Am J Cardiovasc Dis 2014;4(2):58-69
www.AJCD.us /ISSN:2160-200X/AJCD0000488

Original Article

Influence of dyslipidemia in control of arterial hypertension among type-2 diabetics in the western region of the Republic of Macedonia

Ylber Jani[1], Amet Kamberi[1], Fatmir Ferati[2], Atila Rexhepi[2], Bekim Pocesta[3], Nikola Orovcanec[4], Dali Lala[5], Gafur Polisi[6], Mair Iseni[7], Arben Mirto[8], Agim Zeqiri[9]

[1]Department of Cardiology, Faculty of Medicine, "Mother Teresa" University, Tirana, Republic of Albania; [2]Department of Internal Medicine, Faculty of Medicine, Tetov; [3]Department of Cardiology, Faculty of Medicine, "Ss Kiril and Metodij" University, Skopje, Republic of Macedonia; [4]Institute of Biostatistics, Faculty of Medicine, "Ss Kiril and Metodij" University, Skopje, Republic of Macedonia; [5]Private Health Institute of Family Medicine "Florenc", Tetovo; [6]Private Health Institute of Family Medicine "Polisi", Struga; [7]Private Health Institute of Family Medicine "Poli-Medika", Gostivar; [8]Private Health Institute of Family Medicine "DR Mirto", Gostivar; [9]Department of Internal Medicine, General Hospital "DR Ferit Murat", Gostivar

Received April 8, 2014; Accepted May 31, 2014; Epub June 28, 2014; Published July 1, 2014

Abstract: Objective: To determine the influence of dyslipidemia in control of blood pressure in patients with type 2 Diabetes. To test the hypothesis that, blood pressure and lipid levels are not sufficiently controlled in patients with type 2 Diabetes, in the western region of the Republic of Macedonia. Background: Abnormalities of lipid and lipoprotein levels in the serum (dyslipidemia) are recognized as major modifiable cardiovascular disease risk factors and have been identified as independent risk factors for essential hypertension, giving rise to the term dyslipidemic hypertension. While patient-related data from primary care that demonstrate an under-treatment of blood pressure and dyslipidemia in type 2 Diabetics are vastly available in clinical practice, results from population-based studies are scarce. Material and methods: The study was conducted on outpatients in Primary Health Care Clinics in 8 cities on the western region of the Republic of Macedonia. Prospectively the tests were performed on 600 (45.6% women and 54.4% men) participants with a mean age of 62 ± 5.8. Study participants were selected among primary care patients, who were actively on therapy for diabetes mellitus and hypertension during the period of March 2013 - March 2014. Patients' demographic characteristics, clinical laboratory and drug usage data were obtained. The patients were classified according to the BP control, into 2 groups. Results: A total of 600 patients, of which 45.6% female and 54.3% male, completed the survey and had data for a 1-year medical record review. It was observed that a high percentage, 65.3% of patients, did not have controlled blood pressure despite the ongoing medical treatment, according to evidence and current guidelines in a cohort of hypertensive diabetics. (Chi-square: 19.85, p<0.001). Among participants with controled BP, untreated or insufficiently treated dyslipidemia was recorded in 23% of them, whereas among participants with uncontrolled BP, untreated or insufficiently treated dyslipidemia was recorded in 67% of the participants. (Chi-square: 15.01, p=0.0001). Conclusion: A significant influence of dyslipidemia on the control of blood pressure in patients with type 2 Diabetes, was observed in our study. In a small country as Republic of Macedonia (with a population of around 2.000.000, especially the western region with approximately 1/2 of the overall population), this study highlights the considerable lack of awareness and insufficient management of the most important preventable and treatable cardiovascular risk factors (hypertension and dyslipidemia). These findings provide a possible explanation of the steadily high cardiovascular mortality rate despite the clinical and therapeutic progress and accessibility. Besides current hospital-based prevention and pharmaceutical control measures, mass education campaigns, lifestyle interventions etc., emphasis should be given to the role of family doctor as a primary-care health provider.

Keywords: Control, dyslipidemia, arterial hypertension, Type-II diabetics

Introduction

The frequent clustering of hypertension, diabetes and lipid abnormalities, in an individual has been clearly demonstrated to be synergistic in accelerating atherosclerosis, development of premature micro-vascular and macro-vascular complication and substantially increase the risk

Table 1. Basic demographic, clinical and laboratory characteristics of study groups (with controlled and uncontrolled BP) (No 600)

	Group with controlled B.P. (n-208)			Group with uncontolled B.P. (n-392)			
Variables	Mean	S.D.	C.I. ± 95%	Mean	S.D.	C.I. ± 95%	P
Age (y)	59.9	± 5.8		62.4	± 5.4		<.003
BMI (kg/m)	24.8	± 2.4		28.8	± 4.3		<.000
BP-d (y)	5.7	± 2.1		7.1	± 1.5		<.000
DM-d (y)	3.6	± 1.2		5.4	± 2.0		<.000
No- of visits.	4.4	± 0.6		4.3	± 0.7		>.05
Glic. (mmol/dl)	5.7	± 0.1		6.1	± 0.4		<.000
Chol.tot. (mmol/dl)	5.6	± 0.1		5.9	± 0.3		<.000
LDLchol. (mmol/dl)	2.6	± 0.4		3.2	± 0.5		<.000
HDLchol. (mmol/dl)	1.5	± 0.4		1.1	± 0.6		>.05
Trig- (mmol/dl)	1.7	± 0.05		2.0	± 0.3		<.000
Ser.Creatin. (mmol/l)	82.8	± 7.9		82.1	± 7.2		>.05

Values are mean ± SD; y=year; No- of visits=number of measures of BP during 1-year; BW=body weight; BH=body height; BMI=body mass index; BP-d=blood pressure duration; D.M-d=diabetes mellitus duration; Glic=glicemia; Kre=creatinin; Chol-tot=total holesterol; LDL-chol=low density holesterol; HDL-chol=hight density holesterol; Trig=trigicerides.

for coronary heart disease, stroke, nephropathy and retinopathy [1-3]. Abnormalities in serum lipid and lipoprotein levels (dyslipidemia) are recognized as major modifiable cardiovascular disease (CVD) risk factors and have been identified as independent risk factors for essential hypertension giving rise to the term dyslipidemic hypertension [4-6]. Dyslipidemia is more common in untreated hypertension and lipid levels increase as BP increases [7]. It has also been documented that the presence of dyslipidemia substantially worsens the prognosis in hypertensive patients [8]. The risk of CVD associated with concomitant hypertension and dyslipidemia is more multiplicative than the sum of the individual risk factors [3, 7].

