Assessment of cardiovascular morbidity and mortality of Hungarian patients with Type 2 diabetes

PhD thesis

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List of abbreviations

AMI	Acute myocardial infarction
CI	Confidence Interval
CV	Cardiovascular
CVD	Cardiovascular disease
HR	Hazard Ratio
NEAK	National Health Insurance Fund
T2DM	Type 2 Diabetes
T1DM	Type 1 Diabetes
OAD	Oral antidiabetics
MI	Myocardial infarction
IDF	International Diabetes Federation
HDL	High density lipoprotein
LDL	Low density lipoprotein
NO	nitrogen-monoxid
DAN	diabetic autonomous neuropathy
IRAS	Insulin Resistance Atherosclerosis Study
TNF-α	tumor-necrosis-factor alfa
ROS	reactive oxygen species
PAI-1	plasminogen activator inhibitor-1
MRR	mortality rate ratio
SMR	standardized mortality ratio

1. Introduction

Type 2 diabetes (T2DM) is one of the most significant public health problem in modern societies, having leading position among the diseases of civilization (1). In recent decades, the prevalence of diabetes has continued to rise worldwide, approaching 10% in some countries. Diabetes was estimated 60 million European adults in 2017. According to an analysis by the International Diabetes Federation (IDF) by 2045 there will be more than 600 million patients with diabetes worldwide and about the same number of pre-diabetic people are predicted (2). In the absence of a diabetes registry, there is no accurate survey of the prevalence of adult-onset diabetes in Hungary; however, based on global trends and prevalence data from neighbouring countries, the incidence of diabetes was previously estimated at 6.0–7.0% (3). Based on the results of a representative screening study, a prevalence of 7.47% was found for the entire population of 20-69 age of years (4). According to a NEAK database research, the number of diabetics receiving treatment between 2001 and 2016 increased from 422.707 persons per year to 743.797 persons/year and similar rise was found in this 16 years timeframe in the crude prevalence from 5,29%-to 9,30% (5). The standardized prevalence rate was 4949,9 per 100.000 (95%CI: 4935,0–4964,9/100.000) in 2001, which increased to 8135,3/100.000 persons (95%CI:8116,7–8153,8/100.000) in 2011 and decreased moderately in the following years (1). During the same period the incidence of T2DM decreased from 76,645 persons to 29,122 persons between 2001 and 2016. (1)

Cardiovascular morbidity in T2DM

The increase in the number of diabetics is accompanied by an increase in the morbidity and mortality as a consequence of the disease. These includes

cardiovascular diseases such as myocardial infarct (MI) and ischemic stroke, which largely contributes to worldwide health problem caused by cardiovascular morbidity and mortality. A meta-analysis of 102 prospective studies by the Emerging Risk Factor Collaboration has shown that diabetes doubles the odds ratio for cardiovascular events (6).

The pathophysiology of the relationship between diabetes and cardiovascular disease (CVD) is complex. The long-term presence of T2DM leads to the damage of micro- and macrovasculature, besides the inflammation, activated leukocyte reaction, oxidative stress and hypercoagulability contributes to the development of cardiovascular complications.

The role of diabetes in the development of macrovascular complications

Diabetes plays a significant role in the development of atherosclerosis. Dyslipidemia is one of the major causes of atherosclerosis that is found in the majority of diabetic patients (up to 97%) (7). In diabetes, blood triglyceride levels increase and HDL cholesterol levels decrease, but there is also a change in the levels of different types of LDL cholesterol. In diabetes, the dominant form of LDL-cholesterol is small dense LDL (8). A small dense LDL-particles have more prominent atherogenic effect than bigger LDL-particles, as they penetrate more easily the endothelium, and able to bind stronger to the arteries, and also more prone to oxidation (9). Oxidized LDL is pro-atherogenic. As soon as the particles are oxidized, the immune system recognizes them as "foreign", thus oxidized LDL attracts leukocytes to the vascular wall, increases the lipid uptake of white blood cells that leads to the formation of foam cells. It also stimulates the proliferation of white blood cells, endothelial cells, and smooth muscle cells, which are the steps that results in the formation of the

atherosclerotic plaques (10). In diabetes, LDL-particles are also glycated, which prolongs their half-life (11), therefore this process also leads to the development of atherosclerosis. In contrast, glycation of HDL–particles shortens their half-life, therefore their antiatherosclerotic, protective function is decreased (12).

In addition, triglyceride level is also elevated in diabetic patients, which leads to hypertriglyceridemia (13). Hypertriglyceridemia increases the level of small dense LDL-cholesterol and lowers HDL-cholesterol transport to the liver (14).

In the natural course of diabetes, through the mechanisms mentioned above, the process of atherosclerosis is accelerated and all this leads to the development of macrovascular complications.

2. Objectives

The goal of our first investigation was to define the excess risk of mortality, stroke and myocardial infract in patients with new onset of T2DM between January 2010 and 31 December, 2013 in Hungary compared to control non-diabetic patients matched according to age, gender, and zip code of residence. We also analysed a subgroup of patients according to age decades and sex for outcome analyses. The results were assessed in terms of the results of studies with similar methods available in international literatures.

The aim of our second research was to compare changes of risks for stroke and myocardial infarction in patients with type 2 diabetes in Hungary between the two periods of 2001–2004 and 2010–2013.

3. Methods and statistical analysis

The Hungarian National Health Insurance Fund (NHIF - NEAK) has a large, centralized electronic database available for research that contains prescription data of all reimbursed medicinal products and in- and outpatient care data for all Hungarian patients. Data is collected at an individual level for each patients who has social security identification number (TAJ), therefore insured persons have data linked to their social security identification number and date, which make it possible to follow certain illnesses, their interventions in outpatient and inpatient care, and reimbursed therapies. NHIF provides the research data in an aggregated, anonymous format.

The NHIF database was available January 1, 2000 to October 31, 2014 to conduct our study. Those T2DM patients were included into our retrospective cohort study, who received anti-diabetic therapy for the first time during this period. Patients on antidiabetic treatment (ATC A10) who did not meet the criteria for T1DM were considered to be T2DM patients. Coding of T1DM was not always coherent in the documentation, therefore we developed a hierarchical system to identify T1DM, and T2DM patients were identified if they did not meet the T1DM disease criteria.

In our first research, we focused on patients with new onset of diabetes in order to investigate the effect of diabetes on cardiovascular morbidity and mortality. The onset date of diabetes was either the first occurrence of the diabetes BNO code (E10-E14) or the date of the first antidiabetic treatment, whichever was recorded earlier. The combination of these two parameters guaranteed that all Hungarian T2DM patients will be enrolled into the research.

First research work - methodology established to measure the excess cardiovascular risk of T2DM patients

Patients diagnosed between 1 January 2010 and 31 December 2013 (n= 152,678) formed the baseline population. Only those patients were included in the analysis, who matched the enrolment criteria only between 01-01-2010 and 31-12-2013, but not before. The control population (n = 305 356) was randomly selected from NHIF database from age, sex and residence-matched non-diabetic population so that each diabetic patient had two matching control at the time of diagnosis.

NHIF data source included information on overall mortality, cardiovascular complications of diabetes diagnosed in outpatient or inpatient care, such as acute myocardial infarction (ICD I21-24) ischemic or hemorragic stroke (ICD I61-63, G4630, G4640, G4580, G4590). Cause of death is not recorded in NHIF database, therefore all-cause mortality data has been analysed.

The incidence of myocardial infarction, stroke, and all-cause mortality was followed for a total of 58 months from January 1, 2010 to October 31, 2014 in both the newly diagnosed T2DM patients and the control group. We then compared the survival of the two arms.

Second research work – methodology established to measure changes of cardiovascular risk in T2DM patients

New onset of type 2 diabetic patients in 2 timeframes were compared to each other:

1) incident patients between 1 January 2010 and 31 December 2013. (n=152 678)

2) incident patients between 1 January 2001 and 31 December a 2004. (n=274 109).

The incidence of cardiovascular events and mortality in the two T2DM populations was examined at 48 months post-diagnosis.

In both timeframes we created subgroups for outcome analysis based on age at diagnosis in 10 years cohorts, and by sex.

The study was approved by the Regional Research and Ethics Committee of the Medical Faculty of University of Pécs (study approval number: 6962/2017). The study protocol was also reviewed and approved by the National Health Insurance Fund (NEAK identification number: S04 / 161/2016).

Statistical analysis

In the first research survival analysis was conducted with Cox -regression analysis, adjusted for age and sex. According to literature data, the risk of death is higher in the first four months after the diagnosis of diabetes and the risk of stroke and myocardial infarction within the first month, therefore we separated the initial effects from the long-term effects using a dummy – variable. Simultaneous confidence intervals were calculated using contrast- matrix. Mean age and follow-up time were compared using Welch's two-sample t-test. The incidence of infarction or stroke was compared using chi-square test. The analysis was performed with R-statistical software 3.4.2 (2017-09-28) version with survival - , survminer – and the multcomp add-ins.

In our second research Cox -regression model was used to define risk of death, MI, and stroke among newly diagnosed patients in the 2 periods between 2001-2004 and 2010-2013. The model was adjusted for baseline differences between gender and age group. Because the proportional risk assumption was not satisfactory in the model, we used a time-dependent covariance: the model included a linear function of

the onset of diabetes in the 2010–2013 group. In this case, a Cox - model estimates that the risk ratio is a function of the time constant.

The main advantage of this statistical approach is that we are able to estimate such differences in risk at any point of patient-life from diagnosis comparing the periods of 2010-2013 to 2001-2004. Therefore, we are able to evaluate the risk around diagnosis-time, as well. Additionally, if we compare the same time points of the later phase of complications of diabetes, we are able to estimate the impact of diabetes care during a decade.

Although the MI time dependency was not significant, we were including it into the model to show the mild observed changes.

Data were available for our analysis October 31, 2014 as a follow-up period. We followed the patients from diagnosis to the event or death or till the end of a 48 months long follow-up period.

The risk at first month was much higher, probably because diabetes has been diagnosed just at the occurrence of the event. To eliminate the possible bias we started the follow-up after the first month from the diagnosis.

The analysis was performed with the use of R Software, version 3.4.2 (2017-09-28) - R Core Team (2017). R Foundation for Statistical Computing, Vienna, Austria.

