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Original article

Importance of metabolic factors in determining cardiovascular risk in romanian patients with type 1 diabetes: A pilot study

Andreea Herascu [1, 2, 3], Vlad Avram [2, 3, 4] *, Laura Gaita [2, 3, 4], Adina Braha [2, 3, 4], Alexandra Sima [2, 3, 4], Bogdan Timar [2, 3, 4]

[1] Doctoral School of Medicine, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania

[2] Department of Diabetes, Pius Brinzeu Emergency Hospital, Timisoara, Romania

[3] Centre for Molecular Research in Nephrology and Vascular Disease, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania

[4] Second Department of Internal Medicine, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania

* Correspondence to: Vlad Avram, Department of Diabetes, Pius Brinzeu Emergency Hospital, 300723 Timisoara, Romania. Phone: 0040749037787; E-mail: avram.vlad@umft.ro

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Abstract

A major cause of morbidity and mortality in patients with type 1 diabetes is cardiovascular disease. Cardiovascular risk in these patients should be periodically evaluated, and the Steno T1 Risk Engine can be a useful tool in determining five- and ten-year cardiovascular risk in patients with type 1 diabetes. The current aim of this study was to evaluate the link between cardiovascular risk in a population of Romanian patients with type 1 diabetes and metabolic control. The current study is a non-interventional, population-based, retrospective, single-center study in which 38 patients were enrolled on a consecutive case basis from the Diabetes Clinic of the Pius Brinzeu Emergency County Hospital Timisoara. Anthropological and laboratory tests were collected in order to cluster patients into three cardiovascular risk categories. Statistical analysis was performed using GraphPad Prism Software version 10.4.0. The threshold for statistical significance in this study was a p-value under 0.05. In most cases, patients were at a medium five-year cardiovascular risk (47.37%), while in the case of ten-year cardiovascular risk, most patients were in the high category (78.38%). No difference was found in cardiovascular risk levels between male and female patients, and achieving glucose control was shown to improve cardiovascular risk significantly more than achieving lipid control. Improving glucose and lipid control by achieving and maintaining the target for HbA1c and LDLc, respectively, reduces cardiovascular risk, with the former having a greater magnitude to the impact.

Keywords: type 1 diabetes mellitus, Steno T1 Risk Engine, cardiovascular risk, HbA1c, LDL- cholesterol.

Introduction

Cardiovascular disease (CVD) represents a leading cause of mortality among patients with type 1 diabetes (T1DM). Compared to the non-diabetic population, these people have a higher chance of developing cardiovascular disease earlier in life, which has been shown to shorten life expectancy by at least 11 years. Patients who develop T1DM at a younger age (less than 10 years old) have an increased risk of cardiovascular disease [1]. Cardiovascular disease is 1.5–2 times more likely to occur in people with type 2 diabetes (T2DM) than in people without T2DM, while the risk of cardiovascular death is 2–4 times higher [2, 3]. "SCORE2-Diabetes" is a useful tool in estimating the probability of developing a cardiovascular event in this group of patients, but it cannot be used for patients with T1DM.

According to early research on cardiovascular mortality in patients with T1DM, risk only rises noticeably once nephropathy develops, which is usually associated

with a worsening of blood pressure and lipid profile [4]. Long-term hyperglycemia can substantially affect cardiovascular risk because it determines an increase in oxidative stress, monocyte adhesion, vascular inflammation, and arterial wall thickening and also promotes endothelial dysfunction [1].

T1DM is more frequently seen in younger patients, and as such, the cardiovascular risk remains underestimated. The Steno T1 Risk Engine is a risk calculator that can be used to estimate the risk of non-fatal and fatal cardiovascular disease in individuals with T1DM over the next five and ten years, respectively. This risk engine uses information from the Danish National Patient Register and Cause of Death Register, as well as comprehensive clinical data from the electronic medical records of the roughly 5,000 type 1 diabetic patients treated at the Steno Diabetes Center in Copenhagen. The risk engine has been verified in the population with type 1 diabetes in Denmark's Funen (regional) Diabetes Database [5].

Taking into account that there are few studies evaluating cardiovascular risk in patients with T1DM, this study aims to evaluate the correlation between cardiovascular risk and metabolic control in a population of Romanian patients with type 1 diabetes.

