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Insulin and C-Peptide Levels, Pancreatic Beta Cell Function, and Insulin Resistance Across Glucose Tolerance Status in Thais

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Impaired pancreatic beta cell function and insulin sensitivity are fundamental factors in the pathogenesis of type 2 diabetes; however, the predominant defect appears differ among ethnic groups. We conducted a cross-sectional study to evaluate the contribution of impaired beta cell function and insulin sensitivity at different stages of the deterioration of glucose tolerance in Thais. The study involved 420 urban Thais of both sexes, 43–84 years old. A 75-g oral glucose tolerance test was performed on all of the subjects. Indices of insulin resistance and beta cell function were calculated with the use of a homeostasis model assessment. The subjects were classified as having normal glucose tolerance (NGT), isolated impaired fasting glucose (IFG), isolated impaired glucose tolerance (IGT), combined IFG and IGT, or type 2 diabetes mellitus according to the American Diabetes Association (ADA) criteria. There were no differences between groups with regard to gender and age. The percentage of obesity was significantly greatest in the diabetic group. Fasting serum insulin and C-peptide levels progressively increased from the NGT to the diabetic subjects. Serum C-peptide was more strongly associated with newly diagnosed diabetes than insulin, and was an independent factor associated with newly diagnosed diabetic subjects. The insulin resistance index progressively increased when the glucose tolerance stage changed from NGT through diabetic subjects. Beta cell function did not change significantly in any other group compared to the NGT group. An increase in fasting serum C-peptide may be a risk factor for type 2 diabetes. Obesity and insulin resistance are the predominant features in the deterioration of glucose tolerance in Thais. J. Clin. Lab. Anal. 21:85–90, 2007.

Key words: diabetes; obesity; homeostasis model assessment; beta cell function; insulin resistance

INTRODUCTION

The prevalence of type 2 diabetes in Thai adults was reported to be 9.6% in 2000 (1). This prevalence is higher than the projection for diabetes worldwide, which predicts an increase from 4.0% in 1995 to 5.4% in 2025 (2). Despite the growing prevalence of diabetes in Thailand, to date no study has examined the pathogenesis of diabetes in Thais. It is important to understand the pathophysiology in order to develop prevention and therapy strategies for subjects who are at risk of developing diabetes. It is well known that both impaired pancreatic beta cell function and decreased insulin sensitivity are fundamental factors in the pathogenesis of type 2 diabetes. However, the contribution of these two abnormalities has been reported to vary among ethnic groups (3–5). In addition, body fat has been reported to not only affect insulin sensitivity but also to compensate for impaired beta cell function (6). In Caucasians, obesity is a major predictor for type 2 diabetes and is closely associated with insulin resistance (7,8). Although there is a lower prevalence of obesity in Asians compared to Caucasians (9), the prevalence of

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diabetes is comparable between Asian and Caucasian populations (10,11). A progression in the prevalence of diabetes with increasing body mass index (BMI) and waist circumference is being seen in all populations.

Several previous studies used insulin concentration to infer pancreatic insulin secretion. However, a substantial and variable uptake of newly secreted insulin by the liver, and a short but variable plasma halflife of insulin have a confounding effect in such studies. In recent studies, C-peptide measurement has been used as an alternative, reliable surrogate for assessing pancreatic insulin secretion. Both insulin and C-peptide originate from the pancreatic cells, and both are secreted in equimolar amounts from the beta cell; however, C-peptide is only minimally extracted or metabolized by the liver (12). Therefore, the purpose of this study was to estimate insulin secretion by measuring both serum insulin and C-peptide levels, the contribution of impaired pancreatic beta cell function and increase in insulin resistance across the range of glucose tolerance, and their relations to body fat in Thais who have never been diagnosed with diabetes.

