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Original research

Characteristics of patients with hypertension in a population with type 2 diabetes mellitus. Results from the **T**urkish Nationwide Surv**E**y of Glycemic and Other **M**etabolic Parameters of Patients with **D**iabetes Mellitus (**TEMD** Hypertension Study)

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ABSTRACT

Background: The present survey aimed to find out the demographical and clinical characteristics of patients with hypertension in a population with type 2 diabetes mellitus (T2DM) in Turkey.
Methods: Patients with T2DM who were followed-up in tertiary endocrine units for at least last one year were recruited. Demographic, clinical and biochemical data of the patients were collected. Hypertension was defined as taking anti-hypertensive medications or having office arterial blood pressure (ABP) ≥140/90 mmHg or home ABP ≥ 130/80 mmHg.
Results: A total of 4756 (58.9% women) diabetic patients were evaluated. The percentage of patients with hypertension was 67.5% (n = 3212). Although 87.4% (n = 2808) of hypertensive patients were under treatment, blood pressure was on target in 52.7% (n = 1479) of patients. Hypertension proportions were higher in woman (p = 0.001), older, more obese, and those who had longer diabetes duration, lower education levels, higher frequency of hypoglycemic events (all p < 0.001) and higher triglyceride levels (p = 0.003). LDL cholesterol level and the percentage of smokers were lower in hypertensive group than in non-hypertensive group (both p < 0.001). The percentage of macro and microvascular complications was higher in the hypertensive group than in the normotensive one (both p < 0.001). In multivariate logistic regression analysis, being a woman (OR: 1.26, 95% CI: 1.04–1.51, p = 0.016), smoking (OR: 1.38, 95% CI: 1.05–1.80, p = 0.020), regular physical activity (OR: 1.24, 95% CI: 1.01–1.53, p = 0.039) and the presence of macrovascular complications (OR: 1.38 95% CI: 1.15–1.65, p = 0.001) were the significant predictors of good ABP regulation. The ratios of masked and white coat hypertension were 41.2% and 5.7%, respectively.
Conclusion: Our findings indicate that two-thirds (67.5%) of adult patients with T2DM have hypertension. Co-existence of hypertension increases the frequency of macro and microvascular diabetic complications in these patients. Despite the critical role of hypertension in morbidity and mortality, only half of the patients have favorable ABP levels. Masked hypertension seems to be another important issue in this population.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is a common and a serious public health problem with chronic complications and a leading cause of cardiovascular disease [1]. T2DM and hypertension are interrelated diseases and diabetic complications are significantly increased with the coexistence of hypertension [2,3]. Not only hypertension prevalence is increased among patients with diabetes, but also hypertensive patients are more prone to develop T2DM [4–6].

Many studies reported increased hypertension rates among patients with T2DM [4–7]. It is estimated that hypertension is about two-fold increased in individuals with T2DM compared to those without hypertension [8]. T2DM and hypertension share common risk factors, such as obesity, increased visceral adiposity and insulin resistance. Although several findings help to understand this coexistence, the whole pathogenic mechanisms are not well understood [9].

The current study was designed to evaluate the prevalence of hypertension, and the achievement rates of treatment goals of arterial blood pressure (ABP) among Turkish adult patients with T2DM. The socio-demographic and biochemical predictors that affect the control of hypertension were also investigated. This study is the first multi-centered nation-wide study that enrolled patients from 37 cities in Turkey to evaluate the prevalence of hypertension, and assess the characteristics of hypertensive compared to normotensive T2DM patients. The results of our study with these features also contribute to global evaluation.

2. Methods

2.1. Study design

This cross-sectional, nationwide, multicenter study was carried out between 01 April and 30 June 2017 in 68 tertiary endocrine units of university hospitals from 37 cities throughout Turkey. Patients were allocated according to the 12 NUTS (Nomenclature of Territorial Units for Statistics) regions of the country, and maximum 100 patients per unit were enrolled. The local and central ethics committees approved the study protocol defined as in our previous study [10]. All patients signed informed consents prior to data collection. This study was registered at ClinicalTrials.gov (NCT03455101).

