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Metabolism Clinical and Experimental 55 (2006) 135–141

Metabolism
Clinical and Experimental

www.elsevier.com/locate/metabol

Insulin secretory defect plays a major role in the development of diabetes in patients with distal pancreatectomy

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Received 12 November 2004; accepted 24 August 2005

Abstract

To investigate the pathogenesis of distal pancreatectomy (d-Px)–induced diabetes in Korean patients, we investigated insulin secretory and sensitivity indexes obtained by oral glucose tolerance testing in 20 patients that had received d-Px (10 with d-Px–induced diabetes and 10 with normal glucose tolerance with d-Px [NGT d-Px]) and in 164 control subjects (77 with type 2 diabetes mellitus and 87 with NGT) that did not receive d-Px. The pancreatectomized subjects had lower fasting serum insulin, homeostasis model assessment of pancreatic beta-cell function (HOMA-β) levels, and insulinogenic indices than the NGT controls. The HOMA-β values of nonobese NGT d-Px– and d-Px–induced diabetic subjects were 73.7% and 38.7% of those for nonobese NGT controls, respectively, and HOMA-β was significantly lower only for d-Px–induced diabetic subjects ($P < .01$). In obese subjects, the HOMA-β values of obese d-Px–induced diabetic subjects were significantly lower than those of obese NGT controls ($P < .05$). The insulin sensitivity was significantly lower in nonobese type 2 diabetes mellitus controls than in nonobese NGT d-Px or in nonobese d-Px–induced diabetic subjects ($P < .001$ and .05, respectively). These results show that a reduced insulin secretory function is a typical feature of glucose homeostasis in distal pancreatectomized patients and that insulin secretory defect plays a major role in the development of diabetes in these patients. In addition, the study suggests that pancreatic resections of 60% or less and body mass index are not the main causes of diabetes onset after d-Px in this study.

1. Introduction

The hormonal abnormalities that follow pancreatic resection are dependent on the extent and location (ie, proximal or distal) of resection [1]. Insulin-producing beta cells are distributed evenly throughout the pancreas, but alpha and PP cells are believed to be localized selectively in the pancreatic tail and head, respectively [2]. Earlier studies have shown that distal pancreatectomy (d-Px) causes iatrogenic hypoglycemia and deficient glucagon secretion by alpha cells, whereas proximal resection reduces pancreatic polypeptide secretion from PP cells and leads to hyperglycemia due to an impaired hepatic insulin function [1,3]. The incidence of diabetes after pancreatectomy, however, is unpredictable and depends on preoperative metabolic insufficiency, the amount of pancreatic tissue resected, and obesity [1,4-6]. Diabetes associated with pancreatic resection is termed *pancreatogenic diabetes*, and patients with this condition have lower serum insulin levels and show little insulin response after consuming food, which differentiates them from those with adult-onset type 2 diabetes mellitus (T2DM) [1,7,8]. However, insulin secretion and insulin sensitivity are not well understood in Korean distal pancreatectomized subjects.

In this study, we undertook to assess insulin and glucose regulation after d-Px in Korean subjects.

2. Subjects and methods

2.1. Subjects

From 1995 to 2002, 334 patients underwent d-Px at the Samsung Medical Center. Of these 334 patients, 84 subjects who had undergone d-Px satisfied the following criteria: (1)

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0026-0495/$ – see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2005.08.005

younger than 60 years at pancreatectomy; (2) no evidence of cancer recurrence or metastasis (at >48 months after d-Px); (3) no history of chemotherapy/radiotherapy or steroid medication; (4) no history of hepatic surgery (which rules out the possibility of hepatic metabolic effects); and (5) no coexisting malignancy in another organ. Of the 84 patients, 41 subjects were also excluded because (1) 24 subjects were pre- or postoperative diabetic patients and (2) 17 subjects were lost to follow-up after d-Px. Finally, 23 subjects (11 men and 12 women) provided informed consent and were enrolled in this study. Oral glucose tolerance testing was carried out on these 23 subjects at least 12 or 24 months after d-Px in benign and malignant conditions, respectively.

