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Risk of Malignancies in Patients with Insulin-treated Diabetes mellitus

Results of a Population-based Trial with 10-Year Follow-up (JEVIN)

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Abstract
Background: Studies involving diabetes mellitus and malignancies show contradictory results: Many of them have found incidences of malignancies that are comparable or lower, other studies have found higher rates than those of non-diabetic subjects. Hence, the goal of the present trial was to study the possible association between diabetes mellitus and the incidence of malignancies and its outcome in a selection-free population over a longer period of time.
Patients and methods: All the patients (n = 291) who participated in the JEVIN (Jena's St. Vincent)- trial (a prospective, 10 year follow-up, population-based intervention survey of all insulin-treated patients with type 1 and type 2 diabetes mellitus aged 16 to 60 years and living in the city of Jena [about 100,000 inhabitants], Thuringia, Germany) were assessed. The baseline examination took place in 1989/90, follow-up examinations were performed in 1994/95 and 1999/2000.
Results: Up to 1999/2000, 2 patients with type 1 and 5 patients with insulin-treated type 2 diabetes mellitus developed a malignancy (incidence 0.0241). The most frequent malignancies were cancer of the colon and rectum (3 of 291 patients, incidence 0.0103). Comparing these data with the incidence of carcinoma of the colon and rectum reported by the Robert-Koch-Institute of Germany (incidence 0.0012) diabetic patients showed a 9.9-fold increased risk (p = 0.042). There were no significant differences regarding incidence of total malignancies or carcinoma of the breast, the lung, renal cells or gonads. Correlation and multivariate analyses revealed no associations between the development of malignancies and patients' outcome and diabetes duration, the duration of insulin therapy, insulin dosage, the quality of diabetes control or the presence of diabetes-related long-term complications.
Conclusions: Conclusive to other data derived from selected cohorts, population-based the JEVIN-trial demonstrate an increased incidence of malignancies of the colon and rectum in insulin-treated patients with diabetes mellitus. However, for further confirmation of these interesting results more studies in larger populations over longer periods of time are necessary to explain the heterogeneous findings in patients with diabetes mellitus of an increased incidence for some cancer entities, but not for others. Knowledge of these mechanisms should have important implications for the direction of strategies to prevent the development of malignancies, or to enhance ability to make an earlier diagnosis and more effective therapies.

Key words: Diabetes mellitus, malignancy, carcinoma, colon cancer, rectum cancer, HbA1c, insulin therapy

Introduction

Up to the present the studies published involving diabetes mellitus and malignancies show contradictory results: Many of them have found incidences of malignancies that were comparable (Green and Jensen 1985; O'Mara et al. 1985; Kopp et al. 1990; Janeczko et al. 1998; Gullo 1999; Kath et al. 2000) or even lower (Nerlich et al. 1998) than those of non-diabetic subjects. In contrast, some studies conclude that diabetes mellitus is linked to a higher incidence of malignancies (Widerhoff et al. 1997; Lindblad et al. 1999; Liu and Koo 2001; Yang et al. 2004) and/or a predictor of mortality from cancer (Coughlin et al. 2004; Folsom et al. 2004; Huo et al. 2004). In particular there are striking studies demonstrating an elevated relative risk of patients with diabetes mellitus for breast and colon cancer, even without poorer survival rates after cancer therapy. In a meta-analysis published in 2001 Liu and Koo (2001) revealed a 1.2- to 1.6-fold increase in the relative risk for patients with type 2 diabetes mellitus to develop colon cancer.

To clarify the relationship between diabetes mellitus and the development of malignancies the pathogenesis of type 2 diabetes must taken into account: Type 2 diabetes mellitus is either caused predominantly by insulin resistance with relative insulin deficiency (Polonsky et al. 1988; Reaven 1995; Yki-Järvinen 1995; Del Prato and Bruttomesse 1996) or by a deficit in insulin secretion (Davies et al. 1993; Pimenta et al. 1995; The expert committee on the diagnosis and classification of diabetes mellitus 1997). Following the pathophysiological concept of a relative insulin deficiency, patients show not only hyperinsulinaemia, but also elevated concentrations of insulin precursors (i.e. pro-insulin, pre-pro-insulin) (Davies et al. 1993a; Davies et al.