Material and methods

In this non-interventional, population-based, retrospective, single-center study, 38 patients from the Diabetes Clinic of the Pius Brinzeu Emergency County Hospital Timisoara were enrolled. Patients were admitted for metabolic control evaluation. Enrolment was based on a consecutive case principle. The hospital's standard of care for T1DM patients was followed in the collection of all data. All study participants gave their informed consent for the gathering of data and the secondary use of their medical records for scientific purposes.

To cluster patients with T1DM in cardiovascular risk categories, specific laboratory data was collected: HbA1c, urinary albumin to creatinine ratio (UACR), estimated glomerular filtration rate (eGFR using KGD-EPI creatinine equation 2021), LDL- cholesterol. Data collected by taking patient history and physical examination included age, duration of diabetes, systolic blood pressure, height, weight, smoking status, and whether regular exercise (≥3.5 hours/week) was performed. Screening for chronic diabetes complications was performed: dilated eye examination, foot examination, electrocardiogram ankle-brachial index and neuropathy tests.

The body mass index (BMI) was calculated as weight (kg)/height 2 (m) [6]. Moreover, the estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI Creatinine Equation (2021), as follows: eGFR = 142 x min (standardized Scr/K,1) α * max (standardized Scr/K,1) -1.200 * 0.9938 age in years * 1.012 [if female], where Scr = serum creatinine in mg/dL, K = 0.7 (females) or 0.9 (males), α = -0.241 (females) or -0.302 (males), min (standardized Scr/K,1) = the minimum of Scr/K or 1 and max (standardized Scr/K,1) = the maximum of Scr/K or 1 [7].

Statistical analysis

Statistical analysis was performed using GraphPad Prism Software version 10.4.0. The magnitude of the reduction in cardiovascular risk by achieving a target HbA1c and target LDLc was calculated as the difference between the cardiovascular risk upon achieving the desired target and the initial cardiovascular risk. Data is presented as means±standard error of the mean (continuous variables with Gaussian distribution), medians (continuous variables with non-parametric distribution) and Spearmen correlation coefficient was used to assess potential factors that may contribute to improving cardiovascular risk. The Wilcoxon test was used for matched pairs of data, and the Mann-Whitney test for unmatched pairs. The threshold for statistical significance in this study was a p-value under 0.05.

Results

This study encompassed 38 patients with T1DM, of whom 57.9% (22) were female and 42.1% (16) male. Patients were screened for microvascular complications of type 1 diabetes and evaluated for five—and ten-year cardiovascular risk, respectively, as well as metabolic control. The general characteristics of the study population have been summarized in Table 1.

Cardiovascular risk was determined for each individual patient. Patients were categorized within 3 risk groups: high (>20%), medium (10–20%), and low (<10%), according to the probability of developing a cardiovascular event in the following 5 or 10 years, respectively. Regarding the 5-year cardiovascular risk, most patients, 47.37%, were at medium risk of developing a cardiovascular event, while 18.42% were at low risk and 34.21% were in the high-risk category. Looking at

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Table 1: General characteristics of the study population.

Variable	Men		Women		p*
	N	Median	N	Median	
Age (years)	16	57.5	22	63	ns
Duration of diabetes (years)	16	17.5	22	8.5	ns
BMI (kg/m²)	16	31.1	22	31.12	ns
HbA1c (%)	16	8.6	22	8	ns
LDL (mg/dl)	16	84.5	22	90	ns
eGFR (ml/min/1.73 m²)	16	90.5	22	76.5	ns
UACR (mg/g)	16	22.45	22	22.55	ns

Note: * – Mann–Whitney test was performed between the two groups.

the 10-year cardiovascular risk, most patients (78.38%) were at high risk of suffering a cardiovascular event, while 13.51% were at medium and 8.11% at low cardiovascular risk, respectively. This data has been summarized in Figure 1.

Glycemic control was evaluated using HbA1c. Only 21.05% of patients reached a target HbA1c of under 7%, while most patients (78.95%) had poor glycemic control. Moreover, it must be noted that only 14 study participants were statin users (13 atorvastatin users and

