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Leptin and adiponectin in pancreatic cancer: connection with diabetes mellitus

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The aim of this study was to analyze the relationship of serum leptin as well as adiponectin and the manifestation of pancreatic cancer (PC). Serum leptin, adiponectin, glucose homeostasis and insulin resistance (expressed as HOMA-IR) were investigated in 64 patients with newly diagnosed PC and compared with 64 healthy controls (CON group) and 75 patients with type 2 diabetes (DM2).

Seventy percent of newly diagnosed PC patients had DM2. The levels of leptin were lower, whilst adiponectin/leptin ratio was higher in PC patients (both with and without DM2), in comparison with CON and DM2 groups ($P < 0.001$) independently of age, BMI and waist circumference.

Newly diagnosed PC is characterized with lower leptin concentrations and higher adiponectin/leptin ratio in comparison with CON or DM2 individuals. Analysis of these parameters could help in the screening of persons in high risk for PC, especially in those with DM2.

Key words: adiponectin, leptin, pancreatic cancer, type 2 diabetes mellitus

The worldwide prevalence of pancreatic carcinoma is continually growing. The malignant tumors of pancreas are 4th most often death cause for cancer in the Czech Republic[1] and 5th in Europe [2]. The five-year survival rate is only 4 % [3]. The vast majority of PC cases is diagnosed in advanced stages III – IV with affected lymphatic nodes and distant metastases. Therefore, much effort has been paid to the search for marker enabling to identify the patients with high risk for PC.

In the pathogenesis of pancreatic ductal adenocarcinoma and some other cancers, such as colorectal or endometrial, as well as in obesity and type 2 diabetes mellitus, chronic hyperinsulinemia, insulin resistance and the polymorphisms within the promoter of *Ins* gene could play a role [5, 6, 7]; the confounding mechanisms have not been elucidated yet. Recently, new-onset diabetes was suggested as important marker for pancreatic cancer screening [8, 9], because of significant associations between PC and diabetes mellitus. Only a few papers dealt with the association of PC to the concentrations of leptin and adiponectin; these proteins play a role in the pathophysiology of insulin resistance and probably influence some mechanisms of the cancerogenesis [10].

Leptin, the product of the *ob* gene, belonging to cytokine family, is produced mainly by adipocytes, circulates in the plasma proportionally to the volume of body fat and acts centrally in the hypothalamus to suppress appetite and increase energy expenditure [11]. It plays important roles in angiogenesis, immune function, fertility, as well as bone formation [12]. The effects of leptin are mediated through the transmembrane leptin receptor. Leptin expression has also been found in other tissues, such as the fundus of the stomach [13], colonic epithelial cells, the skeletal muscle, the liver, and the placenta [14, 15] Changes in leptin expression and its concentrations are associated with various cancers including breast, endometrial, gastric, and prostate cancers [16].

Adiponectin is a 244 amino acid protein that is synthesized by adipose tissue. Its plasma concentrations are negatively associated with obesity and insulin resistance [17, 18]. Serum levels of adiponectin *in vivo* are inversely associated with the risk of colonic cancer, prostate, breast and endometrium [19]. On the contrary, in one study it was found that lower leptin but higher adiponectin levels were associated with PC before and after controlling for age, gender, body mass index (BMI),

smoking status, alcohol consumption, history of diabetes, and family history of pancreatic cancer [20].

The aim of this pilot study was to analyze the concentrations of leptin, adiponectin, basic parameters of glucose homeostasis in patients with newly diagnosed PC, diabetic individuals without PC, and healthy controls.

Patients and methods

Subjects. The study comprised in total of 203 individuals; of these, 64 were control persons (29/35 men/women) (CON), 75 patients with DM2 (47/28 men/women) and 64 had newly diagnosed PC (35/29 men/women). Seventy per cent patients with PC were diagnosed also with DM2. The diagnosis for DM2 was based on recommended guidelines [21] and all the PC patients had the tumor presence verified by histology (from aspiration biopsy or chirurgical resection sample). None of the investigated probands suffered from chronic pancreatitis. For further purposes, the PC group was divided into group with DM2 and the group without DM2. Both groups had similar distribution of tumor staging (P = 0.867, $\chi 2$ test) and location (P = 0.170, $\chi 2$ test) – see Table 2 for further information.

