Rate of blood pressure control and antihypertensive treatment approaches in diabetic patients with hypertension

Hipertansiyonu olan diyabetik hastalarda kan basıncı kontrolü ve antihipertansif tedavi yaklaşımları

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ABSTRACT

Objectives: Hypertension is a common co-morbidity in patients with type 2 diabetes. Management of hypertension is of paramount importance in reducing macro- and microvascular complications of diabetes. The aim of this study is to determine the rate of blood pressure control (<140/85 mmHg) in diabetic patients with hypertension, and to evaluate the prescribing pattern of antihypertensive medications.

Study design: This was a prospective, cross-sectional, observational study conducted in a tertiary centre in Turkey. Of 707 patients with diabetes, 500 hypertensive patients were evaluated to determine control of hypertension and treatment attitudes. Logistic regression analysis was used to evaluate the likelihood of prescription of each class of antihypertensive medications for the presence of macro- and microvascular complications.

Results: Most of the patients (95%) were on antihypertensive therapy. Only 41% achieved target blood pressure values (<140/85 mmHg). Renin angiotensin system (RAS) blockers were the most frequently (82.4%) prescribed antihypertensive agents, and a combination of RAS blockers and diuretics were the most commonly preferred combination therapy. Most of the patients were on 1 antihypertensive drug or a combination of 2 drugs (39.5% and 44.7%, respectively). Patients with coronary artery disease were more likely to receive beta blockers (Odds ratio=3.6, 95% confidence interval=2.3-5.6; p<0.001).

Conclusion: Although most of the diabetic hypertensive patients were on hypertensive therapy, more than half had uncontrolled blood pressure.

ÖZET

Amaç: Hipertansiyon, tip 2 diyabeti olan hastalarda sık olarak eşlik eden bir hastalıktır. Hipertansiyonun tedavisi, diyabetin makro- ve mikrovasküler komplikasyonlarının azaltılmasında oldukça önemli bir yere sahiptir. Bu çalışmanın amacı hipertansiyonu olan diyabetli hastalarda kan basıncı kontrol (<140/85 mmHg) düzeyini saptamak ve antihipertansif ilaçların reçetelenme biçimini değerlendirmektir.

Çalışma planı: Bu çalışma, Türkiye'de üçüncü basamak bir merkezde yürütülen ileriye dönük, kesitsel, gözlemsel bir çalışmadır. Yediyüz yedi diyabetli hasta içinden hipertansiyonlu 500 hasta hipertansiyon kontrolü ve tedavi yaklaşımlarının belirlenmesi için değerlendirildi. Lojistik regresyon analizi kullanılarak her bir antihipertansif ilaç sınıfının makro- ve mikrovasküler hastalıkların varlığı açısından reçetelenme olasılığı araştırıldı.

Bulgular: Hastaların çoğu (%95) antihipertansif ilaç kullanmakla birlikte sadece %41'i hedef kan basıncı değerlerine (<140/85 mmHg) ulaşmıştı. Renin anjiyotensin sistemi (RAS) blokerleri en sık (%82.4) reçete edilen antihipertansif ajanlardı ve RAS blokerleri ile diüretik kombinasyonu en sık tercih edilen kombinasyon tedavisi idi. Hastaların çoğu bir veya iki antihipertansif ilaç kullanmaktaydı (sırasıyla, %39.5; %44.7). Koroner arter hastalığı olan hastalarda beta bloker kullanımı daha olası idi (Odds oranı=3.6; %95 güvenlik aralığı=2.3-5.6; p<0.001).

Sonuç: Diyabetli hipertansif hastaların çoğu hipertansiyon tedavisi almalarına rağmen, yarıdan fazlasında kan basıncı kontrol altında değildir.

