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SURVIVAL ASPECTS IN PATIENTS DIAGNOSED WITH TYPE II DIABETES MELLITUS BETWEEN 1970 AND 1999 IN THE DIABETES CENTER TIMIŞOARA

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Abstract

Background. *Diabetes mellitus is a serious pathological state, which shortens the lifespan, with severe complications and increased mortality.* ***Objective.*** *To study the main aspects regarding the survival for a period of 30 years, in patients newly diagnosed with T2DM in the Diabetes Center Timişoara.* ***Material and methods*** *The study enrolled 4,913 subjects, 2,742 women (55.81%) and 2,171 men (44.19%), mean age at diagnosis of 58.2± 11.5 years, diagnosed with T2DM between 1970 and 1999.* ***Results*** *We observed a decreasing trend of the all cause death between the analyzed groups as well as within the same group, during the study periods.* ***Conclusion*** *Our data support the results of numerous longitudinal descriptive studies indicating a decrease of the secular mortality trend, but especially of mortality in the last decades in diabetic patients.*

key words: *diabetes mellitus, mortality, death causes.*

Background

Diabetes mellitus (DM) is a public health problem and one of the main chronic illnesses affecting the human kind, regardless the social and economical status and the geographical area. It is a serious pathological state, which shortens the lifespan, with severe complications and increased mortality. The analysis of the current causes of death in diabetic patients could lead to a more judicious evaluation of the medical measures to improve the disease's immediate and long-term evolution.

There is numerous data regarding the DM mortality trend worldwide. Regardless of the statistic manner in which this issue was addressed, all the longitudinal descriptive studies performed on various continents indicate a reduction of the secular mortality trend in diabetic patients, especially in the last decades. A decrease of mortality from cardiovascular diseases (CVD) in most developed countries was noticed, and the

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excess of CVD mortality which characterizes the diabetic population also decreased during the last decades [1,2].

The mortality by non-cardiovascular causes continued to affect, in a greater degree, the females with DM as opposed to those without DM, leading to an all cause mortality, significantly higher in diabetic patients [3]. On the other hand, the Framingham study, performed between 1950 and 2005 in the US, has brought to attention the reduction of the general mortality, without gender differentiation, with or without DM, the phenomenon being valid only for the CVD mortality.

Numerous population studies analyzing the DM-related mortality have been performed in Europe, comparative or not with the general population [1,2,4-7], but on periods shorter than 2-4 decades. Their majority took into account the main morbidity: coronary heart disease (CHD) or the cardiovascular pathology (CVP), since this pathology is the main cause of death both in diabetic as well as non-diabetic patients.

Aim

The present paper aim was to perform an observational, retrospective study, which attempts to describe the main aspects regarding the survival of patients newly diagnosed with T2DM in the Diabetes Center Timişoara for a period of 30 years. Moreover, it aimed to identify and compare the mortality causes, both cardiovascular and non-cardiovascular, during the three decades.

Material and Method

A total of 4,913 subjects with T2DM have been enrolled, 2,742 women (55.81%) and 2,171 men (44.19%), with an average age at diagnosis of 58.2±11.5 years (limits between 21 and 89 years), diagnosed and registered at the Diabetes Center Timişoara between 1970 and 1999.

A series of clinical and biological parameters have been extracted from the subjects' observation charts (from the archives of the Diabetes Center and Timişoara County Hospital): sex, date of birth, registration date, date of the last examination (for the active subjects – the date of the last performed examination; for the possibly active subjects: date of the last examination performed within at least one year from the appointment date; for the deceased patients - date of death), causes of death (extracted from the patient charts at the diabetes center, from the death certificates, from the hospital admission charts in case of subjects deceased in the hospital or from the data provided by the next of kin) fasting or postprandial glycemia. Regarding possibly still living patients, we don't have precise data about them: part of them might be alive and some could have died. They were not present on the last appointment date and the family members have not contacted us.

