Glucose and Lipid Metabolism in Patients with Advanced Pancreatic Cancer Receiving Palliative Chemotherapy

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Abstract. *Background: The role of diabetes mellitus (DM) in the pathogenesis of pancreatic cancer (PC) and its prognostic role on patients with advanced disease remain undefined. Patients and Methods: Within a prospective single-center pilot study, 30 consecutive patients with advanced PC underwent metabolic profiling for glucose (fasting glucose level, oral glucose tolerance test (oGTT), serum insulin levels) and lipid metabolism (cholesterol, triglycerides, lipoprotein a) at the initiation of and two months after chemotherapy. Subgroups (DM vs. non-DM) were analyzed with regard to metabolic and outcome parameters. Results: Sixteen patients (53%) had DM, in seven of whom DM was newly-diagnosed by an oGTT. Patients in the DM subgroup had a higher prevalence of hypertension (p=0.05) and a higher BMI (p=0.01), but with no significant differences in pre-treatment cholesterol (p=0.55) and triglyceride levels (p=0.37). Regarding baseline oncological parameters, patients with DM more often had a reduced performance status (p=0.06), and were more likely to present with metastatic disease (p=0.09). The median overall survival was 3.9 months in the DM group and 8.3 months in the non-DM group (hazard ratio=0.67, 95% confidence interval=0.31-1.45, p=0.31), respectively. Conclusion: The incidence of DM is high in patients with PC and the lipid profile associated with DM may be different from that of patients with metabolic syndromes. The role of DM as a negative prognostic factor in advanced PC remains to be determined.*

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Pancreatic cancer (PC) remains a disease with a dismal prognosis: in 2008, an estimated 165,100 new cases were diagnosed worldwide in developed countries, with a nearly identical number of annual deaths due to PC (161,800). The 5-year survival rate thus still remains low, at approximately 5% (1). Establishing the diagnosis of PC is often notably hindered by non-specific early symptoms such as nausea, weight loss, fatigue and abdominal pain. It has been reported that patients with known diabetes mellitus (DM) have a higher incidence of PC compared to a non-DM control group (2-4). Thus, several groups have proposed that the onset of DM might also serve as a potential meaningful screening tool to detect PC at an early stage of disease (4, 5). Furthermore, it is known that up to 80% of patients with PC have abnormal levels of fasting glucose (6, 7). To date, only limited evidence from large studies exists on the profile and the clinical course of DM associated with a malignant exocrine pancreatic disease such as pancreatic adenocarcinoma (also known as DM type 3c), compared to the metabolic profile of the classical DM type 2 within the metabolic syndrome (7).

Some pre-clinical and early-clinical studies indicate that hyperglycemia and hyperinsulinemia might play an important role in the association between DM and the pathogenesis of gastrointestinal cancer (8-10). An experimental mouse model of PC showed a relationship between high levels of insulin and a higher proliferation rate of tumor cells (11). Thus, DM associated with PC may further enhance tumor initiation, as well as tumor growth, and thus may also represent a potential prognostic factor in patients with PC (12). However, most previous data on the correlation between DM and PC were generated from large epidemiological case control or cohort studies on unselected patients, or from studies including patients with PC undergoing surgery for resectable disease (3, 7). Prospective investigations on this topic for homogenous PC populations such as patients with advanced disease receiving modern gemcitabine-based chemotherapy regimens including anti-

epidermal growth factor receptor treatment with the novel oral tyrosine kinase inhibitor erlotinib are still lacking.

Therefore, this prospective single-center pilot study was designed in order, firstly, to provide the metabolic profile of a homogeneous patient population with advanced exocrine PC undergoing palliative first-line chemotherapy with regard to glucose and lipid metabolism; and secondly to obtain hypothesis-generating data on the prognostic role of hyperglycemia in this patient population, thereby providing evidence for future prospective studies investigating the associations between DM and PC.