4. Results

4.1 First study part – Number and characteristics of Hungarian T2DM patients

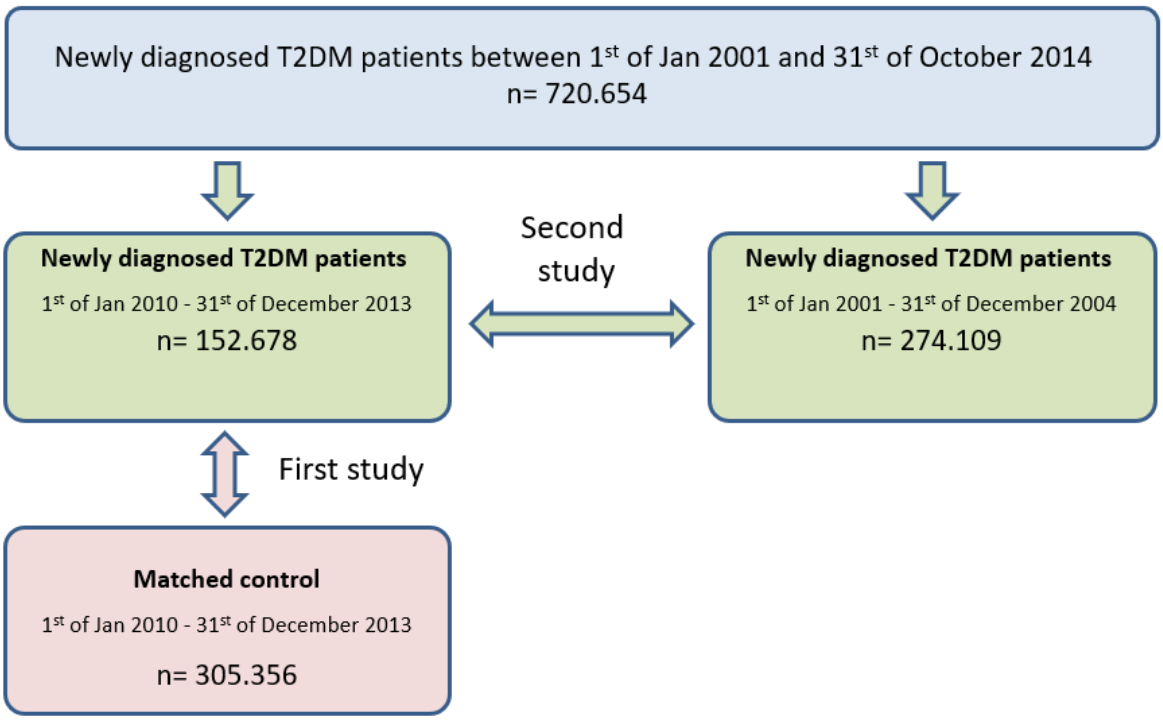


Figure 1 Design of the study

Based on the inclusion and exclusion criteria detailed in the methodology, a total of 720,654 T2DM patients were diagnosed in the NEAK(NHIF) database between 1 January 2001 and 31 October 2014 and were not in this database between 1 January and 31 December 2000, hence could be considered as a newly diagnosed T2DM patient (Fig. 1). Our first study was based on the 152,678 individuals diagnosed with diabetes between 1 January 2010 and 31 December 2013.

Age	2001-2004 T2DM patients				2010-2013 T2DM patients				2010-2013 Matched Control			
	Total	Male	Female	% of female	**Total**	Male	Female	% of female	**Total**	Male	Female	% of female
0-18	**583**	175	408	69.98%	**394**	78	316	80.20%	**788**	156	632	80.20%
19-30	**3,088**	1,379	1,709	55.34%	**2,852**	702	2,150	75.39%	**5,704**	1,404	4,300	75.39%
31-40	**12,215**	6,881	5,334	43.67%	**8,621**	4,707	3,914	45.40%	**17,242**	9,414	7,828	45.40%
41-50	**51,583**	28,767	22,816	44.23%	**21,827**	13,345	8,482	38.86%	**43,654**	26,690	16,964	38.86%
51-60	**79,821**	39,204	40,617	50.89%	**46,659**	24,422	22,237	47.66%	**93,318**	48,844	44,474	47.66%
61-70	**72,044**	31,555	40,489	56.20%	**42,243**	19,738	22,505	53.28%	**84,486**	39,476	45,010	53.28%
70<	**54,775**	20,433	34,342	62.70%	**30,082**	10,448	19,634	65.27%	**60,164**	20,896	39,268	65.27%
Total	**274,109**	**128,394**	**145,715**	**53.16%**	**152,678**	**73,440**	**79,238**	**51.90%**	**305,356**	**146,880**	**158,476**	**51.90%**

Table 1 Age and gender distribution of studied patient population (not published table)

Matched control for the established base population had double the size, 305.356 persons. Share of females was 51.9% in both population (table 1), higher between age of 30 and 70-year-old.

In the second phase of the research, the baseline group is the same as the group of T2DM patients in the first phase (January 31, 2010 - December 31, 2013 n = 152,678). T2DM patients diagnosed between January 1, 2001 and December 31, 2004 were compared to this group. Size of population in this group was 274,109, of which 53.16% were women. The highest proportions of women were in the 0-18 and 70 <age groups (69.9% and 62.7%, respectively).

According to Figure 2, more than half of the study populations were in the 51-60 and 61-70 age groups (29.12% and 26.28% and 30.56% and 27.67%, respectively). However, the 41-50 age subgroup of the 2001-2004 T2DM population is significantly higher than that of the 2010-2013 population (18.82% and 14.30%, respectively).

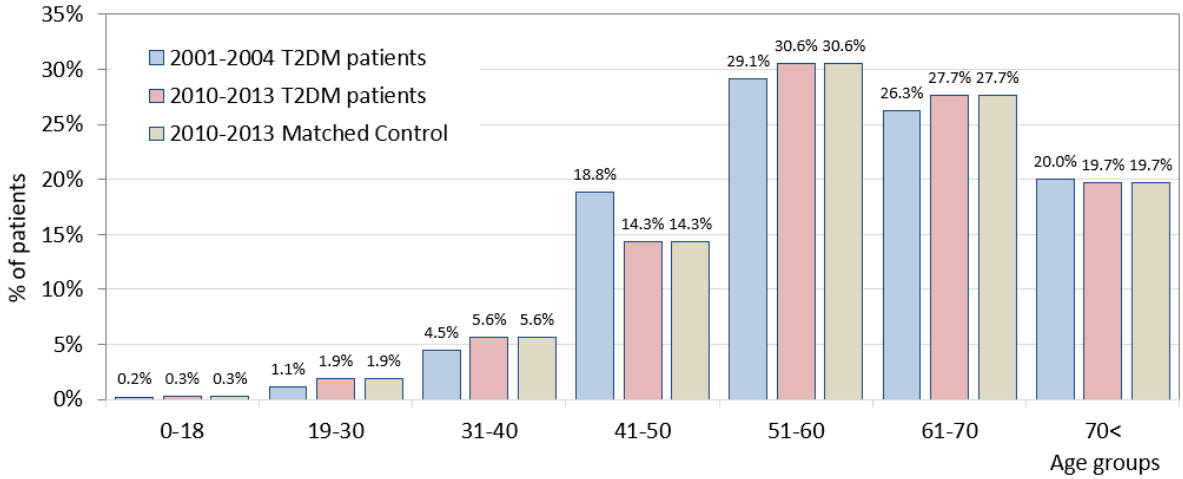


Figure 2 Age distribution of studied patient population in different arm of the study

4.2 Analysing the excess risk of T2DM population

4.2.1 First study phase: Risk of T2DM patients diagnosed between 2010-2013 (71)

T2DM patients diagnosed between January 1, 2010 and December 31, 2013 were matched to two controls of the same age, sex, and address of residence, and then their survival was assessed for 58 months. The characteristics of the two populations in our comparative study are presented in **Table 2** in detail.

	T2DM	Control	p value
Population (n)	152,678	305,356	
Age (years)	59.43 (59.4–59.5)	59.43 (59.3–59.4)	1
Female-no. (%)	79,238 (51.9)	158,476 (51.9)	1
Age (years—95% CI)	60.89 (60.8–61.0)	60.89 (60.8–61.0)	1
Male—no. (%)	73,440 (48.1)	146,880 (48.1)	1
Age (years—95% CI)	57.9 (57.8–57.9)	57.9 (57.8–57.9)	1
Year of diagnosis (range)	2010–2013	2010–2013	
Mean follow-up (year—95% CI)	2.3 (2.3–2.3)	2.4 (2.4–2.4)	< 0.0001

2. Table Patient characteristics of T2DM patients diagnosed between 2010 and 2013 and of their contor population (15)

The mean age of 152,678 T2DM patients was 59.43 (SD 59.4) years, which was found to be the same in the control group (n = 305,356) (p = 1.00). 51.9% of the patients were women whose mean age at diagnosis was higher, 60.89 (60.8) years, than that of men (57.9 years; 57.8).

Mortality-, stroke-, and myocardial infarction-free survival of patients were followed for an average of 2.3 years in the T2DM group and 2.4 years in the control group.

There is an initial drop in survival of the T2DM group (**Fig. 3**). The 12-month event-free survival was 96.36%. In contrast, the survival of the control group during this period was 97.74%. The absolute difference between the two curves at month 12 was 1.37% and the relative risk difference was 37.74% ($p < 0.0001$) at the end of the first follow-up year (higher in T2DM group). The relative risk differences in mortality at the end of the second, third, and fourth years were less, 27.89%, 24.78%, and 22.66%, respectively (p in all three cases <0.001; also higher in T2DM group). By the end of the fourth year, 2.54% more T2DM patients died than non-diabetic controls. The hazard ratio (HR) calculated over the entire follow-up period was 1.26 (95% CI: 1.22-1.29; $p < 0.0001$).

