a biomarker of circadian dysregulation that could be used in epidemiologic studies of the effects of circadian disruption in humans would be most useful and perhaps even used as a tool for monitoring the effects of change in lifestyle designed to reduce the risk of these types of cancer. Circulating melatonin level is one such biomarker and is preferable to other circadian markers (e.g., core body temperature) because it is comparatively robust in the presence of various external influences (2). For example, other circadian markers such as core body temperature and heart rate can be significantly affected by excessive carbohydrate intake (3); cortisol and thyrotropin-releasing hormone, as well as core body temperature, can be masked by sleep, stress, and activity (4). In contrast, melatonin concentration remains relatively uninfluenced by these factors (3, 4). Furthermore, because the onset of melatonin production is also unaffected by the factors described above, it has greater reliability to measure circadian phase position over other circadian markers (4, 5). This article reviews several key considerations in considering circulating melatonin level as a biomarker of circadian disruption.

Pineal Gland and Actions of Melatonin: An Overview

Melatonin is a primary circadian pacemaker; its purpose is to synchronize the internal hormonal environment to the light-dark cycle of the external environment. It is primarily produced and secreted by the pineal gland, a neuroendocrine transducer that is stimulated during the dark period of the external environment and suppressed by light as perceived by the retina (6). The retina hypotalamic tract carries information from the retina to the suprachiasmatic nuclei, which generates the signal to the pineal gland to regulate melatonin production accordingly. In effect, melatonin secretion acts as the “arm” of the biological clock: the timing of the melatonin rhythm indicates the status of the internal clock, with regard to phase position (the internal clock time versus the external clock time) and amplitude (2). Further, melatonin acts as a chemical code for the night: longer nights correlate positively with longer duration of secretion (7), reaching an upper limit of ~12+ h (8). Hence, during the typical sleep-wake period of the non-nightshift worker, circulating melatonin concentrations are low during the day and higher at night, exhibiting a characteristic rise in concentration after darkness and a peak near the midpoint of the dark interval (9).
Melatonin as a Regulator of Gonadal Function.
Melatonin appears to be involved in the regulation of gonadal function by influencing the hypothalamic-pituitary-gonadal axis. Animal studies indicate that melatonin can modify the firing frequency of the hypothalamic gonadotropin-releasing hormone pulse generator, thereby affecting the release of gonadotropins (luteinizing hormone and follicle-stimulating hormone) from the pituitary (10-13) and stimulating testicular testosterone or ovarian estrogen production and release (14, 15). Animal studies have also shown that melatonin can inhibit luteinizing hormone-induced testosterone production in rats (16-18), inhibits prolactin cell activity in male and female hamsters (19), and suppresses several aspects of reproductive physiology in male hamsters (20). Human studies indicate that decreased concentrations of circulating melatonin (such as those brought about by circadian disruption) can result in increased release of the gonadotropins luteinizing hormone and follicle-stimulating hormone from the pituitary and estrogen release by the ovaries (21-25). There is also evidence from clinical studies of a relationship between melatonin and male reproductive hormones (26-29). Thus, through its control over gonadal hormone production, melatonin may have an inhibitory effect on hormone-dependent tumors.

Melatonin as a Direct Oncostatic Agent. Melatonin may also have a direct effect on the development of cancer. Growth-inhibitory and oncostatic properties of melatonin have been well described (reviewed in ref. 30). Several in vitro studies have reported a reduction in the growth of malignant cells and/or tumors of the breast (31-35) prostate (36-41), and other tumor sites (42-46) by both pharmacologic and physiologic doses of melatonin. In rodent models, pinealectomy has been found to enhance tumor growth (47), and exogenous melatonin administration has shown anti-initiating (48) and oncostatic (49-52) activities in various chemically induced cancers as well as in virus-transmitted tumors in mice (53). It has recently been reported that exposure of rats with hematomas or human breast cancer xenografts to light during each 12-hour dark phase resulted in a dose-dependent suppression of nocturnal melatonin blood levels and a stimulation of tumor growth (54). Sainz et al. (55) have also recently shown that treatment of prostate cancer cells with pharmacologic concentrations of melatonin significantly reduced the number of prostate cancer cells and stopped cell cycle progression in both androgen-dependent (LNCaP) and androgen-independent (PC3) epithelial prostate cancer cells and induced cellular differentiation.