Patients and Methods

Patient population and study design. This prospective single-center study was conducted at a German university hospital; all included patients were recruited from the Pancreatic Cancer Center at the Department of Internal Medicine III, Ludwig-Maximilians-University of Munich, Germany. Adult patients (>18 years of age) with a histologically- or cytologically-confirmed diagnosis of advanced exocrine PC [Union internationale contre le cancer (UICC) stage III and IV] and adequate organ function were eligible for this study. In order to generate a homogenous patient population, only patients receiving palliative first-line gemcitabine-based chemotherapy were included. Patients receiving adjuvant chemotherapy were excluded (however, previous treatments for PC such as surgery or adjuvant chemo-/chemoradiotherapy were allowed). The study was approved by the Ethics Committee of the Medical Faculty of the Ludwig-Maximilians-University of Munich, Germany. All participants gave written informed consent before any study-specific procedure was performed.

Data collection. From all included patients, data on medical history [*e.g.* age, gender, Karnofsky performance status (KPS), DM history, body mass index (BMI), hypertension and smoking status] were recorded based on medical records. A patient was also categorized as having pre-diagnosed DM if they were taking oral anti-diabetic medications or insulin at the time of inclusion in the study. Similarly, taking antihypertensive drugs regularly was also defined as arterial hypertension. Oncological baseline data included first diagnosis of PC, histology, stage of disease, and previous treatment. The applied first-line chemotherapy regimen was selected based on the decision of the treating oncologists (SB and VH), with all patients receiving standard-dose gemcitabine-based therapy. Response-to-treatment was monitored by performing regular computed tomography (CT) and/or magnetic resonance imaging (MRI) scans of the involved organs; response evaluation was made according to the Response Evaluation Criteria In Solid Tumors (RECIST, version 1.0) (13). Survival estimates were calculated based on the time from first PC diagnosis to death from any cause and also from the time frame of study entry (defined by the collection date of the pre-treatment baseline laboratory) to death from any cause.

A baseline fasting blood sample was obtained before the start of chemotherapy from each patient. Concentrations of plasma glucose, glycosylated hemoglobin (HbA1c), cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, very low-density lipoprotein (VLDL) cholesterol, high-density lipoprotein (HDL) cholesterol (including a calculation of the LDL/HDL-cholesterol ratio), Lipoprotein a [Lp(a)], carbohydrate-antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) were determined. In patients without pre-diagnosed DM, a standardized oral glucose tolerance test (oGTT; glucose measurements at 0, 30, 60 and 120 min) was performed. Insulin levels were measured during the oGTT in the fasting sample at baseline and after 30 min. After two months of chemotherapy, a follow-up fasting blood sample was collected and the same parameters as at baseline were determined. Furthermore, an oGTT was repeated after two months in patients who still did not meet the criteria for DM. For this study, patients with manifest DM (defined as fasting plasma glucose >126 mg/dl or 2-h glucose >200 mg/dl within the oGTT), impaired fasting glucose (defined as fasting plasma glucose of 100-125 mg/dl) or impaired glucose tolerance (defined as 2-h glucose of 140-200 mg/dl) were all classified as having impaired glucose metabolism (DM group). All other patients were included in the non-DM group.

Statistical analyses. Patients' and laboratory characteristics of the study population are given as percentages or as medians with their corresponding ranges. Survival probabilities were estimated by the Kaplan Meier method with 95% confidence intervals (CI) and differences in survival time were compared by the log-rank test. Mann-Whitney *U*-test and Fisher's exact test were used to compare different variables between groups, where appropriate. For describing the strength of association between two binary variables, an odds ratio (OR) was calculated. Due to the small sample size, no multivariate analyses were performed in this study. The data generated should be regarded as descriptive and hypothesis-generating.

Results

Patients' characteristics. Between September 2009 and November 2010, 30 consecutive patients with confirmed locally advanced or metastatic PC were recruited; 29 received gemcitabine-based chemotherapy, one patient had a rapid decline in KPS and therefore was unable to receive the planned treatment. Seven of the 30 patients (23%) had undergone previous surgical resection of the pancreatic tumor. The database was locked for final survival analysis in May 2012, with a median follow-up of 5.8 months (range=0.9-23.5 months).