Every participant was completely clinically and biochemically examined. The study was approved by the Joint Ethical Committee of 1st Faculty of Medicine and General Teaching Hospital in Prague and it conforms to the provisions of the Helsinki Declaration. The tumor staging was evaluated by the combination of criteria issued by Union International Contre le Cancer (UICC) and American Joint Committee on Cancer [22]. The control group was recruited from apparently healthy persons (personnel and students from 1st Faculty of Medicine). Blood samples were collected after overnight fasting. The plasma concentrations of leptin and adiponectin were assessed by RIA (DRG International, Inc., U.S.A., www.drg-international.com). In each set of RIA samples, both the controls and the patients were included to minimize the effect of inter-assay error on group comparison. Values of other parameters examinated were assessed using routine biochemical and immunochemical methods. The homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated as fasting glucose (mmol/l)*fasting insulin (mUI/l)/22.5.

Statistics. The statistical analyses were performed in STATISTICA for Windows Cz, version 7.1. (www.statsoft.cz). Results are presented as average and standard deviation or as a median with interquartile range (IQR, 25th – 75th percentile) in case of non-Gaussian distribution of data. For the latter type of data we used the logarithmic/double logarithmic transformation to normalize the data for further analyses. As the distribution of both sexes was similar in all groups (Table 3) and the effect of gender interaction was not significant in three-way ANCOVA design including gender, tumor presence and DM2 as grouping variables (data not shown), data were further processed by means of the two–way analysis of covariance (ANCOVA) by adjusting for age, BMI and waist circumference as covariates using presence of tumor and DM2 as factors. We also used the chi-square test for comparison of dichotomic and ordinal variables. We evaluated the determinants of adipocytokines using forward stepwise regression analyses. The variables introduced into the model were HOMA-IR, waist to hip ratio (WHCR), BMI, triacylglycerols (TAG), HDL-C, age, leukocytes count and C-reactive protein (CRP). Associations with p-values less than 0.05 were considered statistically significant.

Results

Basic clinical and biochemical characteristics of the studied groups are shown in Tables 1 and 3. Among the patients with PC, 45 (27M/18F) of them (70 %) were characterized by DM2 at the time of the diagnosis. In 67 % of these cases, diabetes

Table 1. Laboratory data in the studied groups

Parameter	CON	DM2	PC without DM2	PC with DM2	P effect tumor	P effect DM2	P effect DM2*tumor
N	64	75	19	45			
CRP (mg/l)	4.7 (3.0-5.6)	4.6 (3.7-7.6)	6.6 (2.3-30.0)	12.7 (7.0-44.0)	0.0001	0.2162	0.1059
glycaemia (mmol/l)	5.0 (4.7-5.3)	7.0 (6.3-9.2)	5.2 (4.6-5.6)	7.8 (6.5-10.6)	0.1772	0.0001	0.0713
HOMA-IR (ratio)	1.41 (1.04-2.44)	4.20 (2.83-7.12)	1.46 (0.99-1.95)	2.59 (1.44-5.26)	0.8709	0.0001	0.4699
total bilirubin (μmol/l)	11.0 (9.0-16.5)	10.8 (8.3-14.8)	11.1 (10.1-88.9)	18.7 (11.0-61.4)	0.0001	0.6435	0.2784
alkaline phosphatase (μkat/l)	0.9 (0.8-1.1)	1.0 (0.8-1.3)	3.1 (1.3-5.2)	2.9 (1.6-5.0)	0.0001	0.7423	0.2422
leukocytes (10^9/l)	6.2 (5.5-7.4)	7.5 (6.6-8.7)	7.6 (7.0-9.3)	8.0 (7.1-9.4)	0.0120	0.1432	0.1900
insulin (mIU/l)	6.5 (4.9-9.9)	11.7 (8.6-20.5)	5.9 (3.8-9.8)	7.4 (4.5-11.4)	0.4375	0.2597	0.9451
C-peptide (nmol/l)	0.66 (0.54-0.86)	1.10 (0.73-1.37)	0.77 (0.49-1.00)	0.78 (0.51-1.04)	0.4962	0.7709	0.0548
CEA (μg/l)	0.76 (0.50-1.43)	1.00 (0.50-1.67)	3.88 (1.45-7.50)	3.78 (1.82-6.45)	0.0001	0.6551	0.7536
CA 19-9 (kIU/l)	8.3 (5.9-15.1)	7.3 (2.0-14.3)	254 (24-3239)	309 (47-2283)	0.0001	0.9937	0.2162
CA 72-4 (kIU/l)	1.6 (1.0-4.2)	1.1 (1.0-1.6)	7.0 (1.6-23.8)	2.3 (1.7-7.3)	0.0001	0.0963	0.7268

Abbreviations: CON – control group, PC – pancreatic carcinoma, DM2 – diabetes mellitus type 2. CEA – carcinoembryonal antigen, CRP – C reactive protein, the values represent median (25^{th}-75^{th} percentiles). P – ANCOVA adjusted on age, BMI and waist circumference as covariates).