Of these 23 patients, 10 subjects had normal glucose tolerance (NGT), 3 had glucose tolerance impairment (impaired fasting glucose or impaired glucose tolerance), and 10 developed pancreatogenic diabetes. In 10 subjects that received less than 40% pancreatectomy, 6 patients had NGT and 4 had developed d-Px–induced diabetes. Of the 11 subjects who underwent a 40% pancreatectomy, 4 had NGT, 3 had glucose tolerance impairment, and 4 developed diabetes. Both subjects who received a 60% pancreatectomy developed diabetes. The underlying pathologies were 7 mucinous cystic neoplasms (30.4%), 5 solid cystic papillary epithelial neoplasms (21.7%), 6 endocrine neoplasms (2 islet carcinoma, 2 insulinoma, 1 endocrine carcinoma, and 1 glucagonoma) (26.1%), 4 pseudocysts (17.4%), and 1 schwannoma (4.3%).

One hundred sixty-four subjects who did not receive d-Px were enrolled in the study as a control group. These subjects had visited our health promotion center or diabetes clinic between 1997 and 2002 and included most of the subjects described in our previous study [9]. Subjects with or without d-Px were classified according to glucose tolerance degree as having NGT, that is, fasting plasma glucose (FPG) of less than 6.1 mmol/L and 2-hour glucose during oral glucose tolerance test of less than 7.8 mmol/L, or as having diabetes, that is, FPG of 7.0 mmol/L or higher or 2-hour plasma glucose of 11.1 mmol/L or higher during an oral glucose tolerance test, in accordance with the criteria of the America Diabetes Association [10].

2.2. Distal pancreatectomy

The amounts of pancreatic resection were estimated as 40% if the pancreas was divided to the left border of the portal vein, 50% if in front of the portal vein, 60% if along the right border of the vein with intact uncinate, and as 70% to 80% if the uncinate process was removed [6,11,12].

2.3. Calculations and statistical analyses

Two variables were used to estimate insulin secretion [13-17]. First, the kinetics of insulin response to glucose, the insulinogenic index (INS index), was calculated by dividing

Table 1
Characteristics of subjects according to the obesity and pancreatectomy percentage

	Nonobese		Obese	
	<40% Px (n = 7)	40%-60% Px (n = 10)	<40% Px (n = 3)	40%-60% Px (n = 3)
Age (y)	44.0 (37.0-56.0)	48.0 (40.5-56.0)	53.0	50.0
Sex (M/F)	5:2	3:7	0:3	3:0
BMI (kg/m^2)	22.95 (20.19-23.85)	22.50 (20.15-24.24)	27.00	26.60
WHR	0.85 (0.84-0.91)	0.85 (0.82-0.88)	0.94	0.92
SBP (mm Hg)	126.0 (119.0-133.0)	130.0 (125.5-138.5)	127.0	126.0
DBP (mm Hg)	84.00 (77.0-87.0)	76.50 (69.0-92.0)	79.00	85.00
Duration of follow-up	3.82 (2.55-5.09)	3.42 (2.32-4.52)	3.12	4.06
FPG (mmol/L)	5.72 (5.50-7.33)	5.99 (5.02-7.13)	5.44	6.44
2-h Glucose (mmol/L)	8.88 (5.66-11.99)	9.38 (5.66-14.82)	7.27	12.77
A_{1c}	6.0 (4.85-6.80)	5.9 (5.45-6.45)	5.8	5.0
Glucose tolerance				
NGT (%)	57.1 (4/7)	40.0 (4/10)	66.7 (2/3)	
IFG (%)/IGT (%)		0 (0/10)/20.0 (2/10)		
IFG and IGT (%)				33.3 (1/3)
DM (%)	42.9 (3/7)	40.0 (4/10)	33.3 (1/3)	66.7 (2/3)
Cholesterol (mmol/L)	4.68 (4.27-5.42)	5.33 (4.33-5.68)	4.89	4.81
Triglyceride (mmol/L)	1.62 (0.86-3.17)	1.14 (0.62-1.26)	1.14	1.85
HDL-C (mmol/L)	1.07 (0.88-1.24)	1.22 (1.13-1.71)	1.20	0.88
LDL-C (mmol/L)	3.09 (2.61-3.58)	3.08 (2.11-3.94)	2.74	3.10
Insulin (μIU/mL)	4.20 (3.40-6.00)	6.35 (3.40-9.55)	6.90	6.80
C-peptide (ng/mL)	1.71 (1.06-2.50)	1.42 (1.12-1.99)	1.72	2.36
INS index	0.22 (0.13-0.44)	0.32 (0.19-0.36)	0.54	0.22
HOMA-β	32.2 (29.0-40.0)	47.9 (23.9-93.9)	73.0	46.2
HOMA-IR	1.07 (0.85-1.97)	1.41 (0.97-2.65)	1.72	1.95
IS ratio$_0$	0.73 (0.61-0.81)	1.14 (0.53-1.44)	1.29	1.06
IS ratio$_{120}$	2.66 (1.76-4.57)	2.39 (1.36-4.10)	3.78	2.48

