AMBULATORY BLOOD PRESSURE MONITORING AND CIRCADIAN RHYTHM OF BLOOD PRESSURE IN DIABETES MELLITUS

Elena Matteucci, Ottavio Giampietro

Dietology Unit, Department of Clinical and Experimental Medicine, Pisa University, Italy

Disclosure: No potential conflict of interest.
Received: 03.09.13 **Accepted:** 28.10.13
Citation: EMJ Diabet. 2013;1:38-43.

ABSTRACT

Systolic and diastolic blood pressures display a circadian rhythmicity that can be assessed by 24-hour ambulatory blood pressure monitoring and analysed using the cosinor procedure. Altered characteristics to the circadian rhythm of blood pressure, which may result in adverse health outcomes, have been observed in both prediabetes and diabetes. We have investigated the circadian variability of blood pressure in patients with type 1 and type 2 diabetes. Chronobiologically interpreted ambulatory blood pressure monitoring uncovered not only midline estimating statistic of rhythm (MESOR)-hypertension and circadian hyper-amplitude-tension, but also circadian ecphasia (an odd timing of the daily blood pressure swing). Diastolic blood pressure acrophases were found to be phase shifted to earlier along the time axis only in patients with diabetes, but not in those with essential hypertension. Several mechanisms, from changes in nutrient-dependent signalling pathways to diabetic autonomic neuropathy, can contribute to alterations of circadian time structures in diabetic people. The chronology of blood pressure changes in animal models of diabetes and hypertension suggests that a chronobiological approach to the diagnosis of blood pressure disorders could offer advantages, but longitudinal studies in humans are needed to determine its potential relevance in hypertension associated with diabetes.

Keywords: Ambulatory blood pressure monitoring, circadian rhythm, midline estimating statistic of rhythm, acrophase, type 1 diabetes mellitus, type 2 diabetes mellitus, essential hypertension.

INTRODUCTION

Systolic and diastolic blood pressures display a circadian rhythm with a surge at the end of the night on arousal. The term 'circadian rhythm' refers to a periodically repeated sequence of events occurring in cycles of approximately 24 hours. Chronobiology is the study of biological rhythms. Time series of blood pressure measurements can be analysed by the cosinor (e.g. cosine and vector) method where a model consisting of cosine curves with known periods can be fitted by least squares to the data as an estimate of the pattern of the smooth rhythm.[1] The midline estimating statistic of rhythm (MESOR) is the value midway between the highest and lowest values of the cosine function best fitting to the data, the amplitude is half the value of the range of oscillation, and acrophase is the time at which the peak of a rhythm occurs.[2] Chronic circadian misalignment has been implicated in the development of metabolic and cardiovascular diseases, which in turn can modify intrinsic circadian rhythmicity.[3,4] The central circadian clock is located in the suprachiasmatic nuclei of the anterior hypothalamus in the brain of mammals, but similar clock oscillators have been found also in peripheral tissues. The biological clock regulates metabolic responses; on the other hand, metabolism, food consumption, timed meals, and nutrients feed back to the circadian system (Figure 1).[5] Time-related changes in cardiovascular parameters, such as blood pressure and heart rate have long been known, but only 24-hour ambulatory blood pressure monitoring (ABPM) has enabled an accurate

assessment of circadian blood pressure patterns. Many indices can be derived from ABPM recordings: average daytime, night-time, and 24-hour blood pressures (calculated by the arithmetic mean of all measurements and/or by the mean of hourly averages in the respective periods) are the most commonly used variables in clinical practice.[6] Otherwise, MESOR is a rhythm-adjusted mean based on the parameters of a cosine function fitted to the raw data and differs from the arithmetic mean when the data are not equidistant and/or do not cover an integer number of cycles.[1]

ABPM IN DIABETES MELLITUS

The guidelines of the American Diabetes Association do not recommend the use of ABPM for the management of hypertension in diabetes.[7] However, this tool was superior to the traditional clinic measurement in many respects: higher reproducibility, absence of placebo and white coat effect, better correlation with organ damage and cardiovascular events, and possibility to estimate heart rate variability.[4,8]

MESOR and mean of systolic and diastolic blood pressure were found higher in diabetic patients