Depending on the registration date, subjects have been divided into three sub-groups: 1970-1979 (Group 1), 1980-1989 (Group 2) and 1990-1999 (Group 3). The following parameters were calculated: age at diagnosis, disease duration until the last examination and the age of the subjects at that moment, date of death and diabetes duration until death and the average age at death. The study group has been monitored until 2011.

Statistical analyses were performed using GraphPad Prism 5. Data are expressed as mean and standard deviation for parametric

variables. Differences between median of the groups were studied using the Mann-Whitney test or the Student's t-test for differences between means. Pearson's correlation coefficient (r) was used to measure the strength of the association between two variables and its significance with t-distribution test. Fisher's exact test was used in the analysis of contingency tables. For the statistical tests α=0.95 significance levels was accepted and for means and risk estimates a 95% confidence interval was computed.

Results

Survival status of the patients from the three analyzed sub-groups is given in Figure 1.

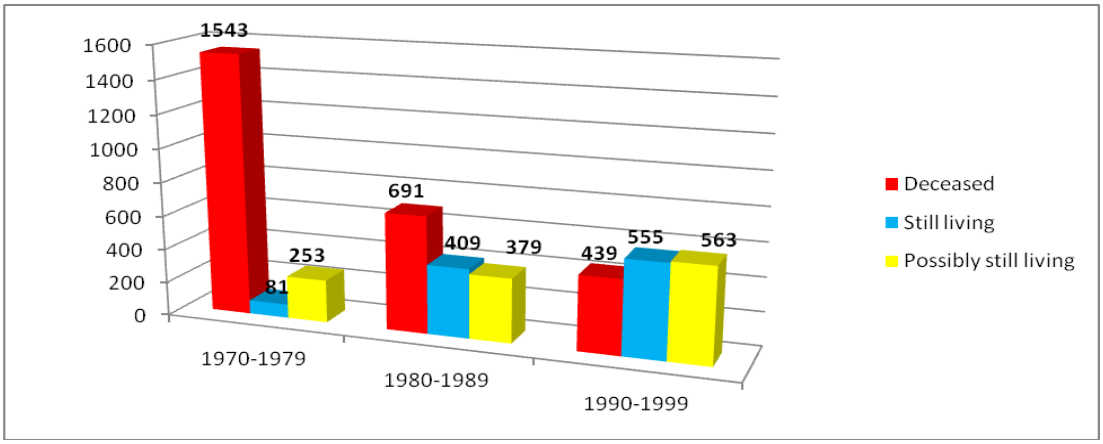

Figure 1. Repartition of subjects from the three study groups.

Table 1. Main characteristics of the subjects for the whole study group and for the three sub-groups.

Characteristics	Total	Group 1	Group 2	Group 3
Total number Female (%) Male (%)	4913 2742 (55.8) 2171(44.2)	1877 1039 (55.3) 838 (44.7)	1479 820 (55.5) 659 (44.5)	1557 883(56.7) 674 (43.3)
Still living subjects Female (%) Male (%)	1045(21.3) 608 (58.2) 437 (41.8)	81(4.3) 37(45.7) 44 (54.3)	409 (27.6) 227 (55.5) 182 (44.5)	555 (35.7) 344 (62) 211 (38)
Possibly still living female (%) Male (%)	1195 (24.3) 659 (55.1) 536 (44.9)	253 (13.5) 142 (56.1) 111(43.9)	379 (25.7) 214 (56.6) 165 (43.4)	563 (36.1) 303 (53.8) 260 (46.2)
Deceased patients female (%) Male (%)	2673 (54.4) 1475 (55.2) 1198 (44.8)	1543 (82.2) 860 (55.7) 683 (44.3)	691 (46.7) 379 (54.8) 312 (45.2)	439 (28.2) 236 (53.7) 203 (46.3)
Average age at registration[1]	58.2±11.5	59.4±10.8	55.0±12.2	59.8±11.1
Average age at the last visit for still living patients[1]	72.0±9.3	77.7±8.2	73.4±8.3	70.±9.6
Average age at the last visit for possibly still living patients[1]	65.9±12	66.8±7.6	62.0±13.6	68±11.9
Avearage age at death[1]	72.4±9.1	71.0±8.9	73.1±8.8	73.4±10.0
Average duration of disease for still living patients	21.5±6.9	35.6±2.8	26.1±3.1	16.0±2.7
Average duration of disease for possibly still living patients[1]	8.5±7.4	13.9±8.7	8.4±7.8	6±4.8
Average duration of disease for deceased patients[1]	10.7±7.7	10.5±6.7	12.2±8.9	9.2±4.9

