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Serum omentin-1 and chemerin concentrations in pancreatic cancer and chronic pancreatitis

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Abstract: Pancreatic ductal adenocarcinoma (PDAC) is characterized by very poor prognosis. It is caused by asymptomatic course of the disease at early stage. Symptomatic PDAC means usually advanced stage of the disease, making radical treatment impossible. Finding of biological PDAC marker could improve PDAC treatment through early diagnosis. In our study, we investigated two adipokines: omentin and chemerin concentration in PDAC, chronic pancreatitis (CP) and healthy individuals. We examined 27 PDAC patients, 10 CP patients and 36 controls. To determine concentration of adipokines we used ELISA immunoenzymatic assay. Level of both adipokines was increased when comparing control group to PDAC patients. Additionally, chemerin concentration in CP group was elevated comparing to control. To evaluate both adipokines as potential PDAC biomarkers we performed ROC analysis. Chemerin (AUC = 0.913) displayed better discriminant ability than omentin-1 (AUC = 0.73). Some authors believe that chemerin may promote tumour growth by stimulating angiogenesis and is supposed to be a factor recruiting mesenchymal stroma cells (MSC) in tumour regions. Omentin-1 can inhibit tumourigenesis by TP53 stimulation. On the other hand, according to some studies, omentin-1 may promote cancer proliferation via Akt signalling pathway. Results from our study showed significantly elevated level of chemerin and omentin-1 in PDAC patients. Therefore, we believe that both investigated adipokines may provide promising and novel pharmacological insights for oncological diagnosis in the near future.

Key words: omentin-1, chemerin, pancreatic cancer, adipose tissue, adipokine, pancreatitis.

Introduction

Pancreatic cancer (PDAC) is characterized by very poor prognosis. Anatomical localization of the pancreas limits surgical accessibility to even very small tumours. Radical operation can be performed only in 20% of patients [1, 2]. Course of the disease is rather asymptomatic at early stage, which makes it difficult to establish the diagnosis early [2]. Discovering a new biological PDAC screening marker may accelerate the diagnosis and enable the delivery of appropriate treatment at an early disease stage. Currently, the only appropriate marker available is CA 19-19, however, unsuitable for asymptomatic cases. Therefore, CA 19-9 may not be introduced into screening, however, it might be applied along with other markers, such as CEA and CA-125, to monitoring of PDAC [3].

Chronic pancreatitis (CP) is a long-standing inflammation of the pancreas, altering its normal structure and function. CP may present at imaging examination as masslike lesion difficult to differentiate from PDAC. As CP is not treated by surgery, misdiagnosis may bring unnecessary risk associated with surgical intervention. Finding a plasma/serum marker allowing to differentiate CP from PDAC would facilitate surgical decision-making [4].

Obesity is associated with pancreatic cancer risk [5]. Yellow adipose tissue synthetizes number of biologically active substances, called adipokines such as leptin, resistin, omentin and chemerin. They are involved in regulation of metabolism, angiogenesis [6] and secretory function of adipose tissue, as well as liver, heart, pancreas, and skeletal muscles [7].

Adipokine concentration is elevated in neoplastic diseases, such as pleural mesothelioma, lung cancer, colorectal cancer and prostate cancer [8].

Omentin-1 is an adipokine with an anti-inflammatory function; it decreases expression of C-reactive protein and tumour necrosis factor. It increases insulin--induced glucose uptake in yellow adipose tissue and nitric oxide synthesis, therefore preventing the development of diabetes and ischaemic heart disease. Its link to neoplastic diseases remains unknown. Some authors believe omentin-1 has an antiproliferatory effect, whereas some claim that it stimulates proliferation. Omentin-1 concentration is increased in colon and prostate cancer [9, 10].

Chemerin takes part in the development of inflammation by stimulating the immune system, particularly cells responsible for non-specific immunity: dendritic cells, macrophages, NK cells and monocytes [11]. Its concentration is positively correlated with insulin resistance, hypertension, elevated patient's BMI, free triglycerides, glycated haemoglobin and metabolic syndrome markers such as leptin and resistin [12–14]. Its high plasma level has been observed in pleural mesothelioma,

adrenal gland tumour and lung cancer, while it decreased in hepatocellular carcinoma [8, 14, 15]. However, the more specific effect of chemerin on neoplasm progression has not been discovered yet. We may hypothesize, that it is linked with proangiogenic activity of chemerin, which is stimulation of endothelial cells migration during angiogenesis [6, 16]. Furthermore, chemerin may stimulate mesenchymal stem cells migration [17]. Both pro- and anti-inflammatory function of chemerin has been confirmed [18].

The aim of our study was to compare plasma level of two adipokines: omentin-1 and chemerin, in patients suffering from pancreatic ductal adenocarcinoma (PDAC), chronic pancreatitis (CP) and in a control group.

