Original Research

METABOLIC DISEASES

The predictive risk factors associated with non-dipper profile in patients with type 2 diabetes and hypertension

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Abstract

Background and aims. The non-dipper status represented by blood pressure reduction by less than 10 percent during sleep is present in about 50 percent of patients with type 2 diabetes (T2D) and hypertension, a pattern associated with more frequent cardiovascular complications and reserved prognosis. This study analyzed the predictive risk factors associated with the different dipper profiles, especially with the nocturnal pattern, following the mean arterial pressure (MAP), the mean heart rate (MHR), and the mean pulse pressure (MPP) in patients with T2D and hypertension, established by ambulatory blood pressure monitoring (ABPM).

Method. 166 consecutive patients with type 2 diabetes mellitus and hypertension were included in a cross-sectional study, and they underwent 24-hour ABPM. We excluded patients with secondary hypertension, acute coronary disease and heart failure, with oncologic or endocrine disease. The simple and multiple linear regression models were performed predicting 24-hour, day and night MAP, MHR, and MPP according to various predictors, using software R version 4.3.1.

Results. There were 80 non-dippers (48.20%), 57 dippers (34.34%), 22 reverse-dippers (13.25%) and seven extreme-dippers (4.21%). A statistically significant association was observed between MAP 24-hour and total cholesterol (TC) (higher TC values were associated with higher MAP /24 h values): adjusted coefficient B of the regression slope: 0.09, 95% confidence interval CI (0.04-0.15), p=0.003. In the multivariate analysis: adjusted B: 8.64, 95% CI (-14.67--2.61), p=0.006, beta-blockers reached the threshold of statistical significance in relation to MHR/24 h, their presence decreasing the heart rate. PP/24 hours was associated in the multivariate analysis with age: adjusted B: 0.45, 95% CI (0.05-0.85), p=0.28; abdominal circumference: 0.26, 95% CI (0.03-0.49), p=0.028, and total cholesterol: 0.1, 95% CI (0.02-0.17), p=0.013. Diabetic nephropathy was statistically significantly associated with PP/24 h: adjusted B: 10.19, 95% CI (1.24-19.14), p=0.027.

Conclusions. High cholesterol was associated with higher values of MAP and PP. Beta-blocker treatment lowered non-dipper MHR. Age and AC were correlated with increased PP values. These are predictive risk factors associated with the status of non-dippers established by ABPM, and they represent a veritable link to the non-dipper pattern in patients with T2D and hypertension.

Keywords: non-dipper; type 2 diabetes, pulse pressure, heart rate, hypertension

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Introduction - background and aims

Non-dipper hypertension is a subtype of high blood pressure (hypertension) characterized by a less-than-normal reduction in blood pressure during nighttime sleep.

Ambulatory blood pressure monitoring (ABPM) is an important method in the evaluation and management of arterial hypertension in patients with type 2 diabetes. ABPM is the gold standard for detecting non-dipper pattern and for determining associated cardiovascular risk factors and other cardiovascular conditions. Night-time blood pressure (BP), especially non-dipper, is a stronger predictor of adverse cardiovascular outcomes. Predictive factors associated with ABPM may be useful in determining patients' risk and making treatment decisions [1].

In the case of the non-dipper profile, the nocturnal drop in blood pressure is less than 10 percent, compared to the normal (dipper) where is between 10 and 20 percent.

Insulin resistance, hyperinsulinemia, and elevated blood glucose are associated with atherosclerotic cardiovascular disease (CVD). In addition to the importance of diabetes as a risk factor, diabetics have increased other atherogenic risk factors than non-diabetics, including hypertension, obesity, total to HDL cholesterol ratio, hypertriglyceridemia, and plasma fibrinogen [2].

Advanced age, obesity, diabetes mellitus, and overt cardiovascular or renal disease were associated with a blunted nocturnal BP decline ($P<0.001$). The non-dipping pattern is common in hypertensive patients. A clinical pattern of high cardiovascular risk is associated with non-dipping, suggesting that the blunted nocturnal BP dip may be a marker of high cardiovascular risk.

Non-dipping was associated with advanced age, obesity, and type 2 diabetes mellitus, conditions that increase cardiovascular risk. Furthermore, a history of previous cardio- vascular or renal disease was more common in non-dippers than in dippers [3].

Hypertension is often associated with other risk factors, including dyslipidemia, impaired glucose tolerance and type 2 diabetes, which further increase cardiovascular (CV) risk. The large number of factors influencing CV risk in patients with hypertension (environmental, lifestyle and clinical CV risk factors plus hypertension mediated organ damage (HMOD) and established CV disease (CVD) or chronic kidney disease (CKD) categories).

In hypertensive patients, HMOD indicates a high risk regardless of the organ where the damage is located, and its assessment is important for management, especially in patients who – according to age and general risk stratification – are at low risk [4].