This has been recognized in the recent treatment guidelines that emphasize the need to quantify a person's overall CVD risk [3, 7, 9]. Studies have consistently indicated that hypertension and hypercholesterolemia frequently coexist, causing what is known as dyslipidemic hypertension.

The relationship between cholesterol and hypertension is still under investigation, with evidence to date conflicting as to whether statins provide additional cardiovascular benefit through blood pressure lowering effects [4, 5].

Although most deaths among patients with type 2 diabetes (T2D), are attributable to cardiovascular disease, modifiable cardiovascular risk factors appear to be inadequately treated in medical practice [10, 11].

According to the intervention studies, the benefit from treatment of hypertension and dyslipidemia in diabetics, is evidence based [7, 9].

Guidelines recommend aggressive goal for blood pressure and lipid reduction for high risk patients with diabetes mellitus [12-15]. However, it remains unclear how many patient achieve treatment goal versus the number of people merely placed on treatment. BP is poorly regulated in most European countries [10].

The discrepancy between recommended blood pressure, dyslipidemia in T2D patients targets, actual lower control rate and reasons, has been broadly debated [10, 16, 18-22]. Therefore, treated but unregulated hypertension and dyslipidemia, is a major problem in preventive health care. Primary healthcare physicians play a very important role in treating hypertension and dyslipidemia in diabetic patients, as most of them are being followed up at primary healthcare clinics.

While patient-related data from primary care that demonstrate an under-treatment of blood pressure and dyslipidemia in type 2 Diabetics are vastly available in clinical practice, results from population-based studies are scarce. Such data, however, are important to generalize knowledge on the treatment status of specific populations.

It would therefore be worthwhile to investigate the control of blood pressure, dyslipidemia and influence of dyslipidemia in the control of BP, in the pursuit of recommended targets, in a cohort of hypertensive diabetics, who were under general practitioners care in our region.

Table 1A. Basic demographic and clinical characteristics of study group (with controlled and uncontrolled BP) (No 600)

Diabetic group		Gr. with contr. BP (n-208)		Gr. with uncontr. BP (n-392)			
VARIABLES		Num. (No)	Rate (%)	Num. (No)	Rate (%)	Total (No.%)	P
Gender	F	102	49	172	43.8	274 (100%)	.87
	M	106	51	176	44.8	326 (100%)	.89
Artery.scler.disease	AP	14	6.7	6	1.5	20 (100%)	.000
	IM	104	50	32	8.1	136 (100%)	
	HF	2	0.09	0	0	2 (100%)	
	IC	12	5.7	6	1.5	18 (100%)	
Educational level	E	4	1.9	140	25.7	144 (100%)	.008
	H	40	19.2	218	55.6	258 (100%)	
	C	158	76	40	10.2	198 (100%)	
Knowl. of goal BP	Y	160	47.6	100	36.2	260 (100%)	.000
	NO	176	52.3	164	59.4	340 (100%)	
Exercise	NO	44	21.1	166	42.3	210 (100%)	.000
	Y (2-3 d/w)	40	19.2	200	51	240 (100%)	
	Y (5 d/w)	116	55.7	50	12.7	150 (100%)	
Heredity of BP	Y	28	13.6	170	43.3	198 (100%	.001
	NO	180	86.5	222	56.6	402 (100%)	
Heredity of DM	Y	88	42.3	216	55.1	304 (100%)	.31
	NO	120	57.6	176	44.8	196 (100%)	
Medication Noncompliance	Y	10	4.8	62	15.9	72 (100%)	.007
	NO	180	95.1	538	88.2	528 (100%)	
Medication Nonadherence	Y	12	5.7	64	16.3	76 (100%)	.01
	NO	196	94.2	328	83.6	524 (100%)	
Side effect atribu. to medication.	Y	6	2.8	52	13.2	58 (100%)	.007
	NO	202	97.1	334	85.2	542 (100%)	

Gr-group; contr-controlled; uncontr-uncontrolled; F-female; MI-Male; M-maried; Un-unmarried; D-divorced; W-widowed; AP-history of angina pectoris; IM-history of myocardial infarcttion; HF-history of heart faillure; IC-histori of stroke; E-elemntary school; H-high scholl; C-college; Y-jes; NO-no; d/w-day in weeks.

In this study, we tried to determine the influence of dyslipidemia in control of blood pressure in patients with T2D, and to test hypothesis that, blood pressure and lipid levels are not sufficiently controlled in patients with T2D, in the western region of the Republic of Macedonia.

Material and methods

The study was conducted on outpatients in Primary Health Care Clinics in 8 cities on the west region of Republic of Macedonia. Prospectively the tests were performed on 600 (45.6% women and 54.4% men) participants with a mean age of 62 ± 5.8. Study participants were selected among primary care patients, who were actively on therapy for diabetes mellitus and hypertension during the period of 1 calendar year.

Inclusion criteria

A patient was eligible for inclusion in the study if they were between 45 and 79 years of age, were under treatment for diabetes mellitus and hypertension and were diagnosed by using validated criteria [13].

We recorded information from all healthcare encounters during a 1 calendar year. (March 2013 - March 2014).

Exclusion criteria

It included a diagnosis of dementia senilis, secondary hypertension, serum creatinine level >2 mg/dl, age under 45 or above 79.

