CAUSE-SPECIFIC MORTALITY AND SURVIVAL AFTER MAJOR COMPLICATIONS IN TYPE 1 DIABETES

DOCTORAL THESIS

Zsolt Bosnyák MD

University of Pittsburgh
Graduate School of Public Health, Department of Epidemiology

University of Pécs
School of Medicine, Department of Pediatrics

Program leader: Prof. Judit Nagy MD, PhD, DSc
University of Pecs, Department of Medicine

Tutor: Prof. Gyula Soltész MD, PhD, DSc
University of Pecs, Department of Pediatrics

2009, Pécs

Introduction

Type 1 diabetes (T1D) is one of the most common serious chronic diseases of childhood. The majority of cases are classified as autoimmune diabetes, which usually is due to destruction of the B-cells of the Langerhans islets, however, non-autoimmune forms (e.g. maturity-onset diabetes of youth – MODY) have been recognized more often in the recent years.

Epidemiology of Type 1 diabetes

Among children, Type 1 diabetes is usually the most prevalent form of the disease. This disorder occurs with an annual incidence of 17 to 18 cases per 100,000 persons younger than 19 years. The prevalence rate is increasing because the incidence is rising and mortality rates are decreasing. One of the more intriguing aspects of the studies in the field of epidemiology of Type 1 diabetes is the remarkable variation in prevalence and incidence in various parts of the world. Incidence figures are lowest in Asia; Japan, Korea, and China report approximately one case per 100,000 people each year. Rates are highest in the Scandinavian countries, especially Finland, and in Sardinia, with incidence rates approaching 40 cases per 100,000 children and adolescents per year. The explanation for these geographic differences is still unclear. Although the frequency of genetic susceptibility haplotypes probably plays a major role among the different races, other populations have very similar gene frequencies. Thus, geographic variations and the rising incidence of T1D around the world point to the role of yet-to-be-determined environmental factors in precipitating insulin deficiency.

Approximately 5-15% of patients with known diabetes have Type 1 diabetes. A large proportion of these patients (probably >60%), acquire the disease before the age of 20 years, recognition is increasing that the disease may present in adulthood. In childhood, the mean age of onset is ~8 years. A peak is seen in adolescence, which occurs somewhat earlier in girls than in boys. A rise in incidence has been reported among children younger than 5 years. No significant difference is seen in sex distribution of diabetes during childhood.

Future for a child with Type 1 diabetes

In the last one and a half decades, important research advances have been made in patient management. One of the most significant in terms of convenience for the patient with diabetes, particularly the school-age child and adolescent, is the availability of modern analogue insulin short-acting and long-acting insulins, the new easy-to-use insulin delivery devices, the smaller glucose-monitoring meters and continuous glucose sensor systems and, last but not least, the convenient subcutaneous insulin infusion pumps are becoming widely available.

Unfortunately, despite the development of new technology in diabetes health care, individuals who develop T1D remain at substantially greater risk of early mortality. Children with T1D appear to be still much more likely to die than comparably aged individuals in the general population. The complications of diabetes markedly contribute to this.

The Diabetes Control and Complication Trial (DCCT) results unequivocally documented that sustained metabolic improvement in diabetes control is associated with highly significant reductions in the frequency, severity, and rate of progression of the serious microvascular complications. But there are only few large, consistent studies that have accurately quantified the mortality risk associated to acute and chronic complications of Type 1 diabetes. Little is known about the underlying causes of this mortality excess and the temporal changes in mortality by different T1D complications.

Epidemiological research is expected to reveal also the causes behind the excess mortality and worse survival that might explain the interrelationships between demographic data, early markers, risk factors, complications and mortality patterns.

Objectives

In the present studies we aimed to determine and analyze cause-specific mortality and complication related survival patterns in patients with T1D, specifically:

1. mortality rates related to acute and chronic diabetes complications and to analyze to role of CAD and nephropathy in the underlying causes of death in the Pittsburgh Metropolitan Area (Allegheny County, Pennsylvania, USA)

2. to compare two T1D populations living under considerably different social and health care circumstances in terms of cause-specific mortality patterns (Allegheny County registry vs Havana cohort)

3. to estimate the relative mortality of patients with T1D as compared to the general population in relation to age and duration of diabetes, and to analyze the effects of age at diagnosis, year of diagnosis in both populations

4. to examine racial (Caucasian, African-American, Hispanic) and gender differences in cause-specific mortality in both cohorts

5. to analyze the incidence and predictors of CAD and different stages of nephropathy (microalbuminuria (MA), overt nephropathy (ON), end-stage renal disease (ESRD)), as well as the survival after these complications, and their invasive treatment (coronary revascularization (PTCA, CABG) and renal replacement therapy (dialysis, kidney transplant)) in Allegheny County.