[1] Continuous variable are mean±SD

The first group included 1877 subjects diagnosed with T2DM between 1970 and 1979. At the end of the monitoring period (year 2011), 1543 (82.2%) subjects were deceased, 253 (13.5%) subjects were possibly still living and 81 (4.3%) subjects were still living (Table 1 and Figure 1).

The second group included 1,479 subjects diagnosed with T2DM between 1980 and 1989. At the end of the monitoring period, 691 (46.7%) subjects were deceased, 379 (25.7%) subjects were possibly still living and 409 (27.6%) subjects were still living (Table 1 and Figure 1).

The third group included 1,557 subjects diagnosed with T2DM between 1990 and 1999. At the end of the monitoring period, 439 (28.2%) subjects were deceased, 563 (36.1%) subjects were possibly still living and 555 (35.7%) subjects were still living (Table 1 and Figure 1).

Comparing the three groups, we noticed a significant decrease ($p<0.01$) of the average age at registration (4.4 years) between 1970-1979 and 1980-1989, from 59.4±10.8 to 55.0±12.2 years but a significant increase ($p<0.01$) of the average age at registration (4.8 years) between 1980-1989 and 1990-1999, from 55.0±12.2 to 59.8±11.1 years. There was no significant difference between the average age at registration between subjects diagnosed between 1970-1979 and 1990-1999 (Table 1).

We found that the average duration of disease evolution until death has significantly ($p<0.01$) increased (1.7 years) from Group 1 (10.5±6.7 years) to Group 2 (12.2±8.9 years). It has significantly ($p<0.01$) decreased (1.3 years) from Group 1 (10.5±6.7 years) to Group 3 (9.2±4.9 years) and it has significantly ($p<0.01$) decreased (3 years) from Group 2 (12.2±8.9 years) to Group 3 (9.2±4.9 years) (Table 1).

This led to a significant ($p<0.01$) increase (2.1 years) of the average age at death between 1970-1979 and 1980-1989 (from 71.0±8.9 years to 73.1±8.8 years). It has also significantly ($p<0.01$) increased (2.4 years) between 1970-1979 and 1990-1999 (from 71.0±8.9 years to 73.4±10.0 years). There was no significant difference regarding the average age at death between subjects diagnosed between 1980-1989 and 1990 and 1999 (Table 1).

Analysis of mortality for the subjects deceased during the first 10 years since diabetes onset

Significant differences ($p<0.0001$, Chi-square test) were noticed between the three groups regarding the all cause death: out of the total subjects diagnosed between 1970-1979, 48.7% have died in the first 10 years from disease onset; subsequently, this percentage has diminished, reaching 21.8% in those diagnosed between 1980-1989, and respectively 14.9% in those diagnosed between 1990-1999 (Table 2). A decreasing trend of all cause death was registered both in females (49% for 1970-1979, 19.4% for 1980-1989 and 14.4% for 1990-1999) and males (48.4% for 1970-1979, 24.9% for 1980-1989 and 15.6% for 1990-1999) (Table 2).

By comparing the average age at death for subjects deceased in the first 10 years after diagnosis, we found a significant increase (2.3 years), from 70.3±8.6 years in subjects diagnosed between 1970-1979 up to 72.0±10.5 years ($p<0.05$) in subjects diagnosed between 1990-1999. This trend was found in females (increase from 70.8±7.9 years in those diagnosed between 1970 -1979

up to 73.6±10.2 years in those diagnosed between 1990 -1999, p<0.01) but not in males (Table 2).

Table 2. Comparison between the number of deaths, average age at disease onset for deceased subjects, average age at death and duration of disease until death for subjects deceased within 10 years from disease onset in the three groups.

