Original Article

OPEN

INFOGRAPHIC

Assessing the relationship between short-term blood pressure variability and glycation profile in young and middle-aged nondiabetic hypertensive individuals

Nestor Vazquez-Agra[a,b,c,*], Lucia Barrera-Lopez[a,b,*], Ana-Teresa Marques-Afonso[a,b], Anton Cruces-Sande[b,c,*], Jose-Enrique Lopez-Paz[a], Antonio Pose-Reino[a,b,c,†], and Alvaro Hermida-Ameijeiras[a,b,c,†]

See related paper on page 1146

Introduction: Elevated short-term blood pressure (BP) variability (BPV) has been associated with a poorer cardiovascular prognosis. The glycation profile is related to BPV in diabetic and prediabetic individuals. However, little is known about the relationship between glycation levels and BPV in hypertensive patients with optimal glycemic control.

Objectives: This observational study aimed to elucidate the relationship between glycated hemoglobin (HbA1c) levels and short-term BPV in young and middle-aged hypertensive patients over 18 years with HbA1c levels below 5.7%.

Methods: We collected and analyzed data on 24-h ambulatory BP monitoring, demographic, epidemiological, clinical, and laboratory variables from 143 hypertensive patients. BPV was measured as the standard deviation (SD) and average real variability (ARV) in millimeters of mercury, as well as the dimensionless coefficient of variation (CV).

Results: Depending on the index, each one unit increase in nighttime SD and CV indices was associated with a 17–24% higher likelihood of elevated HbA1c levels (higher than 5.2%). Regarding BPV dipping, each 1% decrease in nighttime SD and CV dipping was associated with a 10–20% higher risk of increased HbA1c levels. Additionally, each 1% decrease in nighttime ARV DBP dipping was also associated with a 10% higher risk of elevated HbA1c levels. A one-standardized-unit increase in the overall combined BPV index, as a pooled measure of BPV, was associated with a 45% higher likelihood of raised HbA1c levels.

Conclusion: Even within the optimal range, elevated HbA1c levels may reflect an underlying increase in BPV, which may be particularly relevant given the prognostic implications of short-term BPV.

Graphical abstract: http://links.lww.com/HJH/C716

Keywords: blood pressure variability, glycated hemoglobin, glycation, hypertension, short-term

Abbreviations: 24-hDBP, 24-h average DBP; 24-hSBP, 24-h average SBP; ABPM, ambulatory blood pressure monitoring; AGEs, advanced glycation end products; ARV, average real variability; BP, blood pressure; BPV, blood pressure variability; CV, coefficient of variation; dDBP, daytime DBP; dSBP, daytime SBP; HbA1c, glycated hemoglobin; MACE, major cardiovascular events; nDBP, nighttime DBP; nSBP, nighttime SBP; PCA, principal component analysis; RAAS, renin–angiotensin–aldosterone system; SD, standard deviation

BACKGROUND

Elevated blood pressure (BP) is the leading cause of death worldwide [1]. Ambulatory BP monitoring (ABPM) has shown that 24-h SBP and DBP levels are more reliable predictors of prognosis than conventional measurements. Additionally, nighttime BP indices have proven to be stronger predictors of major cardiovascular events (MACE) compared to daytime readings [2].

Beyond average BP levels, fluctuations in BP also carry significant prognostic implications [3]. BP variability (BPV) can be categorized chronologically into very short-term

Journal of Hypertension 2025, 43:1148–1157

[a]Department of Internal Medicine, University Hospital of Santiago de Compostela, [b]Health Research Institute of Santiago de Compostela (IDIS) and [c]University of Santiago de Compostela (USC), Santiago de Compostela, A Coruña, Spain

Correspondence to Nestor Vazquez-Agra, Medical Physician, Postdoctoral Researcher. Department of Internal Medicine, University Hospital of Santiago de Compostela, A Choupana Street, no number, 15706 Santiago de Compostela, A Coruña, Spain. Tel: +0034981950000; e-mail: nestor.vazquez.agra@sergas.es

*N.V.-A., L.B.-L., and A.C.-S. are co-corresponding authors.

†A.P.-R. and A.H.-A. contributed equally to this work.

Received 28 October 2024 **Revised** 14 March 2025 **Accepted** 16 March 2025

J Hypertens 43:1148–1157 Copyright © 2025 The Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

DOI:10.1097/HJH.0000000000004029

(seconds to minutes), short-term (24 h), and long-term (days to years). Short-term BPV is particularly important as it reflects daily BP dynamics in response to external factors, such as postural changes, wake–sleep cycles, physical activity, emotional stress, and treatment adherence; as well as internal factors, including arterial wall biomechanics and autonomic function [4]. Short-term BPV has been associated with all-cause mortality, cardiovascular death, and MACE [3]. In terms of subclinical organ damage, short-term BPV has been linked to higher levels of left ventricular mass, arterial stiffness, carotid atherosclerosis, and renal dysfunction, suggesting it as a potential therapeutic target [5–7].

Hyperglycemia and oxidative stress, characterized by an imbalance favoring pro-oxidant species over antioxidant defense systems, enhance glycation processes that have been shown to impact metabolism and hemodynamics in diabetes mellitus (DM) complications [8]. Glycation is a nonenzymatic process in which sugars, primarily glucose, covalently bind to organic molecules, altering their structure and function. The final stage of this process leads to the formation of advanced glycation end-products (AGEs), which directly and indirectly contribute to endothelial dysfunction, chronic inflammation, and arteriosclerosis [9,10].

Multiple studies have demonstrated a link between an unfavorable glycation profile and abnormalities in both average BP levels and BPV in diabetic and prediabetic patients [11,12]. Emerging evidence has also highlighted the impact of glycation processes on nighttime BP levels in nondiabetic and prediabetic individuals [13,14]. However, there is still limited understanding of whether the glycation profile and BPV are related in hypertensive patients with optimal glycation levels. To address this, we evaluated the relationship between glycated hemoglobin (HbA1c) levels and BPV indices in young and middle-aged hypertensive patients with strictly normal HbA1c levels.

MATERIAL AND METHODS

Study design, setting, and participants

This was an observational, cross-sectional study conducted in the Department of Internal Medicine at the University Hospital of Santiago de Compostela during the first half of 2023. We assessed the relationship between HbA1c, as a relevant marker of glycation, and a set of independent variables, including clinical-anthropometric aspects, laboratory parameters, and BP indices. The inclusion criteria were outpatients aged 18–70 years with HbA1c levels below 5.7% and a confirmed diagnosis of essential hypertension, based on 24-h ABPM results according to the European Society of Hypertension (ESH) guidelines. Exclusion criteria included current smoking (within 6 months prior to recruitment), high-risk alcohol consumption (defined as more than 10 g per day for women and 20 g per day for men), and the presence of DM and pre-DM [15–17].

Clinical and laboratory baseline variables

We collected data on participants' age, sex, alcohol consumption (categorized as nondrinker vs. low-risk drinker), history of tobacco use (categorized as no/yes), and physical activity, following ESH guidelines [15]. BMI was calculated as weight divided by height squared (kg/m^2). Waist circumference (WC) was measured just above both iliac crests using a standardized tape measure and recorded in centimeters [18,19]. Blood samples were obtained at 8 a,m, after a 12-h overnight fast, ensuring at least 12 h had passed since the last dose of antihypertensive medication. HbA1c levels were quantified using high-performance liquid chromatography with the HbNEXT system (Menarini Diagnostics, Barcelona, Spain).