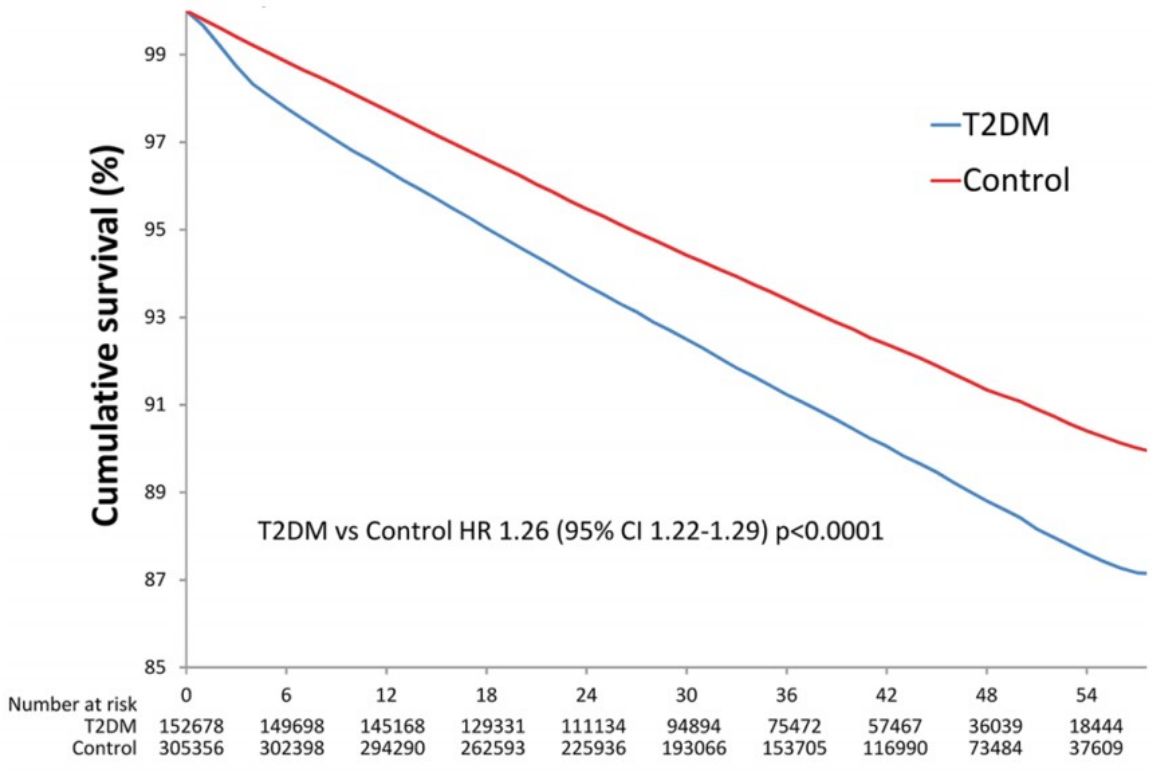


Figure 3 Mortality-free survival of T2DM patients diagnosed between 2010 and 2013 compared to matched control

Myocardial infarction-free survival in the diabetic group dropped to 99.14% in the first month (**Fig 4**), while in the control group, 99.96% of the subjects survived without MI, consequently, the time of myocardial infarction was at the same time of diagnosis of T2DM. At the end of the first year, there were 1.07% more T2DM patients with myocardial infarction than in the control group, the relative risk difference was 79.61% (p <0.001; higher in T2DM group), which was 61.06% by the end of the fourth year. The hazard ratio (HR) for the total period was 1.81 (95% CI: 1.69-1.94; p <0.0001). The risk of stroke in the first month after diagnosis - similarly to MI in the diabetic arm - occurred in 1.79% of patients compared to only 0.28% in the control group (**Fig. 5**). The relative risk difference was 57.65% in the first year, 49.20% at the end of second, 43.70% at the end of third and finally 41.11% in the fourth year (p

in all cases <0.001; higher in T2DM group). The hazard ratio for the whole period was 1.40 (95% CI: 1.35-1.46; p <0.0001).

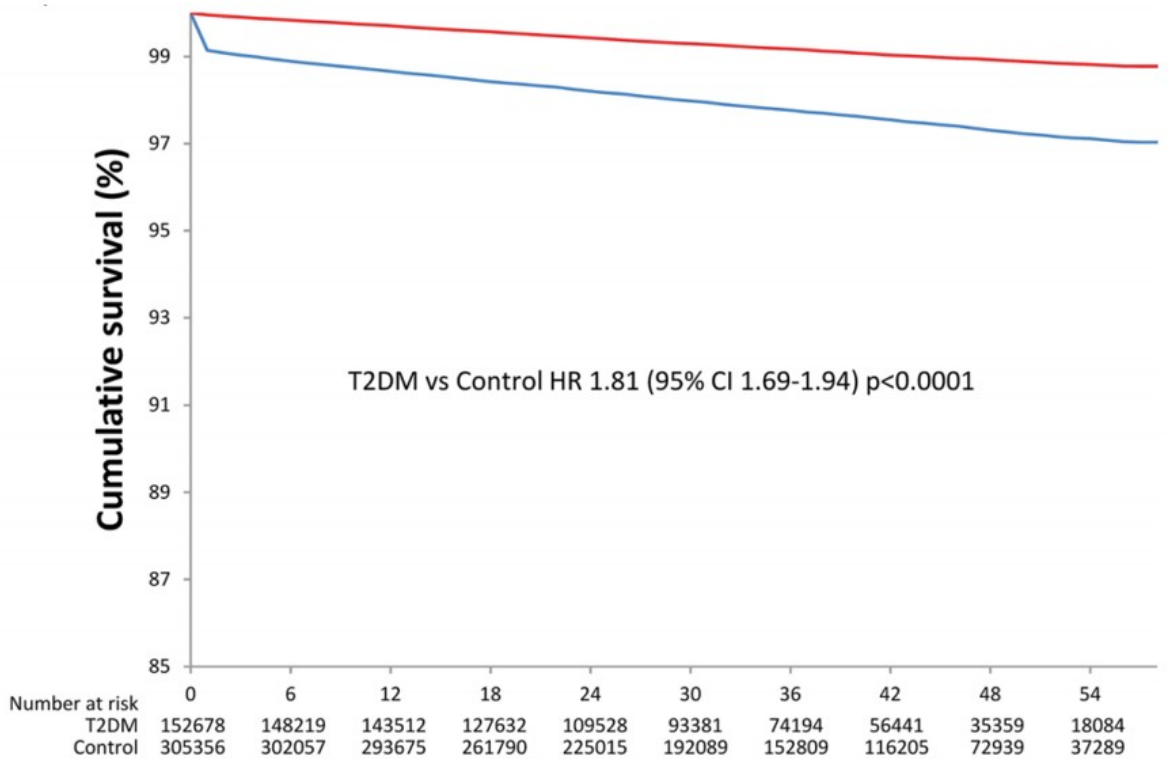


Figure 4 Myocardial infarction free survival of T2DM patients diagnosed between 2010 and 2013 compared to matched control

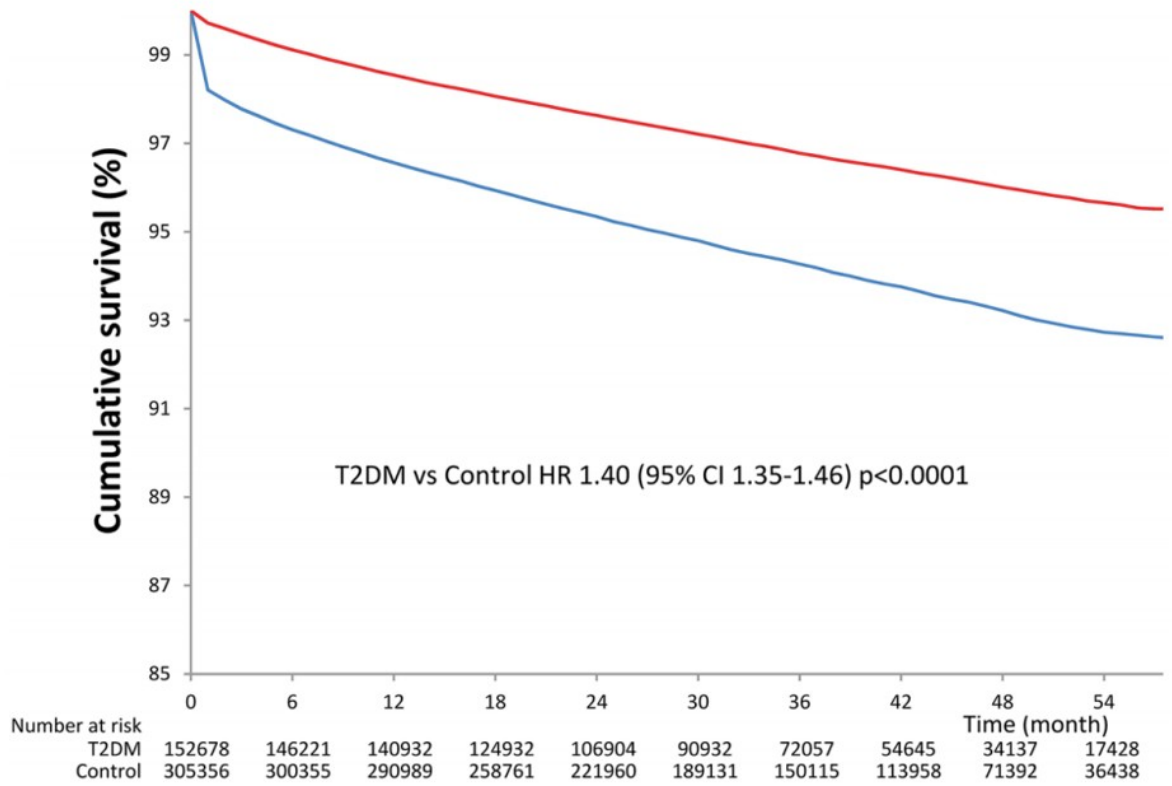


Figure 5 Stroke free survival of T2DM patients diagnosed between 2010 and 2013 compared to matched control

4.2.2. Results according to age group

Age-dependent change of mortality and cardiovascular risk is detailed in **Figure 6**. The hazard ratio for mortality was 1.29 over 70 years (95% CI: 1.14-1.26; p <0.0001), while between 61-70 and 51-60 years it was 1.20 and 1.22 (p in both cases <0.0001). HR increased to 1.48 and 1.98 in the 40s and 30s (p values <0.0001 and = 0.0002). Interaction analysis was significant in terms of age dependence of mortality risk (p = 0.01).