Sixteen patients (53%) were allocated to the DM group based on the criteria defined above, whereas 14 patients had no evidence of abnormal glucose metabolism (non-DM group). Out of the 16 patients in the DM group, nine had pre-existing DM, whereas in seven patients, the diagnosis of impaired glucose metabolism was first established by the pre-treatment oGTT at baseline (three patients with manifest DM, four patients with impaired glucose tolerance). Six out of the 30 study participants were taking oral anti-diabetics at study entry and one patient was being treated with insulin; these seven patients were (by definition) included in the DM group, the remaining nine patients allocated to the DM group did not receive oral anti-diabetics or insulin at baseline. Furthermore, 19 out of 30 patients received oral antihypertensive drugs (12/16 in the DM group *vs.* 7/14 in

Table I. *Baseline patients' characteristics.*

Parameter	n	Non-DM group	DM group	*p*-Value
Patients, n	30	14	16	
Gender				
Male	17	6	11	
Female	13	8	5	
Age (years)				
Median	69	67	71	
Range	41-82	41-82	60-76	
KPS				
Median	90	90	85	0.06
Range	70-100	80-100	70-100	
Previous surgery	7	4	3	
Stage of disease				0.09
Locally-advanced	3	3	0	
Metastatic	27	11	16	
Smoking status				0.34
Current smoker	1	1	0	
Never smoker	15	8	7	
Ex-smoker	12	4	8	
Tumor localization				0.90
Head	12	6	6	
Body	8	4	4	
Tail	10	4	6	
Baseline CEA (ng/ml)				0.07
Median	9	5	12	
Range	0.6-1145	0.6-62	2-1145	
Baseline CA19-9 (U/ml)				0.37
Median	1548	712	2482	
Range	3-336000	11-51722	3-336000	
Chemotherapy				1.00
Gemcitabine	11	5	6	
Gemcitabine/erlotinib	18	9	9	

CEA: Carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; DM: diabetes mellitus; KPS: Karnofsky performance status.

Table II. *Comparison of the non-DM vs. the DM subgroup based on risk factors for metabolic syndrome and baseline lipid levels (n=30).*

		Non-DM group (n=14)	%	DM group (n=16)	%	*p*-Value
Hypertension						
Yes	21	7	50	14	88	0.05
No	9	7	50	2	12	
BMI						
Median	24	23		26		0.01
Range	16-35	16-35		21-34		
HbA1c (%)						
Median	5.6	5.5		6.3		0.05
Range	4.4-9.5	4.4-6.5		4.8-9.5		
Cholesterol (mg/dl)						
Median	195	210		185		0.55
Range	106-309	106-260		137-309		
Triglycerides (mg/dl)						
Median	110	122		106		0.37
Range	60-281	60-175		83-281		
HDL-cholesterol (mg/dl)						
Median	43	49		42		0.17
Range	16-83	16-83		25-64		
LDL-cholesterol (mg/dl)						
Median	128	136		125		0.56
Range	68-244	68-195		90-244		
VLDL-cholesterol (mg/dl)						
Median	19	18		20		0.23
Range	8-40	8-29		11-40		
LDL/HDL-cholesterol						
Median	3	3		3		0.13
Range	2-7	2-7		2-5		
Lp(a)-cholesterol (mg/dl)						
Median	21	24		19		0.65
Range	5-119	5-94		5-119		

BMI: Body mass index; DM: diabetes mellitus; HbA1c: glycosylated hemoglobin; HDL: high density lipoprotein; LDL: low density lipoprotein; Lp(a): lipoprotein a; VLDL: very low density lipoprotein.

the non-DM group), and six patients were on lipid-lowering medications (three patients in each group, respectively).

Baseline patient characteristics (grouped by DM *vs*. non-DM patients) are summarized in Table I. Compared to the non-DM group patients in the DM subgroup had a trend towards a lower KPS and higher median pre-treatment levels of the serum tumor markers CEA and CA19-9. Furthermore, all patients with locally-advanced disease were allocated to the non-DM subgroup.

