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Review

Circadian Dynamics of Blood Cell Parameters: A Review

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Abstract: The authors conducted a retrospective analysis of international publications devoted to the effects of endogenous and exogenous factors on the circadian rhythms of circulating blood cells. More than thirty studies were analyzed. No unequivocal conclusion regarding the 24-hour dynamics of blood cell parameters was reached. These parameters showed substantial interindividual variability, especially against the background of sleep deprivation. In addition, the absence of a standardized approach to the quantitative assessment of circadian rhythms considerably complicates cross-study comparisons. Nevertheless, most authors agree that total or partial sleep deprivation results in circadian misalignment (desynchronosis), including disturbances in blood cell regulation. Circadian dynamics of blood parameters need further investigation, particularly within a personalized framework. The emphasis on developing wearable devices for prolonged monitoring should be put. Researchers should also aim to standardize study designs and to investigate post-illness alterations in circadian rhythms of blood parameters.

Keywords: circadian rhythms, blood parameters, sleep, circadian misalignment.

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Rhythmic changes in the human body occur throughout the 24-hour day-night cycle which are commonly referred to as circadian biological rhythms. It is well established that such rhythms are generated by an internal timing system, which comprises the central endogenous biological clock in the suprachiasmatic nuclei of the hypothalamus and local oscillators present in nearly all peripheral tissues [1].

Dysregulation of biological rhythms may arise under the influence of both endogenous and exogenous factors. Repeated shifts of endogenous circadian clock negatively affect human health. Night-shift work is the most illustrative example, which is currently considered a probable carcinogen and an independent risk factor for several cardiometabolic conditions, including obesity, arterial hypertension, and cardiovascular events [2-5].

Nearly every patient encounter involves measuring laboratory parameters. Considering their circadian fluctuations, correct interpretation of the results is essential. An understanding of variations in biological fluid parameters is crucial for diagnostics and treatment methods to be more effective and personalized. The novelty of this review lies in its synthesis of data on circadian fluctuations of white and red blood cell populations in response to sleep deprivation. Unlike previous studies, which have typically addressed either the influence of single factors on blood components or the impact of multiple factors on specific blood elements, this work offers an integrated perspective.

In this review, we conducted a retrospective analysis of international publications focusing on the impact of endogenous and exogenous factors on circadian rhythms of blood cells. The analysis included studies with comparable design and cohorts, predominantly involving healthy volunteers (19-35 years old) of both sexes, without a history of night-shift work.

Circadian rhythms were established for different circulating blood cells. Lymphocyte levels peaked at night [6-15] while findings regarding neutrophils and monocytes remained controversial [7, 10, 13, 16-18].

Minors and Waterhouse observed prominent circadian dynamics for all investigated cell populations, regardless of the experimental condition [19]. Young colonies of CD4 cells demonstrated the most stable and high-amplitude rhythm, whereas monocytes showed the least stable and low-amplitude rhythm. For the first time, it has been demonstrated that the circadian rhythm of granulocytes is altered under conditions of sleep deprivation, showing reduced amplitude, loss of rhythmicity, and an overall increase in cell count. These changes may reflect the body's immediate immune response to stress, as sleep deprivation acts as a stressor that can contribute to the development of immunodeficiency.

Overall, the peak times of different cell populations identified in this study were consistent with other publications [6-16, 18]. Lymphocytes and their subpopulations, as well as monocytes, exhibited peak levels at night, except for NK/dendritic cells, which peaked in the late afternoon. Circulating granulocytes reached their peak at approximately 17:30, whereas other studies reported peak times for neutrophils around 20:00 [13, 16].

Notably, differences were observed in the correlations of oscillatory patterns across various cell types. Granulocytes exhibited very weak correlations with all other studied cell types, whereas lymphocyte subpopulations displayed significant intercorrelations, particularly between T- and B-cells ($p<0.05$). Monocytes showed stronger correlations with lymphocytes than with granulocytes ($p<0.05$).

Several studies [3, 6, 12, 20] reported no substantial differences in circadian blood count changes during normal sleep versus sleep deprivation. Other researchers [8, 16] described an increase in leukocytes or their subpopulations under sleep deprivation. Another study [21] reported an elevation of granulocyte levels at the end of a 64-hour period of total sleep deprivation, based on samples collected once daily.