Patients with T2DM also had increasing risk of myocardial infarction and stroke with decreasing age: in those aged 31-40 years, the HR was 3.50 (CI 95%: 1.70-7.23; p = 0.0002), while the stroke was 4.64 (CI 95%: 2.55-8.45; p <0.0001). The same risks over 70 year were 1.78 (CI 95%: 1.59-2.00; p <0.0001) and 1.31 (95% CI: 1.24-1.39;

p <0.0001). P-interaction tests showed a significant correlation of age with respect to myocardial infarction and stroke (p-interaction = 0.003 and <0.0001)

T2DM vs Control	Number of population			Number of events			Hazard ratio (95% CI)	p value
Mortality	**T2DM**		**Control**	**T2DM**		**Control**		
71 and over	30 082	vs.	60 164	6 753	vs.	9 875	1.29(1.24-1.34)	p<0.0001
61-70	42 243	vs.	84 486	3 571	vs.	5 716	1.20(1.14-1.26)	p<0.0001
51-60	46 659	vs.	93 318	2 379	vs.	3 699	1.22(1.14-1.30)	p<0.0001
41-50	21 827	vs.	43 654	621	vs.	783	1.48(1.30-1.69)	p<0.0001
31-40	8 621	vs.	17 242	85	vs.	70	1.98(1.34-2.92)	p=0.0002
19-30	2 852	vs.	5 704	6	vs.	10	1.20(0.44-3.30)	p=0.725
Total	152 678	vs.	305 356	13 417	vs.	20 154	1.26(1.22-1.29)	p<0.0001
Interaction								p=0.01
Myocardial Infarction	**T2DM**		**Control**	**T2DM**		**Control**		
71 and over	30 082	vs.	60 164	1 041	vs.	872	1.78(1.59-2.00)	p<0.0001
61-70	42 243	vs.	84 486	948	vs.	763	1.57(1.39-1.79)	p<0.0001
51-60	46 659	vs.	93 318	922	vs.	628	1.85(1.62-2.11)	p<0.0001
41-50	21 827	vs.	43 654	360	vs.	162	2.76(2.16-3.52)	p<0.0001
31-40	8 621	vs.	17 242	55	vs.	16	3.50(1.70-7.23)	p=0.0002
19-30	2 852	vs.	5 704	4	vs.	1	8.02(0.90-71.71)	p=0.0627
Total	152 678	vs.	305 356	3 330	vs.	2 442	1.81(1.69-1.94)	p<0.0001
Interaction								p=0.003
Stroke	**T2DM**		**Control**	**T2DM**		**Control**		
71 and over	30 082	vs.	60 164	3 326	vs.	4 220	1.31(1.24-1.39)	p<0.0001
61-70	42 243	vs.	84 486	2 707	vs.	3 114	1.30(1.21-1.39)	p<0.0001
51-60	46 659	vs.	93 318	1 958	vs.	1 799	1.62(1.49-1.76)	p<0.0001
41-50	21 827	vs.	43 654	440	vs.	319	2.12(1.77-2.55)	p<0.0001
31-40	8 621	vs.	17 242	68	vs.	21	4.64(2.55-8.45)	p<0.0001
19-30	2 852	vs.	5 704	3	vs.	2	3.00(0.50-7.96)	p=0.229
Total	152 678	vs.	305 356	8 502	vs.	9 475	1.40(1.35-1.46)	p<0.0001
Interaction								p<0.0001

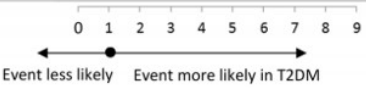
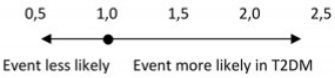


Figure 6 Mortality, Myocardial infarction and Stroke free survival by age groups of T2DM patients diagnosed between 2010 and 2013 compared to matched control (*95%CI is not presented)

4.2.3. Comparison of female and male patients

Fifty-five percent of T2DM patients were male, 48% were female. Higher rates of mortality and cardiovascular morbidity were found in men and women with diabetes compared to non-diabetic control group (mortality rates: 9.2% and 8.5%, myocardial infarction 2.8% and 1.6%, stroke 5.7% and 5.5%). The mortality and cardiovascular risk of the T2DM population compared to the control group were significantly higher in both sexes (Fig. 7). Interaction analysis showed a higher effect of T2DM on mortality and stroke risk in females than in males, whereas this sex difference was not detectable in myocardial infarction.

Male vs Female	Number of population			Number of events			Hazard ratio (95% CI)	Interaction p value
Mortality	**T2DM**		**Control**	**T2DM**		**Control**		
Male	73 440	vs.	146 880	6 725	vs.	10 905	1.17(1.12-1.21)	p<0.000
Female	79 238	vs.	158 476	6 692	vs.	9 249	1.37(1.31-1.42)	
Myocardial infarction								
Male	73 440	vs.	146 880	2 042	vs.	1 473	1.83(1.68 -2.00)	p=0.64
Female	79 238	vs.	158 476	1 288	vs.	969	1.77(1.59-1.98)	
Stroke								
Male	73 440	vs.	146 880	4 171	vs.	4 688	1.33(1.26-1.41)	p=0.01
Female	79 238	vs.	158 476	4 331	vs.	4 787	1.47(1.40-1-55)	



Event less likely Event more likely in T2DM

Figure 7 Mortality, Myocardial infarction and Stroke free survival by sex of T2DM patients diagnosed between 2010 and 2013 compared to matched control

4.3. Changes in cardiovascular and mortality risk in T2DM patients diagnosed between 2001-2004 and 2010-2013

Result of second study phase (16)

Patients characteristics diagnosed in the two periods (2001-2004 and 2010-2013), are presented in **Table 3**. Patients diagnosed in the two different periods differed in all parameters except the incidence of prior myocardial infarction.

	Type 2 diabetes 2001–2004	Type 2 diabetes 2010–2013	*p*-value
Population (*n*)	274.109	152.678	$p < 0.0001$
Age (years)	59.33 (±12.43)	59.43 (±2.92)	$p = 0.0088$
Female - no. (%)	145.715 (53.2)	79.238 (51.9)	$p < 0.0001$
Age (years)	60.74 (±12.61)	60.89 (±13.70)	$p = 0.0127$
Male - no. (%)	128.394 (46.8)	73.440 (48.1)	$p < 0.0001$
Age (years)	57.72 (±12.01)	57.9 (±11.82)	$p = 0.0094$
Prior Myocardial Infarction (%)	1.427 (0.5)	814 (0.5)	$p = 0.9608$
Prior Stroke (%)	2.989 (1.1)	2.599 (1.7)	$p < 0.0001$

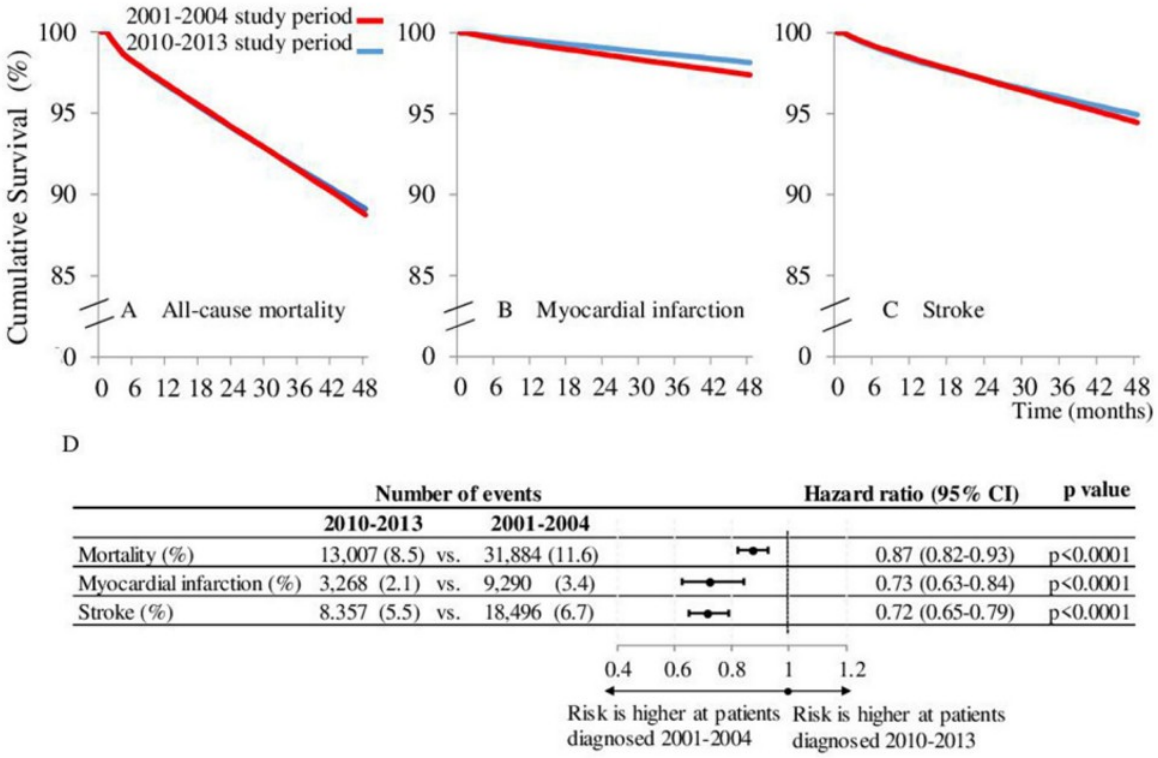
3. Table Patient characteristics of T2DM population diagnosed between 2001-2004 and 2010-2013

Between 2001 and 2004, 274,109 T2DM patients were diagnosed in Hungary who received antidiabetic therapy in the follow-up period (**Table 3**). The mean age of the patients was 59.33 years (95% CI: 59.3-59.4), 53.2% of them were female. During the period of 2010-2013, 152,238 T2DM patients were diagnosed with a mean age of 59.43 years (95% CI: 59.4–59.5). During the first period, 0.5% of new patients had a myocardial infarction in the pre-diagnosis period, 1.1% had stroke, while in the second period, these comorbidities occurred in 0.5% and 1.7% prior to diagnosis.

Among T2DM patients diagnosed between 2001 and 2004, 31,884 deaths (11.63%) were recorded during the follow-up period, while 13,007 (8.52%) deaths occurred in 152,668 patients enrolled between 2010 and 2013. At 48 months, 88.73% of the 2001-2004 arm and 89.11% of the 2010-2013 arm were alive (**Figure 8**).