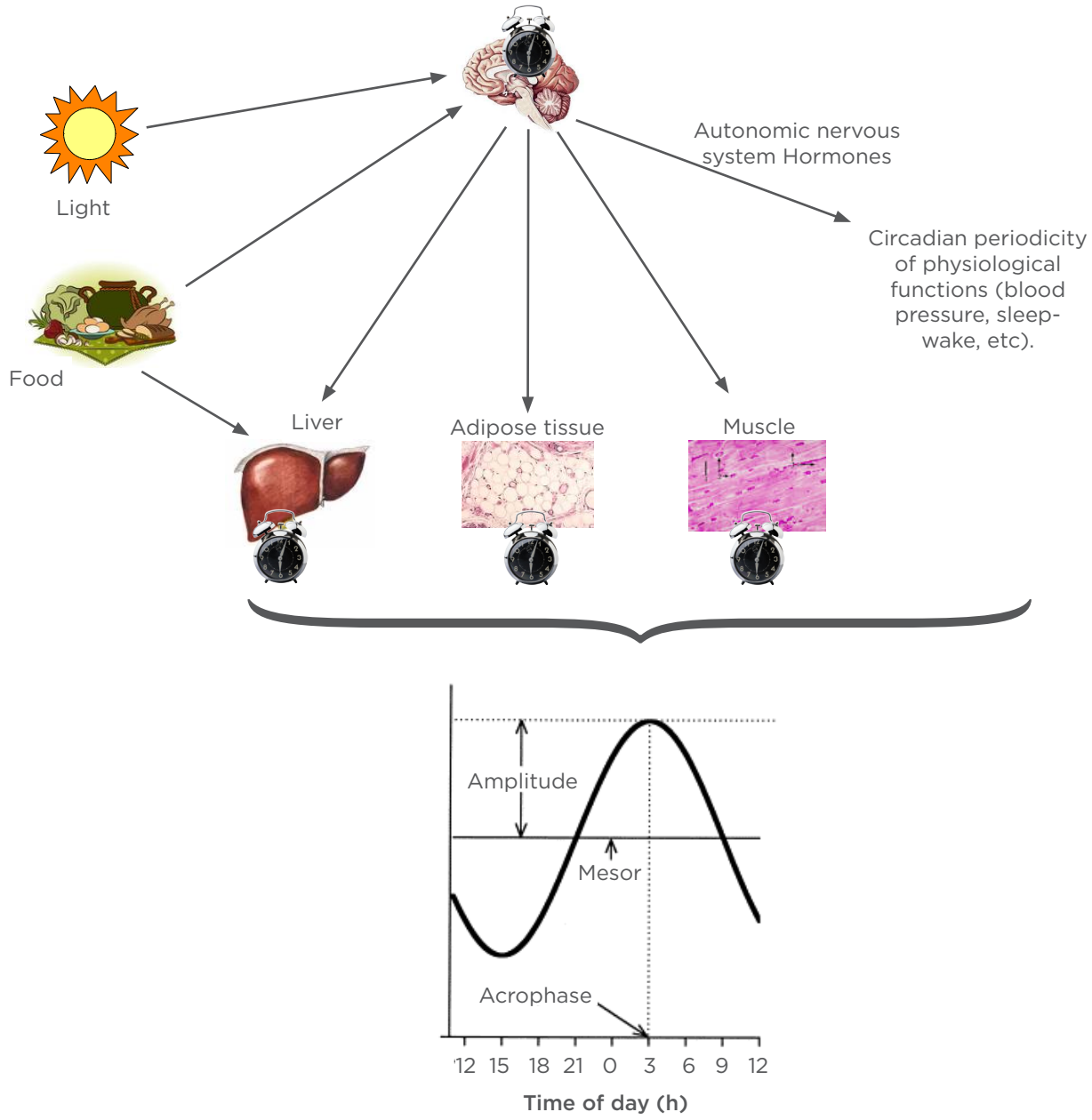

Figure 1. Central and peripheral clocks with some of their resetting signals.
Adapted from Froy et al.[4]

than in healthy subjects with a high prevalence of increased night time blood pressure (so-called non-dipping profile). This could reflect the presence of autonomic neuropathy and/or breathing-related sleep disorders, such as obstructive sleep apnoea in obese subjects with type 2 diabetes (Figure 2).[4,9] So far, few researches have evaluated abnormalities in blood pressure circadian patterns in diabetes mellitus using cosinor approach and a classification system based on the phase and amplitude of the human circadian rhythm.[10,11] After an average 4-year follow-up in 325 patients with type 2 diabetes, Nakano et al.[12] found that the circadian