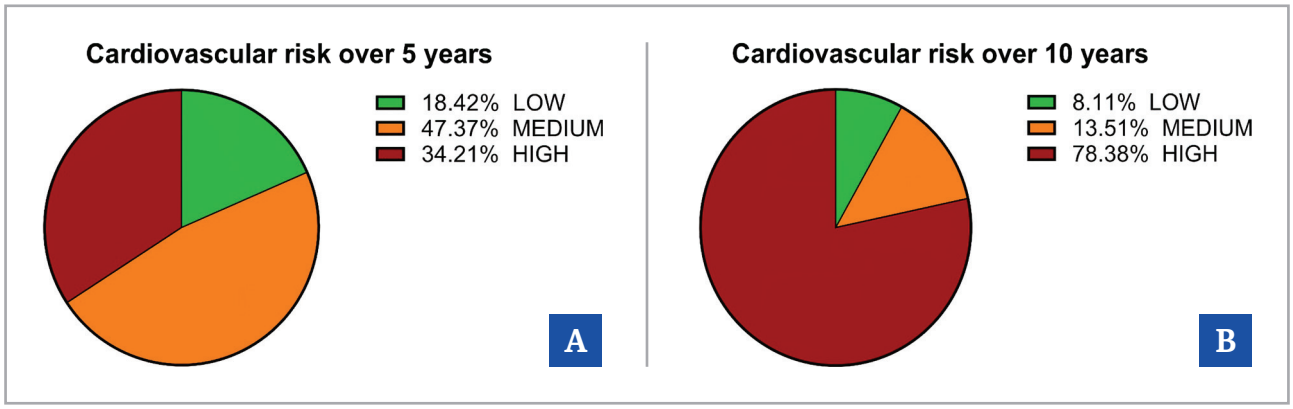

Figure 1: Cardiovascular risk within the study group. A – Risk of developing a cardiovascular event over the next 5 years. B – Risk of developing a cardiovascular event over the next 10 years. Red – high (>20%), orange – medium (10–20%), and green – low (<10%), according to the probability of developing a cardiovascular event in the following 5 or 10 years, respectively. Data is expressed as % of the total number of cases.

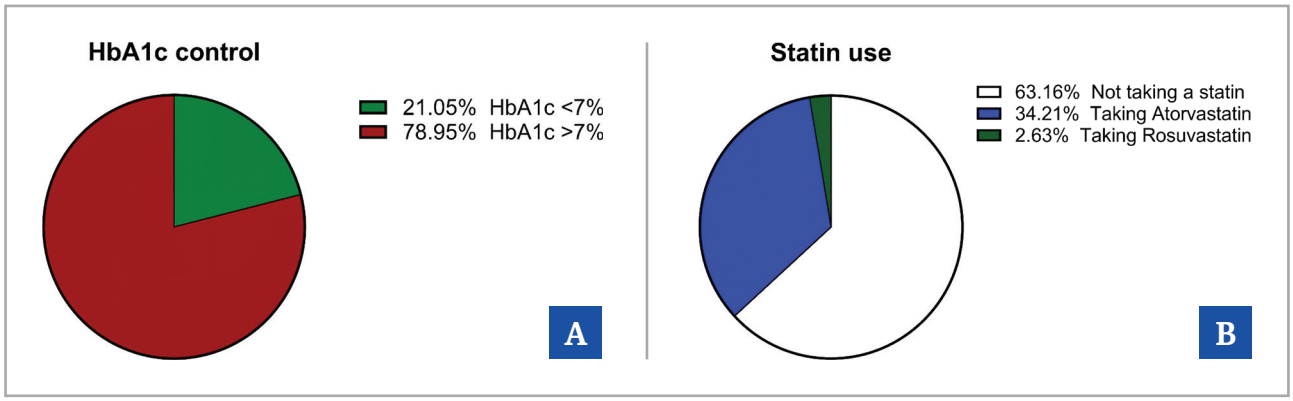

Figure 2: Glycemic control and statin use. A – HbA1c control within the study group; green – HbA1c under 7%; red – HbA1c over 7%. B – Statin use within the study group: white – not taking a statin; blue – taking atorvastatin; green – taking rosuvastatin.

