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ORIGINAL ARTICLE

Serum leptin levels may have diagnostic and predictive roles in patients with pancreatic adenocarcinoma treated with gemcitabine-based chemotherapy

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Summary

Purpose: *Leptin is a highly pleiotropic adipokine. Pancreatic adenocarcinoma (PA) and leptin relationship is important. Our aim was to investigate the serum levels of leptin in patients with PA, the relationship of leptin with tumor progression and known prognostic parameters and its diagnostic, predictive and prognostic role.*

Methods: *Thirty-three patients with PA were investigated. Serum samples were obtained on first admission before treatment and follow-up. Both serum leptin levels were determined using enzyme-linked immunosorbent assay (ELISA). Age, sex, and body mass index (BMI) matched to 20 healthy controls were included in the analysis.*

Results: *The median patient age at diagnosis was 59 years (range 32–84) and 20 (61%) patients were men. The tumor was located in the head of pancreas in 21 (63%) patients. The most common metastatic site was liver in 23 patients with metastasis (N=19; 83%). The median follow-up time was 26.0 weeks (range 1.0-184.0). At the end of the observation period, 32 patients (97%) had died. The baseline serum leptin levels were significantly higher in patients with PA than in the control group (p=0.02). Thirty-nine percent of 23 metastatic patients who received palliative gemcitabine-based chemotherapy (gCTx) were gCTx–responsive. Serum leptin levels were significantly higher in the gCTx-unresponsive patients compared with gCTx -responsive (median 5.32 vs 1.16 ng/mL, p=0.004). Conversely, serum leptin concentration was found to have no prognostic role on survival (p=0.20).*

Conclusion: *Serum leptin levels may be a good diagnostic and predictive tool on the response to gCTx in PA patients.*

Key words: *gemcitabine, leptin serum levels, pancreatic adenocarcinoma, predictive*

Introduction

PA is the fourth leading cause of cancer mortality in the United States among both men and women. The majority of these tumors (85%) are adenocarcinomas arising from the ductal epithelium. PA has an extremely high mortality rate due to its aggressive metastatic nature [1,2].

Numerous epidemiologic studies describe an association between diabetes mellitus, glucose metabolism, insulin resistance and pancreatic cancer [3-9]. Several environmental risk factors have been implicated in the risk of PA, including tobacco use, diet, alcohol, and high caloric intake. Several studies suggest a link between high body mass, lack of physical activity, and pancreatic cancer risk [10-16].

Leptin is a highly pleiotropic adipokine that is synthesized primarily in white adipose tissue [17]. It is important in the neurological regulation

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of physiological processes and behaviors including appetite, metabolism, and body weight and glucose homeostasis [17]. Obesity creates a pathological state whereby high leptin concentrations downregulate leptin receptors and signaling, thus fostering leptin resistance and contributing to greater adiposity [17]. Body mass index (BMI) and body fat are strongly correlated with leptin production [18]. Under conditions of regular food intake, leptin concentrations reflect the proportion of adipose tissue [18].

Leptin has been shown to enhance tumor vascularization, promote cellular proliferation, migration, invasion, and inhibit apoptosis of tumor cells, raising the possibility that the epidemiologic association between BMI and pancreatic cancer might in part be mediated by leptin [18,19]. Leptin receptors have been identified in many cancers and cell lines, including breast, colon, esophagus, genitourinary system, lung, prostate, pancreas and in lymphomas and leukemias [20,21]. In vitro studies have demonstrated a mitogenic effect of leptin on cell lines of breast, colorectal, ovarian, lung, prostate, and esophageal cancer [21].