Table 2.

Parameter	CON	DM2	PC without DM2	PC with DM2	P*
Smoking status (N)	64	70	17	45	
non-smokers	35 (55%)	35 (50%)	4 (24%)	11 (26%)	
ex-smokers	13 (20%)	19 (27%)	3 (18%)	2 (4%)	
smokers	16 (25%)	16 (23%)	10 (59%)	32 (70%)	0.0001
packets/day					
0.5	9	7	4	7	
1	7	6	4	15	
1.5	0	0	1	8	
2	0	2	0	2	
3	0	1	1	0	0.6605
Alcohol consumption (N)	64	70	18	45	
no alcohol	8	28	7	11	
less than 1 glass/day	44	35	4	23	
1 glass/day	10	5	4	4	
2 glasses/day	2	2	0	3	
3 and more glasses/day	0	0	3	4	0.0001
Tumor staging (N)			19	45	
T1			0	0	
T2			3 (16%)	7 (15%)	
T3			8 (42%)	22 (50%)	
T4			8 (42%)	16 (35%)	0.8674
Localization of tumor (N)			19	45	
head			16 (84%)	29(63%)	
body			3 (16%)	10(24%)	
neck			0 (0%)	6 (13%)	0.1697
Duration of diabetes (N)		60		45	
less than 3 years		26 (43%)		30 (67%)	
more than 3 years		34 (57%)		15 (33%)	0.0177

**-P – Pearson χ2, Abbreviations: CON – control group, (N) – actual size of the studied group, PC – pancreatic carcinoma, DM2 – diabetes mellitus type 2.*

lasted less than 3 years, while in the DM2 group, only in 43% patients DM2 lasted less than 3 years, P = 0.018, χ2 test. Within all observed groups, the patients with PC were more often smokers (P < 0.0001, χ^2 test) (see Table 2). As expected, the effect of tumor was highly significant (P < 0.0001) for values of CA 19-9, CEA, CA 72-4 and activity of alkaline phosphatase, which was observed as higher values (P < 0.001) of respective analytes in the patients with PC (both with DM2 and without DM2) vs. CON and DM2 group. The concentrations of the fasting glucose were significantly higher in the DM2 group and in the PC with DM2 group in comparison with other groups. In C-peptide concentrations, we observed only borderline effect for the interaction of tumor with DM2, which was pronounced as higher C-peptide concentrations in DM2 group vs. other groups.

The concentrations of adiponectin, leptin and the ratio adiponectin to leptin and the effect of PC and DM2 are shown in Table 3. The levels of leptin and adiponectin/leptin ratio were significantly influenced by the effect of tumor (P < 0.0001), which resulted in lower leptin concentrations (higher adiponectin/leptin ratio) in both groups of PC (with DM2 as well as without DM2), in comparison with the CON and DM2 groups (P < 0.001) adjusted for age, BMI and waist circumference. The concentrations of adiponectin were not influenced by tumor presence or DM2.

To evaluate the determinants of adipokine levels, the forward stepwise regression (Table 4) was performed with selected indices of lipid (TAG, HDL-C) as well as glucose (HOMA-IR) metabolism, anthropometric (WHCR, BMI) parameters, age, and CRP as predictor variables. We found that in CON group, the levels of adiponectin were determined by the parameters of central obesity, IR, dyslipidemia and inflammation (WHCR, HDL-C, HOMA-IR and CRP, respectively). The model for DM2 group included HOMA-IR, age, HDL-C and BMI. On the contrary, the PC patients with and without DM2 did not reveal any dependence on the parameters introduced into the model.

