Abstract: The medical literature of the last decade enables us to estimate survival of diabetics. Insulin dependent diabetics (IDDM) present a 3 to 6-fold mortality and die after age 30, the most frequent causes being end stage renal and vascular diseases. Non insulin-dependent diabetic (NIDDM) mortality is 1.4 to 3.7 times that of non-diabetics. Cardiovascular events and strokes are the major causes of death. Pancreatic carcinoma occurs twice as frequently in NIDDM compared to non-diabetics. Early markers of late severe complications are hypertension and proteinuria. Retinopathy has little influence on mortality if other risk factors are considered. Yet, glaucoma and lens changes are associated with three- and twofold mortalities. One of five IDDM with microalbuminuria progresses to overt nephropathy in 5 years. In NIDDM micro-albuminuria predicts cardiovascular disease with a mortality of up to 2 times. Careful treatment of cardiovascular risk factors and of microalbuminuria combined with optimal metabolic control substantially reduces mortality of diabetics.

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Introduction
Diabetes mellitus (DM) remains one of the major concerns in life insurance. This disease is responsible for premature death since its first description by Aretaeus in the third century. The discovery of insulin in 1921 brought about an essential improvement insofar as survival became possible for diabetic children. Progress in understanding normal insulin secretion in healthy individuals in the course of the last century facilitated a more refined treatment of diabetics with this hormone. The present article reviews the literature published over the last ten years on juvenile and adult onset type diabetes mellitus focussing on mortality brought about by the various complications of the illness. Special attention is paid to early manifestations indicative of severe complications in the late course of the disease.

Methods
The medical literature between 1984 and 1995 was searched through medline for diabetes, mortality and survival. In addition, the journals DIABETOLOGIA and DIABETES CARE were reviewed for these subjects. Finally, Diabetes Vital Statistics 1993, a publication by the American Diabetes Association, was analyzed.

Results and Discussion
1. General mortality due to diabetes
The population statistics of the US, published by the Center of Disease Control in 1988, reports the number of deaths to be caused by diabetes in the death certificates. For both insulin dependent and non-insulin dependent diabetics as the explicitly declared cause of death, the age adjusted mortality rate was 15 per 100,000 living US population per year. When, however, diabetes related deaths were studied, the figure was more than 4 times higher, namely 4 per 100,000 per year. The deaths caused by diabetes and diabetes-related conditions among Americans generally occurred above age 45. In the elderly over age 70, the mortality rate related to diabetes is reported to be between 0.5 and 1 percent per year. Over the last decade, there has been no significant change in the US death rate per year. In other
words, diabetes mortality in the US is, at present, rather constant. In view of much higher prevalence of Non-Insulin-Dependent Diabetes mellitus (NIDDM) the great majority of the cases reported in these statistics are due to this type of disease.

Worldwide, one of the best studies of diabetes mortality has been undertaken by the World Health Organization Multinational Study of Vascular Disease in Diabetes. Among 10 diabetes centers across the world (London, Switzerland, Warsaw, Berlin, Zagreb, Hong Kong, Tokyo, Havana, Oklahoma and Arizona) a stratified random sample of 4,714 diabetic patients aged 35 to 55 years were followed from 1975 up to 1987. Excess mortality was compared with the respective background population and assessed in terms of standardized mortality ratios (SMRs). Overall, Figure 1 shows for Insulin-Dependent Diabetics (IDDM) SMR’s are approximately 600 for all female age groups as well as for the young males studied. With increasing age, the mortality of diabetic men decreased somewhat to reach an SMR of 360 for the age group 55 to 64 years. For the NIDDM the figures were lower; young men had SMRs of 300, older ones approximately 200, whereas for women the comparative values were 400 and 280. This study also analyzed the influence of disease duration on mortality in both genders and found no statistical difference for IDDM, but a time dependent increase in mortality for NIDDM (Figure 2), confirming earlier publications. Proteinuria and hypertension increased SMRs in both types of diabetes and in a cumulative manner.

