Original Article

Comparison of adiponectin concentration between pancreatic cancer and colorectal cancer

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ABSTRACT

Introduction: Adiponectin (ADP) is an adipocytokine secreted by the adipose tissue which can be a useful marker in oncogenesis. Preliminary studies suggest that adiponectin rates differ according to the type of cancer.

Aim of study: Compare ADP plasma levels in pancreatic cancer (PC) and colorectal cancer (CRC) in a prospective monocentric study.

Patients and methods: The study included all the incident cases of PC gathered from a university hospital in France from January 2006 till September 2007. A control population of incident cases of colorectal cancer (CRC), matching on age, gender, and tumor staging was set in the same period. In addition to demographic data, the other parameters analyzed were: ADP rate, insulinoresistance (Homa-test), presence of a dysmetabolic syndrome, evolution of weight and data concerning the tumor (staging, tumor markers: ACE, CA19.9).

Results: 33 CRC and 53 PC were analyzed. Type 2 diabetes was found in 18.2% of the CRC cases and 39.6% of the PC ($p = 0.037$). The mean ADP level was significantly higher in PC versus CRC (20.9 microgram/l versus 15.9 microgram/l; $p = 0.03$). In multivariate analysis , after adjusting for gender, age, bilirubinemia and weigth loss, the variables independently associated with a high level of ADP (> 10 microG/L) were type 2 diabetes (OR = 0.05, $p = 0.01$), insulinoresistance (OR = 0.42, $p = 0.05$) and PC (OR = 12.03, $p = 0.047$).

Conclusion: ADP concentration is higher in PC patients than in CRC patients. ADP concentration > 10 microgram/l was independently associated with pancreatic cancer. Our data confirm that adiponectin rates differ strongly according to the type of cancer.

KEY WORDS pancreas cancer, colorectal cancer, mellitus diabetes, adiponectin

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Introduction

In Western countries pancreatic cancer represents the fourth cause of cancer death and its incidence rates, between 6 and 10 per 100000 populations, has increased in the last 30 years.

In 2007, in the United States, pancreatic cancer was responsible for one out of 75 deaths caused by cancer (1). Prognostic is very modest with an overall 5 years survival rate at less than 4%, the lowest of all solid tumours. Medical or surgical palliative treatment can significantly increase the comfort of life, but only modestly increases survival.

Only in a subset of patients, with T1 tumour (TNM classification), resectional surgery can be curative, with a 5 year survival rate reported was 20% (3).

Adiponectin is an adipokin product of mature adipocyte, reduced in the case of insulin resistance and positively correlated with insulin sensitivity. Adiponectin regulates intracellular pathways of protein kinase activated by AMP (AMP-kinase), of c-JUN and c-JUN N-terminal kinase (JNK) and of the signal that transcribes and activates transcription 3 (STAT3). Therefore, adiponectin is an anti-inflammatory, anti-angiogenic and a block for cell growth.

No potential conflict of interest.

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Circulating concentrations of adiponectin are inversely correlated to the risk of several cancers: breast cancer (4), endometrium (5), prostate (6), clear cell cancer kidney (7), stomach cancer (8) and leukemia (9). Prospective studies have shown that there is, at distance, a major risk of breast cancer (10), endometrial (11) and colo-rectal cancer (12) in postmenopausal women if adiponectin serum level is low.

Adiponectin present a direct antitumor (13) and proapoptotic effect. Conversely, in pancreatic cancer, results about ADP are conflicted (14,15).

The principal aim of our study was to compare ADP concentrations in two groups of cancer (colorectal cancer and pancreas cancer) matched on age, sex and tumour staging (metastatic or non metastatic).

Patients and methods

This prospective study included all consecutive patients with a new diagnosis of pancreatic adenocarcinoma followed in a referent university hospital between January 2006 and September 2007. The control group included patients with new diagnosis of colorectal carcinoma diagnosed in the same period and matched for sex, age and tumour staging (metastatic or non metastatic tumour), according to the sixth edition of American Joint Committee on Cancer: tumour, node, metastasis (TNM) classification system.

In all cases diagnosis was histological or cytological. All patients were informed and signed a consent paper. Patients on chemotherapy or on antidiabetic treatment were excluded from the study. All patients were characterized by age, sex, body mass index (BMI) before and at the moment of diagnosis, the presence of diabetes according to the criteria of the American Diabetes Association.

When diabetes was pre-existing, we evaluated the interval between diagnosis of diabetes and diagnosis of pancreatic cancer.