Parameters of 24-h ambulatory blood pressure monitoring collection

We followed the methodology used in our previous studies, consistently adhering to the recommendations outlined in major consensus documents [15,20–22]. Patients underwent 24-h ABPM in compliance with STRIDE BP standards, using one of the following validated oscillometric devices: SpaceLabs 90207 (Space-Labs Inc., Redmond, Washington, USA), Microlife WatchBP O3 (Microlife Corporation, Widnau, Switzerland), and Cardioline Walk 200b (AB Medica Group, S.A., Barcelona, Spain) [20]. BP readings were taken every 20 min during the daytime and every 30 min at night, with time periods based on patients' self-reports. The test was considered reliable if more than 70% of the expected measurements were valid. On the day of monitoring, patients completed a form detailing their sleep times, medication use, and any issues experienced during the recording process. When the patient explicitly reported disrupted sleep during the test, the 24-h ABPM was repeated.

The following average indices were obtained: 24-h SBP (24-hSBP), daytime SBP (dSBP), and nighttime SBP (nSBP); 24-h DBP (24-hDBP), daytime DBP (dDBP), and nighttime DBP (nDBP). Similarly, short-term BPV indices were calculated for 24-h, daytime, and nighttime SBP and DBP standard deviation (24-hSBP-SD, dSBP-SD, nSBP-SD, 24-hDBP-SD, dDBP-SD, nDBP-SD), coefficient of variation (24-hSBP-CV, dSBP-CV, nSBP-CV, 24-hDBP-CV, dDBP-CV, nDBP-CV), and average real variability (24-hSBP-ARV, dSBP-ARV, nSBP-ARV, 24-hDBP-ARV, dDBP-ARV, nDBP-ARV) according to the literature [3,23,24]. As for the relationship between daytime and nighttime BP levels, nSBP dipping and nDBP dipping were calculated as the ratio of the difference between daytime and nighttime indices, to the daytime index, expressed as a percentage. Regarding the relationship between daytime and nighttime BPV (nighttime BPV dipping), nSBP-SD, nDBP-SD, nSBP-CV, nDBP-CV, nSBP-ARV and nDBP-ARV dipping were also calculated as the ratio of the difference between daytime and nighttime indices, to the daytime index, expressed as a percentage [25,26].

Glycation profile: glycated hemoglobin levels

To evaluate the relationship between HbA1c levels and the remaining variables, we divided the patients into two categories based on an optimal cutoff point for HbA1c levels in order to facilitate the analysis and interpretability of the results. In a preliminary analysis of the sample, we did not identify optimal cutoff points for 24-h or daytime BPV indices. However, HbA1c values of 5.15 and 5.25% emerged as the optimal cutoffs for distinguishing differences between the groups in nocturnal DBP and SBP variability indices, respectively. This led us to select a general HbA1c cutoff of 5.2%, equivalent to the 25th

percentile (p25) [27]. To avoid losing information in the analysis, we also studied the continuous relationship between the BP indices and HbA1c levels.

Ethical statement

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and the standards of good practice (NBP) in research. Before participation, all patients received comprehensive information about the study to ensure their understanding and voluntary consent, and written informed consent was obtained. The study protocol was formally approved by the Research Ethics Committee of Santiago-Lugo, underscoring our commitment to ethical standards in biomedical research (code 2021/401).

Statistical analysis

Statistical analysis was performed using SPSS 22.0 (SPSS Inc., Chicago, Illinois, USA). Descriptive analyses were conducted, with qualitative variables expressed as number (percentage) and quantitative variables as median (interquartile range).

For the univariate analysis, qualitative and quantitative variables were compared using the chi-squared test and the Mann–Whitney *U* test, respectively. To explore linear relationships between HbA1c levels and BPV indices, a partial correlation analysis was conducted, with results reported as Spearman's correlation coefficients. A *P* value of less than 0.05 was considered statistically significant.

Multivariate analysis was performed using binary logistic regression, with HbA1c levels dichotomized (above or below 5.2%). Predictor variables were the BPV indices. Before constructing the final multivariate model for each BPV index, a bivariate analysis was conducted using binary logistic regression to identify potential interactions with other covariates. Interaction terms were considered relevant if their coefficients were statistically significant. Confounding variables were identified as those that altered the odds ratio by 10% or more. The selection of the optimal model for each BP index involved a thorough evaluation, including the omnibus test of model coefficients for initial validation, the Hosmer–Lemeshow test for goodness of fit, and adherence to the assumptions of binary logistic regression. In the final models, only coefficients with statistical significance ($P < 0.05$) were deemed relevant.

Principal component analysis (PCA) was applied to reduce the dimensionality of BPV individual indices, aiming to minimize the risk of multicollinearity and explore variability patterns. This methodology decomposes the data matrix into orthogonal principal components (PCs) that maximize explained variance in descending order. From the generated PCs, those with the highest cumulative variance were selected based on Kaiser's criterion (eigenvalues >1) and the ecree plot. Factor loadings were calculated to evaluate each variable's contribution to the selected PCs, enabling the interpretation of their influence on the data structure. We employed open-source Python resources available at https://anaconda.org/ [28]. The PCA principles have been applied by solving the characteristic equation and polynomial, with the methodology detailed in Supplementary Appendix 1, http://links.lww.com/HJH/C708 [29]. First, the individual BPV indices that yielded relevant results ($P < 0.05$) in the multivariate analysis were included in a PCA to build the best overall combined BPV index. Then, the individual indices of SD, CV, and ARV were included in a PCA to construct the combined SD, CV, and ARV indices, respectively, in order to assess the performance of each group of BPV indices for HbA1c levels.

The sample size was calculated using the EPIDAT software, available at https://www.sergas.es/Saude-publica/EPIDAT?idioma=es. The calculations were based on the objective of detecting a standardized mean difference of 0.5 in the evaluated BP indices between the groups, as a common benchmark in many areas of biomedical research, often considered a 'medium' effect size according to Cohen's conventions, with a 95% confidence level and a statistical power of at least 80% [30].

RESULTS

Sample overview and general results

A total of 143 well controlled hypertensive patients participated in the study, with a median age of 55 years, of whom 82 (57%) were women. Nearly half of the participants engaged in moderate physical activity, while one-fifth reported low-risk alcohol consumption and one-quarter had a history of former smoking. All patients adhered to lifestyle recommendations, and just under 80% of the patients were receiving antihypertensive medications, with drugs targeting the renin–angiotensin–aldosterone system (RAAS) being the most commonly used. The detailed results are provided in Table 1.

Relationship between glycated hemoglobin levels and 24-h ambulatory blood pressure monitoring indices: univariate analysis

Patients with HbA1c levels above 5.2% were generally older, taking antihypertensive medications, and had higher fasting plasma glucose (FPG) levels. The group with lower HbA1c levels included 10% more women and patients with moderate physical activity, although these differences did not reach statistical significance. No relevant differences were observed between the groups regarding laboratory variables (Table 1).

Regarding 24-h BP indices, the groups were comparable in 24-h, daytime, and nighttime SBP and DBP. We found no relevant differences between the groups regarding 24-h and daytime BPV. However, patients with higher HbA1c levels showed a greater nighttime systolic and diastolic BPV for SD, CV and ARV indices. In terms of nighttime BP dipping, no differences were observed between the groups. Nevertheless, patients with higher HbA1c levels exhibited a blunted decrease in nighttime systolic and diastolic BPV for SD, CV and ARV indices. The results are illustrated in Fig. 1. A detailed breakdown of all findings is provided in Table 2 and Supplementary Table 1, http://links.lww.com/HJH/C712.