Characteristics		Number of patients at follow-up initiation	No. of deaths during the first 10 years of disease	Average age at disease onset	Average age at death	Average diabetes duration until death
1970-1979	T	1877	915 (48.7%)	64.8±8.6	70.3±8.6	5.5±3.0
Group 1	F	1039	509 (49%)	65.4±8.1	70.8±7.9	5.4±2.9
	M	838	406 (48.4%)	64.0±9.2	69.6±9.3	5.6±3.0
1980-1989	T	1479	323 (21.8%)	67.1±8.0	71.4±7.9	4.3±3.1
Group 2	F	820	159 (19.4%)	68.2±5.7	72.4±5.9	4.2±2.9
	M	659	164 (24.9)	66.0±9.6	70.5±9.3	4.4±3.3
1990-1999	T	1557	233(14.9%)	66.3±11.6	72.0±10.5	5.5±3.2
Group 3	F	883	128 (14.4%)	68.4±11.3	73.6±10.2	5.0±3.2
	M	674	105 (15.6%)	63.7±11.6	70.7±10.2	6.3±3.0

T=total; F=female; M=male

Table 3. Comparison between the number of deaths, average age at disease onset for the deceased subjects, average age at death and duration of disease until death in subjects who died between 10 to 20 years from the disease onset in the three groups.

Characteristics		Number of living patients after 10 years of disease	Number of deaths between 10 to 20 years from disease onset	Average age at disease onset	Average age at death	Duration of disease until death
1970-1979	T	866	454 (52.4%)	58.8±8.8	73.1±8.7	14.3±2.7
Group 1	F	473	262 (55.4%)	59.5±8.0	74.0±8.2	14.5±2.8
	M	393	192 (48.8%)	57.7±9.7	71.9±9.2	14.1±2.6
1980-1989	T	892	215 (24.1%)	57.8±9.8	73.3±10.0	15.1±3.1
Group 2	F	521	140 (26.9%)	58.6±9.2	74.1±9.1	15.0±3.1
	M	371	75 (20.2%)	56.3±10.7	71.6±11.2	15.3±3.0
1990-1999	T	883	190 (21.5%)	61.5±8.9	75.3±9.2	13.7±2.0
Group 3	F	374	104 (27.8%)	61.8±8.8	75.2±9.8	13.8±2.0
	M	509	86 (16.9%)	61.1±9.2	75.4±8.6	13.6±2.1

T=total; F=female; M=male;

Significant differences regarding average duration of the disease until death were noted between Group 1 and Group 2 (p<0.01), and between Group 2 and Group 3 (p<0.01). In females we found a significant difference for diabetes duration until death between Group 1 and Group 2 (p<0.01). In men, a significant decrease of the average duration of the disease until death was found from Group 1 to Group 2 (p<0.01) and from Group 2 to Group 3 (p<0.01) (Table 2).

Analysis of mortality for subjects deceased between 10 and 20 years of diabetes evolution

Similarly to the deaths occurred within 10 years from diagnosis, we found a decrease of the all cause death percentage from 52.4% in those diagnosed between 1970-1979, to 24.1% and 21.5% in those diagnosed between 1980-1989 and 1990-1999 respectively (Table 3). This trend was noticed in males with a decrease from 48.8% in those diagnosed

between 1970-1979 to 20.2% in those diagnosed between 1980 -1989 and 16.9% in those diagnosed between 1990-1999. In females we noticed a decrease of the all cause death percentage between 10 to 20 years of disease evolution, from 48.8% in women diagnosed between 1970-1979 to 26.9% in those diagnosed between 1980-1989, but this decreasing trend did not continue in the decade 1990-1999 (Table 3).

A significant increase ($p<0.05$) of the average age at death was noticed (2.2 years), from 73.1±8.7 years in those diagnosed between 1970-1979 up to 75.3±9.2 in those diagnosed between 1990-1999. There were no significant differences regarding the average age at death in females while in males we found a significant increase ($p<0.01$) of the average age at death (3.8 years), from 71.6±11.2 years in those diagnosed between 1980-1989 up to 75.4±8.6 years in those diagnosed between 1990-1999 (Table 3).