Several mechanisms have been proposed to explain such direct anticancer activity: melatonin may have antimitotic activity by its direct effect on hormone-dependent proliferation through interaction with nuclear receptors; it may affect cell-cycle control; and it may increase the expression of the tumor suppressor gene p53 (35, 56). Furthermore, some clinical trials suggest that melatonin, either alone or in combination with standard therapy regimens, exhibits a favorable response in the treatment of human cancers (57).

Whether low nocturnal melatonin levels predisposes one to an increased risk of cancer is difficult to determine; several studies of breast cancer in women have been attempted to answer this question. Three studies measured urinary melatonin levels in women before their development of breast cancer (58-60). Two of the three reported decreased premenopausal and postmenopausal breast cancer risk among women with higher melatonin levels using nocturnal or "first morning void" urine samples (58, 59). The third study found no relationship between melatonin level and breast cancer risk (60); however, a primary concern with that study was the use of a 24-h urine sample to assess melatonin levels, which has several concerns as described by Hrushesky and Blask (61). There is evidence that melatonin levels are decreased in patients with breast cancer, although, in each of these studies, melatonin levels were measured after diagnosis; therefore, it is uncertain whether the disease itself and/or treatment might have affected melatonin levels among the cases (62-67). Nighttime plasma melatonin levels have been reported to be lower in women with estrogen receptor-positive breast cancer than in estrogen receptor-negative breast cancer, which in turn are lower than in healthy control women, and women with the lowest peak melatonin concentrations had tumors with the highest concentrations of estrogen receptors (66). Melatonin levels have also been found to be lower in cases of primary breast cancer than in women with benign breast disease (63, 67). Although these findings are consistent with the results of laboratory studies and melatonin levels are in the direction of what might be predicted, it is difficult to assess their biological relevance due to the presence of disease and its possible effect on blood melatonin levels.

Methods of Measuring Circulating Melatonin
Melatonin in Serum and Plasma. Plasma melatonin, which has a very short biological half-life and is rapidly metabolized by the liver, reflects the amount of melatonin circulating during the time of sample collection. Thus, measurement of melatonin in plasma at regular intervals (e.g., hourly) will show a circadian rhythm, enabling identification of the onset of melatonin secretion, the duration of melatonin secretion, peak levels of circulating melatonin and the time at which peak secretion occurred, and the total amount of melatonin secreted.

Initially, assays of plasma melatonin were based on gas chromatography/mass spectrometry (68). These were later replaced by more specific and sensitive radioimmunoassays (RIA) suitable to the clinical environment (4). Several techniques have been described for measuring melatonin in plasma and serum via RIA. Graham et al. (69) performed comparative studies of the Buhlmann RIA kit (ALPCO), the Rollag and Niswender assay (70), and the Elias USA assay (71). The three techniques were found to be in very high agreement with one another, with Pearson’s R correlations equal to 0.98 and higher over a wide range of concentrations.

Despite the advantages of having such detailed information about the circadian rhythm by direct measurement of melatonin in blood using the highly reliable techniques that are currently available, such measurement is possible only in a controlled setting (e.g., sleep laboratory), making it impractical in other applications such as an epidemiologic study or other widespread population use.
Melatonin in Saliva. Several techniques have been described to measure melatonin levels in saliva, including use of an iodinated tracer and solid-phase second antibody (72), high-performance liquid chromatography-tandem mass spectrometry using stable isotope dilution (73), column-switching semi-microcolumn liquid chromatography/mass spectrometry with online analyte enrichment (74), and, most recently, automated solid-phase extraction, high-performance liquid chromatography and fluorescence detection (75).