Clinical and demographic characteristics

The survey obtained data on age, gender, calculated body mass index, educational level,

Table 2. Degree of Blood Pressure control among studied group (No-600)

Pearson Chi-square: 19.85, df=1, p=0.000***			
	Blood Pressure control		
	Controlled BP (<130/80 mmHg.)	Uncontrolled BP (>130/80 mmHg.)	Totals
Count (No)	208	392	300
Percent (%)	34.67%	65.33%	100%

SBP-systolic blood pressure; DBP-diastolic blood pressure; count-number of patient; percent (%)-percent of patient; p=0.000***-Statistical Significance.

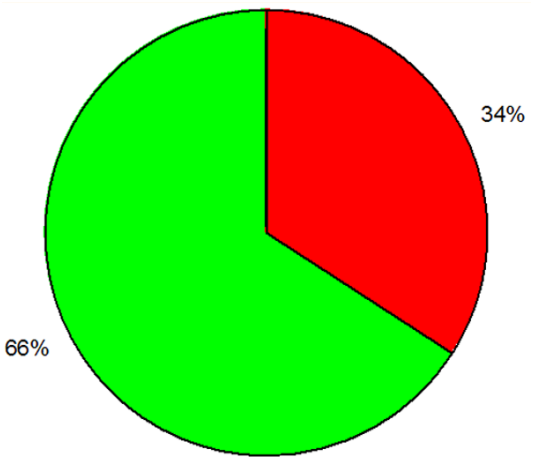

Figure 1. Frequencies of controlled and uncontrolled BP among the studied group.

marital status, health habits, duration of hypertension and diabetes, knowledge of target blood pressure, drugs side effects, compliance and adherence to the drugs treatment. An external electrocardiogram (ECG with lab version 3.0) was done to all the participants in the study. In the blood samples, we determined the values of: glycaemia, lipid status (Tot-chol, LDC, HDC, triglyc), creatinine, in the morning, after 12 hour starvation.

Blood pressure

Measurement of blood pressure according to standard protocol [13]. The mean systolic and diastolic blood pressure recordings were calculated during the study period. Patient were classified according to the value of their systolic and diastolic blood pressure control into 4 groups. Systolic BP groups: I: (<120 mmHg), II: (120-129 mmHg), III: (130-139 mmHg), IV: (>140 mmHg) and diastolic BP group: I: (<80 mmHg), II: (80-84 mmHg), III: (85-89 mmHg), IV: (>90 mmHg). Controlled BP, was defined as systolic BP (SBP) <130 mmHg and diastolic BP (DBP) <80 mmHg.

Uncontrolled BP, was defined as SBP >130 mmHg and DBP >80 mmHg. (The blood pressure was considered to be controlled if the current reading was found to be less than 130/80 mmHg [13].

Dyslipidemia

Total cholesterol (Tot-Chol), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol levels and triglycerides (Trig), were measured from random blood samples.

Dyslipidemia was defined analogous to hypertension using information on lipid-lowering medication intake, self-reported information on physician's diagnoses. According to the recent data, in patient with high ACV risk and those with atherosclerotic cardiovascular disease, high-intensity statin therapy—such as rosuvastatin 20 to 40 mg or atorvastatin 80 mg have been used to achieve at least a 50% reduction in LDL cholesterol. For those with diabetes aged 40 to 75 years of age, a moderate-intensity statin, defined as a drug that lowers LDL cholesterol 30% to 49%, have been used [9, 15].

Statistical analysis

The continuous data were acquired from the examinations for each group shown as average value ± for standard deviation (SD). At the series with attributive marks, the percentage of structure is determined (%); The differences at the series with attributive marks are tested with Difference tests; At the series with numerical marks, we used Descriptive statistics (Mean, 95%; CI; Min., Max, Std.Dev.); At the series with numerical marks where there is no deviation from the normal distribution, the difference is tested with t-test for independent samples (t); Logistical regressive analysis is used to test the association between the categorized variables. A *p*-value of <0.05 or less was considered as the indication for statistical significance. The data are shown in tables and graphics. The statistical processing of data is done by the statistical programs STATISTICA 7.1 and SPSS 20.0.

Table 3. Logistic Regression Model: Association of (Age/Gender/BMI/Level of education/Knowl. of goal BP/Art.CVD/Adherence, Compliance/Med.Side efects) and BP control

			B	S.E	Wald	df	Sig.	Exp (B)	95% CI for Exp (B)	
									Lower L.	Upper L.
1.	Step 1(a)	Gender (1)	-.059	.314	.035	1	.851	.943	.510	1.744
		Age	-.205	.034	36.079	1	.000	.814	.761	.871
		Age	-.351	.101	12.204	1	.000	.704	.578	.857
		Constant	13.16	2.140	37.846	1	.000	315441.82		
2.	Step 1(a)	Constant	1.997	.754	7.010	1	.008	7.368	1.680	32.315
		College (1)	5.007	.761	43.285	1	.000	149.474	33.632	664.328
		College (1)	-3.570	.717	24.785	1	.000	.028		
3.	Step 1(a)	Knowl. of goal BP	-1.678	.290	33.358	1	.000	.187	.106	.330
		Knowl. of goal BP	.153	.460	.111	1	.739	1.166		
4.	Step 1(a)	Art.cvd. AP (1)	2.580	.716	12.977	1	.000	13.198	3.242	53.722
		Art.cvd. AP (1)	3.613	.406	79.196	1	.000	37.080	16.732	82.172
		HF (1)	2.426	.733	10.964	1	.001	11.313	2.691	47.554
		Constant	-1.733	.192	81.644	1	.000	.177		
5	Step 1(a)	Exercise 2-3 d/w (1)	-.393	.338	1.355	1	.244	.675	.348	1.308
		5 d/w (1)	2.603	.371	49.321	1	.000	13.500	6.529	27.912
		Constant	-1.216	.232	27.394	1	.000	.296		
6.	Step 1(a)	Adherence	-1.253	.641	3.817	1	.051	.286	.081	1.004
		Compliance	2.640	1.031	6.556	1	.010	14.012	1.857	105.72
		Constant	-3.056	1.025	8.885	1	.003	.047		
7.	Step 1(a)	Med.Side Efektets (1)	-1.639	.623	6.929	1	.008	.194	.057	.658
		Constant	-.521	.126	17.177	1	.000	.594		

1. Variable(s) entered on step 1: Gender, Age; BMI=body mass index, BP-blood. 2. Variable(s) entered on step 1: a Level of education. 1: High school (1); college (1); BP-blood presure. 3. Variable(s) entered on step 1: a Knowledge of goal BP. 4. Variable(s) entered on step 1a: Artaeriosclerotic Cardiovascular Disease; AP=Angina Pectoris; IM=Myocardial Infarction; HF=heart failure; 5. Variable(s) entered on step 1a: Exercise to lower BP (2-3 day in week and 5-day in week). 6. Variable(s) entered on step 1a: medication compliance, and adherence. 7. Variable(s) entered on step 1a: Side effect atributed to medication.