We noted a family history of diabetes, and the presence or absence of an associated dysmetabolic syndrome: hypertension, dyslipidemia, obesity.

Tumour data were: stage, size and tumour markers (CEA and CA 19-9); patients were divided into two groups: resectable cancer or locally advanced/metastatic.

Clinical Chemistry

Folate and vitamin B12 were assessed at the time of inclusion into the study. The HOMA index was calculated after the dosage of insulin.

Adiponectin level

All biological samples were harvested in the morning before breakfast, and the serum was immediately separated by centrifugation and stored at -80°C until dosage was completed.

This process was completed with recombinant human adiponectin by standard (Human Adiponectin RIA Linco Research® 6 research Park Dr St Charles, Missouri 63304 USA) using the instructions of manufacturer.

Statistical analysis

Statistical analysis was performed by using SPSS software (version 11, SPSS Inc, Chicago, IL, USA). Quantitative variables were expressed as median and range, or as mean ± standard deviation when normally distributed. Parametric student's test or non parametric Mann-Whitney's test when appropriate were used to compare quantitative variables between the 2 groups. The relationship between the type of cancer and the other variables, especially the presence of diabetes and the rate of adiponectin was analyzed using χ^2 test. A p value less than 0.05 was considered to indicate a significant difference.

The threshold of adiponectin level was investigated by analysis of ROC curves and measuring the areas under the curves for a better sensitivity and specificity.

For multivariate analysis, we used binary logistic regression to find the independent factors significantly associated with adiponectin level (low or high comated with a threshold level of ADP) and diabetes with pancreatic cancer.

The variables were analyzed in the multivariate model for a risk $\alpha < 10\%$. Values of $p < 0.05$ were considered statistically significant.

Results

Characteristics of patients

Between January 2006 and September 2007, 53 consecutive patients with pancreatic adenocarcinoma and 30 with colorectal adenocarcinoma were analyzed. Mean age for the two groups was 69 years (range, 11.9 years). The mean HOMA index was 2.54 and the mean adiponectin level was 18.7 μg/L (range 2.9-74.5).

The main demographic and clinical characteristics of all included patients are presented in Table 1. Table 2 shows the factors associated with the type of cancer. The two groups (pancreatic cancer and colorectal cancer) were comparable for age, sex, BMI, the rate of cholestérol and tumour staging.

In the pancreatic group there was however an increased incidence of hypertriglyceridemia (35.8% vs 9.1%, p = 0.05). Pancreatic cancer was associated with severe weight loss (BMI < 20) in 1/3 of the cases against 1/10 in the second group. At the moment of diagnosis, diabetes was two times more frequent in the group of patients with pancreatic

Table 1 Characteristics of patients

	Min	Max	Mean	Standard deviation
Age (years)	34	93	69.48	11.83
Weigth Loss (%)	0	28	6.76	5.22
Glycemia (mmol/L)	3.1	5.0	7.05	5.42
HbA1c	4.1	14.5	6.34	1.51
Triglyceride (g/L)	0.4	3.1	1.34	0.67
Cholesterol (g/L)	0.68	8.23	1.94	1.06
HOMA IR	0.20	11.13	2.54	2.42
Adiponectin (µg/L)	2.948	74.487	18.706	12.329

HbA1C: haemoglobin glycosylated; HOMA IR: HOMA insulinoresistance.

Table 2 Factors associated with the type of cancer, pancreatic vs colo-rectal (univariate analysis)

				Cancer
		Colorectal (N = 33)	Pancréas (N = 53)	p
Age	≤ 75	57.6%	64.2%	0.542
	> 75	42.4%	35.8%	
Sex	M	51.5%	60.4%	0.420
	F	48.5%	39.6%	
Diabetes	No	81.8%	60.4%	0.037
	Yes	18.2%	39.6%	
Weigth loss	≤ 10%	90.9%	71.7%	0.033
	> 10%	9.1%	28.3%	
BMI	< 25	48.5%	52.8%	0.494
	25 < BMI < 30	39.4%	28.3%	
	> 30	12.1%	19.9%	
Cholesterol	Normal	93.9%	84.9%	0.149
	Increased	6.1%	15.1%	
Triglyceride	Normal	90.9%	64.2%	0.005
	Increased	9.1%	35.8%	
Index HOMA	≤ 3.5	78.6%	76.7%	0.862
	> 3.5	21.4%	23.3%	
Adiponectin	≥ 10 µg/L	69.6%	82.9%	0.235
	< 10 µg/L	30.4%	17.1%	

BMI: body mass index.

cancer compared to patients presenting with colorectal cancer (39.6% vs 18.2%, p = 0.037).