1993b). However, since insulin and its precursors have been shown to have some homology to the insulin-like growth factors (IGF-1, IGF-2) the role of diabetes mellitus and hyperinsulinaemia in carcinogenesis appears plausible (Rodeck et al. 1987; Hofmann et al. 1989; Kath et al. 1990; Bornfeldt et al. 1991; De Meyts et al. 1993; De Meyts 1994; Rosskamp and Park 1999). Thereby an association between type 2 diabetes mellitus, its treatment modalities (i.e. insulin therapy, therapy with insulin-secretagogues), but also type 1 diabetes mellitus and the incidence of malignancies should be analyzed. Moreover, the problem gains further complexity: On the other hand there are some data demonstrating a lower risk for cancer in patients with diabetes mellitus. These contradictory data are based on the concept of an alteration in the cell/matrix interaction. In patients with diabetes mellitus this alteration leads to an concomitant change in expression of the transforming growth factor ß expression (Nerlich et al. 1998).

The main goal of the present trial was to study the possible association between insulin-treated diabetes mellitus and the incidence of malignancies in a selection-free population over a longer period of time (Schiel et al. 1997; Schiel et al. 2001; Schiel et al. 2003; Schiel et al. 2005): Not only the incidences and types of cancer were analyzed, but also diabetes therapy including diabetes duration, duration of insulin therapy, insulin dosage, the quality of diabetes control and the prevalence of diabetes related long-term complications.

Patients and Methods

All the patients who participated in the JEVIN (Jena's St. Vincent)- trial (a prospective, 10 year follow-up, population-based intervention survey of all insulin-treated patients with type 1 and type 2 diabetes mellitus aged 16 to 60 years and living in the city of Jena [about 100,000 inhabitants], Thuringia, Germany) were assessed. The baseline examination took place in 1989/90 (Müller et al. 1993), follow-up examinations were performed in 1994/95 (Schiel et al. 1997) and 1999/2000 (Schiel et al. 2001; Schiel et al. 2003; Schiel et al. 2005).

In 1999/2000 a total of 291 patients with type 1 and insulin-treated type 2 diabetes mellitus were identified. Of these patients (type 1: n = 114, type 2: n = 147) 90% were examined by a physician (R.S.). The characteristics of these patients are shown in Table 1.

Table 1. Characteristics of patients with type-1- and insulin-treated type-2-diabetes mellitus aged 16 to 60 years and living in Jena (BMI= Body-mass Index).

	Type 1	Type 2
Number (n)	114	147
Women (%)	43	37
Age (years)	42.5 ± 11.2	52.5 ± 6.7
Diabetes duration (years)	15.6 ± 11.3	11.4 ± 7.2
BMI (kg/m2)	25.9 ± 3.7	30.4 ± 5.6
Relative HbA1c	1.48 ± 0.30	1.47 ± 0.25

Since 1990 twenty-nine insulin-treated registered patients have died. Of the remaining 30 patients, 9 refused to take part and the rest (n = 21) were unable to be contracted (address missing, no response).

Assessment of Quality of Care

To assess the quality of diabetes care the haemoglobin A1c was measured: HbA1c, HPLC, Diamat, (laboratory tests were performed at the Department of Clinical Chemistry, University of Jena Medical School, Jena, Germany.). The normal range (4.5-6.3%) of the method was assessed measuring 100 healthy subjects.

Investigation of diabetic long-term complications was done by

1. funduscopy through dilated pupils by an ophthalmologist. Retinopathy was diagnosed and classified according to the guidelines of the „Airlie-House"-classification used in the „Early Treatment Diabetic Retinopathy Study Group" (ETDRS) (Early treatment diabetic retinopathy study group 1991).
2. screening for peripheral polyneuropathy according to Young et al. (1993).
3. screening for nephropathy by measuring the urine albumin concentration (immunoturbidimetry 1989/90, nephelometry 1994/95 and 1999/2000, normal range <20 mg/l). For calculating the mean three early morning test results within a period of 6 weeks were used. In the case where only two specimens were available the results were used only if both were in the normal range or both were elevated. Infected urine specimens (bacterial counts $>10^5$/ml) were excluded. The serum creatinine was measured using the Jaffé reaction.

Height and body weight were assessed with the patients wearing light clothing and without shoes.

