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INCREASED TYPE 2 DIABETES MELLITUS RISK (ASSESSED BY FINDRISC SCORE) IS ASSOCIATED WITH SUBCLINICAL ATHEROSCLEROTIC MARKERS IN ASYMPTOMATIC ADULT POPULATION

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Abstract

Background and Aims. *Risk score questionnaires for the screening of type 2 diabetes mellitus (DM) present high accuracy, especially the Finnish Diabetes Risk Score (FINDRISC). The aim of the study was to assess the FINDRISC score and its correlations with multiple markers of subclinical atherosclerosis in an asymptomatic urban population.* ***Material and Methods***. *In the current prospective study, 111 randomized asymptomatic subjects, aged 35-75, were evaluated. FINDRISC score, the cardiovascular and metabolic risk profile were evaluated. Multiple markers of subclinical atherosclerosis were assessed including carotid intima-media thickness (IMT), ankle-brachial index (ABI), pulse wave velocity (PWV) and left ventricular mass index (LVMI).* ***Results***. *Mean age was 51.87 ± 10.64 years while FINDRISC score was 10.53 ± 4.53. 77% of the subjects were overweight and all parameters of obesity were well associated with FINDRISC score ($p<0.001$). This asymptomatic population was dyslipidemic (total cholesterol 212.79±44.99 mg/dl). DM risk correlated with age, blood pressure, fasting plasma glucose and glomerular filtration rate. Increased FINDRISC was associated with IMT ($r=0.24$, $p=0.01$), PWV ($r=0.26$, $p=0.008$) or LVMI ($r=0.23$, $p=0.01$).* ***Conclusions***. *This asymptomatic population was metabolically uncontrolled. Easily administered type 2 DM screening questionnaires should be routinely performed as increased risk score values are associated with subclinical atherosclerosis.*

key words: *FINDRISC, type 2 diabetes mellitus, subclinical atherosclerosis, obesity, asymptomatic population.*

Background and Aims

Type 2 diabetes mellitus (DM) represents one of the leading causes of mortality and morbidity worldwide and it is in continuously growing. According to the latest data, more than 415 million people already have DM and it is predicted a 50% growing by 2040 [1]. Known as the forerunner of DM, obesity will definitely influence this augmentation and it is expected

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that the estimation for diabetes prevalence will be underestimated as the prevalence of obesity is dramatically increasing. In Romania, the numbers are even more alarming: almost 30% of the population present impaired glucose regulation, with 11.6% being diabetic out of whom more than 2% being unaware of this diagnosis [2].

Measuring fasting plasma glucose (FPG) or performing an oral glucose tolerance test represent methods for the early diagnosis of DM. However, in the asymptomatic population these measurements are rather difficult to be regularly performed and, moreover, the blood glucose levels present high variability. Thus, easily determined scores for detecting subjects at high risk of DM have been developed, most of them with good sensitivities and specificities [3].

In most cases, the patients newly diagnosed with DM already present different markers of target organ damage and almost 20% have developed subclinical atherosclerosis and with a significantly increased 10-year risk for cardiovascular diseases (CVD) [4]. In the last years, early detection of subclinical atherosclerosis is highly emphasized since actual risk scores (e.g. Framingham or SCORE) often misclassify high-risk individuals as intermediate or low risk and thus prevention is improperly performed [5].

The aim of the current study was to evaluate the risk of type 2 DM in an asymptomatic adult population, the cardiovascular risk profile of these subjects and the association between the diabetic risk score and different markers of subclinical atherosclerosis.

Material and methods

We performed a cross-sectional study, over a two year period. From the medical subjects' data lists of the local general practitioners, more than 600 subjects have been randomized. Out of all these, only 111 met the inclusion criteria, accepted and presented to the clinic for further investigation.

All participants had fulfilled the following inclusion criteria: age 35-75 years, urban residence, and women not being pregnant. Most important, the subjects did not have any known diseases (e.g. CVD or type 2 DM) or received any treatment in the last 12 months for any metabolic, cardiovascular, renal, respiratory or cerebral diseases. Thus, we have included only apparently healthy individuals, treatment naïve at the beginning of the study. The research was approved by the University Ethics Committee and all subjects have agreed and signed an informed consent in order to take part in this study.