Patients and Methods

The present mortality, survival and complication analyses have been conducted on four, well described registries and prospective epidemiological studies: **1**. The Diabetes Epidemiology Research International (DERI) Study; **2**. The Pittsburgh Epidemiology of Diabetes Complications (EDC) Study; **3**. The Havana City cohort; **4**. University of Pecs, albuminuria follow-up

1. The DERI study is one of the largest population based prospective cohort study of T1D mortality initiated in 1986 to test the hypothesis of cross-population differences in diabetes prognosis. The study has evaluated mortality in comparable population-based cohorts from four distinctly different countries, but for present research purposes only the US cohort has been used. Inclusion in the study was based on the following criteria: 1. subjects were diagnosed with diabetes (all forms of secondary-cause diabetes excluded) before 18 years of age between January 1, 1965 and December 31, 1979; 2. placed on insulin at diagnosis; 3. residing in Allegheny County, Pennsylvania.

For this registry, the degree of ascertainment is well over 95 percent. 1,075 eligible cases were identified as of January 1, 1980.

2. The EDC study is a representative, originally 10-year prospective study examining the prevalence, incidence, interrelationships and risk factors of the various complications of T1D, now entering its 20th year of follow-up. The baseline examinations were conducted between 1986 and 1988, and participants were examined biennially thereafter. A total of 1,124 patients were eligible for the study, having been diagnosed or seen within 1 year of diagnosis at Children's Hospital of Pittsburgh between January 1950 to May 1980 and living within 100 miles or 2.5 hours from Pittsburgh. All were receiving insulin therapy at the time of initial discharge from the hospital. Of the 1,124 eligible patients, 658 subjects met eligibility criteria (325 women and 333 men) and participated in the baseline examination in 1986 to 1988 where the mean age was 28 years and diabetes duration was 19 years.

For wider mortality analyses the patient group of the DERI study was extended with EDC individuals based on a standardized procedure. Subjects involved into the combined cohort were identified from the Allegheny County, PA Registry and the Children's Hospital of Pittsburgh Registry (population and hospital based, respectively). 754 subjects came from the Allegheny County registry alone, 245 from the Children's Hospital and a further 262 subjects were members of both cohorts, giving a total of 1261 subjects. The eligibility criteria for the current combined analysis were: 1. a diagnosis of T1D between January 1, 1965 and December 31, 1979; 2. age <17 years old at diagnosis; 3. receiving insulin therapy at discharge from diagnosis hospital admission; and 4. residence of Allegheny County, Pennsylvania or living within 100 miles from Pittsburgh at diagnosis.

3. The Havana city cohort is created to determine the survival pattern and the underlying cause of death in a cohort of childhood-onset T1D subjects from Havana City Province, Cuba. The cohort was defined by 1. age at diagnosis of T1D (<15 years of age), 2. place of residence at diabetes diagnosis (Havana City Province), and 3. date of diagnosis (January 1, 1965 to December 31, 1980). Inclusion into the cohort began at the onset of T1D, and the patients were followed until they died, emigrated, or until January 1, 1991. Emigrated subjects were censored at the date of migration. Due to a unique identification system in Cuba, this registry is considered to be virtually complete with an ascertainment

rate of 100%. For further examine and compare the mortality in Havana, Cuba and in the Allegheny County, USA, a standardized cohort from these two population-based registries was created. Cases diagnosed with T1D between 1965 and 1980 in the Havana cohort and between 1965 and 1979 in the Allegheny County cohort were included. The inclusion criteria for both registries were: 1. diagnosed by a physician as having diabetes, 2. placed on daily insulin injection before the 15th birthday and 3. resident of the registry caption area at the time of first insulin administration.

4. To examine early microalbuminuria (MA) in children (age<18 years) with T1D, a standardized screening method and 5-year follow-up visits were initiated in 1997 at the University of Pecs, Department of Pediatrics. Beyond the general metabolic assessment and insulin dose optimization being done during the control visits in the hospital, the children underwent regular complication (e.g. ophthalmologic) examination as well. A total of 107 patients (44 boys and 63 girls) were followed.