In a recent study, the concentration of leptin and BMI was found to be similar in the PA and control groups [22]. In another study, an association between increasing leptin concentration and PA was found; however, long term follow-up is necessary to observe the relationship [17]. Wallace et al. demonstrated a significant positive correlation between body fat loss and increase in leptin levels of healthy subjects and cancer patients (r_s = 0.731) [23]. In advanced PA daytime serum leptin concentration appeared to be lower in the cachexia group, albeit without statistical significance [24]. In another study, patients with PA had significantly lower plasma leptin levels as compared to controls. No significant differences between serum level of leptin, age, gender, BMI, smoking status, tumor localization, distant metastases and pain has been found in this study.

The aim of the present study was to investigate the serum levels of leptin in patients with PA, the relationship of leptin with tumor progression and known prognostic parameters and its diagnostic, predictive and prognostic role.

Methods

The data of 33 patients with histologically confirmed PA diagnosis, treated and followed up in our clinic were retrieved from medical charts. Patients were evaluated for history of diabetes, and those with diabetes before the diagnosis of cancer or who developed diabetes after the diagnosis were excluded from the study. The exclusion criteria included patients who had undergone oncological therapy before the surgical treatment, and patients with other than adenocarcinoma or inflammatory tumor lesions in the pancreas. There was no coincidence of PA in the control patients' group. Localization of the tumor was determined surgically, endoscopically or radiologically. Pathologic confirmation of pancreatic cancer was obtained by surgery or fine needle aspiration biopsy. The staging of metastatic patients was done by using various imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission computed tomography (PET/CT) scan. Patients were staged according to the International Union Against Cancer TNM classification system.

gCTx was given to the majority of the patients with metastatic disease as single-agent or combination therapy (N=20; 61%). Regimens of single or combination chemotherapy were selected based on the ECOG performance status (PS) of the patients (ECOG PS 0 in 10 patients and 1 in the remaining) and disease extension. The following regimens were administered: combination of gemcitabine with platinum or capecitabine (N=6 and N=3, respectively), or gemcitabine alone (N=11). Response to treatment was determined radiologically after 2-3 cycles of gCTx according to the revised RECIST criteria, version 1.1., and classified as follows: complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Tumor response after 2 months of gCTx was used for statistical analysis. Follow-up programs of metastatic disease consisted of clinical, laboratory examinations, and usage of CT or MRI depending on which imaging methods were used at baseline and performed at 8-week intervals during gCTx or every 12 weeks for patients not taking chemotherapy. Patients with either PR or SD were classified as responders, and patients with PD were considered non-responders.

The possible prognostic variables were selected based on those identified in previous studies. Serum carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19.9 levels were determined by microparticle enzyme immunoassay (Abbott Diagnostics, Chicago, IL). Serum erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH) levels, albumin and whole blood count assessments were measured at presentation in our biochemical laboratory. Serum LDH activity was determined immediately after collection by the kinetic method on a Targa-3000 autoanalyzer (Pointe Scientific Inc., Lincoln Park, MI, USA) at 37°C.

For comparison of serum levels of leptin, age, sex, and BMI matched 20 healthy controls were included in the analysis. Blood samples were obtained from patients with PA three weeks after surgery, just before

adjuvant or palliative treatment. Institutional Review Board approval was obtained from each individual prior to the commencement of the study.

Measurement of serum leptin levels

This assay is a direct Sandwich ELISA based, sequentially, on: 1) capture of human leptin by a polyclonal rabbit anti-human leptin antibody immobilized on a 96-well microtiter plate; 2) washing away unbound materials; 3) binding of a biotinylated monoclonal antibody to the captured human leptin; 4) washing away unbound materials; 5) binding of streptavidin-horseradish peroxidase to the immobilized biotinylated antibodies; 6) washing away free enzyme conjugates; and 7) quantifying bound streptavidin-horseradish peroxidase with the substrate 3,3',5,5'-tetramethylbenzidine. The enzyme activity was measured spectrophotometrically by absorbance at 450-590 nm after acidification of the formed products. Since the increase in absorbance is directly proportional to the amount of captured human leptin in the unknown sample, the latter can be derived by extrapolation from a reference curve generated in the same assay with reference standards of known concentrations of human leptin. After putting the substrate, stop solution was added and the change of color was terminated. The intensity of the color was measured using an automated ELISA reader (Chro-Mate, 4300 Microplate Reader, Palm City, FL, USA). The results were expressed as ng/mL.

