BLOOD PRESSURE AND HYPERTENSION IN TYPE 1 DIABETES MELLITUS PATIENTS WITH LONG DURATION

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АРТЕРИАЛНО НАЛЯГАНЕ И ХИПЕРТОНИЯ ПРИ ПАЦИЕНТИ СЪС ЗАХАРЕН ДИАБЕТ ТИП 1 С ДЪЛГОСРОЧНА ДАВНОСТ

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Abstract. Type 1 diabetes mellitus (T1DM) has significantly better prognosis which has led to increased cardio-vascular diseases (CVD) prevalence. The detection of CVD risk factors and their treatment become tasks of paramount importance. Among them, high blood pressure (BP) is a target of primary purpose. Aim: to explore the blood pressure values, the prevalence of hypertension (HTN) and its management in patients with T1DM with long duration and without overt CVD, in comparison to matched controls. Participants and methods: totally, 124 patients with T1DM were matched to 59 controls by sex, age and approximate body mass index (BMI). All participants filled in questionnaires with information on demographics, physical activity, life style, concomitant diseases, treatments, presence of complications, etc. Blood samples were taken for laboratory and biomarkers investigation. Blood pressure was measured by investigators twice and the mean of the two measurements was used. HTN was accepted using standard definitions. BP values were compared using t-test. Multiple linear regression models with dependent variable BP measures and age, sex, BMI, presence of T1DM, glycated hemoglobin levels, creatinine levels as independent variables were created. ANOVA method was used to test the interaction of sex and presence of T1DM. Results: The mean age of the participants was 43.47 ± 10.1 years, 54% were males. The mean duration of T1DM was 25.31 ± 8.2 years and the mean HbA1c was 8.42 ± 1.8% for diabetic patients. The mean blood pressure measures in T1DM groups were higher than in controls, both in males and females. The difference reached significance for SBP and pulse pressure (PP). The presence of T1DM independently affected the BP values, after adjusting for major confounders. The mean adjusted differences between T1DM and controls were 8.37 mm Hg for SBP, 4.92 mm Hg for DBP, and 5.19 mm Hg for PP ($p < 0.001$). HTN was significantly more frequent in T1DM patients than in controls – 54% vs. 27%, $p = 0.0001$, mainly due to already known hypertension. BP control was insufficient – in only 36% and 13% of the treated hypertensive participants, respectively, for BP < 140/90 and < 130/80 mm Hg. The majority of the patients with HTN were treated with combination therapy, mostly single-pill fixed dosage but 30% of the hypertensive patients with diabetes did not take antihypertensive medications. Inhibitors of the renin-angiotensin system were the preferred class of medications. Conclusions: SBP and PP were significantly higher in middle-aged patients with T1DM with long duration than their control counterparts. The presence of HTN was significantly more common in T1DM. Although treated according to the current recommendations, the control of BP was far from effective. These results show the need for constant screening of patients with T1DM for HTN and other risk factors and for more aggressive antihypertensive treatment to prevent future CVD events.

