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ORIGINAL PAPER

Differences in insulin sensitivity, pancreatic beta cell function and circulating adiponectin across glucose tolerance status in Thai obese and non-obese women

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Abstract Although adiponectin levels are associated with obesity and insulin insensitivity, the role of adiponectin in the progression to diabetes in non-obese subjects is unclear. Therefore, 289 women aged 50–80 years without previous history of diabetes or impaired glucose tolerance (IGT) were studied. They were classified as normal glucose tolerance (NGT), IGT or diabetes based on WHO criteria. Insulin sensitivity (S) and beta cell function (B) indices were calculated using homeostasis model assessment (HOMA). In obese women with BMI $\geq$ 25 kg/m^2 ($n = 161$), there were declines in HOMA-%S ($P < 0.001$), HOMA-%B ($P < 0.05$) and circulating adiponectin ($P < 0.001$) across glucose tolerance status. In non-obese women with BMI $<$ 25 kg/m^2 ($n = 128$), there was no significant change in HOMA-%S in women with IGT and diabetes as compared to women with NGT. However, HOMA-%B ($P < 0.05$) and serum adiponectin levels ($P < 0.001$) were significantly decreased across glucose tolerance. Serum adiponectin levels were correlated to HOMA-%S in both obese and non-obese women while negative correlations between circulating adiponectin and HOMA-%B were demonstrated only in obese women. We have demonstrated in the present study the predominant role of beta cell dysfunction as compared to that of insulin resistance in the deterioration of glucose tolerance in non-obese women. Circulating adiponectin appears to be inversely related to beta cell dysfunction in addition to insulin resistance only in obese women.

Keywords Insulin sensitivity · Beta cell function · Adiponectin · Obese

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Introduction

Type 2 diabetes is characterized by impaired beta cell secretory function in the presence of insulin resistance. The question of which defects is the predominant determinant of diabetes is debatable although studies in a number of ethnic groups suggest the predominant role of insulin resistance [1–3]. In individuals with impaired glucose tolerance, the impairments of insulin sensitivity together with beta cell function have also been demonstrated, albeit to a lesser degree [4, 5]. In most populations, obesity is highly prevalent in subjects with type 2 diabetes and there is a correlation between the degree of adiposity and insulin sensitivity [6]. However, in Asian populations, most diabetic patients are less obese when compared with other ethnic groups [7]. It has also been demonstrated that beta cell secretory dysfunction can play a relatively more important role in some Asian populations [8–10]. Nevertheless, the relative roles of insulin resistance versus beta cell function with regard to impaired glucose tolerance and diabetes in obese as compared to non-obese subjects in Asian populations are unclear.

Recently, circulating adiponectin has been reported to be low in obese subjects [11, 12] and those with type 2 diabetes [13, 14]. Besides the degree of adiposity, adiponectin levels are also determined by the regional distribution of adipose tissue with circulating adiponectin

being suppressed to a greater extent in subjects having high waist-to-hip ratios [15]. However, it is unclear whether adiponectin decreases similarly, in obese and non-obese subjects, with the progression to impaired glucose tolerance and diabetes. It is therefore the purpose of the present study to investigate the relation of adiponectin to the progression to type 2 diabetes in obese and non-obese subjects.

Subjects and methods

Subjects

Two hundred and eighty nine women aged at least 50 years without previous history of IGT or diabetes were recruited by advertisement to have oral glucose tolerance screening at Ramathibodi Hospital, Bangkok, Thailand. Weight, height and waist circumference were measured in each subject. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters. Based on the recent World Health Organization Asia Pacific criteria [16], obesity was defined as BMI $\geq$ 25 kg/m^2, and abdominal obesity was defined as waist circumference $\geq$ 80 cm in female. Fasting blood samples were drawn for the determinations of plasma glucose, serum insulin and adiponectin. The study was approved by the Ethics Committee of Ramathibodi Hospital and written informed consent was obtained from each participant before entering the study.

Oral glucose tolerance test

After an overnight fast, subjects were given 75 g of oral glucose dissolved in 250 ml of water. Blood samples were drawn at baseline and 2 h after the administration of glucose. Plasma glucose levels were measured by the glucose oxidase method using the Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA, USA). The glucose tolerance was classified according to the current American Diabetes Association criteria [17] for fasting and 2-h glucose levels. Normal glucose tolerance (NGT) was defined as having a fasting plasma glucose (FPG) level <5.6 mmol/l and 2 h plasma glucose (PG) level <7.8 mmol/l. Impaired glucose tolerance (IGT) was defined as 2 h PG levels between 7.8 and 11.1 mmol/l. Type 2 diabetic patients were those with FPG $\geq$ 7.0 mmol/l or 2 h PG levels $\geq$11.1 mmol/l.