Statistics

Continuous variables were categorized using median values as cut-off point. For group comparison of categorical variables, Chi-square or One-Way ANOVA tests were used and for comparison of continuous variables, Mann-Whitney U test or Kruskall-Wallis test were performed. Overall survival (OS) was calculated from the date of first admission to the clinic to disease-related death or date of last contact with the patient or any family member. Univariate analysis and Kaplan-Meier method were used for the estimation of survival distribution and differences in OS were assessed by the log-rank. In all statistical tests a two-sided p value ≤0.05 was considered statistically significant. Statistical analysis was carried out using SPPS 21.0 (SPSS Inc., Chicago, IL., USA) software.

Results

From February 2010 to July 2013, 33 patients with pathologically confirmed diagnosis of PA were enrolled in this study. The baseline histopathological and demographic characteristics of the patients are listed in Table 1. The median age at diagnosis was 59 years (range 32–84); the majority of the patients were men (N=20; 61%). The tumor was located in the head of pancreas in 21 (64%) patients. Thirty-nine percent of 23 metastatic patients who received palliative gCTx were gCTx-responsive. The most common metastatic site was the liver in 23 patients with metastasis (N=19; 83%). Surgery was performed to 10 of the non-metastatic patients; 5 (15%) patients underwent pancreaticoduodenectomy and 3 (9%) had palliative surgery.

BMI was 22.2 kg/m^2 (range 16.2-32.3 in the

Table 1. Patient and disease characteristics

Characteristics	*N*
No. of patients	33
Age (years), median (range)	59 (32-84)
Gender Male/Female	20/13
ECOG PS[a] 0/1/2/3	4/19/5/4
BMI (kg/m^2), median (range)	22.2 (16.2-34.3)
Jaundice[a] Yes/no	9/22
Surgery type[aa] Whipple /palliative	5/3
(pT) size[a] <Small (<40 mm)/≥ large (≥40 mm)	14/14
Site of lesion[a] Head/corpus-tail	21/10
Response to CT Yes (PR+SD)/no (PD)	9/11
Metastasis Yes/no	23/10
HSR[a] Normal (<40/h)/high (>40/h)	11/12
WBC[a] Normal (<10.000/mm^3) /high (>10.000/mm^3)	22/9
Hb[a] Low (<12 g/dl)/normal (>12 g/dl)	12/19
PLT[a] Low (<150.000/mm^3) /normal (>150.000/mm^3)	5/26
LDH[a] Normal (<450 IU/l)/high (>450 IU/l)	21/8
Albumin[a] Low (<4 gr/dl)/normal (>4 gr/dl)	10/17
CEA[a] Normal (<5 ng/ml)//high (>5 ng/ml)	19/10
CA 19.9[a] Normal (<38 U/ml)/high (>38 U/ml)	7/22

[a] Patients with unknown data concerning the variables are not included in the analysis, [aa] In 10 patients with non-metastatic disease

PS: performance status, BMI: body mass index, ESH: erythrocyte sedimentation rate, Hb: hemoglobin, WBC: white blood cells, PLT: platelets, LDH: lactate dehydrogenase, CT: chemotherapy

Table 2. Leptin levels in pancreatic cancer patients and healthy controls

	Patients (N=33)		*Controls (N=20)*		
Marker	*Median*	*Range*	*Median*	*Range*	*p value*
Leptin (ng/mL)	3.51	0.11-14.64	0.90	0.08-4.33	0.02

