Adiponectin as a Potential Differential Marker to Distinguish Pancreatic Cancer and Chronic Pancreatitis

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Objectives: Serum adiponectin (ADP) levels are reported inversely related to the risk in breast, endometrial cancer, and gastric cancer. Serum ADP as a potential marker compared with CA-19-9 in pancreatic carcinoma (PC) and chronic pancreatitis (CP) was studied. Adiponectin and CA-19-9 levels were examined at the time of diagnosis in patients with CP and PC.

Methods: Serum ADP and CA-19-9 levels were measured by immunoassays in 72 patients with PC and 39 with CP and 290 control subjects.

Results: The median levels of ADP for PC were significantly higher than those for CP and control subjects ($P = 0.0035$). Increasing the upper reference value of ADP allowed for better discrimination between CP and PC. The introduction of 28 ng/mL as a cutoff for ADP significantly improved its specificity. At an elevated cutoff level for ADP (28 ng/mL), a better discrimination between PC and CP was obtained.

Conclusions: Adiponectin might be useful in the differential diagnosis of PC and CP with elevated CA-19-9. This gives rise to the possibility that ADP has a potential role in differentiating CP and PC.

Key Words: adiponectin (ADP), CA-19-9, pancreatic carcinoma, chronic pancreatitis, tumor marker, differential diagnosis

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Pancreatic carcinoma (PC; ductal adenocarcinoma) is one of the most lethal malignant tumors with poor survival. Most of the patients with PC are diagnosed with advanced diseases.[1] Because chemotherapy and radiotherapy still could not significantly improve the survival of patients with PC, early diagnosis of PC is the key to improve the overall survival in this dismal disease.[2] Chronic pancreatitis (CP) is one of the reported risk factor for PC.[3–5] Even with the tremendous improvement of diagnostic imaging modalities, it is still difficult to distinguish malignant pancreatic tumor from CP, especially in cases involving inflammatory enlargement of the pancreatic head.[6] Therefore, more and more molecular markers are disclosed to try to distinguish them.[2,7,8] The serum marker sialylated Lewis[a] blood group antigen, CA-19-9, is widely used in monitoring responses to therapy in PC. However, the role of CA-19-9 as a diagnostic marker of PC is still undetermined.[9,10] Besides, elevated CA-19-9 could also be noted in CP, cholestasis.[9–13] On the other hand, false-negative results of CA-19-9 could be noted in patients who do not express Lewis antigens but with heavy tumor burden of PC.[11,12] CA-19-9 is also unable to differentiate patients with PC from those with CP accurately, and it is reported that up to 40% of patients with CP will have increased level of CA-19-9.[14] Other tumor markers have also been evaluated, including carcinoembryonic antigen (CEA), CA-242, CA-50, and CA-72-4 in the diagnosis of PC.[8] However, the sensitivity and specificity of these markers appeared to be insufficient for the differentiation of PC and CP.

Up to now, there is no good marker available for screening of high-risk population to detect early PC or to differentiate CP from PC.[6] It is mandatory to search markers to facilitate the diagnosis of PC, especially in risk populations of PC.

Adipose tissue is a now considered to be a genuine endocrine organ producing various adipocytokines, including adiponectin (ADP).[15] Plasma ADP levels have been shown to decrease in patients with cardiovascular diseases,[16] hypertension or obesity,[17] type 2 diabetes mellitus, and metabolic syndrome.[17–20] Interestingly, previous studies have shown that serum ADP levels are inversely related to body mass index (BMI), and decreased ADP level will increase the risk in breast, endometrial,[21–23] and gastric cancer.[24] It is hypothesized that low serum ADP levels may underlie the association between breast cancer and obesity/insulin resistance. Furthermore, the level of ADP was reported to be associated with the tumor aggressiveness in prostate cancer.[25] In recent report, ADP was found to be related to cancer cachexia in breast and colon cancer patients.[26] To our knowledge, whether lower ADP is associated with more aggressive PC is unknown. In the present study, we examined

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the association of the serum ADP levels in patients with PC and CP.

