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Management of macrovascular diabetic complications: a single-center case series analysis of consecutively attending patients in primary care

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ABSTRACT

Introduction. The prevalence of diabetes mellitus is increasing, with type 2 diabetes (T2DM) being a major health priority for any public health system. Increased arterial stiffness in patients with diabetes will lead to the appearance of vascular complications. Increased arterial stiffness in patients with diabetes usually leads to vascular complications. Any earlier diagnosis of impaired macrovascular evidence may lead to improved outcomes in patient care. The objective of our study was to assess and evaluate the finger-toe pulse wave velocity (ftPWV), as a measure of arterial stiffness, in order to assist with early detection of macrovascular diabetic complications. *Materials and Methods*. The observational case series included 140 patients who are registered in a primary care office, of whom 73 were previously diagnosed with diabetes mellitus (study group). The age-matched non-diabetic group included 67 consecutive registered patients who visited the practice for other reasons. *Results*. The mean age of all patients was 51.42±11.57 years, with DM patients being with 4.5 years older than the non-DM patients (CI 95% and CI 95%). There was a significantly higher mean value of ftPWV in the DM group (p = 0.0039) although the study presented some limitations. *Conclusions*. The mean value of ftPWV was statistically significant higher in diabetic patients. The assessment of ftPWV is a non-invasive test, and the data can be used as a useful marker of vascular stiffness in primary care, thus providing an early diagnosis of macrovascular complications during the monitoring and care of the diabetic patient.

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Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is constantly increasing and is a major priority of any public health system [1]. The latest estimates show that in 2017 the global prevalence of diabetes mellitus was of 451 million registered cases. Moreover, it is expected that in 2045 there will be more than 693 million diabetic patients [2]. These observations are determined by the growing prevalence of obesity and the modern lifestyle, which includes cardiovascular and metabolic risk behaviors (sedentarism), as well as the diet rich in carbohydrates and animal fats [3]. Health education programs are needed for patients with T2DM), to reduce the risk factors and prevent or delay the development of complications [4].

Type 2 diabetes mellitus is a chronic, non-communicable disease, associated with decreased quality of life and increased mortality, being considered one of the top 10 causes of disabilities worldwide [1,5]. Diabetes mellitus leads to macrovascular and microvascular complications, which in some cases involve an association between hyperglycemia, dyslipidemia, hypertension and possibly tobacco consumption, factors that determine or mediate the development of vascular changes [6,7]. One macrovascular complication, with multiple implications, is peripheral artery disease (PAD). The evolution of PAD in diabetic

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patients has been shown to be worse with a long history of diabetes, the uncontrolled glycemic level finally leading to the administration of insulin [8]. Arterial stiffness is an independent prognostic marker for morbidity and mortality in diabetic patients [9]. A longitudinal study conducted by Zheng et al. (2020) that enrolled over 14,000 participants, has shown, after adjusting for potential confounders, that the hazard ratio for the risk of diabetes was associated with increased arterial stiffness [10]. A prospective cohort study of Lou et al. (2020) suggested that brachial-ankle pulse wave velocity (PWV) 'might be a useful and independent predictor of new-onset type 2 diabetes', especially among younger individuals and for current smokers [11].

Hyperglycemia, inflammation and oxidative stress reduce vascular compliance and promote the development of aggressive atherosclerosis [12]. Especially during the asymptomatic period of this disease, the family physician has an important role in its prevention and in advising on how to avoid the development of the disease, or how to delay the onset of complications once the disease is diagnosed. This role includes identifying any of risk factors, by providing the patient with proven preventive advice and interventions and by regularly monitoring the diabetic patients. The preventive interventions coming from family physicians must begin in adolescence, by promoting low carbohydrate diets, with a beneficial effect on one or more components of the metabolic syndrome [13]. The family physician must also have a multifactorial approach of diabetes' management, due to the fact that the combined reduction of mediating factors such as high serum glucose, high systolic blood pressure and control of serum lipids decreases the risk of cardiovascular events [6,7].

Obesity is a major risk factor both for arterial hypertension and type 2 diabetes [3,14]. The assessment of abdominal fat tissue accumulation, either by measuring abdominal circumference or by calculating the waist/hip ratio, appears to be an independent predictor of the risk of high blood pressure [15,16]. Arterial stiffness, the consequence of diabetes mellitus, is an independent predictor of mortality [17]. The positive diagnosis of PAD can be determined through history, clinical examination, and by measuring the ankle-brachial index (ABI). The imaging techniques, such as Doppler ultrasound and angiography, are important for evaluating disease severity.