MATERIALS AND METHODS

This cross-sectional study included 420 urban Thai subjects of both sexes (age range = 43–84 years). Subjects were excluded from the study if they were known to have diabetes. After an overnight fast, the subjects underwent a 75-g oral glucose tolerance test. The glucose tolerance was classified according to the current American Diabetes Association (ADA) criteria (13) for fasting and 2-hr glucose levels. Normal glucose tolerance (NGT) was defined as having a fasting plasma glucose (FPG) level <5.6 mmol/L and 2-hr plasma glucose (PG) level <7.8 mmol/L. Subjects with FPG levels between 5.6 and 6.9 mmol/L and 2-hr PG levels <7.8 mmol/L were considered to have isolated impaired fasting glucose (IFG). Isolated impaired glucose tolerance (IGT) was defined as FPG levels <5.6 mmol/L and 2-hr PG levels of 7.8–11.1 mmol/L. Subjects with FPG levels of 5.6–6.9 mmol/L and 2-hr PG levels of 7.8–11.1 mmol/L were considered to have combined IFG and IGT (IFG/IGT). Type 2 diabetic patients had FPG levels ≥ 7.0 mmol/L or 2-hr PG levels ≥ 11.1 mmol/L. Anthropometric measurements (weight, height, and waist circumference) were obtained in each subject. The BMI was calculated as weight in kilograms divided by height in meters squared. According to recent World Health Organization Asia-Pacific criteria (14), obesity is defined as a BMI ≥ 25 kg/m^2, and abdominal obesity is defined as a waist circumference ≥ 90 cm in males and ≥ 80 cm in females. PG was measured by means of the glucose oxidase method with a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). Fasting serum insulin was analyzed by chemiluminescent immunometric assay (Diagnostic Products Corp, Los Angeles, CA). Fasting serum C-peptide was determined by electrochemiluminescence immunoassay (Roche Diagnostic GmbH, Mannheim, Germany). The homeostasis model assessment for insulin resistance (HOMA-IR) and beta cell function (HOMA-B) were calculated by the HOMA calculator from pairs of FPG and serum insulin levels as a surrogate measure for insulin resistance, and from pairs of FPG and serum C-peptide concentrations as a surrogate measure for beta cell function (15). The study was approved by the institutional review board, and written informed consent was obtained from all participants before they entered the study.

Statistical Analysis

The results are expressed as the percentage, mean $\pm$ SD, for normal distribution of continuous values or as the median and range for abnormal distribution. Differences in proportions were evaluated by means of a chi-squared test. Comparisons among groups were analyzed by analysis of variance (ANOVA), followed by Scheffe's test or the Kruskal-Wallis test followed by Mann-Whitney's U-test. Pearson's correlation analysis was used to determine the relationships between variables. Stepwise logistic regression was used to evaluate the significant factors associated with diabetes. A receiver operating characteristic (ROC) curve was used to determine the cutoff value for serum C-peptide. A P-value of <0.05 was considered statistically significant.

RESULTS

The baseline characteristics of the study subjects across glucose tolerance levels are shown in Table 1. Using the recently revised ADA criteria, 42.4%, 15.2%, 13.6%, 12.6%, and 16.2% of the subjects had NGT, isolated IFG, isolated IGT, IFG/IGT, and newly diagnosed type 2 diabetes, respectively. Gender and age were equally represented across the diagnosed groups. BMI and waist circumference were gradually significantly increased from subjects with NGT through prediabetes (isolated IFG, isolated IGT, and IFG/IGT) to diabetes. Using the revised criteria for Asia-Pacific populations, the proportion of obese subjects with prediabetes and diabetes was more than 50%. However, the increment in proportion of abdominal obesity was significant in diabetic subjects compared to subjects with NGT or isolated IFG. The mean fasting serum insulin and C-peptide levels progressively increased from the

subjects with NGT through prediabetes to newly diagnosed diabetes.

With regard to insulin resistance, there was a progressive increase in HOMA-IR across glucose tolerance levels (Table 1). At each step in the deterioration of glucose tolerance, HOMA-IR increased by about 35%, 25%, 92% and 126%, respectively. However, there was no significant change in beta cell function as estimated by HOMA-B in all category subjects when compared to NGT. Subjects with isolated IFG and diabetes had a significantly lower HOMA-B than those with isolated IGT.

As a whole, BMI and waist circumference correlated positively with fasting serum insulin, serum C-peptide, HOMA-IR, and HOMA-B (Table 2). Stepwise logistic regression showed that both serum insulin and C-peptide levels were important factors associated with diabetes (Table 3). However, C-peptide (odds ratio (OR) = 10.85) was more strongly associated with newly diagnosed diabetes than insulin (OR = 1.03). Therefore, a cutoff value of C-peptide at 0.65 ng/mL was chosen according to the ROC curve for use in diabetes screening, which yielded a sensitivity and specificity of 82% and 74%, respectively (Fig. 1).

DISCUSSION

In the present study we found that fasting serum insulin and C-peptide progressively increased from subjects with NGT through prediabetes, and was highest in subjects with newly diagnosed diabetes. This could be explained by the higher level of insulin resistance and a consequent compensatory increase in beta cell mass and hypertrophy of existing beta cells to meet the increased demand and to avoid more severe hyperglycemia (16). As the beta cell mass and function reach their thresholds to compensate, the burden of insulin resistance can no longer be overcome (17), resulting in the development of type 2 diabetes. Additionally, fasting serum C-peptide was found to be an important factor in newly diagnosed diabetes. These results suggest that we can identify individuals at high risk of developing type 2 diabetes without expensive and labor-intensive oral glucose tolerence test (OGTT) by measuring fasting serum C-peptide with a cutoff value of 0.65 nmol/L.

