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Relationship between pancreatic cancer-associated diabetes and cachexia

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Abstract

Background Pancreatic cancer-associated diabetes mellitus (PCDM) is a paraneoplastic phenomenon characterized by worsening hyperglycaemia and weight loss. Galectin-3 and S100A9, mediators of PCDM, have pro-inflammatory functions and might thereby induce systemic inflammation and cachexia. We aimed to examine whether PCDM directly mediates cachexia.
Methods Consecutive pancreatic cancer (PC) patients with and without PCDM (n = 88 each) with complete information were included. Cachexia was defined as weight loss >5% within 6 months or weight loss >2% and body mass index <20 kg/m^2 or sarcopenia. Skeletal muscle mass was measured with lumbar skeletal muscle index (SMI) using computed tomography images. Cachexia-related parameters (prevalence of cachexia, weight loss, and SMI) were compared between patients with and without PCDM. Relations between cachexia-related parameters and fasting blood glucose or serum levels of galectin-3 and S100A9 were analysed by Spearman correlation and logistic regression analyses.
Results One hundred two (58.0%) patients had cachexia at diagnosis. No significant differences existed between patients with and without PCDM in prevalence of cachexia (64.8% vs. 51.1%, P = 0.093), percentage of weight loss (median 6.8 vs. 4.0, P = 0.085), and SMI (median 45.8 vs. 45.3 cm^2/m^2 in men, P = 0.119; 34.9 vs. 36.3 cm^2/m^2 in women, P = 0.418). In patients with cachexia, the percentage of weight loss and SMI were also similar between patients with and without PCDM. In patients with PCDM, fasting blood glucose was comparable between patients with and without cachexia (P = 0.458) and did not correlate with the percentage of weight loss (P = 0.085) or SMI (P = 0.797 in men and 0.679 in women). Serum S100A9 level correlated with fasting blood glucose (correlation coefficient 0.213, P = 0.047) but not with the percentage of weight loss (P = 0.977) or SMI (P = 0.247 in men and 0.458 in women). Serum galectin-3 level also did not correlate with the percentage of weight loss (P = 0.226) and SMI (P = 0.201 in men and 0.826 in women). Primary tumour size was associated with cachexia (adjusted odds ratio per 1 cm increase 1.28, 95% confidence interval 1.02–1.60, P = 0.034), whereas PCDM, fasting blood glucose, and levels of galectin-3 and S100A9 were not predictors of cachexia.
Conclusions Neither fasting blood glucose nor levels of galectin-3 and S100A9 were associated with cachexia-related parameters. Mediators of PCDM and hyperglycaemia do not directly mediate PC-induced cachexia.

Keywords Pancreatic cancer; Diabetes; Cachexia; Sarcopenia

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Introduction

Pancreatic cancer (PC) is the fourth leading cause of cancer deaths in the United States and is projected to become the second leading cause of cancer deaths by 2030.[1] PC is the most lethal cancer, with a 5 year survival rate of only 7.7%.[2] Besides a high risk of recurrence after surgical resection and limited response to systemic therapies, an important contributor to the poor survival of PC is cancer cachexia.[3] Cancer cachexia is a paraneoplastic syndrome triggered by cancer-induced systemic inflammation and characterized by pronounced weight loss and muscle wasting.[4,5] Cachexia develops in approximately 80% of PC patients during the disease course,[3] and weight loss often commences before the tumour is clinically apparent in PC patients.[4] Cachexia negatively impacts treatment response and survival of PC patients,[6,7] with one-third of PC patients dying from cachexia-associated complications including impaired immunity and cardiopulmonary dysfunction.[7] However, the mediators of PC-induced cachexia remain elusive, and no effective treatments exist. A better understanding of the mechanisms and novel treatment strategies for PC-induced cachexia are urgently needed to improve the dismal prognosis of PC.

Pancreatic cancer-associated diabetes mellitus (PCDM) may be a major contributor to PC-induced cachexia.[8,9] PCDM is a paraneoplastic syndrome occurring in approximately 40% of patients within 24 months preceding the diagnosis of PC[10–13] and characterized by rising blood glucose levels concurrent with progressive weight loss.[8,9] At the onset of PCDM, the tumour is generally early or even radiologically undetectable,[14] and resection of the PC results in improved insulin resistance and resolution of diabetes.[15,16] *In vitro*, tumour extracts from patients with PCDM reduce insulin-mediated glycogen synthesis in skeletal muscle,[16] and conditioned media of PC cell lines impair peripheral glucose metabolism *in vitro*[17] and reduce glucose tolerance *in vivo*.[18] Circulating PC-derived exosomes from patients have also been found to induce paraneoplastic beta-cell dysfunction and to inhibit insulin secretion.[19] Significant weight loss has also been found to emerge since 1 year before the diagnosis of PC,[13] with approximately 40% of patients reaching the degree of cachexia at the time of PC diagnosis.[7] PCDM might mediate cachexia through direct and indirect mechanisms. Poorly controlled diabetes induces muscle wasting and unintentional weight loss.[20,21] Insulin resistance, the hallmark of PCDM,[16,22] might play important roles in cancer cachexia-associated muscle wasting.[23] Furthermore, PCDM is mediated by PC-secreted pro-inflammatory factors, suggesting that the mediators of PCDM might underlie the systemic inflammation which drives PC-induced cachexia.[3] A recent study has shown that galectin-3 and S100A9, both with potent pro-inflammatory functions, are differentially overexpressed in the tumour and systemic circulation of PC patients with PCDM and induced insulin resistance by inhibiting insulin-simulated glucose uptake of skeletal muscle cells.[24] Furthermore, binding of S100A9 with toll-like receptor 4 induces activation of NF-κB,[25] which has been shown to induce profound muscle wasting through upregulation of ubiquitin-mediated proteasome degradation.[26] These possible mechanistic links and the fact that progressive weight loss accompanies worsening hyperglycaemia in PCDM[8,13] suggest that increased levels of diabetogenic factors and/or blood glucose in PCDM might directly drive PC-induced cachexia.