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Hypertension (HT) is a common co- morbidity in diabetes, affecting more than 50% of diabetic patients.[1-3] This coexistence of the two conditions carries an excessive risk for both micro- and macrovascular complications, and they work synergistically to increase cardiovascular morbidity and mortality.[4] Blood pressure lowering in diabetic patients has a remarkable cardiovascular protective effect.[5] Lowering blood pressure is associated with greater reduction in cardiovascular event rates and mortality in diabetic patients than in non-diabetic people.[6,7] Most recent European guidelines on management of HT recommend maintaining blood pressure <140 mmHg systolic and <85 mmHg diastolic in patients with type 2 diabetes as a means of reducing cardiovascular events in this high-risk population.[8] Despite the critical role of HT management in the prevention of cardiovascular complications in patients with diabetes, previous studies have shown that treatment goals are often not met in 'real-life' practice.[9-11]

The aim of this study is 1) to identify the gaps between current HT management in 'real life' and evidence-based treatment targets and 2) to determine the patterns of antihypertensive medications in patients with type 2 diabetes.

PATIENTS AND METHODS

This is prospective cross-sectional study conducted at cardiology and endocrinology outpatient clinics in a tertiary hospital in Turkey. Consecutive type-2 diabetic patients were invited to participate in the study, and a total of 707 patients willing to provide informed consent were recruited. Of the 707 patients with type 2 diabetes, 500 with coexisting HT were analysed with respect to blood pressure control and treatment attitudes. Physicians were instructed to perform a routine visit and compile a standard questionnaire specifying the following: demographic data and lifestyle habits (cigarette smoking, ongoing dietary therapies, and regular physical activity ≥30 minutes at least three times a week), anthropometric data, diabetes duration, history and duration of HT, pharmacological therapies, laboratory data and data on microvascular (retinopathy, nephropathy) and macrovascular (coronary, cerebral, and peripheral arterial disease [PAD]) complications.

Systolic and diastolic blood pressure values were measured with standard sphygmomanometers after the patient had been seated for at least 5 minutes. Hypertension was defined by the presence of antihypertensive therapy and/or a blood pressure reading of ≥140/90 mmHg in at least 2 blood pressure measurements. Each patient had had a fasting plasma glucose and lipid profile, haemoglobin A1c (HbA1c), serum creatinine and spot urinanalysis for proteinuria no more than 3 months prior to interview, as well as an eye examination by an ophthalmologist.

Abbreviations:

ACEI	*Angiotensin converting enzyme inhibitors*
ARB	*Angiotensin receptor blockers*
BB	*Beta blockers*
BMI	*Body mass index*
CAD	*Coronary artery disease*
DBP	*Diastolic blood pressure*
HT	*Hypertension*
PAD	*Peripheral arterial disease*
RAS	*Renin angiotensin system*
SBP	*Systolic blood pressure*

Body mass index (BMI) was calculated as kg/m^2. Microalbuminuria was defined as albumin excretion in urine of ≥30 mg/l assessed by spot urinanalysis, and creatinine clearance was estimated by the Cockcroft-Gault formula.

The patients were classified as having coronary artery disease (CAD) if there was a history of previous myocardial infarction, angiographically-documented coronary stenosis of ≥50%, percutaneous coronary intervention, or coronary bypass surgery. The patients were classified as having PAD if there was a history of previous peripheral bypass or percutaneous intervention, amputation, angiographically-documented peripheral vascular stenosis of ≥50%. Patients were identified as having cerebrovascular disease if they had suffered from a neurological dysfunction associated either with temporary or permanent brain injury.

The study was approved by the local ethics committee and was conducted in accordance with the Declaration of Helsinki.

Statistics

Continuous variables were presented as mean±standard deviation or median as appropriate, and categorical variables were presented as percentages. Comparisons of categorical variables between groups were made with a chi-square (x^2) or Fisher's exact test. Multivariate logistic regression analysis was used to identify the likelihood of prescription of antihypertensive agents for the presence of micro- and macrovascular complications, and to identify the

possible demographic or clinical characteristics that could be predictors for achievement of target blood pressure levels.

All statistical comparisons were two-tailed, and p values of <0.05 were considered to be statistically significant.