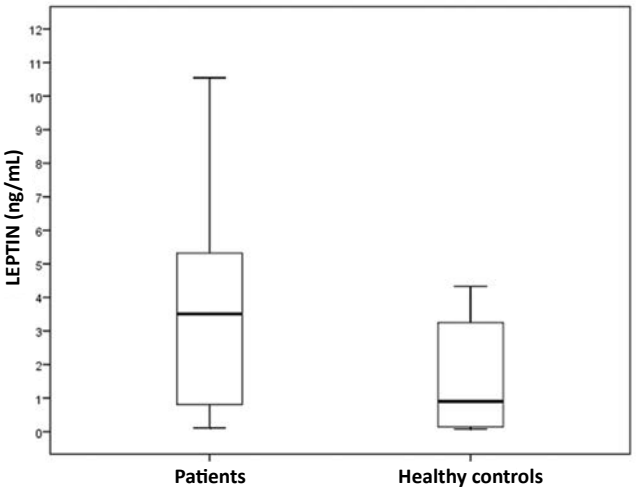

Figure 1. Serum leptin values in pancreatic cancer patients and controls (p=0.02).

patient group) BMI was 24.0 kg/m^2 (range 21.4-36.5 in the control group). There was no statistically significance between the two groups (p=0.21). The levels of serum leptin in patients with PA and healthy controls are shown in Table 2. The baseline serum leptin levels were significantly higher in patients with PA than in the control group (p=0.02) (Figure 1).

Table 3 shows the correlation between the leptin serum levels and clinico-pathological factors. Serum leptin levels were significantly higher in the gCTx-unresponsive patients compared with gCTx-responsive (p=0.004).

The median follow-up time was 26.0 weeks (range 1.0-184.0). At the end of the observation period, 32 patients (97%) had died. Median OS of the whole group was 41.3±8.3 weeks [95% confidence interval (CI)=25-58 weeks], while 1-year OS rate was 24.2% (95%CI=9.5-38.9). Older patients, worse performance status, metastatic disease, lack of liver metastases, and the gCTx-unresponsiveness were found to be significant prognostic factors (p=0.008, p=0.002, p=0.008, p=0.02, and p=0.03, respectively). However, serum leptin levels had no significant impact on OS (p=0.20) (Table 4 and Figure 2).

Discussion

PA is a lethal malignancy which is related with obesity and high BMI. It is diagnosed at advanced stages with metastasis to distant organs and is preceded by significant weight loss which could affect circulating leptin concentrations.

In the present study no statistical significance between the PA and the control group (p=0.21) was found in relation to BMI. The baseline serum leptin levels were significantly higher in patients with PA than in the control group (p=0.02), but leptin levels showed no statistically significance according to BMI median levels as shown in Table 3. It was higher in PA patients whose leptin levels were higher but without statistical significance.

In the literature there are reports with different and conflicting results about the relationship of serum leptin concentrations and PA. Some have found that even relatively modest weight loss in PA has been shown to substantially reduce blood leptin levels [26]. In another study serum leptin concentrations were similar between the PA and control group, but lower in the chronic pancreatitis group [22].

There might be processes independent of BMI related to latent PA and there are biologically plausible reasons why higher leptin concentrations may be associated with risk of PA [17]. Leptin can promote tumor vascularization, as well as proliferation, migration, and invasion of tumor cells [19]. In rodent models obesity promotes both pancreatic carcinogenesis and increase of leptin concentrations [27-30].

Several authors have reported that median leptin levels showed substantial intra-day variations in PA patients with cachexia and in those without cachexia [24]. There are two recent reports which emphasize the importance of leptin on PA tumorigenesis [31,32]. In one of them leptin contributed to pancreatic tumor growth through activation of the PI3K/AKT/mTOR pathway, which promotes pancreatic tumor cell migration [31]. The other one found that leptin enhanced the invasion of PA through the increase in matrix metalloproteinase-13 (MMP-13) production, and targeting the leptin/MMP-13 axis could be a therapeutic strategy for PA [32].