Clarifying the relationship between PCDM and PC-induced cachexia has important research and clinical implications. If PCDM directly mediates cachexia, aggressive glycaemic control in patients with PCDM may attenuate weight loss/muscle wasting and improve survival and quality of life, and PC-produced diabetogenic factors (galectin-3 and S100A9) may serve as novel therapeutic targets for PC-induced cachexia. However, if cachexia and PCDM are mediated through separate mechanisms, optimizing glycaemic control may not alleviate cachexia, and further search for mediators and therapies of PC-induced cachexia is warranted. A causal link between PCDM and PC-induced cachexia is plausible if PC patients with PCDM have a higher risk of cachexia or a greater degree of weight loss and muscle wasting compared with PC patients without PCDM, and the degree of weight loss and muscle wasting correlate with blood levels of glucose and mediators of PCDM in patients with PCDM. This study aimed to verify these inferences to clarify the relationship between PCDM and PC-induced cachexia.

Material and methods

Patients

The PCDM group included 88 PCDM patients (histology-confirmed/cytology-confirmed pancreatic adenocarcinoma with fasting blood glucose >126 mg/dL or HbA1c > 6.5%/48 mmol/mol at diagnosis, without a history of diabetes or with a history of diabetes diagnosed within 24 months preceding the diagnosis of PC[11]) diagnosed at a tertiary referral centre (National Taiwan University Hospital) who were consecutively enrolled between January 2006 and September 2018[24] and had complete information for the study. Among the PC patients consecutively enrolled during the same period who did not have PCDM (fasting blood glucose <126 mg/dL or HbA1c < 6.5%/48 mmol/mol without the use of antidiabetic medication) and had complete information for the study, 88 patients with the lowest fasting blood glucose levels were selected as the non-PCDM comparison group. The presence or absence of diabetes was determined based on fasting blood glucose and HbA1c levels measured at the recruiting centre. Tumour stage was defined according to the eighth edition of the tumour, node, metastasis system of the combined American Joint Committee on Cancer/Union

for International Cancer Control.[27] The study was approved by the Institute Research Ethical Committee of National Taiwan University Hospital and performed in accordance with the Declaration of Helsinki. All participants provided informed consent.

Ascertainment of weight loss, skeletal muscle mass, and cachexia

Cachexia was defined as weight loss >5% within 6 months, or weight loss >2% in individuals with body mass index <20 kg/m^2, or the coexistence of weight loss >2% and sarcopenia.[28] Information on usual body weight and degree of weight loss was obtained by patient recall at the time of diagnosis before treatment for PC. Medical records at the recruiting centre, if available, were reviewed to minimize inaccuracies in patient recall. The percentage of weight loss was calculated as body weight lost (i.e. difference between usual body weight and weight at diagnosis) divided by usual body weight. Lumbar skeletal muscle index (SMI), the preferred method for muscle mass assessment,[28] was calculated from computed tomography images obtained at the diagnosis of PC as previously described.[29] In brief, two consecutive computed tomography images containing the third lumbar vertebrae (L3) were used for measurement. Skeletal muscles at the L3 level including psoas, paraspinal muscles (erector spinae and quadratus lumborum), and abdominal wall muscles (transversus abdominis, external and internal obliques, and rectus abdominis) were identified using Hounsfield unit thresholds of −29 to +150.[30] The sum of cross-sectional areas of these muscles on each image was computed, and the mean value of the two images was taken as total area of L3 skeletal muscles and further normalized for stature to yield the L3 SMI.[29] Lumbar SMI is linearly correlated with whole-body muscle mass, with values <55 cm^2/m^2 in men and < 39 cm^2/m^2 in women considered as sarcopenia.[29,30]

Measurement of serum levels of galectin-3 and S100A9

Blood samples were collected before treatment for PC after an overnight fast. Serum was separated by centrifugation and stored at −80 °C until use. All samples were coded for blind analysis. Serum levels of galectin-3 and S100A9 were analysed in the 88 patients with PCDM by sandwich ELISA (R&D Systems) as previously described.[24]

Statistical analysis

Mann–Whitney *U*-test and Fisher exact test were used to compare continuous and categorical variables, respectively. The relationships between tumour stage or size and prevalence of cachexia, the percentage of weight loss, or lumbar SMI were assessed with trend tests. Spearman correlation coefficient was used to assess correlations between fasting blood glucose or serum levels of galectin-3 and S100A9 and the percentage of weight loss or lumbar SMI. Relations between the risk of cachexia and PCDM status, fasting blood glucose, or serum levels of galectin-3 and S100A9 at diagnosis were analysed with logistic regression model. Variables with *P* values <0.2 in univariable analyses were included in the multivariable analysis. All tests were two-sided and *P* values less than 0.05 were considered as statistically significant. Statistical analyses were performed using Stata14 (StataCorp, College Station, TX).