**FIGURE I.**

![Graph A](image1.png)

![Graph B](image2.png)

*All cause standardized mortality ratio (SMR) according to age and gender for A: Insulin-dependent and B: Non insulin-dependent diabetics; baseline is by sex of the normal reference population Reprinted with the permission of the authors and the publishers.*
1.1. Mortality of Insulin-Dependent Diabetes (IDDM)

During the last decade, ten research groups have investigated the relation of diabetes deaths with that of the normal population comparing gender and geographic trends. They thereby obtained risk ratios which range from 3 to 15. The differences originate from varying cohorts with respect to geographical or racial provenience and to frequency of already existing complications at the beginning of the individual studies. Accordingly, large international series which relate to the individual local background mortality are much more representative. As outlined above, Wang and coworkers report similar absolute mortality figures for males and females. Yet, the relative values comparing patient mortalities to baseline population mortalities become almost twice as high for female IDDM. The reason for this gender difference stems from the fact that normal (nondiabetic) female mortality is only half that of males. An exception to this feature is reported for the former German Democratic Republic and Yugoslavia: in these countries, the absolute values for diabetic male mortality are almost twice that for diabetic females.

With respect to the influence of geography, Matsushima et al reported substantial variations in mortality. These authors investigated IDDM mortalities in 24 regions of the world and related them to the incidence of IDDM in each individual country. The Indexes thereby obtained ranged from zero (Luxembourg, Iceland and Australia) to 1.0 for Norway (defined as comparison standard), rising to 4.8 for Japan.
and as high as 9.9 for Romania and Bulgaria. These adapted mortality indexes correlated with infant mortality and inversely correlated with population life expectancy, gross national product and IDDM incidence rate. This indicates that on one hand knowledge of the disease (high incidence) and on the other financial resources allow a better outcome for this type of diabetes.

1.2. Mortality of Non insulin-dependent Diabetes mellitus (NIDDM)
For NIDDM the mortality risk ratios are placed between 1.4 and 3.7. Although these figures have been reported recently, they are not really different from those of earlier publications. Accordingly, they are not discussed here in detail. However, the reader’s attention is drawn to the fact that a possibly favorable effect of new treatment schemes on mortality are counterbalanced by an equally decreasing all cause mortality of the general population in most countries.

2. Prevalence and Incidence of Diabetes Mellitus
Both prevalence and incidence are factors underlying overall mortality. The work of Matsushima et al reported above is a valuable illustration to this issue: worldwide, there are substantial differences in these figures. With respect to the juvenile type of the disease, 30 Finnish children below age 15 per 100,000 become diabetic every year. For the US, the annual incidence for this age class reported for 1989 was 18 per 100,000. Lipton et al., however, found in 1995 rates for the high risk of children of African-American and Hispanic origin of 13.2 per 100,000 for Chicago and 10.8 per 100,000 for Philadelphia. The lowest numbers are reported from Japan where 2 children (per 100,000) become diabetic every year. Two papers from 1996, one from Denmark, the other from Manitoba, Canada show data that incidence of IDDM has remained constant over the last decade, whereas the prevalence has increased steadily. This implies that at the same time mortality is decreasing. In contrast, Austria, Norway and The Netherlands report an increase in the incidence. In Austria, it was 6.4 per 100,000 in 1979/81 and 9.8 per 100,000 in 1992/93. For NIDDM the prevalence is particularly elevated in the American Indian populations. E.g in Arizona, diabetes is found in 70 per cent of Pima Indian women age 45 to 74 years. Very low prevalence of 0.5 per cent is reported for certain rural areas of China and Africa. Muggeo et al find 2. 5 per cent in Verona, Italy, a rather low number compared to the rest of Europe and the US. In this careful study the prevalence increases with age up to 10 per cent above age 65.

3. Fatal Complications in IDDM
In order to recognize how deleterious the individual complications may be, it is useful, first, to study the causes of death. In an earlier study Dorman et al reported the causes of 80 deaths in IDDM. Under the age of 20 years, 10 of 18 deaths were due to acute complications such as hypoglycemia, diabetic ketoacidosis and/or infections. Above age 20, the major cause of death became renal disease. This complication accounted for half of the fatalities. Thus, in the age group interested in life insurance coverage, nephropathy is the major concern of IDDM.