Key words: type 1 diabetes mellitus, blood pressure, hypertension

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Резюме. Прогнозата при тип 1 захарен диабет (Т13Д) се е подобрила значимо през последните десетилетия, което води до по-висока честота на сърдечно-съдовите заболявания (ССЗ). Откриване на рисковите фактори за ССЗ става задача от първостепенно значение. Сред тях високото артериално налягане (АН) е една от най-важните цели. **Цел:** да се проучат стойностите на АН, наличието на артериална хипертония (АХ) и лечението ѝ при болни с Т13Д с дълга давност и без известни ССЗ в сравнение с подбрани контроли. **Материал и методи:** Общо 124 болни с Т13Д са сравнени с 59 контроли, подбрани по сходна възраст, пол и индекс на телесна маса (ИТМ). Всички участници са интервюирани за демографски характеристики, физическа активност, начин на живот, придружаващи заболявания, лечение, наличие на усложнения и др. Взети са кръвни проби за изследване на лабораторни показатели и биомаркери. АН е измерено двукратно и е взета средната стойност от двете стойности. АХ е дефинирана по стандартен начин. Стойностите на АН са сравнени с помощта на t-тест. Приложен е множествен линеен регресионен анализ, с независима променлива АН и с независими променливи възраст, пол, ИТМ, наличие на Т13Д, нива на гликиран хемоглобин и стойности на креатинин. Методът ANOVA е използван за изследване на интерактивна връзка между пол и наличие на Т13Д. **Резултати:** средната възраст на участниците е 43,47 ± 10,1 години, като 54% са мъже. Средната давност на Т13Д е 25,31 ± 8,2 год. и средните нива на HbA1c са 8,42 ± 1,8% за диабетиците. Средните стойности на АН в групата с Т13Д са били значимо по-високи, отколкото в контролната, еднакво и при двата пола. Разликата достига статистическа значимост за ситолното АН (САН) и за пулсовото налягане (ПН). Наличието на Т13Д независимо повлиява стойностите на АН, след корекция за основни замъгляващи фактори. Средната коригирана разлика в АН между лицата със и без Т13Д е била 8,37 mm Hg за САН, 4,92 mm Hg за ДАН и 5,19 mm Hg за ПН ($p < 0,001$). АХ е значимо по-честа при болните с Т13Д отколкото при контролите – 54% vs. 27%, $p = 0,0001$, основно за сметка на вече известна хипертония. Контролът на АН е бил незадоволителен – стойности на АН < 140/90 и < 130/80 mm Hg са били достигнати съответно само при 36% и 13% от лекуваните хипертоници. Мнозинството от участниците с АХ са на комбинирана терапия, главно фиксирана комбинация в една таблетка, но 30% от хипертониците с Т13Д не са били лекувани въобще за повишеното си АН. РАС-инхибиторите са били най-използваният клас медикаменти. **Изводи:** САН и ПН са значимо по-високи при болни с Т13Д на средна възраст и с дълга давност на заболяването. АХ е сигнификантно по-честа при наличие и на Т13Д. Въпреки че са лекувани според съвременните препоръки, постигнатият контрол на АН е далеч от оптималния. Резултатите показват необходимостта от постоянен скрининг на болните с Т13Д за АХ и други рискови фактори и за по-агресивно антихипертензивно лечение с цел намаляване на бъдещи ССЗ инциденти.

Ключови думи: тип 1 захарен диабет, артериално налягане, артериална хипертония.

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Introduction

Since the invention of insulin 100 years ago, patients with Type 1 Diabetes Mellitus (T1DM) are constantly improving their prognosis and life expectancy [1, 2]. At the same time, the incidence is constantly and steadily rising [3-5], especially in certain geographical regions and ethnical minorities [6-8]. The patients with T1DM still have higher mortality and morbidity than the general population [9-11]. As the life-expectancy in T1DM patients is rising, they become more prone to developing atherosclerotic cardiovascular diseases (ACVD) [12-16]. The search for CVD risk factors becomes of crucial importance, especially in patients with long duration of T1DM and at middle age. Previous studies have shown that the prevalence of such CVD risk factors is higher in patients with T1DM than their aged-matched healthy controls [17-22], like hypertension (HTN), dyslipidemia and others.

Hypertension is the most common health problem in humans over 18 years [23]. Its frequency is increasing with age, more evident in females [24-26]. HTN is the most important independent risk factor for CVD morbidity and mortality in the community worldwide [23, 27-29]. High blood pressure is also a major contributing factor for the development of diabetic nephropathy [30]. The occurrence of HTN was found to be about one in fifth patients with T1DM in earlier study [31], with younger population but more recent data showed that the prevalence of HTN is almost twice more and is about 43% [32]. The effective management of HTN in diabetic patients reduces the adverse cardiovascular events [33-38].

The aim of the present study is to evaluate the blood pressure, the presence of HTN, and its management in patients with long-lasting T1DM compared to controls without glycemic excess.

Material and methods

We invited the patients with T1DM who were included in the register of T1DM children in the Department of Pediatrics of the University Hospital “Sveta Marina” – Varna, Bulgaria, to participate in a survey

for the presence of CVD risk factors. The register is the only one in the region of Eastern Bulgaria. We have **included** only these patients at age > 18 years, with disease duration > 15 years, and without history of CVD. The other source were local endocrinology practices, both ambulatory and hospital. **Exclusion criteria** were: T2DM; duration of T1DM < 15 years; participation in clinical trials; major psychiatric problem which affects the ability to take informed consent by him/herself; significant disability and/or invalidation; more than 3% increase in body weight during the last 3 months; known present CVD (myocardial infarction or other vascular event); acute disease or other acute condition at inclusion (except diabetic ketoacidosis (DKA) or hypoglycemic event), with option to postpone the inclusion for later time; pregnancy; for patients with T1DM – severe hypoglycemic or DKA events in the past 3 months; documented severe microvascular diabetic complications; unwilling to sign informed consent. Overall, 124 patients with T1DM agreed to participate and signed informed consent. Then, we invited 59 participants who were matched to be at similar age ± 2 years, were of the same sex, and had similar body mass index (BMI) but did not have history of DM or CVD to become controls of the cases. Thus, the pre-specified ratio 2:1 between cases and controls was fulfilled.

