The American Journal of Medical Sciences and Pharmaceutical Research
ISSN 2689-1026 | Open Access

TYPE Original Research
PAGE NO. 76-79
DOI 10.37547/tajmspr/Volume07Issue10-10

Circadian Rhythm Alterations And Melatonin Secretion Dynamics In Young Adults With Metabolic Syndrome

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OPEN ACCESS

SUBMITTED 31 August 2025
ACCEPTED 25 September 2025
PUBLISHED 31 October 2025
VOLUME Vol.07 Issue 10 2025

CITATION

Akmal Gaybiyev, & Shaxboz Bobojonov. (2025). Circadian Rhythm Alterations And Melatonin Secretion Dynamics In Young Adults With Metabolic Syndrome. The American Journal of Medical Sciences and Pharmaceutical Research, 7(10), 76–79.
https://doi.org/10.37547/tajmspr/Volume07Issue10-10

Abstract

Metabolic syndrome (MS) in young adults has emerged as an increasingly prevalent health challenge, with recent studies reporting a 4.8–7.0% occurrence among individuals aged 18–30 years, primarily associated with decreased HDL cholesterol levels. The progressive rise in obesity and related metabolic disorders underscores the importance of early identification of neuroendocrine and circadian disturbances contributing to MS pathogenesis. Melatonin, a key regulator of circadian homeostasis and a potent endogenous antioxidant, plays a crucial role in metabolic regulation, including glucose control, lipid balance, and anti-inflammatory defense. This study examines the features of daily melatonin secretion in young patients with MS, emphasizing its diagnostic and pathogenetic significance. A reduction in nocturnal melatonin release and flattening of its circadian rhythm were observed, correlating with increased insulin resistance, dyslipidemia, and endothelial dysfunction. Altered melatonin excretion patterns, assessed through urinary 6-sulfatoxymelatonin profiles, reflect an early manifestation of chronobiological imbalance or "chronodissonance." The findings highlight that disruption of melatonin rhythm may serve as an early biomarker of metabolic and vascular risk, supporting the role of circadian regulation in preventive and therapeutic strategies for metabolic syndrome in young adults.

Keywords: Melatonin, metabolic syndrome, circadian rhythm, chronodissonance, insulin resistance, dyslipidemia, endothelial dysfunction, young adults, 6-sulfatoxymelatonin.

Introduction

A systematic review has estimated the prevalence of metabolic syndrome in young adults (18–30 years) to be 4.8% to 7.0%, with low HDL cholesterol being the most common component of the syndrome in this age group (6). At the same time, the global prevalence of obesity and related metabolic disorders continues to increase, making MS a major public health problem for young people (1,2). Melatonin is a potent antioxidant and chronobiotic that influences the phase and amplitude of circadian rhythms, as well as metabolic processes such as glycemia, lipid metabolism, and inflammatory responses (4,5).

Experimental and clinical observations have revealed a persistent decrease in endogenous melatonin levels in patients with MS, which is associated with the severity of metabolic disorders and endothelial dysfunction.

The circadian profile of melatonin excretion (most often as 6-sulfatoxymelatonin in urine) is a reliable noninvasive marker of circadian hormone secretion. Disturbances in the shape and phase of this profile indicate chronodissonance, which is associated with an increased risk of developing insulin resistance, dyslipidemia, and other components of MS (3). Assessment of changes in the amplitude and phase shifts of melatonin excretion allows the detection of subclinical chrono- and metabolic disorders at an early stage.

Despite extensive studies of melatonin in adults and elderly people with MS, data on 24-h melatonin excretion in young patients (under 40 years of age) with metabolic syndrome are almost nonexistent. Identification of a specific 24-h melatonin profile in this group will allow for a better understanding of the underlying mechanisms of chronometabolic disorders and the development of targeted preventive and therapeutic strategies to reduce the risk of cardiovascular and neurodegenerative complications.

Objective: To determine the characteristics of daily melatonin secretion in young patients with metabolic syndrome, to identify differences in the secretion profile between the hypertensive, dyslipidemic and insulin-resistant phenotypes of MS, and to establish the relationship between the rate of 6-sulfatoxymelatonin secretion and clinical and laboratory parameters and the severity of metabolic disorders.

Methods

A comprehensive examination of 118 young patients with metabolic syndrome (MS) was conducted, of which 57 were male (48.3%) and 61 were female (51.7%). The age of the patients was in the following range: according to the WHO definition of young adults (2023): 18-44 years (mean age 29.6 ± 9.2 years). Based on the patient history and medical records, the duration of the disease at the beginning of the examination ranged from 5 to 11 years, with a mean of 6.1 ± 5.2 years.

During the study, we identified three phenotypes of metabolic syndrome:

1. Hypertensive phenotype (CO + AG) - in patients with this phenotype of metabolic syndrome, in addition to central obesity (CO), arterial hypertension (AG) was the main symptom.

2. Dyslipidemic phenotype (CO + DL) - this phenotype is characterized by CO and impaired lipid metabolism and severe dyslipidemia (DL).

3. Insulin-resistant phenotype (CO + IR) - this phenotype is characterized mainly by CO and severe insulin resistance (IR), which leads to impaired carbohydrate metabolism.

In this regard, all examined patients were divided into 3 groups depending on the MS phenotype.