Nocturnal hypertension and non-dipping are highly prevalent and associated with increased CV risk. Non-dipping is an unreliable prognostic indicator and may be inferior to nocturnal hypertension alone, as defined by a nighttime ≥120/70 mmHg [5].

Hyperuricemia and a higher high-sensitivity C reactive protein level tended to be associated with nocturnal non-dipping [6].

A systematic review and meta-analysis enrolling 10438 untreated hypertensive patients established that these patients may benefit more from evaluation of reverse dippers rather than non-dippers [7].

Non-dipping blood pressure pattern has been associated with metabolic changes and cardiovascular events, it is associated with incidence of new-onset diabetes in over 20 years of follow-up. ABPM provides information of nighttime BP and could be a valuable additional tool for identifying patients in future risk for diabetes. Those with non-dipping pattern of BP could benefit from regular screening of glucose metabolism for early detection of diabetes [8].

The reverse dipping is a more extreme phenotype of non-dipping, having higher severity of autonomic dysfunction, increased risk of subclinical organ damage, and reduced survival probability. They have higher 24-hour BP values than other groups and a higher prevalence of concentric left ventricular remodeling and microvascular complications in type 2 diabetes [9]. Untreated type 2 diabetes causes cardiovascular, renal and retinal pathological changes and affects the life quality of patients. Type 2 diabetes may influence BP due to sympathetic excitation by hyperinsulinemia and activated intrarenal renin-angiotensin system by hyperglycemia. BP and its circadian variations serve as risk factors for type 2 diabetes [10].

A majority of patients with type 2 diabetes had an abnormal pattern of BP that included non-dippers and reverse-dippers. Duration of type 2 diabetes and severity of glycosylated hemoglobin had a direct correlation with non-dippers and reverse-dippers. Thus, ABPM is an important tool to assess the BP variability and the complications of type 2 diabetes [11]. There are not too many studies in medical publications related to various risk factors such as age, sex, weight, abdominal circumference, antecedents and cardiovascular complications, blood sugar, glycosylated hemoglobin, cholesterol level, creatinine, and others, on patients with type 2 diabetes with hypertension and non-dipper profile who performed ABPM.

The aim of this study was to evaluate the role of risk factors in the prediction of non-dipping patients and to find possible practical and clinical implications.

The objectives our study were to investigate the predictive factors associated with the circadian variation of BP in patients with type 2 diabetes mellitus (DM) and hypertension, especially with the nocturnal non-dipper profile, as well as the identification of risk factors correlated with mean arterial pressure (MAP) over 24 hours, per day and per night, with 24-hour average heart rate (FCM), day and night, and 24-hour pulse pressure (PP), day and night.

Methods

Ethics statement

This study was approved by the Ethics Committee of the Emergency County Hospital Baia Mare, Romania (Decision Nr 3034/ 21.11.2019). A written informed consent form was signed by all the enrolled patients to publish the data and participate. Patients' records/information were de-identified and anonymized before the analysis.

Study design and setting

Our research was a cross-sectional prospective study carried out between February 2020 and May 2021, enrolling 166 consecutive hypertensive patients with type 2 DM and ambulatory follow-up at the Diabetes, Metabolic and Nutrition and Cardiology Department of Emergency County Hospital Baia Mare, Romania.

Population

We included patients with type 2 diabetes mellitus and hypertension. Patients with endocrine or oncologic diseases, secondary hypertension, acute heart failure, and acute coronary disease were excluded.

Variables and measurement

Hypertension status was diagnosed following European Society of Cardiology Hypertension Guidelines (2018), while diabetes was diagnosed following European Society of Cardiology Diabetes Guidelines (2019).

The Blood Pressure (BP) values were measured with a validated BTL-08 ABPM II machine (BTL Industries, UK), as recommended by the 2018 ESC Hypertension guidelines; before installing the ABPM, values of BP were measured [4]. A minimum of 70% usable BP recordings are required for a valid ABPM measurement session.

General data, height, weight, abdominal circumference, and body mass index (BMI) details were noted. The medical history was recorded for each patient, especially high blood pressure (HBP) and other cardiovascular diseases (CVD), dyslipidemia, the type 2 diabetes (T2D), and the recording of its complications – nephropathy, polyneuropathy, peripheral chronic arterial disease (PAD), retinopathy. Each patient had electrocardiography (ECG) done to show any possible left ventricular hypertrophy (LVH) and possible rhythm or ischemic disorders.

Current blood test results were recorded – glucose, glycated hemoglobin (HbA1C), urea, creatinine, total cholesterol, LDL and HDL-cholesterol, triglycerides, and uric acid. A morning spot sample of urine was collected and checked for the presence of albuminuria and urinary albumin/creatinine ratio (ACR). Microalbuminuria was established as an ACR from 30 to 299 mg/g.

For each patient, the antihypertensive and antidiabetic treatment was recorded – beta-blockers (βB), angiotensin-converting enzyme inhibitors (ACEI), calcium channel blockers (CCB), angiotensin receptor blockers (ARB), diuretics (Diur), alpha-blockers (AB), or their combinations.