Vital status and determination of causes of death

In the US cohort, living status as of January 1, 1999, was verified by letter or if needed, telephone contact (DERI) or by attendance at biennial examinations for subjects participating in the EDC study. The living status was determined for 1183 (94 percent) patients of whom 200 have died. In Cuba, a unique identity number in Population Registry (all deaths and migrations in Cuba are registered here) was used to obtain the subjects' vital status at January 1, 1991.

The underlying cause of death was determined by the review of death certificates, hospital records, coroner's records, and autopsy reports using the standardized protocol of DERI and verified by a committee of physicians based on a standardized protocol. For mortality analysis, the underlying cause of death was grouped into acute diabetes complications (deaths from diabetes ketoacidosis, hyperglycemia, hypoglycemia, and unspecified coma); chronic complications (deaths from renal, cardiovascular diseases, infection and other diabetes related problems), and other causes (deaths from non-diabetes related problems, e.g. accident/suicide, cancer and post-surgical complications). Cause-specific mortality rates per 100 000 person years of follow-up and 20-year cause-specific rates as well as temporal trends by sex and race were determined. Lifetable analyses by the Kaplan–Meier method were performed and the log-rank test was used to determine the statistical difference between the hazard curves. Mortality rates per person-

year of follow-up by country and race were determined. Standardized Mortality Ratio was also calculated. Survival analysis and Cox proportional hazard model were also included in the analysis.

Complication status

In DERI, living status as of 1999 was updated with the addition of a complication survey with nine new questions concerning renal, retinal, cardiovascular and peripheral artery status with asking also about the date of complications' onset. The diagnosis of coronary artery disease (CAD) was based on history of myocardial infraction and/or revascularization therapy as well as CAD related death confirmed by death certificate. Similarly, onset of end-stage renal disease (ESRD) was defined as the introduction of renal replacement therapy (dialysis or transplantation (kidney or pancreatic-kidney)).

In EDC, CAD was defined by a history of myocardial infarction, confirmed by electrocardiographic changes at time of examination, or review of previous medical records by use of standardized criteria, angina diagnosed by the clinic physician, ischemic ECG or coronary artery stenosis ≥50% by angiogram. Overt nephropathy was defined by renal failure or an albumin excretion rate >200 μg/min in at least two of three timed urine specimens. Cox regression modeling was used to examine relationships between T1D complication status and independent variables.

In the Pecs cohort, diagnosis of microalbuminuria (MA) was based on the results of three consecutive 24-hour urine collections (mean AER ≥ 30mg/day). Median-albuminuria was defined on the individual basis if the mean AER reached the median AER level of the total cohort (≥14.5mg/day). Logistic regression modeling was used to examine relationships between MA and median-MA status and independent variables.

Results

Mortality and underlying causes of death in the Pittsburgh Metropolitan Area

Overall, 200 deaths were observed (16.8 percent). Those dying were significantly ($p<0.001$) younger, had a shorter duration of diabetes, were older when they developed diabetes and their year of diagnosis was earlier. No difference was found by gender, however, African Americans had a greatly increased risk of death (hazard ratio= 3.3, 95% confidence interval: 2.2-5.0) compared to Caucasians. In the Cox regression models, age at onset, diagnosis year, and race predicted total mortality with the hazard ratios of 1.1

(95% CI=1.0-1.3), 0.90 (0.86-0.94), 3.3 (2.2-5.0), respectively. Among the 164 deceased whose causes of death were verified, 19 percent (n=31) died from acute diabetes complications, 101 from chronic diabetes related complications, 15 percent (25) died from other non-diabetes related causes. The leading cause of deaths was the group of cardiovascular diseases, mainly heart disease and coronary artery disease, followed by acute complications mainly diabetic ketoacidosis. Infection and renal disease played also a big role in the causes of death, while other causes involve diabetes and non-diabetes related problems, post-surgical complications, but mainly cancer. No major difference was seen by gender, however, based on the 20-year cause-specific mortality rates males died more frequently from non-diabetes related causes (especially accident/suicide) than females. African Americans had a higher mortality from acute complications (mainly ketoacidotic coma) compared to Caucasians. The increased mortality from acute complications in African Americans was apparent in both genders though only significant in women. No difference was seen by age or duration while the major underlying cause of death from acute complications was diabetic ketoacidosis in both races. The rates regarding the other diabetes-related and non-related causes did not differ significantly between the racial groups. The cumulative hazard curve for acute complication death was significantly worse in African Americans, started separating from the hazard curve of Caucasians already after 10 year of diabetes duration. No difference was seen, however, in the chronic complication hazard curves between the two races. Twenty-year cause specific mortality rates by diagnosis cohort showed a major, significant decline in both overall and chronic complication mortality as well. Though, a decreasing trend was apparent for both Caucasians and African Americans for each cause, only the decline in chronic complication mortality of Caucasians reached the level of significance.