Data are expressed as medians (interquartile ranges). IFG indicates impaired fasting glucose; IGT, impaired glucose tolerance; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; IS ratio$_0$, insulin-to-glucose ratio at fasting; IS ratio$_{120}$, insulin-to-glucose ratio at 120 minutes.

the increase in insulin level (μIU/mL) from baseline to 30 minutes after glucose challenge (Δinsulin = $I_{30} - I_0$) by the increase in glucose level (mg/dL) over the same period (Δglucose = $G_{30} - G_0$). Second, beta-cell function was obtained by homeostasis model assessment (HOMA) using HOMA of pancreatic beta-cell function (HOMA-β) = fasting insulin × 3.33/(fasting glucose − 3.5). Insulin sensitivity was assessed using HOMA of insulin resistance (HOMA-IR) [15], which was calculated from fasting glucose and insulin levels, using HOMA-IR = fasting insulin/(22.5 × $e^{-\ln \text{ fasting glucose}}$). To estimate beta-cell sensitivity to glucose, we used the insulin-to-glucose ratio at fasting or at 2 hours after glucose challenge according to the HOMA model [18].

Body measurements were taken to determine body mass indexes (BMIs) and waist-to-hip ratios (WHRs). Obesity was defined as BMI of 25 kg/m^2 or more. HbA_{1c} levels were measured by high-performance liquid chromatography using a Tosoh G7 (Tosoh Bioscience, Inc, Tokyo, Japan). The reference HbA_{1c} range was 4.5% to 6.5%. Serum levels of total cholesterol, high-density lipoprotein cholesterol, and triglyceride were measured using an automated multianalyzer (7600; Hitachi, Tokyo, Japan). Serum C-peptide (Immunotech, Marseille, France) and insulin (Medgenix, Niveles, Belgium) levels were measured in duplicate using an immunoradiometric assay method.

Values are expressed as means ± SD or as medians and interquartile ranges. One-way analysis of variance (ANOVA) with the Bonferroni post hoc multiple comparison test or the Kruskal-Wallis test with Dunn multiple comparison test were used as appropriate to compare variables of the 4 groups (ie, the NGT control, the T2DM control, the NGT d-Px, and the d-Px–induced diabetes groups). Linear regression analysis was performed using diabetes as a dependent factor. Several clinical and laboratory factors (eg, preoperation glucose level, BMI, obesity, and resection percentage, etc) were entered as independent factors. All statistical analyses were conducted using PRISM version 3.0 (GraphPad Software, San Diego, CA).

3. Results

The clinical characteristics of pancreatectomy patients classified according to obesity and pancreatic resection extent are shown in Table 1.

