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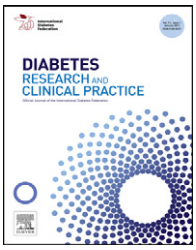

Indexes of β-cell function from the oral glucose tolerance test can modestly predict pancreatic β-cell area in Korean

Soo Kyoung Kim [a,1], Jae Hyeon Kim [a,1], Ji Young Park [a], Hee Sung No [b], Kee-Taek Jang [c], Jin Seok Heo [d], Seong Ho Choi [d], Dong Wook Choi [d], Kwang-Won Kim [a,*]

[a] Division of Endocrinology and Metabolism, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, #50, Irwon-dong, Gangnam-gu, 135-710 Seoul, Republic of Korea
[b] Samsung Biomedical Research Institute, Seoul, Republic of Korea
[c] Department of Pathology, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
[d] Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

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ABSTRACT

Aims: Pancreatic β-cell function indexes have been suggested using the oral glucose tolerance test (OGTT). Here, we investigated whether β-cell function index from the OGTT reflects pancreatic β-cell area in Korean patients.

Methods: The study consisted of 45 patients who underwent pancreatectomies. Before operation, a 75-g OGTT was performed. Immunohistochemical staining was performed, and indexes of β-cell function from the OGTT data were compared with the pancreatic β-cell area.

Results: The β-cell area of the pancreas was 1.07 ± 0.33% in the normal glucose tolerance group, 1.71 ± 0.85% in the pre-diabetes group (impaired glucose tolerance and impaired fasting glucose), and 1.08 ± 0.57% in the diabetes group. The β-cell area of the pre-diabetes group was significantly higher than that of the diabetes group. Pancreatic β-cell area showed a significant correlation with a homeostasis model assessment of β-cell function ($r = 0.358$, $P = 0.016$), disposition index ($r = 0.336$, $P = 0.024$), fasting glucose ($r = -0.359$, $P = 0.015$), and the C-peptide/glucose 30 min ratio ($r = 0.319$, $P = 0.035$).

Conclusions: Some parameters of β-cell function from the OGTT showed a significant relationship with the β-cell area of pancreas.

1. Introduction

Type 2 diabetes mellitus is characterized by progressive declines in β-cell number and function that contribute to insulin deficiency [1–4]. It is associated with both quantitative and qualitative defects of insulin secretion, such as impaired acute insulin response to glucose and an exaggerated proinsulin-to-insulin ratio [5]. Regulation of blood glucose concentrations requires an adequate number of properly functioning β-cells that respond appropriately to blood glucose levels.

It is known that the pancreatic β-cell mass is decreased in type 2 diabetic patients [6], but the results of several reports

* *Corresponding author*. Tel.: +82 2 3410 3430; fax: +82 2 3410 6956.
E-mail address: kw1234@skku.edu (K.-W. Kim).

[1] These two authors contributed equally to this work.

Abbreviations: AUC_{glu}, the area under the glucose curve; DI, disposition index; HOMA-β, homeostasis model assessment of beta cell function; HOMA-IR, homeostasis model assessment of insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; SMBG, self-monitoring of blood glucose.

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have reached variable conclusions, from no significant differences to marked decreases [2,7]. These differences may be attributed to variation in pancreas specimen sampling, quantification techniques, and other confounding factors, such as obesity and ethnic differences.

Pathophysiological questions have underscored the need to measure pancreatic β-cell mass, especially considering the role of apoptosis and neogenesis of β-cells in the onset of type 2 diabetes mellitus. Replacement or regeneration of β-cell mass may restore endogenous insulin secretion and normalize of hyperglycemia in type 2 diabetic patients. However, sensitive and specific *in vivo* measurements of β-cell mass have not been carried out, and the majority of studies have examined β-cell mass under *in vitro* or in rodent models. There have been several attempts to find correlations between β-cell mass and clinical parameters of β-cell function in animals and humans [8–11] and some parameters of metabolic tests have been found to be correlated with β-cell mass ($r = 0.6–0.8$).

The oral glucose tolerance test (OGTT) is widely used to diagnose diabetes mellitus. Various simplified indexes of β-cell function from the OGTT have been suggested as indicators of β-cell function [12]. Meier et al. reported a significant relationship between pancreatic β-cell area and different functional measures of insulin secretion. In addition, they reported a C-peptide-to-glucose ratio after oral glucose ingestion to be a better predictor of pancreatic β-cell area than other parameters of β-cell function from the OGTT [11]. In addition, Ritzel et al. reported that β-cell volume is correlated with fasting blood glucose concentration [3].