Results

Clinical features and information on weight loss and muscle mass are summarized in Table 1. Among all 176 PC patients, 102 (58.0%) had cachexia at the time of PC diagnosis.

Table 1 Patient characteristics

	With PCDM (n = 88)	Without PCDM (n = 88)	*P* value	With cachexia (n = 102)	Without cachexia (n = 74)	*P* value
Age (years)	63.6 ± 11.0	64.7 ± 11.9	0.335	64.5 ± 11.1	63.5 ± 11.8	0.532
Male, *n* (%)	55 (62.5)	47 (53.4)	0.285	59 (57.8)	43 (58.1)	1.000
Stage I/II/III/IV (%)	12.5/27.3/ 23.9/36.3	10.2/25.0/ 27.3/37.5	0.923	7.8/28.4/ 25.5/38.3	16.2/23.0/ 25.7/35.1	0.369
Primary tumour size (cm)	3.4 (2.8–5.0)	3.5 (3.0–4.8)	0.881	3.8 (3.0–5.0)	3.3 (2.7–4.4)	0.027
BMI (kg/m^2)	23.3 (21.3–25.5)	23.0 (20.5–24.9)	0.213	23.1 (20.6–24.8)	23.1 (20.5–25.4)	0.900
Weight loss (%)	6.8 (0–14.6)	4.0 (0–11.8)	0.085	12.0 (7.4–16.9)	0 (0–0)	<0.001
Lumbar SMI (cm^2/m^2)						
Male	45.8 (40.7–51.1)	45.3 (38.0–48.4)	0.119	43.4 (37.6–50.4)	47.0 (42.7–51.4)	0.033
Female	34.9 (31.6–40.7)	36.3 (33.2–40.7)	0.418	34.9 (30.2–39.4)	37.9 (33.6–41.5)	0.135
Cachexia, *n* (%)	57 (64.8)	45 (51.1)	0.093	—	—	—
PCDM, *n* (%)	—	—	—	57 (55.9)	31 (41.9)	0.093

BMI, body mass index; PCDM, pancreatic cancer-associated diabetes mellitus; SMI, skeletal muscle mass index.

Eighty-nine (50.6%) patients lost more than 5% of body weight, and 144 (81.8%) met the definition of sarcopenia. Patients with and without cachexia were comparable in demographics and cancer stage. Compared with patients without cachexia, cachectic patients had greater weight loss (median 0 vs. 12.0%, $P < 0.001$) and slightly larger primary tumour (median 3.3 vs. 3.8 cm, $P = 0.027$). In men, lumbar SMI was significantly lower in patients with cachexia compared with those without cachexia (median 43.4 vs. 47.0 cm^2/m^2, $P = 0.033$). A similar trend was noted in female patients, but the difference did not reach statistical significance.

Weight loss and muscle mass in patients with and without pancreatic cancer-associated diabetes mellitus

The percentage of weight loss and lumbar SMI according to PCDM status are summarized in Table 1. PC patients with and without PCDM were comparable with regard to demographics, primary tumour size, and cancer stage. No significant differences existed between PC patients with and without PCDM with respect to the prevalence of cachexia at diagnosis (64.8% vs. 51.1%, $P = 0.093$), the percentage of