Metabolic profile of PC-associated DM. Study patients with an abnormal glucose metabolism (DM group) were characterized by a higher prevalence of hypertension (88% *vs*. 50%; OR=7.0, 95% CI=1.1-43.0, p=0.05) and a higher BMI (26 *vs*. 23, p=0.01) with no significant differences regarding cholesterol (185 *vs*. 210 mg/dl, p=0.53) or triglyceride levels (106 *vs*. 122 mg/dl, p=0.37; Table II) compared to non-DM patients. No difference was obvious for baseline LDL-cholesterol (median 125 *vs*. 136 mg/dl) and for the protective HDL-cholesterol levels (median 42 *vs*. 49 mg/dl). The pro-atherogenic median Lp(a) levels were 19 mg/dl in the DM group and 24 mg/dl in the non-DM group, respectively (p=0.65).

Fourteen (46%) out of the 30 included study patients were being followed-up for a period of two months after the start of chemotherapy. Within this timeframe, a trend towards an increase in the median baseline fasting glucose level from 135 mg/dl (95% CI=75-267 mg/dl) to 158 mg/dl after two months (95% CI=91-219 mg/dl) in patients with DM was detected. By contrast, no differences were obvious for fasting glucose levels at baseline (83 mg/dl, 95% CI=78-93 mg/dl) and

after two months of chemotherapy (80 mg/dl, 95% CI=72-94 mg/dl) in the non-DM group. Thus there were significant differences in the median fasting plasma glucose levels of the DM group *vs*. the non-DM group both in the baseline blood sample (135 *vs*. 83 mg/dl, $p<0.01$) and after two months of treatment (158 *vs*. 80 mg/dl, $p=0.01$). The course of changes in lipid levels (baseline *vs*. two months after treatment initiation, grouped with regard to DM) is summarized in Table III.

Metabolic parameters and outcome. At the time of final study analysis in May 2012, 26 out of the 30 patients had died. The median overall survival for all patients was estimated to be 6.0 months (95% CI=3.4-8.6 months) from the time of study entry. Patients in the DM group had a median survival of 3.9 months compared to 8.3 months for patients in the non-DM subgroup (hazard ratio, HR=0.67, 95% CI=0.31-1.45, $p=0.31$, Figure 1). The median overall survival time calculated from the initial diagnosis of PC to death was 11.3 months (95% CI=2.7-19.9 months) for all recruited patients; in the DM group it was estimated to be 5.2 months, whereas in the non-DM group, the median survival from initial diagnosis was 14.1 months (HR=0.85, 95% CI=0.39-1.88, $p=0.69$).

After two months of gemcitabine-based chemotherapy, patients in the non-DM group showed disease stabilization by the RECIST criteria in 9/12 of the available cases, compared to 3/9 in patients allocated to the DM subgroup (OR=2.4, 95% CI=0.4-15.3, $p=0.39$). For nine patients, no results for objective response (evaluated by RECIST) after two months of treatment were available: one patient scheduled for treatment did not start chemotherapy due to a rapid decline in KPS; two patients died early; in two patients, progressive disease was determined clinically; and four patients were lost to follow-up or refused further treatment.

When a subgroup of the study cohort was divided according to pre-treatment fasting insulin levels as a dichotomous variable [measured only in patients who underwent a baseline oGTT (n=15); fasting insulin ≥10 U/l *vs*. <10 U/l)], patients with higher insulin levels had a median survival (calculated form study entry) of 7.1 months compared to 6.8 months for patients with a lower baseline fasting insulin (HR=1.03, 95% CI=0.35-2.98, $p=0.96$; Figure 2). When analyzing the survival time from PC diagnosis to death for this 'insulin cohort', patients with a baseline fasting insulin level ≥10 U/l had a median overall survival of 7.4 months compared to 14.8 months for patients with pre-treatment insulin levels of <10 U/l (HR=1.67, 95% CI=0.55-5.04, $p=0.37$).

Table III. *Changes in lipid status during the first two months of chemotherapy (n=14; grouped by DM status).*

	Non-DM group		DM group	
	Baseline (n=9)	After 2 months (n=9)	Baseline (n=5)	After 2 months (n=5)
Cholesterol (mg/dl)				
Median	221	182	193	178
Range	132-253	139-265	148-255	131-236
Triglycerides (mg/dl)				
Median	96	115	100	132
Range	60-175	68-191	98-281	74-205
LDL (mg/dl)				
Median	150	130	124	113
Range	83-195	86-172	100-168	83-145
VLDL (mg/dl)				
Median	16	20	20	18
Range	10-29	7-27	11-40	8-33
HDL (mg/dl)				
Median	55	58	42	45
Range	35-83	32-94	28-59	36-74
LDL/HDL				
Median	2	3	3	2
Range	1.8-5	1-4	2-4	1-3
Lp(a) (mg/dl)				
Median	55	39	13	11
Range	12-94	7-106	5-11	5-65

DM: Diabetes mellitus; HDL: high density lipoprotein; LDL: low density lipoprotein; Lp(a): lipoprotein a; VLDL: very low density lipoprotein.