Most authors define diabetic nephropathy as proteinuria above 300 mg/24 hours or 200 mg/min. Indeed, diabetic nephropathy was followed in the seventies by endstage renal disease in 80 per cent of patients within 10 years. Figure 3 shows that there has been substantial improvement in survival of diabetic nephropathy over the last 25 years. In particular, Parving et al showed in 1991 that careful treatment of hypertension in 45 such patients reduced their 10 year mortality from 80 per cent in 1971 (without such therapy) to 20 per cent, yet still a respectable figure. It is very difficult to distinguish between the causes of death by nephropathy and coronary heart disease, as Jensen et al found in individuals with IDDM that coronary heart disease was 7 times more frequent in those who also suffered from nephropathy. Likewise, diabetic nephropathy is associated with a 40 fold risk of cardiovascular-
Death from diabetic nephropathy in insulin-dependent diabetics. Solid line, $n = 45$, Knowles 1971;\textsuperscript{44} Finely dotted line, $n = 360$, Andersen et al. 1983;\textsuperscript{46} Dotted line, $n = 67$, Krolewskiet al. 1985 (37). Comparison with broken line, $n = 45$ patients with effective antihypertensive treatment, Parving et al. 1989.\textsuperscript{35} Reprinted with the permission of the authors and the publishers.\textsuperscript{45}

Survival in insulin-dependent diabetics with (lower, dotted line, $n = 23$) and without (upper, solid line, $n = 21$) cardiac autonomic neuropathy. Reprinted with the permission of the authors and the publishers.\textsuperscript{40}

Metaanalysis showing relative risks and 95 per cent confidence intervals of pancreatic cancer for diabetics in case-control and cohort or nested case-control studies. Reprinted with the permission of the authors and the publishers.\textsuperscript{46}
lar mortality. Indeed, analyzing the mortality of cardiovascular disease in IDDM, Krolewski et al. reported that cardiovascular death occurred beyond age 30, causing a cumulative mortality of approximately 30 per cent by age 55. There was no difference between female and male mortalities, whereas in the general population cardiovascular mortality of males is twice that of females (see also under 1.1.). The Pittsburgh Group published data with IDDM deaths from cardiovascular causes starting already in the twenties. Stroke is another endpoint of vascular disease. Here again, diabetic patients present 4 times more cerebrovascular accidents than nondiabetic. Yet another IDDM complication with a very poor prognosis is the cardiac autonomic neuropathy. O'Brien and coworkers reported a 5 year survival of 72 per cent in patients with this complication versus 92 and 96 per cent in the controls without neuropathy (Figure 5). Five other recent publications confirm this finding with figures between 70 and 80 per cent survival at 5 years. It has to be noted, though, that the patients of O'Brien had been diabetic for 20 years and, therefore, suffered from several other complications as well. His and other such studies do no allow to separate statistically the influence of this pathology on death from the other eventually coexisting complications.

4. Fatal complications in NIDDM
The major cause of death in NIDDM is coronary artery disease (CAD). Krolewski reported for NIDDM for diabetic men between age 35 and 64 a mortality from CAD of approximately twice that of the male Framingham population: for the females, in turn, diabetic mortality was 4 times that of nondiabetics. As seen already for IDDM, this male-female difference in ratio is based on the lower female mortality in the normal (Framingham) population and yet a similar one (male=female) in the presence of diabetes. - The second vascular cause of death, stroke, is 4.4 times more frequent in diabetic males and 5.1 times in diabetic females. Apart from vascular deaths, some authors reported an association of NIDDM and pancreatic cancer. Others questioned their findings. In 1995, Everhard carried out a meta-analysis on this problem. Figure 5 summarizes the results of 20 publications and yields an overall risk ratio of 2.1. Accordingly, pancreatic cancer appears to be twice as frequent in the NIDDM when compared to normals.