Results

Study characteristics

A total of 600 patients (45.6% female and 54.4% male), completed the survey and had data for a 1-year medical record review. Their mean age was 62 ± 5.8 years. A mean of 4.51 ± BP recordings were obtained for each subject. The basic demographic, clinical and laboratory information of the study population were presented in **Tables 1**, **1A**.

Frequency of hypertension

It was observed that a small percentage of 34.7% of patients had their blood pressure controled according to evidence and current guidelines, in a cohort of hypertensive diabetics, while a high percentage 65.3% of patients have uncontrolled blood pressure, despite an ongoing medical treatment. The difference was found to be statistically significant. (Chi-square: 19.85, df=1, p=0.000, p<0.001). (**Table 2**, **Figure 1**).

Based on the mean SBP during the study year, 45.2% patient had high normal blood pressure, 18.6% patient had stage I hypertension, and 1.6% patients had stage II or higher blood pressure. Whereas, based on the mean DBP during the study year, 7.6% patients had high normal blood pressure, 10% patients had stage I hypertension, and 17.9% had stage II or higher blood pressure.

Multi variety analysis were used to identify the association of blood pressure control and demographic, clinical and laboratory characteristics (**Table 3**).

Participants with uncontrolled BP were significantly older than participants with controlled BP. (59 ± 5.8 vs. 62 ± 5.4 and p<0.003).

Table 4. Blood Lipids (LDL-chol.) control among studied group (No-600)

Pearson Chi-square: 0.22, df=1, p=0.63			
	Lipids control		Total
	Controlled Lipids (LDL-chol. <2.6 mmol/dl)	Uncontrolled Lipids (LDL-chol >2.6 mmol/dl)	
Count (No)	290	310	300
Percent (%)	48%	52%	100%

count-number of patient; percent (%)-percent of patient; p<0.05-Statistcal Significance.

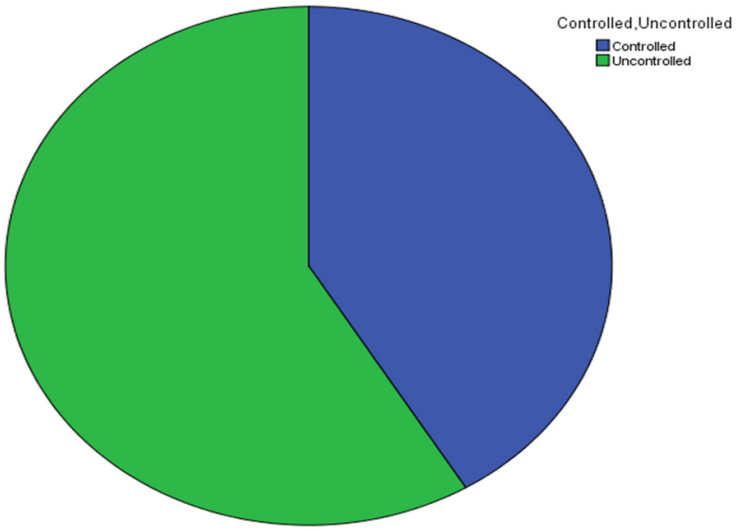

Figure 2. Frequences of controlled and uncontrolled Lipids.

Significant participants with uncontrolled BP had a BMI of 28.8 ± 2.4 kg/m^2, compared to 24.8 ± 2.1 kg/m^2 in participants with controlled BP (Mann-Whitney U Test Z-9.01 and p=0.000); participants with controlled BP smoked less (Chi-square: 31.3, df=5, p=0.008).

Participants with uncontrolled BP were less physically active than participants with controlled BP. (Chi-square: 94.05, df=5, p=0.000). They were also characterized by lower educational status. (Chi-square: 131.39, df=5, p=0.000).

Participants with uncontrolled BP had low adherence and compliance to prescribed treatment. (Chi-square: 5.47, df=1, p=0.01: Chi-square: 12.11.39, df=3, p=0.007). Participants with uncontrolled BP had lack of awareness and knowledge of appropriate target blood pressure. (Chi-square: 32.28, df=7, p=0.0036). Participants with uncontrolled BP, experienced a specific side effects attributed to antihypertensive medication and uncontrolled glycaemia (Chi-square: 7.13, df=1, p=0.0076: Mann-Withney U Test Z-7.28, p=0.000).

Fitting logistic regression models including all study participants without missing values (N= 600), we found the following factors to be significantly associated with poor blood pressure control: age, gender, body mass index, low literacy rates, poor adherence and compliance to prescribed treatment, lack of awareness and knowledge of appropriate target blood pressure, low physical activity, presence of arteriosclerotic disease, experience of a specific side effects attributed to antihypertensive medication.

Frequency and medical treatment of dyslipidemia

Of all participants (n=600), with complete data on: intake of lipid modifying medication, physician's diagnosis and laboratory measurements, it was observed that, untreated or insufficiently treated dyslipidemia was recorded in 52% of all participants, whereas 48% of participants, were treated (according to evidence and current guidelines). The difference was found not to be statistically significant. (Chi-square: 0.22, p=0.63). (**Table 4**, **Figure 2**).