In nonobese subjects (Table 2), no significant differences in age, BMI, WHR, systolic blood pressure (SBP)/diastolic blood pressure (DBP), cholesterol, or triglyceride

Table 2
Characteristic of nonobese subjects

	NGT control (n = 47)	T2DM control (n = 37)	NGT d-Px (n = 8)	d-Px–induced diabetes (n = 7)	*P*
Age (y)	48.04 ± 11.72	49.70 ± 9.42	42.75 ± 8.70	50.71 ± 9.59	NS
Sex (M/F)	31:16	27:10	3:5	5:2	
BMI (kg/m^2)	22.83 ± 1.84	23.17 ± 1.81	22.11 ± 2.09	22.07 ± 1.69	NS
SBP (mm Hg)	128.20 ± 18.33	126.60 ± 18.84	127.90 ± 8.46	128.4 ± 2.70	NS
DBP (mm Hg)	78.02 ± 10.82	77.39 ± 12.35	78.50 ± 8.05	82.29 ± 7.54	NS
Cholesterol (mmol/L)	4.96 ± 1.06	5.16 ± 1.02	5.08 ± 0.66	4.70 ± 0.89	NS
Triglyceride (mmol/L)	1.59 ± 0.92	1.76 ± 0.96	0.99 ± 0.34	1.72 ± 1.12	NS
FPG (mmol/L)	5.34 ± 0.49	7.81 ± 0.74[a]	5.38 ± 0.40[b,c]	7.51 ± 0.81[d]	<.05*
A_{1c}	5.67 ± 0.62	6.56 ± 0.69[a]	5.40 ± 0.60[b,e]	6.45 ± 0.36[f]	<.001***
Insulin (μIU/mL)	6.90 ± 3.57	10.51 ± 4.31[a]	5.21 ± 2.45[g]	6.36 ± 3.02	<.001***
C-peptide (ng/mL)	1.90 ± 0.91	3.01 ± 0.97[a]	1.51 ± 0.51[b]	1.86 ± 0.89[h]	<.001***
INS index	0.82 ± 1.06, 0.58 (0.21-0.99)	0.19 ± 0.15[i], 0.15 (0.09-0.26)[i]	0.31 ± 0.15, 0.27 (0.19-0.41)	0.28 ± 0.17, 0.33 (0.08-0.42)	<.01**<.0001[j]
HOMA-β	81.20 ± 47.45	50.38 ± 23.34[i]	59.84 ± 35.16	31.44 ± 14.19[k]	<.001***
HOMA-IR	1.64 ± 0.85	3.63 ± 0.25[a]	1.23 ± 0.19[b]	2.17 ± 1.18[h]	<.001***

The data except INS index of the NGT controls were normally distributed, and statistical significances were tested by 1-way ANOVAs among groups. *P* values by ANOVA are provided for the 4-group comparisons.

[a] $P < .001$ vs NGT control.
[b] $P < .001$ vs T2DM.
[c] $P < .001$ vs d-Px–induced diabetes.
[d] $P < .001$ vs NGT control.
[e] $P < .05$ vs d-Px–induced diabetes.
[f] $P < .05$ vs NGT control.
[g] $P < .01$ vs T2DM.
[h] $P < .05$ vs T2DM.
[i] $P < .01$vs NGT control.
[j] Statistical significances of INS indexes were analyzed using the Kruskal-Wallis test.
[k] $P < .01$ vs NGT control.
* $P < .05$.
** $P < .01$.
*** $P < .001$.