Patients diagnosed between 2010 and 2013 had a 13% higher chance of survival 4 years after diagnosis (HR 0.87 95% CI 0.82-0.93; <0.0001). A total of 9,220 myocardial infarctions and 18,496 stroke events were recorded in the 2001–2004 study period, while 2,368 MI and 8,357 stroke cases were recorded in the 2010–2013 period. Myocardial infarction was diagnosed in 1.85% of patients with T2DM in the later period, at 48 months, compared with 2.61% of the population diagnosed between 2001 and 2004. Stroke was diagnosed in 5.08% (2001–2004) and 5.55% (2010-2013) of patients in the two arms of the study over 4 years.

At the end of the fourth year, the hazard ratio for myocardial infarction was 0.73 (95% CI: 0.63-0.83; p <0.0001), while the HR for stroke at month 48 was 0.72 (95% CI : 0.65-0.79; p <0.0001).



D

	Number of events			Hazard ratio (95% CI)	p value
	2010-2013		2001-2004		
Mortality (%)	13,007 (8.5)	vs.	31,884 (11.6)	0.87 (0.82-0.93)	p<0.0001
Myocardial infarction (%)	3,268 (2.1)	vs.	9,290 (3.4)	0.73 (0.63-0.84)	p<0.0001
Stroke (%)	8.357 (5.5)	vs.	18,496 (6.7)	0.72 (0.65-0.79)	p<0.0001

Figure 8 Kaplan-Meier mortality (panel A), myocardial infarction (panel B) and stroke (panel C) free survival curve compared patients diagnosed between 2010-2013 to patients diagnosed between 2001-2004 during 48 months survival period. Panel D represents the hazard ratios of the events after 48 months of the diabetes onset.

To rule out the effect of late diagnosis of diabetes in our analysis, events of the first month, i.e., mortality recorded at the time of diagnosis, myocardial infarction, and stroke events were excluded from our Cox regression analysis.

The risk ratios measured at the beginning at the and end of the study do not accurately describe the nature of the change. Therefore, data on HR values over the entire 48-month follow-up period were also presented as continuous variables on a monthly basis (**Figure 9**). We found a steady decrease in HR values of mortality and stroke over the study period, while a significantly unchanged curve was found for myocardial infarction. There was no difference in the risk of death in the second month after the onset of diabetes (HR 1.03 95%CI 0.99-1.07; p = 0.208), while HR crossed 1 value at the 8th month, similarly as in case of stroke. From the second

year, the mortality HR value of the two periods became significantly different, after 48 months of follow-up the HR value was 0.87 (95% CI 0.82-0.93; p <0.001).

In the second period (2010-2013) the risk of myocardial infarction was 37% lower than in the first (2001-2004) (HR: 0.67 95% CI 0.61-0.74; p < 0.001) and was not significantly time-dependent during the study period.

In case of stroke, the risk was higher in T2DM patients diagnosed in the period 2010–2013 (HR: 1.06 95%CI 1.00–1.12; p = 0.035), whereas by the 4-year study period this difference decreased continuously and was 32% lower at 48 months (HR: 0.72 95%CI 0.65-0.79; p <0.001). The absolute reduction in hazard ratio over the 48-month study period was 0.16 for mortality and 0.35 for stroke, both changes being significant. In the case of myocardial infarction, on the other hand, the increase in the absolute hazard ratio was 0.05, this change was not significant (p = 0.6418).

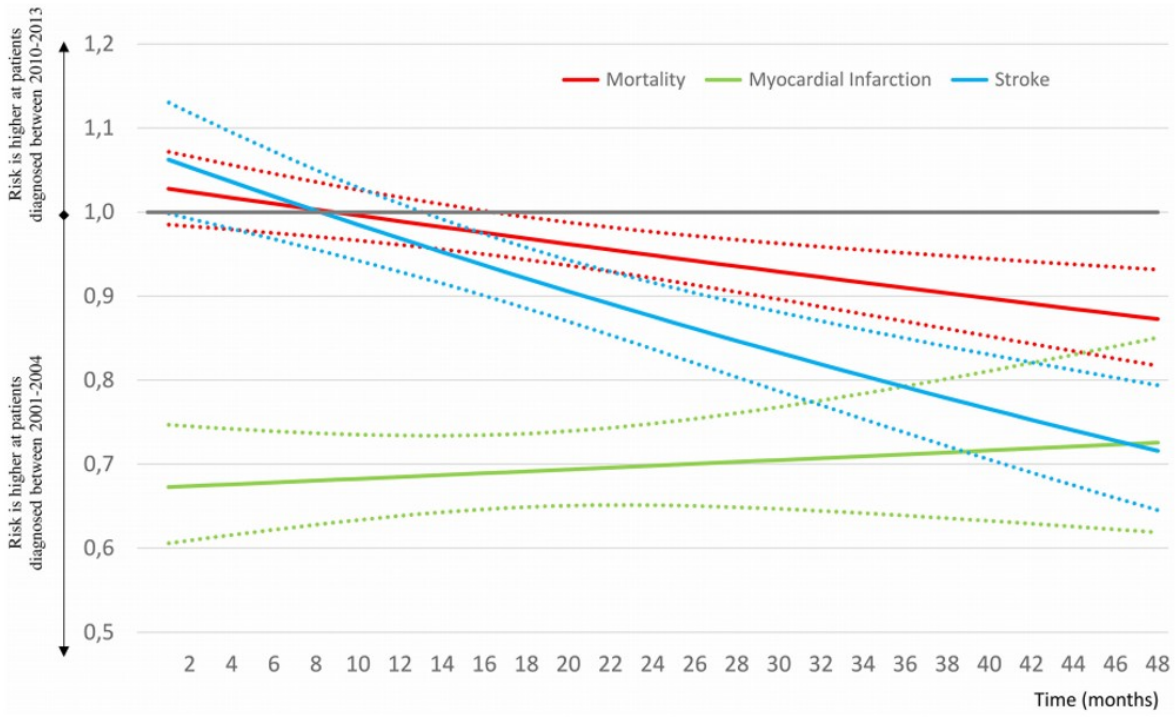


Figure 9 Changes of hazard ratios of all-cause mortality, myocardial infarction and stroke by month from diagnosis, comparing type 2 diabetes patients diagnosed during 2010-2013 vs. 2001-2004 period. The continuous lines represent the mean of HR, and the dotted lines the 95% CI values.

5. Summary of the results, importance of new results

5.1. Main results of our study

Main findings of our study are as follows:

1. The risk of myocardial infarction, stroke and mortality was significantly higher in T2DM population than in the age and gender-matched, non-diabetic control group.

2. This excess risk was age-dependent, with a greater increase in hazard ratio at younger patients than in older patients.

3. The effect of diabetes on the risk of stroke and total mortality was higher in female patients than in male. No such a sex difference was found at myocardial infarction.

4. At diagnosis of diabetes, the risk of mortality was the same in both the 2010-2013 and 2001-2004 study populations. However, during the follow-up, the risk of all deaths slowly decreased in the group of patients diagnosed between 2010 and 2014 compared to the 2001–2004 population.

6. During follow-up, stroke risk showed a rapid decrease, by the 48th month, in favor of the 2010-2013 group.

7. As expected, the risk of myocardial infarction was lower in the 2010-2013 population than in patients diagnosed between 2001 and 2004. The slope of the myocardial infarction risk curve did not change during the study period.

5.2 Discussion

5.2.1 Comparison of mortality and cardiovascular risk of Hungarian T2DM patients with international results

The excess cardiovascular and mortality risks found in our study were consistent with the results of similar studies found in the international literature, such as at Norhammar (17) and Tancredi (18) in Sweden or at Gregg (19) in the United States (20) and at Lind (21) in Canada, at the Latvian Pildava (22) or at English Zhegbi et al. (23) and at Magliano in Australia (24). The results of our study were also confirmed by a previous publication based on Hungarian data, but using a different methodology, in which Jermendy at. al compared the mortality rates of the T2DM population and non-T2DM cohorts in male and female separately (24). Comparing our results with the cited literature data, we can conclude that the excess mortality of Hungarian T2DM patients is in the same range as the international results.

There are a number of factors behind diabetic excess mortality. The majority of T2DM mortality is due to the increase of cardiovascular morbidity (26,27). Within this, myocardial infarction is one of the most common causes of cardiovascular death (28). Sharma et al. in a retrospective analysis of the TECOS study found 1,084 deaths over 3 years of the study period, 49% of this mortality was cardiovascular deaths, 31% non-cardiovascular deaths (including those of malignant tumor origin), and 20% of deaths of unknown origin (89). Within cardiovascular mortality, 21% was due to MI or stroke, 27% due to sudden cardiac death, and 12% had heart failure in cause of death.

In 2019, Sattar et al. listed the causes of T2DM mortality in the light of the control population based on the Swedish T2DM registry. The proportion of cardiovascular causes increases with age, becoming more than a 50% in the cause of diabetic mortality over the age of 90. Tumor plays a significant role in mortality in the 50-70 age group, being more significant in the 50-60 age group than cardiovascular

morbidity (29). Overall, the cardiovascular cause plays a larger role in mortality in T2DM, than in the non-diabetic population.

Thus, the increased cardiovascular risk in diabetic patients has a significant impact on mortality (30). The higher cardiovascular risk confirmed in our study also emphasise the need of effective treatment.

5.2.2. Age dependent risk of cardiovascular morbidity and mortality

Based on our study results, among young, the impact of diabetes on cardiovascular events and mortality is greater than in older age. In the 31-40 age group, the risk of mortality is 98% higher for T2DM than without it, while the same risk difference over 70 year is only 29%. The inverse increase in mortality risk with age was statistically significant (p-interaction = 0.01). The same inverse proportionality is seen for myocardial infarction and stroke (p-interaction = 0.003 and p-interaction <0.001). The age-related effect of cardiovascular risk in diabetic population has been described since two decades (31). In the Swedish T2DM registry, Sattar found 181% higher mortality in T2DM patients under 55 years, while over 75 years of age it was found to be only 25% higher (18).