Differences in mortality between Cuba and USA

Cumulative survival by registry demonstrated a worse survival in Havana (84% at 20 years) than in Allegheny county (91% at 20 years).

Mortality in Cuba was higher than in the US in both genders (males, $p<0.01$; females, $p=0.05$). Standardized Mortality Rates were significantly higher in Cuba in both sexes. More deaths in US were attributed to acute complications than to any other cause, while in Havana the leading cause of death was nephropathy, which accounted for nearly half of the deaths. Interestingly the mortality rate for acute complications was lower in Cuba

than in the US (although not significant) while renal mortality was eight times higher in Cuba (430 vs. 53 /100,000 person-years). There was an excess mortality among African-Americans attributed to acute complications (406/100,000) and infections (271/100,000) when compared to the Hispanics in Cuba or the Caucasians in the US. The cumulative survival analysis by race suggests that mortality for African-Americans was worse than for Caucasians but similar to that seen in Hispanics. SMRs showed similar pattern with regard to race differences. For African-Americans the risk of any cause mortality was 2.8 (95%-CI=1.5-5.4, p=0.002) times higher compared to Caucasians which was not determined by sex, year of diagnosis, year of birth or age at diagnosis. Mortality in Cuba was generally higher irrespective of age at diagnosis (p=0.08 for 0–4 years; p<0.01 for 5–9 years; p<0.01 for 10–14 years). The difference in crude mortality and SMR between the Havana and Allegheny County became even more dramatic in the 1970s (p=0.28 for 1965–1970; p<0.01 for 1971–1980.), however, a nice decreasing trend in the standardized mortality ratios could be seen in both cohorts with the later years of diagnosis.

Incidence of coronary artery disease (CAD) and nephropathy (MA, ON, ESRD)

In the DERI study, cumulative incidence rate of CAD was determined as 9.1% at 25 years, while other rates were 0.7% at 15; 3.0% at 20; and 28.1% at 30 years, respectively. Incidence density was calculated as 325/100,000 person-years. No differences by gender or race were seen in the incidence rates. When sub-cohorts by year of diabetes onset (1965-69, 1970-74 and 1975-79) were compared, the mean age at onset (11.5±5.6 yrs) for subjects diagnosed between 1975-79 was significantly (p=0.01) higher than for those diagnosed between 1965-69 (10.6±4.4 yrs) and 1970-74 (10.7±4.1 yrs), however, differences were not seen in sex and race. The cumulative incidences of CAD were not different significantly between patients diagnosed in earlier calendar years and those diagnosed more recently. During the observation, 104 individuals (13.0%) developed ESRD (incidence density: 521/100,000 person-years, cumulative incidence rate: 11.3 % at 25 years of diabetes, mean duration of diabetes: 25.0±5.6 years). The 20-year cumulative incidence rates of ESRD for the subjects diagnosed between 1965-69, 1970-74 and 1975-79 were 9.1%, 4.7% and 3.6% respectively, and differences between 1965-69 vs. 1970-74 (p=0.0073) and 1965-69 vs. 1975-79 (p=0.0091) were statistically significant (p value for 3 survival curves=0.006). The 20-year cumulative incidence rate of ESRD in African Americans was statistically higher than that of Caucasians (21.9% vs.

5.2%: p<0.0001). Cox proportional modeling indicated that a lower age at onset (OR=0.90/year, 95% CI: 0.85-0.95, p=0.001), a diagnosis in recent years (OR=0.55 (1970-74 vs. 1965-69), 95% CI: 0.34-0.88, p=0.013, and OR=0.39 (1975-79 vs. 1965-69), 95% CI: 0.20-0.74, p=0.0041) and being Caucasian (OR=0.60 (Caucasian vs. African-American), 95% CI: 0.46-0.77, p<0.0001) were protective against ESRD.

In the EDC follow-up, after excluding baseline cases (n=53) and those with no follow-up (n=19), 15% (56/382) of individuals developed new onset CAD during the 6-year observation. Similarly, 29 incident cases (10%) of ON were diagnosed out of 294 eligible subjects. During complication follow-up with a total of 2113 person-years for CAD and 1620 person-years for ON, somewhat higher incidence density was seen for CAD than ON (24.6/1000 person-years vs. 17.3/1000 person-years).