were found between nonobese NGT controls, nonobese T2DM controls, nonobese NGT d-Px patients, and nonobese d-Px–induced diabetic patients. Fasting insulin was statistically higher in nonobese T2DM controls (10.51 ± 4.31) than in nonobese NGT controls or in nonobese NGT d-Px subjects (6.90 ± 3.57 and 5.21 ± 2.45; $P < .001$ and .01, respectively). In addition, fasting C-peptide was significantly higher in nonobese T2DM controls (3.01 ± 0.97) than in nonobese NGT controls, nonobese NGT d-Px patients, and nonobese d-Px–induced diabetic patients (1.90 ± 0.91, 1.51 ± 0.51, and 1.86 ± 0.89; $P < .001$, .001, and .05, respectively). Insulinogenic index, a measure of early-insulin secretion response to stimulation, was significantly lower only in nonobese T2DM controls (median, 0.15; interquartile range, 0.09-0.26) than in nonobese NGT controls (median, 0.58; interquartile range, 0.21-0.99; $P < .01$). The INS indexes of nonobese NGT d-Px patients (median, 0.27; interquartile range, 0.19-0.41) and nonobese d-Px–induced diabetic patients (median, 0.33; interquartile range, 0.08-0.42) were lower than that of nonobese NGT controls, but without significance. In addition, pancreatic beta-cell function, expressed as HOMA-β, was significantly lower in both nonobese T2DM controls and nonobese d-Px–induced diabetic patients (50.38 ± 23.34, 31.44 ± 14.19) than in nonobese NGT controls (81.20 ± 47.45; $P < .01$ for both). The mean HOMA-β values of nonobese NGT d-Px patients and nonobese d-Px–induced diabetic patients were 73.7% and 38.7% of that of the nonobese NGT controls (Fig. 1A). Moreover, the insulin sensitivity index, HOMA-IR, was significant lower for nonobese T2DM controls (3.63 ± 0.25) than for subjects in the other 3 groups (NGT controls, NGT d-Px, d-Px–induced diabetic patients: 1.64 ± 0.85, 1.23 ± 0.19, and 2.17 ± 1.18; $P < .001$, .001, and .05, respectively) (Fig. 1B).

For obese subjects (Table 3), no significant differences were found with respect to age, sex, BMI, WHR, SBP/DBP, cholesterol, triglyceride, insulin, or C-peptide among obese NGT controls, obese T2DM controls, obese NGT d-Px patients, and obese d-Px–induced diabetic patients. Moreover, the INS index was significantly lower only in obese T2DM controls than in obese NGT controls ($P < .001$). However, the mean INS index of obese NGT d-Px patients and obese d-Px–induced diabetic patient were lower than that of obese NGT controls. In addition, beta-cell function, as assessed by HOMA-β, was significantly higher in obese NGT controls than in obese T2DM controls and in obese d-Px–induced diabetic subjects ($P < .001$ and .05, respectively). Moreover, the insulin sensitivity index, HOMA-IR, was significantly lower for obese T2DM controls than for obese NGT controls ($P < .001$).

During linear regression analyses, diabetes was used as a dependent factor, and age, sex, BMI, obesity, WHR, SBP, DBP, resection percentage, preoperation fasting glucose level, glucose levels at 0, 30, 60, 90, and 120 minutes, insulin and C-peptide at 0, 30, and 120 minutes, lipid