Type 2 DM risk evaluation. In order to assess the type 2 DM risk, the Finnish Diabetes Risk Score (FINDRISC) was used [6]. FINDRISC is a well validated tool, having the advantages that it can be easily administered, is time saving and brings valuable data regarding the risk of developing DM over the next 10 years. FINDRISC is an eight-question score and takes into account the following items: age, body mass index (BMI), waist circumference (WC), physical activity level, daily consumption of vegetables, fruits or berries, history of antihypertensive drugs, history of increased FPG, family history of DM. Depending on the answer, each item receives point/points that finally sum and confer the final risk score that varies between 0-26. By obtaining the total risk score, the subject is placed into one of the following risk categories, with different recommendations for prevention and management (Table 1).

Cardiovascular risk factors assessment. All patients were assessed according to the following cardiovascular and metabolic risk factors: age, gender, smoker status, resting

systolic and diastolic blood pressure (SBP, DBP) and heart rate (HR). Family history of premature CVD was established if acute atherosclerotic events occurred in first degree relatives at < 55 years in men, respectively < 65 years in women according to the latest guidelines [7]. Chronic alcohol consumption was defined as an intake of more than 20 g of alcohol for men and 10 g for women [7].

Table 1. FINDRISC score and interpretation. (Adapted after [6])

Total FINDRISC score	10-year risk	Risk class
0 – 14 points	1 – 17%	Low to moderate
15 – 20 points	33%	High
21 – 26 points	50%	Very high

Obesity was evaluated by various anthropometric measurements: BMI (using the weight (kg) / height (m)^2 formula); WC measured halfway between the lowest ribs and the top of the hip bone; hip circumference; Waist to hip ratio (WHR); Waist to height ratio (WHtR); abdominal skinfold measured at 5 cm lateral from the umbilicus.

The following biochemical markers have been analyzed: lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, non HDL cholesterol), FPG, uric acid, glomerular filtration rate (GFR) using CKD-EPI formula for calculation and inflammatory status by determining fibrinogen and erythrocyte sedimentation rate (ESR).

Subclinical atherosclerosis assessment. In order to establish the best correlations and predictors for DM risk, subclinical atherosclerosis was evaluated through multiple methods: carotid intima-media thickness (IMT), ankle-brachial index (ABI), left ventricular mass index (LVMI) determined by echocardiography and parameters of arterial stiffness: central pulse wave velocity (PWV), augmentation indexes, aortic SBP (SBPao). Each investigation was performed by a single experienced operator minimizing the risk of inter-observer bias.

IMT was assessed using ultrasonography and interpreted according to the Mannheim criteria [8]. Measurements were manually performed on the common carotid artery at 1 cm below its end or, in case of vessel tortuosity, proximal to the carotid bifurcation. IMT value more than 0.9 mm was considered as having pathological significance. The carotid plaque was defined as thickness > 1.5 mm or a focal structure encroaching into the lumen > 0.5 mm.

ABI was evaluated by using continuous wave Doppler signal and pneumatic cuffs, at rest and in supine position. SBP was measured at the lower limbs, retaining the highest value obtained at posterior tibial or dorsalis pedis arteries for each leg and this was the numerator in the ABI calculation. The higher of the two brachial SBPs was assumed for denominator in the final equation. An ABI $\leq$ 0.9 was considered the threshold for a diagnosis of lower extremity peripheral artery disease while values > 1.4 indicated incompressible tibial arteries due to important calcification [9].

By echocardiography, we measured LVMI, left ventricular ejection fraction (LVEF) and the presence of aortic atheromatosis. The LVM was indexed for body size and calculated using M mode echography. Thresholds of 95 g/m^2 for women and 115 g/m^2 for men were considered as cut-off values for left ventricular hypertrophy [10].