Adiponectin rate

The mean level of adiponectin was significantly different by univariate analysis (Table 3): between the two groups (20.95 g/L in pancreatic cancer group versus 15.98 g/L in the colorectal cancer, p = 0.03).

After analyzing the ROC curves in the PC group, we selected as threshold a rate of adiponectin of 10 µg/L, with the best sensitivity/specificity ratio for the association between high ADP level and PC. The area under the receiver operating characteristic curve (ROC) for the highest ADP concentration was 0.81 (OR = 21.1; 95%CI = 1.4-150; p = 0.031). A specificity of 87% was seen at the cut-off level of 10 microG/L but with a sensitivity of 75%. In this study, the threshold value could be part of the diagnosis of pancreatic cancer in diabetes mellitus, with a sensibility of 87%.

There was no significant difference between both groups in univariate analysis for the portion of patients above this

Table 3 Factors associated with high levels of adiponectin (> 10 microG/L) (univariate analysis)

				Adiponectin
		< 10 µg/L (N = 19)	≥ 10 µg/L (N = 67)	p
Age	≤ 75	84.6%	60.0%	0.10
	> 75	15.4%	40.0%	
Sex	M	69.2%	48.9%	0.195
	F	30.8%	51.1%	
Diabetes	No	42.9%	77.8%	0.013
	Yes	57.1%	22.2%	
Cancer	Colorectal	53.8%	35.6%	0.235
	Pancreas	46.2%	64.4%	
Weigth loss	≤ 10%	92.8%	82.2%	0.134
	> 10%	7.1%	17.8%	
BMI	< 25	35.7%	60.0%	0.064
	25 < BMI < 30	35.7%	33.3%	
	> 30	28.6%	6.7%	
Glycemia at the diagnosis	≤ 5.8 mmol/L	42.9%	60.0%	0.259
	> 5.8 mmol/L	57.1%	40.0%	
Bilirubinemia	≤ 20 µmol/L	85.7%	77.8%	0.519
	> 20 µmol/L	14.3%	22.2%	
Cholesterol	Normal	85.7%	91.1%	0.730

threshold (adiponectin > 10 µg/L: 69.6% vs 82.9%, p = 0.195). The HOMA indexes were comparable between the two groups.

In the pancreatic cancer group, adiponectin levels were lower (less than 10 g/L) in the presence of type 2 diabetes (44.4% vs 14.6%, p = 0.013) and in the presence of insulin resistance measured by HOMA index (50.0% vs 11.5%, p = 0.049).

In multivariate analysis (Table 4) , after adjustment on sex, age (< 75 years), bilirubin (> 20 µmol/L) and weight loss (> 10%), the variables independently associated with high levels of adiponectin (> 10 µg/L) were : the presence of pancreatic cancer (OR = 12.03, p = 0.047), diabetes (OR = 0.07, p = 0.01) and the insulin resistance (OR = 0.42, p = 0.05).

In conclusion, adiponectin is twelve times higher (> 10 µg/L) in patients presenting with pancreatic cancer than in patients with colorectal cancer after adjustment on diabetes mellitus (Table 4).

Adiponectin-Diabetes Relationship

The low number of diabetic patients in the colorectal cancer group has not allowed analysis and comparison with the group with pancreatic cancer. We therefore focused on the characterization of diabetes in patients with adenocarcinoma of the pancreas. Diabetes was present in 21 patients (39.6%) with pancreatic cancer. It was present of PC within 3 months before diagnosis in 34% of cases and in 43.0% of cases within 3 years preceding the diagnosis of pancreatic cancer. One half of patients were men (p = 0.857).

The age at the time of diagnosis of pancreatic cancer was not statistically different according to the presence or absence of diabetes. Diabetic patients under 75 years represent 59.3% of cases (p = 0.760).

In univariate analysis, the presence of diabetes was associated with obesity (over-weight : 42.9% vs 18.8%, obesity : 33.3% vs 9.4%, p = 0.002), hypercholesterolemia (28.6% vs 6.3%, p = 0.037) and insulin-resistance (HOMA > 3.5 : 50.0% vs 0%, p = 0.001).

Non-diabetic patients did not show insulin resistance; 55% of diabetic patients presented a HOMA index higher than 3.5. An adiponectin rate < 10 µg/L was not statistically linked to type 2 diabetes, but there was a trend because 33.3% of diabetic patients had lower adiponectin levels (only 8.7% of non diabetics, with p = 0.07) (Table 5).