All participants filled in questionnaires with demographic data, their socioeconomic status, the family history, everyday activities, diet, treatment, concomitant diseases, etc. The physical activity was measured by accelerometers. Fasting blood samples were taken for laboratory assessment.

For the purpose of this study, BP was measured twice by trained physicians (K.T., T.C) after at least a 5-minute rest and with 2-minute intervals between the two measurements. The BP was measured using a digital electronic device Omron M6 AC (OMRON Healthcare, Japan) with the appropriate cuff for each participant. The mean of the two separate measurements was used in the analysis. The pulse pressure (PP) was calculated as the difference between systolic BP (SBP) and diastolic BP (BP). The pulse was measured for 60 seconds in sitting position during the interval between the two BP assessments. Presence of HTN was defined as BP > 140/90 mm Hg, positive history of HTN, or antihypertensive treatment in the questionnaire. Each individual drug used was classified according to the pharmacological group it belonged to. Control of HTN was assessed using both the ESH [39] and AHA [40] guidelines criteria.

The study was approved by the Ethical Committee of Medical University, Varna, Bulgaria #75/07 June 2018. Every participant signed informed consent.

Statistical analysis

BP values are presented as mean ± standard deviation. The categorical data are presented as numbers and percent. Continuous variables are compared using independent samples t-test and Kolmogorov-Smirnov's test for non-normally distributed variables. For categorical data, chi-square test or Fisher's exact test in case of small cell numbers are used. The univariate ANOVA analysis is used to assess the interaction on BP between sex and disease presence. A linear regression analysis with SBP, PP and DBP as dependent variables, and age, sex, BMI, presence of T1DM, glycated haemoglobin levels, creatinine levels, as independent predictors, is applied. Stepwise approach for selection of the predictors is used, with $p < 0.05$ for entry in the model and < 0.1 to remove from the model.

Statistical significance is accepted at $p < 0.05$, unless otherwise stated.

Results

A total of 124 patients with T1DM, at a mean age 43.47 ± 10.1 years and 53% males, and 59 controls, at a mean age 42.68 ± 10.4 years and 56% males, were enrolled in the study. The mean duration of T1DM was 25.31 ± 8.2 years, 95% CI 23.85-26.78 years, and median 24 years. The average glycated haemoglobin in the diabetic group was 8.42 ± 1.8% (68.5 ± 8.8 mmol/mol), 95% CI 8.11-8.73% (65.1-71.9 mmol/mol).

Blood pressure in diabetic and control subjects

The BP values of T1DM and control participants are shown on Table 1.

The presence of T1DM independently affected the BP values, after adjusting for major confounders. The linear regression models for SBP, DBP and PP are presented on Table 2. The presence of T1DM significantly and independently increased the BP measures. The mean estimated by the models difference in SBP to controls was 8.37 mm Hg, in DBP – 4.92 mm Hg and in PP – 5.19 mm Hg.

Prevalence of hypertension

HTN was present in 84 (45.4%) of all patients. It was significantly more frequent in patients with T1DM than in controls – 67 (54%) vs. 17 (27.1%), $p = 0.001$ by χ^2 test, as well as in males than in females – 55(55.6%) vs. 28(33.3%), $p = 0.003$ χ^2 test. There was significant interaction between sex and T1DM (Fig. 1).

Previous history of HTN had 63 (34%) of all participants. It was twice more common among T1DM patients than in the controls – 51(41.1%) vs. 12 (20.3%), $p = 0.001$. High BP values for the first time were detected in 15 (25.4%) of the T1DM participants vs. 4 (25%)

Table 1. Blood pressure in patients with and without Type 1 Diabetes Mellitus by sex categories

	Type 1 DM			Controls			p*
	All	Males	Females	All	Males	Females	
SBP (mm Hg)**	128.17 ± 18.9	135.26 ± 18.4	120.09 ± 16.1	121.13 ± 15.3	127.23 ± 13.1	113.38 ± 14.5	0.005
DBP(mm Hg)**	80.28 ± 10.0	83.14 ± 9.5	77.03 ± 9.6	77.98 ± 10.7	80.42 ± 11.2	74.88 ± 9.3	0.123
PP (mm Hg)**	47.89 ± 13.5	52.13 ± 12.8	43.06 ± 12.6	43.14 ± 11.3	46.8 ± 9.2	38.5 ± 12.1	0.011

DM – diabetes mellitus; **SBP** – systolic blood pressure; **DBP** – diastolic blood pressure; **PP** – pulse pressure

*significance level for the difference between all cases vs all controls, univariate ANOVA analysis.