MATERIALS AND METHODS

Patients

A total of 72 patients with PC who were histologically proved to have ductal adenocarcinoma consecutively collected at the Department of Internal Medicine and Surgery, National Taiwan University Hospital, Taiwan, between January 1999 and December 2001 were enrolled. None of the PC patients had been treated by chemotherapy or radiation therapy before resection. The study was approved by the ethics committee, and informed consent was obtained from each patient. The clinicopathologic features of the patients were recorded. Of the 72 patients with PC, 3 were classified as stage I, 8 as stage II, 27 as stage III, and 34 as stage IV according to the Union International Cancer classification. In addition, we examined several discrete histological parameters, including lymphatic invasion, venous invasion, lymph node metastasis, and tumor markers including CEA and CA-19-9 antigens. A fasting morning blood sample was obtained for ADP assay after admission. Serum ADP concentration was also examined in 39 patients with CP collected during the same period.

The diagnosis of CP was confirmed by the presence of at least one of the following criteria: calcification of the pancreas, or histopathologic confirmation (surgical or biopsy samples). None of the patients with CP had PC in the follow-up period (at least 3 years). A total of 290 control subjects participating in 1 cardiovascular examination for a health promotion program were included and were confirmed as free from PC and CP from July to December 2002.[27] These control subjects also showed no abnormality in routine blood tests, urine and stool occult blood tests, chest radiograph examination, and abdominal ultrasonography and thus were considered to be free of malignancy and CP. For each patient, written informed consent was obtained.

Anthropometrics and Biomedical Measurements

The measurements, including serum levels of ADP, fasting concentrations of glucose, total cholesterol, and triglyceride, were performed as described.[28] Diabetes mellitus was diagnosed on the basis of a fasting plasma glucose value of more than 126 mg/dL and a postprandial 2-hour plasma glucose value of more than 200 mg/dL or requirements for insulin or oral hypoglycemic drugs. Hypertension was measured as systolic pressure of 140 mm Hg or higher or diastolic pressure of 90 mm Hg or higher. Dyslipidemia was measured as fasting triglyceride of 2.25 mM or more; hypercholesterolemia was measured as total cholesterol of 6.0 mM or more. Weight and height measurements were obtained. Body mass index was calculated as weight (in kilograms) divided by height (in meters) squared.

Serum ADP Analysis

All blood samples were obtained at fasting early in the morning, and the sera were immediately separated by centrifugation and stored at −80°C until use. Serum ADP levels were determined using a commercial enzyme-linked immunoassay assay with recombinant human ADP as standard (Human Adiponectin Enzyme-Linked Immunoassay kit; R&D Systems Inc, Minneapolis, Minn) according to the manufacturer's instructions.

Statistical Analysis

The statistical calculations were carried out using StatView-J 5.0 statistical software (SAS Institute, Cary, NC). The relationship between the serum ADP level and various clinicopathologic characteristics of PC was evaluated by using analysis of variance or χ^2 test for binary variables. We used logistic regressions to estimate the odds ratio of ADP after adjusting factors that were reported to possibly influence the level of ADP. Differences with a P value of less than 0.05 were considered to be statistically significant. The specificity of each marker

TABLE 1. Clinical Characteristics of Patients With PC and CP and Control Subjects

