https://doi.org/10.46389/rjd-2023-1290
www.rjdnmd.org

Rom J Diabetes Nutr Metab Dis
2023; volume 30, issue 2, pages 215-221

Original Article

Definition of the relationships between ambulatory blood pressure characteristics and blood glucose levels in type 2 diabetes patients with well-controlled arterial hypertension

Nataliia Pertseva [1], Kateryna Moshenets [1] *

[1] Department of Endocrinology, Dnipro State Medical University, Dnipro, Ukraine

* Correspondence to: Kateryna Moshenets, Department of Endocrinology, Dnipro State Medical University, 26 Pasteur str., Dnipro, Ukraine, 49038. Phone: +380509719488; E-mail: k.moshenets@gmail.com

Received: 16 January 2023 / Accepted: 3 June 2023

Abstract

Arterial hypertension is the most common comorbidity in patients with type 2 diabetes mellitus (T2DM). The combined effects of hyperglycemia and elevated blood pressure (BP) may increase the risk of macro- and microvascular complications. This study aimed to investigate BP characteristics over a 24-hour period and to evaluate the relationship between continuous glucose monitoring (CGM) parameters and ambulatory BP monitoring (ABPM) indicators in T2DM patients with well-controlled BP. 53 T2DM patients and 10 controls were examined. All subjects were conducted with CGM and ABPM. Disturbances of BP circadian rhythm were observed in 81.1% of patients. Compared with controls, the patients with T2DM had significantly higher average daily systolic BP, diastolic BP and pulse BP and their variabilities. Glucose variability, together with hypoglycemia, affects the ABPM indicators and determines them by 60.55%, with the greatest impact on the systolic pressure area index and systolic pressure time index ($R=0.82$ ($\chi^2=261.76$; $p=0.001$). Thus, the patients with T2DM and well-controlled arterial hypertension have disturbances in circadian BP rhythm with the predominance of "non-dipper" and the appearance of "night-peaker" patterns. We indicated a strong significant relationship between systolic BP load indicators and high glucose variability together with hypoglycemia.

Keywords: type 2 diabetes mellitus, blood pressure, glucose variability.

Introduction

The number of patients with diabetes mellitus (DM) worldwide constantly increases. According to the International Diabetic Federation (IDF), in 2021, the number of people with diabetes mellitus (DM) is 537 million, which covers 10.5% of the world's population as a whole, while about 90% belong to type 2 DM (T2DM). The predicted incidence of DM in 2030 is 643 million people, which corresponds to 11.3% of the entire human population and will increase to 783 million people (12.2%, respectively) by 2045, making it possible to call DM a non-infectious epidemic of the 21st century [1].

T2DM shortens life expectancy by 10 years, and cardiovascular complications are the main cause of death in these patients. A recent meta-analysis of 57 studies about the prevalence of cardiovascular disease (CVD) in type T2DM, which included over 4.5 million, found that their overall proportion was 32.2%. CVD was the cause of death in 50.3% of all deaths in patients with T2DM during 10 years of observation [2].

The cardiovascular risk varies according to several clinical characteristics like age, sex, ethnicity, type and duration of DM, quality of glycemic control, type of hypoglycemic treatment, presence of nephropathy or previous cardiovascular events [3].

Arterial hypertension and T2DM are common comorbidities because of similar risk factors, such as endothelial dysfunction, vascular inflammation, arterial remodeling, atherosclerosis, dyslipidemia, and obesity. High blood pressure (BP) occurs in 50–80% of patients with T2DM; therefore, the normalization of

BP is extremely important to prevent the progression of cardiovascular complications [4, 5].

This study aimed to investigate BP characteristics over a 24-hour period and to evaluate the relationship between CGM parameters and ABPM indicators in T2DM patients with well-controlled BP.

Material and methods

In our comparative study, 53 adult T2DM patients with different levels of glycemic control were examined. These patients aged between 51-65 years with a disease duration of 9.0 (5.0-14.0) years were examined from January 2022 to December 2022 in the endocrinology department of the University Clinic in Dnipro, Ukraine.

The diagnosis of T2DM was confirmed in accordance with the American Diabetes Association (ADA) diagnostic criteria, 2022 [6].