**P for interaction between sex and study group: 0.798 for SBP, 0.858 for DBP, 0.654 for PP.

Table 2. Linear regression models using stepwise approach for selection of predictors. Independent variables: sex, age, presence of T1DM, BMI, creatinine, glycated hemoglobin

Model	Beta coefficient	Standard error	p
SBP			
Constant	111.75	9.70	<0.0001
Sex male/female	-11.84	2.34	<0.0001
T1DM yes/no	-8.37	2.45	0.001
BMI	0.84	0.27	0.002
Age	0.29	0.12	0.013
Creatinine	0.10	0.05	0.023
DBP			
Constant	72.41	5.16	<0.0001
BMI	0.72	0.16	<0.0001
Sex male/female	-4.92	1.40	0.001
T1DM yes/no	-3.24	1.49	0.031
PP			
Constant	40.38	5.86	<0.0001
Sex male/female	-7.07	1.72	<0.0001
Age	0.36	0.08	<0.0001
Creatinine	0.10	0.03	0.004
T1DM yes/no	-5.19	1.80	0.004

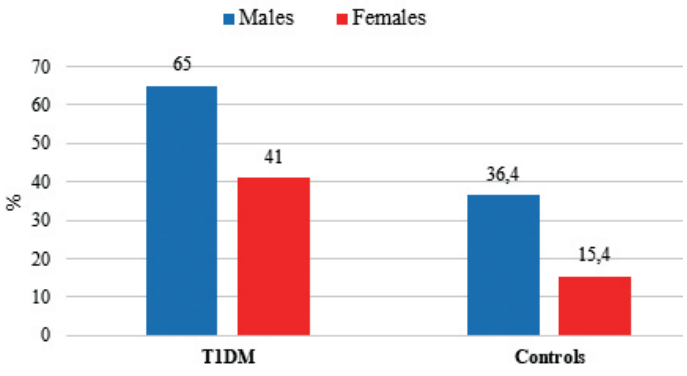

Fig. 1. Hypertension frequency by study group and by sex. Testing for gender differences: p = 0.008 for T1DM and p = 0.085 in controls

of the controls, p = NS. In the diabetic group, there was no difference in the newly detected BP levels between the patients with good or insufficient glycemic controls – 20% vs. 13% (p = 0.275), as well as between various modes of Insulin treatment (p = 0.243)

Hypertension was controlled in only 30 (36%) of all participants with HTN according to the ESH/ESC targets, with no difference between T1DM and control groups – 35.8% vs. 37.5%, p = 0.9. If the more stringent targets were used according to AHA/ACC guidelines, then only 13.25% had BP control, again without difference between the two groups.

There was no difference in BP control for patients with poor or excellent T1DM control according to their HbA1c levels – 20% vs. 19%, p = 0.85. The same was true for various treatment Insulin regimens (p = 0.57, Kendall's tau b test)

Treatment of hypertension

No therapy at all had 28% of all hypertensive participants and was more common in T1DM than in the control group – 30% vs. 19%, p = 0.485. Monotherapy was used overall in 32%, 30% vs. 37% in the subgroups, while combination therapy was used in 40% of

all hypertensive patients, more often in controls (43%) than in T1DM (39%). All comparisons were non-significant. The most common antihypertensive class of drugs used in HTN patients was ACE-inhibitors (37%), followed by beta-blockers (31%), ARBs (23%), diuretics (22%), calcium-channels blockers (19%), central acting drugs (10%). There was no significant difference between T1DM and controls. Single-pill fixed combinations were preferred in the majority of the patients using combinations – in 20 (61%) of those using more than one drug. The controls were more often on fixed single-pill treatment – 6 (86%), than the patients with T1DM – 14 (54%) but probably due to the small numbers this difference was not significant (p = 0.2, Fisher's exact test).