Characteristics	PC (n = 72)	Control (n = 290)	CP (n = 39)
Age (yrs)	64.63 (12.21)	49.54 (10.03)*	52.38 (12.67)†
Sex (male)	55.56	70.34	82.05†
Glucose	140.78 (58.92)	97.12 (18.77)	123.46 (41.40)
AST	75.22 (76.96)	25.83 (17.78)*	27.77 (23.56)†
ALT	104.62 (122.09)	27.98 (23.488)*	32.95 (41.77)†
Bil(T)	5.3 (6.26)	0.68 (0.527)*	0.73 (0.383)†
T-cho	170.35 (70.03)	211.0 (51.59)*	142.46 (37.75)†
TG	137.96 (81.93)	121.37 (97.12)	95.92 (65.53)†
BMI (kg/m^2)	21.39 (2.56)	24.30 (3.00)*	21.55 (1.82)
ADP (ng/mL)	21.14 (10.61)	5.86 (4.86)*	13.74 (7.12)†
CA-19-9 (U/mL)	207.34 (150.347)	8.83 (8.33)*	125.77 (117.86)
CEA (ng/mL)	18.19 (43.56)	1.15 (0.08)*	3.93 (10.67)

Values are given as mean (SD), except sex, which is given in %.
*$P < 0.05$, between PC and control subjects.
†$P < 0.05$, between PC and CP.
ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; Bil(T); total bilirubin; T-cho, total cholesterol; TG, triglyceride.

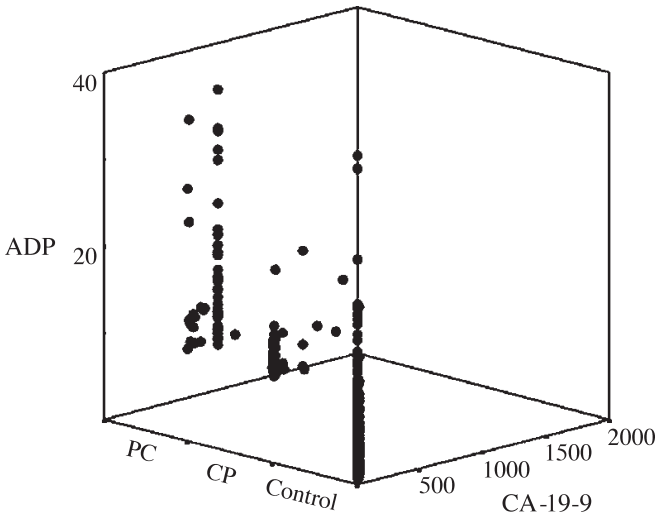

FIGURE 1. The scatter diagram of serum ADP (ng/mL) and CA-19-9 (U/mL) of PC, CP, and control subjects.

in diagnosis of PC and CP was calculated by using control subjects. The optimal cutoff points for each marker for discriminating between PC and CP were sought by constructing receiver operating characteristic (ROC) curves, which were generated by calculating the sensitivities and specificities of CA-19-9 and ADP data at several predetermined cutoff points.

RESULTS

Serum ADP Level Increased in Patients With PC and CP

Clinical demographic characteristics of PC patients, CP patients, and control subjects are shown in Table 1. The intra-assay coefficient of variation for ADP was less than 5%. Serum ADP level was significantly higher (21.14 ± 10.61 ng/mL) in patients with PC than that in CP patients (13.74 ± 7.12 ng/mL) and control subjects (5.86 ± 4.86 ng/mL) as shown in Figure 1 ($P < 0.0001$). The BMI was lower in both the PC and CP groups than in the control subjects ($P < 0.0001$). The BMIs in our study patients with PC and PC were similar.

Multivariate analysis was performed to evaluate the role of age, sex, fasting glucose, transaminases, bilirubin, total cholesterol, triglyceride, and BMI to predict ADP levels in PC patients (Table 2). Results of the model indicated that only bilirubin and BMI were significant independent predictors of ADP levels.