Malignancies were assessed either by interview in patients examined, or by the death certificates of those patients who died during the follow-up period. In all the patients the diagnosis was controlled by comparison with hospital or primary care physicians' records. The TNM system was used for the classification of malignancies (Mendelsohn 1995). Therapy of malignancy, outcome and the quality of diabetes control were assessed at the time of the last examination.

The results found in the population of insulin-treated patients with diabetes mellitus were compared to data of a cohort of diabetic patients out of a similar, but larger geographical area (city of Jena and the counties nearby), studied between January 1995 and April 1999 (Kath et al. 2000). Moreover, the data were compared to data reported by the Robert-Koch-Institute, Berlin, Germany regarding the incidence of colon and rectum carcinoma (personal information to Dr. R. Kath, 22.12.2002, No. 4245).

Statistical Analysis

Statistical analysis was performed using SPSS, (Statistical Package for Social Science). All data are presented as mean±standard deviation (SD) or, if the data did not show normal distribution, as median and range. For comparisons the Student's t-test, chi-square test,

Fisher's exact test for frequencies at or below 5 and Wilcoxon's rank sum test were used. Significance was defined at the 0.05 level.

RESULTS

Up to the follow-up examination in 1999/2000, out of the total of 114 patients with type 1 two patients and out of the total of 147 patients with insulin-treated type 2 diabetes mellitus, five patients developed a malignancy (total incidence 0.0241). The characteristics of the patients with versus without malignancy are presented in Table 2. In both type 1 and type 2 diabetes mellitus there were no differences between the groups regarding diabetes duration, duration of insulin therapy, daily insulin dosage or the quality of diabetes control (HbA1c). However, the type 1 patients with malignancy were significantly older than the patients without carcinoma.

The most frequent malignancies occurring within the population of insulin treated patients with diabetes mellitus were cancer of the colon and rectum (3 of 291 patients, incidence 0.0103). In the rest different tumor entities were found. Table 3 shows the entity of the malignoma and the classification according to the TNM system, the therapy, the outcome and patients' quality of diabetes control.

Comparing the data of the 291 patients with insulin-treated diabetes mellitus studied in the present JEVIN-trial with those derived from a similar, but larger geographical area (Kath et al. 2000), the results were conclusive, but there were some discrepancies comparing the data about the incidence of carcinoma of colon and rectum of JEVIN and those reported for all of Germany by the Robert-Koch-Institute, Berlin, Germany:

1. Data reported by Kath et al. (2000) for the similar geographical area:
   In this study malignancies were reported in 28 of 2720 patients with insulin-treated diabetes mellitus. Thus, the total incidence of malignancies in the trial of Kath et al. (2000) tended to be lower, but was statistically comparable to the incidence found in the present JEVIN-trial (0.0103 versus 0.0241, p = 0.073).
2. For Germany, the Robert-Koch-Institute, Berlin, Germany, reported a number of newly detected malignancies of the colon and rectum in 98,262 out of 85,000,000 inhabitants (one newly diagnosed carcinoma per 865 inhabitants, incidence 0.0012) for the period from 1989/90 up to 1999/2000. Comparing these data with the results of the JEVIN-trial (incidence 0.0103), diabetic patients showed a 9.9-fold increased risk for malignancies of the colon and

Table 2. Characteristics of patients with versus without malignancy.

	Type 1 without malignancies	Type 1 with malignancies	p-value	Type 2 without malignancies	Type 2 with malignancies	p-value
Number (n)	112	2		142	5	
Age (years)	42.3±11.2	53.9±2.4	0.030	52.4±6.7	54.4±6.1	0.511
Diabetes duration (years)	15.4±11.4	21.5±8.2	0.463	11.4±7.2	11.9±7.2	0.856
Duration of insulin therapy (years)	15.4±11.5	21.5±8.2	0.454	5.2±3.8	5.75±5.6	0.765
Insulin dosage (I.U./d)	0.64±0.24	0.35±0.14	0.085	0.59±0.31	0.60±0.50	0.933
HbA1c (%)	1.47±0.30	1.28±0.03	0.251	1.46±0.25	1.60±0.25	0.220

Table 3. Malignancies, their classification according to the TNM system and the outcome in 7 patients with insulin-treated diabetes mellitus. („NED: no evidence of disease").

