THE PROSPECTIVE ANALYSIS OF MORTALITY IN TYPE 2 DIABETES SUBJECTS IN BUCHAREST, ROMANIA

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We performed a perspective study of 16941 patients with noninsulintreated type 2 diabetes mellitus, 7889 (46.7%) males and 9052 (53.34%) females, over an average follow-up period of 3.52±0.75 years. By statistical analysis of the data, we have found that comparing with controls, the presence of diabetes is associated with higher mortality and a significant decrease in life expectancy. The masculine gender, disease duration at inclusion and age at onset were all independent significant predictors of mortality in the Cox regression analysis.

Key words: Mortality; Survival; Age at death; Cause of death; Type 2 diabetes.

INTRODUCTION

Diabetes mellitus is a major problem of public health, not only in Romania, but also all over the world because of its increasing prevalence, severe disease complications and high social costs. The diabetes prevalence has increased four times in the last 40 years[13]. The worldwide estimated prevalence in 2003 was 5.1% (194 million cases) and the projection for 2025 is 6.3% (333 million cases). The increase in diabetes prevalence is mostly due to obesity, ageing of the population, sedentary lifestyle, improper diet, urbanization and industrialization.

The mortality in patients with diabetes without myocardial infarction is similar with that of non-diabetes patients with myocardial infarction and the association between diabetes and myocardial infarction leads to a further two to three times increase of mortality rate[4].

The mortality rate is a very important index, maybe the only one that is able to reveal the real social impact of a disease and the efficiency of its treatment. Comparing with the general population, patients with diabetes have a relative risk of mortality of 3.8[2].

The aim of the present study is to analyze the main mortality aspects of the diabetes mellitus patients receiving oral antidiabetics medications (OAD), based on the data recorded at the "N. Paulescu" National Institute of Diabetes, Nutrition and Metabolic Diseases, Bucharest, "Ion Pavel" Diabetes Centre, Bucharest and the National Institute of Statistics. The primary *end-point* of the study is mortality during the 2001–2004 period.

MATERIALS AND METHODS

Generally, the mortality analysis is performed by sampling the diabetes population and the general population and regarding them as representative samples for the corresponding populations. A retrospective or a prospective study over a different number of years of these samples is then performed. Finally, the resulting data is extrapolated to the initial populations from where the samples were extracted. There are multiple errors in the process of sampling and extrapolating, their presence and amplitude being difficult to anticipate.

The originality of our study is that we manage to eliminate the sampling and other biases by including in the analysis all diabetes mellitus subjects and the whole general population (minus, of course, the diabetes group) from in the same space (Bucharest) and time (2001–2004).

In the 2001–2004 period the only drugstores for free diabetes medication in Bucharest were the "Ion Pavel" Diabetes Centre drugstore and the "Malaxa" Centre drugstore. Each patient that received medication from this sites from January 1st, 2001 until December 31, 2004 was recorded in a database that also contains the information of the medical prescriptions.

The inclusion criteria were:

– patient has received OAD medication from the "Ion Pavel" Diabetes Centre drugstore at least once in the period January 1st, 2001 to December 31, 2001;
– patient has permanent residence in Bucharest.

The exclusion criteria were:

– lack of or no valid personal numeric code (CNP)
– lack of medical record number (i.e. basic information are not available)
– lack of diabetes type information
– permanent residence outside Bucharest
– subject received insulin treatment during the observation period.

We analyzed 131983 medical prescriptions released between January 1st, 2001 and December 31, 2001 to a total number of 35169 subjects. After applying the inclusion/exclusion criteria we retained for this study 16941 noninsulin treated type 2 diabetes patients (T2DM), 7889 (46.57%) men and 9052 (53.43%) women.

The start date of follow-up is the day of the first medical prescription in 2001. At this moment the demographical and anthropometrical information are recorded. All subjects were follow-up until December 31, 2004 or until death. During follow-up we obtained data concerning the subject's medical prescriptions for diabetes, the survival status or the death circumstances and cause. The mean follow-up was 3.54±0.75 years, or 59563.4 person-years.

The data concerning mortality were analyzed by cross linking with the mortality database of the National Institute of Statistics. The Ethics Committee of "N. Paulescu" National Institute of Diabetes, Nutrition and Metabolic Diseases approved the study.

The data available for analysis are: gender, birth date, age at diabetes onset, disease duration, height, weight, the content of each medical prescription released during the study, death date, age at death, cause of death in the ICD10 (International Code Disease 10) codification.