Discussion

In this study, significantly higher SBP and PP and a trend to higher DBP were found in patients with T1DM compared to controls, irrespective of their gender. The mean difference in BP between the two groups was 8.4/4.9 mm Hg. It is known that the higher the blood pressure, the higher is the risk of CVD which doubles with each 20/10 mm Hg rise of BP above 115/75 mm Hg [41]. There is a vast amount of data which shows that SBP and PP are more important prognostic factors of CVD morbidity and mortality than DBP [42-44]. This is especially true for diabetic patients with HTN [45]. One important explanation is the increased arterial stiffness in patients with T1DM, compared to healthy controls. It increases with age and duration of T1DM [46, 47]. The increased arterial stiffness could result from insulin resistance, collagen increase due to inadequate enzymatic glycation, and endothelial and autonomic dysfunction. It positively correlates with systolic blood pressure, obesity, glycated hemoglobin, waist circumference [48-50]. Due to the fact of arterial stiffness, there is an early vascular aging in patients with DM, in our study with approximately 15 years (not shown) [51,52].

The patients with T1DM had significantly higher HTN prevalence than in matched controls – every second compared to one in four. These results are consistent with the data from other studies. In the CACTI study [32] the prevalence of HTN was 43% in T1DM vs. 15% in the control group, although their cohort was younger (mean age 38 years) but the T1DM was similar – 23 years. The prevalence of HTN is reported to be lower in the EURODIAB IDDM Complications study where about one quarter of the patients in this cross-sectional study were hypertensive [31, 53]. But, again, the population of T1DM was younger (mean age of 32 years) and with much lower disease duration – 14 years. The Pittsburgh Epidemiology of Diabetes Complications Study prospectively followed patients with T1DM for 10 years. The HTN frequency was 29% [54]. In our study, 25% of the hypertensive patients were newly diagnosed. We didn't find relation of incident HTN with HbA1c levels (patients vs controls) or diabetic treatment. In the DCCT/EDIC study 44% of the participants met the criteria for incident HTN but over a follow-up period of more than 15 years [55]. The intensive diabetes treatment reduced the HTN occurrence by 24% (HR 0.76, 95% CI 0.64-0.92). In the Scottish national study, about 37% of all patients reported to have BP > 140/90 mm Hg [56]. In a retrospective study of children and adolescents with T1DM compared to healthy controls the prevalence was significantly higher in the T1DM group – 35.2 vs. 11.4%, p<0.001, after 20 years of follow-up [57]. In a cross-sectional study of T1DM in Brazil at the average age of 21 years and mean disease duration 9 years, the HTN prevalence was expectedly low – 19%. The hypertensive patients were older, with longer T1DM duration, higher BMI and serum lipids. The prevalence rate reached 31% in the older subgroup [58].

Patients with HTN were treated in 70% but control was achieved in only 36% of them according to the more conservative cut-off < 140/90 mm Hg and only less than 15% if more stringent criteria < 130/80 mm Hg were applied. Our results are similar to that from other studies in T1DM – treatment was applied in 75% in Pittsburgh, 87% in CACTI, 69% in EURODIAB [32, 53, 54]. However, in younger populations the treatment prevalence was lower – only 26% had HTN treatment and about 50% of T1DM with HTN remained with no antihypertensive medication for 2-5 years during the 20-year follow-up in the retrospective study [57]. In the Brazilian study, only 53.7% of HTN patients received medication [58]. That T1DM patients are undertreated for their high BP showed the Golden Years cohort where only 29% report taking antihypertensive drugs in this much older and with very long duration population [59].

The BP control frequency depends on the cut-off values and varies from guideline to guideline. In the European guideline which we follow the target BP is < 140/90 mm Hg in patients over 65 and < 130/80 mm Hg in younger population [39]. The same conservative approach was accepted by the American Diabetic Association [37]. However, in the current American Heart Association guideline on HTN management the lower target < 130/80 mm Hg was set up for all patients [38]. Some reported that the risk of the diseases is lowest if SBP < 120 mm Hg and DBP is < 80 mm Hg among patients with diabetes [60]. The BP control in our participants is similar to the Bulgarian general hypertensive population – about 37% [61] and to global trends in the HTN at target [62, 63]. In other T1DM studies, the control was much better than in our cohort. In CACTI

study the hypertensive T1DM patients were controlled in 55%, significantly more than the non-T1DM group – 32% ($p < 0.0001$), and reached 64% among the treated T1DM patients with HTN [32]. The control prevalence decreased in a similar way with the change of BP goals – from 64% to 48%, as our observations showed. In the Pittsburgh T1DM cohort, 49.5% of the treated hypertensives were under control [54]. In Europe, the control was poor in the early studies – only 11.3% in EURODIAB [31]. The result improved significantly in later research – from 32% to 41% after 7 years of follow-up [53]. In the younger T1DM population in Brazil, the HTN control was found in only 22.9%, although the awareness of HTN was relatively good (66%) [58].