Lipid lowering medication was used by 61% of participants, whereas 39% of participants were untreated with Lipid lowering medications. The difference was found to be statistically significant. (Chi-square=7.81, df-1, P<0.0052). Lipid lowering medications-Statins, were used by 52.3% of participants, while a high percentage 47.7% of participants, were not using it (Fibrates were used by 3% of participants and no medications 47.4% of participants). The difference was found not to be statistically significant. (Chi-square=0.33, df-1, P-0.567). High-intensity Statins and moderate-intensity Statins were

Table 5. Lipid lowering medications vs Not Lipid lowering medication among studied group (No-600)

Pearson Chi-square: 7.81, df=1, p=0.005				
used Lipid lowering medications (No-600)				Totals
Lipid lowering medication (No. 368)			Not Lipid lowering medication (No. 232)	
(high + moderate intensity Statins)		Others med.		
Count (No)	314	54	232	600
Percent (%)	52.3%	9%	38.6%	100%

count-number of patient; percent(%)-percent of patient; med-medications; p<0.05-Statistical Significance.

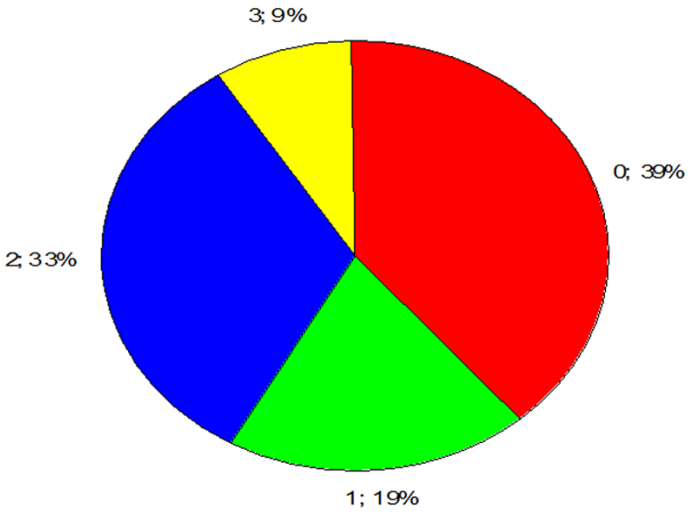

Figure 3. Lipid lowering medication used (0-nomedications, 1-intensive Statins used, 2-subintensive Statin sued, 3-Fibrate used).

used by 52.3% of participants, whereas Lipid lowering medications- Statins, were not used by 48% of participants.The difference was found not to be statistically significant (Chi-square: 0.33, df=1, p=0.56). (**Table 5**, **Figure 3**). Among participans with controlled BP, untreated or insufficiently treated dyslipidemia was recorded in 23% of participants, whereas 77% of participants, were treated (according to evidence and current guidelines). The difference was found to be statistically significant. (Chi-square: 6.63, df=1, p=0.01). Among participans with uncontrolled BP, untreated or insufficiently treated dyslipidemia was recorded in 67% of participants, whereas 33% of participants, were treated (according to evidence and current guidelines). The difference was found to be statistically significant. (Chi-square: 15.01, df=1, p=0.0001). High-intensity Statins and moderate-intensity Statins, were used by 86% of participants with controlled BP and by 32% of participants with uncontrolled BP. The difference was found to be statistically significant (Chi-square: 24.81, df=1, p=0.000). (**Tables 6**, **7**). Fitting logistic regression models including all study participants without missing values (N=600), we found that dyslipidemia was negatively associated with BP control. Participants with uncontrolled lipids had significantly higher odds of failing to reach the blood pressure target (OR=0.035; 95% CI 0.012-0.101). Also, participants with poor glycemic control had significantly higher odds of failing to reach the BP target (OR=0.019; 95% CI 0.03-0.119) (**Table 8**).

Discussion

Dyslipidemia and Hypertension are well-established risk factors for CVD, and the coexistence of both of these conditions has proved to have adverse outcomes [1-3]. However, new guidelines have been published to stress the importance of aggressive treatment of blood pressure and dyslipidemia in diabetics [5-7]. Our study showed that, only a small percentage of 34.7% had controlled blood pressure under according to the evidence and current guidelines, in a cohort of hypertensive diabetics, while a high percentage 65.3% of patients have uncontrolled blood pressure, despite ongoing medical treatment. Also, untreated or insufficiently treated dyslipidemia in our study was recorded in 52% of all participants, while 48% of participants, and were treated (according to evidence and current guidelines). Treated but uncontrolled BP and dyslipidemia in hypertensive diabetics is a common problem. Numerous studies have revealed poor awareness and unsatisfactory treatment and control in many countries. As in other European settings, our findings indicate that the management of these pathologies is far from being optimal [23-28]. Recently, Berthold et al. [17], described that approximately 60% of T2D patients from the German T2DSD-registry DUTY had uncontrolled systolic blood pressure and about 50% had uncontrolled LDL cholesterol values. The German ESTHER Study, found that 78% of dia-

Table 6. Lipids control among participants with controlled BP (No. 208)

Lipids and Blood Pressure control					
Pearson Chi-square: 6.63, df=1, p=0.01			Pearson Chi-square: 15.01, df=1, p=0.0001		Totals
Controlled Lipids			Uncontrolled Lipids		
Gr. with controlled BP (No. 208)		Gr. with uncontrolled BP (No. 392)	Gr. with controlled BP (No. 208)	Gr. with uncontrolled BP (No. 392)	
Count (No)	160	130	48	262	600
Percent (%)	77%	33%	23%	67%	100%

Gr.-group; count-number of patient; percent(%)-percent of patient. BP-Blood Pressure; p<0.05-Statistcal Significance.