Salivary samples were employed by Nowak et al. (76), who compared the melatonin concentrations in blood samples collected from five subjects every 2 to 4 h over a 26-h period, with the melatonin concentrations in saliva. They reported a significant correlation between serum and salivary melatonin concentrations \( R = 0.81 \) and concluded that salivary melatonin concentrations are reliable indices of serum melatonin concentrations (76). Leibenluft et al. (77) measured the onset of melatonin production and proposed this measurement as a practical and reliable method for assessing circadian phase. In their study, plasma onset. Similarly, the acrophase (the time at which the peak of the rhythm occurs) of the saliva and plasma melatonin rhythms were significantly correlated (78).

However, Laakso et al. (79) compared salivary and serum melatonin levels and found that saliva and serum measurements were not highly correlated in individuals with low serum melatonin levels and that the proportion of melatonin found in saliva decreased with increasing serum melatonin levels. They concluded that melatonin concentrations measured in saliva do not always consistently reflect the absolute concentrations in blood. Gooneratne et al. (80) reported similar results in that serum and saliva melatonin levels were less correlated in individuals with low serum melatonin levels.

The development of salivary melatonin assays has contributed to the adoption of salivary testing as a useful method for measuring melatonin, given that it is relatively noninvasive and generally acceptable to study participants. Furthermore, with proper training, study subjects can collect their own samples at home to be later delivered to the laboratory for assay. Although one study described above reported a problem with inadequate saliva volume for analysis for some individuals (80), the primary drawback to measuring melatonin in saliva is that, similar to plasma and serum measurements, salivary melatonin reflects the amount of melatonin circulating in the body at a given point in time. To capture details of the rhythm of melatonin secretion, such as the time of onset, peak levels, and cumulative secretion, one has to collect saliva samples at regular intervals throughout the subject’s night.

Melatonin in Urine. Arendt et al. (81) suggested that measurement of a major metabolite of melatonin excreted in urine would allow noninvasive study of pineal function useful in a broad range of applications. If appropriately executed, measurement of melatonin in the urine would reflect the cumulative amount of circulating melatonin corresponding to the period between the prior urine void and the collection of the subsequent urine sample.

Quantifying melatonin levels in urine is typically accomplished through measurement of 6-sulfatoxymelatonin (aMT6s), the primary metabolite in urine, although some studies directly measure urinary melatonin. Although exact laboratory methods differ from one study to the next, the basic methods for determination of urinary aMT6s include assay by either RIA or ELISA; commercial kits are available for both methods. Measurement of aMT6s by RIA depends on competition of aMT6s in the urine and \( ^{125}\)I-labeled aMT6s for a limited number of high-affinity binding sites on Stockgrand (Guildford) ultraspecific sheep anti-aMT6s antiserum. Determination of aMT6s by ELISA uses a commercially available kit distributed by ALPCO, using the Buhlmann aMT6s ELISA, a competitive immunoassay using a capture second antibody technique. Regardless of the laboratory technique employed, concentrations of aMT6s are often adjusted by urinary creatinine concentrations to account for differing output from one individual to the next and for separate urine collections within individuals (82). It should be noted, however, that urinary creatinine concentration itself can be influenced to some degree by age (83, 84), body weight and lean muscle mass (83, 85), sex (83), and race (83, 86), requiring careful consideration of the effects of these factors on creatinine concentrations in interpretation of individual studies of urinary melatonin that are adjusted for urinary creatinine concentration.