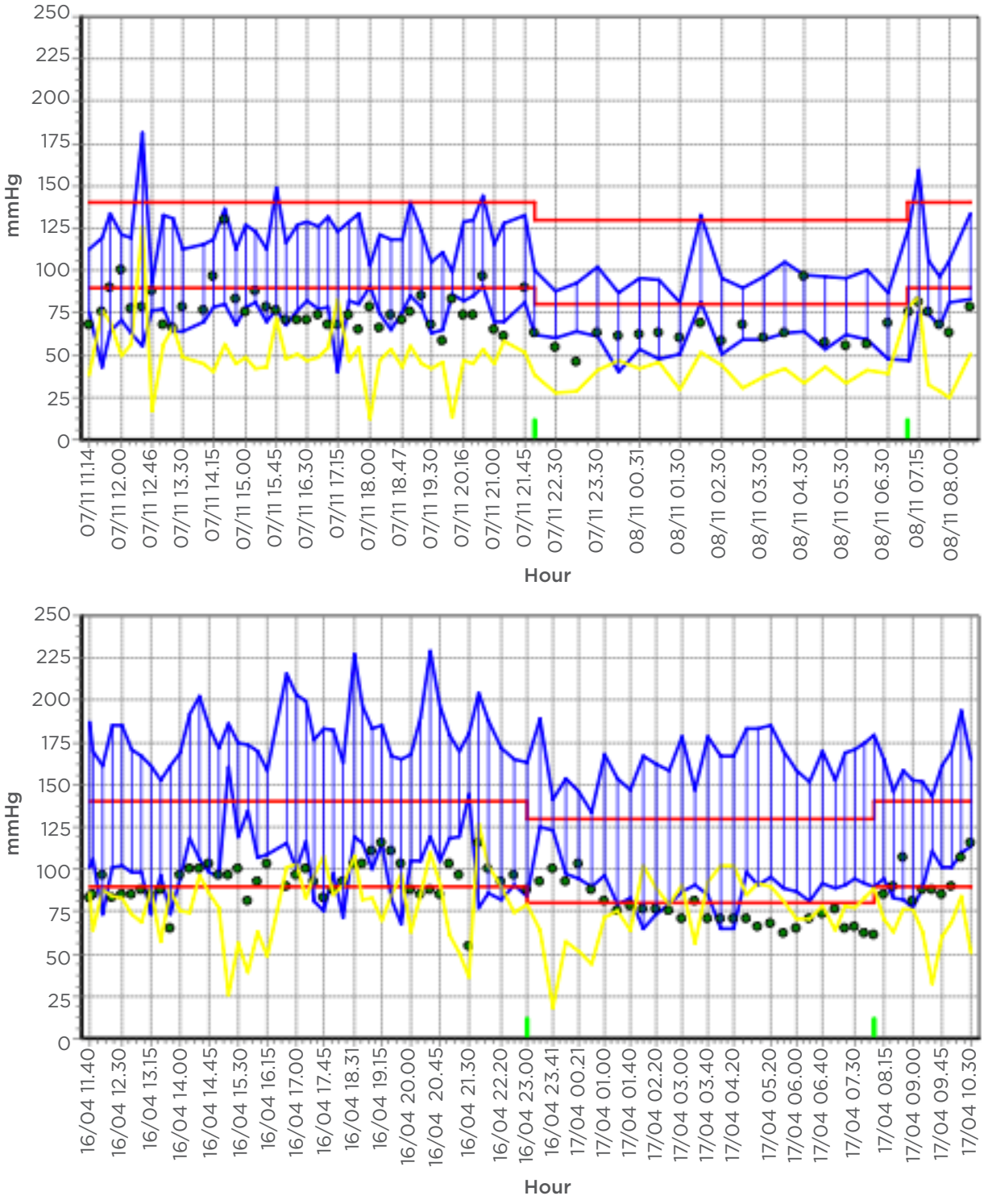

Figure 2. Example graphs from 24-hour ambulatory blood pressure monitoring report of a normotensive patient (upper panel) and a non-dipper hypertensive patient with type 1 diabetes and diabetic nephropathy (lower panel).

blood pressure patterns (analysed by the cosinor method) exhibited a statistically significant adjusted relative risk for fatal and nonfatal events.