Partial correlation analysis between glycated hemoglobin levels and blood pressure variability indices

According to BPV indices, we found that HbA1c levels were positively correlated with nSBP-SD ($\rho = 0.228$, $P = 0.006$),

TABLE 1. General results and group comparisons based on glycated hemoglobin levels

Variables	Total	Groups[a]		
	($n = 143$)	HbA1c (%) $\leq$ 5.2 ($n = 47$)	HbA1c (%) $>$ 5.2 ($n = 96$)	*P* value
Age (years)†	55 (17)	48 (11)	59 (15)	<0.001
Sex (women) ‡	82 (57)	31 (66)	51 (53)	0.155
Alcohol intake[b] ‡	28 (20)	9 (19)	19 (20)	0.999
Former smokers[c] ‡	49 (34)	14 (30)	35 (37)	0.459
Physical activity[d] ‡	65 (46)	25 (54)	40 (42)	0.208
BMI (kg/m^2) †	27.5 (7)	26.8 (9)	28.1 (7)	0.128
WC (cm) †	101 (20)	96 (23)	102 (20)	0.128
AHT drugs ‡	112 (78)	31 (66)	81 (84)	0.017
RAAS blockers ‡	77 (54)	23 (49)	54 (56)	0.476
Diuretics ‡	36 (25)	12 (26)	24 (25)	0.999
CCBs ‡	61 (43)	19 (40)	42 (44)	0.723
B-blockers ‡	21 (15)	5 (11)	16 (17)	0.453
Hb (g/dl) †	14.5 (1.8)	14.1 (1.8)	14.5 (1.7)	0.089
FPG (mg/dl) †	97 (15)	93 (16)	99 (13.5)	0.017
HbA1c (%) †	5.3 (0.3)	5.1 (0.2)	5.5 (0.3)	<0.001
Creatinine (mg/dl)†	0.81 (0.3)	0.83 (0.2)	0.80 (0.3)	0.595
TG (mg/dl) †	83 (64)	82 (70)	83 (59)	0.574
TC (mg/dl) †	191 (43)	187 (42)	192 (46)	0.817

Results expressed as † refer to the median and interquartile range, and results expressed as ‡ refer to the number and percentage. AHT, arterial hypertension; BMI, body mass index; CCBs, calcium channel blockers; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; Hb, hemoglobin; RAAS, renin–angiotensin–aldosterone system; TC, total cholesterol; TG, triglycerides; WC, waist circumference.
[a]Patient groups according to HbA1c levels.
[b]Low-risk alcohol consumption defined as less than 10 and 20 g per day for women and men, respectively.
[c]Former smokers for more than 6 months at the time of recruitment.
[d]Moderate physical activity equivalent to 150 min of moderate-intensity walking per week.

and nDBP-SD ($\rho = 0.204$, $P = 0.015$), with similar results for the CV indices. However, nighttime BPV indices based on ARV did not show a relevant correlation with HbA1c levels. Partial correlation analysis showed that age and waist circumference influenced the correlations of nighttime SD and CV indices with HbA1c levels. The overall correlation results are illustrated in Fig. 2, and the detailed partial correlations are provided in Supplementary Table 2, http://links.lww.com/HJH/C713.

In terms of nighttime BPV dipping, HbA1c levels were negatively correlated with nSBP-SD dipping ($\rho = -0.194$, $P = 0.020$) and nDBP-SD dipping ($\rho = -0.239$, $P = 0.004$), with similar results for the CV indices. Regarding nocturnal ARV parameters, only nDBP-ARV dipping showed a relevant correlation with HbA1c levels ($\rho = -0.211$, $P = 0.012$). Partial correlation analysis revealed that sex and waist circumference were influential factors in the correlation between HbA1c and nSBP-CV dipping. For the remaining BPV dipping indices (nSBP-SD, nDBP-SD, nDBP-CV, and nDBP-ARV dipping) the partial correlation analysis did not influence the results identified in the unadjusted analysis (Fig. 2, Supplementary Table 2, http://links.lww.com/HJH/C713).

Association between individual blood pressure variability parameters and combined blood pressure variability indices based on principal component analysis with glycated hemoglobin levels: multivariate analysis

Binary logistic regression analysis examining the relationship between HbA1c levels (cutoff point 5.2%) and nighttime BPV confirmed that patients with higher HbA1c levels were more likely to show an increased nighttime BPV and reduced BPV dipping. Regarding BPV, each 1 unit increase in nighttime SD and CV indices was associated with an approximately 17–24% higher likelihood of elevated HbA1c levels, without relevant results for ARV indices. According to BPV dipping, each 1% decrease in nighttime SD and CV dipping was associated with a 10–20% higher risk of elevated HbA1c levels. Additionally, each 1% decrease in nDBP-ARV dipping was also associated with a 10% increased risk of high HbA1c levels. The detailed results are provided in Table 3.

The PCA technical results of the overall combined BPV index are detailed in Fig. 3, while the findings of the other combined BPV indices are shown in Supplementary Figure 1, http://links.lww.com/HJH/C709, Supplementary Figure 2, http://links.lww.com/HJH/C710, and Supplementary Figure 3, http://links.lww.com/HJH/C711. Multivariate analysis (Table 3, bottom) revealed a stronger association between the overall combined BPV index and HbA1c levels (cutoff point 5.2%) compared to individual BPV indices. Indeed, a one-standardized-unit increase in the overall combined BPV index was associated with a 45% higher likelihood of elevated HbA1c levels. The PCAs performed on the sets of SD, CV, and ARV indices demonstrated that the combined SD and CV indices outperformed the combined ARV index in their association with HbA1c levels. Indeed, a one-standardized-unit increase in the combined SD and CV indices was associated with over a 50% higher likelihood of elevated HbA1c levels. The ROC curves in Fig. 4 illustrate the performance of the combined BPV indices for HbA1c levels.