Discussion

Increasing evidence exists for a significant role of impaired glucose metabolism in the pathogenesis and biology of gastrointestinal cancer (4, 7, 14). In exocrine PC, it remains unclear if DM is a risk factor (as is smoking status) for this disease, a secondary result of the pancreatic disorder (DM type 3c) or if diabetic metabolism pathways (*e.g.* hyperglycemia, hyperinsulinemia) are in fact more deeply involved in the biology, initiation and progression of this highly malignant tumor (4, 9, 10, 15, 16).

Based on the data generated from this prospective singe-center pilot study, we hypothesize that the proportion of patients with advanced PC (undergoing palliative chemotherapy) with a relevant glucose metabolism disorder is higher than what is determined by the patients' histories, that PC-associated DM might have a different lipid metabolic profile compared to DM type 2, and that hyperglycemia might have a negative prognostic role in advanced PC. Of note, patients allocated to the DM group in this study, also had negative baseline prognostic factors, including a lower KPS and a more advanced stage of disease; they also had a higher incidence of arterial hypertension and a higher median BMI. Thus, at this time point, it remains unclear if well-known prognostic factors in advanced PC, such as KPS and stage of disease, are dependent on or independent of DM. Due to the design and the sample size of our pilot study, no

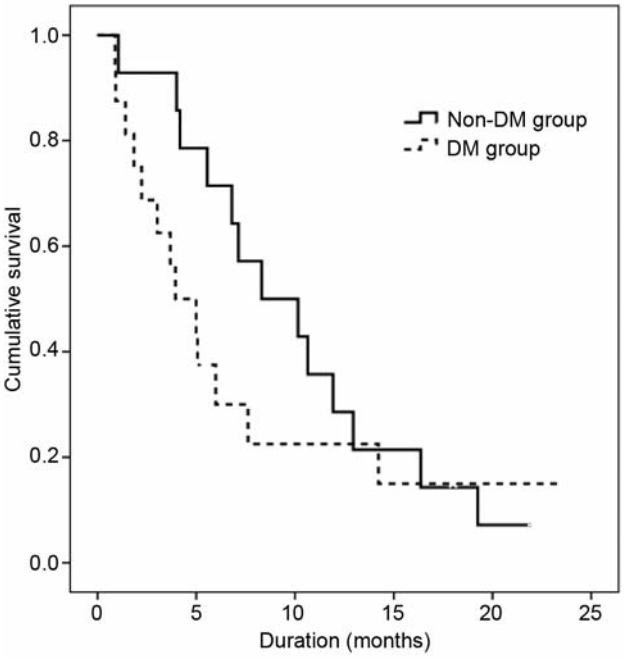

Figure 1. *Kaplan Meier curve for overall survival of all study patients based on the diabetes mellitus (DM) subgroup (n=30; DM group median 3.9 months vs. Non-DM group 8.3 months, p=0.31).*