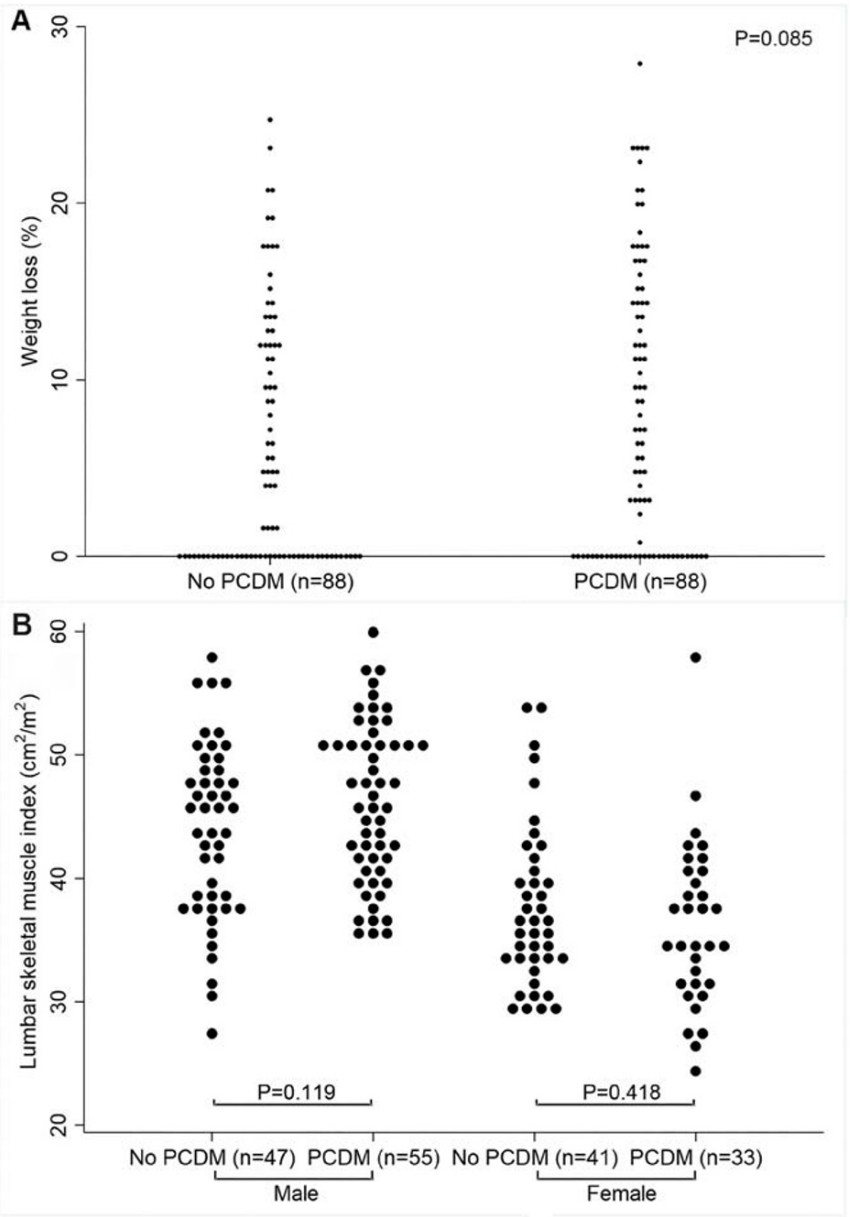

Figure 1 Weight loss *(A)* and muscle mass index *(B)* in patients with or without pancreatic cancer-associated diabetes. PCDM, pancreatic cancer-associated diabetes mellitus.

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weight loss (median 6.8% vs. 4.0%, P = 0.085), and lumbar SMI (median 45.8 vs. 45.3 cm^2/m^2 in men, P = 0.119; 34.9 vs. 36.3 cm^2/m^2 in women, P = 0.418) (Table 1 and Figure 1). In the 102 patients with cachexia at PC diagnosis, patients with and without PCDM also did not differ significantly in the percentage of weight loss (median 12.2% vs. 11.8%, P = 0.625) and lumbar SMI (median 43.9 vs. 41.7 cm^2/m^2 in men, P = 0.062; 34.9 vs. 35.1 cm^2/m^2 in women, P = 0.451).

Relation between diabetogenic factors, blood glucose, and cachexia in pancreatic cancer-associated diabetes mellitus patients

Clinical features and cachexia-related parameters in patients with PCDM are summarized in Table 2. Among the 88 patients with PCDM, 57 (64.8%) had cachexia at diagnosis. Primary tumour size was slightly larger in patients with cachexia. Fasting blood glucose did not differ significantly between PCDM patients with and without cachexia (median 172 vs. 160 mg/dL, P = 0.458) (Table 2 and Figure 2(A)). There were also no significant correlations between fasting blood glucose level and percentage of weight loss (Spearman correlation coefficient r = 0.18, P = 0.085) or lumbar SMI (r = 0.036, P = 0.797 in men and r = 0.075, P = 0.679 in women, respectively) (*Figure 3(A)* and *3(B)*).

Serum levels of S100A9 and galectin-3 were comparable in PCDM patients with and without cachexia (P = 0.634 and 0.487, respectively) (Table 2 and *Figure 2(B)* and *2(C)*). While serum S100A9 level was positively correlated with fasting blood glucose level (r = 0.213, P = 0.047) (Figure 4 (A)), it did not correlate with the percentage of weight loss (r = 0.00, P = 0.977) or lumbar SMI (r = −0.16, P = 0.247 in men; r = 0.13, P = 0.458 in women) (*Figure 4(B)* and *4 (C)*). Serum galectin-3 level also did not correlate with the percentage of weight loss (r = 0.13, P = 0.226) and lumbar SMI (r = −0.18, P = 0.201 in men; r = −0.04, P = 0.826 in women).

Predictors of cachexia

The relation between tumour size/cancer stage and cachexia-related parameters is summarized in Table 3. Primary tumour size was positively associated with the prevalence of cachexia and the percentage of weight loss (P_{trend} = 0.047 and 0.011, respectively) but not with lumbar SMI. Multivariable logistic regression analysis also showed that only primary tumour size was associated with the risk of cachexia (adjusted odds ratio per 1 cm increase 1.28, 95% confidence interval 1.02–1.60, P = 0.034) (*Table 4*). PCDM, fasting blood glucose, and levels of galectin-3 and S100A9 were not associated with cachexia.

Discussion

This study clarified the relationship between PCDM and PC-induced cachexia. The results showed that compared with PC patients without PCDM, patients with PCDM did not have a higher risk of cachexia, a greater degree of weight loss, or lower skeletal muscle mass. Among patients with cachexia, weight loss and skeletal muscle mass were also comparable between those with and without PCDM. Furthermore, fasting blood levels of glucose and PC-derived diabetogenic factors (galectin-3 and S100A9) neither correlated with the degree of weight loss or muscle mass nor predicted the risk of cachexia in patients with PCDM. These results supported that mediators of PCDM and hyperglycaemia do not directly mediate PC-induced cachexia.