Diagnostic Role of ADP in PC and CP

The ROC analyses of ADP and CA-19-9 between different are shown in Figure 2. Table 3 shows the area under the curve (AUC) of ADP and CA-19-9. Table 3 shows the sensitivity, specificity, positive predictive value, and negative predictive value of each marker determined at different cutoff levels. Increasing the CA-19-9 cutoff value from 37 to 240 increases the specificity and decreases its sensitivity from 86.5% to 4.1% as the specificity increased from 71.8% to 89.7%. As to ADP, if we use the mean of ADP in CP (13.7 ng/mL) as the reference cutoff, the sensitivity and the specificity are 70.3% and 74.4%, respectively. When the reference limit set at 21.14 ng/mL (mean of ADP in PC patients) was used for ADP, the specificity and sensitivity for discrimination between PC and CP were 29.7% and 92.3%, respectively. Raising the discrimination level for ADP to 28 U/L (the mean of ADP in CP plus 2 SDs) significantly increased the specificity of ADP to 97.4%. Using the higher cutoff value for ADP allowed ruling out the false-positive results for CP-facilitated discrimination of pancreatic adenocarcinoma and CP.

Adiponectin and Clinicopathologic Characteristics, Staging, and Prognosis in PC Patients

In our study, there was no correlation between ADP level and tumor TNM stage and survival in the PC group. Besides, the CA-19-9 levels did not correlate with either TNM stage or survival (Table 4).

DISCUSSION

This is the first study to disclose the ADP level in PC and CP. Previous reports in endometrial cancer[22] and breast cancer[29] showed an inverse association of cancer risk and levels of ADP. The proposed mechanisms mostly rely on the relationship of obesity, insulin resistance, or sex hormone

TABLE 2. Multivariate Analysis as Predictors of Serum ADP Levels Among PC and CP

Characteristics	Regression Coefficient	SE	OR (95% CI)	*P*
Age	0.665	0.380	1.94	0.083
Sex	−2.911	10.831	0.05	0.789
Diabetes mellitus	−0.125	0.095	0.88	0.188
AST	0.010	0.141	1.01	0.943
ALT	−0.068	0.087	0.93	0.433
Bil(T)	3.346	1.128	28.39 (1.59–62.9)	0.004*
T-cho	−0.137	0.097	0.87	0.161
TG	0.011	0.087	1.01	0.897
BMI (kg/m^2)	−4.841	2.173	0.01 (0.0001–0.878)	0.028*

*$P < 0.05$.
ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; Bil(T); total bilirubin; CI, confidence interval; OR, odds ratio; T-cho, total cholesterol; TG, triglyceride.