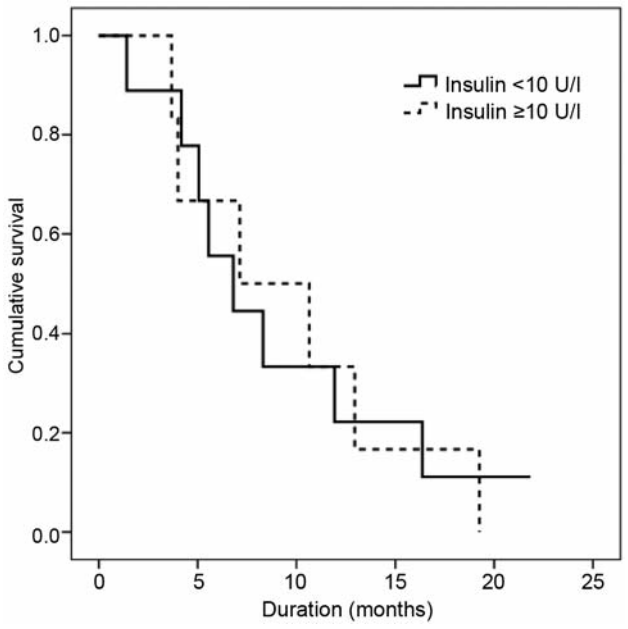

Figure 2. *Kaplan Meier curve for overall survival of study patients related to fasting pre-treatment insulin levels (cut off=10 U/l) (n=15; median 7.1 months for those with ≥10 U/l vs. 6.8 months for those with <10 U/l, p=0.96).*

multivariate analyses were performed. However, the observation that the objective disease control rate by imaging may differ depending on DM status supports the assumption that an impaired glucose metabolism may apparently have an adverse effect on the treatment response and outcome in solid tumors, including PC (4). No trend for an influence of hyperinsulinemia on survival was obvious in our patient population. Based on pre-clinical findings, a prospective clinical evaluation of a correlation between hyperinsulinemia and outcome in PC nevertheless seems warranted (4). Interestingly, the lipid levels of cholesterol, triglycerides, HDL and LDL seem to be equal (or potentially even favorable) in the DM subgroup compared to the non-DM group of patients.

Several groups already have discussed the potential of antidiabetic drugs such as metformin, not only in treatment of PC-associated DM, but also with regard to its effects on glucose and insulin metabolism (15). These (mainly pre-clinical) data are currently supported by a recent large retrospective single-center study which found that metformin use was associated with an improved outcome for patients with DM and PC. Interestingly, the beneficial effect of metformin was significant only in patients with resectable or locally advanced disease, and not in patients with metastatic PC (17). To date, the largest prospective study on the clinical profile of PC-associated DM was conducted by Pannala and colleagues (7): within their 'Mayo Clinic Pancreas Cancer Specialized Program of Research Excellence' cohort study, the authors found that DM associated with PC was often new-onset and may resolve following PC surgical resection. Similar to our data, the Mayo Clinic investigators found that DM in PC appeared to be associated with conventional risk factors (such as age, BMI and family history of DM) for type 2 DM. Data on lipid metabolism or on outcome end-points were not assessed in their study (7). Similarly to our findings, Aggarwal and colleagues very recently reported on a high prevalence (68%) of DM in 100 consecutive patients with PC (any stage of disease); however, the authors did not asses the impact of DM on patient characteristics and outcome (18).

Of note, the metabolic profile of a patient with advanced PC undergoing palliative chemotherapy may be affected by the aggressive course of the disease, and these patients often present with cancer-induced cachexia even at their first presentation (19). This progressive cancer-related cachexia and the associated malnutrition often remain significant medical problems in daily clinical practice during the natural course of the disease. As lipolysis is increased in cancer-related cachexia, these mechanisms also may influence the metabolic profile of such patients (20).

The main limitations of the current study include the small number of patients studied, the design of the trial (single-

center analysis from a university cancer center) and based on these factors, the potential for selection bias. Furthermore, due to the sample size, multivariate analyses were not performed and we therefore are not able to determine if, for example, abnormal glucose metabolism may represent an independent prognostic factor in this patient population. Thus the obtained data should rather be regarded as hypothesis-generating than definitive. The strength of this prospective study is based on its unique patient selection, with the inclusion of patients with confirmed locally-advanced or metastatic PC receiving a standard first-line gemcitabine-based treatment approach only. Data on metabolic profiling for such a patient population have, at least to our knowledge, not been published to date and we strongly recommend such an approach be taken in future prospective treatment trials in advanced PC, in order to generate valid data and to confirm the hypotheses obtained from the current pilot study.

In conclusion, DM seems to play an important role in the pathogenesis of advanced PC and further studies should specifically address the association between abnormal glucose metabolism and PC biology and prognosis.

Conflicts of Interest

Authors declare they have no conflicts of interest in regard to this study.

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