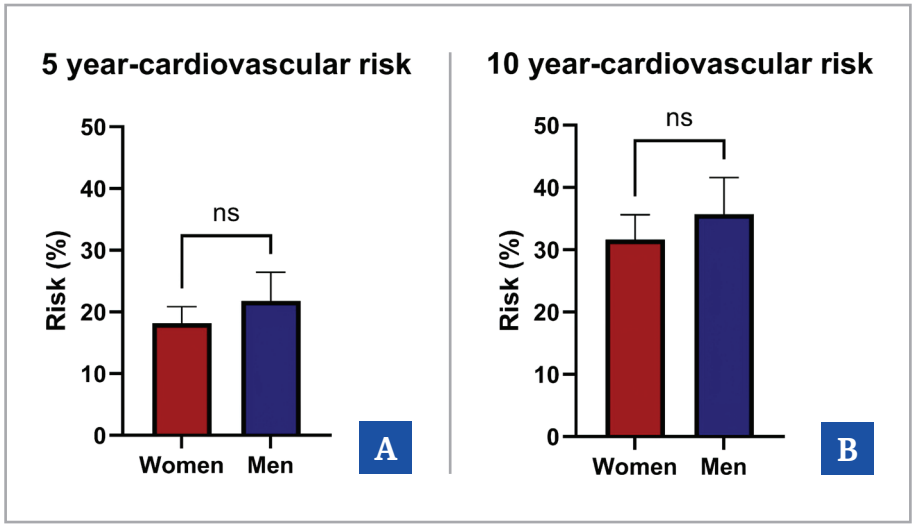

Figure 3: Cardiovascular risk in men *vs*. women. A – 5-year risk of developing a cardiovascular event. B – 10-year risk of developing a cardiovascular event. Data is expressed as mean±SEM; red – women; blue – men; Mann-Whitney test was performed between the two groups; ns – no significance.

1 rosuvastatin user), while the other 24 participants (63.16%) did not take a statin (Figure 2).

Five- and ten-year cardiovascular risk was evaluated in both male and female participants. Men presented a higher 5-year cardiovascular risk of 21.83%±4.59 *vs*. 18.19%±2.65 as well as an increased 10-year cardiovascular risk of 35.73%±5.86 *vs*. 31.63%±4, but there was no significance between the two groups (Figure 3).

Seeing as glycemic control is an essential component in the management of T1DM, and in the prevention of complications, we calculated the magnitude of reduction in cardiovascular risk (5 and 10-year respectively) determined by achieving an HbA1c of under 7%. This resulted in a mean reduction of 3.06±0.53 percentage points of the 5-year cardiovascular risk and a reduction of 4.76±0.81 percentage points of the 10-year