The age-related impact of cardiovascular risk can be caused by the following factors. The incidence of obesity increases with age, and also increase is found in body fat ratio, especially in case of abdominal obesity, which is often associated with aging, which consequently contribute to the development of insulin resistance (32,33). Decreased insulin sensitivity in older age plays a known key role in the development of T2DM (34). Aging also correlates with a decrease in the proliferative capacity of beta cells (35), and it is also known that age-related decreases in mitochondrial

function contribute to insulin resistance in the elderly (36). Other metabolic diseases are closely associated with aging, and with coronary artery disease, cancers, Alzheimer-disease and deficiency vitamin D (37). Thus, obesity, T2DM, the incidence of cardiovascular disease, the risk of mortality increase with age, but in the presence of diabetes, these risks are inversely related to the non-T2DM population, hence, the younger the age of diabetes, the greater the cardiovascular risk of morbidity and mortality.

In a study reported by Tancredi at al., this inverse relationship was explained by a significantly higher incidence of obesity in young T2DM population (56% and 14%, respectively) (18). Sattar also highlighted the higher BMI of younger age groups at the diagnosis of T2DM (29), the poorer lipid profile, including higher triglyceride levels, but also emphasized the importance of lower socioeconomic status in the background of higher cardiovascular risk. Beside, the higher HbA_{1c} levels seen in younger diabetics could also play a role in the development of higher morbidity and mortality risk. Thus, obesity and related risk factors are more closely associated with the development of diabetes at a younger age, which in turn leads to a greater relative increase in CV risks. In a previous study based on the NEAK (NHIF) database, we also found an age-related difference in statin adherence (38).

5.2.3. Gender dependent differences in the risk of cardiovascular morbidity and mortality

Assessing the sex differences in mortality and cardiovascular morbidity within the T2DM population, we found a 41% higher risk of death in male than in female. However, T2DM patients have higher risk in both sexes than in the paired control population, but this relative increase in risk is significantly higher in women in case of

stroke and mortality. This seemingly contradictory result shows that diabetes increases the risk of death and cardiovascular events to a greater extent among females.

Tancredi (18), Magliano (39) and Tönnies (40) also found similar results to our results. In our own study, the female and male excess risk ratio (ratio of HRs) was 17.09% (1.37 HR and 1.17 HR, for female and male respectively). In other words, our research reached the same conclusion as the results of international studies also in case of sex dependent excess risk. In 2020, Jermendy also examined the excess mortality of Hungarian T2DM patients and found that female patients had a higher increased risk of mortality than non-diabetic patients (25). This rate (17.09%) is comparable to our own research, despite that our study measured the excess risk of newly diagnosed T2DM patients during 2.3 years of follow-up, while Jermendy reported this result for all diagnosed T2DM patient compare to total non-T2DM Hungarian population within a calendar year, thus, he examined this difference in a prevalent T2DM population.

The reasons behind the higher increase in cardiovascular and mortality risk measured in the female sex are complex, genetic and biological components are both playing a significant role. The full background to this difference is still unclear, though a number of factors have been studied in the recent decades: the role of estrogens, muscle strength, gender-specific prediabetic conditions, obesity, lipid profile, HbA_{1c} levels, and drug interaction (41,42).

5.2.4. Changes in cardiovascular and mortality risk after diagnosis of diabetes

In previous publications, there were no evaluable data on the changes of cardiovascular and mortality risk during the years following the diagnosis of diabetes. Using a new methodology, our analysis compares the excess risk of T2DM on a monthly basis during the 48 months follow-up period in two patient populations: diagnosed in 2001-2004 or in 2010-2013.

With this methodology, it was possible to evaluate several phase of diabetes management, the period of diagnosis as well as the effectiveness of longer-term 4-year treatment period within a 10-year perspective.

Our data show that the rate of excess mortality, measured at the time of diagnosis did not improve in the 10 year perspective (among T2DM patients diagnosed between 2001–2004 compare to those diagnosed in 2010–2013). This means, that at the time of diagnosis, a T2DM patient had the same mortality risk due to diabetes in 2001 as, for another patient diagnosed in 2010. However, at the end of the four year follow-up, mortality was 10% better among T2DM patients diagnosed in the second study period (2010-2013). Hence, the effectiveness of 4 years of treatment has improved over a decade. If we analyze the cardiovascular events, which also play a role in the mortality, we see that the risk of initial myocardial infarction was 20% lower in the second population (2010-2013), which risk improved by -37% at the end of study period (follow-up), though the change in excess risk of MI was not significant.

However, we found different results for stroke, with the initial risk of stroke at diagnosis was 10% higher after 2010 than in patients diagnosed before 2004, consequently, patients were more likely to have stroke at the beginning of the study period (follow-up).

However, comparing the two periods, this increased excess risk disappeared in the 2010-2013 study arm by the end of the first year after diagnosis. By the end of the 4th year follow-up, we found a 30% lower risk of stroke in this arm. This excess of initial stroke risk may contribute to excess of initial mortality risk. The initial risk of mortality did not improve in 10 years, but by the end of the fourth-year follow-up, both the risk of stroke and myocardial infarction improved, resulting in a 10% mortality risk improvement within a decade.

It is important to note that previous studies have documented improvements in overall cardiovascular and mortality risk over the decades but have not provided detailed analysis of the excess risk in aspect of a diabetic patient's life. Yet these literature findings provide evidence of risk development. Risk of stroke and MI as well as mortality has decreased significantly in recent decades (17,18,19). Overall, we also observed a significant reduction in risk of myocardial infarction (27%) and stroke (28%) in T2DM patients over a decade, with 13% of mortality risk reduction for the whole studied period. However, this decrease was not equal across the diabetic patient's life, we did not see a reduction in mortality risk at the time of diagnosis due to the increased risk of stroke, despite with a significant reduction in MI risk.

The lack of initial improvement may be due to the fact that the number of newly diagnosed T2DM patients decreased significantly between 2001 and 2014 (43). This decline is significant after 2006, especially in the middle-aged cohorts. Though, based on international results, the incidence of T2DM has been declining or declining in recent years, the change in the incidence of middle-aged Hungarian T2DM patients may be due to a negative change in the number of screenings delaying the diagnosis of active diabetes phase.

6. Summary

Despite to the declining trend in the incidence of type 2 diabetes (T2DM), its prevalence has increased significantly in the last 2 decades in Hungary (1) leading to a high social and health burden. Therefore, the assessment of diabetes impact on mortality and morbidity risk of the Hungarian T2DM population is important.

In our first study part, we assessed the excess mortality and cardiovascular morbidity of newly diagnosed T2DM patients (n = 152,678) identified between 2010 and 2013 compared to a control group (n = 305,356) during a 48-month follow-up, based on the NHIF (National Health Insurance Fund) database .

In the second part of the study, we examined how these mortality and cardiovascular risks changed during the 4 years following diagnosis, using the group of patients diagnosed between 2001–2004 (n = 274,109 individuals) and 2010–2014 (n = 152,678 individuals).

In our first study, we found that the risk was significantly higher for myocardial infarction (+81%), stroke (+40%), and mortality (+26%) in the diabetic population compare to the control group. This excess risk was age-dependent, with a greater risk increase in younger than in older patients. The risk of mortality and cardiovascular events was higher in the T2DM group at both sexes, however, the effect of diabetes on the risk of stroke and mortality was higher in female diabetic patients. No such a sex difference was found for myocardial infarction.

In second part of our study, the risk of mortality was the same at diagnosis of T2DM both for those diagnosed between 2010-2013 and 2001–2004. However, at follow-up, the risk of mortality slowly decreased in the group of patients diagnosed between

2010 and 2014 compared to the 2001–2004 population. The initial risk of stroke in patients diagnosed in the period 2010-2013 was similar to those, involved in the earlier period. However, during follow-up, this stroke risk showed a rapid decrease during the 48 months follow-up. The risk of myocardial infarction was lower in the 2010-2013 population than in diabetic patients diagnosed between 2001 and 2004. The size of myocardial infarction risk did not change significantly during the follow-up study period.

8. Conclusion

The results of our studies have confirmed the findings of previous international data. The extent of excess cardiovascular and mortality risk observed in Hungarian T2DM group was consistent with the results of publications using similar methodology in UK, USA, Sweden. We also found the same size in age and sex dependent excess risk of diabetes. Consequently, Hungarian diabetologists achieved similar size of results with diabetes management at the Hungarian T2DM population (diagnosed between 2010 and 2013) as their colleagues in Western countries. However, in the initial (post-diagnosis) risk of stroke and mortality in T2DM patients did not improved significantly within 10 years, emphasizing the need of increased attention on the early diagnosis of diabetes.

9. New findings

1. The risk of myocardial infarction, stroke and mortality was significantly higher in the studied Hungarian T2DM population compare to age and gender-matched non-diabetic control group.

2. This excess risk was age-dependent, we found a higher increased risk in younger than in older patients.

3. The impact of diabetes on the risk of stroke and total mortality was higher in female than in male T2DM patients. No such gender-dependent difference was found for myocardial infarction.

4. In the period immediately following the diagnosis of diabetes, the risk of mortality was the same in both the 2010-2013 and 2001-2004 study populations.

5. However, at follow-up, the risk of all deaths slowly decreased in the group of patients diagnosed between 2010 and 2014 compared to the 2001–2004 population.

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11. Authors publications

Related to this thesis:

1. **Dissimilar impact of type 2 diabetes on cardiovascular outcomes according to age categories: a nationwide population study from Hungary.** Zoltán Kiss, György Rokszin, Zsolt Abonyi-Tóth, György Jermendy, Péter Kempler, Dániel Aradi, István Wittmann. Cardiovasc Diabetol. 2018;17(1):107. Published 2018 Jul 27. doi:10.1186/s12933-018-0751-7 (Impact factor: 5.948)
2. **Different Changes of Risks for Stroke and Myocardial Infarction in Patients With Type 2 Diabetes in Hungary Between the Two Periods of 2001–2004 and 2010–2013.** Zoltan Kiss, György Rokszin, Zsolt Abonyi-Tóth, György Jermendy, Péter Kempler, István Wittmann. Front Endocrinol (Lausanne). 2019;10:170. Published 2019 Mar 21. doi:10.3389/fendo.2019.00170 (Impact factor: 3.644)

Not related to recent thesis:

3. Bogos, K., **Kiss, Z**., Kerpel Fronius, A., Temesi, G., Elek, J., Madurka, I., Cselkó, Z., Csányi, P., Abonyi-Tóth, Z., Rokszin, G., Barcza, Z., & Moldvay, J. (2021). Different Trends in Excess Mortality in a Central European Country Compared to Main European Regions in the Year of the COVID-19 Pandemic (2020): a Hungarian Analysis. Pathology oncology research : POR, 27, 1609774.
4. Bogos, K., **Kiss, Z**., Tamási, L., Ostoros, G., Müller, V., Urbán, L., Bittner, N., Sárosi, V., Vastag, A., Polányi, Z., Nagy-Erdei, Z., Daniel, A., Vokó, Z., Nagy, B., Horváth, K., Rokszin, G., Abonyi-Tóth, Z., Barcza, Z., Gálffy, G., & Moldvay, J. (2021). Improvement in Lung Cancer Survival: 6-Year Trends of Overall Survival at Hungarian Patients Diagnosed in 2011-2016. Pathology oncology research : POR, 27, 603937.