2.2. Study population

Patients older than 18 years with T2DM and followed up in the same center for at least a year were enrolled in the study. They were selected consecutively in each outpatient clinic according to the order of admission. Patients with pregnancy, decompensate liver disease, psychiatric disorders interfering with cognition or compliance, bariatric surgery or renal replacement therapy were excluded.

2.3. Data collection

A specifically designed data collection form was applied to all patients by their physicians. The data form included social and demographic features (age, marital status, education, occupation and monthly income), concomitant diseases, diabetic macro and microvascular complications, family history (T2DM, obesity, hypertension, dyslipidemia and cardiovascular death at an early age), individual lifestyle and diabetes management (smoking, diet, exercise, self-monitoring of blood glucose (SMBG) and frequency of hypoglycemia) and all medications. Current and previous laboratory data were also collected. Presence of macro and microvascular complications were confirmed with hospital records.

2.4. Anthropometric and blood pressure measurements

Height, weight and waist circumference (WC) were recorded in patients with underwear. Body mass index (BMI) was calculated from measured weight and square of height (kg/m^2). WC was measured from the horizontal line between the lower ribs and the upper iliac crests after the patients exhaled. Office ABP was obtained by using the same model automatic blood pressure monitors (Omron M2, HEM-7121-E) in the sitting position after at least 5 min rest. For study participants, office BP was measured three times consecutively on the same arm at 2 visits before and after home measurements, and the mean of the measurements was recorded. Specific home ABP forms were given to patients who were educated about how to measure blood pressure and fill in the form. Patients measured ABP with automated blood pressure monitors at home twice a day for a week (total 14 records). The mean of measurements were recorded during their control visits and used for analysis.

2.5. Laboratory data

For biochemical analyses, all blood samples were collected from the antecubital vein in the morning of after overnight fasting. Laboratory measurements were made with automated analyzers in the hospitals where the patients were followed. The levels of fasting blood glucose, triglycerides (TG), total and HDL-cholesterol (HDL-C) were measured enzymatically. LDL cholesterol (LDL-C) was calculated using Friedewald's equation (LDL-C = Total cholesterol − [HDL-C + TG/5]) if TG was less than 400 mg/dl. Glycohemoglobin (HbA1c) was measured with the one of the methods certified by the National Glycohemoglobin Standardization Program (NGSP) including high-performance liquidchromatography (HPLC), turbidimetric inhibition immunoassay or enzymatic methods.

2.6. Definitions

Hypertension was defined as taking anti-hypertensive medications or having at least twice office ABP $\geq$ 140/90 mmHg or home ABP $\geq$ 130/80 mmHg. Normotensive patients taking anti-hypertensive medications for proteinuria or any other purpose were not included. White coat hypertension (WCH) was defined as office ABP $\geq$ 140/90 mmHg with home ABP < 130/80 mmHg and masked hypertension (MH) as office ABP < 140/90 mmHg with home ABP $\geq$ 130/80 mmHg. Sustained hypertension was defined as office ABP $\geq$ 140/90 mmHg with home ABP $\geq$ 130/80 mmHg. Controlled hypertension was defined as office ABP < 140/90 mmHg and home ABP < 130/80 mmHg [11]. Hypoglycemia was defined by the presence of classic symptoms and a capillary glucose level of 70 mg/dl or less at that time.

2.7. Statistical analyses

Statistical analyses were performed in SPSS 18.0 (SPSS Inc., Chicago, IL, USA). Data were expressed as mean ± SD for continuous variables or as percentage for categorical variables. Independent sample t-test was used for comparisons among continuous variables, and Chi-square test for categorical variables. Binominal logistic regression was performed to ascertain the association between different variables and the presence of hypertension or the control of hypertension. The p value was two tailed with a significance level of 0.05.

