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AGE-SPECIFIC REFERENCE VALUES OF NOCTURNAL SALIVARY MELATONIN IN THE POPULATION OF THE REPUBLIC OF UZBEKISTAN

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Annotation
This study aimed to establish age-specific reference intervals for nocturnal salivary melatonin in apparently healthy individuals from the Republic of Uzbekistan. A total of 200 participants aged 6–69 years were divided into five age groups. Nocturnal salivary melatonin concentrations were measured by enzyme-linked immunosorbent assay under standardized low-light conditions. A pronounced age-related decline in melatonin secretion was observed, with mean concentrations decreasing from 150.60±5.64 pg/mL in children aged 6–12 years to 19.47±3.50 pg/mL in participants aged ≥60 years. Differences between age groups were statistically significant ($F=192.7$; $p<0.001$). Age-specific P5–P95 intervals were established for all five age categories. The findings demonstrate substantial age-related variability in nocturnal salivary melatonin concentrations and support the use of age-adapted reference intervals for clinical and research interpretation.

Keywords: melatonin, salivary melatonin, circadian rhythm, age-related changes, reference intervals, nocturnal secretion, Uzbekistan.

Background

Melatonin is a major neuroendocrine hormone involved in the regulation of circadian rhythms, sleep–wake cycles, energy metabolism, glucose and lipid

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homeostasis, and several age-related physiological processes [1,2]. Its secretion follows a pronounced circadian pattern, with low concentrations during daytime and a marked increase during the evening and night. The magnitude and timing of nocturnal melatonin secretion may be influenced by multiple factors, including age, exposure to artificial light, sleep schedule, environmental conditions, lifestyle, and geographical location [2,3]. Age is considered one of the most important physiological determinants of melatonin production, as pineal melatonin secretion gradually declines throughout life. Despite increasing clinical and research interest in salivary melatonin as a non-invasive marker of circadian function, population-specific reference data remain limited. In particular, age-specific reference intervals for nocturnal salivary melatonin have not been sufficiently established for the population of the Republic of Uzbekistan. The availability of such reference values may improve the interpretation of melatonin measurements in clinical endocrinology, sleep medicine, chronobiology, and metabolic research.

Objective

To establish age-specific reference values and reference intervals of nocturnal salivary melatonin in apparently healthy individuals from the Republic of Uzbekistan and to assess the pattern of age-related changes in nocturnal melatonin secretion.

Materials and Methods

The study included 200 apparently healthy individuals aged 6–69 years. Participants were stratified into five age groups according to major developmental and adult age categories: 6–12 years (n=40), 13–18 years (n=42), 19–44 years (n=38), 45–59 years (n=40), and ≥60 years (n=40). Individuals with known endocrine disorders, severe chronic diseases, or other conditions potentially affecting melatonin secretion were excluded from the study.

Saliva samples were collected during the nocturnal period under standardized low-light conditions to minimize the suppressive effect of light exposure on melatonin production. Melatonin concentration in saliva was determined using enzyme-linked immunosorbent assay (ELISA). The

obtained data were analyzed using descriptive statistical methods. Mean values and measures of variability were calculated for each age group. Differences in melatonin concentrations between age groups were evaluated using one-way analysis of variance (ANOVA). Age-specific reference intervals were defined using the 5th and 95th percentiles (P5–P95). A value of $p<0.05$ was considered statistically significant.

Results

A clear and statistically significant age-associated decline in nocturnal salivary melatonin concentration was observed across the studied age groups. The highest mean melatonin level was detected among children aged 6–12 years and amounted to 150.60±5.64 pg/mL. In adolescents aged 13–18 years, the mean level decreased to 122.13±7.98 pg/mL. A further reduction was observed in adults aged 19–44 years, with a mean concentration of 94.96±7.66 pg/mL.

The decline became more pronounced in the older age groups. Among participants aged 45–59 years, the mean nocturnal melatonin concentration was 53.98±4.14 pg/mL, while the lowest level was recorded in individuals aged ≥60 years, reaching 19.47±3.50 pg/mL. Differences between the five age groups were highly statistically significant ($F=192.7$; $p<0.001$).

The corresponding age-specific P5–P95 reference intervals were 142.67–159.45 pg/mL for participants aged 6–12 years, 98.37–129.09 pg/mL for those aged 13–18 years, 83.42–107.67 pg/mL for individuals aged 19–44 years, 46.84–61.78 pg/mL for the 45–59-year age group, and 12.89–24.36 pg/mL for participants aged ≥60 years.

Overall, mean nocturnal salivary melatonin concentration decreased approximately 7.7-fold between the youngest and oldest age groups. The reduction was progressive across consecutive age categories, indicating a strong physiological association between age and nocturnal melatonin secretion.

Discussion

The present findings demonstrate a pronounced age-related decline in nocturnal salivary melatonin among apparently healthy individuals in Uzbekistan. The highest concentrations were observed in childhood,

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followed by a gradual reduction during adolescence and adulthood and a more substantial decline in middle-aged and older participants. This pattern is consistent with the established physiology of the pineal gland and previously reported age-related changes in melatonin production [2,4].

The progressive decrease in nocturnal melatonin may reflect age-associated alterations in pineal gland function, circadian regulation, and the responsiveness of the circadian system to environmental light–dark signals. Previous studies have shown that both the amplitude and timing of nocturnal melatonin secretion change with advancing age, and these changes may become particularly evident from middle age onward [4,5]. The marked reduction observed in participants aged ≥60 years in the present study is therefore physiologically plausible and supports earlier observations of attenuated nocturnal melatonin secretion in older adults.

An important finding of this study is the considerable difference in reference intervals between age categories. The reference range established for children was substantially higher than that observed in adults and elderly individuals. Consequently, the application of a single reference range to all age groups may result in inaccurate interpretation of laboratory findings. A melatonin concentration that could be considered physiologically normal for an elderly individual may represent a markedly reduced value in a child or young adult.

The results also support the use of salivary melatonin measurement as a practical, non-invasive method for evaluating circadian endocrine function. Saliva collection is less invasive than repeated blood sampling and is particularly convenient in pediatric populations and in studies requiring nighttime sampling. At the same time, melatonin concentrations are highly sensitive to the timing of sample collection, ambient light exposure, sleep schedule, and other pre-analytical conditions. Therefore, strict standardization of sampling procedures remains essential for reliable interpretation.

The establishment of population- and age-specific reference intervals may have practical value for future studies investigating circadian rhythm disorders, sleep disturbances, obesity, metabolic syndrome, endocrine disorders, and other conditions potentially associated with altered melatonin secretion. However, the proposed intervals should be interpreted within the

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context of the present study population. Further multicenter studies involving larger samples, different regions of Uzbekistan, seasonal observations, and stratification by sex may help refine these reference values.

Conclusion

Nocturnal salivary melatonin concentrations demonstrate a pronounced and statistically significant age-dependent decline in apparently healthy individuals from Uzbekistan. The highest levels were observed in children aged 6–12 years, whereas the lowest values were recorded in participants aged ≥60 years. Age-specific P5–P95 reference intervals were established for five age categories. These findings indicate that age should be considered a major factor when interpreting nocturnal salivary melatonin measurements and support the use of age-adapted rather than universal reference ranges in clinical and research practice.

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