Materials and Methods

The fast and noninvasive method that can be used by the family physician is the measurement of finger-toe pulse wave velocity (ft-PWV), which reflects the degree of vascular stiffness, by using a pOpmétre® device [18,19]. This device has two sensors with photodiodes, which are put in contact with the index finger, respectively with the patient`s hallux for 20 seconds. The infrared beam emitter must be in contact with the pulp of the finger in order to capture the data. During this time, each pulse wave is recorded from the point of view of the required time to transition (TT) from the aorta to the arteries of the index`s pulp, respectively the hallux`s pulp. The device's software calculates the time differential, a result that will automatically be used in a mathematical formula, to render the value of the PWV, which represent the velocity, estimated by the device`s software, at which the pulse wave travels from the aorta to the periphery of the vascular system. This parameter is considered by various studies to be useful for the assessment of arterial stiffness [20,21]. The evaluation of distal PAD of the ankle using ABI is limited, and the ft-PWV measurement in primary care could bring additional data for an early diagnosis [8]. Moreover, the investigation is non-invasive, evaluates arterial stiffness faster than ABI calculation and allows the assessment of patients at cardiovascular risk by the family physicians. The device is easy to use by the family physician. One doctor and two nurses were trained to proceed with measurements and recording of the readings in a database. The cross-sectional study was conducted between May 2 – September 30, 2019 in one setting primary care office from Bucharest, Romania.

The objective of our study was to evaluate the ftPWV in patients with diabetes mellitus, to explore the association between ft-PWV value and arterial stiffness, for monitoring and prediction of PAD in patients with type 2 of diabetes mellitus. Assessing arterial stiffness by measuring ft-PWV is simple, fast, and easily accepted by patients [21,22]. We aimed to perform a quick assessment of the cardiovascular risk factors in patients with and without diabetes mellitus, using only available tools to the family physicians.

A group of 73 consecutive patients previously diagnosed with type 2 diabetes mellitus, undergoing treatment and being in the records of the office, was included in the study. The non-diabetic group included 67 age-matched by intention consecutive patients, without diabetes, who also presented to the same family medicine office. Main variables' values were collected from the medical files and ft-PWV was measured in all 140 patients to assess and evaluate the arterial stiffness. Several variables were set for a detailed description of included patients, given that logistics required enrollment of consecutive patients in which the ft-PWV reading device was available to the primary care office for only five months. Before enrolling all patients read and signed an informed study consent form.

Microsoft Office Excel 2013 and IBM SPSS Statistics 23 were used to analyse the data. Confidence intervals (CI95%) were calculated for estimates. Continuous variables were analysed with mean ± standard deviations and t-student test for differences in means and with one-sample statistics for testing differences in each sample against the reference optimal values from the literature (ft-PWV). As these reference values used reported results by age group we also grouped both T2DM and non-T2M patients in same referenced age-groups for comparative

purposes of ft-PWV measurements. Differences were described with CI 95%. The lower and upper limits of these intervals may indicate that such reading ranges generally require attention when evaluating ft-PWV in the follow-up measurements (Table 2). A linear regression analysis was used where arterial stiffness (ft-PWV) was selected as the dependent variable and systolic blood pressure (SBP) and age as independent variables. Due to to the logistics encountered only cross-sectional measurements were assessed and results are indicative. The diastolic blood pressure (DBP) was also chosen as an independent variable, but due to its high correlation with SBP it was dropped from the independent variables list. This linear regression function was used to explore and point out to possible estimate points of changes in the dependent variable (ft-PWV) when the independent covariates would have registered a change as given by standardised regression coefficients (covariation). Smoking status was dropped from the independent list due to a high missing value rate (30% in the T2DM group and 66% in the non-T2DM group). Independent and the dependent variable underwent a correlation analysis (coefficients can take values from -1 to 1). Direct or indirect correlation is given by the arithmetic sign (Table 2). Results in Table 3 are the intermediate step for the multivariate (linear) regression equation. Assumptions were made for 1) linearity (for every pair of X1 and X2, the independent variables), the mean of the corresponding Y values (dependent variable) lies on a flat surface and, 2) no interaction, where the effect of changes in X1 on Y is independent of the level of X2.