Inclusion criteria: patients with T2DM aged ≥18 years with HbA1c ≤10% and stable glucose-lowering regimen during the previous 3 months with well-controlled BP (by home and office measurements).

Exclusion criteria: presence of short-acting insulin or rapid-acting analog in patient's treatment regimen; body mass index (BMI) <40 kg/m^2; acute diabetic complications at the time of inclusion; heart failure class III–IV, according to the New York Heart Association classification, uncontrolled hypertension, congenital and acquired heart defects, severe vascular complications, estimated glomerular filtration rate (eGFR) <45 ml/min/1.73 m^2, thyroid gland dysfunction and pregnancy.

In our study, we included 10 age-, sex- and BMI-matched controls without T2DM but with well-controlled BP. All T2DM patients and the control group received antihypertensive therapy: angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists (ARBs) as monotherapy or in combination with calcium channel blockers (amlodipine).

Informed consent was obtained from all subjects. All procedures of our study were conducted in accordance with the ethical standards of the responsible committee on human experimentation and with the Declaration of Helsinki of 1964 and later versions. The study protocol was approved by the Dnipro State Medical University Bioethical Committee.

Biochemical measurement parameters

Glycated hemoglobin (HbA1c), serum creatinine level and albumin-to-creatinine ratio (ACR) were determined by immunoturbidimetry using an automatic biochemical analyzer "SAPPHIRE 400" (Tokio Boeki, Japan, 2009). The eGFR was estimated using the CKD-EPI equation (Chronic Kidney Disease Epidemiology Collaboration) [7].

Instrumental research methods

For continuous glucose monitoring (CGM), the The Guardian™ Connect system (Medtronic, USA) was used. The time above range (TAR), time below range (TBR), time in range (TIR), as well as indicators of glycose variability (SD, standard deviation), were analyzed. Hypoglycemia for T2DM was considered at a blood glucose level to be <3.9 mmol/l [6].

Simultaneously with the CGM, ABPM was performed 24 hours with an SDM23 automatic cuff-oscillometric device (manufacturer: X-Techno Ukraine). Measurements were obtained every 15 minutes during the day and every 30 minutes at night. ABPM parameters were analyzed automatically using ARNIKA software version 8.3.9.

Indicators of systolic BP (SBP), diastolic BP (DBP) and pulse BP (PBP), in combination with their variability, were analyzed. BP load indicators were automatically calculated: systolic pressure area index (SPAI24), systolic pressure time index (SPTI24), diastolic pressure area index (DPAI24) and diastolic pressure time index (DPTI24).

Statistical analysis

Data were analyzed using biostatistics methods implemented in Microsoft Excel software packages (Office Home Business 2KB4Y-6H9DB-BM47K-749PV-PG3KT) and STATISTICA 6.1 (StatSoftInc., Serial No. AGAR909E415822FA). The median and interquartile range of Me (25%; 75%) were used to describe the central trend of continuous data. Relative (%) values were calculated to describe qualitative characteristics. Calculation of Spearman's rank correlation coefficients and canonical correlation analysis (CCA) was used to analyze relationships between the studied traits, as well as their sets. A p-value below 0.05 was considered statistically significant.

Results

We analyzed ABPM indicators and found that the patients with T2DM had significantly higher average

https://doi.org/10.46389/rjd-2023-1290

daily values of SBP, DBP, PBP and their variabilities compared with the control group. The results of CGM were anticipated. In the control group, nondiabetic subjects' glucose levels were within the normal range. The patients with T2DM had significantly higher HbA1c TBR, TAR and glucose variability (SD) then controls. A decrease in eGFR and an increase in ACR in T2DM patients indicate the formation of chronic kidney disease (Table 1).

CGM detected hypoglycemia level 1 in 11 (20.1%) patients with T2DM with an average TBR of 6.0 (3.0; 10.0)%. We analyzed the frequency and causes of hypoglycemia. It was established that eight cases were associated with the prescription of intermediate-acting insulins, and three other cases were associated with sulfonylurea therapy.