Only limited data exists on the relationship

Table 3. Results (median and range) of comparisons between the leptin levels and various clinical parameters

Parameters	*N*	*Leptin (ng/mL) Median (range)*	*p value*
Age, years			
Young (<60)	18	2.93 (0.13-14.64)	0.33
Older (>60)	15	4.80 (0.11-12.49)	
Gender			
Male	20	3.09 (0.11-10.55)	0.43
Female	13	3.52 (0.13-14.64)	
ECOG PS			
Good (0-1)	23	3.34 (0.13-14.64)	0.65
Worse (2-4)	9	4.89 (0.11-12.49)	
BMI			
High (>median)*	15	4.07 (0.11-7.58)	0.53
Low (<median)	18	3.34 (0.81-14.64)	
Jaundice			
Yes	9	2.43 (0.11-5.32)	0.24
No	22	3.56 (0.13-14.64)	
Surgery			
Yes	8	3.25 (0.11-14.64)	0.81
No	25	3.56 (0.13-14.64)	
Localization			
Head	21	3.34 (0.11-12.49)	0.92
Corpus-tail	10	3.38 (0.13-14.64)	
pT size			
Small	14	3.25 (0.13-12.49)	0.84
Large	14	3.18 (0.11-14.64)	
Metastasis			
Yes	23	3.61 (0.11-14.64)	0.14
No	10	1.16 (0.36-12.49)	
Liver metastasis			
Yes	19	4.80 (0.13-14.64)	0.41
No	4	2.79 (0.11-10.55)	
ESH			
Normal	11	3.09 (0.13-7.89)	0.21
High	12	4.80 (0.20-14.64)	
Hb			
Low	12	4.48 (0.11-14.64)	0.86
Normal	19	3.51 (0.20-10.55)	
WBC			
High	9	4.89 (0.13-14.64)	0.29
Normal	22	3.34 (0.11-12.49)	
PLT			
Low	5	4.07 (0.20-7.58)	0.66
Normal	26	3.43 (0.11-14.64)	
Albumin			
Low	17	2.48 (0.11-12.49)	0.33
Normal	10	4.07 (0.13-10.55)	
LDH			
High	8	3.86 (0.11-7.40)	0.68
Normal	21	3.52 (0.13-14.64)	
CEA			
High	19	3.38 (0.11-14.64)	0.91
Normal	10	3.52 (0.13-12.49)	
CA 19.9			
High	22	3.52 (0.11-14.64)	0.38
Normal	7	4.07 (0.45-10.55)	
Response to CT			
Yes	8	1.16 (0.13-4.80)	0.004
No	7	5.32 (0.20-10.55)	

* BMI, median (range) = 22.2 (16.2-34.3) kg/m^2, PS: performance status, BMI: body mass index, ESH: erythrocyte sedimentation rate, Hb: hemoglobin, WBC: white blood cells, PLT: platelets, LDH: lactate dehydrogenase, CT: chemotherapy

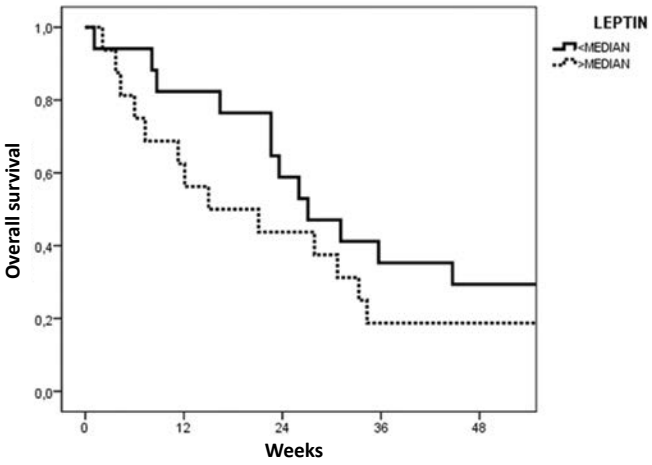

Figure 2. Kaplan-Meier overall survival in pancreatic cancer patients according to serum leptin levels (p=0.20)