Results

The T2DM group, all previously diagnosed with type 2 diabetes, enrolled 73 patients with a mean age of 54±9 years (minimum value 37 years old, maximum 78 years old). The non-T2DM group enrolled 67 consecutive non-diabetic patients who visited the family doctor's office for other conditions, unrelated to metabolic syndrome or diabetes, such as acute respiratory, digestive or urinary infections, or annual preventive check-ups. The mean age of the patients in this group was 48±13 years (minimum 22 years old and maximum 81 years old). Difference in means of age between groups was not statistically significant. Overall the mean age of the patients included in the study was 51.42±11.57 years, with a minimum age of 22 years and a maximum age of 81 years.

From the total number of patients (140), 76 (54%) were women and 64 (46%) were men, but by group there was an imbalance in the sex ratio with T2DM registering a M:F of 2.65 and the non-T2DM a ratio of 0.20 (Table 1). The imbalanced ratio led to separate reporting of regression coefficients (Table 4).

Excess body weight was measured with abdominal circumference levels (Table 1). Among all 140 patients in our study, the mean value of the body mass index (BMI) was 28.16±5.67 Kg/m^2, with a maximum value of 49.05 kg/m^2 and a minimum value of 16.46 kg/m^2 All the observed (some expected) differences between T2DM and non-T2DM groups are shown in Table 1 and these differences are further discussed in the Discussion Section. Regarding the onset of type 2 of diabetes mellitus, most of the patients, 54.2% (39 patients), had a history of type 2 diabetes mellitus of 5-10 years. 13.7% (10 patients) were diagnosed more than 10 years before, and 30.1% (22 patients) had been suffering from type 2 diabetes mellitus for 1–5 years. Two patients (2.7%) have been diagnosed with diabetes less than a year before. The majority of diabetic patients received oral antidiabetic agents (biguanides and sulfonylureas). Only 6 patients had the serum glucose levels controlled by diet, without pharmacological treatment. No patient required insulin administration.

The abdominal circumference, weight and height of the patients have been measured. BMI has been calculated for each patient. Systolic blood pressure (SBP) and diastolic blood pressure (DBP), while supine, have also been measured, as well as the ft-PWV. The values of the lipid profile and fasting serum glucose were obtained from patients' files. The clinical characteristics of the study group and control group are presented in Table 1. The mean BMI was 31.04 kg/m^2, with a standard deviation of 4.52 kg/m^2, in the T2DM group higher than in the non-T2DM group, 25.00 kg/m^2, standard deviation of 5.10 kg/m^2 ($p<0.001$) (Table 1). Patients in the T2DM group had a mean abdominal circumference of 116.3±20.7 cm (CI95% 111 to 121 cm), higher than patients in the non-T2DM group, who had a mean abdominal circumference of 83.7±24.1 cm ($p=0.028$) (CI95% 78 to 90 cm); a difference of 32 cm was observed (CI95% 26.5 to 38.2 cm) (Table 1).

The mean SBP value was 143±9 mmHg in the T2DM group, while it was lower in the non-T2DM group at 128±12 mmHg (Table 1). Similarly, the mean DBP value observed in the T2DM group was 86±8 mmHg, also higher than in the control group, 74±10 mmHg. For these mean readings SBP correlates highly and significant with DBP at $r=0.816$ in T2DM and 0.893 in the non-T2DM groups. Given that age is a variable which must be controlled for in analyses such as arterial stiffness assessments and given that DBP correlates highly with SBP, we selected age and SBP as covariates for a simple linear regression model to explore more the role of arterial stiffness assessment in T2DM.

The mean value of cholesterol in the study group was 319±62 mg/dL, higher than in the control group 245±72 mg/dL ($p=0.0392$). The mean value of triglycerides in the study group was 415±94 mg/dL, while in the control group was 294±106 mg/dL ($p=0.0407$). The mean low-density lipoprotein cholesterol (LDL-C) in the study group was 197±48 mg/dL, and in the control group 145±58 mg/dL ($p=0.0471$). The mean high-density lipoprotein cholesterol (HDL-C) in the study group was 39±10 mg/dL, and in the control group 42±10 mg/dL, without statistical significance

(p=0.1786). The mean value of fasting plasma glucose in smoking patients was 98±17 mg/dL versus the non-smokers group, 96±18 mg/dL (p=0.0108). The mean value of pack-year index recorded in smoking patients from the study group was 27±7, compared to 11±7 pack - year recorded in the control group (p=0.000114) (Table 1).