The mortality analysis was detailed by gender and 5 years age groups. We also have taken into account that some subjects moved from one age group into the next one during the study period. For example, for a subject followed-up for 3.2 years, he could be included 1.6 years in a certain age group and 2.6 years in the next one.

Data regarding the mortality of diabetes mellitus subjects included in our study were compared with a control group, built as the **true conventional value of the investigated group**. The control group is represented by the entire population of Bucharest, during 2001-2004 (data from the National Institute of Statistics) minus all known subjects with diabetes. The exposure (years of observation) and number of death encountered during this exposure was available by gender and five-year age group. The reference group was built at the end of the study.

The percent of all deaths attributable to diabetes in the general population of Bucharest was computed using the formula proposed by Miettinen [11]:

$$PA = \frac{P(RR-1)}{P(RR-1)+1} \times 100$$

where: PA = percent attributable to diabetes;
P = diabetes prevalence;
RR = the relative risk of death comparing with the population without diabetes.

The statistical analysis used parametric and nonparametric tests according to the data set. The statistical difference between the Kaplan-Meier survival curves was tested using the Log Rank test. The relative risk (RR) of death compared with the control group was computed based on the 2x2-stratified tables according to the age groups distribution, using the *Mantel-Haenszel weighted relative risk* method, with Greenland / Robins confidence interval.

The life expectancy at birth and at the age *x* (for example 40 years) was computed using an Excel spreadsheet for automatic computation provided by „*US Census Bureau*" in the population analysis package „*Population Analysis Spreadsheets (PAS)*" (*www.census.gov*). The mortality table was computed using the age specific mortality rates and the death expected coverage in each age group (considered to be 100% in the present study). The

life expectancy analysis takes into account the gender, age at diabetes onset of and the disease duration at inclusion.

The *Proportional hazard [Cox] regression* uses the method *"ENTER"*. The time is defined by the diabetes evolution in years.

Data presented in this study represents the first preliminary report of this prospective study of mortality.

RESULTS

We analyzed 16941 patients with T2DM treated with OAD, 7889 (46.7%) males and 9052 (53.3%) females. The mean age at inclusion was 63.7±10.44 years (range 11.28–98.67 years), with an average age at diabetes onset of 58.26±10.15 years (range 9.29–94.11 years) and disease duration of 5.44±6.31 years (range 0–59.06 years).

Comparing with males, females had an higher age at onset (59.06±10.08 years for females and 57.36±10.15 years for males, $p<0.01$), at inclusion in the study (64.25±10.16 years for females and 63.08±10.71 years for males, $p<0.01$) and BMI (30.63±6.03 kg/m^2 for females and 29.12±4.63 kg/m^2 for males, $p<0.01$); we also found a small but significantly lower disease duration at inclusion in females (5.19±5.92 years for females and 5.72±6.72 years for males, $p<0.05$).

Mortality rates

We had prospectively followed-up 16941 subjects with T2DM over an average period of 3.52±0.75 years, with a total of 59563.4 person-years of follow-up. During this period, 2027 subjects died (11.97%), 1088 males (13.79% of all males) and 939 females (10.37% of all females). There were 14914 (88.03%) surviving subjects at December 31, 2004. See Table 1 for the average gender and age groups mortality rates.

The mortality rate for 1000 person-years for the 40+ years old group increases from 27.32‰ for subjects with < 1 year of evolution at inclusion in the study, to 29.72‰ for subjects with 1–9 years of disease duration and 58.24‰ for those with ≥ 10 years of evolution at inclusion in the study.

The standardized mortality rates

In order to perform a comparative study of mortality between heterogeneous groups of subjects, the differences in the distributions of gender and age groups of the populations to be studied must be eliminated. Therefore, the standardized mortality rates were computed, using as reference the WHO Standard European population.

Table 1

The average gender and age groups mortality rates:

The age group	**The mortality rate T2DMo (‰)**		
	Male	Female	Total
30-34	–	–	–
35-39	*5.27*	–	*2.83*
40-44	9.30	3.63	**6.69**
45-49	8.20	6.66	**7.50**
50-54	12.90	5.08	**9.13**
55-59	18.44	13.27	**15.75**
60-64	28.80	12.36	**19.62**
65-69	38.01	23.90	**29.97**
70-74	56.91	38.04	**46.21**
75-79	69.64	57.62	**63.22**
80-84	118.45	90.93	**102.35**
85+	116.18	135.56	**126.88**
30+	–	–	–
40+	**40.04**	**29.47**	**34.33**

For the subjects with age ≥ 40 years old, the standardized mortality rate was 22.56‰, and on gender groups, we found 27.07‰ for males and 18.61‰ for females. The standardized mortality rate in the control group for the 40+ age group was 20.28‰, 26.17‰ for males and 15.98‰ for females.