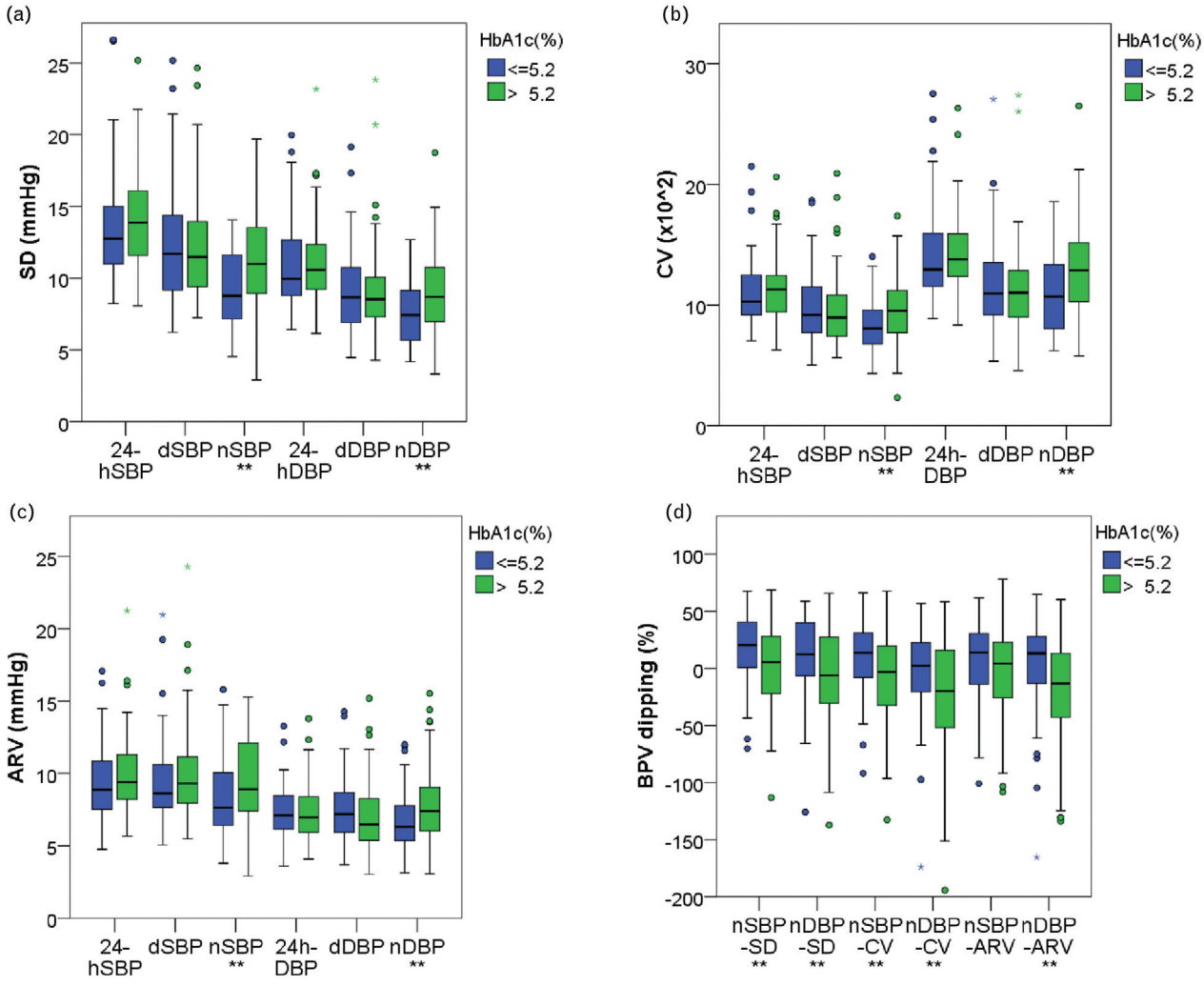

FIGURE 1 Comparison of blood pressure variability between patients with glycated hemoglobin levels below (blue) and above (green) 5.2%. (a) SD indices; (b) CV indices; (c) ARV indices; (d) nighttime BPV dipping. Results marked with ** reached a *P* value of less than 0.05. The numerical values of all indices are shown in Supplementary Table 1, http://links.lww.com/HJH/C712. %, percentage; 24-hDBP, 24-h DBP; 24-hSBP, 24-h SBP; ARV, average real variability; BP, blood pressure; BPV, blood pressure variability; CV, coefficient of variation; DBP, diastolic BP; dDBP, daytime DBP; dSBP, daytime SBP; HbA1c, glycated hemoglobin; nDBP, nighttime DBP; nSBP, nighttime SBP; SBP, systolic BP; SD, standard deviation.

TABLE 2. Comparison of groups attending to 24-h ambulatory blood pressure monitoring average indices

Variables	Total	Groups[a]		
	(*n* = 143)	HbA1c (%) ≤ 5.2 (*n* = 47)	HbA1c (%) > 5.2 (*n* = 96)	*P* value
24-hSBP (mmHg) †	125 (16)	122 (22)	126 (16)	0.189
dSBP (mmHg) †	129 (17)	127 (23)	129 (16)	0.186
nSBP (mmHg) †	114 (20)	109 (20)	116 (19)	0.135
nSBP dipping (%) †	14.3 (13)	13.8 (14)	14.4 (13)	0.578
24-hDBP (mmHg) †	77 (14)	78 (13)	76 (13)	0.542
dDBP (mmHg) †	80 (14)	82 (13)	80 (15)	0.535
nDBP (mmHg) †	68 (12)	68 (12)	68 (13)	0.928
nDBP dipping (%) †	11.7 (10)	11.4 (10)	11.8 (11)	0.981
24-hHR (bpm) †	71 (11)	73 (10)	69 (12)	0.022
dHR (bpm) †	74 (13)	76 (10)	72 (12)	0.016
nHR (bpm) †	62 (11)	64 (12)	61 (11)	0.120

24-hDBP, 24-h DBP; 24-hHR, 24-h HR; 24-hSBP, 24-h SBP; BP, blood pressure; DBP, diastolic BP; dDBP, daytime DBP; dHR, daytime HR; dSBP, daytime SBP; HbA1c, glycated hemoglobin; HR, heart rate; nDBP, nighttime DBP; nHR, nighttime HR; nSBP, nighttime SBP; SBP, systolic BP.
[a]Groups based on HbA1c levels; results expressed as † refer to the median and interquartile range.

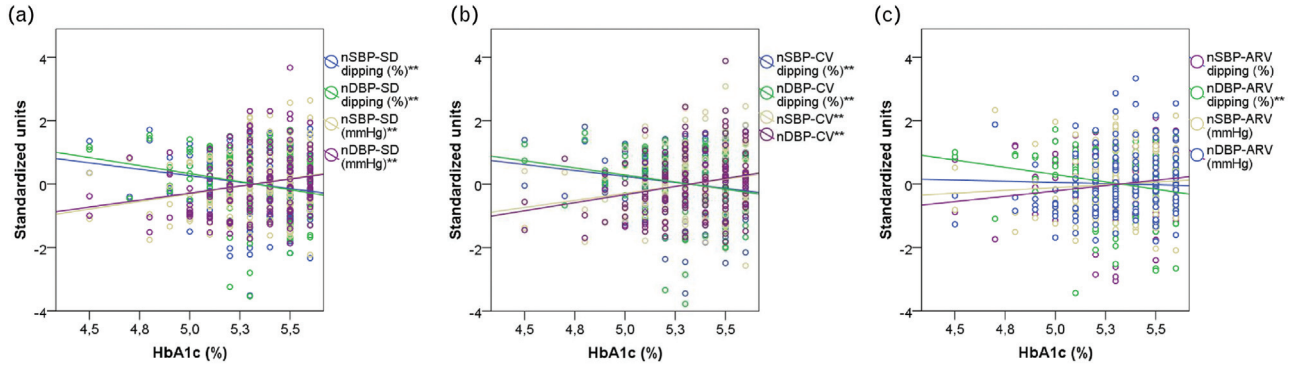

FIGURE 2 Overall linear correlation analysis for blood pressure variability indices and glycated hemoglobin levels. (a) Correlation between HbA1c levels and nighttime SD indices; (b) correlation between HbA1c levels and nighttime CV indices; (c) correlation between HbA1c levels and nighttime ARV indices. Equations: nDBP-SD = −4.69 + 0.88∗HbA1c; nSBP-SD = −5.1 + 0.96∗HbA1c; nDBP-SD dipping= 5.38 + (−1.01)∗HbA1c; nSBP-SD dipping= 4.31 + (−0.81)∗HbA1c; nDBP-CV= −5.41 + 1.02∗HbA1; nSBP-CV= −4.74 + 0.89∗HbA1c; nDBP-CV dipping= 4.75 + (−0.89)∗HbA1c; nSBP-CV dipping= 3.99 + (−0.75)∗HbA1c; nDBP-ARV= −3.57 + 0.67∗HbA1c; nSBP-ARV = −1.86 + 0.35∗HbA1c; nDBP-ARV dipping = 4.88 + (−0.92)∗HbA1c; nSBP-ARV dipping = 0.8 + (−0.15)∗HbA1c. Results marked with ** reached a *P* value less than 0.05. The complete results of the linear correlation analysis are presented in Supplementary Table 2, http://links.lww.com/HJH/C713. ARV, average real variability; BP, blood pressure; CV, coefficient of variation; HbA1c, glycated hemoglobin; nDBP, nighttime DBP; nSBP, nighttime SBP; SD, standard deviation.

DISCUSSION

This study provides one of the first insights into the relationship between HbA1c levels and BPV indices in otherwise healthy young and middle-aged individuals. The key findings can be summarized as follows: elevated HbA1c levels were associated with increased BPV and a reduced nocturnal BPV dipping; some of these relationships even demonstrated a linear correlation between HbA1c and BPV indices; the combined BPV indices showed a stronger association with HbA1c levels than the individual BPV indices they are derived from.