Materials and Methods

Study group consisted of 20 males, aged 35 to 76 (mean 58.65 ± 11.2) and 17 women aged 37 to 80 (mean 63.76 ± 10.93); difference in age between male and female age was not significant ($p > 0.05$). All patients were recruited from the Department of General and Bariatric Surgery of Medical university of Silesia in Zabrze. They were qualified for surgical treatment due to duodenopancreatic region tumour, pancreatic cancer of tail and body. Diagnosis was made based on computed tomography (CT) of abdominal cavity according to pancreatic protocol CT [19]. Resection was performed based on a consensus statement by the International Study Group on Pancreatic Surgery (ISGPS) [1, 20, 21]. Inclusion criteria included: age >18 yo, pancreatic tumour found in CT, histopathological confirmation for PDAC or CP and informed consent of patient for participation in study Exclusion criteria included: pregnancy, age <18 yo, localization of tumour other than pancreas, histopathological diagnosis other than CP or PDAC, lack of patient consent or limited state of consciousness for full consent.

35 patients with histopatologically confirmed postoperative PDAC or CP were included in final analysis. Group I consisted of 25 PDAC patients and group II consisted of 10 CP patients. Due to a small number of serum samples collected, control group for omentin-1 consisted of 18 samples, while the examined group consisted of 20 PDAC patients and 10 CP.

Characteristics of patients are presented in Table 1. Control group consisted of 36 healthy males, recruited randomly from among miner rescuers, aged from 25 to 50 (mean 37.64 ± 6.39).

Tumour staging was determined in accordance with TNM [22] classification; 14 patients underwent tumour resection, 11 were qualified as unresectable. Tumours were considered unresesectable based on consensus of ISGPS [21]. TNM Classification for all cancer patients is presented in Table 2.

Table 1. Patients' characteristics; number of patients in omentin-1 group is given in brackets.

	PDAC	CP	Control	p
n	25 (20)	10	36 (18)	–
Age	62.96 ± 9.76	56 ± 14.45	37.64 ± 6.39	<0.05*
BMI	24.5 (21.70–27.80)	23.25 (21.20–24.50)	26.13 (24.19–29.53)	>0.05
Omentin-1	582.49 (422.59–663.68)	604.16 (439.86–711.03)	461.71 (345.42–494.42)	<0.05**
Chemerin	272.01 (221.18–313.98)	260.26 (204.65–312.37)	193.32 (173.32–213.87)	<0.05***

* RIR Turkey test, significant difference for: control vs PDAC, control vs CP.
** Kruskall Wallis test: significant difference for: Control vs PDAC.
*** Kruskall Wallis test: significant difference for: Control vs PDAC, vs CP.

Table 2. TNM staging for PDAC.

T value	Patients n (%)	N value	Patients n (%)	M value	Patients n (%)
T1	2 (8%)	N0	12 (48%)	M0	23 (92%)
T2	3 (12%)	N1	13 (52%)	M1	2 (8%)
T3	7 (28%)				
T4	13 (52%)				

Samples collection was performed in 2014 and 2015. Fasting blood samples were drawn from the ulnar vein in morning hours. Serum samples were frozen in –80°C. To measure concentrations of adipokines, ELISA test kit (BioVendor, Czech Republic) was used, in adherence with the manufacturer's instructions. Concentrations were determined based on the calibration curves for series of dilutions of the standard adipokines available in the kit. To determine absorbance of the samples Universal Microplate Spectrophotometer (μQUANT, Biotek Inc. Winooski, VT, United States) at 450 nm wavelength was used. The sensitivity of the kit for omentin-1 was 0.5 ng/ml. The inter- and intra-assay coefficients of variations were 4.1% and 4.4%, respectively. For chemerin, the sensitivity of the kit was 0.1 ng/ml. The inter- and intra-assay coefficients of variations were 5.1% and 8.3%, respectively.

The study was ethically approved by Bioethics Committee of Medical University of Silesia in Katowice (Act No. KNW/0022/KB1/38/I/14 from 17.06.2014).

Statistical analysis

Continuous variables are presented as the mean ± SD or the median with the inter-quartile range, if not normally distributed. The Shapiro-Wilk test was used for all continuous variables to test for a normal distribution. Statistical comparisons were achieved by using the Mann-Whitney U test for independent groups: resectable vs unresectable patients group. Differences in each variable at the three group (PDAC, CP and control) were calculated by analysis of variance (ANOVA) test followed by Tukey's post hoc test or by Kruskall Wallis test for non-normal distribution data. Spearman correlation was performed to analyse link between adipokines concentrations, age and BMI. To evaluate adipokines as potential biomarkers ROC analysis was performed. P-value <0.05 was considered to be significant. Statistical analysis was performed using STATICTICA 12.5 (StatSoft Inc., Tulsa, OK, USA, License SUM JPZP510A903822AR-A).

