Evaluation of Biochemical and Clinical Parameters of Hypertension with Type 2 Diabetes Mellitus

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The aim of this study was to assess the basic biochemical and clinical characteristics of patients with hypertension and type 2 diabetes mellitus (T2DM), office blood pressure (BP) and 24-h BP profile, their risk factors and associated comorbidities. Compared with non-diabetics, hypertensive patients with T2DM were older, with a longer duration of hypertension (5.9 vs. 4.7 years), greater office blood pressure and ambulatory BP values, increased incidence of multiple risk factors, target organ damage and cardiovascular disease. Biochemical data in hypertension with T2DM revealed significantly high levels of LDL cholesterol, triglycerides, creatinine, micro- and macro-albuminuria and a reduced estimated glomerular filtration rate. The presence of diabetes was associated with obesity, represented by a BMI >30 kg/m^2 (OR 2.08 [95% CI 1.26-3.45], p = 0.004), abdominal obesity (OR 1.85 [95% CI 1.11-3.04], p = 0.016), high LDL cholesterol (OR 2.02 [95% CI 1.22-3.35], p = 0.006) and high triglycerides (OR 1.86 [95% CI 1.11-3.11], p = 0.017).

Keywords: Hypertension, type 2 diabetes, clinical and biochemical characteristics

The rising prevalence of hypertension (HT) and diabetes worldwide and in Romania, along with their association, expose patients to a severe clinical condition. Hypertension is a common comorbidity of type 2 diabetes mellitus (T2DM), obesity, old age and chronic kidney disease (CKD) representing consecrated risk factors [1-3]. Hypertension further aggravates the progression of microvascular disorders and renal function decline [4-7]. This association creates a vicious circle that causes earlier and frequent cardiovascular (CV) events, such as coronary heart disease (CHD), heart failure and stroke [8-10]. Romania has a high prevalence of hypertension [11] and a high CV risk [12, 13]. Despite recent advancements in medicine and socio-economic status, cardiovascular mortality in Romania is extremely high [14, 15]. The situation, compared to Western-European countries, where CV disease and deaths decreased more than 50-60% during the last decade, is worrying and imposes a better management [16]. This means a better control of blood pressure (BP) and risk factors such as obesity, smoking, sedentary life, diabetes and dyslipidaemia [17]. Data from the second and third national *Epidemiological Studies on Prevalence of Arterial Hypertension and Cardiovascular Risk in Romania* (SEPHAR) II [12] and III [14] indicated a rising trend of HTs prevalence, from 40.41% in 2012 to 45.10% in 2016. As noticed in the *Prevalence of diabetes mellitus and prediabetes in the adult Romanian population*, PREDATORR STUDY [18], 11.66% of our population has diabetes. Comorbidities such as kidney disease, cerebrovascular, heart disease and dyslipidaemia are common [19, 20], but national literature data are scarce about this issue.

The objectives of the study were to assess the 24-h BP profile, the biochemical and clinical characteristics of patients with hypertension and T2DM.

Experimental part

Material and methods

This is a prospective cross-sectional study of a database of hypertensive patients from twelve primary care offices in Timi' and Mures Counties, Romania. The recruitment was done between January 2015 and February 2016 at the visits to the GPs. Inclusion criteria were: adult patients over 18 years, diagnosed with essential HT, who underwent treatment for at least three months and had a recent (less than one month ago) ambulatory BP monitoring (ABPM). Exclusion criteria were secondary HT and severe chronic kidney disease (CKD). In accordance with the rules of the Helsinki Declaration, International Ethical Regulations and some published models and guidelines, each participant signed a written and informed consent before entering the study [21-23]. The Ethics Committee of Victor Babes University of Medicine and Pharmacy Timisoara approved the present study.