5. Tamási, L., Horváth, K., **Kiss, Z.,** Bogos, K., Ostoros, G., Müller, V., Urbán, L., Bittner, N., Sárosi, V., Vastag, A., Polányi, Z., Nagy-Erdei, Z., Daniel, A., Nagy, B., Rokszin, G., Abonyi-Tóth, Z., Moldvay, J., Vokó, Z., & Gálffy, G. (2021). Age and Gender Specific Lung Cancer Incidence and Mortality in Hungary: Trends from 2011 Through 2016. Pathology oncology research : POR, 27, 598862.
6. Liszkay G, **Kiss Z**, Gyulai R, Oláh J, Holló P, Emri G, Csejtei A, Kenessey I, Benedek A, Polányi Z, Nagy-Erdei Z, Daniel A, Knollmajer K, Várnai M, Vokó Z, Nagy B, Rokszin G, Fábián I, Barcza Z, Polgár C. Changing Trends in Melanoma Incidence and Decreasing Melanoma Mortality in Hungary Between 2011 and 2019: A Nationwide Epidemiological Study. Front Oncol. 2021 Feb 12;10:612459. doi: 10.3389/fonc.2020.612459. PMID: 33643913; PMCID: PMC7908827.
7. Magliano DJ, Chen L, Islam RM, Carstensen B, Gregg EW, Pavkov ME, Andes LJ, Balicer R, Baviera M, Boersma-van Dam E, Booth GL, Chan JCN, Chua YX, Fosse-Edorh S, Fuentes S, Gulseth HL, Gurevicius R, Ha KH, Hird TR, Jermendy G, Khalangot MD, Kim DJ, **Kiss Z**, Kravchenko VI, Leventer-Roberts M, Lin CY, Luk AOY, Mata-Cases M, Mauricio D, Nichols GA, Nielen MM, Pang D, Paul SK, Pelletier C, Pildava S, Porath A, Read SH, Roncaglioni MC, Lopez-Doriga Ruiz P, Shestakova M, Vikulova O, Wang KL, Wild SH, Yekutiel N, Shaw JE. Trends in the incidence of diagnosed diabetes: a multicountry analysis of aggregate data from 22 million diagnoses in high-income and middle-income settings. Lancet Diabetes Endocrinol. 2021 Feb 23:S2213-8587(20)30402-2. doi: 10.1016/S2213-8587(20)30402-2. Epub ahead of print. PMID: 33636102.
8. Sütő G, Molnár GA, Rokszin G, Fábián I, **Kiss Z**, Szekanecz Z, Poór G, Jermendy G, Kempler P, Wittmann I. Risk of morbidity and mortality in patients with type 2 diabetes treated with sodium-glucose cotransporter-2 inhibitor and/or dipeptidyl peptidase-4 inhibitor: a nationwide study. BMJ Open Diabetes Res Care. 2021 Jan;9(1):e001765. doi: 10.1136/bmjdrc-2020-001765. PMID: 33472796; PMCID: PMC7818813.
9. Bogos K, **Kiss Z**, Gálffy G, Tamási L, Ostoros G, Müller V, Urbán L, Bittner N, Sárosi V, Vastag A, Polányi Z, Nagy-Erdei Z, Vokó Z, Nagy B, Rokszin G, Abonyi-Tóth Z, Moldvay J. A tüdőrák hazai epidemiológiai adatai új megközelítésben [Novel approaches to the epidemiology of lung cancer in Hungary]. Magy Onkol. 2020 Sep 23;64(3):175-181. Hungarian. Epub 2020 Sep 14. PMID: 32966347.
10. Bogos K, **Kiss Z**, Gálffy G, Tamási L, Ostoros G, Müller V, Urbán L, Bittner N, Sárosi V, Vastag A, Polányi Z, Nagy-Erdei Z, Vokó Z, Nagy B, Horváth K, Rokszin G, Abonyi-Tóth Z, Barcza Z, Moldvay J. Lung Cancer in Hungary. J Thorac Oncol. 2020 May;15(5):692-699. doi: 10.1016/j.jtho.2019.11.001. PMID: 32340676.

11. Jermendy G, **Kiss Z**, Rokszin G, Fábián I, Wittmann I, Kempler P. Changes in mortality rates and ratios in people with pharmacologically treated type 2 diabetes mellitus between 2001 and 2016 in Hungary. Diabetes Res Clin Pract. 2020 May;163:108134. doi: 10.1016/j.diabres.2020.108134. Epub 2020 Apr 6. PMID: 32272189.

12. Barkai L, **Kiss Z**, Rokszin G, Abonyi-Tóth Z, Jermendy G, Wittmann I, Kempler P. Changes in the incidence and prevalence of type 1 and type 2 diabetes among 2 million children and adolescents in Hungary between 2001 and 2016 - a nationwide population-based study. Arch Med Sci. 2019 Oct 7;16(1):34-41. doi: 10.5114/aoms.2019.88406. PMID: 32051703; PMCID: PMC6963129.

13. Bogos K, **Kiss Z**, Gálffy G, Tamási L, Ostoros G, Müller V, Urbán L, Bittner N, Sárosi V, Vastag A, Polányi Z, Nagy-Erdei Z, Vokó Z, Nagy B, Horváth K, Rokszin G, Abonyi-Tóth Z, Moldvay J. Revising Incidence and Mortality of Lung Cancer in Central Europe: An Epidemiology Review From Hungary. Front Oncol. 2019 Oct 23;9:1051. doi: 10.3389/fonc.2019.01051. PMID: 31709174; PMCID: PMC6819432.

14. Jermendy G, **Kiss Z**, Rokszin G, Abonyi-Tóth Z, Wittmann I, Kempler P. Decreasing incidence of pharmacologically treated Type 2 diabetes in Hungary from 2001 to 2016: A nationwide cohort study. Diabetes Res Clin Pract. 2019 Sep;155:107788. doi: 10.1016/j.diabres.2019.107788. Epub 2019 Jul 19. PMID: 31326457.

15. Jermendy G, **Kiss Z**, Rokszin G, Abonyi-Tóth Z, Wittmann I, Kempler P. Persistence to Treatment with Novel Antidiabetic Drugs (Dipeptidyl Peptidase-4 Inhibitors, Sodium-Glucose Co-Transporter-2 Inhibitors, and Glucagon-Like Peptide-1 Receptor Agonists) in People with Type 2 Diabetes: A Nationwide Cohort Study. Diabetes Ther. 2018 Oct;9(5):2133-2141. doi: 10.1007/s13300-018-0483-4. Epub 2018 Aug 17. PMID: 30120754; PMCID: PMC6167279.

16. Jánosi A, Ofner P, Kiss **Z, Kiss** L, Kiss RG, Dinnyés J, Járai Z, Nagy G, Veress G, Ferenci T. Szívinfarktust túlélt betegek terápiahűsége a másodlagos megelőzés szempontjából fontos gyógyszeres kezelésekhez [Adherence to medication after myocardial infarction and its impact on outcome: a registry-based analysis from the Hungarian Myocardial Infarction Registry]. Orv Hetil. 2017 Jul;158(27):1051-1057. Hungarian. doi: 10.1556/650.2017.30795.

17. Jermendy G, **Kiss Z**, Rokszin G, Abonyi-Tóth Z, Wittmann I, Kempler P. Persistence to Treatment with Novel Antidiabetic Drugs (Dipeptidyl Peptidase-4 Inhibitors, Sodium-Glucose Co-Transporter-2 Inhibitors, and Glucagon-Like Peptide-1 Receptor Agonists) in People with Type 2 Diabetes: A Nationwide Cohort Study. Diabetes Ther. 2018 Aug 17. doi: 10.1007/s13300-018-0483-4.

18. **Kiss Z**, Nagy L, Reiber I, Paragh G, Molnar MP, Rokszin G, Abonyi-Toth Z, Mark L. Persistence with statin therapy in Hungary. Arch Med Sci. 2013 Jun 20;9(3):409-17.
19. Mark L, Paragh G, Karadi I, Reiber I, Paragh Gy, Pados Gy, **Kiss Z**. and Jermendy Gy. Statin Therapy in Patients with Type 2 Diabetes Mellitus in Hungary Cardiology and Angiology: An International Journal 4(4): 147-155, 2015, Article no.CA.2015.038
20. Mark L, Paragh G, Karadi I, Reiber I, Paragh Gy, **Kiss Z**. Comparison of patients' adherence and ldl-cholesterol goal attainment in 2010 and 2013 in the Hungarian multi gap 2012 study Atherosclerosis 235(2):e278-e279 · August 2014.
21. Mark L, Paragh G, Karadi I, Reiber I, Pados G, **Kiss Z**. How can we further improve the LDL-cholesterol target level achievement rate based on the Hungarian MULTI GAP 2011 study results and considering the new European dyslipidemia guidelines? Arch Med Sci. 2012 Sep 8;8(4):608-13.
22. Jermendy G, Wittmann I, Nagy L, **Kiss Z**, Rokszin G, Abonyi-Tóth Z, Katona L, Paragh G, Karádi I, Merkely B. Persistence of initial oral antidiabetic treatment in patients with type 2 diabetes mellitus. Med Sci Monit. 2012 Feb;18(2):CR72-77.
23. Mark L, Paragh G, Karadi I, Reiber I, Pados G, **Kiss Z**. An attempt to make lipid-lowering therapy more effective in Hungary. The results of MULTI GAP 2010 and the PLUS Program. Arch Med Sci. 2011 Oct;7(5):760-6.