Assessment of insulin sensitivity, beta cell function and adiponectin

Fasting serum insulin was measured by chemiluminescence immunoassay (Diagnostic Products Corporation, Los Angeles, CA, USA) with an intra-assay precision of 8.0%. Homeostasis model assessment of insulin sensitivity (HOMA-%S) and beta cell function (HOMA-%B) were used. The indices were calculated using the computer program HOMA2 calculator from pairs of fasting glucose and insulin levels [16]. Fasting serum adiponectin were measured by a human adiponectin radioimmunoassay kit (LINCO Research, St Louis, MO, USA). The assay has intra- and inter-assay precision of 1.7% and 9.3%, respectively.

Statistical analysis

Results were expressed as percentage or mean $\pm$ SD. Differences in proportions were evaluated by Chi-square test. Analysis of variance was used to evaluate differences among groups followed by Scheffe's method for pairwise comparisons. Pearson's correlation analysis was used to examine the relationships between variables. A P value < 0.05 was considered statistically significant. All statistical analyses were performed using the SPSS package version 11.5 (SPSS Inc., Chicago, IL, USA).

Results

Two hundred and eighty nine women were grouped according to their BMI and glucose tolerance status (Table 1). Of the 161 obese women with BMI $\geq$ 25 kg/m^2, 46.0%, 29.2% and 24.8% were NGT, IGT and diabetics, respectively. In non-obese women with BMI $<$ 25 kg/m^2, the percentage of subjects with IGT (39.1%) was more than that of the obese subjects. However, the percentage of lean subjects with diabetes (12.5%) was about 2-fold lower than in obese subjects. In both lean and obese subjects, the age, BMI, waist circumference and the proportion of abdominal obesity did not differ across the various glucose tolerance status. Fasting serum insulin levels progressively increased from subjects with NGT through IGT to diabetes, but statistical significance was found only in obese subjects.

In obese subjects, there was a progressive decline in HOMA-%S in the progression from NGT to diabetes (Table 2). The significant difference in HOMA-%S was found between subjects with diabetes and those with NGT. However, the significant decline in HOMA-%B was also found in subjects with diabetes as compared to subjects with IGT. On the contrary, in lean subjects, there was no significant change in HOMA-%S across the glucose tolerance status. However, HOMA-%B significantly declined in subjects with diabetes as compared to those with NGT.

The levels of adiponectin in subjects with IGT or diabetes (Table 2) were significantly lower than those with NGT, both in obese and non-obese subjects. No difference

Table 1 Baseline characteristic of the subjects according to BMI and glucose tolerance status

	BMI ≥ 25 (kg/m^2)				BMI < 25 (kg/m^2)			
	NGT	IGT	Diabetes	*P* value	NGT	IGT	Diabetes	*P* value
Number	74 (46.0%)	47 (29.2%)	40 (24.8%)		62 (48.4%)	50 (39.1%)	16 (12.5%)	
Age (years)	62.0 ± 8.7	64.2 ± 7.0	63.3 ± 8.2	NS	65.6 ± 7.6	65.4 ± 6.6	65.5 ± 4.6	NS
BMI (kg/m^2)	28.0 ± 2.5	28.3 ± 3.2	28.7 ± 3.3	NS	22.5 ± 1.9	22.5 ± 1.9	22.9 ± 2.7	NS
Waist circumference (cm)	88.1 ± 7.4	89.3 ± 8.2	90.9 ± 8.4	NS	78.9 ± 7.3	77.9 ± 9.3	80.2 ± 10.5	NS
Abdominal obesity (%)	88.9	89.4	95.0	NS	41.7	44.0	62.5	NS
Fasting blood glucose (mmol/l)	5.2 ± 0.5	5.4 ± 0.5	7.0 ± 1.6*,**	<0.001	5.0 ± 0.4	5.3 ± 0.4*	6.1 ± 0.9*,**	<0.001
2-h blood glucose (mmol/l)	6.5 ± 0.9	8.9 ± 1.0*	15.1 ± 3.1*,**	<0.001	5.9 ± 1.1	8.8 ± 0.9*	14.1 ± 2.5*,**	<0.001
Fasting insulin (pmol/l)	62.6 ± 27.8	79.5 ± 49.8	102.3 ± 62.3*	<0.001	48.2 ± 20.2	52.2 ± 24.0	59.6 ± 28.1	NS

Values are mean ± SD or percentage

*$P < 0.001$ vs. NGT; ** $P < 0.001$ vs. IGT

Table 2 HOMA-%S, HOMA-%B and adiponectin levels in obese and non-obese subjects according to glucose tolerance status