Baseline sociodemographic data (age, gender, urban/rural residence, educational level), lifestyle (physical activity, salt intake, smoking), and history data (family history of diabetes, of premature CV disease, HT, dyslipidaemia) and current treatment were collected from interviewer-administered questionnaires. The physical examination included office BP, ambulatory blood pressure monitoring (ABPM), weight, height and waist measurements and body mass index (BMI). The laboratory analyses consisted of fasting plasma glucose (FPG), glycated haemoglobin (HbA1c), oral glucose tolerance test (OGTT), total cholesterol (TC), low density lipoprotein cholesterol (LDL-c), high density lipoprotein cholesterol (HDL-c), triglycerides (TG), uric acid, creatinine, estimated glomerular filtration rate (eGFR), urine analysis and urine albumin/creatinine ratio (UACR).

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Definitions

The diagnosis of HT relied on the recommendations of the Hypertension Guidelines of the European Society of Cardiology [24]. Office BP values ≥ 140/90 mmHg on at least two separate visits confirmed the diagnosis. Validated and calibrated devices OMRON HEM 7251G were used for office BP measurement and Meditech monitors ABPM04 for ambulatory measurement. ABPM with ≥70% accurate readings, minimum 20 measurements during daytime and 7 during night-time were accepted as good [25]. Office BP goal for treatment was < 140/90 mmHg for non-diabetics and < 140/85 mmHg for T2DM. HT control was obtained when BP reached or dropped below targets. The normal nocturnal dipping pattern was represented by nocturnal fall of systolic BP (SBP) > 10% till to 20% of the daytime SBP. Diagnostic criteria for diabetes were (according to the American Diabetes Association Guidelines [4]): fasting plasma glucose (FPG) levels ≥ 126 mg/dL, a plasma glucose ≥ 200 mg/dL at 2 h after glucose ingestion during oral glucose tolerance test (OGTT), plasma level of gycated haemoglobin - isoform A1c (HbA1c) > 7%, or previously diagnosed T2DM with antidiabetic medication, regardless of HbA1c or FPG. Prediabetes was diagnosed whenever FPG values of 100-125 mg/dL or plasma glucose between 140-199 mg/dL at 2 h after glucose ingestion during OGTT. Lipid disorders were: hypertriglyceridemia, defined by TG ≥ 150 mg/dL or under hypolipemiant pharmacologic treatment; hypercholesterolemia was defined by total cholesterol (TC) ≥ 190 mg/dL or under hypolimemiant pharmacologic treatment; low HDL-c ≤ 40 mg/dL in men and ≤ 46 mg/dL in women. Overweight was diagnosed by a BMI of 25-30 kg/m^2, obesity by a BMI ≥ 30 kg/m^2 and abdominal obesity by waist circumference > 102 cm in men and > 88 cm in women. Mild renal damage was represented by a reduced eGFR (MDRD formula) of 60-90 mL/min/1.73 m^2 and/or microalbuminuria (MAU) with urine albumin/creatinine ratio (UACR) 30-300 mg/g. Moderate renal damage was present with eGFR 58-30 mL/min/1.73 m^2 and/or macroscopic proteinuria with UACR >300 mg/g.

Statistical analysis

Statistical analysis was carried out using Graph Pad Prism 6 for Windows, version 6.01 and MedCalc. Descriptive statistics was applied for the analysis of quantitative variables, including mean with standard deviation (SD) and qualitative variables were represented as numbers and percentages. Differences between mean values were evaluated using Student's *t*-test and qualitative variables were compared respectively with chi-square test. Statistically significant value for p was < 0.05. Using MedCalc Program, based on Altman formula, odds ratio, 95% confidence interval and p value were obtained. Variables which were found to be significantly different between groups were included in univariable logistic regression analysis, the association of independent variables with the dependent variable being investigated.