The average duration of the disease up to death has significantly increased from Group 1 to Group 2 ($p<0.01$) and significantly decreased from Group 1 to Group 3 ($p<0.05$). It has significantly decreased from Group 2 to Group 3 ($p<0.01$). In females, the duration of the disease until death has significantly decreased from Group 1 to Group 3 ($p<0.01$) and significantly decreased from Group 2 to Group 3 ($p<0.01$). In males, the disease duration until death has significantly increased from Group 1 to Group 2 ($p<0.01$) and significantly decreased ($p< 0.01$) from Group 2 to Group 3 (Table 3).

Table 4. Comparison between the number of deaths, average age at ~~the~~ disease onset for the deceased subjects, average age at death and duration of disease until death in subjects who died between 20 to 30 years from diabetes onset in the two groups.

Characteristics		Number of living patients after 20 years of diabetes	Number of subjects who died 20 to 30 years from diabetes onset	Average age at disease onset	Average age at death	Duration of disease until death
1970-1979	T	324	132(40.7%)	52.6±8.3	77.0±8.3	24.3±2.9
Decade I	F	162	65 (40.1%)	51.8±7.5	76.6±7.9	24.7±3.1
	M	162	67 (41.3%)	53.3±8.9	77.4±8.6	24.0±2.7
1980-1989	T	621	141 (22.7%)	50.7±7.7	77.2±7.1	25.8±2.9
Decade II	F	353	76 (21.5%)	50.4±7.6	78.2±5.8	26.5±2.7
	M	268	65(24.2%)	51.0±7.9	76.1±8.2	25.0±2.9

T=total; F=female; M=male

Analysis of mortality for subjects deceased between 20 and 30 years of diabetes evolution

It should be noted that the 1990-1999 group did not fulfill the "minimum period of follow-up" criteria, thus was excluded from the analysis.

A decrease of the all cause death percentage was noticed in the whole group of subjects surviving >20 years from disease onset: from 40.7% in Group 1 to 22.7% in Group 2 (Table 4). This was noticed both in females (decrease from 40.1% to 21.5%) and males (decrease from 41.3% to 24.2%). There were not significant differences in average age at death. The average diabetes duration until death has significantly ($p<0.01$) increased (1.5 years), from 24.3±2.9 years in those diagnosed between 1970-1979 up to 25.8±2.9 years in those diagnosed between 1980-1989. This significant increase was noticed both in females ($p<0.05$) and males ($p<0.01$).

The analysis of the causes of death for each monitored period, 0-10 years, 10-20 years, 20-30 years and 0-30 years highlights in all the monitored groups a greater percentage of cardiovascular death (CHD + stroke) as opposed to the non-cardiovascular death causes (infections, tumors, diabetic ketoacidosis, hypoglycemic coma and other causes) as shown in Table 5 and Figure 2.

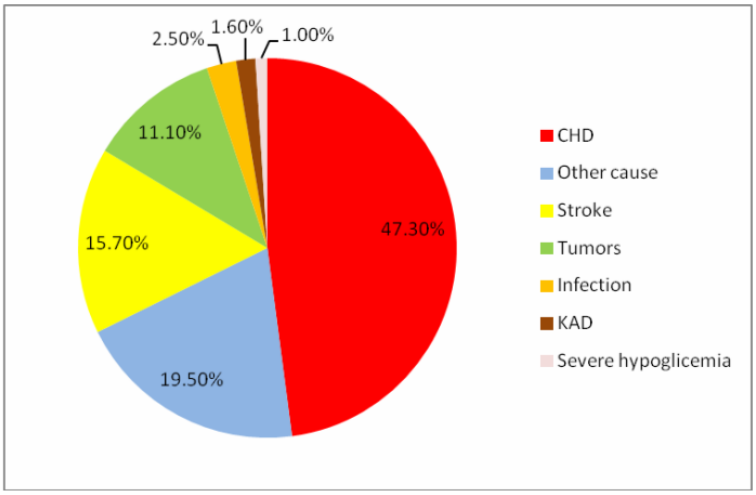

Figure 2. Causes of death in the whole group of subjects diagnosed between 1970-1999.