Since normotensive non-diabetic siblings of patients with type 1 diabetes had abnormal blood pressure response to exercise testing that was associated with indices of metabolic syndrome and increased oxidative stress,[13] we investigated the circadian variability of blood pressure in patients with type 1 diabetes, their healthy siblings, and healthy control subjects who had no first-degree relative with type 1 diabetes.[14] Secondary aims of the study were to explore the influence of cardiovascular autonomic function and erythrocyte electron transfer activity on the ambulatory blood pressure profile. For this purpose, autonomic function was assessed using four standardised autonomic function tests and erythrocyte transplasma ferricyanide reductase activity was measured as the erythrocyte velocity of ferricyanide reduction.[15,16]

24-hour ABPM in type 1 diabetes families showed evidence that: 1) systolic blood pressure, MESOR and pulse pressure were higher in patients with type 1 diabetes; 2) diastolic blood pressure acrophase was 3 hours earlier in the diabetic than in normal subjects, and diastolic blood pressure ecphasia was more pronounced in patients with lower heart rate variability during deep breathing test; 3) non-diabetic siblings of patients with type 1 diabetes, who showed signs of reduced insulin sensitivity, had larger circadian amplitude of systolic blood pressure and higher ambulatory arterial stiffness index. Thus, not only diabetes but also prediabetes seemed to be associated with abnormal circadian blood pressure variability; 4) daytime systolic blood pressure was positively, independently associated with body mass index and erythrocyte transplasma ferricyanide reductase activity. This transplasma membrane electron transport system transfers reducing equivalents from intracellular reductants, such as NADPH, to extracellular oxidants, such as ferricyanide, and protects cells against oxidative damage. Transplasma membrane electron transfer systems have been found in all tested cells (including endothelial cells) and implied in antioxidant defence, cell growth, redox signal transduction, etc. The redox activity of the endothelial surface is likely to be involved in modifying the redox status of other bloodborne substances, thus influencing blood composition and vascular and organ function.[15,16] Our finding confirmed, in a clinical setting, the proposed role of transplasma membrane electron transport systems in vascular pathobiology.[14]

Recently, in order to compare the circadian rhythm characteristics of blood pressure among different groups, we have retrospectively evaluated ABPM records in normotensive control subjects, patients with type 1 and type 2 diabetes, and patients with essential hypertension who were well matched regarding age, gender, and body mass.[17] The MESOR of systolic and diastolic blood pressure was higher in patients with type 1 diabetes, type 2 diabetes, and essential hypertension. Diastolic blood pressure ecphasia was present only in the diabetic individuals: the acrophase of diastolic blood pressure occurred 4 hours earlier than normal in type 1 diabetes, whereas 2 hours earlier in type 2 diabetes. In a multiple-regression analysis, only HbA1c and systolic blood pressure acrophase were statistically significant and correlated with diastolic blood pressure acrophase. We concluded that altered circadian timing of diastolic blood pressure characterises diabetes mellitus and correlates with the previous 2-3 months of glycaemic control.[17]

CHANGES IN CIRCADIAN RHYTHMS

Due to the feedback loop between components of circadian and metabolic cycles in mammals,[18] changes in nutrient-dependent signalling pathways typical of diabetes may affect cardiovascular rhythmicity through transcriptional and non-transcriptional mechanisms. Indeed, evidence has linked cellular metabolism, epigenetic state, and the circadian clock: NAD+ is considered a critical signalling metabolite with effects on epigenetic state.[18] In this regard, our finding of a relationship between daytime systolic blood pressure and erythrocyte transplasma membrane electron transport activity that maintains appropriate intracellular NADH/NAD ratios is noteworthy.[14] The coupling mechanisms between core clock circuitry and metabolism should include NAD-dependent enzymes, redox and/or temperature-dependent transcription factors, nutrient-sensing transcriptional regulatory proteins, and protein kinases.[19]

Additionally, the pineal hormone melatonin that is involved in the phasing of circadian rhythms appears to have an antagonistic relation with

insulin.[20] For example, the circadian rhythm of insulin secretion can be phase-shifted by melatonin, polymorphisms of the melatonin MT2 receptor locus have been associated with type 2 diabetes, and increased melatonin levels in type 1 diabetic rats are normalised by insulin therapy. Catecholamines, which decrease insulin levels and stimulate melatonin synthesis, might control insulin-melatonin interactions.[20] Finally, diabetic autonomic neuropathy can contribute to the changes in the time structures of melatonin[21] and blood pressure.[22]