Results and discussions

Complete data were obtained from 252 patients with HT, of which 124 with T2DM forming the study group and 128 without T2DM, forming the control group. The age of the subjects ranged from 23 to 80 years, the mean age of the study group was 57.12 ±13.14 years (95% CI 54.78-59.45) and of the control group 53.46±16.36 years (95% CI 50.59-56.32), p = 0.051. Male gender was present in 54.84% in the study group vs 51.56% in the control group. The mean duration of HT in the study group was 5.94±3.27 years (95% CI 5.36-6.52) compared with 4.71±3.27 years (95% CI 4.14-5.28), p = 0.003 in the control group. The duration of HT was more than 5 years in 70.1% of the study group participants and 54.70% of the control group. Comparing diabetes with non-diabetes patients, family history of premature CVD was present in 29.03% vs 19.53%, p = 0.079, smoking was present in 16.21 vs 17.97, p = 0.711, sedentary lifestyle in 59.68% vs 53.90%, p = 0.355. A BMI (kg/m^2) between 18-24.99 was present in T2DM group in 14.51% vs 40.62, p < 0.001, a BMI between 25-30 was present in 29% vs 21.10, p = 0.145 and a BMI > 30 was present in 56.46 vs 38.28, p=0.003. Abdominal obesity was noticed in 60.48% vs 45.31%, p = 0.015. Prediabetes was present in 13.28% of the control group and T2DM had a duration of more than 5 years in 41.1%. Hypertensive patients with T2DM exhibited higher prevalence of risk factors, target organ damage and established CV disease, but no significant differences regarding family history of premature CV disease, educational level, living area, smoking, sedentary lifestyle and diet salt intake (table 1).

Table 1
RISK FACTORS, TARGET ORGAN DAMAGE AND CARDIOVASCULAR DISEASE

Parameters	Study group HT + T2DM Nr, %	Control group HT Nr, %	P-value
High LDL-c	67 (54.03%)	47 (36.72%)	0.005
Low HDL-c	44 (35.48%)	33 (25.78%)	0.095
High Triglycerides	58 (46.77%)	41 (32.03%)	0.016
Hyperuricemia	18 (14.60%)	17 (13.80%)	0.855
LVH ECG	10 (8.06%)	5 (3.90%)	0.164
LVH echocardiography	29 (23.39%)	15 (11.72%)	0.015
MAU	19 (15.32%)	9 (7.03%)	0.036
Macroalbuminuria	3 (2.60%)	1 (1.28%)	0.376
eGFR > 90 (mL/min/1.73 m^2)	71 (57.26%)	95 (74.22%)	0.004
eGFR = 89-60 (mL/min/1.73m^2)	28 (22.58%)	22 (17.18%)	0.283
eGFR= 59-30 (mL/min/1.73m^2)	25 (20.16%)	11 (8.59%)	0.008
Coronary heart disease	38 (30.64%)	24 (18.75)	0.028
Heart failure	18 (14.52%)	7 (5.46%)	0.016
Cerebrovascular disease	9 (7.25%)	5 (3.90%)	0.246

The laboratory data of the two study groups are presented in table 2. There were statistical significantly differences between the diabetes and non-diabetes groups concerning high glucose level, HbA1c, TG, LDL-c and creatinine levels, low HDL-c, but not regarding the serum concentration of potassium, sodium and uric acid (fig.1).

The evaluation of the renal function by determination of eGFR demonstrated in the T2DM group a higher prevalence of moderate renal impairment, expressed as chronic kidney disease stage 2 and 3 and a higher prevalence of MAU and macro-albuminuria, data presented in figures 2 and 3.

The association of different risk factors with hypertension and T2DM was studied in a logistic univariate

Table 2
LABORATORY DATA

Biochemical data mg/dL	Study group HT + T2DM N=124	Control group N=128	p-value
Potassium	4.51±0.39	4.46±0.47	0.3598
Sodium	139.60±3.16	139.9±2.33	0.3908
Glucose	134.74±40.72	94.25±13.10	<0.0001
HbA1c (%)	8.10±3.42	5.40±1.12	<0.0001
LDL-c	139.50±41.2	108.40±32.10	<0.0001
HDL-c	42.20±11.5	45.60±12.20	0.0238
TG	176.10±89.4	139.0±71.20	0.0003
Creatinine	1.09±0.21	1.02±0.19	0.0059
Uric acid	5.40±1.90	5.30±1.80	0.6683

Abbreviations: ECG, electrocardiogram; eGFR, estimated glomerular filtering rate; HDL-c, high-density lipoprotein cholesterol; HT, hypertension; LDL-c, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; n, number; T2DM, type 2 diabetes mellitus.