In our patients, BP load indicators were significantly higher than in the control group. SPTI24 in T2DM patients was 27 (5.3; 50.1)% *vs*. 4.7 (0; 15.2)% in controls ($p<0.05$); SPAI24 – 47 (9.3; 149.8) *vs*. 7.9 (0; 20.5)% in controls ($p<0.05$); DPTI24 – 20 (13.9; 30.7)% *vs*. 4 (0.2; 9.8)% in controls ($p<0.05$); DPAI24 – 34.5 (12.6; 62.8) *vs*. 3.1 (0.1; 7.6) of the control group ($p<0.05$).

Disturbances of BP circadian rhythm were observed in 81.1% of patients with T2DM, with predominance of pathological patterns of "non-dipper" and "night-peaker" types. The study revealed significant differences compared to the structure of the control group with a predominance of the "dipper" pattern ($p<0.05$) (Figure 1).

We found many relationships between ABPM indicators and blood glucose characteristics, as well as eGFR and ACR using Spearman's rank correlation (Table 2).

Due to the presence of a significant number of correlations, a canonical correlation analysis was performed to assess the complexity of these relationships. A strong significant correlation between ABPM indicators (average SBP, DBP, PBP and their variabilities, SPTI24, SPAI24, DPTI24, DPAI24) and complex laboratory and CGM parameters (HbA1c, SD, eGFR, ACR TAR, TIR and TBR,) was determined: $R=0.82$ ($\chi^2=261.76$; $p=0.001$).

The first canonical root extracts 100% of the variance from the left set of variables (laboratory and CGM parameters) i 66.22% – from the right set of variables (ABPM indicators). The total redundancy of the left values is 60.55%, and of the right values is 49.17%. These indicators are strongly and moderately correlated with the combined factor – laboratory and CGM parameters.

Based on the evaluated loadings of the variables for the first canonical function from the laboratory values set, the most important were ACR (loading: 0.972), TBR (0.420), SD (0.425), and HbA1c (0.409). From the ABPM values set, the most important were SPAI24, SPTI24, DPAI24, and DPTI24 (evaluated loadings 0.770, 0.711, 0.625, 0.600, respectively).

In the left set of variables, the highest canonical weights in the module relate to SD and TBR (the absolute value of the canonical weight – 2.763 and 2.630,

Table 1: The characteristics of the analyzed parameters in T2DM patients and the control group (median and interquartile range Me (25%; 75%).

Values	T2DM patients (n=53)	Control (n=10)
HbA1c (%)	8.1 (6.6; 9.7)	4.8 (4.4; 5.2)*
eGFR (ml/min/1.73 m²)	82.5 (72.5; 95.5)	94,5 (85; 102)*
ACR (mg/mmol)	5.5 (3.2; 10.4)	1.4 (0.9; 2.2)*
SD (mmol/l)	2.8 (1.7; 3.8)	0.9 (0.7; 1)*
TBR (%)	6.0 (3.0; 9.0)	0*
TAR (%)	39.0 (19; 41.0)	0*
TIR (%)	49.0 (39; 64.0)	100*
Average SBP (mm Hg)	129 (119; 138)	117 (114; 124)*
SBP variability (mm Hg)	14 (12; 16)	11 (10; 12)*
Average DBP (mm Hg)	78 (74; 81)	73 (71; 74)*
DBP variability (mm Hg)	10 (9; 13)	8 (7; 10)*
Average PBP (mm Hg)	53 (44; 58)	44.5 (42; 50)*
PBP variability (mm Hg)	12 (9; 16)	9 (7; 10)*

Note: * – $p<0.05$ compared to control.