Table 1. Characteristics of patients at enrollment in the study - T2DM and non-T2DM groups

		T2DM group (n=73)	Difference (by sex)	CI95% for difference	Non-T2DM group N=67	Difference (by sex)	CI95% for difference
Gender	Male	53	M:F=2.65		11	M:F=0.20	
	Female	20			56		
Mean age (years)	Male	52±8	-9.6	-14.7 to -4.5	58±13	11.2	2.2 to 20.2
	Female	61±10			47±12		
Weight							
BMI (kg/m^2)		31.04±4.52	.048	-2.9 to 3	25±5.10	4.8	2.3 to 7.2
Underweight		0/73			8/67		
Normal weight		7/73			26/67		
Overweight		24/73			21/67		
Obesity grade 1		31/73			12/67		
Obesity grade 2		10/73			0/67		
Obesity grade 3		1/73			0/67		
Abdominal circumference (cm)		116.3±20.7	3.2	-8.5 to14.8	83.7±24.1	24.1	12 to 36
Smoking							
Missing value		30%			66%		
Blood Pressure (mmHg)							
Systolic blood pressure (SBP)		143±9	3	-2 to 7	129±12	14	9 to 20
Diastolic blood pressure (DBP)		86±8	1	-3 to 5	74±11	12	7 to 17
Triglycerides (mg/dL)		415.±94	5	-44 to 55	294±106	5	-44 to 55
Total cholesterol (mg/dL)		319±62	8	-24 to 40	245±72	50	7 to 93
HDL cholesterol (mg/dL)		39±10	1	-5 to 7	42±10	3	-5 to 11
LDL cholesterol (mg/dL)		197±48	6	-19 to 31	145±58	39	5 to 74
Glycaemia (mg/dL)		112±9.5	-1.5	-6.9 to3.8	84±8.5	10	5 to 15
HbA1c (%)		6.2±0.3	-.06	-0.27 to 0.15	4.7±0.3	0.21	0.1 to 0.32
Ft-PWV (m/s)		8.3±2.3	-0.91	-2.2 to 0.4	7.2±2.3	0.51	-0.48 to 1.5
T2DM status		Yes			No		

BMI = body mass index; HDL cholesterol = high-density lipoprotein cholesterol; LDL cholesterol = low-density lipoprotein cholesterol; HbA1c = hemoglobin A1c; ft-PWV = finger-toe pulse wave velocity

The mean pulse wave velocity value in patients from the study group was 8.3±2.3 m/s. This value was higher than in the control group, 7.2±2.3 m/s (p=0.0039) (Table 2, Figure 1).

Table 2. Summary of ft-PWV comparative results by study group, age group and reference (based on optimal values)

Age group	ft-PWV Reference (optimal values ®)	Mean		Difference from reference (optimal value) (One-sample statistics)		CI95% for difference		Sig (2-tailed)	
		T2DM (n=73)	Non T2DM (n=67)	T2DM (n=73)	Non T2DM (n=67)	T2DM (n=73)	Non-T2DM (n=67)	T2DM (n=73)	Non-T2DM (n=67)
<40	<6.47	6.9	5.9	0.43	-0.60	-12.3 to 13.1	-1.33 to 0.16	0.74	0.11
40-49	<7.03	6.9	6.6	-0.13	-0.39	-0.50 to 0.32	-1.44 to 0.66	0.55	0.45
50-59	<8.33	8.38	8.03	0.05	-0.31	-0.60 to 0.70	-1.57 to 0.96	0.88	0.61
60-69	<8.68	10.4	8.6	1.72	-0.08	-0.89 to 4.33	-1.44 to 1.28	0.17	0.89
>70	<9.76	10.98	9.9	1.22	0.14	-2.35 to 4.78	-7.84 to 8.12	0.36	0.95

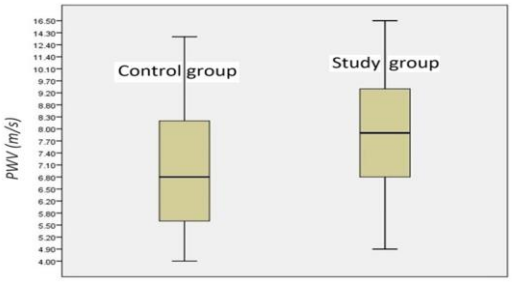

Figure 1 (right)**.** Distributions of ft-PWV values: non-T2DM ('control') and T2DM ('study') groups

Correlation indices for the variables included in the linear regression are presented in the Table 3. Given the observed correlation indices, we used only age and SBP as independent variables in the regression equation. Age appears the only consistent covariate in our study, with high correlation indices across both analyzed groups. Furthermore, the standardised beta coefficient takes positive values and gives the slope an ascendent order: the higher the ft-PWV readings, the older the person (Table 4, Figures 2-4).