Comparison between Blood and Urinary Melatonin Levels. Urinary melatonin concentration shows a circadian rhythm, much like melatonin levels in the blood (87-90). Because melatonin is secreted primarily at night, many studies have focused on nocturnal samples when evaluating the correlation between melatonin levels in blood and urine. Wetterberg (91) first reported a high correlation between plasma melatonin level at 2:00 a.m. and morning urine melatonin level and pointed out the potential clinical significance of urinary melatonin levels. Since then, many other studies have shown a high degree of correlation between nocturnal measurements of urinary aMT6s and plasma and serum melatonin (69, 90, 92-94). In addition to observing the circadian rhythm of urinary melatonin, Lang et al. (90) reported a correlation of 0.74 between plasma melatonin levels at midnight and urine collected from 9:00 p.m. to 7:00 a.m. the following morning. They also found that correlations were somewhat lower when plasma levels were compared with urine samples from 9:00 p.m. to midnight \( (r = 0.61) \) and from midnight to 8:00 a.m. \( (r = 0.51) \), perhaps indicating the importance of collecting a urine sample over the entire night. Fernandez et al. (93) analyzed serum melatonin collected between 8:00 and 9:00 a.m. with nocturnal urinary aMT6s collected the preceding night over a 12-h period and found a significant positive correlation in each of the three groups of women studied (premenopausal, perimenopausal, and post-menopausal). Graham et al. (69) found a significant relationship between total nocturnal plasma melatonin and both urinary aMT6s corrected for creatinine and...
urinary melatonin. Combining the two urinary measures of aMT6s and melatonin accounted for 72% of the variance in total plasma melatonin. Furthermore, peak nocturnal levels of plasma melatonin were significantly related to morning levels of urinary melatonin and aMT6s (69). Cook et al. (92) assessed the differences in melatonin levels between blood and urine samples collected in a laboratory-based setting with nocturnal urine samples collected in a field study and found a very high correlations (r < 0.001) between first morning void melatonin and creatinine-corrected aMT6s and both total nocturnal plasma melatonin output and peak nocturnal plasma melatonin and (b) that the ranges of urinary melatonin levels were very similar between the laboratory and field studies.

Similarly high correlations have been found in studies that compared melatonin in plasma and serum with urinary melatonin over a 24-h period (76, 81, 94-97). Markey et al. reported a significant correlation (r = 0.76) between 24-h levels of conjugated 6-hydroxymelatonin and nighttime peak plasma melatonin (95). Nowak et al. collected blood and urine samples every 2 to 4 h over a 26-h period and found significant correlations between serum melatonin and urinary aMT6s (76). Baskett et al. reported high agreement between 24-h plasma melatonin and urinary aMT6s levels in a group of elderly participants (96). Bojkowski et al. found that total 24-h urinary excretion of aMT6s was significantly correlated with the area under the curve of the respective profiles for plasma melatonin (r = 0.75) and plasma aMT6s (r = 0.70; ref. 97). Although the temporal pattern of nighttime circulating melatonin levels is lost when a single morning urine sample is used in lieu of repeated measurement of plasma or serum melatonin throughout the night, the studies described above form a convincing argument that circulating levels of melatonin in the blood can be adequately measured in urine samples of the appropriate duration, suitable in most epidemiologic settings.

**Reproducibility of Urinary Melatonin Measurements.** Several studies have evaluated whether measurement of urinary melatonin within an individual is stable over time. The stability of such measurements further promotes the usefulness of this technique, because long-term levels of hormones are often of interest in diseases with long latency periods.

A few studies have investigated whether creatinine-standardized urinary melatonin measurements are stable over time. Davis et al. (98) evaluated nocturnal aMT6s levels in a group of women ages 20 to 74 years over 3 consecutive days and then repeated the measurement protocol 3 to 6 months later. Urinary aMT6s concentrations were highly and significantly correlated on consecutive days (r > 0.85) as well as between measurements sessions (r = 0.75; ref. 98). Levallois et al. (99) measured urinary aMT6s concentrations over 2 consecutive days and found similarly high correlation (r = 0.92). Schernhammer et al. (100) evaluated the reproducibility of aMT6s in three urine samples collected from women over a 3-year period and reported a correlation of 0.72 between the measurement periods. The longest period of urinary melatonin reproducibility investigated to date is a study by Travis et al. (101), which evaluated urinary aMT6s at three different points over a 5-year period and reported a correlation of 0.56.