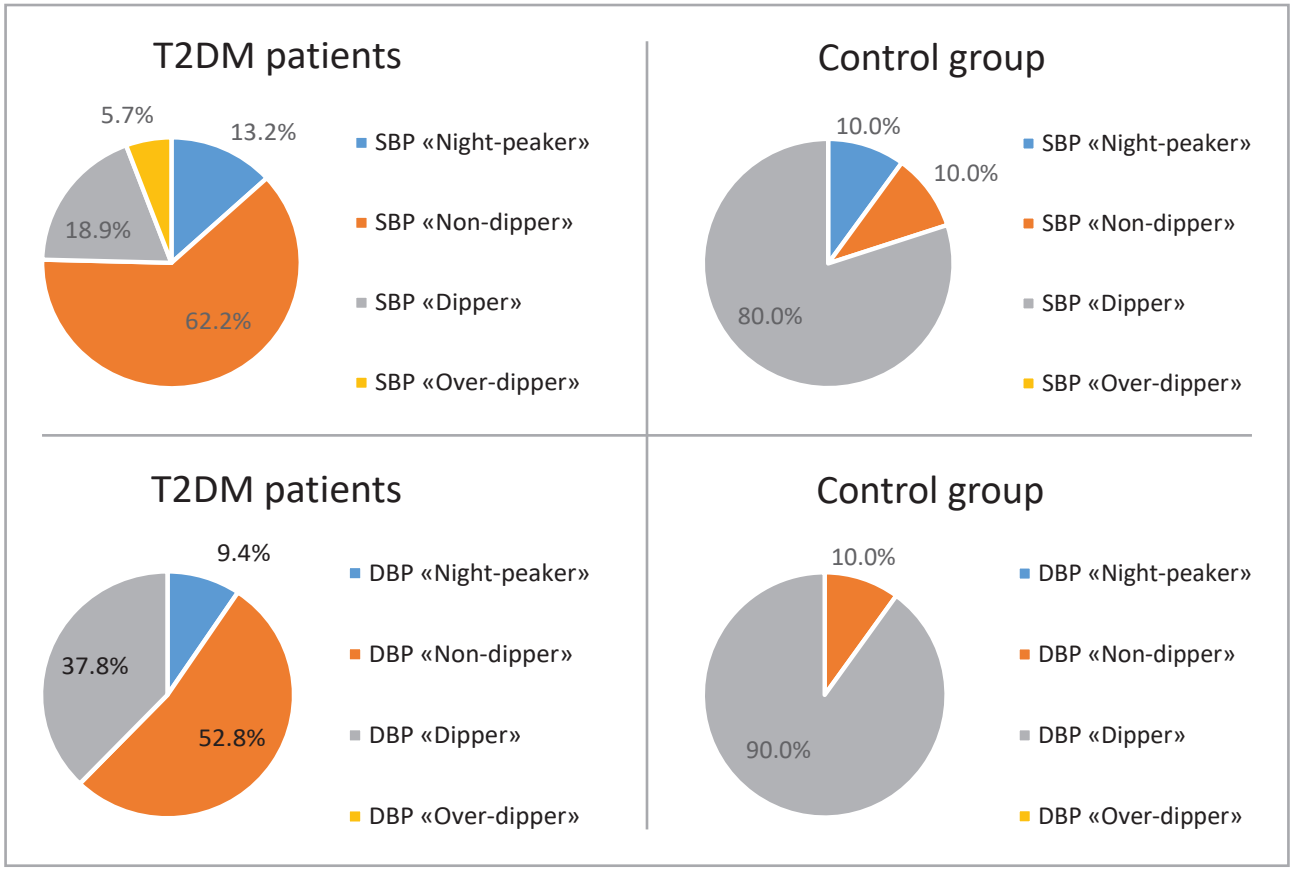

Figure 1: Distribution of T2DM patients and the control group by circadian blood pressure patterns.

respectively). SPAI24 and SPTI24 made the greatest contribution to the right set of values (the absolute value of the canonical weight – 4.488 and 4.401, respectively) (Figure 2).

Therefore, based on the performed canonical correlation analysis, we conclude that glucose variability, together with hypoglycemia, affects the ABPM indicators and determines them by 60.55% with the greatest impact on the SPAI24 and SPTI24.

Discussion

Our study analyzed ABPM indicators in well-controlled hypertensive patients with T2DM compared with well-controlled hypertensive nondiabetic controls. We found several significant differences, apparently due to the presence of carbohydrate metabolism disorders.

Our observations show that parameters such as average daily values of SBP, DBP, and PBP and their variabilities are significantly higher in T2DM patients. It can be explained by the mechanisms by which T2DM (precisely, insulin resistance) contributes to the development of hypertension. In the literature review, Jia G. *et al.* considered the issues of diabetes-related hypertension and identified the most important mechanisms of its development. This complex of processes includes molecular and cellular mechanisms of the inappropriate renin-angiotensin-aldosterone system and

Table 2: Correlations between ABPM indicators and laboratory parameters, including CGM, in T2DM patients (Spearman's rank correlation coefficient – rs).

