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Defects in alpha-cell function in patients with diabetes due to chronic pancreatitis compared to patients with type 2 diabetes and healthy individuals

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Short title: Mumme et al. hypoglycaemia counter-regulation in chronic pancreatitis

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Supplementary Table 1. Characteristics of subjects with chronic pancreatitis, type 2 diabetes mellitus, and healthy controls participating in hyperinsulinaemic, hypoglycaemic clamp experiments

Parameter	[unit]	Chronic pancreatitis	Type 2 diabetes	Healthy controls	P-value
Age	[years]	52 ± 12	64 ± 7 ^a	45 ± 18 ^b	0.004
Gender	female/male [% female]	0/10 (0)	2/11 (15.4)	6/4 (60.0) ^{a,b}	0.005
HbA _{1c}	[%]	7.5 ± 0.9	7.2 ± 0.8	5.2 ± 0.3 ^{a,b}	<0.0001
Diabetes duration	[years]	8 ± 6	17 ± 6 ^a	n.a.	0.0014
Hypoglycaemic episodes	[per month]	1.2 ± 2.0	0.0 ± 0.0 ^a	0.0 ± 0.0	
Severe hypoglycaemia	yes/no (% yes)	1/9 (10.0)	1/12 (7.7)	0/10 (0)	0.61
Body-mass-index	[kg/m ²]	26.4 ± 3.8	31.7 ± 5.2 ^a	25.9 ± 2.9 ^b	0.003
Waist circumference	[cm]	96 ± 9	113 ± 14 ^a	93 ± 12 ^b	0.0007
Hip circumference	[cm]	101 ± 10	112 ± 11 ^a	103 ± 9 ^b	0.021
Pancreatic calcifications ^c	yes/no (% yes)	6/4 (60.0)	n.a.	n.a.	n.a.
Pancreatic duct dilatation ^d	yes/no (% yes)	3/7 (30.0)	n.a.	n.a.	n.a.
Exocrine pancreatic atrophy ^e	yes/no (% yes)	6/4 (60.0)	n.a.	n.a.	n.a.
Septation/lobulation (fibrosis) ^f	yes/no (% yes)	3/7 (30.0)	n.a.	n.a.	n.a.
Exocrine insufficiency ^g	yes/no (% yes)	5/5 (50.0)	n.a.	n.a.	n.a.
Number of diagnostic criteria for chronic pancreatitis ^h	[n]	2.0 ± 0.80	n.a.	n.a.	n.a.
Pancreatic enzyme replacement	yes/no [% yes]	5/5 (50.0)	0/13 (0) a	0/10 (0) a	0.0011
Lipase	[U/l]	21 ± 16	48 ± 30 a	33 ± 12	0.026
Pancreas-Amylase	[U/l]	17 ± 11	29 ± 13	20 ± 6	0.4
Aspartat-Aminotransferase	[U/l]	25.0 ± 7.3	25.9 ± 8.7	22.3 ± 4.7	0.62
Alanin-Aminotransferase	[U/l]	25.6 ± 3.9	29.8 ± 12.0	21.8 ± 8.1	0.12
Gamma-Glutamyltransferase	[U/l]	53.2 ± 66.5	37.8 ± 19.5	22.6 ± 16.3	0.22
Insulin therapy	yes/no (% yes)	6/4 (60.0)	5/8 (38.5)	0/10 (0) ^{a,b}	0.015
Oral glucose-lowering agents	yes/no (% yes)	4/6 (40.0)	13/0 (100) ^a	0/10 (0.0) ^b	<0.0001

Mean ± standard deviation; n.a.: Not applicable ;^a: significant difference ($p < 0.05$) to patients with chronic pancreatitis; ^b: significant difference ($p < 0.05$) to patients with type 2 diabetes; ^c: pancreatic calcifications demonstrated using endosonography computed axial tomography ; ; ^d: pancreatic duct dilatation by endosonography or magnetic resonance choledocho-pancreatography; ^e: pancreatic exocrine atrophy demonstrated by endosonography, computed axial tomography or magnetic resonance tomography; ^f: pancreatic septation/lobulation (fibrosis) demonstrated by endosonography or magnetic resonance tomography; ^g: exocrine insufficiency treated with pancreatin ; ^h: as diagnostic criteria we used: pancreatic calcifications, pancreatic duct dilatation, pancreatic exocrine atrophy, pancreatic septation/lobulation (fibrosis), exocrine insufficiency requiring pancreatin replacement.