The analysis of disease duration and age at death

The average age at death was 72.29±8.87 years, women having a significant higher age at death than men (73.37±8.52 years for females vs. 71.35±9.06 years for males, $p<0.01$). The average disease duration at death was 9.64±7.83 years, without significant differences by gender.

The relative risk of death compared with the control group

The RR of death compared with the control group, for 40+ years old subjects, adjusted for age, was of 1.14 (CI 95% 1.09–1.19, $p<0.01$).

For the age group 85+ years, there was a sub unitary RR, namely 0.67 (CI 95% 0.56–0.8, $p<0.01$), which is statistically significant even on the analysis by gender. For example, for males the RR was 0.58 (CI 95% 0.43-0.77, $p<0.01$) and just a little higher for females, *i.e.* RR was 0.74 (CI 95% 0.43-0.77, $p<0.01$). For these subjects, diabetes seems to be a protective factor for mortality (see Table 2).

Table 2

Relative risk of death for the T2DM subjects compared with the reference group

The age group	The relative risk of death compared with the reference group (CI 95%)		
	Male (CI 95%)	Female (CI 95%)	Total (CI 95%)
40-44	2.06 (0.93-4.59) ^{NS}	2.05 (0.51-8.22) ^{NS}	2.22 (1.11-4.43)*
45-49	1.07 (0.64-1.77) ^{NS}	2.19 (1.18-4.08)*	1.45 (0.98-2.15) ^{NS}
50-54	1.16 (0.85-1.57) ^{NS}	1.06 (0.64-1.77) ^{NS}	1.18 (0.9-1.53) ^{NS}
55-59	1.11 (0.86-1.44) ^{NS}	1.91 (1.42-2.55)**	1.38 (1.14-1.61)**
60-64	1.16 (0.97-1.39) ^{NS}	1.21 (0.94-1.55) ^{NS}	1.18 (1.02-1.37)*
65-69	1.11 (0.96-1.28) ^{NS}	1.43 (1.22-1.68)**	1.25 (1.13-1.39)**
70-74	1.19 (1.05-1.34)**	1.36 (1.19-1.55)**	1.28 (1.17-1.4)**
75-79	0.96 (0.85-1.09) ^{NS}	1.1 (0.97-1.26) ^{NS}	1.06 (0.96-1.16) ^{NS}
80-84	1.06 (0.9-1.24) ^{NS}	1.03 (0.88-1.21) ^{NS}	1.07 (0.96-1.2) ^{NS}
85+	0.58 (0.43-0.77)**	0.74 (0.58-0.93)**	0.67 (0.56-0.8)**
40+	**1.06 (1-1.12)** ^{NS}	**1.19 (1.12-1.27)****	**1.14 (1.09-1.19)****

^{NS} not significant; *p<0.05; **p<0.01

The analysis of Kaplan-Meier survival curves

The survival curves for patients with <1 year and 1-9 years of disease duration at inclusion does not differ significantly. However, there is a clear and significant (p<0.01) difference shown by the survival curve for subjects with ≥10 years of disease duration at inclusion, whose survival is obviously inferior to the first two categories (see Figure 1).

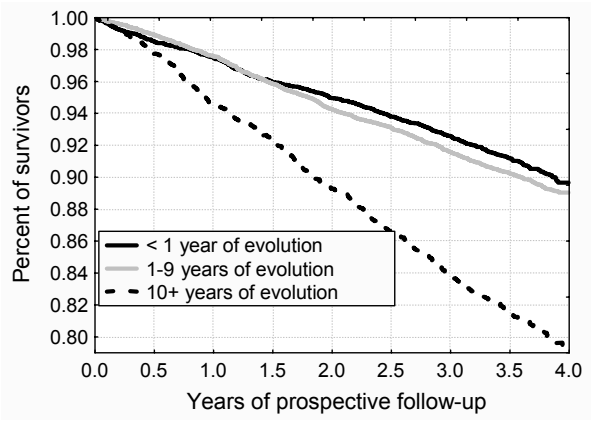

Fig. 1. Kaplan-Meier survival curves for subjects with T2DM, by disease duration at inclusion.