Values	HbA1c	SD	TAR	TIR	TBR	eGFR	ACR
Average SBP	0.22*	0.35*	0.24*	-0.21*	0.42*	-0.36*	0.34*
SBP variability	0.11	0.26*	0.12	-0.1	0.31*	-0.34*	0.31*
Average DBP	0.27*	0.30*	0.28*	-0.32*	0.38*	-0.35*	0.32*
DBP variability	0.14	0.23*	0.13	-0.10	0.25*	-0.22*	0.20*

https://doi.org/10.46389/rjd-2023-1290

Table 2: Continued.

Values	HbA1c	SD	TAR	TIR	TBR	eGFR	ACR
Average PBP	0.23	0.09	0.24	-0.22	0.19	-0.06	0.16
PBP variability	0.18	0.21	0.16	-0.17	0.17	-0.02	0.11
SPAI24	0.22*	0.51*	0.23*	-0.36*	0.53*	-0.52*	0.48*
SPTI24	0.24*	0.54*	0.26*	-0.35*	0.55*	-0.51*	0.49*
DPAI24	0.25*	0.30*	0.22*	-0.29*	0.32*	-0.35*	0.42*
DPTI24	0.21*	0.34*	0.20*	-0.24*	0.30*	-0.32*	0.40*

Note: * – correlation coefficients are statistically significant ($p<0.05$).

sympathetic nervous system activation, increased activation of renal and endothelial sodium channels, mitochondrial dysfunction, oxidative stress, inflammation, abnormal exosomal microRNAs, abnormal gut microbiota and increased renal sodium-glucose cotransporter-2 inhibitors activity [4].

Moreover, significantly higher BP variability in these patients compared to the control group is prognostically unfavorable because it is related to alterations in functional and structural cardiovascular and renal regulatory mechanisms, subclinical or established cardiovascular damage and autonomic dysfunction [8, 9].

The predominant "non-dipper" patterns and emerging "night-peaker" patterns found in our study indicate an increased risk of adverse cardiovascular outcomes independent of average BP level. It forms target organ damage, namely, left ventricular hypertrophy,