Although the frequent co-occurrence of PCDM and significant weight loss has been well recognized,[8,31] their relationship had not been investigated in depth. We found that PC patients without PCDM had comparable weight loss and muscle wasting compared with those with PCDM. The lack of association between fasting blood glucose level and weight loss or muscle mass in patients with PCDM argues against a significant role of hyperglycaemia in mediating cachexia. While the positive correlation between S100A9 level and fasting blood

Table 2 Patients with pancreatic cancer-associated diabetes

	With cachexia (n = 57)	Without cachexia (n = 31)	P value
Age	64.5 ± 10.7	61.8 ± 11.5	0.281
Male, n (%)	36 (63.2)	19 (61.3)	1.000
Stage I/II/III/IV (%)	7.0/28.1/21.0/43.9	22.6/25.8/29.0/22.6	0.074
Primary tumour size (cm)	3.8 (2.8–5.3)	3.0 (2.4–4.0)	0.040
BMI (kg/m^2)	23.4 (21.7–24.9)	23.3 (20.3–26.0)	0.757
Weight loss (%)	12.2 (7.4–17.4)	0 (0–0)	<0.001
Lumbar SMI (cm^2/m^2)			
Male	43.9 (39.5–50.7)	47.5 (43.7–53.4)	0.111
Female	34.8 (31.5–38.6)	37.9 (33.5–42.6)	0.262
Fasting blood glucose (mg/dL)	172 (139–221)	160 (134–202)	0.458
Serum galectin-3 (ng/mL)	8.7 (4.5–12.0)	7.4 (4.4–12.0)	0.487
Serum S100A9 (ng/mL)	63.9 (54.5–68.6)	64.9 (59.4–68.6)	0.634

BMI, body mass index; SMI, skeletal muscle mass index.

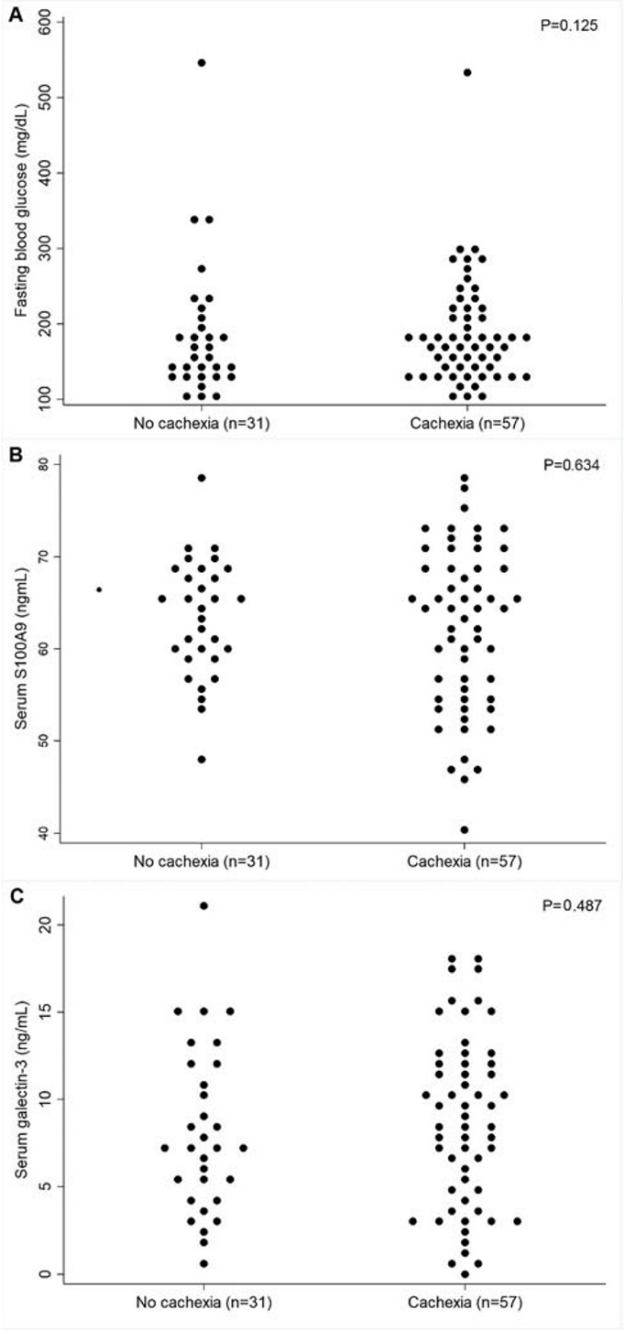

Figure 2 Fasting blood glucose *(A)*, serum S100A9 *(B)*, and serum galectin-3 *(C)* levels in patients with pancreatic cancer-associated diabetes.

glucose reaffirmed the finding that S100A9 mediates PCDM,[24] the lack of association between S100A9 level and weight loss or muscle wasting refuted the hypothesis that increased levels of diabetogenic factors in PCDM directly drives PC-induced cachexia. However, the ability of S100A9 to activate NF-κB through TLR4[25] suggested that S100A9 might contribute to muscle wasting, as NF-κB activation induces profound muscle wasting through MURF1-mediated degradation of myosin heavy chain,[5,32] a major cause of muscle degradation in cancer cachexia.[4] Therefore, our results could not exclude the possibility that PCDM might potentiate muscle wasting induced by elusive PC-derived cachexigenic factors. We also could not rule out a permissive role of S100A9 and galectin-3 in cachexia among patients with PCDM.