Mentioning the diabetes as cause of death in subjects with known diabetes

The percent of mentioning the diabetes as primary or secondary death cause is 23.33% of registered deaths. The percent was lower (20.73%) for a disease duration at death of <5 years and higher (28.13%) for a disease duration at death of >15 years.

Analysis of causes of death

The major causes of death in T2DM subjects were the circulatory system diseases (62.51%), followed by tumors (16.67%), diabetes (6.41%), digestive system diseases (5.33%), respiratory system diseases (4.98%), urinary tract diseases (1.48%), infectious and parasitic diseases (0.30%) and others (2.32%). Please see table 3 for further information.

Death percents attributable to diabetes in the general population

The mortality attributable to diabetes in the general population of Bucharest aged 40 years or more was estimated as 0.7–1% of all deaths, corresponding to an estimated prevalence of 5–7% and a RR of 1.14.

Cox regression analysis

We analyzed the following risk factors for mortality:

1. gender; categorical variable – male versus female;
2. age at onset; continuous variable – increase by one year;
3. diabetes duration at inclusion; categorical variable 1–9 years *versus* <1 year and 10+ years *versus* <1 year.

Table 3

The major causes of death in T2DM subjects

Cause of death	ICD10 code	Death percent N=2027
Circulatory system diseases	**I00-I99**	**62.51%**
– Ischemic heart diseases	I20-I25	27.92%
– Cerebrovasculatory Diseases	I60-I67	19.54%
Diabetes mellitus	E10-E14	6.41%
Tumors	C00-D48	16.67%
Digestive system diseases	K00-K93	5.33%
Urinary tract diseases	N00-N39	1.48%
– Chronic renal failure	N18	0.89%
Respiratory system diseases	J00-J98	4.98%
Infectious and parasitic diseases	A00-B99	0.30%
– Tuberculosis	A15-A19	0.25%
Others	–	2.32%

N – number of cases; ICD10 – International classification of Diseases, 10th revision.

Cox regression analysis reveals a statistically significant model (*Omnibus tests of model coefficients*: p<0.01) where all the analyzed factors contribute (see Table 5). The proportionality assumption necessary in the Cox regression model is verified in our case.

The masculine gender was associated with a 42.8% (CI95% 30.8 – 55.8%, p<0.01) increase in mortality compared with the feminine gender.

Every increase with one year of the age at onset implies an increasing of 6.6% (CI95% 6.1–7.2%, p<0.01) in mortality.

Comparing with the disease duration at inclusion of <1 year (used as reference), an evolution period of 1–9 years at inclusion leads to an increase in mortality of 21.8% (CI95% 8.8–36.4%, p<0.01), while the 10+ years of disease duration at inclusion is responsible for a 3.4 times (CI95% 3–3.9, p<0.01) increase in mortality.

Analysis of life expectancy

The subjects with T2DM, with the onset age ≥ 40 years old had a decrease in life expectancy in the moment of disease onset of 1.47 years for men and 4.18 years for women (see Table 4). This decrease in life expectancy could become much larger if we take into account that the real onset of the disease is placed many years before its discovery. This difference disappears for an onset of T2DM at the age of 60 years for men and 70 years for women.

An unexpected increase in life expectancy relative to the control group appears in men with diabetes over 75 years old, while this phenomenon has a smaller influence for women with diabetes over 80 years old (see Table 4).

Table 5

Cox regression analysis of the principal risk factors of mortality

	Beta exponent	CI95%	Significance
Male versus female	1.428	1.308–1.558	p<0.01
Age at onset (+ 1 year)	1.066	1.061–1.072	p<0.01
1-9 years disease duration#	1.218	1.088–1.364	p<0.01
10+ years disease duration#	3.397	2.988–3.862	p<0.01

#Relative to <1 year disease duration at inclusion.