Aortic stiffness parameters were assessed using the Arteriograph system (Tensiomed, Hungary). It determines PWV, SBPao and augmentation indexes (brachial [AIXbr] and aortic [AIXao]) by oscillometric method, measuring the BP in the upper arm and producing a 35 mmHg cuff pressure over SBP measured. The pressure fluctuations are measured in the brachial artery and, by entering

the distance from the jugulum to the symphysis, the software determines the pulse waves and calculates the PWV. PWV > 10 m/s cut-off value is considered as marker of subclinical atherosclerosis [11].

Statistical analysis. Data analysis was performed using SPSS 20.0 (Statistical Package for the Social Sciences, Chicago, Illinois). Data were expressed as mean ± standard deviation (SD), number of cases with percentage, for continuous, categorical and ordinal variables, respectively. Continuous variables were compared using the t-test for independent samples. Categorical comparisons were performed by chi-square test. Ordinal variables were compared using Mann-Whitney U Test. The correlations between different parameters were analyzed using the Pearson coefficient. A two-sided p value < 0.05 was considered significant for all data analyses.

Results

Mean age was 51.87 ± 10.64 years (between 35 and 75 years), with 33.3% of subjects being males. In the study population, mean FINDRISC score was 10.53 ± 4.53 (varying between 0 and 22), with a median of 11. BMI, WC, WHR and WHtR had high values, over the normal superior limits, while resting arterial BP and HR were in normal ranges. Average parameters of subclinical atherosclerosis were normal, with LVMI reaching higher values. Regarding biochemical markers, most lipid parameters exceeded the upper limit while FPG and uric acid were normal. All subjects' characteristics are found in Table 2.

Table 2. General characteristics of the study population.

Parameter	Value
n	*111*
FINDRISC score	10.53 ± 4.53
Age (years)	51.87 ± 10.64
SBP (mmHg)	131.62 ± 15.82
DBP (mmHg)	82.57 ± 9.09
HR (bpm)	67.78 ± 10.50
Obesity parameters	
BMI (kg/m²)	28.83 ± 5.31
WC (cm)	100.31 ± 12.41
WHR	0.93 ± 0.06
WHtR	0.60 ± 0.07
Abdominal skinfold (mm)	31.86 ± 6.68
Biochemical markers	
Total cholesterol (mg/dl)	212.79 ± 44.99
HDL cholesterol (mg/dl)	51.50 ± 14.07
LDL cholesterol (mg/dl)	132.95 ± 40.22
Non HDL cholesterol (mg/dl)	161.28 ± 43.57
Triglycerides (mg/dl)	142.32 ± 81.75
FPG (mg/dl)	97.48 ± 12.65
Uric acid (mg/dl)	4.41 ± 1.61
GFR (ml/min/1.73m²)	88.27 ± 16.35
ESR (mm/1h)	17.64 ± 12.79
Fibrinogen (mg/dl)	368.76 ± 77.80
Subclinical atherosclerosis markers	
Carotid IMT (mm)	0.86 ± 0.12
ABI	1.07 ± 0.14
PWV (m/s)	8.21 ± 1.71
AIXbr (%)	-1.97 ± 30.56
AIXao (%)	36.54 ± 15.34
SBPao (mmHg)	128.35 ± 20.85
LVMI (g/m²)	101.48 ± 23.30
LVEF (%)	67.66 ± 6.22

ESR – Erythrocytes Sedimentation Rate

Increased FINDRISC values correlated with age (r = 0.24, p = 0.011) (Figure 1) while no differences were found regarding gender. As well, family history of premature CVD, smoking or chronic alcohol intake were not reliable predictors of type 2 DM assessed by risk charts. However, menopausal women exhibited an increased FINDRISC scores compared to non-menopausal ones (12.11 ± 3.84 vs. 8.33 ± 4.24, p < 0.001).

All anthropometric obesity parameters were strongly associated with high FINDRISC values (p < 0.001), BMI and WC having the best statistical significance (Table 3).

Increased BP values were positively associated with DM risk, both SBP (r = 0.20, p = 0.031) and DBP (r = 0.22, p = 0.019) while resting HR present no correlation with FINDRISC.