Results

Among examined groups no statistically significant difference in BMI value was found. However, there was a significant ($p < 0.05$) age difference between subjects (see Table 1).

Omentin-1 and chemerin concentrations in each group are presented in Table 1.

Serum concentration of omentin-1 was significantly higher in PDAC group compared to control. We obtained marginally significant results ($p = 0.057$) when comparing omentin-1 levels of CP and control group. There was no significant difference in either adipokine concentration between CP and PDAC. Chemerin concentration was significantly higher in CP and PDAC than in control group (Table 1). We found no significant difference in omentin-1 and chemerin levels between PDAC patients with resectable (Stage I, II) and unresectable (stage III, IV) tumours (Table 2). Additionally, no difference was observed between omentin-1 and chemerin concentration in different PDAC stages (Table 3). There was no significant correlation between examined adipokines concentration, age and BMI.

Table 3. Adipokines concentrations according to resectability of tumour; values for omentin-1 are given in brackets.

	Resectable (n = 10 (9))	Unresectable (n = 15 (11))	p
Omentin-1	634.53 (438.810–1001.230)	560.65 (416.07–635.92)	>0.05*
Chemerin	275.43 (225.435–302.725)	275.11 (216.47–430.89)	>0.05*

* Mann-Whitney U test.

We evaluated chemerin and omentin-1 as potential PDAC biomarkers. Both adipokines might be considered for use as PDAC biomarkers, however, chemerin displayed better discriminant ability than omentin-1 when comparing healthy volunteers to PDAC patients ($p < 0.05$) (Table 4, Fig. 1).

Table 4. Omentin-1 and chemerin concentrations according to tumour stage; values for omentin-1 are given in brackets.

	IA	IIA	IIB	III	IV	p
N	2 (1)	3	5	13 (10)	2 (1)	—
Omentin-1	378.5	1001.23 (634.53–1633.47)	522.45 (438.81–671.73)	531.01 (416.07–608.3)	655.63	>0.05*
Chemerin	336.10 (278.84–383.64)	281.65 (272.0–287.92)	221.18 (219.67–229.69)	275.11 (226.63–384.68)	321.49 (198.1–444.87)	>0.05*

*Kruskal Wallis test.

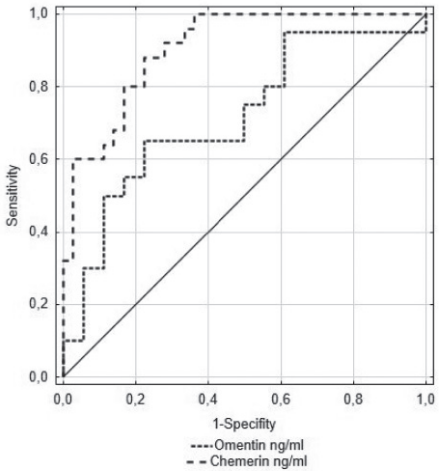

Fig. 1. Omentin-1 and Chemerin ROC curves.

Table 5. Comparison of omentin-1 and chemerin sensitivity and specificity.

	Cutoff value (ng/ml)	Sensitivity	Specificity	AUC (95% CI)
Omentin-1	501.37	0.65	0.78	0.72 (0.55–0.88)
Chemerin	219.67	0.80	0.83	0.91 (0.84–0.98)

Discussion

Concentrations of omentin-1 and chemerin are known to be elevated in colorectal, gastric and prostate cancers [10]. Additionally, omentin-1 concentration was increased in PDAC patients [22]. As far as we know, there are no published studies confirming increased levels of chemerin in PDAC patients.

The role of investigated adipokines in pancreatic cancer carcinogenesis remains unclear. Some authors reported that omentin-1 inhibits neoplastic cell growth *in vitro* via TP53 protein activity stimulation through posttranslational modification [23]. Others suggested a positive influence of omentin-1 on tumour progression via Akt signalling pathway. Stimulating role of adipokine in this pathway was confirmed in a human osteoblast culture *in vitro* [24]. There is also evidence, that Akt signalling inhibition induces neoplastic cell apoptosis [25]. It is uncertain whether neoplastic cells produce omentin-1, which may have an anti-apoptotic affect via stimulation of Akt autocrine pathway, or if elevated adipokine concentration occurs due to its increased secretion in adipose tissue, therefore making adipose tissue presence related to induction of tumour growth.