A notable finding of this study was the consistently high prevalence of cachexia and muscle wasting regardless of tumour size and stage in PC. The prevalence of cachexia/sarcopenia reached 40/60% in patients with stage I cancer (i.e. tumour ≦4 cm without involvement of celiac axis, superior mesenteric artery, or common hepatic artery and without lymph node or distant metastasis) and 50/78.6% in those with tumours ≦2 cm. Similarly, Danai *et al*. found that 65% of PC patients had sarcopenia at diagnosis, and the prevalence of sarcopenia was comparable between stages.[33] In line with these findings, Mayers *et al*. showed that wasting of body protein with increased circulating amino acid preceded cancer diagnosis by 2 to 5 years in PC patients, and increased muscle catabolism in mice with K-ras-driven PCs occurred before tumours were detectable.[34] Collectively, these findings lend further support to the notion that PC-induced cachexia is a paraneoplastic phenomenon mainly attributed to the metabolic phenotype of the cancer cells and begins before the tumour is clinically detectable. The modest association between primary tumour size and weight loss/cachexia might be attributed to a multitude of mechanisms contributing to cachexia as PC progresses, including reduced food intake due to tumour compression of the duodenum and pancreatic exocrine dysfunction in patients with large tumours.[3,33]

Our results suggested that PC-induced cachexia might provide another window of opportunity for early detection of PC. Given the low incidence of PC, screening the general population for PC is not feasible. It is estimated that even if a test with 99% sensitivity and specificity for PC were available, screening individuals aged greater than 50 years with the test would have a positive predictive value of only 3.6%, resulting in many false positives and unnecessary tests.[9,11] Elucidation of the distinctive clinical features and mediators of PCDM has been shown to enable detection of PCDM among patients with new-onset diabetes,[9,24] supporting PCDM as a window of opportunity for early detection of PC. However, only approximately 40% of PC patients develop PCDM, and thus alternative strategies are needed to enable early detection in PC patients without PCDM. Our results support that unexplained weight loss/cachexia is another clue to occult PC, but a screening modality that can identify PC-induced cachexia is needed to take advantage of this opportunity.

Cancer cachexia is characterized by systemic inflammation with resultant skeletal muscle breakdown and increased circulating amino acids to support tumour growth.[4,34] PCDM is also a metabolic strategy employed by PC to fuel tumour