5. Markers for fatal complications in IDDM
Discrete alterations in organ function which may indicate severe complications late in the course of diabetes, are most helpful parameters for underwriting life insurance in these patients. As the true value of these discrete alterations is not yet clearly delimited, the expression, marker, is used rather than, risk angiotensin-I-converting factor. For IDDM, retinopathy, other ocular diseases, hypertension, microalbuminuria, and polymorphism of the angiotensin-I-converting enzyme gene are discussed here. Retinopathy occurs in up to 90 or even 100 per cent of IDDM. The progressive variant, proliferative retinopathy, is found in half of them and is associated with a 5-fold mortality compared to diabetics without retinopathy according to Ratzmann et al. Yet, when other risk factors are considered, particularly hypertension, the retinopathy as such adds little to the mortality accounted for by hypertension. Thus, the independent influence of retinopathy to mortality becomes marginal. Other ocular diseases, however, have been reported to be associated with an increased mortality: glaucoma 3 times, lens changes 2 times. Hypertension is a particularly important marker for the mortality of IDDM. Morish reported a 4-fold age adjusted mortality in IDDM patients with hypertension. As already mentioned, Parving has shown the important reduction in the mortality of nephropathy by appropriate treatment of elevated blood pressure. Several other studies confirm these findings.

Microalbuminuria has been identified 15 years ago as an indicator for later complications. It has been the subject of most intensive investigation. Most authors define it by an albumin
excretion rate of between 20 or 30 and 200 μg/min (equal to 30 or 45 to 300 mg/24 hrs). Its presence is considered to be a precursor of frank proteinuria. Its prevalence in IDDM is approximately 20 per cent. Almdal et al followed 118 juvenile type diabetics with microalbuminuria during 5 years. At the end of this period, 22 patients had progressed to frank proteinuria and a third of them had returned to normal values. Among the 48 per cent remaining microalbuminuria diabetics, half of them showed increasing microalbuminuria values. In 3,046 IDDM patients, from the EURODIAB study, Stephenson showed that microalbuminuria did not occur below diastolic blood pressures of 75 mm Hg (Figure 6). This leads to lowering the target of blood pressure hitherto used in the treatment of IDDM. Angiotensin converting enzyme (ACE) inhibitors have been shown to reduce microalbuminuria independent of and beyond their effect of reducing blood pressure. This lead the American Diabetes Association to recommend a yearly urinary test to search for microalbuminuria and, if positive, to treat it by ACE-inhibitors. Finally, several recent articles have reported that an insertion/deletion polymorphism in the angiotensin-I-converting enzyme (ACE) gene is associated with coronary heart disease. Tarnov et al find that the most favorable gene constellation has a 27 per cent incidence of coronary heart disease, when compared to the more unfavorable ones.

6. Markers for fatal complications in MID

As cardiovascular and cerebrovascular diseases are the most important causes of death in this type of diabetes, the well known other cardiovascular risk factor, smoking, hypertension, lipid abnormalities and obesity have to be paid the closest attention in NIDDM. In order, yet, to compare mortality figures in the diabetic with those of the normal population, one has to know whether these risk factors really operate in a similar way in diabetics and in nondiabetics. The Framingham study shows data from 5,245 diabetic and 350,977 nondiabetic subjects and suggests that this is the case (Figure 7). As a matter of fact, adding the number of risk factors up and comparing this sum with mortality yields a linear relationship for both diabetics and nondiabetics. This comparison was published after a Consensus Conference by the American Diabetes Association, and it implies that DM would just add an excess of (18 units per 1,000) to the previous risk. This is not the experience of Fessel et al, however, whose report on insured subjects found that diabetes has a multiplying effect on mortality. There is no need to repeat the most deleterious efforts of smoking on population mortality, also true for the diabetics. Yet, hypertension has been carefully studied in relation with diabetes: it is observed in almost half of them and doubles their mortality. Dyslipemia, in turn, has been shown to worsen survival also of diabetics and therapeutic reduction of serum cholesterol has been documented to reduce mortality in diabetics with cardiovascular disease. In contrast to the IDDM, where nephropathy is the main outcome of microalbuminuria, in the adult onset diabetics this marker rather predicts CV-death. Microalbuminuria and, if present, should be treated with ACE-inhibitors.
minuria is found in approximately 20 per cent of the NIDDM patients. The mortality figures are related to the quantity of albumin excreted. So far, microalbuminuria is defined as excretion rates above 20 μg/min. Interestingly, this limit appears to be too high according to the data of McLeod et al and those of Schmitz et al. Table 1 illustrates for NIDDM that mortality is elevated already for patients with albumin excretion rates above 10.6 μg/min. If this finding is confirmed by others, the definition of microalbuminuria as a marker in NIDDM would have to be adapted. Meanwhile, Stiegler et al showed an increased mortality at albumin excretions only beyond 30 mg/ (similar to 30 mg/24 hours or 20 μg/min).