RESULTS

Of 707 type 2 diabetic patients, 500 (71%) had co-existing HT. The mean age of the diabetic hypertensive patients was 61.0±9.9 years, and 39% were male. Table 1 shows the demographic and clinical charac-

Table 1. Demographic and clinical characteristics of the study population

	Total (n=500)	
	%	Mean±SD
Men	38.8	
Age (years) (min.-max.)		
		61.04±9.98 (35-90)
Diabetes duration (years)		9.06±7.94
HT duration		
0-1 year	10.4	
≥1.1; and ≤5 years	31.2	
>5 and ≤10 years	15	
>10 years	43.4	
Body mass index (kg/m^2)		31.1±6.09
≥30 kg/m^2	52.2	
Current smoker	14.4	
Physical activity	18.6	
Diet	44.6	
Nephropathy	22.8	
Retinopathy	26.8	
Coronary artery disease	33.2	
Cerebrovascular disease	11.4	
Peripheral artery disease	6.0	
HbA1c (%)		7.58±1.7
Microalbumiuria	20	
Creatinine clearance (ml/min)		102.6±38.6
<30 ml/min	1.8	
≥30 and <60 ml/min	8.8	
≥60 and <90 ml/min	27.4	
≥90 ml/min	62	
Total cholesterol (mg/dl)		206.25±46.06
Low-density lipoprotein cholesterol cholesterol (mg/dl)		128.3±38.1
High-density lipoprotein cholesterol cholesterol (mg/dl)		44.2±12.2
Triglyceride (mg/dl)		182.9±120.9
Statin therapy	40	
Oral antidiabetic therapy	72.2	
Insulin therapy	43	

SD: Standard deviation.

Table 2. Demographic and clinical characteristics of patients with and without blood pressure control

	Patients with uncontrolled blood pressure (n=292)		Patients with controlled blood pressure (n=208)		p
	%	Mean±SD	%	Mean±SD	
Men	39		38.5		0.89
Age(years)		60.6±9.9		61.6±10	0.19
Diabetes duration (years)		8.9±8.0		9.3±7.7	0.42
Hypertension duration (years)		8.9±7.7		9.1±7.5	0.58
Body mass index (kg/m^2)		31.1±5.8		30.9±6.4	0.36
Current smoker	13		16		0.43
Physical activity	19		18		0.87
Nephropathy	22.9		22.6		0.92
Retinopathy	30		25		0.20
Coronary artery disease	32		35		0.40
Cerebrovascular disease	13		9		0.17
Peripheral artery disease	4.5		8.2		0.08
Statin therapy	39		40		0.90

SD: Standart deviation.

teristics of the diabetic hypertensive patients. There were 114 (23%) patients with nephropathy, 134 (27%) had retinopathy and 202 (40.4%) had cardiovascular disease.

Nearly half of the patients reported that they had received dietary advice and were compliant with the recommendations, and 18% reported doing regular physical activity. Most patients (88%) were overweight or obese.

Four hundred and seventy four patients (95%) were on antihypertensive therapy. Overall blood pressure control according to current European guidelines on management of HT (systolic blood pressure (SBP) <140 mmHg and diastolic blood pressure (DBP) <85 mmHg) was achieved in 41.6% of the patients. Systolic blood pressure levels were above target level (≥140 mmHg) in 54% of the patients, and 42% had high diastolic blood pressure levels (≥85 mmHg). In the group with controlled blood pressure mean SBP was 121.0±9.2 mmHg and mean DBP was 72.5±7.2 mmHg. In the group with uncontrolled blood pressure, mean SBP and DBP were 151.2±14.9 mmHg and 89.7±11.6 mmHg respectively. None of the demographic or clinical characteristics (age, gender, diabetes duration, HT duration, body mass index, smoking status, physical activity, nephropathy, retinopathy, coronary artery disease, peripheral artery disease, cerebrovascular disease or statin therapy) was associated with the achievement of recommended targets for blood pressure (Table 2).

Among those who were on antihypertensive therapy, 39.5% were on monotherapy, 44.7% on 2 antihypertensive drugs, and 16% on a combination of 3 or more drugs (Table 3). The mean number of antihypertensive medications among those who were on antihypertensive therapy was 1.7±0.7. Blood pressure control rate was similar in patients on monotherapy and patients receiving multidrug regimens (42.7% vs. 42.8% respectively).