At the University of Pecs in 107 patients with childhood onset T1D (mean age at onset: 6.4±3.9 yrs), the incidence of microalbuminuria was 18 percent (n=19/107) at 5 years of diabetes duration, and 39% of subjects developed median-albuminuria (≥14.5mg/day). The 10-year cumulative incidence rate of MA was found to be 23% (10/44). There was no difference seen in gender. The 5-year incidence of MA was found to be significantly lower (chi square trend p<0.01) among patients with on early diabetes (0-4 years) onset compared to those in higher age groups (5-9, 10-17 yrs) by diabetes onset. In the 5-year longitudinal analysis, progression from normoalbuminuria to MA was revealed in 30% of patients, while improvement from MA to normoalbuminuria was detected only in two cases.

Risk factors and predictors of coronary artery disease (CAD) and nephropathy (MA, ON)

In EDC, those who developed CAD had significantly higher age, duration, HbA1, total and LDL cholesterol, triglycerides, systolic blood pressure, Beck depression score, white blood cell count (WBC), fibrinogen and lower estimated glucose disposal rate (eGDR - a good estimation of insulin sensitivity). HbA1 and triglycerides were statistically higher in incident cases of ON compared to non-cases, although again, eGDR was lower in those who developed overt nephropathy. Significantly more hypertensive individuals were found among both CAD and ON cases then in those did not develop the complications. For incident ON, both PAI-1 and tPA-PAI-1 were higher in those who developed the complication, although only the latter difference was significant. This association became

somewhat stronger (p=0.02) when only those were analyzed who did not develop CAD simultaneously. In addition, a significant trend (p<0.01) for an increased incidence of ON by tPA-PAI-1 tertiles was seen. With regard to their link to insulin resistance, a significant decreasing trend in incidence of both CAD and ON by eGDR tertiles was observed (p<0.01). In the Cox model only age (RR=1.05, 95% CI: 1.0-1.2, p=0.025) and triglycerides (RR: 14.2, CI: 1.5-22.2, p<0.001) were independent predictors of CAD while in the case of ON, HbA1 (RR: 1.4, CI: 1.1-1.9, p=0.022) and eGDR (RR: 0.7, CI: 0.3-0.9, p=0.001) predicted the development of the complication.

In the Pecs cohort, 5-year cross-sectional data showed significant correlation between albuminuria and age (r=0.23, p<0.05). Patients with MA were significantly older and they had significantly higher Tanner-score (p<0.01). Individuals with higher Tanner-score (more mature during puberty) had an almost 3-fold bigger chance (OR=2.7, 95% CI: 1.0-7.8, p=0.05) for developing MA than children with lower maturity degree, but in a multivariate model only age was proved to be an independent predictor of MA (RR=1.4, 95% CI: 1.1-1.8). Markedly higher HbA1c, systolic blood pressure, insulin requirement and Tanner-score was detected in subjects with progression from normoalbuminuria to MA. The mean Tanner-score was found to be significantly higher (p<0.05) among children with an albuminuria progression of 14.5mg/day during the 5-year follow-up.

Survival after coronary artery disease (CAD) and revascularization (RV) therapy

In the DERI study, incidence rates of non-fatal myocardial infarction (MI) and RV increased dramatically after 25-year of diabetes duration, while incidence of fatal MI left far behind the above two in incidence growth. Cumulative survival of subjects with MI followed by RV was 76% at 5 years whereas significantly less (p<0.01), only 53% of patients who developed MI but not treated with any form of RV survived 5 years. Patients who underwent any form of RV (PTCA or CABG), regardless of MI in history, had a significantly higher survival rate compared to those who developed MI but did not have any form of RV (p=0.003, p=0.04, respectively).

Survival after end-stage renal disease (ESRD) and renal replacement therapy (RRT)

Cumulative survival rates after introduction of RRT were 66.5% at 5 years and 51.2% at 10 years, respectively. The 5-year cumulative survival rates after introduction of RRT of the subjects diagnosed between 1965-69, 1970-74 and 1975-79 were 58.8%, 73.5% and 87.5% respectively. Cumulative survival rates at 5 years by groups of dialysis therapy

alone, dialysis followed by kidney transplantation, successful transplantation alone and failed kidney transplantation followed by dialysis therapy were 32.8 %, 85.8%, 62.0% and 80% respectively. Cumulative survival rate of all transplant recipient was 79.6% at 5 year, which was significantly higher than that of the subjects of dialysis therapy alone (32.8%, p=0.0002). Cox modeling revealed that the relative risk of death for all transplantation recipients against dialysis therapy alone was 0.25 (95% CI: 0.13-0.47; p<0.001). In all transplant recipients, the relative risk of death for pancreatic-kidney transplantation recipients compared to those with kidney transplantation only was 0.51 (95% CI: 0.14-1.8; p=0.29).