Figure 7.

![Graph](image)

Effects of 3 major risk factors (hypercholesterolemia, smoking and diastolic hypertension) on age standardized cardiovascular disease mortality in 5'245 diabetic subjects (solid line) and 350'977 nondiabetic subjects (dotted line) between ages 35 and 57 and free of myocardial infarction at baseline. Follow-up 6 years. Reprinted with the permission of the authors and the publishers.

7. Treatment
The type of treatment and the compliance of the patient to his drug and diet regimens are essential parts in the analysis of survival of an individual diabetic. In the IDDM, treatment may reduce mortality by three different parameters: metabolic control, hypertension and microalbuminuria. The Diabetes Control and Complication Trial (DCCT, 72) has clearly shown that intensive insulin treatment schedules leading to a close to normal glycosylated hemoglobin (indicator of good metabolic control) allowed a reduction of all major complications (retinopathy, neuropathy and nephropathy) by half. The Swedish study by Reichard et al, preceding the DCCT reported similar results. Effects on mortality of these treatments have not yet been published, but there is little doubt that it will improve. Indeed, Krolewsky et al already showed a close relationship between glycosylated hemoglobin and microalbuminuria in IDDM. Likewise, Singer et al showed similar results in the cohort of the Framingham study. As optimizing metabolic control often is accompanied by weight gain, Chaturvedi et al have investigated this possible deleterious influence of obesity: increased weight in these patients did not augment mortality. Thus, optimizing metabolic control becomes priority over increased weight.

<table>
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<th>albumin excretion rate (μg/min)</th>
<th>&lt;10.5</th>
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<tr>
<td>n</td>
<td>153</td>
<td>48</td>
<td>31</td>
</tr>
<tr>
<td>dead (n)</td>
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<td>24</td>
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<tr>
<td>dead (%)</td>
<td>41.2</td>
<td>50.0</td>
<td>74.2</td>
</tr>
</tbody>
</table>

cause of death

| ischaemic heart disease (%)    | 18.9  | 25.0   | 32.2   |
| other vascular                | 6.5   | 16.7   | 9.7    |

Deaths and causes of death of non-insulin dependent diabetics according to their albumin excretion rate. Reprinted with the permission of the authors and the publishers.
The importance of elevated blood pressure and that of dyslipemia have already been discussed. For microalbuminuria, ACE-inhibitors have been reported to reduce albumin excretion by half.77 Accordingly, the American Diabetes Association recommends this treatment even in the absence of hypertension.99 Finally, Moy et al.78 show the beneficial effect on mortality of regular physical exercise.

For NIDDM, the individual cardiovascular risk factors have to be treated individually; physical exercise is an additional useful prescription.79,80 As the disease causes no pain, and its deleterious effects become evident only after many years, a change in behavior is possible only by intense educational efforts by the treating physician and his team. Hahnefeld and coworkers82 undertook a double blind study in two groups of 378 NIDDM each comparing conventional treatment with a combination of education, improving metabolic control and treatment of the other cardiovascular risk factors. After 5 years mortality was 25 per cent lower in the intensely treated group. For microalbuminuria the same treatment criteria are valuable as for IDDM.

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