Renin angiotensin system (RAS) blockers were the most frequently prescribed antihypertensive agents both in patients on mono- and polytherapy (Table 3), angiotensin receptor blockers (ARB) being more commonly preferred than angiotensin converting enzyme inhibitors (ACEI) in the overall patient population. Patients on monotherapy were most frequently receiving RAS blockers (67.3%) followed by beta blockers (BB) and calcium channel blockers (CCB) (14.9% and 12.8% respectively). Diuretics were commonly prescribed in patients receiving combination

Table 3. Prescribing patterns in hypertensive diabetic patients along with data related to rate of BP control

Antihypertensive drug	Overall		Monotherapy		2 Drugs		3 Drugs		≥4 Drugs	
	n	%	n	%	n	%	n	%	n	%
ACEI	175	36.9	74	39.5	78	36.8	20	29.8	3	37.5
ARB	218	46	52	27.8	116	54.7	45	67.1	5	62.5
Beta blockers	136	28.7	28	14.9	47	22.1	54	80.6	7	87.5
CCB	106	22.3	24	12.8	52	24.5	23	34.3	7	87.5
Diuretics	196	41.3	5	2.6	129	60.8	54	80.6	8	100
Alfa blocker	13	2.7	4	2.1	2	0.9	5	7.4	2	25
Rate of BP control (%)	41.6		42.7		38.7		52.3		75	
Total	474		187		212		67		8	

BP: Blood pressure; ACEI: Angiotensin converting enzyme inhibitors; ARB: Angiotensin receptor blockers; CCB: Calcium channel blockers.

therapy, and were included in 60.8% of 2 drug regimens and 82.6% of the 3 or more drug combinations. A combination of RAS blockers with diuretics was the most common combination therapy. The presence of micro- or macrovascular complications did not have an effect on the likelihood of prescription of specific antihypertensive agents, except for BB, which were more likely to be prescribed in patients with coronary artery disease (Odds ratio=3.6, 95% confidence interval=2.3-5.6; p<0.001).

DISCUSSION

This study found that 71% of Turkish patients with type 2 diabetes have HT, and less than half reached their target blood pressure values. The high prevalence of HT among diabetic patients has been reported previously in population-based studies, which is in line with our findings.[1-4,9] There is clear evidence that reduction of blood pressure in patients with diabetes and HT results in reduction of cardiovascular and renal complications.[12] Small reductions in blood pressure (6/4.6 mmHg) in patients with diabetes have been associated with a 27% reduction in total mortality and a 25% reduction in total cardiovascular events.[13] Previous guidelines on management of HT recommended aggressive blood pressure lowering in diabetic patients to a target of below 130/80 mmHg.[5,14,15] Studies evaluating the accomplishment of these recommendations for diabetic patients reported low rates of aggressive blood pressure control ranging from 2.66%-56%.[9,11,16-19] The most favourable finding was reported by Gee et al., where the rate of HT control (56%) in Canadians with diabetes was almost twofold that of the rates reported in other studies.[11] This relatively high rate of blood pressure control in Canadian diabetic patients was attributed to the Canadian Hypertension Education Program.

Recent clinical outcomes trials have demonstrated that aggressive blood pressure control in subjects with type 2 diabetes does not provide any additional benefits with respect to cardiovascular outcomes compared to less aggressive blood pressure control.[12,20-22] The most recent European guidelines on management of HT recommend lowering blood pressure to a less aggressive target of <140/85 mmHg in patients with type 2 diabetes.[8] In this study we evaluated the control of blood pressure in type 2 diabetic patients in accordance with these guidelines. Although 95% of the patients received antihypertensive therapy, only 41.6% of the patients reached their target blood pressure levels. In 2004, Abaci et al.[23] investigated the rate of blood pressure control in hypertensive patients attending primary care units in Turkey. The subgroup analysis from this study showed that aggressive blood pressure control (<130/80 mmHg) was achieved in only 7.6% of diabetic patients. If the target blood pressure level was defined as <140/90 mmHg, the rate of blood pressure control was found to be 27.3%. Accordingly, our findings suggest that the rate of blood pressure control in diabetic patients seems to have increased. However, the difference in the rates of blood pressure control between the two studies might be related to the difference in the patient populations. The present study investigated diabetic patients attending

a tertiary centre, while the study by Abaci et al. was conducted in a primary care setting.