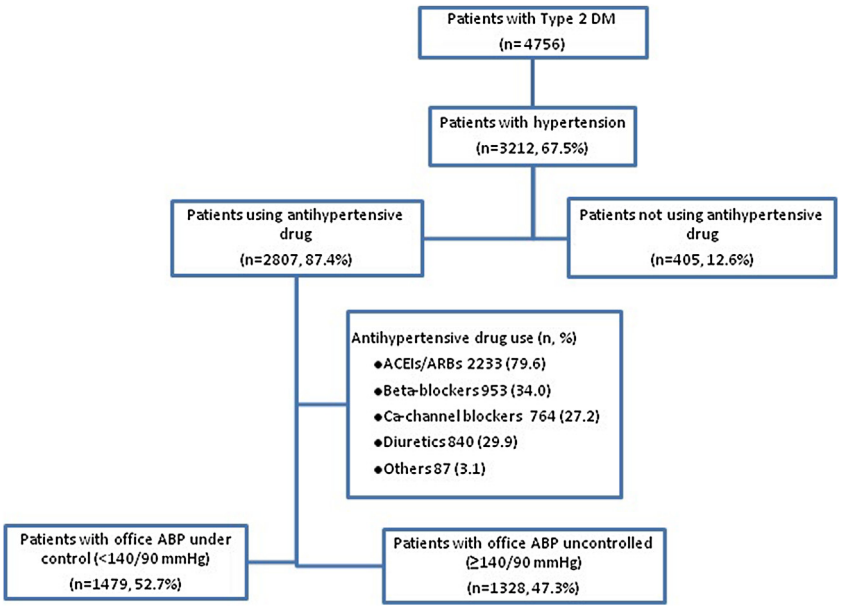

Fig. 1. The CONSORT diagram for the frequency of hypertension and hypertension under control, and the distribution of antihypertensive medications. Abbreviations: ABP, arterial blood pressure; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin ii receptor blockers.

3. Results

A total of 4756 (58.9% women) patients were registered. The ratio of the patients with hypertension was 67.5% (n = 3212). Although 87.4% (n = 2808) of the hypertensive patients were under treatment, blood pressures were on target only in 52.7% (n = 1479) (Fig. 1).

The rate of hypertension was 69.4% in women and 64.7% in men (p = 0.001). Patients with hypertension were older than those without hypertension (60.6 ± 9.8 vs. 54.0 ± 10.4 year, p < 0.001), and were predominantly woman especially after 40 years old (Fig. 2). The rate of overweight or obesity was significantly higher in the hypertensive group compared to the normotensive group (91.7% vs. 84.8%, p < 0.001). Furthermore, the rate of increased WC was higher in patients with hypertension than those of without hypertension (74.3% vs. 68.3%, p < 0.001). Compared to those without hypertension, patients with hypertension had longer diabetes duration, lower education levels, higher frequency of hypoglycemic events and higher TG levels. The mean LDL-C level and the percentage of patients with LDL-C level equal or higher than 70 mg/dL were significantly higher in the normotensive group compared to the hypertensive group. On the other hand, the use of antihyperlipidemic agents was significantly higher in hypertensive patients than in normotensive ones. Additionally, the frequency of smokers was lower in the hypertensive group compared to the normotensive group (Table 1). Furthermore, coronary artery disease, peripheral artery disease, cerebrovascular disease, retinopathy, nephropathy and neuropathy were more frequent in patients with hypertension compared to those of without hypertension (Table 2).

According to the multivariate logistic regression analysis, being a woman (OR: 1.26, 95% CI: 1.04–1.51, p = 0.016), current smoking (OR: 1.38, 95% CI: 1.05–1.80, p = 0.020), performing regular physical activity (OR: 1.24, 95% CI: 1.01–1.53, p = 0.039) and the presence of any macrovascular complication (OR: 1.38, 95% CI: 1.15–1.65, p = 0.001) were the significant predictors of better BP control (Fig. 3). The number of antihypertensive medications in patients with and without macrovascular disease was compared. Accordingly, using more than one antihypertensive drug was higher in patients with macrovascular disease compared to those of without macrovascular disease (61.9% vs. 46.6, p < 0.001).

Of the 3212 hypertensive patients with T2DM, 41.2% had MH and 5.7% WCH. According to the office blood pressure measurements, the vast majority of patients with normotension (86.5%) had MH, and 10.9% of those with hypertension had WCH (Table 3).