Out of lipid parameters, only non HDL cholesterol correlated with increased FINDRISC

score, with total cholesterol and LDL cholesterol being at limit for reaching statistical significance. Type 2 DM risk score was not associated with positive inflammatory markers (fibrinogen, ESR). FPG strongly correlated with FINDRISC scores ($p < 0.001$) as well as high values of uric acid or decreased renal function assessed by GFR. Table 4 presents the correlations between biochemical markers and FINDRISC score.

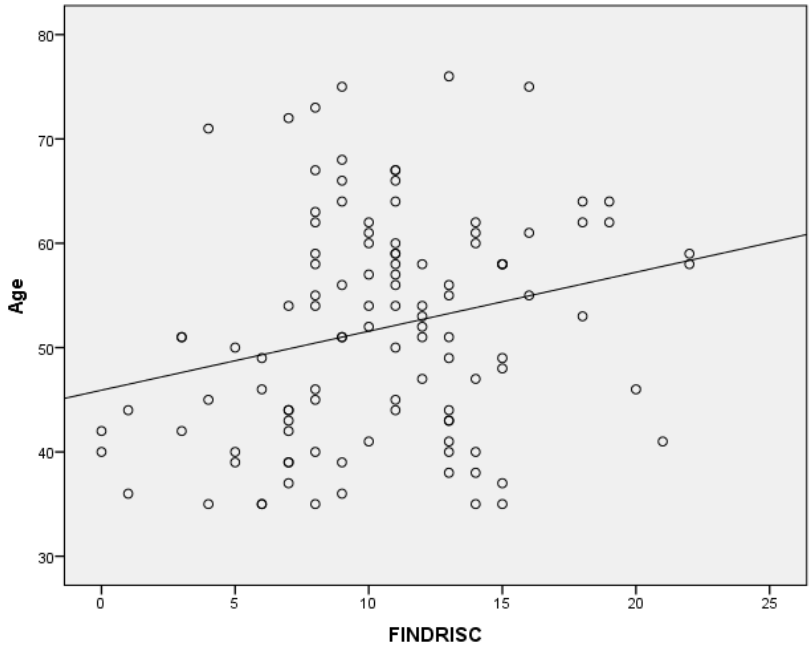

Figure 1. *Direct correlation between increased FINDRISC score and age.*

Table 3. Correlations between FINDRISC score and anthropometric obesity parameters.

Parameter	**FINDRISC**	
	r coefficient	**p value**
BMI	*0.50*	*< 0.001*
WC	*0.51*	*< 0.001*
WHR	*0.41*	*< 0.001*
WHtR	*0.48*	*< 0.001*
Abdominal skinfold	*0.49*	*< 0.001*

Table 4. Correlations between FINDRISC score and biochemical parameters.

Parameter	**FINDRISC**	
	r coefficient	**p value**
Total cholesterol	0.18	0.056
HDL cholesterol	-0.13	0.17
LDL cholesterol	0.18	0.059
Non HDL cholesterol	*0.23*	*0.015*
Triglycerides	0.16	0.084
FPG	*0.42*	*< 0.001*
Uric acid	*0.31*	*0.001*
GFR	*-0.28*	*0.003*
ESR	0.02	0.77
Fibrinogen	0.16	0.092

Regarding subclinical atherosclerosis, an increased IMT correlated with DM risk ($r = 0.24$, $p = 0.01$). Moreover, subjects with IMT ≥ 0.9 mm exhibited higher FINDRISC values

compared to normal IMT individuals (11.61 ± 3.66 vs. 9.90 ± 4.88, p = 0.039). However, the presence of carotid plaques did not influence significantly the risk chart. Increased aortic stiffness determined by PWV correlated with DM risk (p = 0.008) while other stiffness parameters (AIXbr, AIXao or SBPao) showed no significant correlations. ABI had no predictive value for DM risk. Out of the echocardiographic markers, an increased LVMI correlated with high risk chart values (p = 0.016). Moreover, patients with aortic atheromatosis had higher FINDRISC score (11.51 ± 4.11 vs. 8.13 ± 4.66, p = 0.001). All correlations between FINDRISC values and parameters of subclinical atherosclerosis are summarized in Table 5.