The concentrations of leptin were determined in CON group with HOMA-IR, WHCR, leukocytes, BMI, HDL-C and CRP. The same situation was observed for the respective levels in the DM2 group with the exception of CRP, which did not prove to be significant, whereas the TAG and age variables played a role in the model. The patients with PC and DM2

Table 3. Anthropometrical data and adipokines in the studied groups

Parameter	CON	DM2	PC without DM2	PC with DM2	P* effect tumor	P* effect DM2	P* effect DM2*tumor
present tumor	no	no	yes	yes			
present DM2	no	yes	no	yes			
N	64	75	19	45			
males/females	29/35	47/28	8/11	27/18	0.1154**		
age (years)	51.9 ± 9.4	61.6 ± 10.6	59.7 ± 9.1	66.5 ± 9.4			
BMI (kg/m^2)	26.8 ± 4.7	33.4 ± 5.7	23.9 ± 3.6	24.8 ± 5.6			
waist circumference (cm)	90.8 ± 12.4	108.8 ± 13.6	88.8 ± 11.6	92.8 ± 14.6			
adiponectin (μg/ml)	10.7 (7.1-14.2)	7.6 (4.9-9.4)	10.4 (7.2-13.5)	10.7 (7.2-15.0)	0.4053	0.2355	0.2693
leptin (ng/ml)	10.2 (5.4-16.5)	10.8 (6.9-20.4)	3.1 (1.7-7.8)	3.2 (2.4-6.6)	0.0001	0.0519	0.4504
adiponectin/leptin ratio	1.0 (0.6-2.0)	0.6 (0.4-1.1)	3.0 (1.5-5.0)	2.5 (1.1-6.1)	0.0001	0.3920	0.8367

*Abbreviations: CON – control group, PC – pancreatic carcinoma, DM2 – diabetes mellitus type 2. The values represent mean ± standard deviation or median (25th-75th percentiles); *ANCOVA adjusted on age, BMI and waist circumference as covariates; ** -Pearson χ2 test;*

Table 4. Forward stepwise regression models for adipocytokines in studied groups

dependent variable	PC	DM2	regression equation[a]	R^2	p
adiponectin	yes	yes	model not significant		
leptin	yes	yes	-6.48 + 2.01***BMI* – 2.16***WHCR* + 0.02*age + 0.11***HOMA-IR* + 0.19***TAG*	0.5568	0.0001
adiponectin/leptin	yes	yes	9.14 – 2.44***BMI* – 0.53***TAG* + 2.21***WHCR* – 0.24***HDL-C*	0.3448	0.0023
adiponectin	yes	no	model not significant		
leptin	yes	no	-7.76 + 2.72***BMI* + 0.56***TAG* + 0.50***HDL-C*	0.5423	0.0102
adiponectin/leptin	yes	no	model not significant		
adiponectin	no	yes	-2.00 – 0.36***HOMA-IR* + 0.02*age + 0.58***HDL-C* + 0.98***BMI*	0.3437	0.0001
leptin	no	yes	-7.71 + 2.33***BMI* + 0.44***leu* – 1.97***WHCR* + 0.34***TAG* + 0.54***HDL-C* + 0.01*age + 0.14***HOMA-IR*	0.5160	0.0001
adiponectin/leptin	no	yes	4.88 – 0.46***HOMA-IR* – 0.43***TAG* – 1.27***BMI*	0.4846	0.0001
adiponectin	no	no	1.69 – 2.35***WHCR* + 0.80***HDL-C* – 0.18***HOMA-IR* + 0.10***CRP*	0.4588	0.0001
leptin	no	no	-3.79 + 0.32***HOMA-IR* – 2.30***WHCR* + 0.86***leu* + 1.27***BMI* – 0.18***CRP* + 0.40***HDL-C*	0.3558	0.0003
adiponectin/leptin	no	no	6.29 – 0.47***HOMA-IR* – 1.51***BMI* + 0.29***CRP* – 0.89***leu* + 0.40***HDL-C*	0.4688	0.0001

[a] – the variables (log transformed in italics) are ordered according to the decreasing contribution to the coefficient of determination

seemed to have similar model for leptin concentrations as those without PC (HOMA-IR, WHCR, BMI, TAG and age). The model for PC without DM2 had included only the values of BMI, TG and HDL-C.

The adiponectin/leptin ratio in CON group revealed similar correlation with selected parameters as for the leptin (HOMA-IR, BMI, leukocytes, CRP, HDL-C) except WHCR. The DM2 patients exhibited the relationship of the ratio only with HOMA-IR, TAG, and BMI. The ratio in the PC group with DM2 had inverse sense of the correlations with parameters chosen for leptin (BMI, WHCR, and TAG) in the same group; furthermore, HDL-C was also included in the regression equation. No valid model was found for the individuals with PC without DM2 for the ratio.