	BMI ≥ 25 (kg/m^2)				BMI < 25 (kg/m^2)			
	NGT	IGT	Diabetes	*P* value	NGT	IGT	Diabetes	*P* value
HOMA-S (%)	105.0 ± 59.6	88.9 ± 46.4	63.2 ± 34.5*	<0.001	131.1 ± 58.7	137.0 ± 113.1	121.5 ± 91.3	NS
HOMA-B (%)	96.4 ± 27.8	101.5 ± 30.4	81.5 ± 39.9**	<0.05	90.1 ± 28.1	80.4 ± 24.2	69.3 ± 25.1*	<0.05
Adiponectin (μg/ml)	8.3 ± 3.2	6.5 ± 2.4*	6.0 ± 2.2*	<0.001	10.5 ± 4.3	7.3 ± 3.5*	7.4 ± 3.4*	<0.001

Values are mean ± SD

* $P < 0.05$ vs. NGT, ** $P < 0.05$ vs. IGT

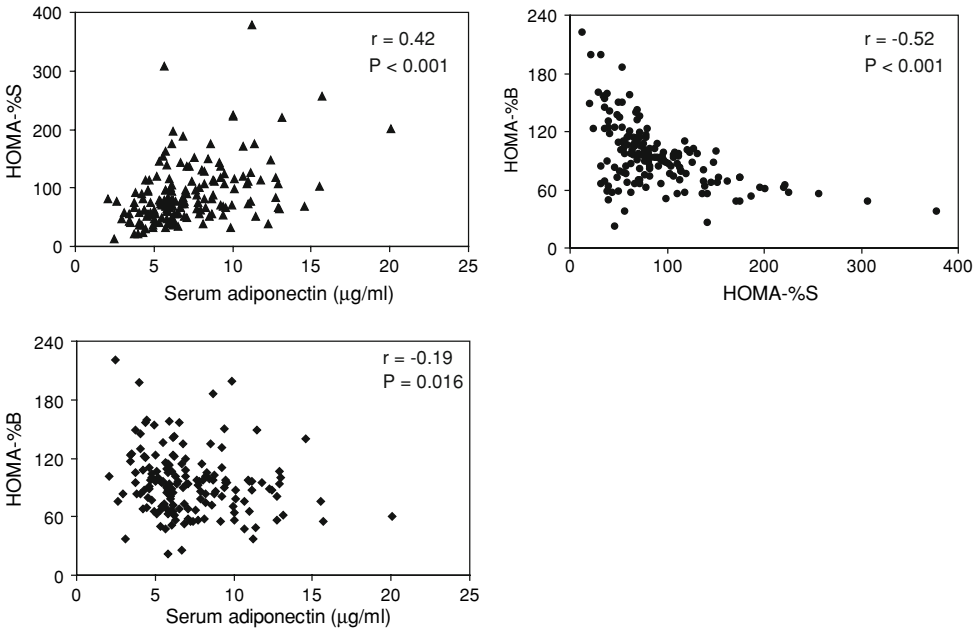

Fig. 1 Correlations between HOMA-%S, HOMA-%B and adiponectin levels in obese subjects

in serum adiponectin was detected between subjects with IGT and diabetes. Figures 1 and 2 demonstrate the correlation among HOMA-%S, HOMA-%B and circulating adiponectin in both obese and non-obese women. Serum adiponectin levels were positively correlated to HOMA-%S in both obese and non-obese women while negative correlations between circulating adiponectin and HOMA-%B were demonstrated only in obese women. In addition, negative correlations between HOMA-%B and HOMA-%S were also observed in both obese and non-obese subjects.

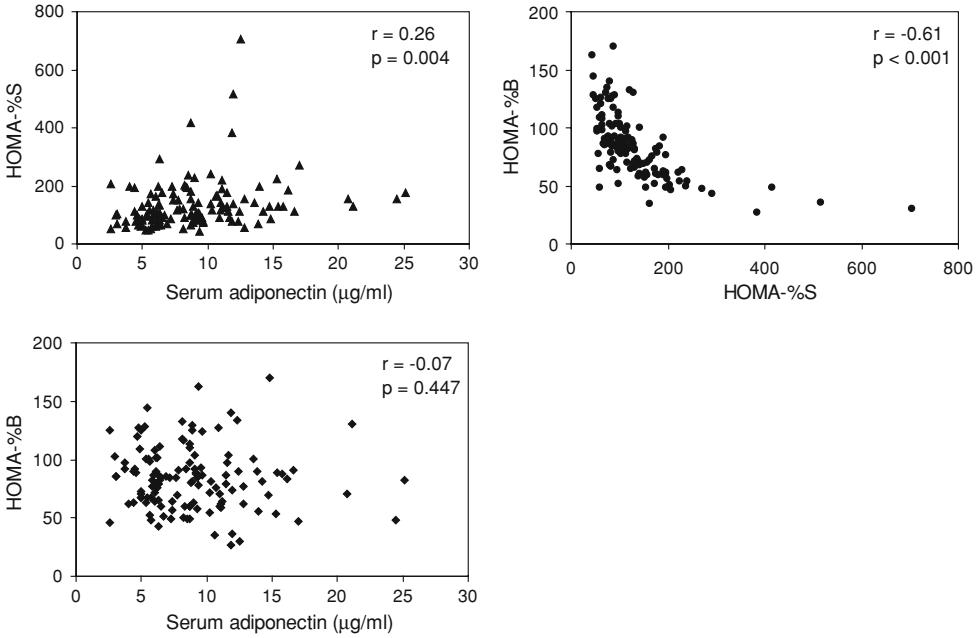

Fig. 2 Correlations between HOMA-%S, HOMA-%B and adiponectin levels in non-obese subjects