4. Discussion

The TEMD Hypertension Study demonstrated that two-thirds (67.5%) of adult patients with T2DM followed in the tertiary center have hypertension in Turkey. Although the vast majority of patients (87.4%) used antihypertensive drugs, BP were on target in less than half of all hypertensive patients (46.0%). Also, the data showed that about 40% of patients with hypertension had MH and 6% had WCH. This is the first nationwide report showing the frequency of hypertension in patients with T2DM in Turkey. In accordance with our results, the prevalence of hypertension among patients with type 2 diabetes has reported to be 50–87 % [7,12–16]. There is hardly enough data about the prevalence of HT in patients with T2DM in Turkey. In a single center study of 707 patients with T2DM, the prevalence of hypertension was reported as 70% [17]. A previous study conducted by our study group found that 58.0% prevalence of hypertension among the 4039 adults from 7 different regions of Turkey [18]. In a study of Sengul et al., the prevalence of hypertension in the adult Turkish population was %30.3, pharmacological treatment rate 47.4%, and the rate of hypertension control was 28.7% [19]. Compared to Sengul et al., the higher rate of hypertension control of in our study may be due to the patients followed up in the tertiary endocrine units for at least a year.

It has been reported that the prevalence of hypertension was higher among men than women until the age of 45, nearly equal between two genders from 45 to 64 years of age, and after that became more prevalent among women [20]. Sengul et al. showed that the prevalence of hypertension was significantly higher among women compared with men in middle age Turkish adults [19]. In our Turkish T2DM population, hypertension was more common in men before the age of 40 years, thereafter became more prevalent in women.

Obesity often accompanies hypertension, either as a causative or a coexisting factor. Furthermore, obesity and particularly visceral adiposity have been reported to have a key role in development

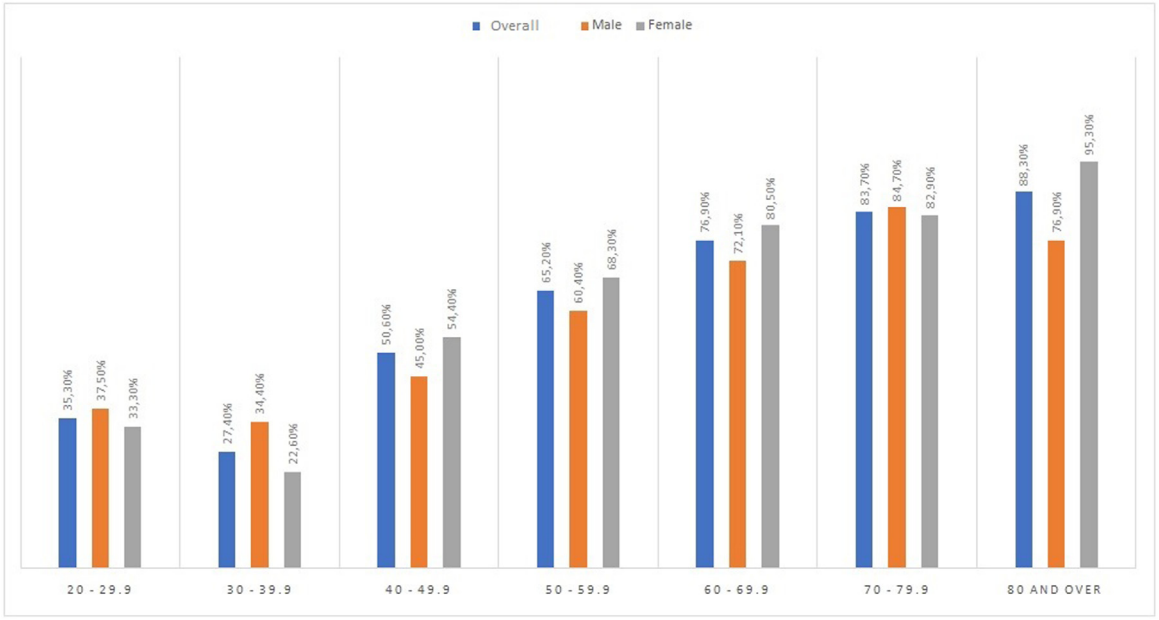

Fig. 2. The prevalence of hypertension according to the age categories and gender.

Table 1
Comparison of demographic, clinical and laboratory findings in patients with T2DM with and without hypertension.