In multivariate analysis, only obesity was an independent factor explaining diabetes (Overweight: OR = 11.35, p = 0.01, obesity: OR = 47.49, p < 0.01). The insulin-resistance

Table 4 Factors associated with high levels of adiponectin (> 10 microG/L) (multivariate analysis)

	Definition	OR	p
Diabetes	No	1	0.10
	Yes	0.007	
Insulino-resistance	Homa Index ≤ 3.5	1	0.05
	Homa Index > 3.5	0.42	
Cancer	Colorectal	1	0.04
	Pancréas	12.03	

Table 5 Factors related to diabetes mellitus associated with pancreatic cancer (univariate analysis)

			Diabetes	
		No (N = 32)	Yes (N = 21)	p
Age	≤ 75	65.6%	61.9%	0.782
	> 75	34.4%	38.1%	
Sex	M	59.4%	61.9%	0.854
	F	40.6%	38.1%	
Weigth loss	≤ 10%	68.8%	76.2%	0.556
	> 10%	31.3%	23.8%	
BMI	< 25	71.9%	23.8%	0.002
	25 < BMI < 30	18.8%	42.9%	
	> 30	9.4%	33.3%	
Cholesterol	Normal	90.6%	61.9%	0,040
	> 2.7 g/L	6.3%	28.6%	
Triglyceride	Normal	65.6%	47.6%	0.351
	> 1.5 g/L	31.3%	42.9%	
HOMA Index	≤ 3.5	100%	50.0%	0.001
	> 3.5	0%	50.0%	
Adiponectin (µg/L)	< 10	8.7%	33.3%	0.07
	≥ 10	91.3%	66.7%	

Table 6 Factors related to diabetes mellitus associated with pancreatic cancer (multivariate analysis)

	Definition	OR	p
BMI	BMI < 25	1	
	25 < BMI < 30	11.35	0.01
	BMI > 30	47.49	< 0.01
Insulino-resistance	HOMA Index ≤ 3.5	1	
	HOMA Index > 3.5	1.2	0.84
Adiponectin	≥ 10 µg/L	1	
	< 10 µg/L	7.11	0.26

and adiponectin level's < 10 μg/L were not statistically associated with diabetes (respectively OR = 1.2, p = 0.84 and OR = 7.11, p = 0.26) (Table 6).

Discussion

Our study confirms that adiponectin level is variable with the type of cancer; and demonstrates that the mean level of ADP is significantly higher in PC than in CRC. In multivariate analysis, ADP concentration of up to 10 microG/l was independently associated with PC. For the first time our results show that serum adiponectin level is 12 times higher in pancreatic cancer than in colorectal cancer.

Published studies showed an inverse correlation between plasma levels of adiponectin and incidence of different cancers (4-9) probably because adiponectin could have an antitumor action through a pro-apoptotic and antiangiogenic pathway.

Data about the association between ADP and colorectal tumours are in agreement with that. In a recent cross sectional study, Okate et al (16) concluded that a decreased level of adiponectin was strongly associated with an increased risk of colorectal adenoma and early cancer but not with advanced cancer. The threeshold level of ADP in this study is comparable to our results (11 microG/l). If we don't demonstrate that the mean of ADP in the CRC is low (15.9 microG/l); more than one third of this group of patients presented an ADP under 11 microG/l. All the patients included presented an advanced cancer in our population. In a case control study, Gonullu et al (17) reported that adiponectin level was negatively correlated with a CRC and with the stage of the cancer. In this study, adiponectin could be responsible for a poor prognosis in colorectal cancer. Moreover serum adiponectin level seem negatively associated with higher risk of colorectal cancer and cancer stage and grade (18,19). In these two recent studies expression of adiponectin receptors was significantly stronger in adenocarcinoma than in normal tissue.

The association between adiponectin and pancreatic cancer is, conversely, more debated. For the first time, Chang et al. (14) reported a significant increase of ADP concentration in patients with operable pancreatic cancer compared to patients with chronic pancreatitis and the control group. In this study, the ADP test used is different from our study, so the threshold isolated cannot be extrapolated. In a case control study, Dalamaga et al (20) demonstrated that higher adiponectin levels were associated with PC ($p < 0.05$) before and after controlling for age, gender, BMI, smoking, alcohol consumption, history of diabetes and family history. Our results demonstrate that diabetes mellitus and pancreatic cancer are independently associated with an ADP concentration up to 10 microG/l. Conversely, Stolzenberg- Solomon et al (21) conducted a nested case control study. They demonstrate that higher ADP concentration (> 10 microG/l) were inversely associated with pancreatic cancer (OR = 0.65; p = 0.04). The inverse association was significant among cases diagnosed 5 or more years after blood concentrations.