Glycated hemoglobin has been associated with BP levels and BPV in diabetic and prediabetic patients, always considering the impact of HbA1c levels exceeding those established in clinical practice guidelines [31,32]. However, glycation intensity exists on a continuum, even at HbA1c levels below the pathological threshold [27,33,34]. When combined with factors such as age, central obesity, hyperglycemia, and insulin resistance, this process ultimately leads to oxidative stress-mediated endothelial dysfunction. This dysfunction affects vasomotor tone, promotes vasoconstriction, and thereby contributes to elevated BP levels [35–37]. Furthermore, the formation of AGEs in arterial wall

TABLE 3. Results of logistic regression models for the association between glycated hemoglobin levels and each blood pressure predictor

Predictor	*B*	SE	*P* value	Exp(B)	95% CI (lower–upper)
Standard deviation (SD)					
nSBP-SD (mmHg)	0.161	0.065	0.014	1.175	1.034–1.335
nDBP-SD (mmHg)	0.214	0.083	0.010	1.238	1.053–1.457
nSBP-SD dipping (%)	−0.018	0.006	0.006	0.982	0.970–0.995
nSBP-SD dipping (%)	−0.015	0.006	0.008	0.985	0.974–0.996
Coeficient of variation (CV)					
nSBP-CV	0.182	0.083	0.028	1.200	1.020–1.412
nDBP-CV	0.166	0.063	0.009	1.181	1.043–1.336
nSBP-CV dipping (%)	−0.018	0.006	0.003	0.982	0.971–0.994
nDBP-CV dipping (%)	−0.013	0.005	0.006	0.987	0.977–0.996
Average real variability (ARV)					
nSBP-ARV (mmHg)	0.070	0.074	0.341	1.073	0.928–1.239
nDBP-ARV (mmHg)	0.167	0.093	0.073	1.182	0.984–1.419
nSBP-ARV dipping (%)	−0.005	0.006	0.367	0.995	0.983–1.006
nDBP-ARV dipping (%)	−0.010	0.005	0.042	0.990	0.980–0.999
Combined BPV indices					
Combined SD index (SU)[a]	0.413	0.135	0.002	1.512	1.159–1.972
Combined CV index (SU)[b]	0.435	0.138	0.002	1.545	1.179–2.025
Combined ARV index (SU)[c]	0.238	0.135	0.077	1.269	0.975–1.653
Overall combined BPV index (SU)[d]	0.370	0.137	0.007	1.447	1.106–1.893

Logistic regression models elucidating the relationship between BPV indices (predictor variables) and HbA1c levels (cutoff point 5.2%) are presented. All models incorporated data from 143 patients, ensuring no missing data. The variables to be controlled were age, sex, waist circumference, antihypertensive drugs, FPG, and hemoglobin. For all the models: Omnibus test of model coefficients (*P* value) <0.05; Hosmer–Lemeshow test (*P* value) >0.05. All comprehensive models including those variables within the final model are detailed in Supplementary Table 3, http://links.lww.com/HJH/C714. ARV, average real variability; BP, blood pressure; BPV, BP variability; CV, coefficient of variation; DBP, diastolic BP; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; nDBP, nighttime DBP; nSBP, nighttime SBP; SBP, systolic BP; SD, standard deviation; SU, standard unit; WC, waist circumference.
[a]This parameter represents a PCA over the SD indices.
[b]This variable represents a PCA over the CV indices.
[c]This index represents a PCA over the ARV indices.
[d]This parameter represents a PCA over all the individual indices.

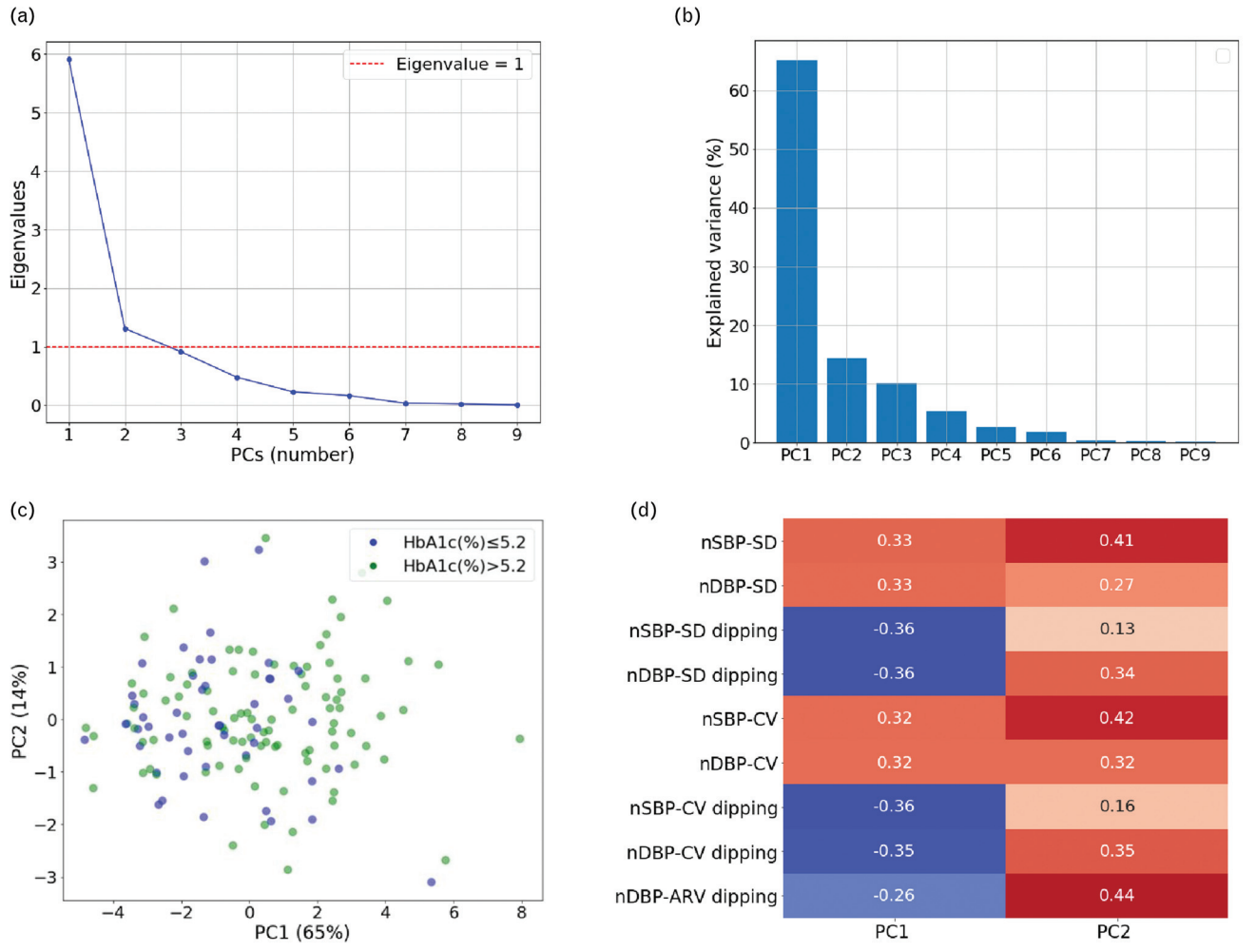

FIGURE 3 Principal component analysis to build an overall combined blood pressure variability index as a composite marker of the individual blood pressure variability parameters that achieved relevant results. (a) Ecree plot showing the PCs and their eigenvalues; (b) bar chart depicting the explained variance of the PCs; (c) scatterplot highlighting the most relevant PCs in relation to HbA1c levels; (d) heat map displaying the individual indices loadings for each PC. Among the components obtained from the PCA, only the first two PCs exhibited eigenvalues greater than 1. Together, these two components account for approximately 80% of the total variance (PC1: 65%, PC2: 14%) (a and b). When considering HbA1c levels categorized by the predefined cutoff of 5.2%, PC1 emerged as the primary differentiator between the two groups (c). This finding suggests that PC1 captures the majority of the variability associated with distinctions in HbA1c levels. Furthermore, the loadings of PC1 revealed balanced contributions from the original variables, indicating that this component proportionally summarizes their variability without disproportionately favoring any specific variable (d). This balance underscores the robustness of PC1 as a comprehensive summary of the dataset's multidimensional variability. ARV, average real variability; BP, blood pressure; CV, coefficient of variation; nDBP, average nighttime DBP; nSBP, average nighttime SBP; PC, principal component; SD, standard deviation.

proteins, particularly collagen, induces detrimental changes in their properties and structure, fostering the long-term development of arteriosclerosis [37,38].