Discussion

In the presented pilot study, 70 % persons with newly diagnosed PC were characterized by the presence of DM2. In the patients with newly diagnosed PC (regardless to the presence of DM2) we have found significantly lower concentration of serum leptin, while we found increased ratio adiponectin to leptin, compared to both control and DM2 groups independently of age, BMI and waist circumference. Leptin was in numerous papers identified as a factor enhancing the growth and invasiveness of several tumors, e.g. breast [23], endometrium [24], and prostate [25] cancer. However, in some gastrointestinal tumors such as colorectal or gastric cancer the leptin concentrations were found to be similar [26] or lower [27, 28] in comparison with controls.

The data about pancreatic carcinoma and leptin are scarce. One study dealing with the relationship between the cachexia and leptin concentrations in 64 patients with PC found BMI adjusted leptin concentrations lower than in control group, and leptin did not correlate with anorexia nor weight loss [29]. Furthermore, in a small group of 7 patients with PC, Barber et al. [30] revealed that lower leptin is accompanied with higher concentrations of glucose, cortisol and IL-6.

Levels of adiponectin in PC have not been extensively studied. One small case-control study showed PC cases to have significantly higher median adiponectin concentrations than controls [31]. Stolzenberg-Solomon et al. [32] have found in a cohort of male Finnish smokers prediagnostic adiponectin concentrations to be inversely associated with PC. Dalamaga et al. [20] have found in case-control study lower leptin but higher adiponectin levels associated with PC before and after controlling for age, gender, BMI, smoking status, alcohol consumption, history of diabetes and family history of pancreatic cancer. Moreover, they documented the presence of both AdipoR1 and AdipoR2 on PC tumor tissue.

It seems that increased adiponectin concentrations may play a role in various malignancies associated with diabetes, as (according to some authors) in non-Hodgkin lymphoma [33], where was observed the association of high concentration of adiponectin with increased levels of IL-10, a growth factor with known antiapoptotic properties in B- cells and T-cells in non-Hodgkin lymphoma [34] which is also overexpressed in PC cells [35].

In PC, it was speculated that increased adiponectin could compensate for insulin resistance, or for the adiponectin resistance produced by a down-regulation of adiponectin receptors or signaling pathways downstream of the receptors AdipoR1 AdipoR2. Increased adiponectin could also be compensatory response to the inflammation [36, 20]. Epidemiological evidence and molecular studies both in vitro and in vivo all support the hypothesis that inflammation plays an important role in the initiation and progression of pancreatic tumors [37]. However, in our study we did not find significantly different concentrations of adiponectin in PC patients in comparison with CON group. Patients with PC and with DM2 had only insignificantly higher adiponectin levels than diabetics without PC. Nevertheless, in type 2 diabetics, plasma adiponectin concentrations are usually lower than in BMI-matched controls [17].

Some experimental papers showed that the simultaneous effect of adiponectin and leptin on the tumor growth (migration of tumor cells) can lead to different results in comparison with the isolated effect of the both adipokines. The balance between adiponectin and leptin can thus have significant impact on the tumor progression [9, 38].

Only a few clinical studies dealt with the relationship of adiponectin/leptin ratio in human cancer. In breast cancer, the leptin/adiponectin ratio was increased in the patients with cancer in comparison with controls; moreover, this ratio showed positive correlation with the progression of tumor [39]. Recent study by Yamaji et al. [40] in colorectal adenoma indicates interactive effects of these two adipokines on the progression of adenoma, which were independent of their involvement in insulin resistance. However, in our study, the PC patients had increased adiponectin/leptin ratio. This finding corresponds with the data by Dalamaga [20], who found association of higher concentrations of adiponectin and lower levels of leptin in pancreatic cancer.

Adiponectin and leptin seem to exhibit complex and concerted effects on tumor cells and leukocytes [9]. In five breast cancer cell lines treated with varying adiponectin/leptin ratio, different effects on the proliferation were observed [38]. Thus, the adiponectin/leptin ratio could bear possible predictive power in some other types of cancer, including PC.

Moreover, in other pathophysiological states the adiponectin/leptin interactions play a role; the ratio was used by several authors as a marker of risk for insulin resistance in DM2 [41], preclinical atherosclerosis [42], and, recently, also as potential marker of depression [43].

To conclude, we found in the presented study low leptin concentrations and high adiponectin to leptin ratio in newly diagnosed PC. Potential significance of adiponectin/leptin ratio in PC could reflect anticipated different roles of leptin and adiponectin in pathogenesis of PC. We suppose that the manifestation of PC is linked with the dysregulation of leptin and adiponectin pathways in the affected individuals regardless to the presence of diabetes. Further studies are needed to elucidate the significance of both adipokines and their ratio in the pathogenesis of PC.

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