Table 3. Pearson's correlation coefficients for independent variables (covariates) included in the linear regression

Variable (coefficient; sig. 2-tailed	T2DM group					Variable (coefficient; sig. 2-tailed	Non-T2DM group				
	Ft-PWV	age	SBP	DBP	Smoking		Ft-PWV	age	SBP	DBP	Smoking
ft-PWV	1	.496**	.025	0.03	-.225	ft-PWV	1	.607**	.484**	.530**	.060
Age	.496**	1	.054	.155	-.369**	Age	.607**	1	.692**	.639**	-.303
SBP	.025	.054	1	.816**	.246	SBP	.484**	.692**	1	.893**	-.290
DBP	0.03	.155	.816**	1	.006	DBP	.530**	.639**	.893**	1	-.170
Smoking	-.225	-.369**	.246	.006	1	Smoking	.060	-.303	-.290	-.170	1

Ft-PWV= finger-toe pulse wave velocity (dependent variable); SBP=systolic blood pressure (independent variable); DBP= diastolic blood pressure (independent variable); age (independent variable); **. Correlation is significant at the 0.01 level (2-tailed).

Table 4. Linear regression – Coefficients [a]

Model	Unstandardised B	Std error	Standardised β	95% CI for B coefficient	Sig. 2-tailed	R2 adjusted (linear)
Men (study group; Fig. 2)						
Age	.132	.037	.468	.058 to 0.206	.001	0.206
SBP	.022	.030	.096	-.038 to 0.082	.467	0.011
Women (study group; Fig. 3)						
Age	.117	.056	.462	-.002 to 0.237	.054	0.213
SBP	-.101	.077	-.292	-.264 to 0.061	.205	0.098
Men (control group) (not shown)						
Age	.032	.034	.330	-.049 to 0.113	.385	0.109
SBP	.043	.060	.256	-.098 to 0.184	.495	0.069
Women (control group; Fig. 4)						
Age	.107	.027	.571	.053 to 0.161	.000	0.235
SBP	.034	.030	.171	-.025 to 0.094	.249	0.026

a. Dependent Variable: ft-PWV= finger-toe pulse wave velocity; SBP=Systolic blood pressure

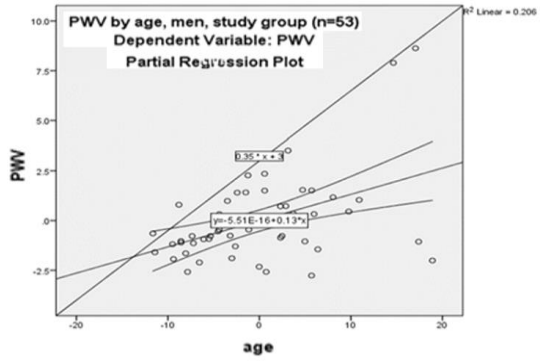

Figure 2. Partial regression plot: ft-PWV and age T2DM group (men, n=53)

Figure 3. Partial regression plot between ft-PWV and age in T2DM (women, n=20)

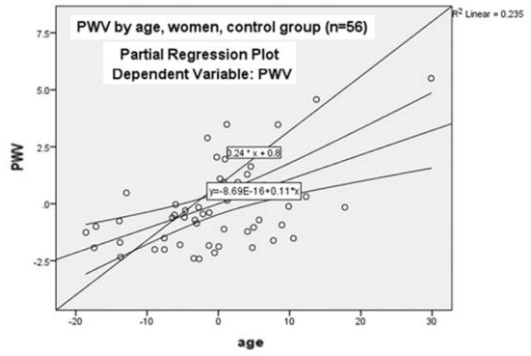

Figure 4. Partial regression plot between ft-PWV and age in non T2DM (women, n=56)