ABPM

In this study, a validated ABPM machine was used. The following were recorded and analyzed: the average values of systolic and diastolic BP with the differences given by the circadian cycles, and average heart rate (HR) for 24 hours, morning, day, and night.

For each patient, we recorded and analyzed MAP (mean arterial pressure) for 24 hours, morning, day, and night, and pulse pressure (PP) for 24 hours, day and night. The BTL-08 monitor was worn for 24 hours, and BP recordings were made at 30-minute intervals from 06:00 to 22:00 and at one-hour intervals from 22:00 to 06:00.

Dippers were defined as those individuals with a >10% drop in 24-hour mean ambulatory BP.

Non-dippers are those individuals with a BP drop of 0–9%. Reverse Dippers are those whose decline is less than 0%, and extreme-dippers are those individuals whose BP decline is greater than 20%. The dipping index was determined as the relative nocturnal decrease in BP, which is defined as the percentage decrease of the average nocturnal BP value compared to the average diurnal BP value.

Normal daytime ambulatory BP is <135/<85 mm Hg (BP threshold is 135/85 mmHg) and <120/<70 mm Hg at night (BP threshold 120/70 mmHg) with a 24 h average of <130/80 mmHg [3]. ABPM values are, on average, lower than office BP values, and the diagnostic threshold for hypertension is ≥130/80 mmHg over 24 hours, ≥135/85 mmHg for daytime average, and ≥120/70 for night time average (all equivalent to office BP ≥140/90 mmHg).

Statistical analysis

To see which predictive factors are associated with non-dipper status, we performed univariate and multivariate logistic regressions. We selected as independent variables characteristics that might be associated with non-dipper status based on clinical judgment and the published literature. For the multivariate model, the application assumptions were evaluated: the Hosmer and Lemeshow goodness-of-fit test, multicollinearity (through the variance inflation factor and correlation coefficients). The classification accuracy of the model was also calculated by the area under the curve, with a 95% confidence interval. For each model, the odds ratio, 95% confidence interval, and p-value were displayed for each individual variable. Simple and multiple linear regression models were performed to predict blood pressure, heart rate, and pulse pressure.

The application assumptions of the models were checked, such as the normality of the residuals, the linearity of the relationship with the dependent variable, and heteroscedasticity.

Multivariate models were tested for multicollinearity. Regression slopes with confidence interval, and p-value were presented for linear models. Logistic regression models were calculated in R version 4.3.1 software and development environment for statistical computing and graphics.

Results

In the group of 166 participants, there were 80 non-dippers (48.20%), 57 dippers (34.34%), 22 reverse-dippers (13.25%) and seven extreme-dippers (4.21%). The median age was 64 years (interquartile range: 58 - 70.75), ranging from 25 to 85 years. There were no significant differences between grouped dippers and non-dippers regarding patients characteristics (Table I).

Non-Dipper Prediction

To visualize the predictive factors associated with non-dipper status, we performed univariate logistic regressions. We selected independent variable characteristics that could be associated with non-dipper status based on clinical judgment and the published literature. Univariate regressions did not identify any variable that was statistically significantly associated with non-dipper status, but beta-blockers were closest to the level of statistical significance (Table II).

When the multivariate logistic regression model was performed, we observed that the chance of having non-dipper status is 2.22 times higher in those who took beta-blockers compared to those who did not take beta-blockers, statistically significant (p=0.045), controlling for all confounding variables present in the model. The multivariate logistic regression model had an area under the curve of 0.68 (95% CI 0.59–0.76), and the Hosmer and Lemeshow goodness-of-fit test gave a p-value of 0.41.

A multiple logistic regression model was performed. 158 observations were available. The result of the Hosmer Lemeshow goodness of fit test, which shows whether there are differences between the observed data and the prediction made by the model, was p = 0.41. Regarding the prediction, the global percentage of correct classification was 65.19%.

BP prediction in non-dipper-TAM/24 h prediction

Simple and multiple linear regression models were performed predicting mean 24-hour blood pressure as a function of various predictors (Table III). In simple analyses, statistically significant associations were observed between mean 24-hour blood pressure and total cholesterol (increased total cholesterol values are associated with higher TAM/24 h values), as well as calcium channel blockers (those consuming blockers of calcium channels have lower TAM/24 h values compared to non-consumers).

Beta-blocker treatment is also associated with simple regression with lower TAM/24 h values.

In the multivariate analysis, the associations between TAM/24 h and total cholesterol were preserved, calcium blockers being close to statistical significance.

Table I. Patients characteristics according to dipper status.