Table 7. Used Lipid lowering medications-Statins, among study group (No. 600)

Pearson Chi-square: 24.81, df=1, p=0.000.			
Used Lipid lowering medications-Statins (No. 600)			Totals
Gr. with controlled BP (No. 208)		Gr. with uncontrolled BP (No. 392)	
Count (No)	180	134	314/600
Percent (%)	86%	34%	52.3%

Gr.-group; count-number of patient; percent(%)-percent of patient. BP-Blood Pressure; p<0.05-Statistcal Significance.

betes patients had hypertension diagnosed by a physician and only 12.8% of those who received anti-hypertensive pharmacotherapy achieved blood pressure levels below 130/85mmHg, physician diagnosed dyslipidemia was reported in 42.5% of all patients [10]. A nationwide French survey, involving 410 diabetologists found that the target blood pressure was attained by 29% of patients and 58% had uncontrolled LDL values. Control of blood pressure and LDL was not considered to be optimal [29]. The authors of a Canadian study concluded that T2D patients with cardiovascular co-morbidities are insufficiently treated with medication, perhaps because of the "glucocentric view" of diabetes. They focused on antiplatelet agents, statins and ACE inhibitors [30]. Godley et al. used insurance claims data of 977 hypertensive T2D patients in the US. Only 19.7% reached the stricter blood pressure goal of <130/85 mmHg and 52% had dyslipidemia [31]. A recently published US investigation by DeGuzman et al. including 926 high risk patients with diabetes and concomitant atherosclerotic CVD found that although the vast majority of patients were prescribed recommended drug therapy and mean cholesterol and BP values were satisfactory, the percentage of patients actually treated to goals of current guidelines was moderate. About 40% had controlled LDL, and about 60% reached a systolic BP of ≤130 mmHg [32]. Data from 9,167 participants of the US NHANES (National Health and Nutrition Examination Survey) survey, showed that alongside an increasing prevalence of diabetes from 1999 to 2008 the frequency of self reported use of lipid lowering medication increased significantly. Accordingly, the proportion of participants reaching the LDL cholesterol goal of <100 mg/dl also increased significantly from about 30% to about 50%. Although the use of antihypertensive preparations increased significantly from about 35% to about 60%, there was no change in the proportion of participants achieving the BP goal of ≤130/80 mmHg (about 50%). Moreover, only one in four people with diabetes attained both the LDL and BP targets simultaneously [33].

The results of our study proved that, there is a statistically significant influence of dyslipidemia on control of BP in a cohort of hypertensive diabetics. There could be a significant role of these lipid abnormalities in causing of hypertension. It has been proved that hypercholesterolemia induced endothelial injury results in superoxide anion production. The resultant excessive degradation of nitric oxide which disrupts the endothelium dependent vasodilatation affects the peripheral vascular resistance. As Type-2 DM is an insulin resistant and hyperinsulinemic state, insulin itself can impair endothelium dependent vasodilatation [34]. Hypertension in turn can impair the glucose metabolism through various mechanisms. The exaggerated action of angiotensin II, inhibits insulin like growth factor-1 (IGF-1) signaling pathway which in turn hampers the vasodilator and glucose transporting actions of IGF-1 and insulin. Inhibited IGF-1 and insulin can accentuate the vasoconstriction by diminishing endothelial nitric oxide synthase activity, impaired nitric oxide metabo-

Table 8. Logistic Regression Model: Association of (Glic/Chol-Tot/LDL-chol, HDL-chol/Trig.) and controlled BP

			B	S.E.	Wald	df	Sig.	Exp (B)	95% C.I. EXP (B)	
									Lower L	Upper L.
1.	Step 1(a)	Glic	-3.978	.942	17.814	1	.000	.019	.003	.119
		Chole.Tot.	-2.067	.782	6.981	1	.008	.127	.027	.586
		Triglic.	-7.421	1.572	22.284	1	.000	.001	.000	.013
		Triglic.	48.058	7.436	41.773	1	.000	7E + 020		
2.	Step 1(a)	LDL	-3.357	.544	38.101	1	.000	.035	.012	.101
		LDL	-.009	.074	.014	1	.906	.991	.858	1.145
		Constant	10.769	1.817	35.114	1	.000	47525.11		

1. Variable(s) entered on step 1a: Glic, Cholesterol Total, Triglycerides. 2. Variable(s) entered on step 1: LDL-chol, HDL-chol.

lism as well as the sodium pump functioning. Dyslipidemia may also cause hypertension by increasing arterial stiffness [35]. Thus diabetes mellitus and hypertension act as vicious cycle and worsen each other.

If lipid disturbances provoke hypertension, it is logical that pharmacological treatment of dyslipidemia lowers blood pressure.

Statins are usually prescribed to treat dyslipidemia. In our study High-intensity Statins and moderate-intensity Statins, were used by 86% of participants with controlled BP and by 32% of participants with uncontrolled BP. They are regarded as safe, provide significant cardiovascular benefits in different populations including the elderly and patients with diabetes [36]. There is some evidence to suggest that treating dyslipidemia has beneficial effects on blood pressure. Patients receiving concomitant antihypertensive and statin therapy experienced a reduction in BP that could not be explained solely by the lipid-lowering effect of the statin or the effect of the antihypertensive medication. These results suggest that the use of statins in combination with antihypertensive drugs may improve BP control in patients, with uncontrolled hypertension and high serum cholesterol levels [37, 38].

In a study of patients taking an ACE inhibitor (enalapril or lisinopril), the value of systolic blood pressure was lowered by double, also the value of diastolic blood pressure was by 25% lower when a statin (either lovastatin or pravastatin) was added to the regimen. The mean cholesterol levels fell by 38% and these results could be attributed to a direct statin effect or to cholesterol lowering. Such differences in blood pressure between patients treated with lipid-lowering therapies and those given a control intervention were not seen in HPS, ASCOT, ALLHAT or several other large clinical trials [39]. Whether blood pressure-lowering drugs have any effect on the circulating lipid levels has been the subject of intense debate for many years. However, there is limited data demonstrating the effect of elevated blood pressure on lipid levels. Clearly, further large-scale trials are needed to examine the BP-lowering effects of the lipid-lowering therapy and to distinguish between the effects that can be directly attributed to reduced serum cholesterol, the pleiotropic effects of lipid-lowering agents or situations in which lipid-lowering medications potentiate the action of concomitant antihypertensive agents. Over and above, insufficient blood pressure and lipid control are not exclusively due to insufficient prescription of medication but to various factors related to the patient and the physician. Important aspects are insufficient awareness and motivation of the patient, reluctance to initiate lifestyle changes, poor compliance (e.g. because of forgetfulness, tolerability problems due to adverse side effects, polypharmacy and dosing schedule, co-payments) and failure to modify therapy, when it is indicated such as use of combination therapy if monotherapy proves to be inadequate [40, 41].