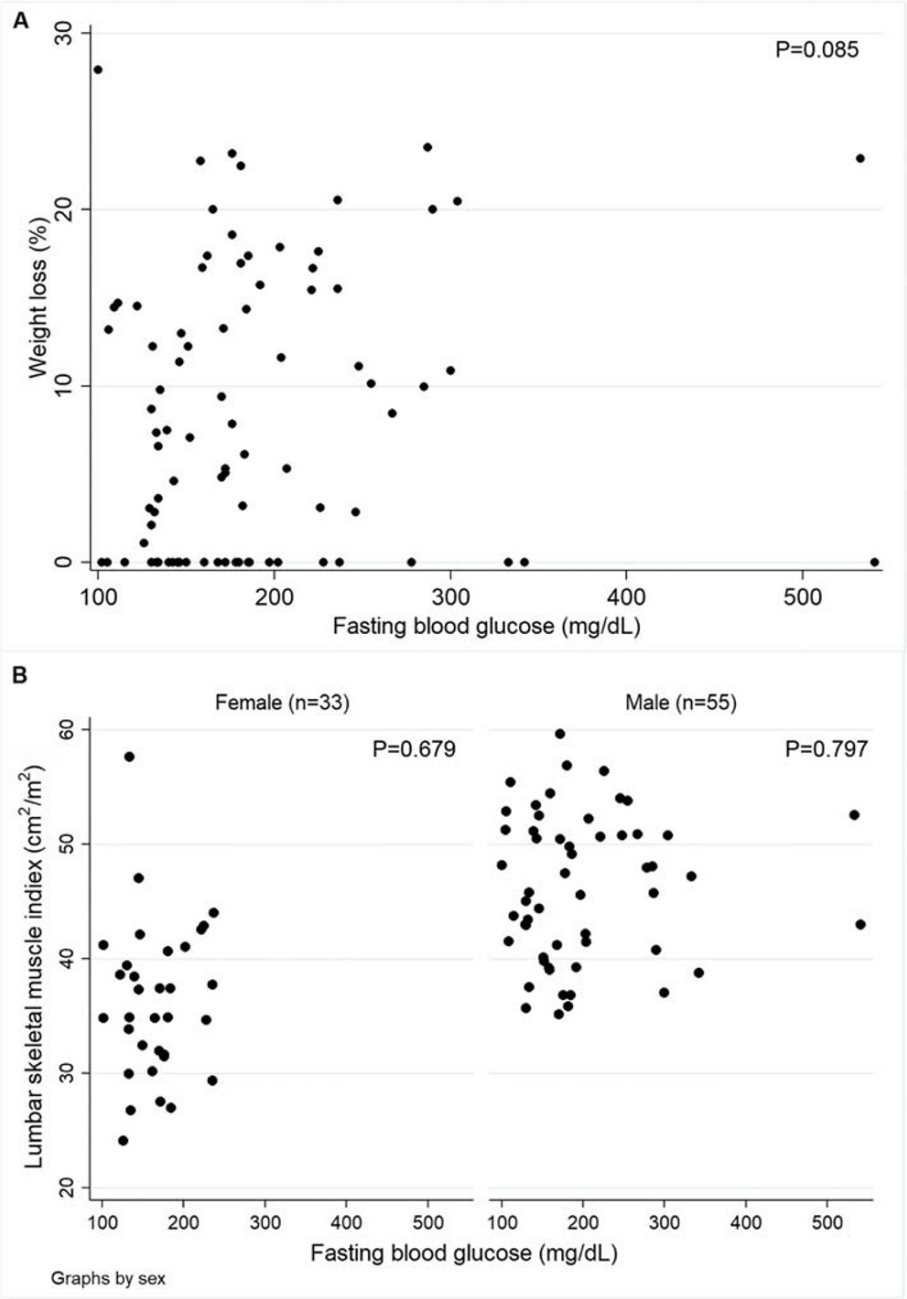

Figure 3 Correlation between fasting blood glucose and weight loss *(A)* or skeletal muscle mass *(B)* in patients with pancreatic cancer-associated diabetes.

growth. PC cells have a high demand for glucose ('glucose addiction') because of their preferential metabolism of glucose through aerobic glycolysis to generate metabolites required for cell proliferation (Warburg effect),[12,35–37] and hyperglycaemia has been shown to promote invasion and migration of PC cells.[38] We have discovered that galectin-3, a β-galactoside-binding lectin with pro-inflammatory functions,[39] and S100A9, which binds TLR4 to amplify the inflammatory responses of phagocytes,[25] are diabetogenic factors overexpressed by PC and mediate insulin resistance by inhibiting insulin-induced glucose uptake of muscle cells.[24] Despite the potential of S100A9 and galectin-3 to induce systemic inflammation and the ability of S100A9 to induce NF-κB activation and subsequent muscle wasting,[25,26] our results suggested that PCDM and PC-induced cachexia are distinct metabolic reprogramming induced by PC cells to secure amino acids and glucose for tumour growth.

This study was the first to investigate the potential link between PCDM and PC-induced cachexia in depth and provided novel insights into the relationship between these two