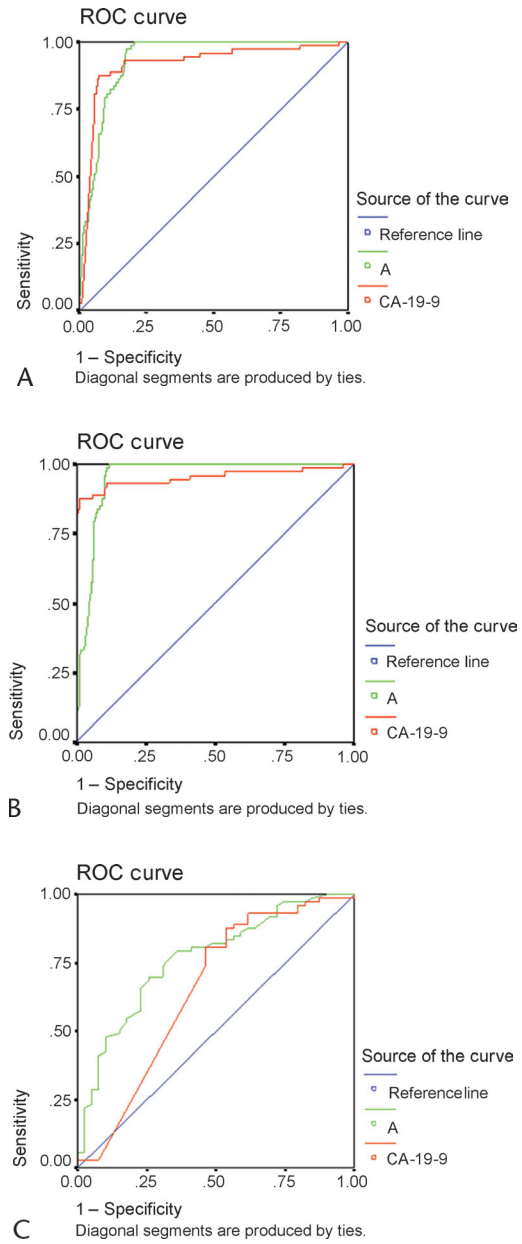

FIGURE 2. A, Receiver operating characteristic analysis of ADP and CA-19-9 (PC vs non-PC): ADP AUC, 0.934 (95% CI, 0.911–0.957); CA-19-9 AUC, 0.917 (95% CI, 0.876–0.958). B, Receiver operating characteristic analysis of ADP and CA–19-9 (PC vs controls): ADP AUC, 0.956 (95% CI, 0.937–0.975); CA-19-9 AUC, 0.953 (95% CI, 0.914–0.991). C, Receiver operating characteristic analysis of ADP and CA-19-9 (PC vs CP): ADP AUC, 0.766 (95% CI, 0.674–0.857); CA-19-9 AUC, 0.648 (95% CI, 0.531–0.765).

status in cancer risk. Adiponectin is reported to have antiangiogenic properties both in vivo and in vitro.[30] In our study, elevated ADP is noted in patients with PC after adjusting possible factors to influence the ADP level including age, sex, BMI, abnormal liver function, and jaundice.[31] It is different from the role ADP is playing in gastric,[2] prostate,[32] and breast cancer.[33] The effects of ADP on these cancer cells are currently under investigation.

In our study, the mean values of ADP level of control subjects, CP patients, and PC patients were different, and an increasing trend among these 3 groups was noted ($P < 0.0001$).

CA-19-9 is the most used traditional serum tumor marker of PC. The sensitivity and specificity to diagnose PC depend on the cutoff value we set.[34] However, the CA-19-9 may also increase in patients with CP. In our study, both CA-19-9 and ADP were elevated in both PC and CP patient groups than control subjects. Adiponectin outperformed CA-19-9 in distinguishing patients with PC from those without PC (AUC in Table 3, $P < 0.0001$). Similarly, in the comparison between patients with CP and those with PC, ADP is still better than CA-19-9 (AUC in Table 3, $P < 0.0001$). These findings suggest that ADPs have a potential role as a marker to differentiate CP from PC, especially those with elevated CA-19-9.

The diagnostic value of ADP for patients with PC has never been studied before. In the current study, the results of ADP and CA-19-9 concentrations were measured in 2 selected patient groups with confirmed PC and CP. Different cutoff levels of ADP and CA-19-9 were considered, and using ROC curve analysis, the sensitivities for both markers were calculated at predetermined specificity values. Using 28 ng/mL as the reference limit value for ADP and 37 U/mL for CA-19-9 demonstrated an elevation in specificity of the markers, which reached 97.4% and 71.8% of PC patients, respectively. Based on these results, the upper reference limit for CA-19-9 was kept at 37 U/mL, because increasing its cutoff value did not improve the differential diagnosis between CP and PC. On the other hand, using higher ADP levels facilitated the discrimination of pancreatic adenocarcinoma and CP.

The result suggested that ADP has a potential advantage over CA-19-9 because of its significantly higher specificity in patients with pancreatic disease, especially in those with elevated CA-19-9. The specificity of the high cutoff point for ADP (28 ng/mL) seems to offer a better opportunity to distinguish between PC and CP.