Discussion

Our mortality data were gathered from both population and hospital based registries of childhood onset T1D. Knowing the well described inadequacy of death certificate classification alone, it is of utmost importance that the DERI mortality classification process itself provided a highly standardized, unique method to make a more appropriate cause-specific mortality analysis that has led to a major redistribution of the causes of death. The proportion of deaths due to acute complications otherwise may have been seriously underestimated. Regarding deaths from chronic diabetes complications, our findings are consistent with the literature in showing that cardiovascular diseases and nephropathy are responsible for most premature mortality in people with 26-year long T1D. Our data showed a dramatically higher mortality among people with childhood onset T1D in Havana, Cuba compared to that in Allegheny County, USA. More deaths in USA were attributed to acute complications than to any other cause, while in the Cuban cohort the leading cause of death was nephropathy, which accounted for nearly half of the deaths. Interestingly the mortality rate for acute complications was lower in Havana than in Allegheny County which might be partly explained by the existence of universal care in Cuba in contrast with a more limited access to care in US. Unavailability of dialyses services were likely to relate the high renal mortality in Havana. The results of our analyses confirm previous reports showing an excess total mortality in African-Americans after 20 years of duration. In addition to this we also demonstrated that the excess rate is largely related to acute complications. Since the total mortality in the general population is also higher in African-Americans, and the standard mortality ratios,

as reported earlier for diabetes are relatively similar in both races, we assume that the poorer prognosis for African-Americans might reflect an underlying general, racial disparity in socio economic status, health care access and/or utilization and behavior. Mortality in USA for African-Americans was similar to that seen in Havana for Hispanics. Acute complication and infection related mortality clustered among African-Americans while Hispanics had much higher mortality rate from nephropathy. This, again, can be explained by the different health care system. Our results also showed an encouraging decline in time regarding chronic complication mortality, which may reflect improvements both in the treatment and prevention of complications. While acute complication mortality did not change much over time among Caucasians, there was a big improvement seen in Africans-Americans for those diagnosed more recently.

We could not show any decline in the cumulative incidences of CAD which is supported by others reporting no difference in the cumulative incidence of CAD according to the year of diagnosis. The benefits of improved diabetes care, therefore, do not (at least as yet) appear to have reduced CAD morbidity, although a nice decline in CAD mortality by the year of diagnosis could be seen. Our findings regarding the 5-year incidence rate of early microalbuminuria is mostly consistent with previous data in the literature. Estimates of the prevalence of MA during childhood are confounded by the effects of puberty which is supported by our data as well. Epidemiological data show major declines in total mortality and renal failure rates in individuals diagnosed after the mid-1960s. In terms of temporal trends of ESRD, the current study also indicates an improving trend in those diagnosed later in time.

In our follow-up analysis, well known traditional risk factors were revealed as independent predictors of CAD while glycemic status and insulin resistance proved to be related to the development of nephropathy. Our data supports previous suggestions that insulin resistance may play a role in the development of complications, particularly overt nephropathy. In contrast with other studies, we found no effect of glycemic control and other traditional risk factors on the development of early microalbuminuria. Our data also prove, however, that hormonal changes in puberty can accelerate the development of microalbuminuria in children with diabetes.

Probably due to the benefits of revascularization and other conservative-preventive therapies in those who developed CAD, the incidence of fatal MI remains relatively

stable after 25 years in spite of the dramatic increase in non-fatal MI. In our results, both forms of revascularization therapy seemed to be beneficial even in patients without myocardial infarction thus providing support for the early revascularization of T1D individuals with CAD. The cumulative survival after end-stage renal disease improved by the year of diabetes diagnosis probably reflecting better access and care in patients with renal disease. Transplant recipients had a better survival than patients on dialysis which is likely to be explained by the fact that healthier patients are placed on the waiting list for transplantation.