Variable	Hypertensive group (n = 3212)	Non-hypertensive group (n = 1544)	p
Gender(female) (n,%)	1944 (60.5)	855 (55.4)	0.001
Age (years)	60.6 ± 9.8	54.0 ± 10.4	<0.001
WC (n(%))			
<90 cm for women; <100 cm for men	682 (22.9%)	399 (28.9%)	<0.001
≥90 cm for women; ≥100 cm for men	2297 (77.1%)	984 (71.1%)	
Smoking (n(%))			
Never smoking	2050 (64.0%)	930 (60.7%)	<0.001
Quit smoking	802 (25.1%)	348 (22.7%)	
Current smoking	349 (10.9%)	253 (16.5%)	
Education level (n(%))			
None	389 (12.3%)	129 (8.5%)	<0.001
Elementary	1617 (51.0%)	748 (49.3%)	
High school	603 (19.0%)	344 (22.7%)	
University	560 (17.7%)	296 (19.5%)	
Monthly income (n(%))			
<1500 ₺	750 (29.3%)	331 (27.8%)	0.482
1501–2000 ₺	535 (20.9%)	252 (21.2%)	
2001–5000 ₺	1061 (41.5%)	497 (41.8%)	
>5000 ₺	211 (8.3%)	110 (9.2%)	
Physical activity (n(%))			
None	1556 (48.9%)	689 (45.3%)	0.069
<60 min per week	949 (29.8%)	483 (31.7%)	
61–150 min per week	325 (10.2%)	154 (10.1%)	
>150 min per week	351 (11.0%)	196 (12.9%)	
Diabetesduration (year)	11.9 ± 7.7	8.57 ± 6.6	<0.001
Hypoglycemic event (n,%)	1425 (45.0)	583 (38.8)	<0.001
BMI (kg/m^2)	32.7 ± 6.6	30.9 ± 6.3	<0.001
SBP office (mmHg)	137.1 ± 19.2)	122.9 ± 11.3	<0.001
DBP office (mmHg)	82.2 ± 11.5	77.0 ± 8.0	<0.001
SBP home (mmHg)	128.5 ± 13.9	119.5 ± 10.8	<0.001
DBP home (mmHg)	78.6 ± 9.0	75.4 ± 7.8	<0.001
HbA1c (%)	7.7 ± 1.7	7.6 ± 1.8	0.520
LDL-C (mg/dl)	112.0 ± 35.8	117.8 ± 36.7	<0.001
LDL-C (n(%))			
<70 mg/dl	323 (10.1%)	106 (7.4%)	<0.001
≥ 70 mg/dl	2889 (89.9%)	1438 (92.6%)	
TG (mg/dl)	186.1 ± 134.6	174.0 ± 117.3	0.003
HDL-C (mg/dl)	46.4 ± 12.9	46.7 ± 12.9	0.482

Abbreviations: ₺, Turkish lira; BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TG, triglyceride; WC, waist circumference.

Table 2
Comparison of macro and micro-vascular complications in patients with T2DM with and without hypertension.

Variable	Hypertensive group (n = 3212)	Non-hypertensive group (n = 1544)	p
Coronary artery disease	871 (29.5%)	131 (9.2%)	<0.001
Peripheral artery disease	147 (5.0%)	39 (2.7%)	0.001
Cerebrovascular disease	118 (3.8%)	23 (1.6%)	<0.001
Retinopathy	730 (24.9)	190 (13.8)	<0.001
Nephropathy	737 (24.8)	127 (8.9)	<0.001
Neuropathy	1196 (37.6)	428 (28.2)	<0.001

Abbreviations: T2DM, type 2 diabetes mellitus.