Study limitations

Several limitations of this study deserve mentioning. The study design was observational, so each patient was managed at the discretion of his or her physician. Study design limited the ability to make causal inferences of the associations between predictors' variables and hypertension control. Although the conflicting inter-

national treatment thresholds complicate comparison with previous studies, we believe that these limitations will not reduce the values of the basic conclusions of the study.

Clinical implications

These data provide further evidence of influence of dyslipidemia on the blood pressure control. Targeted interventions to improve management in such patients could make a substantial difference in stemming the epidemic of poorly controlled hypertension and dyslipidemia. This study provides a framework for identifying hypertensive patients who are at high risk of poor control, and many of the factors identified may be amenable to improvement. Thus, apart from medication and its design, to improve secondary prevention of cardiovascular disease in primary physician health care and especially in T2D patients, the following intervention programs should be emphasized: education sessions for practitioners, medical management guidelines, physician profiling of prescribing patterns, blood pressure and dyslipidemia monitoring kits for patients and patient education.

Conclusions

A significant influence of dyslipidemia on the control of blood pressure in patients with type 2 Diabetes, was observed in our study. In a small country as Republic of Macedonia (with a population of around 2.000.000, especially the western region with approximately 1/2 of the overall population), this study highlights the considerable lack of awareness and insufficient management of the most important preventable and treatable cardiovascular risk factors (hypertension and dyslipidemia). These findings provide a possible explanation of the steadily high cardiovascular mortality rate despite the clinical and therapeutic progress and accessibility. For the majority of the patients with T2D, secondary prevention of cardiovascular disease is not in line with recent recommendations. Though numerous guidelines on the topic have been published, the transfer of theoretical knowledge to practical application appears to be very difficult. The present findings indicate the urgent need for intensive efforts to reduce the gap in prevention strategies and control of clinical cases according to explicit clinical guidelines. A tailored approach to both, prevention and treatment of hypertension and dyslipidemia, is required in this high-risk population. Besides current hospital-based prevention and pharmaceutical control measures, mass education campaigns, lifestyle interventions and more emphasis should be given to the role of family doctor as a primary-care health provider.

Disclosure of conflict of interest

The authors reported no conflict of interest and no funding has been received for this work.

Abbreviations

AGE, Age; BW, Body weight; BH, Body height; BMI, Body mass index; BP, Blood pressure; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; GLYC, Glycaemia; T2D, Diabetes type-2; ACV, Arteriosclerotic cardio vascular disease; CRE, Creatinemia; TCH, Total cholesterol; LDC, Low density cholesterol; HDC, High density cholesterol; Trigl, Triglyceride; ESH, European Society of Hypertension; ESC, European Society of Cardiology; JNC 7, Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure; ACC/AHA, American College of Cardiology; American Heart Association.

Address correspondence to: Dr. Ylber Jani, Department of Cardiology, Faculty of Medicine, "Mother Teresa" University, Tirana, Republic of Albania. E-mail: ylber_jani@hotmail.com

References

[1] UK Prospective Diabetes Study Group. Tight blood pressure contr and risk of macrovascular and microvascular complication in type-diabetes. UKPD38. BMJ 1998; 317: 703-13.

[2] Turnbull F; Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet 2003; 362: 1527-35.

[3] National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. Circulation 2002; 106: 3143-3421.

[4] Kannel WB, Castelli WP, Gordon T, William B. Serum cholesterol, lipoproteins, and the risk of