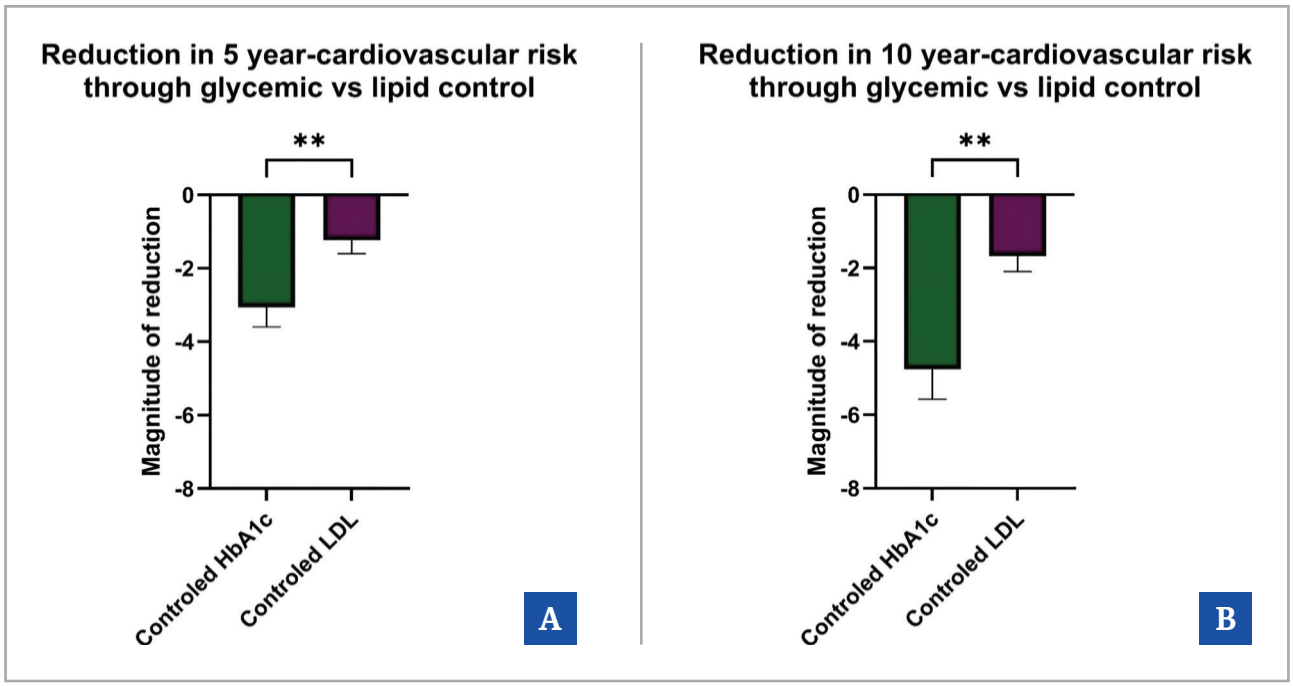

Figure 4: Reduction of cardiovascular risk through glycemic *vs*. lipid control reduction of 5-year (A) and 10-year (B) risk of developing a cardiovascular event by having a HbA1c<7% *vs*. having a target LDL value according to the respective risk category. Data is expressed as mean±SEM; Wilcoxon test was performed between the two groups; **p<0.01, green – controlled HbA1c, purple – LDL within target.

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risk respectively. Spearmen's correlation was used to show that the higher the patients' HbA1c, the greater the magnitude of reduction in cardiovascular risk (both 5-year and 10-year), determined by reaching an HbA1c<7% (p<0.0001). The magnitude of reduction in cardiovascular risk determined by achieving target values for LDLc was also determined, however it has shown a milder reduction in this risk as compared to achieving a target glucose control (p<0.01). These results have been expressed in Figure 4.

Taking into account the known differences in cardiovascular risk between the two genders we also aimed to evaluate whether glucose or lipid control would have a different impact in reducing cardiovascular risk in the two genders. These findings have been summarized in Figure 5.

Discussion

There are limited prediction models for cardiovascular disease in people with T1DM. Steno T1 Risk Engine was created to help clinicians make decisions regarding the primary prevention in patients with