Discussions

An overall mean age of patients included in the study was 51.42±11.57. This informs us in one way, that a threshold of above 45 years might be an important benchmark for a future multi-center study. Standardized beta regression coefficients are consistent across groups (Table 4). Excess weight represents an important, independent risk factor for the development of type 2 diabetes, as well as for an unfavorable evolution [23-25]. The presence of obesity, associated with the onset of type 2 diabetes and cardiovascular disease, represents a major risk factor for cardiovascular complications [3,26]. Different studies support the hypothesis that the treatment of obesity can prevent the progression from pre-diabetes to diabetes and it is an important stage in the treatment of type 2 diabetes [3,14,18,26,27]. Patients with type 2 diabetes have a higher risk of PAD, further associated with the risk of amputations. Therefore, an early diagnosis of vascular complications by non-invasive techniques is of utmost importance. The Maine-Syracuse Longitudinal Study have analyzed seven longitudinal waves of data available for over 1,000 community participants and cross-sectional data available for more than 2,000 study participants, residents of central New York, who have been monitored for 40 years, since 1976. In this study, Elias et al. evaluated the risk factors for cardiovascular disease, data on cardiovascular disease, clinical cognitive performance, and personality and lifestyle measures. This prospective study showed that type 2 diabetes mellitus is associated with increased mean arterial stiffness over a 5-year period. Fasting plasma glucose was positively associated with PWV, and this significant association remained after addition of PWV-related variables, lifestyle factors and cardiovascular risk factors, such as obesity, smoking or sedentarism. An effective management of obesity and hyperglycemia may prevent the increase of arterial stiffness [28]. Abdominal circumference is an indicator of adipose tissue disposition at the central level (elevated values defining android obesity and suggesting perivisceral disposition of excess adipose tissue) and a good predictor of the cardiometabolic risk [3,6]. In our study, the patients from the study group had higher abdominal circumference than patients from the control group, as in other studies, that underline the importance of visceral obesity and the increased metabolic risk associated with obesity [27,29]. The prospective study of Strasser et al. included 146 middle-aged participants and pointed out that abdominal obesity and visceral fat are associated with increased arterial stiffness. These findings support the importance of clinical evaluation, measurement of abdominal circumference and BMI, as risk factors for arterial stiffening in middle-aged adults [30] (Table 1).

Regarding the mean values of SBP and DBP, our study has shown that both hemodynamic parameters have higher values in patients diagnosed with type 2 diabetes. Many clinical studies have shown that a proper treatment of arterial hypertension reduces the risk of cardiovascular events, as well as the risk of microangiopathic complications in patients suffering from diabetes mellitus [3,7,31]. An observational study by Tomiyama et al., of a middle-aged Japanese male cohort, reported a synergistic acceleration of the brachial - ankle PWV in subjects with both higher blood pressure and elevated plasma glucose, compared with subjects with either arterial hypertension or diabetes mellitus alone [32].

Tobacco consumption had a higher prevalence among men. Yet they were also five times more men in the study group than the control group. Smoking status has high missing value levels (30% in study group and 66% in control group). Of 55 smokers, 69% (38) were men and 31% (17) women. The mean values of SBP and DBP recorded in smoking patients were 136±13 mmHg, respectively 80±11 mmHg (p=0.00018). In non-smokers, the mean values of SBP and DBP were lower, 133±13 mmHg, respectively 78±12 mmHg (p=0.00018). These results could not be used with the regression function due to high missing values in reporting of smoking.

The mean ft-PWV value in the study group was higher in the T2DM group, which may indicate vascular stiffness by indication of the presence of peripheral artery disease. This was mentioned in other studies, especially in patients who associate obesity or arterial hypertension [18,33,34]. High blood pressure represents one of the major factors that influences peripheral arterial stiffness and target organ damage; it has been demonstrated a strong correlation between type 2 diabetes mellitus and progressive stiffening of central rather than peripheral arteries, after adjustment for other risk factors [35]. Increased arterial stiffness, as measured by brachial-ankle PWV, predicts the risk of all-cause and cause-specific mortality in type 2 diabetes [36]. The regression function shows positive regression coefficients of SBP; however, the interpretation of statistical significance requires a larger study given that coefficients show statistical significance in men with T2DM and women without T2DM (Table 4).