As part of the Schernhammer et al. study described above (100), they also conducted a small pilot study to evaluate whether delaying urine sample processing by 24 to 48 h affected the results. They found that mean aMT6s levels declined by ~20% when processing was delayed. In contrast, as part of the study conducted by Bojkowski et al. (97), investigators stored urine samples without preservative either at room temperature for 5 days or at -20°C for 2 years and found aMT6s to be stable under both conditions.

**Melatonin as a Biomarker of Circadian Dysfunction**

It is well established that ocular light exposure in humans can affect hormonal secretion either acutely as a direct response to the presence or absence of retinal light exposure or indirectly as a result of the influence of light on circadian mechanisms. Indeed, light is the most powerful circadian synchronizer in humans (102) and can exert a profound effect on the phase and amplitude of the human circadian pacemaker (103). Of particular interest in the context of melatonin as a biomarker is the effect of light on pineal function in humans: nocturnal illumination of sufficient intensity completely suppresses melatonin production (104, 105); there is considerable individual variability in sensitivity to LAN (106-108); there appears to be a dose-response to LAN in that the brighter the light the greater the reduction in nocturnal circulating melatonin (109, 110); bright light shifts the phase of melatonin rhythm, with morning hours being associated with phase advance and evening hours with phase delays (111); and light quality during the day affects night time melatonin production (106, 112-114) as well as the human circadian pacemaker (115).

Because melatonin is a primary circadian pacemaker and is quantifiable in the urine, blood, and saliva via well-proven and reliable techniques applicable to non-laboratory studies, it has become a powerful tool as a biomarker of circadian dysregulation.

**Laboratory-Based Studies of Melatonin and Exposure to LAN.** Using sleep laboratory-based protocols, several studies have used melatonin measurements to determine phase advance and delays resulting from controlled exposure to LAN. Deacon and Arendt (116) simulated circadian rhythm disturbance in a laboratory environment to assess the ability of controlled exposure to moderately bright light and subsequent darkness to delay circadian rhythms. Subjects were exposed to bright light for a 6-h period for 3 consecutive days, at progressively later times each day, with exposure beginning at 8:00 p.m. on day 1, 10:00 p.m. on day 2, and midnight on day 3. Using urinary aMT6s measurements, they detected a delay shift 1 day post-light treatment and a return to baseline phase position by day 4 post-treatment. Furthermore, they reported a high degree of correlation between urine, plasma, and saliva melatonin in detecting these phase shifts (116). The same investigators later used a similar design, this time with bright light exposure for a 9-h period for 5 consecutive days, and reported that urinary aMT6s acrophase took at least 5 days post-treatment to return to normal baseline...
Several studies have used measurements of melatonin in the blood or urine to evaluate and describe the effects of shift work on circadian rhythm. Toutou et al. (122) found that fast-rotating shift work modifies peak values and rhythm amplitudes of serum melatonin. Using data from the Nurses’ Health Study II, Schernhammer et al. (100) reported a significant inverse association between increasing number of nights worked within the 2 weeks preceding urine collection and urinary melatonin levels. Among similar lines, Marie et al. (123) reported lower 24-h urinary concentrations of \( aMT6s \) in nurses working the nightshift compared with nurses working the dayshift; urinary concentrations of \( aMT6s \) were also lower during a day off for nightshift workers, relative to day-off levels in dayshift workers. In a study conducted by Quera-Salva et al. (124, 125), rapid change in sleep time and melatonin acrophase was reported in some nightshift workers but not in others, suggesting that some people have a physiologic ability to readily adapt to rotating shift schedules and reported for the first time a corresponding rapid shift in melatonin secretion. At the time of publication, this study was unique in that it employed melatonin (via urinary \( aMT6s \)) to evaluate the variability in individual responses to shift work on circadian rhythm. Since then, Dumont et al. (126) measured urinary \( aMT6s \) every 2 h during a 24-h period after three consecutive nights of work in another group of nurses. Using a cosinor analysis to estimate phase position, they reported individual variability in adaptation to nightshift work, with 5 participants showing a phase delay, 3 a phase advance, and the remaining 22 showing no phase shift (the timing of their melatonin secretion was typical of a dayshift worker). In a study involving offshore oil workers employed in a weekend alternating shift schedule (one week nights, one week days), Gibbs et al. (127) reported adaptation to the nightshift schedule via a delay of \( aMT6s \) at the end of the week of nightshifts. In another study of offshore oil workers employed in a 2-week alternating shift schedule (two weeks of days, two weeks of nights), Barnes et al. (128) reported similar results, with the delay of \( aMT6s \) occurring during the first week of the nightshift. This same investigative team conducted another study in which urine samples were collected every 2 to 3 h throughout the subjective days and an oversleep sample from a group of offshore oil workers employed in a 1-week alternating shift schedule (one week days, one week nights), and reported differing adaptation to the nightshift depending on season of the year, using measurement of urinary \( aMT6s \) to detect phase shift (129). Before this, Midwinter and Arendt (130) reported differing shifts in the acrophase of melatonin secretion depending on the season of the year using 48-h urine samples collected during a week of nightshift work in a group of workers stationed in the Antarctic; they further reported a slower readaptation to the rhythm following nightshift work during the winter compared with the summer.