New findings

a) Beyond the unexpectedly common acute complications, coronary artery disease and renal disease attributed significantly to premature deaths of patients with Type 1 diabetes.

b) Racial differences in cause-specific mortality from Type 1 diabetes have been revealed. The excess mortality among African-American diabetes patients is particularly linked to acute diabetes complications, mainly diabetic ketoacidosis, in Cuban Hispanics, however, the leading cause of death is nephropathy. While mortality in the US was clearly related to acute care, excess mortality in Cuban patients was mainly attributable to long-term care reflecting the effects of two largely different health care systems on mortality and outcomes. This can lead us to the conclusion that different strategies might be needed to improve survival among individuals with Type 1 diabetes in USA and Cuba.

c) An encouraging improvement has been achieved overall in the mortality rates for all major causes (especially chronic diabetes complications among Caucasians) by calendar year of diagnosis probably due to the better preventive strategies of the recent years, though African-Americans are still more likely to be affected by diabetes-related deaths. Since acute complications of diabetes may be the most amenable to intervention, a focus on their prevention should be a high priority.

d) Incidence of overt nephropathy has been nicely decreasing in recent years, however, the benefits of improved diabetes care do not appear to have reduced morbidity of coronary artery disease, although a nice decline in their mortality by the year of diagnosis can be seen. This might also be explained by different predictors affecting the development of renal disease and coronary artery disease, as glycemia itself can more directly contribute to the former one while insulin resistance rather play a big role in the latter complication.

e) The development of early microalbuminuria might be considerable in children within five years of diabetes duration. Age at onset and pubertal maturity largely contribute to the risk of microalbuminuria. Although HbA1c might be less related to the early development of microalbuminuria, poor glycemic status may have long-term consequences for the risk of subsequent nephropathy and for cardiovascular risk in postpubertal children.

f) Once complication developed, right tertiary prevention strategy should be planned to improve life quality and prolong life-years. Both forms of revascularization therapy might be beneficial for patients with Type 1 diabetes who underwent myocardial infarction. Our data also provide support for early revascularization as a secondary prevention strategy. Survival after renal replacement therapy is greater with transplantation compared with dialysis therapy alone. Combined pancreatic-kidney transplantation seems to be beneficial over renal transplantation alone.

Acknowledgement

I would like to thank my first mentors, ***Professor Gyula Tamás*** and ***Dr. Zsuzsa Kerényi*** for their kind willingness to open the gate for me not only toward the world of diabetes epidemiology and research but also clinical diabetology and practice. I also would like to acknowledge my former mentor, ***Professor Trevor Orchard***, that he gave me the opportunity to work under his mentorship at the University of Pittsburgh, Department of Epidemiology where I started my training in Epidemiology as a young physician. With regard to research projects I was involved in, I also thank *Alberto Barcelo, Rimei Nishimura* for their extensive advice; *Melissa Hagan Hughes, Georgia Pambianco, Lesa Thomas (†), Nancy Silvers, Idamae Gower and Robb Wilson* for their contribution in contacting patients and data management; and of course study participants and their families for their willing assistance during data collection and evaluation. I would like to express my appreciation toward my current mentor, ***Professor Gyula Soltész***, for involving my work into his doctoral program and for giving me the opportunity to take part in epidemiological research at the University of Pecs, Department of Pediatrics. Finally, I dedicate this work to my parents and wife who always supported my commitment toward diabetes research.

Publication list of the author

Publications related to this thesis

Barceló A, **Bosnyak Z** , Orchard T: A cohort analysis of type 1 diabetes mortality in Havana and Allegheny County, Pittsburgh, PA. Diab Research and Clin Pract, Volume 75 (2): 214-219, 2007. **IF: 1.837**

Bosnyák Zs, Kozári A, Erhardt É, Soltész Gy: Korai mikroalbuminuria gyermekkorban diagnosztizált 1-es tipusú diabéteszben: 10 éves követés eredményei (Early Microalbuminuria in Patients with Childhood Onset Type 1 Diabetes: Results of a 10-year Follow-up). Diabetologia Hungarica, Volume 14 (4): 313-321, 2006

Bosnyak Z, Nishimura R, Hughes MH, Tajima N, Becker D, Tuomilehto J, Orchard TJ: Excess Mortality in Black vs White Patients with Type 1 Diabetes: An Examination of Underlying Causes. Diabetic Medicine, Volume 22: 1636-1641, 2005. **IF: 2.725**

Nishimura R, Dorman JS, **Bosnyak Z**, Tajima N, Becker DJ, Orchard TJ: Incidence of End Stage Renal Disease and Survival after Renal Replacement Therapy in Subjects with Type 1 Diabetes. A Report from the Allegheny County Registry. American Journal of Kidney Diseases, Volume 42 (1): 117-124, 2003. **IF: 3.897**

Bosnyak Z, Forrest KY-Z, Maser RE, Becker D, Orchard TJ: Does Plasminogen Activator Inhibitor (PAI-1) or Tissue Plasminogen Activator PAI-1 Complexes Predict Complications in Type 1 Diabetes: The Pittsburgh Epidemiology of Diabetes Complications Study. Diabetic Medicine, Volume 20 (2): 147-151, 2003.**IF: 2.235**