Group 1 (CO + AG) consisted of 41 patients (34.7), their average age was 36.4 ± 4.8 years, of which 25 were men (61.0%) and 16 were women (39.0%) (here and below the percentage is calculated based on the number of patients in a particular group), the male/female ratio was 1.6:1.0.

Group II (CO+DL) included 32 patients with a mean age of 28.6±5.3 years, of whom 15 were male (46.9%) and 17 were female (53.1%) (gender ratio 0.9:1.0). Group III (CO+IR) included 45 patients with a mean age of 24.6±7.1 years, of whom 17 were male (37.8%) and 58 were female (62.2%) (gender ratio 0.6:1.0).

The control group (CG) included 20 patients with a mean age of 25.1±6.4 years, of whom 10 were male and 10 were female.

Circadian markers were studied (daily excretion of 6-sulfatoxymelatonin (urine assay) was determined by

ELISA and serum 25(OH)D levels were determined by chemiluminescence immunoassay). Statistical analysis was performed.

Results

Table 1 shows the peak nocturnal melatonin levels and serum 25-hydroxyvitamin D concentrations in young patients and healthy donors from three clinical groups with different metabolic syndrome phenotypes. The mean and standard deviation (M ± σ) for each group, as well as the statistical significance of differences in paired comparisons (two-tailed t-test), are shown. Melatonin levels were highest in the control group (60.2 ± 15.3 pg/ml). In patients with phenotype I ("CO + AG"), melatonin levels were 45.3 ± 12.4 pg/ml, in patients with phenotype II ("CO + DL") 39.9 ± 11.7 pg/ml, and in phenotype III ("CO + IR") 35.6 ± 10.2 pg/ml. Significant decreases were observed in all MS groups compared to the control group ($p < 0.001$).

The difference between phenotypes I and II was not statistically significant ($p = 0.12$), but between phenotypes II and III, melatonin levels in III were significantly lower ($p = 0.03$), reflecting the increasing disruption of circadian rhythm secretion as insulin resistance worsened.

Table 1. Melatonin and vitamin D levels in young patients with different MS phenotypes

Group		Nocturnal peak melatonin, pg/mL (M ± s)	(Vitamin D), ng/mL (M ± σ)
I (ЦО+АГ), n=41	1	45,3 ± 12,4	17,4 ± 4,8
II (ЦО+ДЛ), n=32	2	39,9 ± 11,7	15,2 ± 5,1
III (ЦО+ИР), n=45	3	35,6 ± 10,2	13,6 ± 3,9
Control, n=20	4	60,2 ± 15,3	25,8 ± 6,2
p 1–2		p = 0,12	—
p 1–3		p = 0,001	p = 0,02
p 1–4		p < 0,001	p < 0,001
p 2–3		p = 0,03	—
p 2–4		p < 0,001	p < 0,001
p 3–4		p < 0,001	p < 0,001

The highest concentration of vitamin D (25.8 ± 6.2 ng/ml) was observed in the control group. Lower levels were observed in the metabolic syndrome groups: 17.4 ± 4.8 in phenotype I, 15.2 ± 5.1 in phenotype II, and 13.6 ± 3.9 ng/ml in phenotype III. The differences between all patient groups and the control group were highly significant ($p < 0.001$). Vitamin D deficiency was not statistically significant between phenotypes I and II ($p = 0.15$), but a significant decrease was observed from phenotype II to III ($p = 0.04$).

Thus, in young patients with metabolic syndrome, significant disturbances in nocturnal melatonin secretion and vitamin D deficiency are observed in the early stages of the disease. The degree of decrease in both parameters is associated with the severity of the metabolic phenotype: the largest deviations were noted in the group with predominant insulin resistance (phenotype III). Circadian rhythm disturbances (melatonin) and vitamin D deficiency may serve as independent predictors of the development of cognitive and vascular complications in this category of patients.

Vitamin D deficiency (25(OH)D) as a common denominator. 25(OH)D levels are deficient (<20 ng/ml) in all MS phenotypes, and in COX + IR they fall to an average of ≈13 ng/ml. Low vitamin D significantly increases the likelihood of having ≥3 MS components in young adults.

Table 2. Pathophysiological associations

Linkage	Mechanism	Clinical outcome

↓ Melatonin → ↑ Insulin resistance	MTNR1B polymorphism, decreased β-cell sensitivity to glucose	Worsening of glycemic profile, failure to lower blood pressure
↓ Vitamin D → ↑	Visceral fat: Decreased adiponectin, increased TNF-α	Chronic inflammation and worsening hypertension
Joint failure	Increased oxidative stress, activation of HIF-1α	Early cognitive decline, cerebral hypoperfusion

Table 2 summarizes the main pathophysiological relationships linking impaired nocturnal melatonin secretion and vitamin D deficiency to the clinical manifestations of metabolic syndrome and early cognitive impairment.

Conclusions

Disturbances in circadian rhythm secretion (melatonin) and vitamin D deficiency are independent but complementary factors in the development of metabolic syndrome. Their effects are mediated by genetically determined and inflammatory-metabolic mechanisms, which increase insulin resistance and atherogenic lipid profiles and, when combined, cause early vascular and neuronal changes. Comprehensive assessment of nocturnal melatonin and 25(OH)D peaks may serve as a valuable screening marker to identify patients at high risk of metabolic and cognitive complications.

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