Patient	**Type of diabetes**	**Age (years)**	**Diabetes duration (years)**	**HbA1c (%)**	**Malignancy**	**TNM**	**Therapy**	**Outcome**
1, female	1	52	16	7.1	Breast	pT2N1M0	Surgery, radiotherapy	Progression
2, male	1	64	21	8.1	Rectum	pT3N0M0	Surgery	NED
3, male	2	58	11	8.7	Colon	pT3N2M0	Surgery, chemotherapy, radiotherapy	NED
4, male	2	44	1	6.7	Rectum	pT2N0M0	Surgery, chemotherapy	NED
5, male	2	57	20	9.7	Lung	Disseminated	Chemotherapy	Died of progression
6, male	2	58	17	8.7	Renal cell	pT2N0M0	Surgery, chemotherapy	NED
7, male	2	54	12	10.2	Gonads	pT1N0M0	Surgery, chemotherapy	NED

rectum ($p = 0.042$). However, there were no significant differences with respect to the incidence of total malignancies or carcinoma of the breast, the lung, renal cells or gonads.

Correlation and Multivariate Analysis

The correlation and multivariate analysis of the patient data assessed in the JEVIN-trial included the following parameters: Patients' age and body-mass index, the duration of diabetes and the duration of insulin therapy at the time of the diagnosis of malignancy, the current insulin dosage per kilogram of body weight, the HbA1c-value, patients' sex and the presence of diabetes-related long-term complications (Table 4). None of the above-mentioned parameters included in the models showed any correlation or revealed an association to the development of malignancies.

Table 4. Prevalence of diabetes-related long-term complications in 114 patients with type 1 and 147 patients with insulin-treated type 2 diabetes mellitus examined in 1999/2000.

Prevalence (%)	**Type 1**	**Type 2**
Retinopathy	25	28
Neuropathy	18	33
Nephropathy	24	38

A multivariate analysis was also performed to investigate the associations between patient-age, body-mass index, the duration of diabetes, the duration of insulin therapy or the insulin dosage and the outcome of the patients after the diagnosis of malignancy: Again, there were no associations between these parameters.

Discussion

Insulin and its precursors pro- and pre-pro-insulin show homology to the insulin-like growth factors IGF-I and IGF-II. Various experimental studies have clearly demonstrated that insulin and its precursors are important mitogens and they are able to stimulate the proliferation rate of cells (Rodeck et al. 1987; Hofmann et al. 1989; Kath et al. 1990; Bornfeldt et al. 1991; De Meyts et al. 1993; De Meyts 1994; Rosskamp and Park 1999). Probably these effects are mediated through the binding of insulin and/or its precursors on the IGF-receptors. This binding results in the activation of tyrosine kinase and a cascade of intracellular responses. These complex mechanisms seem to play an important role in the development and progression of malignancies, in particular in patients with hyperinsulinaemia (Del Guidice et al. 1998). There are also some studies which lend support to the suggestion that patients with diabetes mellitus have higher incidence rates for various cancer entities (Widerhoff et al. 1997; Lindblad et al. 1999; Liu and Koo 2001; Yang et al. 2004) an/or higher mortality rates from cancer (Coughlin et al. 2004; Folsom et al. 2004; Huo et al. 2004).

In contrast to the hypothesis of insulin and its precursors as mitogen and stimulating factors for cell proliferation, based mainly on in vitro studies (Rodeck et al. 1987; Hofmann et al. 1989; Kath et al. 1990; Bornfeldt et al. 1991; De Meyts et al. 1993; De Meyts 1994; Rosskamp and Park 1999), in the present JEVIN-trial of a population of insulin-treated patients with type 1 and type 2 diabetes mellitus, there were no associations between the risk of developing or the outcome of malignancies and the duration of insulin therapy or patients' insulin dosage. There were also no associations between the incidence of malignancies and the quality of diabetes control or the prevalence of diabetes-related long-term complications.