Other publications

Tabák AGy, Tamás Gy, Péterfalvi A, **Bosnyák Zs**, Madarász E, Rákóczi I, and Kerényi Zs: The effect of paternal and maternal history of diabetes mellitus on the development of gestational diabetes mellitus. Journal of Endocrinological Investigation, 2009 under revision **IF: 2.021**

Chang Yu P, **Bosnyak Z**, Ceriello A: The continued importance of improving glycaemic control in patients with type 2 diabetes. Diabetologia, 2009 submitted. **IF: 5.822**

Costacou T, **Bosnyak Z**, Harger GF, Markovic N, Silvers N, Orchard T: Postpartum adiponectin concentration, insulin resistance and the metabolic syndrome among women with pregnancy-induced disturbances. Preventive Cardiology, Volume 11: 106-115, 2008. **IF: 1.423**

Madarász E, Tamás Gy, Tabák Á.Gy., **Bosnyák Zs**, Tóth K, Szalay J, Csákány Gy.M., Kerényi Zs: 2-es típusú diabetes, szénhidrátanyagcsere-zavar és cardiovascularis rizikófaktorok előfordulása korábbi gestatiós diabetest követően: négyéves utánkövetés (Prevalence of Type 2 Diabetes, Glucose Intolerance and Cardiovascular Risk Factors following prior Gestational Diabetes : 4-year follow-up). Diabetologia Hungarica, Volume 14 (2): 153-162, 2006.

Bosnyák Zs, Kerényi Zs: A csökkent glükóztolerancia cardiovascularis következményei – áttekintés a STOP-NIDDM vizsgálat tükrében. (Cardiovascular Aspects of Impaired Glucose Tolerance: overview through the STOP-NIDDM Trial). Lege Artis Medicinae, Volume 14 (1): 57-58, 2004

Bosnyák Zs, Stella P: Az Amerikai Diabetes Társaság 63.Tudományos Konferenciája (Overview about the 63rd Annual Scientific Sessions of the American Diabetes Association). Lege Artis Medicinae Volume 13(6): 471-472, 2003.

Tabák Á.Gy., Kerényi Zs, Nagy E, **Bosnyák Zs**, Madarász E, Tamás Gy: Height and Gestational Diabetes Mellitus. Diabetic Medicine, Volume 19: 344-345, 2002.**IF: 2.678**

Kerényi Z, Stella P, Tabák AGy, Nádasdi Á, Madarász E, **Bosnyák Z**, Baranyi É, Csákány MGy, Karádi I, Tamás G: Gestational Diabetes Mellitus: Early Manifestation or Predictor of the Metabolic Syndrome. Diabetologia Hungarica, Volume 10 (Suppl 2.): 32-36, 2002.

Kerényi Z, Tabák ÁGy, Stella P, **Bosnyák Z**, Simon K, Karádi I, Tamás G: Association Between Socioeconomic Factors and the Metabolic Syndrome in Women with Prior Gestational Diabetes Mellitus. Diabetes Care, Volume 23: 1444-1445, 2000.**IF: 5.076**

Bosnyák Zs, Kerényi Zs, Stella P, Tabák ÁGy, Madarász E, Tóth K, Tamás Gy: Hypertonia gesztációs diabéteszben: a későbbi magasvérnyomás betegség előjelzője? (High Blood Pressure in Gestational Diabetes: Predictor of the Later Hypertension?). Hypertonia és Nephrologia Volume 4 (4): 198-209, 2000.

Kerényi Z, P. Stella, **Bosnyák Z**, Tabák AG, Tamás G: Association Between Central Adiposity and Multimetabolic Syndrome in a Special Cohort of Women with Prior Gestational Diabetes. Diabetes Care, Volume 22: 876-877, 1999. **IF: 5.076**

Kerényi Zs, Pánczél P, Tabák ÁGy, **Bosnyák Zs**, Bíbok Gy, Nádasdi Á, Stella P, Tamás Gy: Terhesség kapcsán észlelt "enyhe" diabéteszformák reklasszifikációja: szigetsejt- és GAD-ellenes antitestek gyakorisága az utánkövetéskor (Reclassification of "Mild" Diabetes Forms detected during Pregnancy: Frequency of Islet Cell and GAD Antibodies at Follow-up). Magyar Belorvosi Archivum 52: 369-374, 1999.

Overall IF: <u>25.0</u>