of predictive markers and chemotherapeutics in PA patients. For example, plasma IL-8 level may be a novel biomarker for the response to chemotherapy in patients with PA [33]. The ribonucleotide reductase (RNR) complex, composed of a catalytic subunit (RRM1) and a regulatory subunit (RRM2), is thought to be a rate-limiting enzymatic complex for the production of nucleotides. In humans, the Rrm1 gene (a tumor suppressor), and RRM1 were found to be predictive markers for PA patients treated with gemcitabine chemotherapy [34] and IL-10 levels in serum can be predictive for 5FU-based chemotherapy in PA patients receiving chemoradioimmunotherapy [35]. In a new study, HEAT repeat containing 1 (HEATR1) gene was found as a possible determinant of cellular sensitivity to different chemotherapeutic drugs in PA patients [36]. In another study, pretreatment C-reactive protein levels were found to be predictive in patients with locally advanced PA who received chemoradiotherapy [37]. The value of LDH serum levels as a prognostic and predictive factor for advanced pancreatic cancer patients receiving sorafenib was shown in another new study [38]. Another predictive situation is mismatch repair status in resectable PA which predicts response to adjuvant chemotherapy [39]. In the present study it was found that leptin is a predictive marker for response to gCTx subgroup treatment but it was not prognostic. To our knowledge the present study is the first to show the predictive role of leptin on the response to chemotherapy.

Taken all these together, one can say that

Table 4. Univariate analyses of overall survival

Parameters	*Overall survival Mean (±SD) (weeks)*	*p value*
Age		
Young	58.3 (13.1)	0.008
Older	21.8 (6.6)	
Gender		
Male	49.9 (12.6)	0.21
Female	29.0 (7.5)	
ECOG PS		
Good	53.6 (10.9)	0.002
Worse	15.6 (3.6)	
BMI		
High	46.0 (13.7)	0.65
Low	35.7 (8.0)	
Jaundice		
Yes	41.6 (18.8)	0.46
No	41.9 (7.8)	
Localization		
Head	48.3 (11.8)	0.54
Corpus-tail	34.4 (10.4)	
pT size		
Small	42.1 (9.4)	0.37
Large	36.4 (8.9)	
Metastasis		
Yes	26.5 (5.9)	0.008
No	76.7 (20.3)	
Liver metastasis		
Yes	30.0 (6.8)	0.02
No	9.5 (4.6)	
ESR		
High	34.3 (7.7)	0.24
Normal	43.9 (12.0)	
Hb		
Low	41.1 (11.5)	0.66
Normal	32.1 (7.0)	
WBC		
High	38.2 (12.2)	0.67
Normal	34.5 (7.2)	
PLT		
Low	27.5 (9.0)	0.59
Normal	37.2 (7.1)	
Albumin		
Low	30.9 (8.8)	0.79
Normal	32.8 (8.7)	
LDH		
High	24.5 (12.2)	0.06
Normal	38.3 (6.8)	
CEA		
High	30.1 (9.4)	0.66
Normal	36.8 (7.7)	
CA 19.9		
High	32.5 (6.0)	0.63
Normal	40.8 (16.0)	
Response to CTx		
Yes	48.1 (11.4)	0.03
No	23.1 (8.9)	
Leptin		
<Mean	48.2 (11.5)	0.20
>Mean	30.8 (8.6)	

PS: performance status, BMI: body mass index, ESH: erythrocyte sedimentation rate, Hb: hemoglobin, WBC: white blood cells, PLT: platelets, LDH: lactate dehydrogenase, CT: chemotherapy

leptin and PA relationship is complex, not only limited to obesity, insulin resistance and BMI but also to the pathways of tumorigenesis. Leptin could act as a predictive marker for PA patients receiving gCTx and this finding should be evaluated in larger clinical trials.

Conflict of interests

The authors declare no confict of interests.

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