These studies seem to indicate a stimulating influence of omentin-1 on carcinogenesis. We found no association between omentin concentration and cancer stage; however, it should be taken into account that limitation of our study is small sample size. Further studies are necessary to clarify the association between omentin and stage of PDAC. Furthermore, chemerin displays chemotactic activity for NK lymphocytes, dendritic cells and macrophages, compounds of anticancer immune response [15, 17]. Lowered concentration of this adipokine was correlated with poor prognosis in human hepatocellular carcinoma [15]. However, simultaneously, it was reported that chemerin plays a part in carcinogenesis by stimulating angiogenesis [25]. Its elevated levels are positively correlated with microvessel density in squamous cell carcinoma of the tongue [14]. Studies confirmed proliferative activity of chemerin in mesothelium and angiogenesis *in vitro* [25, 26]. It may also stimulate angiogenesis in pancreatic cancer. Additionally, chemerin was discovered to be a factor recruiting mesenchymal stroma cells (MSC) in the tumour regions. This mechanism has not been sufficiently investigated yet, however, it may be associated with chemerin action on a G protein ChemR23 receptor. There is evidence, that MSC contribute to tumour progression [17]. Worth mentioning is that chemerin can stimulate angiogenesis via MAPK signalling pathway. Kaur *et al.* discovered that chemerin receptor (ChemR23 or CMKLR1) is associated with MAPK and AKT pathways stimulation, leading to endothelial cell recruitment but also apoptosis inhibition [6].

Our results show that patients suffering from pancreatic cancer display a significantly increased chemerin and omentin-1 plasma levels compared to the

control group. However, we should bear in mind some limitations of the study. The patient age of the group with pancreatic cancer (mean 62.96 years) as well as the group with chronic pancreatitis (mean 56) differed from the age of the control group (mean 37.64). Another limitation of our study is lack of insulin resistance, hypertension, free triglycerides and glycated haemoglobin status.

Further studies are needed to determine potential role of both adipokines in PDAC pathogenesis. However, we assume that chemerin may be involved in tumour angiogenesis. Determining whether chemerin is secreted by adipose tissue or cancer cells is needed for a better understanding of PDAC pathogenesis. Elevated serum chemerin level in other cancers seems to prove its role in tumour angiogenesis, yet this topic requires further research. Lack of association between chemerin and tumour stage should be verified in further studies.

Interestingly, we found no correlation between adipokines concentration and BMI. However, we must bear in mind that BMI is not used to diagnose obesity definitely because it does not take into account muscle mass, bone density and overall body composition [27].

In patients suffering from CP elevated chemerin level was noted as well. The higher concentration of chemerin in CP was previously reported by Adrych *et al.* [28] Literature describes both pro- and anti-inflammatory activity of chemerin. Inhibition of synthesis of inflammatory agents in response to LPS and IFN-γ due to chemerin was observed [29]. On the other hand, the aforementioned influence on NK cells and macrophages recruitment, as well as reported positive correlation of chemerin concentration with CRP and TNF-α concentrations, suggest the proinflammatory role of this adipokine [9]. Additionally, increased chemerin concentration was noted in patients suffering from psoriasis, where chemerin activity is associated with CXCL 10 and CXCL 12, stimulating recruitment of plasmacytoid dendrititic cells to diseased skin [30]. Both in pancreatic cancer and chronic pancreatitis, there are further studies required to determine function of chemerin. However, bearing in mind the fact that chronic pancreatitis is a risk factor of pancreatic cancer, we should consider whether proinflammatory effect of adipokines may influence carcinogenesis [31]. Omentin-1 levels were not significantly elevated in CP patients. However, these results may be related to a small sample size. So far, elevated level of omentin-1 in pancreatitis was demonstrated in a study on rats [32]. Anti-inflammatory function of omentin-1 consists of lowering C-reactive protein (CRP), tumour necrosis factor (TNF-α) and nuclear factor NF-κB expression [33]. We found no difference between CP and PDAC concentrations of both adipokines.

In conclusion, we noted significantly elevated levels of studied adipokines in patients suffering from pancreatic cancer and, in case of chemerin, in chronic pancreatitis. In order to attempt to determine the role of examined adipokines in PDAC and CP pathogenesis, we are going to use greater sample size, consider

additional clinical parameters and analyse the expression of adipokines in tumour tissue in our further research.

Conflict of interest

None declared.

Authors' contributions

- Conception or design of the work — Elżbieta Świętochowska, Paweł Kiczmer, Zofia Ostrowska;
- Data collection — Jerzy Piecuch, Maciej Wiewióra, Janusz Jopek, Elżbieta Świętochowska, Paweł Kiczmer, Błażej Szydło;
- Data analysis and interpretation — Paweł Kiczmer, Maciej Wiewióra, Elżbieta Świętochowska;
- Drafting the article — Alicja Prawdzic Seńkowska, Paweł Kiczmer;
- Critical revision of the article — Elżbieta Świętochowska;
- Final approval of the version to be published — Zofia Ostrowska.

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