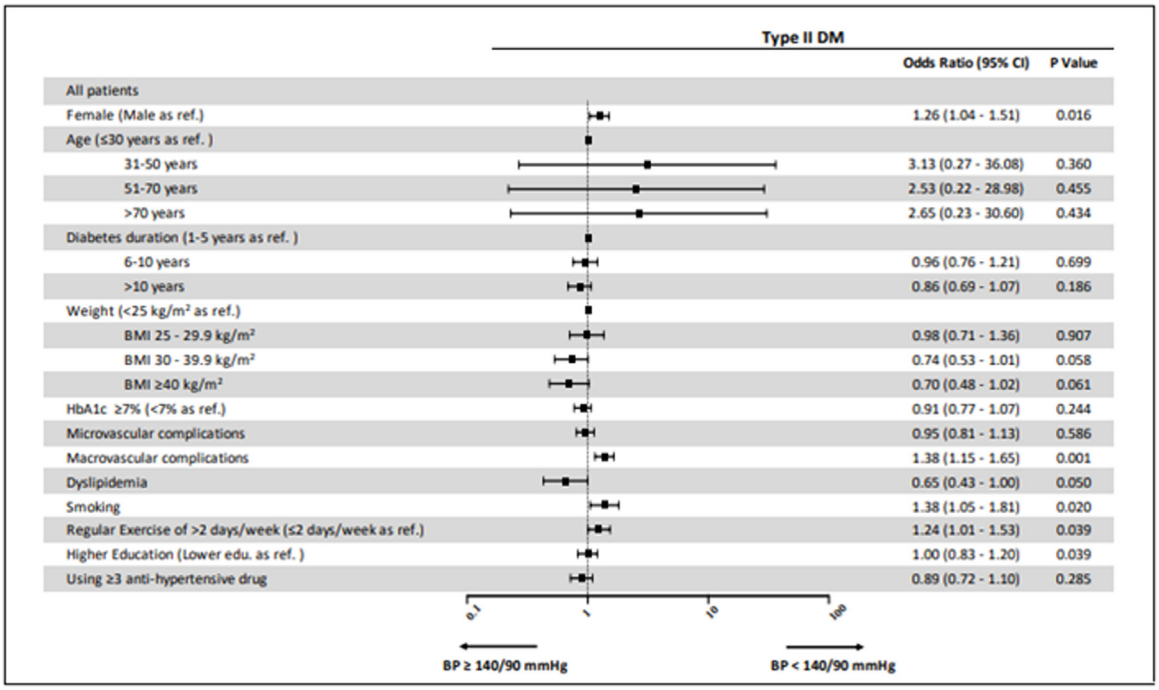

Fig. 3. Factors associated with good blood pressure control in the logistic regression model. Abbreviations: BMI, body mass index.

Table 3
The rates of masked and white-coat hypertension in hypertensive patients with T2DM.

	OfficeABP < 140/90 mmHg	Office ABP ≥ 140/90 mmHg
Home ABP < 130/80 mmHg	ABP at target	White-coat hypertension
Home ABP ≥ 130/80 mmHg	Masked hypertension	Uncontrolled ABP

Abbreviations: ABP, arterial blood pressure; T2DM, type 2 diabetes mellitus.

ofhypertension in patients with diabetes [9,21]. Chronic low-grade inflammation and oxidative stress in visceral adipose tissue lead to renin angiotensin aldosterone system (RAAS) activation and stimulation of aldosterone production [22,23]. Visceral obesity induced oxidative stress augments insulin résistance, which leads to vascular stiffness, hypertrophy, fibrosis and abnormal remodeling [24]. Moreover, hyperinsulinemia enhances sodium reabsorption in the renal tubules, resulting in high blood pressure [25]. In a study, Al-Nimer et al. showed that diabetic patients complicated with hypertension had higher BMI than those of without hypertension [26]. Our study confirmed that obesity and increased WC were more common in T2DM patients with hypertension.

It has been found that prevalence of hypertension increased as the educational status decreased in several studies [27–29]. In a meta-analysis, Leng et al. showed that subjects with lowest education level had two-fold increased risk of hypertension compared to those with highest education [30]. The present study also found that the percentage of patients with low education level was higher in the hypertensive group. Low education level may affect patient's knowledge of hypertension and health behaviors such as diet, exercise, stress management and health care visits [31–35].

In the present study, patients with hypertension had longer diabetes duration, higher frequency of hypoglycemic events and higher TG levels. It has been shown that duration of diabetes was independently associated with macrovascular complications [36,37]. Hypoglycemia leads to activation of sympatho-adrenal system resulting in blood pressure elevation, which may be related with increased cardiovascular risk [38,39]. Saraç et al. found that elderly diabetic patients had more often complicated with dyslipidemia and also had higher systolic and diastolic BP compared to middle-aged diabetic patients [40]. Laaksonen et al. found that elevated LDL-C and TG levels were associated with increased hypertension risk [41]. Moreover, Fu et al. demonstrated that elevated TG levels can increase risk of T2DM complicated with hypertension [42]. Interestingly, percentage of patients with elevated LDL-C and smokers were lower in our hypertensive group. The higher rate of statin use in the hypertensive group may explain the low LDL-C in this group. While blood pressure increases with the acute effect of