In this study we used insulin to compute HOMA-IR, and C-peptide to compute HOMA-B. This is because HOMA-IR determines the resistance to insulin action,

TABLE 1. Baseline characteristic and glucose/insulin homeostasis of the subjects according to glucose tolerance*

	NGT	Isolated IFG	Isolated IGT	IFG/IGT	Diabetes	*P* value
Number	178	64	57	53	68	
Sex (M/F)	24/154	10/54	9/48	9/44	12/56	NS
Age (years)	60.1 ± 7.6	61.0 ± 7.8	62.3 ± 7.1	61.7 ± 6.1	62.2 ± 6.8	NS
BMI (kg/m^2)	24.4 ± 3.8	26.0 ± 3.6	25.9 ± 3.4	26.7 ± 3.1[a]	28.0 ± 4.7[a,b,c]	<0.001
Waist circumference (cm)	78.0 ± 10.1	82.2 ± 8.2[a]	80.5 ± 8.4	83.2 ± 7.6[a]	87.5 ± 9.5[a,b,c]	<0.001
Obesity (BMI ≥ 25 kg/m^2) (%)	44.9	50.8	52.6	69.8[d]	68.7[d]	<0.01
Abdominal obesity (male ≥ 90 cm, female ≥ 80 cm) (%)	39.3	50.8	52.6	56.6	76.1[d,e]	<0.001
Fasting plasma glucose (mmol/L)	5.05 (5.00–5.16)	5.72[f] (5.72–5.83)	5.16[h] (5.11–5.27)	5.83[f,g] (5.77–6.22)	6.94[f,g,h,i] (6.61–7.32)	<0.001
2-hr plasma glucose (mmol/L)	6.19 ± 0.86	6.51 ± 0.95	8.75 ± 0.85[a,b]	9.00 ± 0.98[a,b]	14.34 ± 2.9[a,b,c,j]	<0.001
Fasting insulin (pmol/L)	41.0 (38.9–44.4)	53.5[f] (43.8–62.5)	50.7[f] (43.8–57.6)	75.7[f,g] (64.6–92.4)	86.8[f,g,h] (82.0–100.7)	<0.001
Fasting C-peptide (nmol/L)	0.54 ± 0.23	0.63 ± 0.21	0.66 ± 0.27	0.92 ± 0.44[a,b,c]	1.03 ± 0.48[a,b,c]	<0.001
HOMA-IR	0.77 (0.72–0.84)	1.04[f] (0.85–1.21)	0.96[f] (0.80–1.05)	1.48[f,g] (1.24–1.75)	1.74[f,g,h] (1.68–2.05)	<0.001
HOMA-B	104.7 ± 33.8	89.6 ± 21.3[c]	116.3 ± 32.4	107.1 ± 29.7	92.9 ± 54.6 [c]	<0.001

*Values are mean ± SD, median (95% confidence interval of median), or percentage.
[a]Scheffe $P<0.05$ vs. normal.
[b]Scheffe $P<0.05$ vs. IFG.
[c]Scheffe $P<0.05$ vs. ISOLATED IGT.
[d]Chi-squared $P<0.005$ vs. normal.
[e]Chi-squared $P<0.005$ vs. IFG.
[f]Mann-Whitney $P<0.005$ vs. normal.
[g]Mann-Whitney $P<0.005$ vs. IGT.
[h]Mann-Whitney $P<0.005$ vs. IFG.
[i]Mann-Whitney $P<0.005$ vs. IFG/IGT.
[j]Scheffe $P<0.05$ vs. IFG/IGT.
BMI, body mass index; M, male, F, female.

TABLE 2. Correlation between BMI, waist circumference, and serum C-peptide levels, HOMA-IR and HOMA-B

Parameters	Insulin (pmol/L)	C-peptide (nmol/L)	HOMA-IR (%)	HOMA-B (%)
Body mass index (kg/m^2)	0.514 $P<0.001$	0.488 $P<0.001$	0.485 $P<0.001$	0.272 $P<0.001$
Waist circumference (cm)	0.477 $P<0.001$	0.459 $P<0.001$	0.462 $P<0.001$	0.233 $P<0.001$
Insulin (pmol/L)	1	0.813 $P<0.001$	0.996 $P<0.001$	0.430 $P<0.001$
C-peptide (nmol/L)	–	1	0.818 $P<0.001$	0.631 $P<0.001$