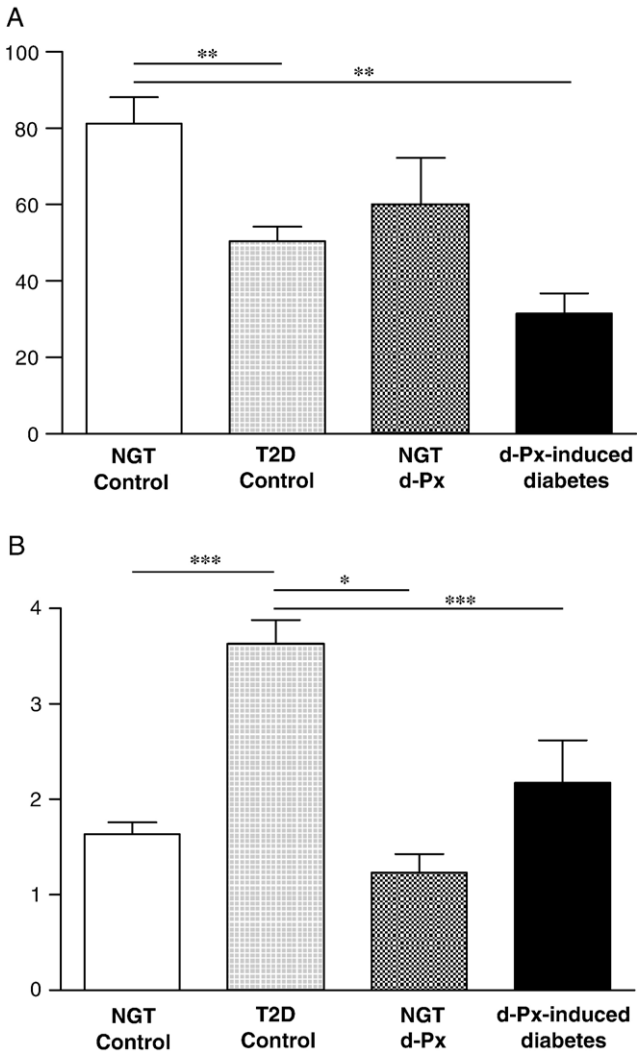

Fig. 1. Insulin secretion and sensitivity variables in all nonobese subjects. Mean HOMA-β values of nonobese NGT d-Px subjects and nonobese d-Px–induced diabetic subjects were 73.8% and 38.7% that of the nonobese NGT controls, respectively. A, Mean HOMA-β values were significantly higher for nonobese NGT controls than for nonobese T2DM controls or for nonobese d-Px–induced diabetic subjects. B, HOMA-IR values were significantly higher for nonobese T2DM controls than for nonobese NGT controls, nonobese NGT d-Px patients or nonobese d-Px–induced diabetic subjects. *$P < .05$, **$P < .01$, ***$P < .001$.

profile, INS index, HOMA-β, HOMA-IR, and insulin-to-glucose ratio at fasting and at 2 hours after glucose challenge were entered as independent factors. We found that the insulin-to-glucose ratio at 2 hours predicted the development of pancreatogenic diabetes ($r^2 = 0.469$, $P = .029$), and that BMI ($r^2 = 0.338$, $P = .078$), obesity ($r^2 = 0.277$, $P = .118$), nondiabetic preoperation fasting glucose level ($r^2 = 0.175$, $P = .229$), and resection percentage ($r^2 = 0.044$, $P = .561$) did not predict diabetes onset.

4. Discussion

In the present study, we investigated glucose homeostasis in Korean subjects without clinical evidence of diabetes

Table 3
Characteristic of obese subjects

	NGT control (n = 40)	Diabetes control (n = 40)	d-Px NGT (n = 2)	d-Px–induced diabetes (n = 3)	*P*
Age (y)	49.0 (43.5-55.5)	53.0 (45.0-58.0)	49.5	54.0	NS
Sex (M/F)	22:18	28:12	0:2	1:2	
BMI (kg/m^2)	26.80 (25.85-29.10)	26.60 (25.60-27.51)	26.65	27.20	NS
SBP (mm Hg)	128.5 (119.5-149.0)	137.5 (126.0-148.5)	126.0	127.0	NS
DBP (mm Hg)	81.0 (75.0-90.0)	84.5 (76.5-94.0)	81.0	79.0	NS
Cholesterol (mmol/L)	5.20 (4.34-6.12)	5.22 (4.66-5.82)	5.07	4.89	NS
Triglyceride (mmol/L)	3.12 (2.28-4.27)	4.68 (2.90-5.69)	2.41	4.24	NS
FPG (mmol/L)	5.52 (5.05-5.88)	7.60 (7.19-8.10)[a]	5.27[b]	7.72	<.0001**
A_{1c}	5.70 (5.50-6.00)	6.65 (6.25-7.25)[a]	5.55	6.20	<.0001**
Insulin (μIU/mL)	9.85 (8.05-14.10)	11.40 (9.30-15.85)	6.85	6.90	NS
C-peptide (ng/mL)	2.61 (2.26-3.47)	3.08 (2.37-3.84)	1.60	2.44	NS
INS index	0.79 (0.49-1.10)	0.20 (0.100-0.28)[a]	0.52	0.22	<.0001**
HOMA-β	111.2 (79.4-156.0)	55.0 (41.4-70.2)[a]	77.5	46.2[c]	<.0001**
HOMA-IR	2.30 (1.97-3.53)	3.84 (2.99-5.73)[a]	1.61	2.47	<.001***