A recent study conducted by Burch et al. (131) compared melatonin levels among workers on permanent day, swing, and night shifts. Urinary \( aMT6s \) was measured in post-work and post-sleep samples, and disrupted circadian melatonin production was evaluated using the sleep/work \( aMT6s \) ratio. They reported that night workers had altered melatonin, disrupted sleep, and elevated symptom prevalence. Subjects grouped by their sleep/work \( aMT6s \) ratio rather than shift had even greater symptom prevalence. Risks for two or more symptoms were 3.5 to 8 times greater among workers with sleep/work ratios of ≤1 compared with those with ratios of >1 (131). Thus, they described an objective means to assess circadian disruption.

Melatonin as an Indicator of Diurnal Type. Several studies have used melatonin measurements to evaluate whether diurnal type (morning versus evening) is associated with cumulative nocturnal melatonin secretion and/or onset of melatonin secretion. A small study conducted by Madokoro et al. (132) reported pronounced interindividual differences in plasma melatonin concentration measured before and 1 year after beginning shift work. They constructed a ratio of melatonin concentration measured at 6:00 a.m. to total melatonin concentration measured during the night and found that higher morningness-eveningness score (indicating morning type; ref. 133) was correlated with this ratio. Gibertini et al. (134) measured nocturnal melatonin levels in blood hourly and assessed the circadian type of each participant; they found that circadian type was strongly related to the melatonin acrophase but not to amplitude of the time of year of assessment and that morning types experienced a more rapid decline in melatonin levels after the peak relative to evening types. Similarly, Liu et al. (135) reported that morning type was associated with an earlier melatonin acrophase. More recently, Griefahn et al. (136) found that the onset of melatonin synthesis was 3 h earlier in morning than in evening types using hourly salivary melatonin measurements; they also reported melatonin measurements to be a better indicator of diurnal type than rectal temperature measurements. In a follow-up study reporting similar results (137), the same investigators concluded that, because morningness is closely related to the ability to cope with shift work, the determination of the melatonin profile might be a valuable element of the criteria when assigning a person to shift work.
Concluding Remarks. Melatonin has been shown to be a useful biomarker of circadian dysregulation and has been associated with nightshift work and exposure to LAN in both laboratory-based and field studies. Among other circadian markers (such as core body temperature), it remains comparatively robust in the presence of various external influences. It can be reliably measured directly and indirectly through its metabolites in urine, blood, and saliva. Urinary melatonin has been shown to be stable over time, making it useful in epidemiologic studies in which laboratory processing is not immediately available; its stability also allows it to be used in studies of cancer with long latency periods. Several studies have shown melatonin to be useful in measuring diurnal type, which is of increasing interest as it becomes more apparent that successful adaptation to shift work may be dependent on diurnal preference.

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