Adiponectin, Obesity, BMI, and PC

Adiponectin levels are reported to be inversely correlated with body weight. Voluntary weight loss, as well as anorexia nervosa, is associated with elevated ADP levels.[26,35] It is still controversial whether obesity is a risk factor for PC. Previous studies only provide a weak association of obesity as a risk factor for PC.[36] A recently published study in South Korea did not show any significant association of excess weight with PC incidence.[28] Our results clearly demonstrated that serum ADP levels were significantly increased in patients with PC as compared with controls. Furthermore, an increasing trend of ADP level in control, CP patients, and PC patients is obvious (Fig. 1). In this report, patients with CP and PC have lower BMI than controls (Table 1), which may partially explain the increased level of ADP. The BMI is similar between the patients with CP and PC ($P = 0.605$ in Table 1). After adjusting for age,

TABLE 3. Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value of ADP and CA-19-9

Markers	No. PC	No. CP	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CA-19-9, U/mL						
<37	9	28	86.5	71.8	85.3	73.7
≥37	63	11				
CA-19-9, U/mL						
<100	15	32	78.4	82.1	89.2	66.7
≥100	57	7				
CA-19-9, U/mL						
<240	18	33	4.1	89.7	42.9	33.0
≥240	54	6				
ADP, ng/mL						
<13.74	22	29	70.3	74.4	83.9	56.9
≥13.74	50	10				
ADP, ng/mL						
<21.14	51	36	29.7	92.3	88.0	40.9
≥21.14	21	3				
ADP, ng/mL						
<28	58	38	18.9	97.4	93.3	38.8
≥28	14	1				

PPV indicates positive predictive value; NPV, negative predictive value.

sex, transaminases, bilirubin, and BMI, ADP is still an independent factor to predict PC. In the literature, ADP is regarded to be related to cancer cachexia.[26] Cancer cachexia is one of the most frequent effects of malignancy, and it is often associated with poor prognosis. Pancreatic cancer is one of the lethal cancers with poor prognosis. Furthermore, patients with cystic fibrosis also have been reported to have high ADP levels, which may also be related to the changes of body composition.[37] It is worthy and interesting to elucidate the mechanism of increased ADP level in cancer in the future.

Adiponectin and Jaundice

In our patients, about half of the PC patients were with jaundice at diagnosis. Previous study described that the elevated ADP level might be related to cholestasis in chronic liver diseases.[31] In multivariate analysis, bilirubin is still an independent factor associated with increased ADP level in our patients. CA-19-9 values were also increased in both groups with PC and CP. However, it could not differentiate PC patients from those with CP after adjusting bilirubin levels. Therefore, ADP is a more promising differential marker in PC and CP.

In conclusion, we have investigated the potential use of ADP levels in patients with PC and found that ADP, compared with CA-19-9, had a significantly higher specificity for differentiating between PC and CP. Our data suggest that ADP provides additional information and is more useful in the differential diagnosis of patients with CP and PC. Further studies are needed to confirm these findings and determine whether ADP may have a role as a tumor marker for PC. In addition, more studies are needed to help us better

TABLE 4. CEA, CA-19-9, and ADP Levels in Patients With PC

	CA-19-9	CEA	ADP
TNM stage			
I	95.60 ± 12.2	2.01 ± 2.01	13.00 ± 2.68
II	57.30 ± 43.01	12.85 ± 24.77	17.00 ± 8.12
III	3486.09 ± 136.07	14.81 ± 41.16	23.24 ± 17.58
IV	2129.192 ± 165.685	23.26 ± 50.75	23.26 ± 50.75
Tumor size			
≤3 cm	109.92 ± 97.19	17.29 ± 50.31	22.30 ± 16.70
>3 cm	4144.92 ± 1514.92	18.60 ± 38.18	20.26 ± 20.09
Lymph node involvement			
Negative	2733.89 ± 1224.56	15.56 ± 40.91	20.47 ± 18.26
Positive	2142.32 ± 122.07	25.31 ± 51.46	23.342 ± 0.31
Distant metastasis			
Negative	108.56 ± 114.40	12.94 ± 33.37	23.16 ± 22.23
Positive	4149.81 ± 1514.42	29.69 ± 60.19	17.23 ± 5.86

understand the potential biological association between ADP and PC.

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