Table 4

Life expectancy in T2DM subjects relative to the control group

Attained age	Life expectancy in control group		Decrease in life expectancy (in years) in T2DM subjects relative to the control group, by different ages at disease onset							
			40 years old		50 years old		60 years old		70 years old	
	M	F	M	F	M	F	M	F	M	F
0	70.50	77.46	1.70	4.08	1.07	3.06	0.03	1.79	-0.82	0.34
1-4	70.34	77.14	1.72	4.11	1.09	3.09	0.03	1.81	-0.83	0.34
5-9	66.49	73.23	1.72	4.12	1.09	3.09	0.03	1.81	-0.83	0.34

Table 4 (continued)

10-14	61.56	68.30	1.72	4.12	1.09	3.09	0.03	1.81	-0.83	0.34
15-19	56.64	63.38	1.72	4.13	1.09	3.10	0.03	1.81	-0.83	0.34
20-24	51.77	58.47	1.73	4.13	1.10	3.10	0.03	1.81	-0.83	0.34
25-29	46.94	53.56	1.74	4.14	1.10	3.11	0.03	1.82	-0.84	0.34
30-34	42.13	48.64	1.74	4.15	1.10	3.11	0.03	1.82	-0.84	0.34
35-39	37.39	43.79	1.75	4.16	1.11	3.12	0.03	1.83	-0.85	0.35
40-44	32.76	39.02	**1.77**	**4.18**	1.12	3.14	0.03	1.84	-0.86	0.35
45-49	28.45	34.34	1.64	3.90	1.15	3.17	0.03	1.85	-0.87	0.35
50-54	24.46	29.83	1.93	4.03	**1.19**	**3.21**	0.03	1.88	-0.91	0.36
55-59	20.72	25.49	1.54	3.79	1.19	3.20	0.03	1.93	-0.96	0.36
60-64	17.29	21.30	1.35	2.70	1.35	2.70	**0.03**	**1.99**	-1.04	0.38
65-69	14.25	17.29	0.56	2.76	0.56	2.76	-0.16	1.89	-1.18	0.40
70-74	11.44	13.58	-0.37	1.57	-0.37	1.57	-0.37	1.57	**-1.40**	**0.43**
75-79	8.88	10.25	-1.61	0.28	-1.61	0.28	-1.61	0.28	-2.02	0.19
80-84	6.69	7.57	-2.41	-0.12	-2.41	-0.12	-2.41	-0.12	-2.41	-0.12
85+	4.95	5.43	-4.70	-0.53	-4.70	-0.53	-4.70	-0.53	-4.70	-0.53

M – male; F – female.

DISCUSSIONS AND CONCLUSIONS

We analyzed 16941 patients with T2DM treated with OAD, 7889 (46.7%) males and 9052 (53.3%) females. The mean age at inclusion was 63.7±10.44 years, with an average age at diabetes onset of 58.26±10.15 years and disease duration at inclusion of 5.44±6.31 years. The average follow-up period was 3.52±0.75 years, representing 59563.4 person-years.

Compared with males, females had a significantly higher age at the onset, age at inclusion in the study and BMI and a significantly lower disease duration at inclusion (although very little in absolute terms).

The mortality rate for 1000 person-years for the 40+ years old group ranged from 27.32‰ for < 1 year of evolution at inclusion and 58.24‰ for those with ≥ 10 years of evolution at inclusion. The relatively high mortality rate in the group with >10 years of evolution at inclusion could be explained by the secondary failure of OAD treatment, with the necessity of insulin therapy, but the lack of its presence in the therapeutic scheme.

The standardized mortality rates were higher in the diabetes group compared with the control group. The same results were obtained by gender analysis. The average age at death was 72.29±8.87 years, women having a significant older age at death than men. The average disease duration at death was 9.64±7.83 years, without significant differences by gender.

The RR of death compared with the control group, for 40+ years old subjects, adjusted for age was 1.14. For the age group 85+ years, there was a sub unitary RR, namely 0.67, which is statistically significant even on the analysis by gender. A possible explanation of this fact is that diabetes patients might receive a more careful treatment of their cardiovascular disease, with a subsequent decrease in the global risk of death. In the case of slowly advancing diabetes, that do not have enough time to develop severe complications, the actual killer of these subjects is the cardiovascular disease, determined mostly by the older age. The relatively better care received by the diabetes patients in these age groups can explain the differences that occur in the life expectancy. However, a more detailed supplementary study is necessary in order to clarify this problem.

The Kaplan-Meier survival curves clearly showed that there is a significant ($p<0.01$) lower survival for subjects with ≥10 years of disease duration at inclusion, compared with both <1 year and 1–9 years of disease duration at inclusion.

The percent of mentioning the diabetes as primary or secondary cause of death was 23.33% of all registered deaths. The percent was lower

(20.73%) for a disease duration at death of <5 years and higher (28.13%) for a disease duration at death of >15 years.