Table 5. Causes of death in subjects from the three analysed sub-groups.

Tracking period	All groups	0-10 years			10-20 years			20-30 years	
Causes of death	1970-1999	1970-1979	1980-1989	1990-1999	1970-1979	1980-1989	1990-1999	1970-1979	1980-1989
CHD[1] (%)	47.3	51.3	32.2	42	63.9	34.3	43.7	48.5	48.2
Stroke(%)	15.7	18.6	15.5	15	11.0	13.5	21.6	17.4	11.3
Infections (%)	2.5	3.3	0.6	0.9	2.4	2.7	1.6	2.3	4.3
Tumors (%)	11.1	10.9	12.0	14.2	7.7	9.50.	14.7	12.9	12.8
DKA[2] (%)	1.6	2.3	0.0	0.0	3.0	0.5	0.0	0.0	5.7
Severe hypoglicemia(%)	1.0	0.8	0.6	0.0	0.7	2.3	0.0	0.7	2.8
Other causes[3] (%)	**19.5**	**12.8**	**39.0**	**27.9**	**11.3**	**38.2**	**18.4**	**18.2**	**14.9**
Total CV+stroke	**63**	**69.9**	**47.7**	**57**	**74.9**	**47.8**	**65.3**	**65.9**	**59.5**

[1] Coronary Heart Disease; [2] Diabetic ketoacidosis; [3] Other causes (chronic renal failure, gastrointestinal, respiratory, trauma, suicide)

Analysis of mortality in patients with CVD death

As depicted in Table 6, in the first 10 years from diabetes onset, we noted a significant increase of the average age at CVD death from Group 1 to Group 2 ($p<0.01$) and a significant increase, from Group 1 to Group 3 ($p<0.01$). The average duration of disease until death has significantly decreased from Group 1 to Group 2 ($p<0.01$) and significantly increased from Group 2 to Group 3 (<0.05). Between 10 to 20 years from disease onset, we noticed a significant increase of the average age at death from Group 1 to Group 3 ($p<0.01$) and a significant increase from Group 2 to Group 3 ($p<0.01$). The average duration of disease until death has been significantly longer in Group 2 in comparison with Group 3 ($p<0.01$)

Table 6. Analysis of mortality in patients with CVD death.

Decade		**1970-1979**	**1980-1989**	**1990-1999**	**1970-1979**	**1980-1989**	**1990-1999**	**1970-1979**	**1980-1989**
Monitoring period		**First 10 yrs**	**First 10 yrs**	**First 10 yrs**	**10-20 yrs**	**10-20 yrs**	**10-20 yrs**	**20-30 yrs**	**20-30 yrs**
Cardiovascular death	T	469	104	98	290	74	83	64	68
	F/M	261/208	47/57	55/43	166/124	47/27	40/43	27/37	28/40
Average age at registration	T	64.3±8.6	68.1±5.9	69.3±9.0	58.4±8.6	57.9±8.0	63.3±6.9	53.7±7.9	51.1±8.3
	F	65.3±8.2	68.6±4.7	71.3±6.7	58.6±7.8	59.3±7.1	64.8±5.2	52.6±8.9	49.2±8.3
	M	63.1±8.9	67.8±6.8	66.9±10.8	58.2±9.7	55.8±9.2	61.9±8.0	54.5±7.0	52.5±8.2
Average age at death	T	70.0±8.5	72.5±6.0	74.9±8.4	72.9±8.3	72.9±8.9	76.9±7.0**	77.3±7.8	76.8±8.0
	F	70.9±8.0	72.8±4.6	76.7±6.3	73.3±7.9	74.0±8.1	78.6±4.7	76.3±9.3	76.4±5.7
	M	68.8±9.0	72.3±6.9	72.7±10.2	72.4±8.9	71.6±10.2	75.2±8.3	78.0±6.6	77.0±9.3
Average duration of disease	T	5.7±3.0**	4.4±3.1	5.6±3.1*	14.4±2.8	15.1±3.3	13.6±2.1**	23.5±2.7	25.0±2.6**
	F	5.6±2.9	4.3±2.9	5.4±3.3	14.7±2.8	14.7±3.2	13.9±2.0	23.5±.2.8	25.8±2.5
	M	5.7±3.1	4.5±3.4	5.8±2.8	14.1±2.7	15.8±3.2	13.3±2.2	23.5±2.7	24.5±2.6