Patients in this study cohort were receiving an average of 1.7±0.7 antihypertensive medications. Most of them were on 1 or 2 antihypertensive drugs, while only 16% received 3 or more drug combinations. Several clinical trials have demonstrated that most patients with diabetes require 3-4 antihypertensive medications to achieve target blood pressure levels.[24,25] Therefore, lack of blood pressure control in more than half the patients in this study appears to be related to underutilization of antihypertensive drugs. Furthermore, half the patients were obese, and only 18% reported doing regular physical activity, demonstrating that modification of unfavourable life style factors were also inadequate.

In the present study, none of the demographic or clinical characteristics were found to be a predictor for blood pressure control. Previous studies reported different results with respect to predictors for blood pressure control in diabetic hypertensive patients. An Italian study in 2007 demonstrated that at multivariate analysis, the only predictor for blood pressure control was the use of ≥3 antihypertensive drugs.[16] Raum et al.[9] reported that older age was associated with poor blood pressure control, while gender, smoking status, BMI, physical activity, coronary artery disease or dyslipidemia were not associated with blood pressure control. Duggirala et al.[26] found that older age, isolated systolic HT, use of oral hypoglycemic agents and use of ≥3 antihypertensive drugs were predictors of poor blood pressure control, while the use of nitrates, history of CAD and at least 1 annual visit to a sub-specialist physician were predictors of better blood pressure control.

Under-treatment of HT in diabetic patients might be related to several factors. Most diabetic patients are old and present with multiple chronic diseases which require multiple treatments. Accordingly, management of diabetic patients is usually complex and challenging. Physicians caring for too many patients usually have insufficient time to refine and intensify treatment options in such complex patients. Therefore, the complex nature of the diabetic patients might be related to suboptimal management of cardiovascular risk factors. Besides, physicians' non-adherence with the current guidelines as well as patients' non-adherence to the prescribed pharmacological therapies might also be related to under-treatment of HT in patients with diabetes.

Randomized controlled trials have demonstrated that RAS blockade is more effective than other antihypertensive agents in reducing albuminuria in diabetic nephropathy.[27,28] RAS blockade is also effective in preventing incident microalbuminuria.[29] Guidelines on management of HT recommend RAS blockers to control HT in diabetic patients, whereas a combination of two different RAS blockers is not recommended.[5,8] Prescription patterns for antihypertensive agents in this study population were concordant with the guidelines. Renin angiotensin system blockers were the most commonly preferred drugs in patients on monotherapy (ACEIs 39.5% and ARBs 27.8%), and were included in most of the multidrug regimens (92.3%). On the other hand, a combination of an ACEI with an ARB was observed in only 2 (0.4%) patients. Beta blockers were preferred for the control of blood pressure, especially in patients with coronary artery disease. These data suggest that the benefits of RAS blockers in the management of diabetic patients with HT, and the benefits of BB in the management of diabetic patients with coronary artery disease are well-translated into clinical practice.

Limitations

This study is a single centre, cross-sectional, observational study, the findings of which cannot be considered as fully representative of all Turkish diabetic hypertensive patients. Additionally, in this study, office blood pressure measurements were evaluated, and therefore white coat HT might have occurred in some patients and uncontrolled HT might be overestimated.

This cross sectional study has provided important real-life insights into the current management of HT in diabetic patients, and demonstrated that more than half of diabetic patients with HT were under-treated. Additionally, physical inactivity and obesity were highly prevalent in this high-risk population. Interventions to increase physician and patient awareness of the high cardiovascular risk of diabetic hypertensive patients, and efforts to refine antihypertensive therapy together with modification of unfavourable life style factors should be implemented.

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Key words: Antihypertensive agents; diabetes mellitus; hypertension/complications/drug therapy.

Anahtar sözcükler: Antihipertansif ilaçlar; diabetes mellitus; hipertansiyon/komplikasyonlar/ilaç tedavisi.