Analyses of living human β-cell are rare, with the exception of autopsy studies especially in Asian populations [4,13]. It is known that impaired insulin secretion is more prominent than insulin resistance in Korean, even in patients with impaired glucose tolerance (IGT) [14], and about 65% of Korean patients with type 2 diabetes are not obese [15]. This suggests an etiologic difference of type 2 diabetes mellitus in Korean patients compared with Caucasians.

Here, we investigated whether the OGTT β-cell function index reflects the pancreatic β-cell area in Koreans. We also studied which OGTT β-cell function index parameter showed the best correlation with pancreatic β-cell area in Koreans.

2. Materials and methods

2.1. Subjects

We collected human pancreatic head tissues from a total of 45 Korean patients who underwent partial or total pancreatectomies for distal common bile duct cancer ($n = 19$), benign pancreatic adenoma ($n = 13$), or pancreatic cancer ($n = 13$) at the Department of Surgery, Samsung Medical Center, Seoul, Korea between 2007 and 2009. Several indexes of β-cell function were calculated and tested for correlations with pancreatic β-cell area.

Total pancreatectomies were performed in 9 patients, while 35 patients were treated with pancreaticoduodenectomies with pylorus preservation. One patient underwent Whipple's operation. All pancreatic sections were taken from the non-pathologic portion of the pancreatic head, and pathological lesions were excluded. All tissues were obtained by a single experienced pathologist. Patients were excluded if (1) type 1 diabetes mellitus or potential secondary causes (except for pancreatic cancer) of type 2 diabetes mellitus were present, including chronic pancreatitis, endocrinopathies causing diabetes mellitus, chronic glucocorticoid treatment, and infection, or (2) the pancreatic tissue had undergone autolysis or showed evidence of pancreatitis or elevated amylase and/or lipase on laboratory findings before 75-g OGTT.

This study was approved by the Ethical Committee of Samsung Medical Center at Sungkyunkwan University School of Medicine in Seoul, Korea.

2.2. Biochemical tests

One week before surgery, a standard 75-g OGTT was performed. After overnight fasting, subjects orally ingested glucose solution (75 g) within 5 min. Insulin and oral hypoglycemic agents were stopped for at least 24 h before OGTT. Blood samples for glucose measurement were obtained before ingestion and at 30, 60, 90, and 120 min thereafter, and insulin and C-peptide levels were measured before ingestion and at 30 and 120 min thereafter.

Several models were used to estimate insulin sensitivity and secretion from plasma glucose, C-peptide, and insulin concentrations measured during the OGTT. For early-phase insulin secretion, the insulinogenic index was calculated as the change in insulin levels ($\Delta insulin_{30}$) divided by the change in glucose levels ($\Delta glucose_{30}$) during the first 30 min [16]. For basal insulin secretion and insulin resistance, homeostasis model assessment of β cell function (HOMA-β) and insulin resistance (HOMA-IR) was calculated [17]. The disposition index (DI) provides a measure of β cell function [18]. DI was calculated as the insulinogenic index × $ISI_{0,120}$ (insulin sensitivity index). $ISI_{0,120}$ is a formula for insulin sensitivity index as follows: [75,000 + (fasting glucose (mg/dl) − 2 h glucose (mg/dl)) × 0.19 × body weight (kg)]/[120 × log(fasting insulin (μU/ml) + 2 h insulin (μU/ml))/2 × (fasting glucose (mg/dl) + 2 h glucose (mg/dl))/2] [19].

The insulin-to-glucose ratios and C-peptide-to-glucose ratios were calculated before and at 30 and 120 min after glucose ingestion. The area under the glucose curve (AUC_{glu}) during the OGTT was calculated. The following parameters were investigated to determine whether they were correlated with β-cell area: (1) HOMA-β cell function index; (2) DI; (3) fasting insulin-to-glucose ratio; (4) fasting C-peptide-to-glucose ratio; (5) insulin-to-glucose ratio 30 min after oral glucose ingestion; (6) C-peptide-to-glucose ratio 30 min after oral glucose ingestion; (7) insulin-to-glucose ratio 120 min after oral glucose ingestion; (8) C-peptide-to-glucose ratio 120 min after oral glucose ingestion; (9) insulinogenic index; (10) glucose levels; and (11) AUC_{glu}.

2.3. Immunohistochemistry

Pancreatic tissues were fixed in formaldehyde and embedded in paraffin. Paraffin sections (4 μm thick) were stained