All in all, the findings of the JEVIN-trial agreed with the results of a trial performed by Kath et al. (2000) in the same geographical area, as well as other trials published to date (Green and Jensen 1985; O'Mara et al. 1985; Kopp et al. 1990; Janeczko et al. 1998; Gullo 1999). However, the total incidence of malignancies in the JEVIN-trial was substantial or tended to be lower than the incidence rates reported by Becker and Wahrendorf (1997) for the population of the Federal Republic of Germany for the period between 1981 and 1990 or found in a population-based cohort in Denmark (Widerhoff et al. 1997) and in the Swedish hospital registry (Lindblad et al. 1999). However, when interpreting the incidence rates derived from the present JEVIN-trial, it must be taken into account that our survey was performed on a relatively young population of insulin-treated diabetic patients: In the mean, patients with type 1 were 43 years, patients with type 2 diabetes mellitus were 53 years old. Considering that incidence of malignancies increases with aging (Becker and Wahrendorf 1997), the results of the JEVIN-trial are perhaps biased in the direction of a lower incidence rate for the younger age of the patients with diabetes mellitus. Thus, looking at the incidence of carcinoma of the colon and the rectum found in our trial, the results gain further importance: In contrast to the relatively low total incidence for malignancies in the population studied, the incidence of cancers of the colon and rectum in this group was significantly higher compared to the German total population (personal information of the Robert-Koch-Institute Berlin, Germany, to Dr. R. Kath, 22.12.2002, No. 4245). With respect to these two cancers, our trial provides more evidence that diabetes is linked to a higher incidence of malignancies; a result which is conclusive to other recently published data (Liu and Koo 2001; Yang et al. 2004; Caughlin et al. 2004).

However, in other ways the findings of the present trial contrast to other published studies: Unterberger et al. (1990) found a significantly higher rate of metastatic diseases in women with both diabetes mellitus and breast cancer, suggesting diabetes mellitus and insulin as unfavourable prognostic factors (Talamini et al. 1997). Similar results were reported by Sellers et al. (1998). They found a higher prevalence of breast cancer risk factors in women with a family history of diabetes mellitus. But, surprisingly, in this study of more than 1,000 women, a family history of diabetes mellitus was not associated with an elevated rate of postmenopausal breast cancer. Other trials show the published data on diabetes mellitus and the incidence of malignancies to be still more contradictory. In pancre-

atic cancer, for example, diabetes mellitus seems not to be a risk factor, but pancreatic cancer can possibly lead to the development of diabetes mellitus or the impairment of the disease (Gullo 1999). Concerning renal cell cancer, in Sweden Lindblad et al. (1999) found an increased risk for patients with diabetes mellitus, whereas Nerlich et al. (1998) found a lower risk of developing cancer in people with diabetes mellitus. In Taiwan, Huo et al. (2004) identified diabetes mellitus as a risk factor for reduced long-term survival in patients with small (≤ 5 cm) hepatocellular carcinoma, but not in patients who underwent resection. Moreover, in the cohort Huo t al. (2004) studied, patients with diabetes mellitus were more susceptible to develop hepatic decompensation suggesting a negative influence of diabetes and/or its therapy on tumoral and/or cirrhosis factors.

However, although the patients studied in the present JEVIN-trial derived from a population of diabetic patients, they represent a relatively small group of only 291 subjects. In contrast, Lindblad et al. (1999) analysed the data of more than 150,000 patients with diabetes mellitus over a period of twenty years to detect an increased risk of developing renal cell carcinoma. It is possible that the lack of any associations between the parameters of diabetes therapy (quality of diabetes control, diabetes duration, duration of insulin therapy, insulin dosage) and outcome of malignancies, but also the relatively low total incidence rate of malignancies is not only due to the young age, but also due to the relatively small number of patients studied. Comparing the data with those given by the "Atlas of Cancer Mortality" for the Federal Republic of Germany (Becker and Wahrendorf 1997), the small number of patients means that there is also an underrepresentation of cancers such as breast and lung.

In conclusion, conclusive with others recently published trials (Yang et al. 2004; Coughlin et al. 2004), an increased risk for malignancies of the colon and rectum was demonstrated by the JEVIN-trial in a population-based survey of insulin treated patients with diabetes mellitus. However, for further confirmation of these interesting results more studies in larger populations over longer periods of time are necessary to explain the heterogeneous findings in patients with diabetes mellitus of an increased incidence for some cancer entities, but not for others. Knowledge of these mechanisms should have important implications for the direction of strategies to prevent the development of malignancies, or to enhance ability to make an earlier diagnosis and more effective therapies.

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