coronary heart disease. The Framingham study. Ann Int Med 1971; 74: 1-12.
[5] Williams RR, Hunt SC, Hopkins PN, Kuida H, Stults BM, Barlow GK, Ash KO. Familial dyslipidemic hypertension. Evidence from 58 Utah families for a syndrome present in approximately 12% of patients with essential hypertension. J Am Med Associat 1988; 259: 3579-3586.
[6] Halperin HD, Sesso J, Buring JE, Stampfer MJ, Gaziano JM. Dyslipidemia and the risk of incident hypertension in men. Hypertension 2006; 47: 45-50.
[7] Borghi C. Interactions between hypercholesterolemia and hypertension: implications for therapy. Curr Opin Nephrol Hypertens 2002; 11: 489-96.
[8] Thomas F, Bean K, Guize L, Quentzel S, Argyriadis P, Benetos A. Combined effects of systolic blood pressure and serum cholesterol on cardiovascular mortality in young (<55 years) men and women. Eur Heart J 2002; 23: 528-35.
[9] Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Lloyd-Jones DM, Blum CB, McBride P, Eckel RH, Schwartz JS, Goldberg AC, Shero ST, Gordon D, Smith SC Jr, Levy D, Watson K, Wilson PW. ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013; [Epub ahead of print].
[10] Ruckert IM, Schunk M, Schipt S, Holle R, Henry V. Blood preassure anlipid management fall far short in persons with type 2 diabetes:results from the DIAB-CORE Consortiom including sex German papolation-baseed studies. Cardiovasc Diabetol 2012; 8: 50.
[11] Hanson L, Zancheti A, Carruthers SG. Effects of intensive blood-presure lowering and low dose aspirin in patient with hypertension: principal results of Hypertension Optimal treatment (HOT) randomized trial. Lancet 1998; 351: 1755-6.
[12] ESH-ESC guidelines for management of hypertension. Herz 2006; 31: 331-8.
[13] The seventh report of Join National Committee on Prevention, Detection, Evaluation and treatment of Hight Blood Pressure. JAMA 2003; 289: 2550-72. The JNC 7 report.
[14] Position Statement. Hypertension management in adult with diabetes. Diabetes Care 2004; 27: S65-S67.
[15] ESC/EAS guidelines for management of Dyslipidemas. Eur Heart J 2011; 32: 1769-1818.
[16] De Guzman PB, Akosah KO, Simpson AG. Suboptimal achivement of guideline-derive lipid goal in management of diabetes patients with CVD,despide high use ofevidence-based therapies. Diab Vasc Dis Res 2012; 9: 138-45.
[17] Berthold HK, Bestehorn KP, Krone W, Gouni-Berthold I. Atherosclerotic disease location and disparities in the control and treatment of cardiovascular risk factors in patients with Type 2 diabetes. Diabet Med 2010; 27: 303-308.
[18] The US Departement of health and human servise in their Helthy Peuple 2010 report.
[19] Leenen FH, Dumain J, Mclnnis NH, Frans HH, Pavel H. Result of Ontario survey on the prevalence and control of hypertension. CMAJ 2008; 178: 1441-9.
[20] Campbell NR, Gilbert RE, Leiter LA, Larochelle P, Tobe S, Chockalingam A, Ward R, Morris D, Tsuyuki RT, Harris SB. Hypertension in people with type 2 diabetes: Update on pharmacologic management. Can Fam Physician 2011; 57: 997-1002, e347-53.
[21] Anver Z, Sharma RK, Garg VK, Abanto Z, Bert J. Hypertension management in diabetic patient. Eur Rev Med Pharmacol Sci 2011; 15: 1256-1259.
[22] Borghi C. Internaction between hypercholesterolemia and hypertension:implication for therapy. Curr Opin Nephrol Hypertens 2002; 11: 489-96.
[23] Wolf-Maier K, Cooper RS, Kramer H, Banegas JR, Giampaoli S, Joffres MR. Hypertension treatment and control in five European countries, Canada, and the United States. Hypertension 2004; 43: 10-17.
[24] Aguado A, López F, Miravet S, Oriol P, Fuentes MI, Henares B, Badia T, Esteve L, Peligro J. Hypertension in the very old; prevalence, awareness, treatment and control: a cross-sectional population-based study in a Spanish municipality. BMC Geriatr 2009; 9: 16.
[25] Danon-Hersch N, Marques-Vidal P, Bovet P, Chiolero A, Paccaud F, Bovet P, Chiolero A, Paccaud F, Pécoud A. Prevalence, awareness, treatment and control of high blood pressure in a Swiss city general population: the CoLaus study. Eur J Cardiovasc Prev Rehabil 2009; 16: 66-72.
[26] Macedo ME, Lima MJ, Silva AO, Alcantara P, Ramalhinho V, Carmona J. Prevalence, awareness, treatment and control of hypertension in Portugal: the PAP study. J Hypertens 2005; 23: 1661-1666.
[27] McDonald M, Hertz RP, Unger AN, Lustik MB. Prevalence, awareness, and management of hypertension, dyslipidemia, and diabetes among United States adults aged 65 and older. J Gerontol A Biol Sci Med Sci 2009; 64: 256-263.
[28] Costanzo S, Di Castelnuovo A, Zito F, Krogh V, Siani A, Arnout J, Cappuccio FP, Miller MA, van

Dongen M, de Lorgeril M, de Gaetano G, Donati MB, Iacoviello L; European Collaborative Group of the IMMIDIET project. Prevalence, awareness, treatment and control of hypertension in healthy unrelated male-female pairs of European regions: the dietary habit profile in European communities with different risk of myocardial infarction the impact of migration as a model of gene-environment interaction project. J Hypertens 2008; 26: 2303-2311.

[29] Charpentier G, Genes N, Vaur L, Amar J, Clerson P, Cambou JP, Gueret P. Control of diabetes and cardiovascular risk factors in patients with type 2 diabetes: a nationwide French survey. Diabetes Metab 2003; 29: 152-158.

[30] Brown LC, Johnson JA, Majumdar SR, Tsuyuki RT, McAlister FA. Evidence of suboptimal management of cardiovascular risk in patients with type 2 diabetes mellitus and symptomatic atherosclerosis. CMAJ 2004; 171: 1189-1192.

[31] Godley PJ, Maue SK, Farrelly EW, Frech F. The need for improved medical management of patients with concomitant hypertension and type 2 diabetes mellitus. Am J Manag Care 2005; 11: 206-210.

[32] Deguzman PB, Akosah KO, Simpson AG, Barbieri KE, Megginson GC, Goldberg RI, Beller GA. Sub-optimal achievement of guideline-derived lipid goals in management of diabetic patients with atherosclerotic cardiovascular disease, despite high use of evidence-based therapies. Diab Vasc Dis Res 2012; 9: 138-145.

[33] Kuznik A, Mardekian J. Trends in utilization of lipid- and blood pressure-lowering agents and goal attainment among the U.S. diabetic population, 1999-2008. Cardiovasc Diabetol 2011; 10: 31.

[34] Sung BH, Izzo JL Jr, Wilson MF. Effects of cholesterol reduction on BP response to mental stress in patients with high cholesterol. Am J Hypertens 1997; 10: 592-99.

[35] Sowers JR. Insulin resistance and hypertension. Am J Physiol Heart Circ Physiol 2004; 286: H1597-602.

[36] Lewis SJ. Lipid-lowering therapy: who can benefit? Vasc Health Risk Manag 2011; 7: 525-534.

[37] Borghi C, Prandin G, Costa V, Bacchelli S, Zimmermann C. Use of statins and blood pressure control in treated hypertensive patients with hypercholesterolemia. J Cardiovasc Pharmacol 2000; 35: 549-55.

[38] Borghi C, Dormi A, Veronesi M, Ambrosioni E. Association between different lipid-lowering treatment strategies and blood pressure control in the Brisighella Heart Study. Am Heart J 2004; 148: 285-92.

[39] Nickenig G, Baumer AT, Temur Y, Kebben D, Jockenhovel F, Bohm M. Statin-sensitive dysregulated AT1 receptor function and density in hypercholesterolemic men. Circulation 1999; 100: 2131-4.

[40] Dusing R. Overcoming barriers to effective blood pressure control in patients with hypertension. Curr Med Res Opin 2006; 22: 1545-1553.

[41] Bailey CJ, Kodack M. Patient adherence to medication requirements for therapy of type 2 diabetes. Int J Clin Pract 2011; 65: 314-322.