The data of NGT/T2DM control subjects were normally distributed, and statistical significances were analyzed using the Kruskal-Wallis test. *P* values determined by the Kruskal-Wallis test are quoted for the 4-group comparisons.

[a] $P < .001$ vs NGT control.

[b] $P < .001$ vs T2DM.

[c] $P < .05$ vs NGT control.

** $P < .0001$.

*** $P < .001$.

before or after d-Px and tried to identify the following: (1) factors that predict the development of pancreatogenic diabetes and (2) the metabolic consequences of abnormal insulin and glucose levels in subjects treated by d-Px.

Glucose tolerance after pancreatectomy is dependent on the extent of pancreas resection and the surgery scope because of variations in alpha- and PP-cell distributions. It has been reported that about one quarter to one third of patients with chronic pancreatitis who underwent intermediate 40% to 75% d-Px, including those with a preoperative diabetes condition, were rendered diabetic by surgery [6,11]. In the present study, of 23 subjects that received 60% or less pancreatectomy, 10 patients (43.48%) became diabetic. Pancreatic resection that spares the duodenum, such as d-Px, is associated with lower rates of de novo diabetes development and glucose intolerance than the Whipple procedure or total pancreatectomy [1]. Other reported factors for the development of pancreatogenic diabetes include preoperative metabolic insufficiency and obesity [1,4-6]. Our study also shows that 60% or less pancreas resection or obesity is not the main cause of diabetes in those with no definitive preexisting endocrine dysfunction condition. Moreover, the only parameter found to be associated with the development pancreatogenic diabetes was the insulin-to-glucose ratio at 120 minutes after oral glucose tolerance testing ($r^2 = 0.469$, $P = .029$). The likely explanations for these contradictory results were the exclusion of newly diagnosed diabetes after d-Px and the inclusion of only those subjects with a nondiabetic preoperative glucose level. Despite its lack of statistical significance, BMI was found to be more associated with diabetes onset after d-Px ($r^2 = 0.338$, $P = .078$) than the other factors.

Type 2 diabetes mellitus control subjects, representing beta-cell quality dysfunction, showed significantly higher fasting insulin secretions, lower insulinogenic indices (early-insulin response to stimulation), lower HOMA-β levels (pancreatic beta-cell function), and higher HOMA-IR levels (insulin resistance) than NGT control subjects (Tables 2 and 3). Unlike adult-onset type 2 diabetes where plasma insulin levels are normal or elevated [19,20], the pathophysiology of diabetes after pancreatectomy is characterized by reduced insulin secretion [7,8]. After pancreatectomy, causing a commensurately absolute β-cell quantity reduction, the pancreatectomized subjects in this study had lower fasting serum insulin levels, INS index, and HOMA-β (Tables 2 and 3 and Fig. 1A). The INS index has been proposed as a means of determining early-insulin response or first-phase insulin secretion. And early-phase insulin secretion has a pivotal role in switching the metabolism from a fasting to a prandial state, which is associated with a deterioration in glucose tolerance [9,13]. The mean INS index of nonobese NGT d-Px subjects was about one third that of nonobese NGT controls. This finding implies that reduced early-phase insulin secretion is not necessarily followed by glucose intolerance in distal pancreatectomized subjects. In an ideal population reference, the young (<35 years old), lean, and healthy white subjects have 100% beta-cell function [15] (HOMA-β). In this study, the HOMA-β value of nonobese NGT controls with a mean age 48 years was 81.2% and the mean value of nonobese d-Px–induced diabetic subjects was about 60%. Moreover, the mean HOMA-β results of those who received 40% pancreatectomies in the d-Px NGT and d-Px–induced diabetes groups, namely, 59.9% and 31.4%, respectively, suggest that there is a need to investigate beta-cell quality