smoking, there is controversial data on the relationship between chronic smoking and hypertension [43–48]. Although our finding that smoking did not have a negative effect on hypertension and that smoking was a good predictor for ABP, there is controversial data on the relationship between chronic smoking and hypertension. Most of the trials that failed to find a positive effect of smoking on hypertension relied on current smoking status to evaluate the effects of smoking on health, while others used the data for smoking in a specific period of time [45,44–48]. Some authors explained that this may be attributed to the fact that smokers are relatively less body weight than non-smokers [49]. However, this can lead to biased and misleading evaluation of the effects of smoking on health. It is well known that smoking generally has a long-term, cumulative negative effect on health, so current smoking may not damage health on a short time. It has been shown that life-course smoking is associated with higher risks of hypertension [50]. Our study evaluated the current smoking status that not reflecting life-course-adjusted cigarettes smoking. In our study, macro and microvascular diseases were more common in hypertensive T2DM population. Many studies have shown that the risk of macrovascular events including cardiovascular, cerebrovascular and peripheral arterial diseases dramatically increased in the coexistence of hypertension and diabetes [51–54]. Moreover, several researchers demonstrated that macrovascular diseases can be prevented via controlling the blood pressure in patients with diabetes [53,55–58]. The additive effect of increased blood pressure on the beginning and progression of microvascular complications of diabetes has been determined previously [55,59–65].

The present study revealed that being a woman, smoking, making regular exercise and having macrovascular complications were associated with good blood pressure control. Although the pathophysiological mechanisms have not been fully elucidated, it has been found that premenopausal women had lower blood pressure compared to men. Inhibitor effects of estrogen on sympathetic nervous system, RAAS, endothelin and oxidative stress have been suggested to lead the blood pressure control in a positive way [66]. Although exercise has been shown to lower BP in non-diabetic individuals, studies in T2DM have yielded inconsistent results [67–70]. Our patients with macrovascular disease were using multiple antihypertensive drugs, which may be the reason of good blood pressure control.

Only few studies with limited number of subjects have explored WCH and MH in T2DM. These studies reported various ratios of 6.8–42.2% for WCH and 18–33.1% for MH with different cut-off values of systolic and diastolic ABP [71–73]. Of these, two studies used 24 h and 30 min intervals ABPM for evaluation of MH and they reported ratio of 18.8% and 18% for MH [71,72]. The other study used self blood pressure measurement for home monitoring reported MH ratio of 33.1% [73]. The frequencies of WCH and MH were found to be 5.7% and 41.2%, respectively in our Turkish patients with T2DM.The different results may be due to the different diagnostic cut-off values (our study used lower cut-off values which was ≥130/80 mmHg for home measurement) and different blood pressure measurement techniques, and the fact that our patients had been followed up in a tertiary center for at least 1 year.

The limitations of the present study were as follows: I) the results may probably not reflect the hypertension prevalence of the overall population with T2DM since they were only followed in the tertiary center. II) Some anti-hyperglycemic agents, such as SGLT-2 inhibitors, may affect blood pressure. Since we did not take this matter into evaluation, the blood pressure might be affected in some patients. III) The study was in cross-sectional design. Therefore, inferring a causal relationship between predictive risk factors and good blood pressure control may be questionable. On the other hand, with large sample size increasing the power of the study, the TEMD survey is the first nationwide hypertension study in T2DM that provides valuable data about hypertension prevalence, blood pressure treatment and control rates and the characteristics of the patients with T2DM living in Turkey. Moreover, the patient population including 37 cities from all region of Turkey reflected the socio-demographic distribution in a homogeneous manner.

In conclusion, the TEMD study data show that the prevalence of hypertension in patients with T2DM is higher than the previously reported prevalence for the Turkish adult population. Micro and macro complications of diabetes are more common in people with hypertension. Despite the critical role of hypertension in morbidity and mortality, and lots of patients was taking antihypertensive treatment, only half of the patients were at the desired blood pressure levels, and masked hypertension was an important problem for these patients. Although the data of our study consisted of national values, the information obtained from this research may have important clinical value that can contribute to optimize HTN and T2DM management in order to prevent or at least reduce their devastating results.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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