Another recent nested-case control study observed a non-significant decrease in pancreatic cancer risk with higher adiponectin serum levels (22.) In our study, the ADP level was determined in patients with a proved PC, many of them presenting with weight loss and high inflammatory status. So, we can explain in part the paradigm.

Our study does not allow demonstrating directly if the ADP level is low in CRC or high in PC because we did not compare our cancer groups with a healthy control group. However, we consider that the level in patients with PC is high. One of our explanations is linked to diabetes mellitus. Pancreatic adenocarcinoma is the cancer most often associated with type 2 diabetes and/or metabolic syndrome, up to 80% in some series (15). It is well recognized that the reduction of adiponectin level in serum is involved in the genesis and the aggravation obesity and type 2 (16). The existence of tumor disease and association of diabetes (in pancreatic cancer) are two factors that should be associated with a significant decrease of adiponectin rate. Our results are concordant with those of Chang et al. (14) : they discovered high levels of adiponectin in patients with pancreatic cancer compared to subjects with chronic pancreatitis or healthy.

For the first time our results demonstrate that adiponectin level is 12 times higher in pancreatic cancer than in colorectal cancer (control group in our study). So, we can speculate that adiponectin doesn't present an antineoplasic property in PC or that diabetes mellitus could be the explanation for the difference of adiponectin in PC. The time between the onset of diabetes and diagnosis of pancreatic cancer is 3 years or less in 43% of cases in our study. This short period does not suggest a causal link between a classic diabetes mellitus and neoplastic disease, as has been described for type 2 "classic" diabetes in general (17, 20). There is certainly a different mechanism linking type 2 diabetes and pancreatic cancer. The most probable mechanism is that diabetes is a direct consequence of pancreatic cancer through a biochemical or mechanical lower insulin levels. Some works have suggested that diabetes associated with pancreatic cancer would be consequence of alterations of insulin secretion in beta cells (21,23). In our study, among diabetic patients with pancreatic cancer, there was a context of insulin resistance in only 50% of the cases; incidence of diabetes was two times

higher than in control group (38% vs 19%). The frequency of diabetes in the control group was comparable to type 2 diabetes in general population (prevalence between 10 and 20% after 35 years). All diabetics in colo-rectal cancer group had an insulin-resistance, characteristic of "classic" type 2 diabetes. This observation suggests that in pancreatic cancer group, 50% of mellitus diabetes was "classic", and 50% of others types of diabetes, directly associated with pancreatic cancer and probably linked to insulin deficiency.

Some weaknesses can be reported in our study. We have not included a healthy group. We have chosen to compare two different tumour populations rather than using a control group of healthy subjects because we wanted to validate the divergent evolution of adiponectin rate during theses cancers. Because of the relatively small population in our study we could not possibly explore in detail the subgroup of diabetic patients and our odds ratio, have wide confidence intervals and are only informative. Our article is a transversal study that allows evaluation of adiponectin rate at the moment when cancer becomes symptomatic, so we can not evaluate the kinetics of adiponectin before apparition of neoplasia. At last, there isn't a consensus between manufacturers of kits for the determination of adiponectin (positivity or increased serum level). The case-controlled studies conducted in various cancers have showed variable rates. The rate of adiponectin was often less than 9 µg/L in cancer cases, and generally between 10 µg/L and 14 µg/L in the control group without cancer. In the study by Chang et al. comparing the rates of adiponectin in pancreatic cancer (14), in chronic pancreatitis and in healthy subjects, the averages were respectively 21.1, 13.7 and 5.8 µg/L. After the analysis of ROC curves, we have chosen 10 µg/L as the threshold of positivity, but this must be confirmed by further studies with a larger numbers of patients.

Conclusion

In summary, we demonstrate that adiponectin concentration is higher in PC than in CRC. Our results confirm indirectly that in CRC, adiponectin is often low and higher in pancreatic cancer. We demonstrated that diabetes could be a factor for PC and differ in function of the natural in PC. Our data can speculate that we have two different mechanisms of natural history on PC. So, we hypothesize that an old diabetes mellitus could be an moderate risk factor of PC associated within an increase of IGF level and low adiponectin concentration and conversely an early diabetes with insulopenia and high level of adiponectin secondary and witness of an new PC. So, we think that other prospective studies must control our results and analyse the real key of adiponectin in these tumors.

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