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Supplementary Table 2. Additional characteristics of subjects with chronic pancreatitis, type 2 diabetes mellitus, and healthy controls participating in hyperinsulinaemic, hypoglycaemic clamp experiments

Parameter	[unit]	Chronic pancreatitis	Type 2 diabetes	Healthy controls	P-value
Type of insulin used					
NPH insulin	yes/no (% yes)	0/10 (0.0)	1/12 (7.7)	0/10 (0.0)	0.45
Insulin <i>glargine</i>	yes/no (% yes)	6/4 (60.0)	4/9 (30.8)	0/10 (0.0) ^a	0.014
Regular insulin	yes/no (% yes)	3/7 (30.0)	2/11 (15.4)	0/10 (0.0)	0.171
Insulin <i>lispro</i>	yes/no (% yes)	0/10 (0.0)	1/12 (7.7)	0/10 (0.0)	0.45
Insulin <i>aspart</i>	yes/no (% yes)	3/7 (30.0)	1/12 (7.7)	0/10 (0.0)	0.45
Type of oral glucose-lowering agents used					
Metformin	yes/no (% yes)	1/9 (10.0)	11/2 (84.6) ^a	0/10 (0.0) ^b	< 0.0001
Sulfonylureas (glibenclamide, glimepiride)	yes/no (% yes)	2/8 (20.0)	2/11 (15.4)	0/10 (0.0)	0.4
DPP-4 inhibitors (vildagliptin,sitagliptin)	yes/no (% yes)	0/10 (0.0)	7/6 (53.9) ^a	0/10 (0.0) ^b	0.0011
Meglitinides (repaglinide)	yes/no (% yes)	0/10 (0.0)	1/12 (7.7)	0/10 (0.0)	0.5
Diabetes complications					
Retinopathy	yes/no (% yes)	0/10 (0.0)	1/12 (7.7)	0/10 (0.0)	0.45
Neuropathy	yes/no (% yes)	0/10 (0.0)	5/8 (38.5) ^a	0/10 (0.0) ^b	0.011
Nephropathy	yes/no (% yes)	0/10 (0.0)	0/13 (0)	0/10 (0.0)	0.0
Cardiovascular disease	yes/no (% yes)	0/10 (0.0)	0/13 (0.0)	0/10 (0.0)	0.0
Peripheral vascular disease	yes/no (% yes)	1/9 (10.0)	1/12 (7.7)	0/10 (0.0)	0.61
Diabetic foot syndrome	yes/no (% yes)	3/7 (30.0)	2/11 (15.4)	0/10 (0.0)	0.17
Creatinine	[mg/dl]	0.8 ± 0.1	0.9 ± 0.1	0.8 ± 0.2	0.45
Nicotin abuse	yes/no (% yes)	6/4 (60.0)	2/11 (15.4) ^a	1/9 (10.0)	0.02
Alcohol abuse	yes/no (% yes)	2/8 (20.0)	5/8 (38.5)	2/8 (20.0)	0.51
Hyperlipidaemia	yes/no (% yes)	4/6 (40.0)	6/7 (46)	0/10 (0) ^{a,b}	0.042
Blood pressure (systolic)	[mmHg]	126 ± 18	143 ± 18	129 ± 22	0.093
Blood pressure (diastolic)	[mmHg]	83 ± 13	85 ± 11	77 ± 9	0.230
Aarterial hypertension (treated)	yes/no (% yes)	2/8 (20.0)	9/4 (69.2) ^a	2/8 (20.0) ^b	0.018
Heart rate	[bpm]	70 ± 14	76 ± 11	74 ± 11	0.86

Mean ± standard deviation; n.a.: Not applicable ;^a: significant difference ($p < 0.05$) to patients with chronic pancreatitis; ^b: significant difference ($p < 0.05$) to patients with type 2 diabetes; ^c: pancreatic calcifications demonstrated using endosonography computed axial tomography ; ; ^d: pancreatic duct dilatation by endosonography or magnetic resonance choledoco-pancreatography; ^e: pancreatic exocrine atrophy demonstrated by endosonography, computed axial tomography or magnetic resonance tomography; ^f: pancreatic septation/lobulation (fibrosis) demonstrated by endosonography or magnetic resonance

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tomography; ^g: exocrine insufficiency treated with pancreatin ; ^h: as diagnostic criteria we used: pancreatic calcifications, pancreatic duct dilatation, pancreatic exocrine atrophy, pancreatic septation/lobulation (fibrosis), exocrine insufficiency requiring pancreatin replacement.

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Supplementary Figure 1. Relationship between the maximum glucagon levels measured during the hypoglycaemic clamp experiment and the difference between glucagon levels at 60 min after oral glucose ingestion and baseline or (B) and the C-peptide/glucose ration determined 20 min after oral glucose ingestion in patients with diabetes due to chronic pancreatitis (filled triangles), subjects with type 2 diabetes (filled circles), and healthy control subjects (open circles). Correlations were performed using linear regression analysis.