Table 5. Correlations between FINDRISC score and markers of subclinical atherosclerosis.

Parameter	FINDRISC	
	r coefficient	p value
Carotid IMT	*0.24*	*0.01*
ABI	-0.04	0.64
PWV	*0.26*	*0.008*
AIXbr	0.05	0.57
AIXao	0.05	0.62
SBPao	0.15	0.11
LVMI	*0.23*	*0.016*

Discussion

In most developed countries, DM prevalence is dramatically increasingly and certain individuals are diagnosed when micro or macrovascular complications have already been installed. Thus, early detection of DM (with presumably positive lifestyle changes) could retard its progression. Regarding the strategy for population based screening, multiple approaches have been suggested and the risk scores have been proved to be well effective for identifying high-risk populations that should benefit of more specific investigations, such as FPG or oral glucose tolerance test [3]. In a recent cross-sectional study that evaluated the performance of 10 diabetes risk scores, FINDRISC proved to be superior for predicting the risk of DM in the general population [12]. Moreover, FINDRISC represents the most commonly used risk chart for evaluating DM risk in Europe with 85% accuracy [13].

CVD is the main cause of mortality in diabetic patients worldwide. Thus, early detection of atherosclerosis is strongly recommended even in asymptomatic individuals. The SHAPE (Screening for Heart Attack Prevention and Education) Task Force calls for noninvasive screening of atherosclerosis in all asymptomatic men (age 45 to 75 years) and women (age 55 to 75 years) [14]. This approach of atherosclerosis imaging proved to have a superior prognostic value compared to the evaluation of traditional risk factors of atherosclerosis. The SHAPE Task Force recommends the use of coronary artery calcium score by computer tomography and carotid IMT by ultrasonography. In the current study, multiple validated methods for detection of subclinical atherosclerosis have been used: IMT and carotid plaque detection, ABI, LVMI and aortic atheromatosis by echocardiography and different parameters of arterial stiffness, PWV being the most important. Up to our knowledge, no study evaluated the association between the DM risk and multiple parameters of atherosclerosis in an asymptomatic population.

Obesity is continuously increasing worldwide both in adults and children. Increased BMI, WC and WHR are associated with high rates of mortality and the parameters of abdominal adiposity can be used in addition to BMI for assessing the risk of death [15]. In our study, more than 77% of the asymptomatic adult population sample was overweight or obese, with an average BMI of almost 29 kg/m². Moreover, all other markers of obesity that have been studied (WC, WHR, WHtR, abdominal

skinfold) exceeded the superior limit, proving that the urban adult population has usually an uncontrolled weight. Increased values of all obesity parameters are associated with high risk of DM, BMI and WC having the best statistical results ($p < 0.001$). However, this result was foreseeable since these obesity parameters are included in the FINDRISC score. Our results are consistent with literature data since a meta-analysis performed by Vasquez et al. showed as well that BMI, WC and WHR are independent predictors of incident diabetes (relative risks: 1.87, 1.87, respectively 1.88) [16].

Major studies showed that increased levels of total cholesterol, LDL, non HDL cholesterol and triglycerides and decreased levels of HDL cholesterol are independent predictors for cardiovascular mortality [7]. In the current study, the asymptomatic population is dyslipidemic, with higher levels of total cholesterol, LDL and non HDL cholesterol. However, out of all lipid markers, only non HDL cholesterol significantly correlated with FINDRISC score though total cholesterol and LDL cholesterol are at limit for being statistically valid. These results suggest that certain lipid parameters may be good predictors for future development of DM.