Group	Diper+extreme dipper (n=64)	Non-dipper+reverse diper (n=102)	P-value
Age (years), median (IQR)	62 (57.75 - 71)	64.5 (59 - 69)	0.46
Female, n (%)	35 (54.69)	54 (52.94)	0.826
BMI (kg/m2), median (IQR)	33.41 (29.52 - 37.92)	33.51 (28.41 - 38.95)	0.89
Abdominal circonference (cm), median (IQR)	115 (105.75 - 124.75)	114 (105 - 124)	0.571
Heart failure, n (%)	21 (32.81)	28 (27.45)	0.461
Acute myocardial infarction, n (%)	7 (10.94)	18 (17.65)	0.239
Stroke, n (%)	9 (14.06)	10 (9.8)	0.402
Diabetic nephropathy, n (%)	29 (45.31)	41 (40.2)	0.516
Diabetic polyneuropathy, n (%)	55 (85.94)	83 (81.37)	0.445
Triglycerides (mg/dL), median (IQR)	174 (140 - 257)	163 (112 - 258.5)	0.062
Total cholesterol (mg/dL), median (IQR)	195.5 (153.5 - 227.25)	183 (149 - 213)	0.147
HDL cholesterol (mg/dL), median (IQR)	45 (38 - 55)	44 (36 - 51)	0.433
Hb A1 c%, median (IQR)	9.3 (8.1 - 10.4)	9.89 (8.88 - 11.1)	0.216
Creatinine (mg/dL), median (IQR)	1.01 (0.81 - 1.3)	0.93 (0.77 - 1.3)	0.359
Betablockers, n (%)	37 (57.81)	73 (71.57)	0.068
CCB, n (%)	24 (37.5)	32 (31.37)	0.416
ARB, n (%)	12 (18.75)	24 (23.53)	0.467
ACEI, n (%)	39 (60.94)	59 (57.84)	0.693
CCI, n (%)	29 (45.31)	50 (49.02)	0.642
Diuretics, n (%)	49 (76.56)	75 (73.53)	0.662
MHR/24 h, median (IQR)	71 (64.75 - 78.25)	73 (67 - 80.5)	0.292
SBP/24 h (mmHg), median (IQR)	128.5 (122 - 139.25)	130.5 (121.25 - 141)	0.582
DBP/24 h (mmHg), median (IQR)	67.5 (61 - 76)	70 (63.25 - 75.75)	0.224
MAP/24 h (mmHg), median (IQR)	89 (82 - 97)	91 (85 - 96.75)	0.299
PP/24 h (mmHg), median (IQR)	61 (51.75 - 72)	61 (51 - 71.75)	0.871

IQR, interquartile range; HbA1c: glycated hemoglobin; ACEI: angiotensin-converting enzyme inhibitors; CCB: calcium channel blockers; ARB: angiotensin receptor blockers; MHR, the mean heart rate; MAP, mean arterial pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure.

Table II. Univariate and multivariate logistic regressions predicting non-dipper according to independent variables.

Characteristics	OR	95% CI	p-value	OR adjusted	95% CI	p
Age: (years)	1.01	0.98 - 1.04	0.624	1.02	0.98 - 1.07	0.281
Sex (M vs. F)	1.07	0.57 - 2.02	0.826	1.07	0.52 - 2.21	0.848
Diabetic polyneuropathy	0.71	0.29 - 1.66	0.446	0.5	0.18 - 1.31	0.173
Diabetic nephropathy	0.81	0.43 - 1.53	0.516	1.19	0.55 - 2.62	0.667
ACEI	0.88	0.46-1.66	0.693	1.2	0.49-2.93	0.683
Betablockers	1.84	0.95 - 3.56	0.07	2.22	1.03 - 4.92	0.045
CCB	0.76	0.4 - 1.47	0.417	0.94	0.42 - 2.13	0.888
ARB	1.33	0.62 - 2.98	0.468	1.67	0.55 - 5.19	0.364
Diuretics	0.85	0.40 - 1.75	0.662	1.37	0.58 - 3.23	0.474
CAD	1.16	0.62 - 2.18	0.642	1.03	0.49 - 2.17	0.945
HF	0.77	0.39 - 1.54	0.462	0.47	0.2 - 1.07	0.074
Stroke	0.66	0.25 - 1.77	0.404	0.77	0.26 - 2.31	0.633
MI	1.74	0.71 - 4.73	0.244	2.03	0.73 - 6.44	0.197
LVH	1.48	0.79 - 2.81	0.226	1.73	0.85 - 3.58	0.134
Creatinine (mg/dL)	0.77	0.42 - 1.4	0.395	0.55	0.25 - 1.18	0.124

OR: odds ratio; CI: confidence interval; ACEI: angiotensin-converting enzyme inhibitors; CCB: calcium channel blockers; ARB: angiotensin receptor blockers; CAD: coronary artery disease; HF: heart failure; stroke: brain attack; MI: myocardial infarction; LVH: left ventricular hypertrophy.