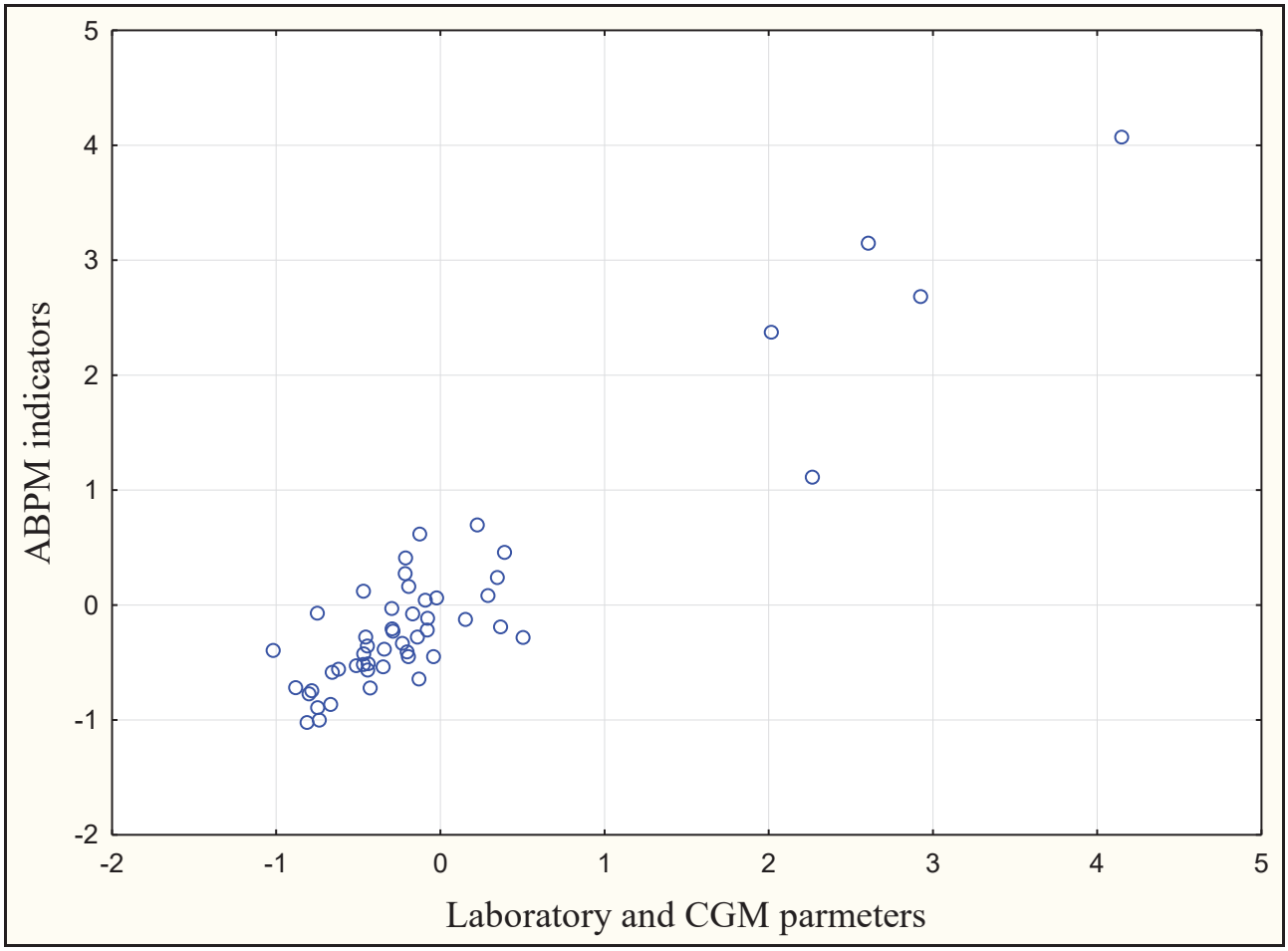

Figure 2: Canonical correlation relationship between laboratory and CGM parameters and ABPM indices in patients with T2DM.

formation of diastolic dysfunction and, increased ACR, increased prevalence of diabetic retinopathy [10].

In addition, Chotruangnapa C. *et al.* concluded that hyperglycemia is associated with a "non-dipper" pattern because hyperinsulinism in an insulin-resistant state causes sodium retention and alteration of arterial structure and function [11]. By the way, BP load has a significant impact on hypertension-mediated organ damage, in addition to arterial hypertension, pathological BP patterns ("non-dipper" and "night-peaker") and increased BP variability. The ARIC (Atherosclerosis Risk in Communities) study showed the importance of the cumulative effect of elevated SBP in the development of heart failure [12].

In our patients, the glycemic profile, to the greatest extent, determined precisely the SBP load. We found a lot of significant correlations between ABPM indicators and glycemic parameters. The largest number of moderate relationships were established between BP load indicators and the following parameters: SD, TBR, eGFR, and ACR.

The mechanisms of influence of kidney function indicators on BP are quite clear, but the relationship between BP and the glycemic profile characteristics requires attention. These relationships have never been fully elucidated because studies are either observational or limited to a retrospective analysis of trials not primarily designed to address this issue.

It is well known that hypoglycemia in diabetes is associated with increased morbidity and constitutes a barrier to glycemic control. The sympathoadrenal response during hypoglycemia increases the release of adrenaline and can lead to high BP, and arrhythmias and contribute to cardiovascular risk [13]. Besides, many researchers have concluded that glucose variability is not only associated with cardiovascular events but is also a causal risk factor for diabetes complications in the presence of persistent ambient hyperglycemia. Study on the influence mechanisms of high glycemic fluctuations on cardiovascular risks revealed their ability to accelerate oxidative stress, the release of inflammatory cytokines and vascular endothelial dysfunction [14, 15].

Due to the establishment of significant relationships in our research, further study of the role of glycemic variability is of paramount importance to achieve optimal glycemic control in T2DM patients.

Conclusions

Thus, our study shows that patients with T2DM, even with well-controlled arterial hypertension, have disturbances in circadian blood pressure rhythm with the predominance of "non-dipper" and the appearance of "night-peaker" patterns.

The findings obtained from the CCA indicated a strong statistically significant relationship between ABPM indicators and high glucose variability together with hypoglycemia. These characteristics of the glycemic profile explained 60.55% of the variance in ABPM indicators, mainly affecting the variability of SBP load indicators.