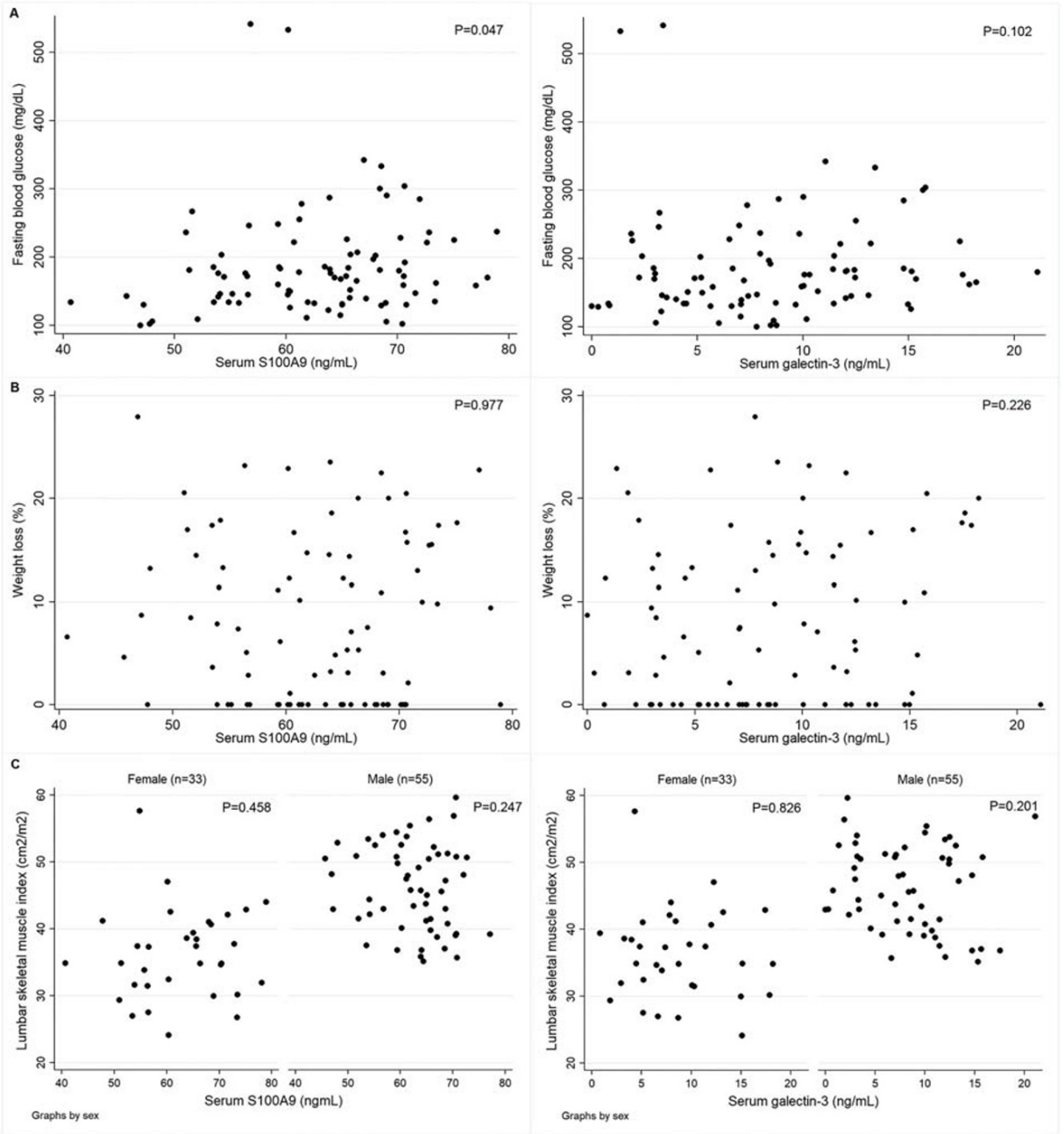

Figure 4 Correlation between levels of S100A9 or galectin-3 and fasting blood glucose *(A)*, weight loss *(B)*, and skeletal muscle mass *(C)* in patients with pancreatic cancer-associated diabetes.

paraneoplastic phenomena. The relations between novel mediators of PCDM and various cachexia-related parameters were comprehensively analysed to verify the cachexigenic potential of PCDM. Our results suggest that optimizing glycaemic control may not alleviate weight loss or muscle wasting, and therapies targeting mediators of PCDM may not protect against the development of cachexia. cAMP response element binding protein (CREB) and CREB-regulated transcriptional coactivators are key cAMP effectors that have been reported to sustain muscle function and represent potential therapeutic targets for cachexia.[40] Whether CREB and CREB-regulated transcriptional coactivators are implicated in PC-induced cachexia should be further studied. A limitation was that this study focused only on cachexia that existed at the time of PC diagnosis, because cachexia that occurred later during disease course might be confounded by factors including treatment-related side effects and cancer-related complications. We could not rule out the possibility

Table 3 Tumour size, cancer stage, and cachexia-related parameters

	Cachexia, *n* (%)	Weight loss (%)[a]	Lumbar SMI—male[a]	Lumbar SMI—female[a]
Primary tumour size				
≦2cm (n=14)	7 (50.0)	2.5 (0–12.5)	45.6 (37.9–47.4)	39.2 (27.5–41.2)
2–4 cm (*n* = 101)	53 (52.5)	3.2 (0–10.9)	45.6 (39.8–50.7)	34.9 (31.6–39.0)
> 4 cm (*n* = 61)	42 (68.9)	9.2 (0–15.7)	45.7 (39.3–50.9)	37.8 (33.9–42.6)
P_{trend}	0.047	0.011	0.552	0.204
Stage				
I (*n* = 20)	8 (40.0)	0 (0–10.5)	47.2 (42.1–50.8)	41.0 (34.9–43.0)
II (*n* = 46)	29 (63.0)	5.1 (0–12.2)	44.0 (38.7–49.8)	33.6 (29.3–36.3)
III (*n* = 45)	26 (57.8)	6.8 (0–14.6)	45.6 (39.8–49.9)	36.8 (31.7–39.1)
IV (*n* = 65)	39 (60.0)	4.6 (0–13.0)	45.4 (40.1–51.0)	38.4 (33.2–42.6)
P_{trend}	0.829	0.258	0.957	0.790

SMI, skeletal muscle mass index.
[a]Median (inter-quartile range).

Table 4 Predictors of cachexia

	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Male	0.99 (0.54–1.81)	0.972	—	—
Age > 60 years	1.13 (0.62–2.06)	0.691	—	—
Stage (I as reference)	1	—	1	—
Stage II	2.56 (0.87–7.51)	0.087	2.32 (0.78–6.96)	0.132
Stage III	2.05 (0.70–6.00)	0.189	1.61 (0.52–4.95)	0.405
Stage IV	2.25 (0.81–6.26)	0.120	1.62 (0.55–4.81)	0.385
Primary tumour size (per 1 cm increase)	1.29 (1.05–1.58)	0.017	1.28 (1.02–1.60)	0.034
PCDM	1.76 (0.96–3.22)	0.068	1.74 (0.93–3.23)	0.082
Fasting blood glucose (per 10 mg/dL increase)	1.00 (0.95–1.06)	0.915	—	—
Serum galectin-3 (per 1 ng/mL increase)[a]	1.03 (0.94–1.13)	0.583	—	—
Serum S100A9 (per 1 ng/mL increase)[a]	0.98 (0.92–1.03)	0.433	—	—

PCDM, pancreatic cancer-associated diabetes.
[a]In patients with pancreatic cancer-associated diabetes.

that PCDM might play a synergistic role with other factors in cachexia that occurred later in disease course. Secondly, because only 16 PCDM patients were receiving regular antidiabetic treatments before the diagnosis of PC, this study was not powered to further analyse whether different classes of antidiabetic drugs exert differential influences on cachexia-related parameters assessed at the time of PC diagnosis. As previous research suggested potential differences in the risk of PC between patients treated with different classes of antidiabetic drugs,[41] further research is needed to assess potential influences of antidiabetic drugs on cachexia-related parameters.

In conclusion, PCDM did not confer a greater risk or severity of cachexia in PC patients, and neither blood glucose nor levels of galectin-3 and S100A9 were associated with cachexia in patients with PCDM. Mediators of PCDM and hyperglycaemia do not directly mediate PC-induced cachexia.

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Conflict of interest

W.-C.L., P.-R.C., C.-C.H., Y.-T.C., B.-S.H., C.-C.C., M.-S.W., and L.-P.C. declare that they have no conflict of interest.

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