Table III. Simple and multiple linear regression models, predicting average blood pressure over 24 hours, according to various predictors:

Characteristics	B	(95% CI)	p	B adjusted	(95% CI)	p
(Intercept)				78.76	40.88 - 116.64	< 0.001
Age (years)	-0.2	-0.43 - 0.04	0.101	-0.06	-0.38 - 0.26	0.688
Sex (M vs. F)	1.53	-3.2 - 6.26	0.52	3.5	-2.34 - 9.33	0.232
Abdominal circumference (cm)	0.04	-0.13 - 0.21	0.663	0.08	-0.1 - 0.26	0.387
MI	-4.72	-11.52 - 2.07	0.17	-1.51	-10.89 - 7.88	0.747
CAD	2.13	-2.59 - 6.86	0.372	3.36	-2.85 - 9.56	0.28
HF	-0.13	-5.6 - 5.34	0.961	-3.83	-11.35 - 3.68	0.308
Diabetic nephropathy	-1.26	-6.06 - 3.54	0.603	3.93	-3.21 - 11.08	0.272
Total cholesterol (mg/dL)	0.08	0.03 - 0.12	<0.001	0.09	0.04 - 0.15	0.003
Hb A1 c%	-1.31	-2.88 - 0.27	0.102	-1.16	-3.08 - 0.77	0.232
Creatinine (mg/dL)	-3.6	-7.93 - 0.73	0.102	-3.65	-13.16 - 5.86	0.442
ACEI	3.04	-1.77 - 7.86	0.212	-1.4	-9.2 - 6.4	0.718
Diuretics	0.93	-4.53 - 6.4	0.735	3.56	-3.39 - 10.51	0.307
Betablockers	-5.37	-10.28 - -0.46	0.033	-0.56	-7.33 - 6.2	0.867
CCB	7.91	2.99 - 12.83	0.002	6.51	-0.66 - 13.68	0.074
ARB	-4.76	-10.73 - 1.21	0.117	-6.71	-16.8 - 3.39	0.187

CI: confidence interval; MI: myocardial infarction; CAD: coronary artery disease; HbA1c: glycated hemoglobin; ACEI: angiotensin-converting enzyme inhibitors; CCB: calcium channel blockers; ARB: angiotensin receptor blockers.

FCM prediction - FCM prediction /24 h

Simple and multiple linear regression models were performed predicting 24-hour MHR according to various predictors (Table IV). In simple analyses, statistically significant associations were observed between 24-hour MHR and beta-blockers, and the CAD approached the threshold for statistical significance. In the multivariate analysis, beta-blockers reached the threshold of statistical significance in relation to MHR/24 h, their presence decreasing heart rate, and the presence of CAD increasing heart rate as well.

PP prediction- PP prediction/ 24 hour

Simple and multiple linear regression models were performed predicting 24-hour PP according to various predictors (Table V). In simple analyses, a statistically significant association was observed between 24-hour PP and age (increased age values are associated with higher PP values), sex (men have lower PP values than women), abdominal circumference (values increased abdominal circumference is associated with increased PP/24 h values), CAD (their presence increasing PP), total cholesterol (increased values being associated with increased PP values), calcium channel blockers (those consuming calcium channel blockers have higher PP/24 h values compared to those who do not consume).

Table IV. Simple and multiple linear regression models, predicting MHR for 24 hours, according to various predictors:

Characteristics	B	95% CI	p	B adjusted	95% CI	p
Intercept				46.12	12.35 - 79.9	0.009
Age: years	0.08	-0.14 - 0.3	0.465	0.27	-0.01 - 0.56	0.059
Sex M vs. F	1.1	-3.28 - 5.49	0.618	-0.49	-5.69 - 4.71	0.85
Abdominal circumference(cm)	0.07	-0.09 - 0.23	0.384	0.12	-0.05 - 0.28	0.155
MI	-6	-12.22 - 0.23	0.059	-7.51	-15.88 - 0.86	0.077
CAD	3.03	-1.32 - 7.38	0.169	6.74	1.21 - 12.28	0.018
HF	-3.48	-8.49 - 1.52	0.17	-5.86	-12.57 - 0.84	0.084
Diabetic nephropathy	0.07	-4.39 - 4.53	0.975	1.74	-4.63 - 8.11	0.583
Total cholesterol mg/dL	0.02	-0.02 - 0.06	0.401	0	-0.05 - 0.06	0.908
Hb A1 c%	-1.07	-2.66 - 0.51	0.18	0.19	-1.52 - 1.91	0.821
ACEI	2.69	-1.77 - 7.16	0.233	1.59	-5.36 - 8.55	0.645
Creatinine mg/dL	2.88	-1.14 - 6.91	0.158	-3.21	-11.69 - 5.27	0.449
Diuretics	1.42	-3.64 - 6.47	0.579	0.62	-5.58 - 6.81	0.841
Betablockers	-5.54	-10.05 - -1.02	0.017	-8.64	-14.67 - -2.61	0.006
CCB	1.77	-3.06 - 6.6	0.469	-0.46	-6.85 - 5.93	0.884
ARB	-2.7	-8.29 - 2.89	0.339	-4.22	-13.22 - 4.78	0.349

CI: confidence interval; MI: myocardial infarction; CAD: coronary artery disease; HF: heart failure; HbA1c: glycated hemoglobin; ACEI: angiotensin-converting enzyme inhibitors; CCB: calcium channel blockers; ARB: angiotensin receptor blockers.