Heiser et al. [22] analyzed blood samples obtained at three day-time points (07:00, 13:00, and 19:00) over three consecutive days. The period included one night of total sleep deprivation and an 8-hour recovery sleep on the third night. A significant increase in granulocytes was reported both after sleep deprivation and after recovery sleep, but only at the 07:00 time point. These results partially coincide with findings from another study [23], which reported a significant rise in neutrophils in the morning following a night of restricted sleep, which persisted even after an 8-hour recovery sleep. However, after a 10-hour recovery sleep, neutrophil levels declined to baseline values.

In another study [24], researchers examined the relationship between sleep regularity, assessed using actigraphy, and the number of leukocytes in a cohort of healthy young adults. It was shown that sleep loss increased leukocyte counts, with residual elevations persisting after recovery sleep. Moreover, irregularity in both sleep duration and sleep onset was associated with significantly higher leukocyte counts. Thus, long-term irregularity of sleep–wake cycle is likely to alter immune system functioning, potentially contributing to the development and progression of various diseases and reducing overall quality of life.

Another study [25] involved participants accommodated in a hospital ward for 24 hours. They spent 15 hours awake under normal indoor lighting. Their daily performance included sedentary activity, such as reading, watching television, and light walking, followed by 9 hours of sleep from 23:00 to 08:00. Sleep was maintained in darkness and interrupted only for three blood-sampling procedures, which were conducted under dim red light to minimize disturbance. Light exposure was assessed using a lux meter and melatonin levels were being determined every 3 hours. Hematocrit, erythrocytes, hemoglobin, serum iron, folate, transferrin, and transferrin saturation, as well as white blood counts were continuously measured.

Most parameters demonstrated distinct 24-hour rhythms, with peaks around 12:00 and nadirs around 00:00. Transferrin peaked in the late afternoon and reached its minimum in the early morning. Similar patterns were observed for other hematology parameters: ferritin, cobalamin, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), platelets, and reticulocytes. Neutrophils, monocytes, lymphocytes, eosinophils, and total white blood counts showed significant 24-hour coupled rhythms, with peaks around midnight and nadirs at midday. Thus, leucocytes demonstrated an inverted phase pattern compared to other hematology parameters. Neutrophils peaked in the evening and were at their lowest values in the morning. Erythrocytes and total leukocyte counts showed low-amplitude circadian rhythms (0 to 0.78 x 10^9/l). However, the 24-hour rhythm range, expressed as relative amplitude, was relatively high for leukocytes (excluding basophils), ranging from 9.75% to 25.0%, compared to erythrocytes (0.06% to 5.05%). Other parameters also exhibited high-amplitude circadian rhythms. Ranking them by “interpretive vulnerability” revealed elevated vulnerability indices and notable 24-hour fluctuations relative to reference intervals.

Similar results were obtained by other authors who assessed oscillatory patterns of erythrocytes, hemoglobin, and hematocrit [26-28], whereas other researchers indicated no significant oscillations [10, 29].

It cannot be excluded that disparities in findings are attributable to differences in analytical methods, study designs, and group heterogeneity. Furthermore, in some studies, the blood-sampling period lasted less than 24 hours, and concentration changes were not analyzed with respect to periodicity or individual circadian rhythm of melatonin [30, 31].

Conclusion

In conclusion, further research in this area is warranted, with greater emphasis on a personalized approach. In particular, the use of next-generation wearable devices enabling continuous monitoring [32] could improve both the quality of collected data and the robustness of derived findings. Equally important is to investigate circadian dynamics in blood parameters following various diseases – primarily acute viral infections – with residual effects on sleep. Active studies are already underway; for example, one scientific group reported no changes in morning blood parameters despite increased vulnerability of circadian rhythms to inadequate light exposure in individuals recovering from COVID-19 [33].

Thus, more than 30 analyzed publications have provided no definitive data on the circadian dynamics of blood cells in response to sleep deprivation, largely due to the lack of a unified study design, including standardized sampling frequency and timing [34]. The lack of data collected during sleep is among the most significant and common methodological limitations, as many night-time studies reported substantial changes precisely during the sleep. Moreover, no standardized approach was employed for the mathematical analysis of the obtained data. Partly for this reason, some studies showed circadian fluctuations of blood cells and correlations between them, while others did not. These findings suggest that study participants were largely similar across many characteristics, yet still exhibited relevant individual differences. To obtain more definitive data, future research may consider participants’ genetic factors, particularly genes involved in sleep regulation.

Conflict of interest

The authors declare no conflict of interest.

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Authors’ contributions

All authors contributed equally to the writing of this article. All authors read and approved the final version of the manuscript and agreed to be responsible for all aspects of the work.

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