*- p value <0.05- statistically significant; **- p value < 0.01-highly statistically significant;

Discussions

On our study population we have noticed a decreasing trend of the number of deaths in the three analyzed subgroups, with the highest number of deaths registered in the subgroup of patients diagnosed between 1970-1979 and the lowest in the subgroup of patients diagnosed between 1990-1999. This observation is valid both for the whole study group and for the female sex, but in males we found a slight increase in the number of deaths was observed within the analyzed three subgroups (Table 1). These results are similar with other literature data supporting a downward trend of mortality due to DM [1,2,4-9].

With regard to the influence of sex on the DM mortality, the literature data are often very different and controversial. The NHANES Study (National Health and Nutrition Examination Survey) showed that, despite the general decrease of all cause mortality in diabetic patients between 1988-2000, the decline is less significant in females [10]. However, a few studies, including one performed in Sweden (1980-2004) [2] and one in Brazil [11] reported an improving tendency of survival in diabetic patients actually higher in women than in men.

As for the mortality due to CV pathology, we concluded that CVD death represents the main cause of death in the analyzed subgroups, irrespective of sex. We noticed however a decreasing tendency along the decades of observation in every subgroup, both for men and for women. These data support those other literature data which have shown a declining tendency of mortality due to CV causes within the diabetic population [5,12], but they differ from data regarding the decrease of CV mortality according to gender. Thus, a longitudinal study performed between 1972-2004 in Sweden on 776 newly registered DM cases has pointed out a decreased of CV mortality in diabetic males similar with that of non-diabetics but has not revealed such a dynamics in diabetic women [4].

A comprehensive mortality study was performed in USA on 3 consecutive representative sub-groups, with or without DM, between 1971-1975, 1976-1980 and 1988-1994, the data beeing evaluated in 1986, 1992, and 2000. The study analysed the annual rate of death/1.000 persons and has

shown a parallel tendency of reduced CV mortality both in the nondiabetic population and in the diabetic male population, while the all cause and CV mortality in women with DM has not shown this tendency of decrease. Thus, the progresses concerning the reduction in the number of deaths were limited only to the male sex [10]. Similar results have been reported in some regional studies in Canada [13] or the USA [14].

This dynamics of the mortality trend is mainly determined by the accessibility to the specific diabetes therapy (modern insulins, oral anti-diabetes drugs), but also by an improved worldwide medical care, which also includes: diet, physical activity regimen, adjustment of the therapy to the glycemic control parameters, self-control, and many others. Another important factor could be the improvement of DM diagnosis in adults and its therapeutic approach.

There are some weak points of our study due to the fact that the analysis was not performed on all patients diagnosed in the respective time periods and the data have not been analyzed in comparison with the general population mortality data. There are no data about the „possibly still living" patients (who are likely to be alive but some of them might be already dead) which could modify the percentage of the registered deaths and the evolution of the mortality within the subgroups. Moreover, an analysis of the mortality tendency based on the dynamics of the risk factors would be useful. However, our study is important because its results provide data about the mortality trend and about the causes of death in a diabetic population from a big diabetes centre.

Conclusions

The decreasing trend of the all cause death percentage comparatively between the analyzed groups registered in our study is similar with those of other longitudinal descriptive studies performed on various continents, indicating a decrease of the secular mortality trend in diabetic patients, especially during the last decades. Our data also support the fact that the cardiovascular pathology represents the main cause of death in the diabetic patient.

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