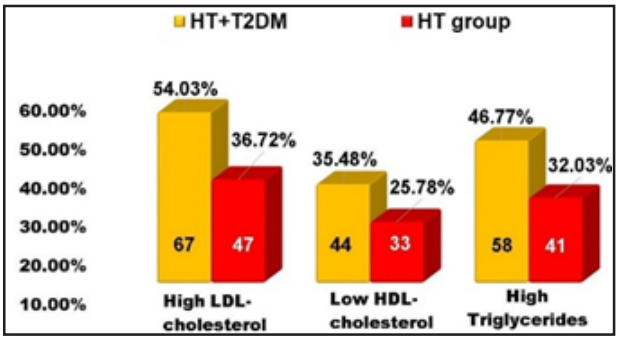

Fig. 1. Lipid profile in hypertension with diabetes

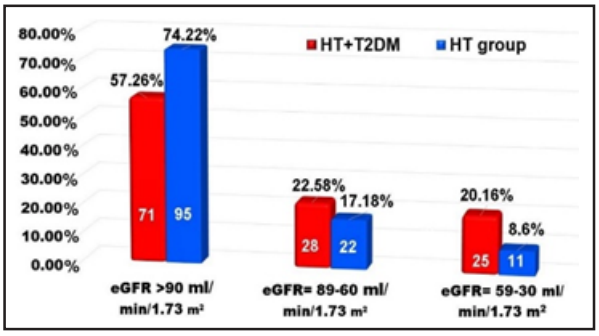

Fig. 2. Evaluation of the estimated glomerular filtration rate in hypertension with diabetes

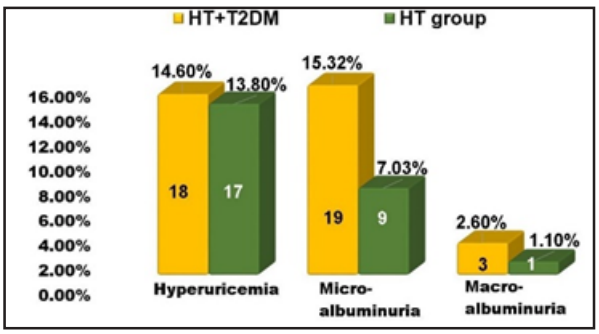

Fig. 3. Hyperuricemia, micro- and macro-albuminuria in hypertension with diabetes

regression analysis. A significant impact was present for obesity with BMI >30 kg/m^2 (OR 2.08 [95% CI 1.26-3.45], p = 0.004), abdominal obesity (OR 1.85 [95% CI 1.11-3.04], p = 0.016), high LDL-c (OR 2.02 [95% CI 1.22-3.35], p = 0.006) and high TG (OR 1.86 [95% CI 1.11-3.11], p = 0.017).

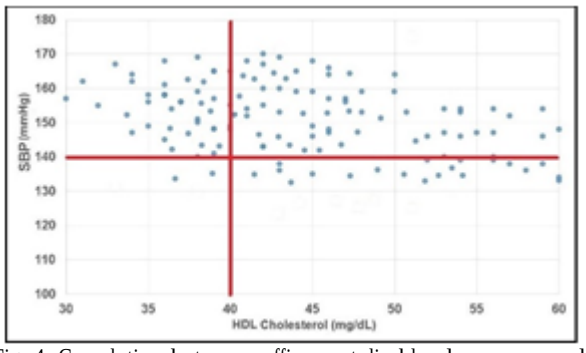

Fig. 4. Correlation between office systolic blood pressure and HDL-cholesterol in hypertension with diabetes

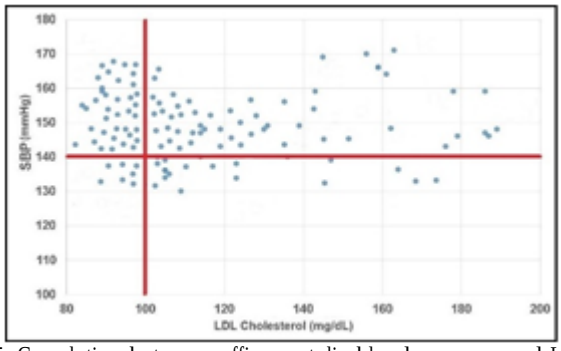

Fig. 5. Correlation between office systolic blood pressure and LDL-cholesterol in hypertension with diabetes