Table V. Simple and multiple linear regression models, predicting PP over 24 hours, according to various predictors

Characteristics	B	(95% CI)	p	B adjusted	(95% CI)	p
Intercept				-11.49	-58.95 - 35.96	0.627
Age years	0.4	0.08 - 0.72	0.016	0.45	0.05 - 0.85	0.028
Sex M vs. F	-7.01	-13.41 - -0.61	0.032	-3.99	-11.3 - 3.32	0.277
Abdominal circumference (cm)	0.26	0.03 - 0.49	0.03	0.26	0.03 - 0.49	0.028
MI	0.96	-8.6 - 10.51	0.843	1.86	-9.9 - 13.61	0.751
CAD	7.94	1.59 - 14.3	0.015	4.56	-3.21 - 12.34	0.242
HF	3.78	-3.77 - 11.34	0.322	-2.58	-12 - 6.83	0.582
Diabetic nephropathy	2.33	-4.34 - 9	0.489	10.19	1.24 - 19.14	0.027
Total cholesterol (mg/dL)	0.07	0 - 0.14	0.037	0.1	0.02 - 0.17	0.013
Hb A1 c%	-0.97	-3.09 - 1.15	0.363	-0.3	-2.71 - 2.11	0.802
Creatinine (mg/dL)	-1.61	-7.72 - 4.5	0.602	-8.79	-20.71 - 3.12	0.144
ACEI	-3.04	-9.77 - 3.68	0.37	-2.76	-12.53 - 7.01	0.571
Diuretics	3.82	-3.74 - 11.37	0.318	6.37	-2.34 - 15.07	0.147
Betablockers	0.24	-6.79 - 7.26	0.947	0.57	-7.91 - 9.04	0.893
CCB	7.71	0.64 - 14.77	0.033	8.51	-0.47 - 17.49	0.063
ARB	1.79	-6.64 - 10.22	0.674	1.09	-11.55 - 13.73	0.863

CI: confidence interval; MI: myocardial infarction; CAD: coronary artery disease; HF: heart failure; HbA1c: glycated hemoglobin; ACEI: angiotensin-converting enzyme inhibitors; CCB: calcium channel blockers; ARB: angiotensin receptor blockers.

In the multivariate analysis, associations with age, abdominal circumference, and total cholesterol were preserved. In addition, diabetic nephropathy became statistically significantly associated with PP/24 h (the presence of nephropathy being associated with increased PP values).

Discussion

Patients with type 2 diabetes who exhibit a non-dipper profile are at an increased risk for various complications. Understanding the predictive risk factors for this specific population is essential for effective management and prevention strategies and can help in reducing the adverse outcomes associated with type 2 diabetes and non-dipper blood pressure profile.

Beta-blockers work by blocking the effects of the hormone epinephrine. They reduce heart rate, the heart's workload, and the heart's output of blood, which lowers blood pressure. Beta-blockers are a valuable tool in managing hypertension, but their effectiveness in addressing

non-dipper blood pressure patterns can be variable.

The result of our study shows a strong association of the non-dipper profile with the beta-blocker treatment, the effectiveness of which is increased in the non-dipper status, the chance of having a non-dipper status is 2.22 times higher in those who took beta-blockers compared to those who did not take beta-blockers.

A review of the currently available literature shows that in patients with uncomplicated hypertension, there is a lack of data or no evidence to support the use of beta-blockers as monotherapy or as first-line agents. However, beta-blockers remain very effective agents for the treatment of heart failure, certain types of arrhythmia, hypertrophic obstructive cardiomyopathy, and in patients with previous myocardial infarction [12].

The UKPDS trial in type 2 diabetics with hypertension showed that first-line beta-blockade is at least as effective as ACEI use in preventing all primary macrovascular and microvascular endpoints. The active ingredient appears to be beta-1 blockade, acting not only to lower blood pressure but also to prevent sudden death and cardiovascular damage resulting from chronic beta-1 stimulation associated with increased noradrenaline activity. Beta-blockers should be considered as a first-line therapeutic option for all diabetics with ischemic heart disease or younger/middle-aged diabetics with hypertension (but co-prescribed with low-dose diuretic therapy in the elderly) [13].

Understanding the relationship between cholesterol and non-dipper blood pressure patterns is crucial for preventing cardiovascular diseases. Both conditions need to be managed proactively through a combination of lifestyle modifications and medical treatments. Regular monitoring of blood pressure patterns and lipid profiles can help in the early identification and better management of at-risk individuals with type 2 diabetes and a non-dipper blood pressure profile.

In the simple analyses in our study, statistically significant associations were observed between mean blood pressure over 24 hours and total cholesterol. Increased values of total cholesterol were associated with higher MAP/24 h values, these CT values having a predictive role for increased BP. In the multivariate analysis, the associations between MAP/24 h and total cholesterol were preserved.