Health Impact of Circadian Blood Pressure Rhythm Alterations

Follow-up studies demonstrate that ambulatory blood pressure predicts target organ damage and cardiovascular prognosis in diabetic patients.[4] Non-dipping, defined as a nocturnal blood pressure fall ([awake blood pressure mean - asleep blood pressure mean]/awake blood pressure mean x 100) of less than 10%, is considered one of the most relevant features of abnormal circadian variability. While the adverse prognostic implications of a blunted day-night blood pressure dip (independent of the average 24-hour blood pressure) have recently been confirmed, those of the morning blood pressure surge are still debated.[23] However, adopting a chronobiological approach to the diagnosis of blood pressure disorders could offer advantages in explaining differential outcomes and deserves more thorough investigation.[10]

Moreover, a classification in term of 'dipping' may not match chronobiological analysis or it may even be misleading.[11,24] The following concordances between studies on animals and humans suggest the clinical meaning of the chronobiological approach. By recording via telemetry the arterial blood pressure in an animal model of spontaneous type 1 diabetes mellitus, changes in circadian cardiovascular and autonomic functions were detected. These included: 1) a phase shift by the second diabetic month in which the diurnal blood pressure peak shifted from the mid-afternoon to late-afternoon but the amplitude of the rhythm was reduced, and 2) a phase shift in the peaks and dips (with the night-time having the lowest dip) by the ninth month that could mark the beginning of irreversible impairment of autonomic and cardiovascular function.[25]

Analogously, patients with type 1 diabetes mellitus showed diastolic blood pressure ecphasia that was more pronounced in those with lower heart rate variability.[14] Furthermore, in longitudinal studies using animal models of hypertension, an increase in the circadian amplitude of blood pressure preceded MESOR hypertension,[26] just as observed in non-diabetic siblings of type 1 diabetic patients who showed signs of reduced insulin sensitivity associated with a circadian hyper-amplitude-tension.[14]

CONCLUSION

Unfortunately, the exact prognostic values of changes in blood pressure MESOR, amplitude, and acrophase remain undetermined. To determine the potential relevance of these parameters in hypertension associated with diabetes, follow-up studies are required that 1) use and compare multiple procedures for the analysis of blood pressure time series, 2) evaluate target organ damage, and finally 3) implement personalised antihypertensive therapy by timing along the circadian scale.

Glossary[2]

Acrophase: Measure of timing of a rhythm in relation to a defined reference time point selected by the investigator (e.g. local midnight for circadian rhythms); used for data which can be described by the fitting of a mathematical model, e.g. a cosine curve, and represents the crest time of the cosine curve best fitting to the data; may be expressed in (negative) degrees as the lag from the acrophase reference (360°C=1 period) or in calendar time units (e.g. hours and minutes for circadian rhythms, days or months for infradian rhythms).

Amplitude: The measure of one half of the extent of the rhythmic change estimated by the mathematical model (e.g. cosine curve) best fitting to the data (e.g. the difference between the maximum and the rhythm-adjusted mean (MESOR) of the best fitting curve).

Chronobiology: The science of investigating and objectively quantifying phenomena and mechanisms of the biological time structure, including the rhythmic manifestations of life.

Circadian ecphasia: an odd timing outside reference limits of the circadian rhythm of blood pressure.

Circadian hyper-amplitude tension (CHAT): condition defined by an excessive circadian amplitude of blood pressure, above a threshold approximated by the upper 95% prediction limit of clinically healthy peers matched by gender, age and ethnicity.

Circadian: About 24 hours. The term describes rhythms with an approximately 24-hour (>20 to <28) cycle length whether they are synchronised with a 24-hour periodic surrounding or not.

Cosinor procedure: A mathematical-statistical method of describing a rhythm by determining by least squares technique the cosine curve best fitting to the data and exploring the presence of a rhythm by examining the null hypothesis for amplitude in an F-test. If a rhythm can be described by this procedure the cosinor yields a rhythm-adjusted mean (MESOR), an amplitude as measure of the extent of the rhythm, and an acrophase as indication of its timing with variance estimates for each.