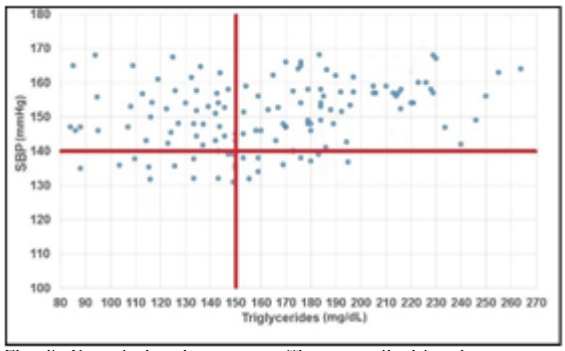

Fig. 6. Correlation between office systolic blood pressure and triglycerides in hypertension with diabetes

Office BP in the T2DM group, compared to the control group, was higher (153.5/89.6 mmHg vs 146.1/86.3 mmHg), the difference being 6.4 mmHg for SBP and 3.25 mmHg for diastolic (DBP). On ABPM, the greatest difference between the 2 groups was 8.3 mmHg regarding night-time SBP. Correlations between office systolic blood pressure and lipidic biomarkers are presented in figures 4 - 6.

The present study is to our knowledge the first Romanian one regarding HT patients with T2DM managed in primary care and evaluated not only with office BP, but also with ABPM. The control rate with office BP measurement was achieved only in less than one fourth of T2DM patients. ABPM control was better, achieved in more than one third of patients, but unsatisfactory, especially during night-time. Office BP targets established for the T2DM group were < 140/85 mmHg, in accordance with the ESC/ESH Guidelines [25] and supported by large clinical trials as Action to Control CV Risk in Diabetes (ACCORD) [26], Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) [27] and International Verapamil SR/Trandolapril Study (INVEST) [24]. BP measurements revealed that patients with T2DM presented higher systolic and diastolic BP values, both in the office and on ABPM. The most specific finding was the higher prevalence of night-time non-dipper and riser pattern, resulting often in nocturnal hypertension, these aspects

being correlated in studies with a worse CV prognostic [29-33].

Assessment of risk factors, as dyslipidaemia, smoking, obesity, reduced eGFR and albuminuria, followed by their correction is important for HT patients with T2DM [34-36]. Many organ damage as MAU, reduced eGFR and comorbidities as CHD, heart failure, cerebrovascular disease and renal impairment had a greater prevalence in the T2DM group. Ayala et al [37] investigated 12,765 patients with HT and diabetes in the Hygia Project, noticing that they were predominantly older, obese males, with obstructive sleep apneea, higher TG, creatinine, uric acid levels, albuminuria and CKD [38-44]. In our diabetes group 42.6% had a reduced eGFR, 15.3% micro- and 2.6% macro-albuminuria, our data being in accordance with literature studies, that show that CKD occurs in 25-40% of diabetics, contributing to a greater morbidity and mortality [45-48]. Some limitations of our study are the relatively small sample size and absence of follow-up and no assessment of prognosis due to the cross-sectional design, aspects that remain to be evaluated in future studies.

Conclusions

The diagnosis of HT in T2DM patients in primary care setting imposes a complete and careful assessment of office BP and ABPM with the entire 24 h BP profile. The most important BP abnormalities observed in hypertension with T2DM were higher BP values both in the office and on ABPM, prevalence of nocturnal non-dipping pattern, association of multiple risk factors, target organ damage and cardiovascular disease. Biochemical data showed significant higher LDL-c, hypertriglyceridemia, low HDL-c and renal evaluation revealed significantly higher prevalence of micro- and macro-albuminuria and reduced eGFR. As hypertension and T2DM are frequent diseases and occur often together, the Romanian GPs must have a greater contribution to an efficient clinical and biochemical evaluation and proper management.

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