9. References

1. NCD Risk Factor Collaboration (NCD-RisC) Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants. The Lancet. 2016;387(10027):1513–1530.
2. International Diabetes Federation. IDF Diabetes Atlas - 8th Edition. http://diabetesatlas.org/resources/2017-atlas.html (June 14 2019)
3. Egészségügyi szakmai irányelv - A diabetes mellitus kórismézéséről, a cukorbetegek antihyperglykaemiás kezeléséről és gondozásáról felnőttkorban. http://www.diabet.hu/upload/diabetes/magazine/dh.2017.1.pdf?web_xml:id=2017

4. Jermendy G, Nádas J, Szigethy E, Széles G, Nagy A, Hídvégi T, et al.: Prevalence rate of diabetes mellitus and impaired fasting glycemia in Hungary – crosssectional study on nationally representative sample of people aged 20-69 years. Croat Med J 2010; 51: 151- 156. doi:10.3325/cmj.2010.51.151
5. Jermendy G, Kiss Z, Rokszin Gy, Abonyi-Tóth Z, Wittmann I, Kempler P. Decreasing incidence of Pharmacologically treated Type 2 diabetes in Hungary from 2001 to 2016: A nationwide cohort study. Diabetes Res Clin Pract. 2019 Sep;155:107788.
6. Emerging Risk Factors Collaboration, Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, Stehouwer CD, Lewington S, Pennells L, Thompson A, Sattar N, White IR, Ray KK, Danesh J. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010;375:22152222.
7. Fagot-Campagna A, Rolka DB, Beckles GL, Gregg EW, Narayan KM: Prevalence of lipid ablormalities, awareness, and treatment in US adults with diabetes [Abstract]. Diabetes 49 (Suppl. 1): A78, 2000
8. Schofield JD, Liu Y, Rao-Balakrishna P, Malik RA, Soran H. Diabetes Ther. 2016 Jun;7(2):203-19. Diabetes Dyslipidemia.
9. Rosenson RS: Clinical role of LDL and HDL subclasses and apolipoprotein measurement. ACC Curr J Rev May, 2004, p. 33–37
10. Ahotupa M. Oxidized lipoprotein lipids and atherosclerosis. Free Radic Res. 2017 Apr;51(4):439-447.
11. Napoli C, Triggiani M, Palumbo G, Condorelli M, Chiariello M, Ambrosio G: Glycosylation enhances oxygen radical-induced modifications and decreases

acetylhydrolase activity of human low density lipoprotein. Basic Res Cardiol 92:96 –105, 1997

12. Bucala R, Makita Z, Koschinski T, Cerami A: Lipid advanced glycosylated pathway for lipid oxidation in vivo. Proc Natl Acad Sci USA91 : 9441–9445,1993
13. Packard C, Olsson AG. Management of hypercholesterolaemia in the patient with diabetes. Int J Clin Pract Suppl. 2002 Jul;(130):27-32.
14. Duell PB, Oram JF, Bierman EL: Nonenzymatic glycosylation of HDL and impaired HDL-receptor-mediated cholesterol efflux. Diabetes40 : 377–384,1991
15. Kiss Z, Rokszin G, Abonyi-Tóth Z, et al. Dissimilar impact of type 2 diabetes on cardiovascular outcomes according to age categories: a nationwide population study from Hungary. Cardiovasc Diabetol. 2018;17(1):107. Published 2018 Jul 27
16. Kiss Z, Rokszin G, Abonyi-Tóth Z, Jermendy G, Kempler P, Wittmann I. Different Changes of Risks for Stroke and Myocardial Infarction in Patients With Type 2 Diabetes in Hungary Between the Two Periods of 2001-2004 and 2010-2013. Front Endocrinol (Lausanne). 2019;10:170. Published 2019 Mar 21.
17. A Norhammar, J Bodegård, T Nyström, M Thuresson, J W. Eriksson, D Nathanson. Incidence, prevalence and mortality of type 2 diabetes requiring glucose-lowering treatment, and associated risks of cardiovascular complications: a nationwide study in Sweden, 2006–2013. Diabetologia (2016) 59:1692–1701.
18. Tancredi M, Rosengren A, Svensson AM, et al. Excess mortality among persons with type 2 diabetes. N Engl J Med. 2015;373:1720-1732.
19. Gregg EW, Li Y, Wang J, et al. Changes in diabetes-related complications in the United States, 1990–2010. N Engl J Med. 2014;370(16):1514–23.
20. Heintjes EM, Houben E, Beekman-Hendriks WL, Lighaam E, Cremers SM, Penning-van Beest FJA, Stehouwer CDA, Herings RMC. Trends in mortality,

cardiovascular complications, and risk factors in type 2 diabetes. Neth J Med. 2019 Dec;77(9):317-329.

21. M. Lind, L. A. Garcia-Rodriguez, G. L. Booth, L. Cea-Soriano, B. R. Shah, G. Ekeroth, L. L. Lipscombe. Mortality trends in patients with and without diabetes in Ontario, Canada and the UK from 1996 to 2009: a population-based study. Diabetologia (2013) 56:2601–2608
22. Kiss Z, Rokszin G, Abonyi-Tóth Z, Jermendy G, Kempler P, Wittmann I. Different Changes of Risks for Stroke and Myocardial Infarction in Patients With Type 2 Diabetes in Hungary Between the Two Periods of 2001-2004 and 2010-2013. Front Endocrinol (Lausanne). 2019;10:170. Published 2019 Mar 21.
23. Gregg EW, Li Y, Wang J, et al. Changes in diabetes-related complications in the United States, 1990–2010. N Engl J Med. 2014;370(16):1514–23.
24. Heintjes EM, Houben E, Beekman-Hendriks WL, Lighaam E, Cremers SM, Penning-van Beest FJA, Stehouwer CDA, Herings RMC. Trends in mortality, cardiovascular complications, and risk factors in type 2 diabetes. Neth J Med. 2019 Dec;77(9):317-329.
25. Jermendy G, Kiss Z, Rokszin G, Fábián I, Wittmann I, Kempler P. Changes in mortality rates and ratios in people with pharmacologically treated type 2 diabetes mellitus between 2001 and 2016 in Hungary [published online ahead of print, 2020 Apr 6]. Diabetes Res Clin Pract. 2020;163:108134.
26. World Health Organization. Global report on diabetes, 2016. Available from http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf?ua=1. Accessed 31 May 2020

27. Beckman JA, Paneni F, Cosentino F, Creager MA. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part II. Eur Heart J. 2013;34:2444-2452.
28. Rao Kondapally Seshasai S, Kaptoge S, Thompson A, et al.; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011;364:829–841
29. Sattar N, Rawshani A, Franzen S, Rawshani A, Svensson AM, Rosengren A, McGuire DK, Eliasson B, Gudbjornsdottir S. Age at diagnosis of type 2 diabetes mellitus and associations with cardiovascular and mortality risks. Circulation 2019;139:22282237.
30. Mehta S, Ghosh S, Sander S, Kuti E, Mountford WK. Differences in all-cause health care utilization and costs in a type 2 diabetes mellitus population with and without a history of cardiovascular disease. J Manag Care Spec Pharm. 2018;24(3):280–90.
31. Hillier TA, Pedula KL. Complications in young adults with early-onset type 2 diabetes: losing the relative protection of youth.Diabetes Care. 2003; 26:2999–3005.
32. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of Obesity Among Adults and Youth: United States, 2015-2016. NCHS Data Brief. 2017 Oct;(288):1-8.
33. Hales CM, Fryar CD, Carroll MD, Freedman DS, Ogden CL. Trends in Obesity and Severe Obesity Prevalence in US Youth and Adults by Sex and Age, 2007-2008 to 2015-2016. JAMA. 2018 Apr 24;319(16):1723-1725.
34. Meneilly GS, Elliott T. Metabolic alterations in middle-aged and elderly obese patients with type 2 diabetes. Diabetes Care. 1999 Jan;22(1):112-8.

35. Maedler K, Schumann DM, Sauter N, Ellingsgaard H, Bosco D, Baertschiger R, Iwakura Y, Oberholzer J, Wollheim CB, Gauthier BR, Donath MY. Low concentration of interleukin-1beta induces FLICE-inhibitory protein-mediated beta-cell proliferation in human pancreatic islets. Diabetes. 2006 Oct;55(10):2713-22.
36. PetersenK. F.BefroyD.DufourS.DziuraJ.AriyanC.RothmanD. L.Di PietroL.ClineG. W.ShulmanG. I.Mitochondrial dysfunction in the elderly: possible role in insulin resistance.Science 20031140 EOF2 EOF
37. Lu L, Yu Z, Pan A, Hu FB, Franco OH, Li H, Li X, Yang X, Chen Y, Lin X. Plasma 25-hydroxyvitamin D concentration and metabolic syndrome among middle-aged and elderly Chinese individuals. Diabetes Care. 2009 Jul;32(7):1278-83.
38. Pavkov ME, Bennett PH, Knowler WC, Krakoff J, Sievers ML, Nelson RG (2006) Effect of youth-onset type 2 diabetes mellitus on incidence of end-stage renal disease and mortality in young and middle-aged pima Indians. JAMA 296:421–426
39. JL. Harding, JE. Shaw, A Peeters, S Davidson, DJ. Magliano. Age-Specific Trends From 2000–2011 in All-Cause and Cause-Specific Mortality in Type 1 and Type 2 Diabetes: A Cohort Study of More Than One Million People. Diabetes Care 2016;39:1018–1026
40. Tönnies T, Hoyer A, Brinks R. Excess mortality for people diagnosed with type 2 diabetes in 2012 - Estimates based on claims data from 70 million Germans. Nutr Metab Cardiovasc Dis. 2018;28(9):887-891.
41. Barrettconnor E. Sex differences in coronary heart disease why are women so superior? The 1995 Ancel Keys Lecture. Circulation. 1997;95:252–64.

42. Robert A, Kloner MD, Culley Carson III, et al. Testosterone and Cardiovascular Disease. JACC. 2016;67:545–57.
43. Jermendy G, Kiss Z, Rokszin G, Abonyi-Tóth Z, Wittmann I, Kempler P. Decreasing incidence of pharmacologically treated Type 2 diabetes in Hungary from 2001 to 2016: A nationwide cohort study. Diabetes Res Clin Pract. 2019;155:107788.