A large study conducted on 54000 subjects over 3 years has shown that older age, male sex, obesity, smoking, psychological distress or medical history of hypertension and dyslipidemia are correlated with higher risk of developing DM [17]. Moreover, systematic reviews have shown that active smoking is associated with an increased risk of DM, especially in heavy smokers (≥ 20 cigarettes/day) but without stating for a direct cause-effect mechanism [18]. In our study, age is well correlated with increased FINDRISC values ($p = 0.01$). However, no significant correlations were obtained for smoking status, sex, family history of CVD or chronic alcohol consumption. These results may be due to the relative small number of individuals included in the research and also to their asymptomatic profile, these individuals being undiagnosed for any diseases at the investigation moment.

DM is the most common chronic disease in post-menopausal women and the main predisposing factor for CVD [19]. Our results are consistent with the existing data since menopausal women presented significantly increased FINDRISC values. This may be explained by the estrogen deficiency which is associated with reduced pancreatic insulin secretion while the age increase predisposes to insulin resistance [19].

Increased DM risk is associated with high BP values, both SBP and DBP. The two pathologies present interconnected mechanisms and more than 60% of diabetic patients have arterial hypertension [13].

Concerning early detection of atherosclerosis in high risk non-diabetic individuals, we have used multiple imagistic methods. IMT, PWV or LVMI proved to be associated with an increased risk of developing DM assessed by FINDRISC questionnaire. A study performed on more than 1500 subjects proved that carotid IMT is higher in diabetic and prediabetic individuals compared to non-diabetic ones after age and sex adjustment; the study concluded that IMT levels were elevated even before the clinical onset of DM [20]. In our research, no correlation was obtained between carotid plaque presence and high FINDRISC score.

No association was found between low ABI and high risk of DM. The literature data is rather inconsistent on this matter as abnormal ABI value is not well established as predictor of future DM. Peripheral artery disease diagnosed by ABI is associated with many CVD risk factors, including diagnosed DM, high BP values

or hyperlipidemia. As well, in patients with type 2 DM, mortality rates are higher when ABI was abnormal. Yet, the predictive value of ABI for future development of DM requires further additional research [9].

PWV represents the 'gold standard' for measuring aortic stiffness with high predictive value for fatal and non-fatal cardiovascular events. Increased PWV values have been obtained in patients with type 2 DM when compared to control groups [21]. Our results bring further additional information as direct correlation was obtained between high PWV and increased risk of DM emphasizing the need for a closer surveillance in certain high risk categories of patients. Other arterial stiffness parameters such as AIXao or SBPao did not correlate with high FINDRISC score. These results suggest the need for further studies in order to clarify whether these parameters are associated with high risk of DM in asymptomatic population.

Left ventricular hypertrophy or LVMI represents important target organ damage, especially in hypertensive patients. Moreover, on a large sample of asymptomatic population, Taylor et al. proved that LV hypertrophy is associated with higher rates of all-cause mortality especially in men [22]. Our results suggest that LVMI determined by cardiac ultrasound can predict a future risk of developing DM. Moreover, the presence of aortic atheromatosis is correlated with increased FINDRISC scores. Thus, the presence and detection of atherosclerotic burden by echocardiography may indicate the risk for the future development of DM and should impose early lifestyle changes.

Limitations of the study. Even though the selection of the population was strictly performed, the limited number of patients (111) may influence some of the results. Furthermore, the risk of DM was evaluated using a single questionnaire which may represent a bias for making certain conclusions between possible associations. However, future research is needed in order to establish the role of certain cardiovascular risk factors (such as smoking, gender or alcohol consumption) and markers of subclinical atherosclerosis (such as ABI, aortic SBP or LVMI) as type 2 DM indicators.

Conclusions

The asymptomatic urban adult population represents a high risk category for CVD and type 2 DM, presenting high rates of obesity and uncontrolled lipid values. FINDRISC score represents a useful and validated tool for DM screening and is well correlated with age, BP values and all markers of obesity. Increased FINDRISC values are associated with high levels of FPG and uric acid and present an inverse relationship with GFR.

Out of all markers of subclinical atherosclerosis, carotid IMT, PWV, LVMI and the presence of aortic atheromatosis are associated with the highest risk for developing type 2 DM. Thus, easily administered type 2 DM screening questionnaires should be routinely performed as increased score risk values are already associated with the presence of subclinical atherosclerosis.

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