Age and physical activity, among other factors, are key contributors to the relationship between HbA1c levels and BPV [39,40]. The decline in metabolic function, pancreatic reserve, and hematopoietic function, along with changes in body composition and reduced physical activity associated with aging, have been shown to significantly influence this relationship [41–43]. Additionally, age plays a critical role in the development of chronic vascular damage and arteriosclerosis, demonstrating a linear relationship with increased nocturnal SBP and pulse pressure, among other indices [44,45]. However, in light of these results, a portion of glycation's impact on the arterial tree may be at least partially independent of other key factors, such as age and physical activity.

It is important to emphasize the notable absence of relevant associations between 24-h and daytime BPV with HbA1c levels, especially considering that, epidemiologically, all indices typically show some degree of alignment according to the literature [4,46]. In this regard, the specific association between nocturnal BPV and HbA1c levels suggests that mechanisms regulating nighttime BPV may be particularly influenced by glycation intensity, even in young and middle-aged hypertensive patients with normal HbA1c levels [47,48]. However, further research is needed.

Additionally, it is well established that the nocturnal resting phase is associated with a physiological decrease in day-to-night average BP indices (the dipping BP profile), due to the predominance of parasympathetic tone, down-regulation of high-pressure systems, and absence of disruptions to restorative sleep, among other conditions [4,49–51]. However, the relationship between day-to-night

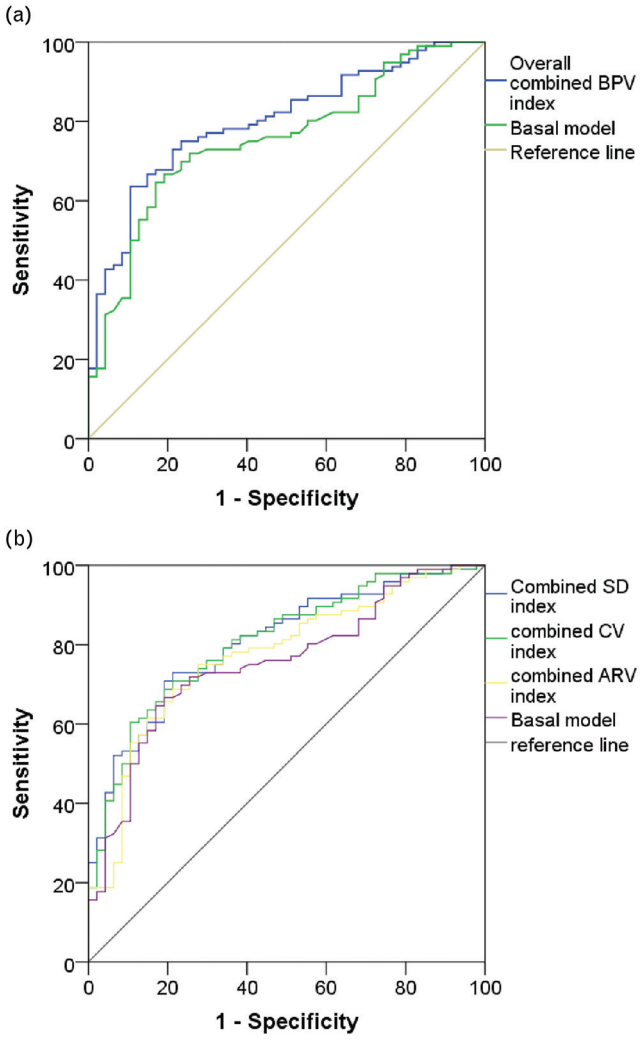

FIGURE 4 Receiver-operating characteristics curve for glycated hemoglobin levels (cutoff point 5.2%) comparing an optimal basal model (age, sex and physical activity) with (a) the overall combined BPV index and (b) the combined SD, CV, and ARV indices. Basal model: AUC = 0.754, SE = 0.042, $P < 0.001$, 95% CI (0.673–0.836), sensibility = 0.66, 1-specificity = 0.21; overall combined BPV index: AUC = 0.800, SE = 0.037, $P < 0.001$, 95% CI (0.727–0.873), sensibility = 0.73, 1 − specificity = 0.21; SD combined index: AUC = 0.807, SE = 0.037, $P < 0.001$, 95% CI (0.735–0.879), sensibility = 0.73, 1 − specificity = 0.21; CV combined index: AUC = 0.807, SE = 0.037, $P < 0.001$, 95% CI (0.734–0.879), sensibility = 0.71, 1 − specificity = 0.21; ARV combined index: AUC = 0.773, SE = 0.041, $P < 0.001$, 95% CI (0.693–0.853), sensibility = 0.69, 1 − specificity = 0.27). ARV, average real variability; AUC, area under the curve; BP, blood pressure; BPV, blood pressure variability; CV, coefficient of variation; HbA1c, glycated hemoglobin; SD, standard deviation; SE, standard error.

BPV (specifically, nighttime BPV dipping) remains a largely unexplored concept. Given that BPV levels also fluctuate throughout the day, with a physiological decline at night, the negative correlation between nighttime BPV dipping and HbA1c levels may indicate a disruption in the circadian rhythm of BPV, extending beyond the mere presence or absence of an abnormal circadian BP profile [6,52,53].

The analysis of the combined BPV indices showed that individual BPV parameters may be complementary and synergistic in the relationship between BPV and HbA1c, further underscoring the importance of a multidimensional approach to studying BPV. This may be because, while SD and CV exhibit a certain degree of correlation, representing global measures of BPV over a given period, ARV specifically captures variability between successive BP measurements. This characteristic allows ARV to better explain BPV behavior in relation to the patient's activity, events, states, and emotions along the day [54,55].

To end with, the relationship between glycation levels and BPV indices in young and middle-aged hypertensive adults remains an ongoing topic of discussion. Based on the findings, elevated HbA1c levels, even within the optimal range, may indicate increased BPV. Thus, as BPV may be considered a potential therapeutic target due to its role as an independent prognostic factor for major adverse cardiovascular events, measuring glycation levels would be worthwhile, even in nondiabetic and nonprediabetic individuals, to properly assess cost-effective interventions such as the early implementation of healthy lifestyle changes and/or antihypertensive medications.

Limitations and strengths

This was a real-world clinical practice study with limitations inherent to its observational, cross-sectional design and consecutive sampling approach. In discussing the results, we assumed that glycation influences BP parameters based on existing literature [56,57]. However, the study lacks a temporal sequence between HbA1c levels and BP indices, while unmeasured confounding factors could potentially affect both the glycation profile and BP indices simultaneously. The study population consisted of hypertensive individuals, meaning they do not represent a completely healthy cohort. Nonetheless, they provide a good representation of young and middle-aged patients with essential hypertension. Additionally, there were notable age differences between the comparison groups, although we took careful measures to minimize the impact of this variable during the analysis phase. Certain clinical variables, particularly sleep quality and stress levels, among others, have a significant influence on BP values and BPV [58,59]. Although we repeated the 24-h ABPM when patients explicitly reported disrupted sleep during the test, we acknowledge the lack of specific characterization of these variables as a limitation. Regarding the glycation profile, we assessed HbA1c at a single point in time; therefore, a more robust approach would have involved evaluating a broader range of glycation markers, such as fructosamine and glycated albumin, across multiple time points to gain a more comprehensive understanding.