Discussion

It is generally believed that insulin resistance is the primary defect and that pancreatic beta cell dysfunction occurs later and contributes to the progression of NGT to IGT and diabetes. However, a number of studies conducted in Asian populations have demonstrated the dominant role of beta cell dysfunction in the pathogenesis of type 2 diabetes [8, 9]. Furthermore, a recent study conducted in Korean population showed no difference in insulin resistance index between subjects with normal glucose tolerance and those with impaired fasting glucose or impaired glucose tolerance [8]. However, a significant decrease in beta cell function was observed. Likewise, the predominant role of beta cell dysfunction over insulin resistance in impaired glucose tolerance has also been demonstrated in another study [19]. In the present study, we have demonstrated the importance of beta cell dysfunction in diabetic subjects. Interestingly, the predominant role of beta cell dysfunction over insulin resistance was more readily apparent in non-obese subjects. Since there was no significant difference in insulin resistance, this suggests that pancreatic beta cell dysfunction may be the determinant for the worsening of glucose tolerance from NGT through IGT to diabetes in non-obese subjects. This raises the possibility of a different pathogenesis of type 2 diabetes in non-obese subjects.

We have also demonstrated in the present study that the levels of adiponectin decreased in subjects with IGT and subjects with diabetes regardless of the degree of adiposity. Due to the cross-sectional nature of the study, it is unclear whether adiponectin actually decreased overtime when individuals progressed from the state of normal to abnormal glucose tolerance or if the lower serum adiponectin was already present in subjects with normal glucose tolerance who were at a higher risk of developing abnormal glucose tolerance. However, it has been demonstrated that adiponectin is a risk factor of developing insulin resistance and diabetes in a number of studies suggesting the more likely possibility of pre-existing low adiponectin in subjects destined to develop abnormal glucose tolerance [20–22]. It should be noted that there was no significant difference in serum adiponectin between subjects with IGT and those with diabetes. This may suggest the roles of other factors rather than adiponectin in the progression from IGT to diabetes.

In keeping with the known effect of adiponectin on insulin sensitivity, we have found that circulating adiponectin was related to insulin sensitivity as measured by HOMA-%S in both obese and non-obese women. However, it was found in the present study that adiponectin was inversely related to pancreatic beta cell function as measured by HOMA-%B only in obese women. Although several studies have established the role of adiponectin in the determination of insulin sensitivity, the influence of adiponectin on beta cell secretory function is less clear. A cross-sectional study has demonstrated the relation of serum adiponectin not only to insulin sensitivity but also to beta cell function [23]. A previous study has shown that thiazolidinediones, which are used in the treatment of type 2 diabetes, improve both insulin sensitivity and beta cell function [24] and there are data suggesting that treating diabetic subjects with the thiazolidinediones could protect human beta cells from apoptosis induced by glucose and interleukin-1 beta (IL1-B) [25]. However, since thiazolidinediones

also increase circulating adiponectin levels [12, 26], it is likely that both beneficial effects of thiazolidinediones are mediated through the increase in adiponectin. More direct evidence has been generated in vitro. Exposure of pancreatic beta cells to glucose induces IL1-B production by the beta cells and IL1-B itself can induce apoptosis of beta cells [27]. In addition, fatty acid-induced beta cell apoptosis has been associated with obesity-related type 2 diabetes [28]. Interestingly, cytokines and fatty acid-induced apoptosis in pancreatic beta cells can be counteracted by adiponectin [29]. However, the protective effect of adiponectin against fatty acid-induced beta-cell apoptosis could not be demonstrated in humans [30]. It should be noted that the association between adiponectin and pancreatic beta cell function in our study does not indicate causation. In addition, the function of adiponectin in this regard cannot be readily generalized from a single basal measurement in a study population consisted of mostly postmenopausal women. More studies to validate such role of adiponectin are apparently required.

Conclusion

In summary, we have demonstrated in the present study the predominant role of beta cell dysfunction as compared to that of insulin resistance in the deterioration of glucose tolerance in non-obese women. Circulating adiponectin appears to be inversely related to beta cell dysfunction in addition to insulin resistance only in obese women.

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