TABLE 3. Independent variables associated with type 2 diabetes

	Dependent variables Diabetes vs. NGT		
Independent variables	Odds ratio	95% CI	*P*-value
Body mass index (kg/m^2)	–	–	0.507
Waist circumference (cm)	–	–	0.085
Insulin (pmol/L)	1.03	1.01–1.04	0.001
C-peptide (nmol/L)	10.85	2.27–51.8	0.001

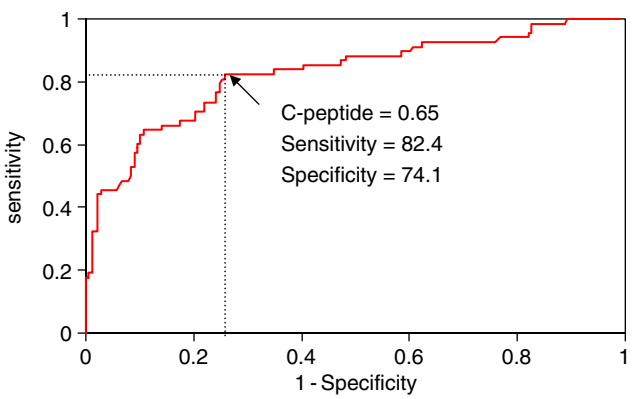

Fig. 1. ROC curve of C-peptide for predicting newly diagnosed diabetes (area under the ROC curve = 0.83, 95% confidence interval (CI) = 0.77–0.89).

while HOMA-B determines pancreatic insulin secretion. C-peptide has been used to reflect pancreatic insulin secretion more accurately than insulin itself because it is cosecreted on an equimolar basis from the beta cell with insulin, but is not extracted or metabolized by the liver as insulin (12). With regard to insulin resistance, there was a marked increase in HOMA-IR with the deterioration of glucose tolerance. The magnitude of the incremental increase in HOMA-IR in subjects with isolated IFG, isolated IGT, IFG/IGT, and newly diagnosed diabetes in the present study was 1.4-, 1.2-, 1.9-, and 2.3-fold greater than in subjects with NGT. These increases in HOMA-IR were nearly similar to those previously found in Japan (18), but lower than those reported for other ethnic groups (19–22). The present results are in accordance with one study that reported that Asian-American diabetes is markedly less insulin-resistant than that of other ethnic Americans or Caucasians (3). In the current study there was only a slightly decline in beta cell function as assessed by HOMA-B in subjects with isolated IFG and newly diagnosed diabetes. However, a large reduction in beta cell function in both prediabetes and diabetes has been observed in Japanese and other ethnic groups (3,18,19,23). The variance between the current study and previous ones in terms of degrees of impaired insulin secretion and insulin resistance may be due to ethnic differences, the different methods used to assess insulin resistance and insulin secretion, and differences in the range of BMIs in each study group. It is well known that obesity and the onset of type 2 diabetes are linked (24). In Caucasians, the majority of diabetic patients are obese and insulin resistance is the dominant factor (25,26). However, most diabetic patients in Asia are not obese (27–29). The contribution of insulin resistance and insulin secretory dysfunction may differ between non-obese and obese diabetic subjects (30–32). Even in the same ethnic group, obese and non-obese diabetic patients have been reported to exhibit differences in their insulin secretory status (33). More than 50% of subjects with abnormal glucose tolerance in this study displayed a higher BMI, waist circumference, and insulin resistance than subjects with NGT. This rate is higher than that in the general population reported in other Asian countries (27,28,34). The increase in obesity could be attributed to the adoption of western culture and lifestyle, which leads to reduced physical activity levels, and other socioeconomic factors. These results indicate that the underlying pathophysiologic abnormalities of type 2 diabetes differ even within the same Asian populations. In addition, each of the measures of adiposity used in this study, including BMI and waist circumference, were more strongly associated with HOMA-IR than HOMA-B. Taken together, these data might imply that diabetic subjects in whom insulin resistance is shown to be the dominant pathogenic factor have a higher degree of obesity compared to those with dominant impaired insulin secretion. Furthermore,

we noted that pathogenesis differed between isolated IFG and isolated IGT. Impaired beta cell function was expressed only in subjects with isolated IFG, whereas there were no significant differences regarding insulin sensitivity between isolated IFG and isolated IGT subjects. This finding suggests that isolated IFG subjects had elevated FPG levels because of impaired insulin secretion, whereas the FPG concentrations in isolated IGT subjects were regulated by a compensatory increase in insulin secretion.

CONCLUSIONS

An increase in fasting serum C-peptide levels may be a risk factor for type 2 diabetes. Subjects with isolated IFG and isolated IGT differ with respect to beta cell dysfunction. Obesity and insulin resistance are the predominant features of type 2 diabetes in Thais.

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