ACKNOWLEDGEMENTS

Ethics approval and consent to participate: the study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Research Ethics Committee of Santiago-Lugo (protocol code 2021/401, 19 October 2021).

Consent for publication: written informed consent was obtained from all subjects involved in the study.

Availability of data and materials: data presented in this study are available on request from the corresponding author. In accordance with Article 18.4 of the Spanish Constitution and the Organic Law on Data Protection and Guarantee of Digital Rights (LOPDGDD) of 6

December 2018, the privacy and integrity of the individual will be protected at all times, so anonymous data are available upon reasonable request.

Grants and funding: the first author holds a Juan Rodés contract (CM23/00018), granted by the Carlos III Health Institute (ISCIII), which has supported the development of this work.

Authors' contributions: conceptualization, N.V.-A. and A.H.-A.; data curation, N.V.-A.; formal analysis, N.V.-A. and A.C.-S; investigation, N.V.-A., L.B.-L., and A.H.-A.; methodology, N.V.-A. and A.H.-A.; project administration, A.H.-A. and A.P.-R; resources, J.-E.L.-P., A.P.-R. and A.H.-A.; software, N.V.-A.; supervision, A.-T.M.-A., A.P.-R., and A.H.-A.; validation, A.-T.M.-A., E.C.-V., A.P.-R., and A.H.-A.; visualization, N.V.-A., J.-E.L.-P.; writing—original draft, N.V.-A.; writing—review and editing, N.V.-A., A.C.-S., and L.B.-L. All authors have read and agreed to the published version of the manuscript.

The authors express their gratitude to the Research Methodology Group (C017) of the Health Research Institute of Santiago de Compostela for their support on methodology and statistical analysis.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. *Lancet* 2021; 398:957–980.
2. Salles GF, Reboldi G, Fagard RH, Cardoso CRL, Pierdomenico SD, Verdecchia P, *et al.*, ABC-H Investigators. Prognostic effect of the nocturnal blood pressure fall in hypertensive patients: the Ambulatory Blood Pressure Collaboration in Patients With Hypertension (ABC-H) meta-analysis. *Hypertension* 2016; 67:693–700.
3. Stevens SL, Wood S, Koshiaris C, Law K, Glasziou P, Stevens RJ, McManus RJ. Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. *BMJ* 2016; 354:i4098.
4. Parati G, Torlasco C, Pengo M, Bilo G, Ochoa JE. Blood pressure variability: its relevance for cardiovascular homeostasis and cardiovascular diseases. *Hypertens Res* 2020; 43:609–620.
5. Madden JM, O'Flynn AM, Fitzgerald AP, Kearney PM. Correlation between short-term blood pressure variability and left-ventricular mass index: a meta-analysis. *Hypertens Res* 2016; 39:171–177.
6. Shintani Y, Kikuya M, Hara A, Ohkubo T, Metoki H, Asayama K, *et al.* Ambulatory blood pressure, blood pressure variability and the prevalence of carotid artery alteration: the Ohasama study. *J Hypertens* 2007; 25:1704–1710.
7. Manios E, Tsagalis G, Tsivgoulis G, Barlas G, Koroboki E, Michas F, *et al.* Time rate of blood pressure variation is associated with impaired renal function in hypertensive patients. *J Hypertens* 2009; 27:2244–2248.
8. Schalkwijk CG, Stehouwer CDA. Methylglyoxal, a highly reactive dicarbonyl compound, in diabetes, its vascular complications, and other age-related diseases. *Physiol Rev* 2020; 100:407–461.
9. Deluyker D, Evens L, Bito V. Advanced glycation end products (AGEs) and cardiovascular dysfunction: focus on high molecular weight AGEs. *Amino Acids* 2017; 49:1535–1541.
10. Vistoli G, De Maddis D, Cipak A, Zarkovic N, Carini M, Aldini G. Advanced glycoxidation and lipoxidation end products (AGEs and ALEs): an overview of their mechanisms of formation. *Free Radic Res* 2013; 47 (Suppl 1):3–27.
11. Iuchi H, Sakamoto M, Matsutani D, Suzuki H, Kayama Y, Takeda N, Utsunomiya K. Association between day-by-day and ambulatory blood pressure variability in type 2 diabetes patients. *Blood Press Monit* 2017; 22:351–354.
12. Takao T, Suka M, Yanagisawa H, Matsuyama Y, Iwamoto Y. Predictive ability of visit-to-visit variability in HbA1c and systolic blood pressure for the development of microalbuminuria and retinopathy in people with type 2 diabetes. *Diabetes Res Clin Pract* 2017; 128:15–23.
13. Huang Q-F, Cheng Y-B, Guo Q-H, Liu C-Y, Kang Y-Y, Sheng C-S, *et al.* Clinic and ambulatory blood pressure in relation to the interaction between plasma advanced glycation end products and sodium dietary intake and renal handling. *Hypertens Res* 2022; 45:665–674.
14. Li Y, Deng B, Guo Y, Peng Q, Hu T, Xia K. Association between glycated hemoglobin and ambulatory blood pressure or heart rate in hypertensive patients. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* 2021; 46:488–496.
15. Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, *et al.* 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). *Journal of Hypertension* 2023; 41:1874.
16. El consumo de alcohol y su salud | Hojas Informativas | Alcohol | CDC 2022. Available at: https://www.cdc.gov/alcohol/hojas-informativas/consumo-alcohol-salud.html. [Accessed 18 September 2022]
17. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, *et al.*, on behalf of the American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of care in diabetes-2023. *Diabetes Care* 2023; 46 (Suppl 1):S19–S40.
18. Flegal KM. Body-mass index and all-cause mortality. *Lancet* 2017; 389:2284–2285.
19. Ross R, Neeland IJ, Yamashita S, Shai I, Seidell J, Magni P, *et al.* Waist circumference as a vital sign in clinical practice: a Consensus Statement from the IAS and ICCR Working Group on Visceral Obesity. *Nat Rev Endocrinol* 2020; 16:177–189.
20. Stergiou GS, O'Brien E, Myers M, Palatini P, Parati G, Kollias A, *et al.*, STRIDE BP Scientific Advisory Board. STRIDE BP international initiative for accurate blood pressure measurement: Systematic review of published validation studies of blood pressure measuring devices. *J Clin Hypertens (Greenwich)* 2019; 21:1616–1622.
21. Vazquez-Agra N, Cruces-Sande A, Barbosa-Gouveia S, Lopez-Paz J-E, Camafort M, Casariego-Vales E, *et al.* Assessing the relationship between lipoprotein(a) levels and blood pressure among hypertensive patients beyond conventional measures. An observational study. *Sci Rep* 2024; 14:14433.
22. Vazquez-Agra N, Cruces-Sande A, Mendez-Alvarez E, Soto-Otero R, Cinza-Sanjurjo S, Lopez-Paz J-E, *et al.* Correlation between blunted nocturnal decrease in diastolic blood pressure and oxidative stress: an observational study. *Antioxidants (Basel)* 2022; 11:2430.
23. Sheikh AB, Sobotka PA, Garg I, Dunn JP, Minhas AMK, Shandhi MMH, *et al.* Blood pressure variability in clinical practice: past, present and the future. *J Am Heart Assoc* 2023; 12:e029297.
24. Mena L, Pintos S, Queipo NV, Aizpúrua JA, Maestre G, Sulbarán T. A reliable index for the prognostic significance of blood pressure variability. *J Hypertens* 2005; 23:505–511.
25. O'Brien E, Sheridan J, O'Malley K. Dippers and nondippers. *Lancet* 1988; 2:397.
26. Parati G, Stergiou G, O'Brien E, Asmar R, Beilin L, Bilo G, *et al.*, European Society of Hypertension Working Group on Blood Pressure Monitoring and Cardiovascular Variability. European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. *J Hypertens* 2014; 32:.
27. Rossello X, Raposeiras-Roubin S, Oliva B, Sánchez-Cabo F, García-Ruíz JM, Caimari F, *et al.* Glycated hemoglobin and subclinical atherosclerosis in people without diabetes. *J Am Coll Cardiol* 2021; 77:2777–2791.
28. Schreiber JB. Issues and recommendations for exploratory factor analysis and principal component analysis. *Res Social Adm Pharm* 2021; 17:1004–1011.
29. Gewers FL, Ferreira GR, Arruda HFD, Silva FN, Comin CH, Amancio DR, *et al.* Principal component analysis: a natural approach to data exploration. *ACM Comput Surv* 2021; 54:1.e34–70.e34.
30. Cohen J. *Statistical power analysis for the behavioral sciences*, 2nd ed New York: Routledge; 1988.
31. Kim JH, Oh S, Hong SJ, Yu CW, Joo HJ, Kim YH, *et al.* Minimum number of readings necessary for determining long-term visit-to-visit blood pressure variability to predict cardiovascular outcomes in people with diabetes. *J Hypertens* 2024; 43:649–656.