Reduction of high glucose variability means the establishment of good glycemic control, in addition to achieving the target HbA1c. Low glucose variability and the absence of hypoglycemic episodes are priorities to prevent the development and progression of vascular complications in T2DM patients.

Conflict of interest

The authors declare no conflict of interest.

References

1. International Diabetes Federation. IDF Diabetes Atlas, 10th edn. Brussels, Belgium: 2021. Available at: https://www.diabetesatlas.org.
2. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. Cardiovasc Diabetol 17(1): 83, 2018. doi: 10.1186/s12933-018-0728-6.
3. González-Clemente JM, Giménez-Palop O, Caixàs A *et al.* Escasa caracterización clínica de los pacientes con diabetes mellitus incluidos en los principales ensayos clínicos sobre hipertensión arterial [Low reporting of clinical characteristics of patients with diabetes mellitus included in the main clinical trials on hypertension]. Med Clin (Barc) 125(5): 173-178, 2005. Spanish. doi: 10.1157/13077140.
4. Jia G, Sowers JR. Hypertension in Diabetes: An Update of Basic Mechanisms and Clinical Disease. Hypertension 78(5): 1197-1205, 2021. doi: 10.1161/HYPERTENSIONAHA.121.17981.
5. Petrie JR, Guzik TJ, Touyz RM. Diabetes, hypertension, and cardiovascular disease: clinical insights and vascular mechanisms. Can J Cardiol 34(5):575-584, 2018. doi: 10.1016/j.cjca.2017.12.005.
6. American Diabetes Association Professional Practice Committee. Standards of Medical Care in Diabetes—2022. Diabetes Care 45(Suppl. 1): S17–S97, 2022. Available at: https://diabetesjournals.org/care/issue/45/Supplement_1.
7. Levey AS, Stevens LA, Schmid CH *et al.* A new equation to estimate glomerular filtration rate. Ann Intern Med 150(9):604-612, 2009. doi: 10.7326/0003-4819-150-9-200905050-00006.
8. Schutte AE, Kollias A, Stergiou GS. Blood pressure and its variability: classic and novel measurement techniques. Nat Rev Cardiol 19(10): 643-654, 2022. doi: 10.1038/s41569-022-00690-0.
9. Parati G, Torlasco C, Pengo M, Bilo G, Ochoa JE. Blood pressure variability: its relevance for cardiovascular homeostasis and

 https://doi.org/10.46389/rjd-2023-1290

cardiovascular diseases. Hypertens. Res 43(7): 609–620, 2020. doi: 10.1038/s41440-020-0421-5.

10. Gavriilaki M, Anyfanti P, Nikolaidou B *et al*. Nighttime dipping status and risk of cardiovascular events in patients with untreated hypertension: A systematic review and meta-analysis. J Clin Hypertens (Greenwich) 22(11): 1951-1959, 2020. doi: 10.1111/jch.14039.
11. Chotruangnapa, C, Tansakun, T, Roubsanthisuk, W. Clinical risk factors and predictive score for the non-dipper profile in hypertensive patients: a case-control study. Clin Hypertens 27(1): 22, 2021. doi: 10.1186/s40885-021-00180-4.
12. Schutte AE, Gnanenthiran SR. Toward a better understanding of why cumulative blood pressure is such a strong predictor of cardiovascular outcomes. Hypertension 78(5): 1267-1269, 2021. doi: 10.1161/HYPERTENSIONAHA.121.18156
13. Nakhleh A, Shehadeh N. Hypoglycemia in diabetes: An update on pathophysiology, treatment, and prevention. World J Diabetes 12(12): 2036-2049, 2021. doi: 10.4239/wjd.v12.i12.2036.
14. Monnier L, Colette C, Owens D. Glucose variability and diabetes complications: Risk factor or biomarker? Can we disentangle the "Gordian Knot"? Diabetes Metab 47(3):101225, 2021. doi: 10.1016/j.diabet.2021.101225
15. Zhang L, Li F, Liu HH *et al*. Glycaemic variability and risk of adverse cardiovascular events in acute coronary syndrome. Diab Vasc Dis Res 19(6): 14791641221137736, 2022. doi: 10.1177/14791641221137736.