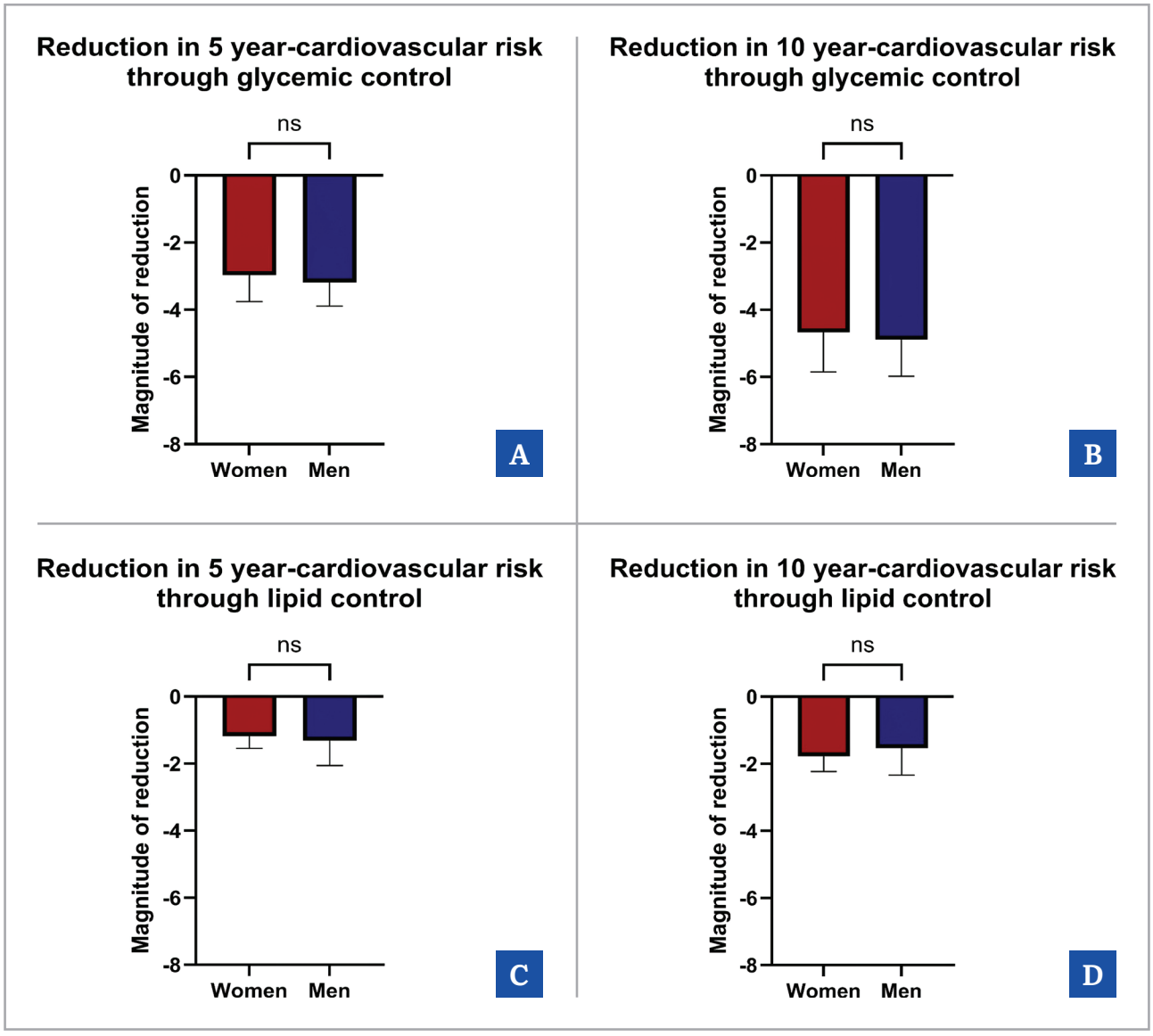

Figure 5: Reduction of cardiovascular risk through metabolic control in men vs women. A – reduction of the 5-year risk of developing a cardiovascular event by having an HbA1c<7%. B – reduction of 10-year risk of developing a cardiovascular event by having a HbA1c<7%. C – reduction of the 5-year risk of developing a cardiovascular event by having an LDLc in target according to the respective risk category. D – reduction of 10-year risk of developing a cardiovascular event by having a LDLc in target according to the respective risk category. Data is expressed as mean±SEM; red – women; blue – men; Mann-Whitney test was performed between the two groups; ns – no significance.

T1DM [8]. Additionally, a prior study demonstrated that the prevalence of long-term microvascular complications of diabetes, including somatic or autonomic neuropathy and retinopathy, gradually rises throughout the Steno T1 Risk Engine categories [9]. In the current study, most patients were in the medium 5-year cardiovascular risk category, while, regarding the 10-year cardiovascular risk, most were in the high-risk category. However, because Steno T1 Risk Engine was created and validated in a group with 90% Danish ancestry in the derivation cohort, its applicability in other populations is still unknown, and prediction models created for one community might not correctly estimate the risk in another [10].

In patients with T1DM, LDLc is a strong predictor of cardiovascular events and mortality; an increase of 1 mmol/l (38.7 mg/dl) in LDLc is linked to a 35–50% higher risk [11]. Young persons with T1D often have LDLc levels that are comparable to or slightly more elevated than those of the control group; those with HbA1c above 7.5% had higher LDLc values [12]. Further research has demonstrated that among people with T1DM, primary prevention with lipid-lowering drugs lowers cardiovascular and all-cause mortality, cardiovascular disease, stroke and acute myocardial infarction [11]. In our study, controlling LDLc did indeed lower cardiovascular risk, however, the magnitude of the reduction was higher by controlling HbA1c, as seen in Figure 4. Similarly, according to the DCCT/EDIC study, mean HbA1c at follow-up was significantly and independently linked to either major acute cardiovascular events (MACE) or cardiovascular disease, and for every 1% increase in HbA1c, MACE increased by 42% [13].

Cardiovascular morbidity and mortality have a lower prevalence in the female gender, mainly due to the natural hormonal differences between men and women [14]. In our study, we have found no difference in cardiovascular risk between male and female patients with T1DM, which would suggest that in this particular category of patients, the female gender no longer benefits from their "natural cardiovascular protection". Other authors have also suggested that women have a higher cardiovascular risk than men when diabetes is present [14, 15]. This is most probably the explanation for why we have found no differences between the two genders when evaluating the magnitude of cardiovascular risk reduction by achieving adequate metabolic control (Figure 5).

A limitation of this study is the fact that it is a preliminary study with a limited number of patients, and it should be expanded in order to validate Steno T1 Risk Engine for Romania's population. However, the study group was limited due to the lower prevalence of T1DM in Romania compared to Denmark or Sweden [16].

Conclusion

Improving glucose and lipid control by achieving and maintaining the target for HbA1c and LDLc, respectively, reduces cardiovascular risk, with the former having a greater magnitude to the impact.

Conflict of interest

The authors declare no conflict of interest.

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