32. Díaz-Cruz C, González-Ortiz M, Rosales-Rivera LY, de Patiño-Laguna AJ, Ramírez-Rodríguez ZG, Díaz-Cruz K, *et al*. Effects of dapagliflozin on blood pressure variability in patients with prediabetes and prehypertension without pharmacological treatment: a randomized trial. *Blood Press Monit* 2020; 25:346–350.
33. Jakubiak GK, Chwalba A, Basek A, Cieślar G, Pawlas N. Glycated hemoglobin and cardiovascular disease in patients without diabetes. *J Clin Med* 2024; 14:53.
34. Xie Y, Kong W, Wang X, Wu Z. Association of glycated hemoglobin with nonalcoholic fatty liver disease patients and the severity of liver steatosis and fibrosis measured by transient elastography in adults without diabetes. *BMC Endocr Disord* 2022; 22:220.
35. Prakash K, Ranjan N, Malhotra AS. Blood pressure variability is better associated with acute relative hyperglycemia than the heart rate variability in healthy young adults. *Exp Clin Endocrinol Diabetes* 2024; 132:444–451.
36. Laucyte-Cibulskiene A, Chen C-H, Cockroft J, Cunha PG, Kavousi M, Laucevicius A, *et al*. Clusters of risk factors in metabolic syndrome and their influence on central blood pressure in a global study. *Sci Rep* 2022; 12:14409.
37. Fuhr JC, Ramos MEK, Piovesan F, Renner LO, de Siqueira LO. Relationship of advanced glycation end-products in hypertension in diabetic patients: a systematic review. *J Bras Nefrol* 2022; 44:557–572.
38. Prasad K, Mishra M. Do advanced glycation end products and its receptor play a role in pathophysiology of hypertension? *Int J Angiol* 2017; 26:1–11.
39. Gülsen , Deniz KE, Başak C, Alper G, Yeşil BS, Betül E. The effect of age and gender on HbA1c levels in adults without diabetes mellitus. *J Med Biochem* 2023; 42:714–721.
40. Roth J, Müller N, Lehmann T, Heinemann L, Wolf G, Müller UA. HbA1c and age in non-diabetic subjects: an ignored association? *Exp Clin Endocrinol Diabetes* 2016; 124:637–642.
41. Boniol M, Dragomir M, Autier P, Boyle P. Physical activity and change in fasting glucose and HbA1c: a quantitative meta-analysis of randomized trials. *Acta Diabetol* 2017; 54:983–991.
42. Noda Y, Goshima S, Tanaka K, Osada S, Tomita H, Hara A, *et al*. Findings in pancreatic MRI associated with pancreatic fibrosis and HbA1c values. *J Magn Reson Imaging* 2016; 43:680–687.
43. Azcoitia P, Rodríguez-Castellano R, Saavedra P, Alberiche MP, Marrero D, Wägner AM, *et al*. Age and red blood cell parameters mainly explain the differences between HbA1c and glycemic management indicator among patients with type 1 diabetes using intermittent continuous glucose monitoring. *J Diabetes Sci Technol* 2023; 18:1370–1376.
44. Benetos A, Petrovic M, Strandberg T. Hypertension management in older and frail older patients. *Circ Res* 2019; 124:1045–1060.
45. Franklin SS, Gustin W, Wong ND, Larson MG, Weber MA, Kannel WB, Levy D. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation* 1997; 96:308–315.
46. Schutte AE, Kollias A, Stergiou GS. Blood pressure and its variability: classic and novel measurement techniques. *Nat Rev Cardiol* 2022; 19:643–654.
47. Dimova R, Tankova T, Chakarova N. Vitamin D in the spectrum of prediabetes and cardiovascular autonomic dysfunction. *J Nutr* 2017; 147:1607–1615.
48. Dimova R, Tankova T, Kirilov G, Chakarova N, Grozeva G, Dakovska L. Endothelial and autonomic dysfunction at early stages of glucose intolerance and in metabolic syndrome. *Horm Metab Res* 2020; 52:39–48.
49. Spallone V. Blood pressure variability and autonomic dysfunction. *Curr Diab Rep* 2018; 18:137.
50. Ozkayar N, Dede F, Akyel F, Yildirim T, Ateş I, Turhan T, Altun B. Relationship between blood pressure variability and renal activity of the renin-angiotensin system. *J Hum Hypertens* 2016; 30:297–302.
51. Liu X, Logan J, Kwon Y, Lobo JM, Kang H, Sohn M-W. Visit-to-visit blood pressure variability and sleep architecture. *J Clin Hypertens (Greenwich)* 2021; 23:323–330.
52. Narita K, Shimbo D, Kario K. Assessment of blood pressure variability: characteristics and comparison of blood pressure measurement methods. *Hypertens Res* 2024; 47:1–11.
53. Bilo G, Dolan E, O'Brien E, Facchetti R, Soranna D, Zambon A, *et al*. The impact of systolic and diastolic blood pressure variability on mortality is age dependent: Data from the Dublin Outcome Study. *Eur J Prev Cardiol* 2020; 27:355–364.
54. Mena LJ, Felix VG, Melgarejo JD, Maestre GE. 24-hour blood pressure variability assessed by average real variability: a systematic review and meta-analysis. *J Am Heart Assoc* 2017; 6:e006895.
55. Pierdomenico SD, Di Nicola M, Esposito AL, Di Mascio R, Ballone E, Lapenna D, *et al*. Prognostic value of different indices of blood pressure variability in hypertensive patients. *Am J Hypertens* 2009; 22:842–847.
56. Okada R, Yasuda Y, Tsushita K, Wakai K, Hamajima N, Matsuo S. Within-visit blood pressure variability is associated with prediabetes and diabetes. *Sci Rep* 2015; 5:7964.
57. Kannenkeril D, Nolde JM, Kiuchi MG, Carnagarin R, Lugo-Gavidia LM, Chan J, *et al*. Retinal capillary damage is already evident in patients with hypertension and prediabetes and associated with HbA1c levels in the nondiabetic range. *Diabetes Care* 2022; 45:1472–1475.
58. de Havenon A, Falcone G, Rivier C, Littig L, Petersen N, de Villele P, *et al*. Impact of sleep quality and physical activity on blood pressure variability. *PLoS One* 2024; 19:e0301631.
59. Tomitani N, Kanegae H, Kario K. The effect of psychological stress and physical activity on ambulatory blood pressure variability detected by a multisensor ambulatory blood pressure monitoring device. *Hypertens Res* 2023; 46:916–921.