In the Framingham Study, coronary heart disease occurred in one in five men and one in 17 women by age sixty. Total cholesterol levels have been shown to be an excellent predictor of coronary heart disease in those under the age of 50. Both systolic and diastolic blood pressure are also related to the risk of coronary heart disease in a linear fashion: the higher the pressure level, the greater the incidence of coronary heart disease. Blood pressure and serum cholesterol are correlated, suggesting that those with higher blood pressure values tend to have higher serum cholesterol levels [14].

In conclusion, among patients with type 2 diabetes and hypertension, regardless of lipid-lowering medication use, increases in CT levels from pre- and post-diagnosis were associated with increased CVD risks, whereas decreases were associated with reduced CVD risk. Management of cholesterol levels among diabetic patients may represent an important clinical goal for CVD prevention [15].

In patients with dyslipidemia, non-dipping hypertension is more closely related to cardiovascular disease compared to dipping hypertension [16].

Treatment with calcium channel blockers and beta-blockers is significantly associated in simple linear regression with MAP, and in multivariate regression CCB almost reach significance. The opposite effects of calcium channel blockers and beta-blockers on blood pressure variability explain the difference between the observed effects on stroke risk and the expected effects based on MAP. To most effectively prevent stroke, blood pressure-lowering drugs should reduce MAP without increasing variability; ideally it should reduce both [17].

In our study in the simple analyses, statistically significant associations were observed between 24-hour FCM and beta-blockers, and MI approached the threshold of statistical significance. In the multivariate analysis, beta-blockers reached the threshold of statistical significance in relation to FCM/24 h, their presence decreasing heart rate, and the presence of CAD increasing heart rate as well.

Beta-blockers refer to a mixed group of drugs with diverse pharmacodynamic and pharmacokinetic properties. They have demonstrated long-term beneficial effects on mortality and cardiovascular disease (CVD) when used in people with ischemic heart disease or heart failure [18].

Previous studies have shown positive associations between heart rate and cardiovascular mortality. Therefore, heart rate may be an independent risk factor for cardiovascular death in people with hypertension [19].

Nocturnal HR pattern without decrease, especially increased HR was associated with increased risk of renal function deterioration and decreased eGFR. The predictive value of HR non-dippers for poor renal outcomes disappeared after further adjustments, while that of HR risers remained stable. The circadian rhythm of HR in hypertensive patients with chronic kidney disease (CKD) deserves further attention and research [20].

Pulse pressure is the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP). Pulse pressure is an important indicator of the health of the arteries. A normal pulse pressure range is typically between 30 to 40 mmHg. A high pulse pressure (e.g., above 60 mmHg) can indicate stiff arteries or other cardiovascular problems. It is often seen in older adults and can be associated with an increased risk of heart disease and stroke. A low pulse pressure (e.g., below 30 mmHg) may indicate poor heart function or other conditions such as heart failure.

Our study shows in a simple analysis a statistically significant association between 24-hour PP and age (increased age values are associated with higher PP values), sex (men have lower PP values than women), abdominal circumference (values increased abdominal circumference is associated with increased PP/24 h values), CAD (their presence increasing PP), total cholesterol (increased values being associated with increased PP values), calcium channel blockers (those consuming calcium channel blockers have higher PP/24 h values compared to those who do not consume).

In the multivariate analysis, associations with age, abdominal circumference, and total cholesterol were preserved. In addition, diabetic nephropathy became statistically significantly associated with PP/24 h (the presence of nephropathy being associated with increased PP values).

Increased pulse pressure (PP) is a marker of increased arterial stiffness and high cardiovascular risk. Pulse pressure was significantly higher in patients with type 2 diabetes and atherosclerotic cardiovascular disease compared with type 2 diabetes without atherosclerotic cardiovascular disease, although mean systolic and diastolic blood pressure and blood pressure variability were similar.

PP might be more relevant to cardiovascular disease risk than mean blood pressure and blood pressure variability in patients with type 2 diabetes [21].

Aging changes vascular stiffness depending on the genetic predisposition, as well as the quality of blood pressure, cholesterol, and blood sugar throughout life. In longitudinal Western population-based studies, concomitant increases in systolic and diastolic blood pressure occur by age 50 to 55 years.

Afterward, the systolic and diastolic blood pressures diverge, with the systolic continuing to rise and the diastolic stabilizing and then falling. These changes result in increased pulse pressure and ultimately, isolation of systolic hypertension [22].

In the simple and multiple linear regression models in our study, age is significantly associated with 24-hour, daytime, and nighttime pulse pressure, increased age values are associated with increased PP/24-hour values

Women's pulse pressure levels were lower than men's in early adulthood and higher in older ages. Women had a steeper and more consistent increase in pulse pressure with age than men , whereas men had a steeper curvilinear increase in pulse pressure with age [23], in our study men in the simple linear regression model have lower pulse pressure values compared to women.