The relationship between carbohydrate and lipid metabolism is a complex one, insulin resistance and insulin secretion deficiency playing an important role [3,6]. Diabetic dyslipidemia forms a complex group of qualitative, quantitative, and kinetic abnormalities of the lipid fractions, dyslipidemia being considered a modifiable risk factor for cardiovascular disease [6]. The changes in lipid profile in patients included in the study group overlap with the nature of diabetes mellitus-associated dyslipidemia. In Romania, in the PREDATORR study, the prevalence of dyslipidemia in patients with prediabetes and diabetes was 83.7% [37]. The status of smoker, regardless of the presence of diabetes mellitus, is associated with higher values of SBP and DBP, a fact also confirmed by our study [3,38]. Chronic hyperglycemia induces arterial wall remodeling and the subsequent increase in arterial stiffness, irrespective of the presence of other cardiovascular risk factors [35]. Arterial stiffness itself is an independent prognostic marker for the evolution of patients with type 2 diabetes [35,36], being an indicator of cardiovascular diseases, micro and macrovascular complications in patients with type 2 diabetes [35].

Even if our study has some limitations, nevertheless we decided that these results deserve to be brought to the attention of the public with the aim to expand ft-PWV measurements in adults in a multi-center study, with a design that includes a follow-up period of T2DM individuals as well as age and sex non-T2DM individuals in order to: 1) detect within patient differences in time or time precedence, 2) possibly capture ft-PWV readings for the incident T2DM patients, 3) adjust for other co-morbidity ('third' factors), 4) include treatment variables (status by exposure with evaluation for immortal time bias).

There are therefore limitations regarding the design of this study. Cross-sectional studies are well known to offer just a picture and also known for being prone to selection bias (inclusive of consecutive attendances and measurements, instead of random allocation to ft-PWV readings). This small study does not include data related to any subsequent monitoring of these two groups, or to have allowed for a time series measurements. All measurements should have been carried out in dynamics, alongside with treatment variables, if they were to point to any 'predictive' role of the two independent covariates (age, SBP). One further challenge is that we were not generally able to observe changes in states even in the pre-diagnosis status, let alone after T2DM diagnosis, that is, at each point in time when we are measuring the ft-PWV, each individual either has had drug exposure or has not. Due to time limitations and logistics of the use of the ft-PWV device, treatment variables were excluded [39].

The proposed test is easy to use; however, there are other criteria to consider if such an early detection as a screening program were to be introduced. But such programs involve substantial additional costs. A feasibility or pilot study must take place first and that must happen in more settings. Scarce resources will have to be further re-deployed if groups of high-risk T2DM patients will undergo recommendations for such screening.

The optimum threshold value, as given by the literature or the manufacturer, has also limitations in information quality (Table 2). Single thresholds for such large age groups denote that wide measurement errors may have occurred when they were set up.

Large scale studies would inform better for future use of this test, including when it comes to conditions such as T2DM. Our results point only to levels which do not differ statistically from the age-adjusted optimum readings. However, results appear inconclusive when it comes to differences observed for the T2DM and the non-T2DM and this fact is due to the many limitations (study design, short period of the study, outlying values pointed by the partial regression, etc.) (Figures 2-4).

T2DM incidence is an essential morbidity public health indicator and a ft-PWV reading at the diagnosis moment would be of great value for both patient and carers. This study could not flag up incident cases in such a short period. One other major limitation is that the study has not taken into account immortal time bias in the T2DM group and this plays a role in the evolution followed by prognosis of disease once diagnosed [40].

Conclusions

The easy testing and recording of the pulse wave at the finger and the toe may be a good alternative for the measurement and monitoring of arterial stiffness evaluation in any primary care office. In our study, T2DM patients had a mean BMI value and a mean abdominal circumference that were statistically significantly higher than non-T2DM individuals. The values of SBP and DBP were higher in T2DM group. Descriptive and exploratory analyses with regression coefficients are guiding us into studying changes in ft-PWV when measurements will be done in dynamics. A more robust study design (observational, prospective, age and sex-adjusted, which would account for immortal time bias and other 'third' variables) is needed with a larger sample base. An improved design may identify the role of SBP in men and women given that this result proved inconclusive with this case series. Early, accessible and non-invasive testing carried out by the family physicians, such as ft-PWV, may lead to an earlier PAD diagnosis in patients with T2DM. This creates prerequisites for a good quality management of the patient with T2DM.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. Informed consent was obtained from all subjects involved in the study.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

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