Changing the treatment target of BP from < 140/90 to < 130/80 mm Hg in the present study significantly reduced the relative share of HTN control in patients with T1DM (from 36% to 13%). This was also noticed by others [64] which reported that the hypertensive population above treatment goal in US rose from 39% to 53% when the new recommendations were introduced. If the targets are set up lower, e.g. < 120/80 mm Hg, the relative share of uncontrolled hypertension will inevitably rise also in our population.

The combination therapy was the preferred mode of treatment of HTN by the participants in the study and the majority used single-pill medications. It is in agreement with the present recommendations and trends in HTN management [36-38, 65]. The fixed dose combinations have several advantages – better results, economic benefit, and, most important, compliance improvement to treatment algorhythms. The same trend of higher combination usage was noticed in the EURODIAB studies. In the earlier study, combination therapy was used only in 19% but in the later study it was applied in 33% [31, 53]. ACE-inhibitors are the preferred class and, together with ARBs, the inhibitors of renin-angiotensin II system accounted for 60% of all treatments. This fact is in agreement with previous studies in T1DM [32, 53, 58]. These drugs have been proven to have substantial renoprotective and cardiovascular protective effects in patients with diabetes mellitus, without deleterious metabolic side effects. Interesting finding from the current study is the relative high share of beta-blockers and central acting drugs which together comprise more than 40% of all medications although they are known to increase severe hypoglycaemia and cardiovascular adverse events [66]. There are several possible explanations of this finding. Another factor is the therapeutic inertia of their physicians who follow older recommendations and are used to consider beta-blockers and diuretics as their first choice of HTN treatment. The high prescription rate is still found in the general population of hypertensive patients [67] and in elderly people [68]. Another possible reason is choosing the beta-blocker because of the presence of initial autonomic neuropathy with higher heart rates at rest.

The strengths of the study include the fact that the participants are patients of one diabetes center for several decades, and that the control group is well matched for variables that affect the hypertension preponderance (e.g., age, gender, BMI). Another important positive feature of the studied group is the lack of known cardiovascular events so far, as well as the absence of severe microvascular diabetes complications.

Limitations

The present study has several limitations. The first is the small number of patients recruited in the study. We managed to include 124 patients with type 1 diabetes mellitus in this complex study which included various measurements, e.g. imaging, laboratory tests and physical activity by accelerometers. However, this number was pre-specified by calculations based on the capture diabetic population of the targeted region. The projected number may have been increased if other centers in the country were affiliated. But this was logistically impossible because of the heavy protocol of the study. Moreover, the study was powerful enough to prove the hypothesis of higher HTN prevalence in T1DM population with long duration than in their age- and sex-matched counterparts. The second limitation is the BP measurement method in the study. There are still discussions whether the electronic devices are more accurate. But the drawbacks of this method may only affect the precision of the results and not the validity of the conclusions, as the method was applied in patients and controls similarly. Vervoort et al. conducted a study comparing various methods of BP measurements in T1DM and controls [69]. They found that sphygmomanometers and ambulatory blood pressure showed similar results with intra-arterial measurements while oscillometric devices overestimated the BP in T1DM. Thus, the measuring method would hardly affect the findings of higher BP and HTN prevalence. Another negative effect may be the lack of blinding of the investigators for the T1DM status that may affect differentially the BP readings. This may result in exaggerating the potential BP difference between T1DM and control subjects but can't affect the difference in the prevalence of HTN. Thus, the lack of blinding impacts only the current BP measurements and not the previous ones.

Conclusions

BP was higher in middle-aged patients with T1DM with long duration than their control counterparts. HTN was significantly more common in T1DM and every one in four diabetic patient had high BP measured in the

study. Although treated according to the current recommendations, the control of BP was far from effective. These results show the need for constant screening of patients with T1DM for HTN and other risk factors, and for more aggressive and suitable for diabetes antihypertensive treatment to prevent future CVD events.

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Не е деклариран конфликт на интереси

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