and the factors associated with the development of diabetes preoperatively. Despite a lack of statistical significance, distal pancreatectomized subjects showed higher insulin sensitivities as assessed by HOMA-IR than NGT controls (Tables 2 and 3 and Fig. 1B). These findings indicate that healthy distal pancreatectomized subjects show a reduced overall beta-cell secretory function (INS index, HOMA-β), and a nonsignificant reduction in insulin resistance.

Glucagon has a major role in maintaining normal concentrations of glucose in blood and is often described as having the opposite effects to insulin by stimulating the breakdown of glycogen stored in liver and by activating hepatic gluconeogenesis. When adequate basal insulin concentrations are present, neither the glucagon-induced stimulation of glucose production nor the glucose-induced suppression of glucose production differs in diabetic and nondiabetic subjects [21]. However, when insulin secretion is defective, a lack of glucagon suppression can cause substantial hyperglycemia by enhancing glucose production rates [21]. Moreover, the magnitude of the defective suppression of hepatic glucose production is correlated with increased plasma glucagon and the glucagon-insulin molar ratio [22-24]. In addition, 48 hours of physiological hyperglycemia, even in NGT subjects, is associated with an increased rate of basal hepatic glucose production, an impaired insulin-mediated suppression of hepatic glucose production, and defective glucose disposal by peripheral tissues [25,26]. Because pancreatic glucagon is predominantly contained in the body and tail of the human pancreas, d-Px is expected to diminished both insulin and glucagon secretion [27,28]. Seaquist and colleagues [8,28] suggested that hemipancreatectomized patients may show increased rather than decreased glucose use after surgery. Thus, it is possible that hormone changes after d-Px can affect insulin secretory function and insulin sensitivity and that the d-Px–induced glucagon secretory defect can compensate for postoperative reductions in insulin secretion by reducing hepatic glucose production and increasing glucose disposal. Moreover, this is quite different from the pathogenesis of type 2 diabetes. In view of these findings and the importance of d-Px–induced reductions in insulin and glucagon secretion, we hypothesize that despite an NGT, a reduced insulin secretory function and an increased insulin sensitivity are typical features of glucose regulation in distal pancreatectomized patients and further that the effect of ineffectively compensating for reduced insulin secretion on glucose homeostasis is an important feature in the development of d-Px–induced diabetes. If these homeostasis hypotheses are correct, uncompensated insulin secretory defect plays a major role in the development of diabetes in d-Px patients.

It appears that the introduction of the nonobese and obese characterizations to our analysis causes unnecessary confusion. Moreover, our linear regression analysis showed that obesity and BMI are not significantly associated with pancreatogenic diabetes development for our study subjects who had no evidence of diabetes before or immediately after d-Px. Thus, to address as directly as possible the influences of known predictors of pancreatogenic diabetes development, we felt that a comprehensive analysis of obesity and pancreatic resection extent was warranted. The major limitation of our study is that glucagon and glucose regulation were not evaluated and that, to some extent, this undermines the validity of our glucose homeostasis analysis. Therefore, the results of the present study should be confirmed by prospective studies before and after pancreatectomy incorporating glucagon-to-glucose and beta-cell reserve assays.

However, despite its limitations, the present result shows that a 60% or less pancreatic resection and BMI are not the main contributors to diabetes development in this study and that insulin secretory defect plays a major role in the development of diabetes in Korean patients that have undergone d-Px. In addition, the study shows that reduced insulin secretory function with a favorable adaptation of insulin sensitivity is a typical feature of glucose-to-insulin homeostasis in distal pancreatectomized patients.

Acknowledgment

This work was supported by grants from the Samsung Biomedical Research Institute (C-98-008 and C-A3-116).

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