The major causes of death in T2DM subjects were the circulatory system diseases (62.51%), followed by tumors (16.67%), diabetes (6.41%), digestive system diseases (5.33%), respiratory system diseases (4.98%), urinary tract diseases (1.48%), infectious and parasitic diseases (0.30%) and others (2.32%).

The mortality attributable to diabetes in the general population of Bucharest aged 40 years or more was estimated as 0.7–1% of all deaths, corresponding to an estimated prevalence of 5–7% and a RR of 1.14. Taking into account that the actual number of diabetes patients is two times the number of registered patients, we consider that the prevalence of diabetes mellitus (especially T2DM) is severe underestimated. Computing the RR on a longer period could provide a higher RR than that given here. Based on these facts we consider that the percent of deaths attributed to diabetes from the total number of registered deaths in the general population of Bucharest is actually much larger.

The masculine gender, disease duration at inclusion and age at onset were all independent significant predictors of mortality in the Cox regression analysis.

For subjects with noninsulintreated T2DM, with the diabetes onset at age ≥ 40 years, there was a decrease in life expectancy at disease onset of 1.47 years for men and 4.18 years for women (see Table 4). This decrease in life expectancy could become much larger if we take into account that the real onset of the disease is placed many years before its discovery. This difference disappears for an onset of T2DM at the age of 60 years for men and 70 years for women. An unexpected increase in life expectancy relative to the control group appears in men with diabetes over 75 years old, while this phenomenon has a smaller influence for women with diabetes over 80 years old. Further investigations in this issue are required, with the extension of the follow-up period.

Our study confirms in the Romanian population the findings of several other international studies showing that the main impact of diabetes as a major public issue is through the steep rise in the cardiovascular diseases incidence and mortality. Comparing with the general population, the relative risk for sudden cardiovascular death in patients with diabetes is 1.5 in males and 3 in females[8]. The presence of diabetes complications further increases the diabetes related mortality. In the very much cited UKPDS study, the mortality in T2DM subjects increases from 1.4% / year in normoalbuminuric patients, to 3% / year in the presence of microalbuminuria, 4.6% / year for macroalbuminuria and 19.2% / year for the end-stage renal disease[1].

Even though in the last years one can remark a decreasing trend in the incidence of cardiovascular diseases, this is not entirely true for diabetes patients, especially for women, where there is an increasing trend[12].

In USA, diabetes mellitus is the fifth cause of death and it shows a 30% rise in the last 20 years[10]. The main causes of death for the T2DM subjects are the cardiovascular diseases, with a variable proportion of 42–75% from all deaths[6, 7, 12].

The mortality excess, shown by diabetes patients relative to reference subjects, increases proportionally with the diabetes duration and decreases with the increasing of the onset age or actual age.

The all cause mortality rate as well as the cardiovascular mortality is higher for men relative to women for all age groups, for diabetes patients as well as in the general population[12]. However, if one computes the relative risk of death comparative to the general population, the mortality excess induced by the presence of diabetes is higher for women then men, especially in the 65–74 age group.

We conclude that, even though men have a younger age at death, the decrease in age at death affects mainly the women, especially increasing the relative risk of death comparative to the general population. Therefore, diabetes "annihilates" the relative advantage of feminine gender for a longer life expectancy.

The real onset of T2DM is impossible to determine because it is often asymptomatic. This leads to a delay, sometimes of 10–15 years, in the disease diagnostic. In the majority of cases, diabetes is discovered with the occasion of a control for another disease that is often a complication of diabetes. Therefore, the life expectancy is shortened from the very beginning.

The medical care received by the patients with diabetes influences their quality of life and therefore their life expectancy. There is evidence that patients treated in a specialized clinic have better results in the control of disease, comparing with the ones treated in a usual clinic[5].

Metabolic syndrome is associated with an increased mortality risk[3]. For the metabolic syndrome patients, the death risk is supplementary increased in the presence of smoking and an increased level of LDL cholesterol[3]. The prevalence of the metabolic syndrome in a Romanian population was recently estimated at 28.51%, with no significant differences by gender[9]. That means that more then one third of the Romanian population (including diabetes) is at a high risk for mortality. Strong preventive interventions are therefore warranted for these categories, with the central role being placed on lifestyle modifications.

Data presented in this study represents the first preliminary report of this prospective study of mortality. The follow-up of the enrolled subjects continues and the next report is scheduled for the last trimester of 2008.

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