Abdominal fat and obesity significantly impacts blood pressure regulation and can contribute to a non-dipping pattern. This relationship underscores the importance of managing abdominal obesity through lifestyle interventions and medical treatments to improve blood pressure patterns and reduce cardiovascular risk. Regular monitoring and comprehensive management strategies are essential for individuals with both conditions.

Abdominal fat distribution, abdominal obesity is associated with a number of adverse health consequences, including an increased risk of cardiovascular and cerebrovascular disease, impaired glucose tolerance, and hypertriglyceridemia, even when BMI is in the "healthy" range. Increased abdominal circumference (AC) is associated with increased BP, independent of increasing body mass index (BMI) and regardless of baseline abdominal obesity and overweight status [24].

In our study, AC is statistically significantly associated in simple and multiple linear regression models with 24-hour, daytime, and nighttime pulse pressure, with increased AC values being associated with higher PP values.

In the simple analyses in our study, statistically significant associations were observed between the average pulse pressure over 24 hours and total cholesterol (TC), increased values of total cholesterol are associated with higher PP/24 h values, and these values of TC having a predictive role for increasing PP.

In the multivariate analysis, the associations between PP/24 h and total cholesterol were preserved. The same trends were also maintained for PP per day and night of association with TC.

Total cholesterol is detrimental to endothelial function, and an elevated serum level of TC leads to arterial stiffness by increasing the response of vascular smooth muscle cells to angiotensin II and reducing the bioavailability of nitric oxide, which consequently leads to increased systolic blood pressure.

Second, oxidized lipids accumulate with the inflammatory reaction and migrate to the tunica intima, causing degradation of collagen, elastic fibers, and proliferation of smooth muscle cells, thus leading to the development of arterial stiffness.

Third, lipids in the blood can lead to plaque buildup, which narrows the artery, worsens arteriosclerosis, and ultimately causes increased systolic blood pressure [25].

A non-dipping blood pressure pattern in normotensive CKD patients does not predict the risk of a rapid decline in estimated glomerular filtration rate (eGFR). This suggests that the control of blood pressure, rather than its circadian rhythm, is essential for the preservation of eGFR [26].

Elevated PP/24 h, day and night values are associated with CAD in simple linear regression, and diabetic nephropathy is statistically significantly associated in multivariate regression analysis.

CCB treatment is significantly associated both in simple and multiple regression analysis with PP per day, with PP per 24 hours significance appearing only in the simple regression, and with PP at night, statistical correlations no longer appear, PP values being generally higher in those with CCB.

Hypertension rarely occurs in isolation, and often clusters with other CV risk factors such as dyslipidaemia and glucose intolerance.

This metabolic risk factor clustering has a multiplicative effect on CV risk. Consequently, quantification of total CV risk (i.e. the likelihood of a person developing a CV event over a defined period) is an important part of the risk stratification process for patients with hypertension [27].

Limitations

Our study's limitations include its limited generalizability due to the small sample size and single-center design, restricted to a specific patient population in Romania, as well as exclusions of certain patient groups. These exclusions are warranted since they could have biased our observations. Additionally, unmeasured factors such as lifestyle behaviors and medication adherence, not monitored or controlled in the study, could influence the outcomes. Due to the observational nature of our study, it is subject to potential confounding. To address this issue, we used multiple regression analyses and adjusted for important confounders. Nevertheless, residual confounding is still a problem. Causality cannot be confirmed or denied due to the observational study design.

Strengths

The use of ambulatory blood pressure monitoring ensures the accuracy of blood pressure measurements. The use of advanced statistical methods, including rigorous multivariate analyses, strengthens the examination of the data and enhances the validity of the results by minimizing confounding.

Clinical implications and future perspectives

The identification of factors such as total cholesterol, increased heart rate, age, abdominal circumference, history of chronic ischemic coronary disease, presence of diabetic nephropathy, and specific medication use (beta-blockers and calcium channel blockers) associated with non-dipper status in patients with T2D and hypertension underscores the need for comprehensive cardiovascular risk management. These insights suggest more stringent monitoring and potentially earlier or more aggressive intervention strategies to manage cardiovascular risk effectively in this selected population.

Future research should focus on confirming these associations in larger, more diverse populations and exploring the mechanisms by which specific treatments influence circadian blood pressure patterns. Longitudinal studies assessing long-term cardiovascular outcomes in non-dipper patients with T2D and hypertension could guide the development of targeted therapies and interventions, ultimately improving clinical outcomes for these high-risk individuals.

Conclusions

The results of statistical analyses showed that total cholesterol values, increased heart rate, age, abdominal circumference, history of chronic ischemic coronary disease, presence of diabetic nephropathy, beta-blocker, and calcium channel blocker treatment were associated with non-dipper status in patients with T2D and hypertension. The presence of several risk factors in clinical practice lead to the state of non-dippers, as highlighted by ABPM.

Therefore, accurate diagnosis of non-dippers in patients with T2D and hypertension will specifically lead to improved blood pressure control and reduced adverse cardiovascular events.

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