MESOR: Midline Estimating Statistic of Rhythm. The value midway between the highest and the lowest values of the (cosine) function best fitting to the data. The MESOR is equal to the arithmetic mean only for equidistant data covering an integral number of cycles.

REFERENCES

1. Refinetti R et al. Procedures for numerical analysis of circadian rhythms. Biol Rhythm Res. 2007;38(4):275-325.

2. http://www.aamcc.net/glossary.htm

3. Litinski M et al. Influence of the Circadian System on Disease Severity. Sleep Med Clin. 2009;4(2):143-63.

4. Matteucci E, Giampietro O. Circadian rhythm of blood pressure in diabetes mellitus: evidence, mechanisms and implications. Curr Diabetes Rev. 2012;8(5):355-61.

5. Froy O. Metabolism and circadian rhythms-implications for obesity. Endocr Rev. 2010;31(1):1-24.

6. 2013 ESH/ESC guidelines for the management of arterial hypertension. J Hypertens. 2013;31:1281-357.

7. Standards of medical care in diabetes – 2012. Diabet Care. 2012;35:S11-S63.

8. Parati G, Bilo G. Should 24-h ambulatory blood pressure monitoring be done in every patient with diabetes? Diabetes Care. 2009;32(suppl 2):S298-304.

9. Sharma S, Kavuru M. Sleep and metabolism: an overview. Int J Endocrinol. 2010;2010:270832.

10. Cornélissen G et al. Ambulatory blood-pressure monitoring. N Engl J Med. 2006;355(8):850.

11. Gupta AK et al. Prediabetes is associated with abnormal circadian blood pressure variability. J Hum Hypertens. 2008;22(9):627-33.

12. Nakano S et al. Reversed circadian blood pressure rhythm is associated with occurrences of both fatal and nonfatal vascular events in NIDDM subjects. Diabetes. 1998;47(9):1501-6.

13. Matteucci E et al. Systolic blood pressure response to exercise in type 1 diabetes families compared with healthy control individuals. J Hypertens. 2006;24(9):1745-51.

14. Matteucci E et al. Circadian blood pressure variability in type 1 diabetes subjects and their nondiabetic siblings - influence of erythrocyte electron transfer. Cardiovasc Diabetol. 2010;9:61.

15. Lane DJ, Lawen A. Ascorbate and plasma membrane electron transport--enzymes vs efflux. Free Radic Biol Med. 2009;47(5):485-95.

16. Merker MP et al. Intracellular redox status affects transplasma membrane electron transport in pulmonary arterial endothelial cells. Am J Physiol Lung Cell Mol Physiol. 2002;282(1):L36-43.

17. Matteucci E, Della Bartola L, Giampietro O. Differences in circadian time structure of diastolic blood pressure between diabetes mellitus and essential hypertension. Diabetol Metab Syndr. 2012;4(1):51.

18. Masri S et al. The circadian clock transcriptional complex: metabolic feedback intersects with epigenetic control. Ann N Y Acad Sci. 2012;1264(1):103-9.

19. Asher G, Schibler U. Crosstalk between components of circadian and metabolic cycles in mammals. Cell Metab. 2011;13(2):125-37.

20. Peschke E et al. Catecholamines are the key for explaining the biological relevance of insulin-melatonin antagonisms in type 1 and type 2 diabetes. J Pineal Res. 2012;52(4):389-96.

21. Tutuncu NB et al. Melatonin levels decrease in type 2 diabetic patients with cardiac autonomic neuropathy. J Pineal Res. 2005;39(1):43-9.

22. Cardoso CR et al. Pattern of 24-hour ambulatory blood pressure monitoring in type 2 diabetic patients with cardiovascular dysautonomy. Hypertens Res. 2008;31(5):865-72.

23. Verdecchia P et al. Day-night dip and early-morning surge in blood pressure in hypertension: prognostic implications. Hypertension. 2012;60(1):34-42.

24. Cornélissen G et al. Chronobiology predicts actual and proxy outcomes when dipping fails. Hypertension. 2007;49(1):237-9.

25. Anigbogu CN et al. Circadian variations in blood pressure, heart rate, and HR-BP cross-correlation coefficient during progression of diabetes mellitus in rat. Int J Hypertens. 2011;2011:738689.

26. Halberg J et al. Schedule shifts, life quality and quantity--modelled by murine blood pressure elevation and arthropod life span. Int J Chronobiol. 1979;7(1):17–64.