The Preservation of Insulin Sensitivity in Obese Women without Diabetes

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Objective: *To assess insulin sensitivity, pancreatic beta-cell function, and compare circulating levels of adiponectin and ghrelin in obese women with and without diabetes.*
Material and Method: *Ninety-nine obese women with a body mass index (BMI) $\geq$ 25 kg/m^2 and age at least 40 years without previous history of diabetes participated in this study. Oral glucose tolerance test was performed in all subjects. Serum for insulin, adiponectin, and ghrelin were obtained at baseline. Data were expressed as mean $\pm$ SEM.*
Results: *Oral glucose tolerance test revealed 66 non-diabetic (ND) and 33 diabetic (D) subjects. Despite a similar degree of obesity, women without diabetes had near normal insulin sensitivity (ND, 105.7 $\pm$ 6.4%; D, 62.3 $\pm$ 5.9%; $p < 0.001$) and beta cell function (ND, 95.4 $\pm$ 3.0%; D, 79.0 $\pm$ 6.1%; $p < 0.001$) as assessed by the HOMA model. Non-diabetic subjects had higher serum adiponectin levels despite similar BMI (ND, 8.3 $\pm$ 0.4 mg/ml; D, 6.3 $\pm$ 0.4 mg/ml; $p < 0.01$). Obese subjects with diabetes had lower serum ghrelin levels than obese non-diabetic subjects (ND, 1027.2 $\pm$ 32.0 pg/ml; D, 875.1 $\pm$ 34.6 pg/ml; $p < 0.05$).*
Conclusion: *Obese women without diabetes have less pancreatic beta cell dysfunction and higher insulin sensitivity than obese women with diabetes. Higher circulating adiponectin may play protective roles in obese non-diabetic subjects, but the significance of higher ghrelin level should be further explored.*

Keywords: *Obesity, Diabetes, Insulin sensitivity, Adiponectin, Ghrelin*

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Type 2 diabetes is an important cause of morbidity and mortality and the extent of the problem is increasing worldwide. Identifying individuals at risk and targeting effective diabetic prevention is therefore highly important. Impairment of insulin secretion and increased insulin resistance characterize the pathogenesis of type 2 diabetes. The decline in beta-cell function rather than increasing insulin resistance is believed to be the determinant for the progression to diabetic stage in subjects with insulin resistance[1-3]. Obesity is a well-known risk factor of type 2 diabetes through increased insulin resistance. However, a number of obese individuals were non-diabetic. It is unclear whether these subjects have more efficient pancreatic beta-cell function in the presence of existing insulin resistance or relatively lower degree of insulin resistance.

Despite the well-established association between obesity and diabetes, the exact mechanism linking the two conditions remains unclear. Recently, there has been much interest in adipocytes and their endocrine-like function. Adipose tissue is discovered to secrete many biologically active substances namely free fatty acid, leptin, tumor necrosis factor-α (TNFα), interleukin-6, resistin, plasminogen activator inhibitor-1, and adiponectin[4-6].

These adipokines may interact with each other in a complex way and influence insulin sensitivity. Adiponectin is abundantly and specifically expressed in differentiated adipocytes and circulates in blood at a high level. Unlike other adipokines of which levels

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increase with increased degree of obesity, level of adiponectin has negative correlation with increased body fat[7,8] and decreased levels of adiponectin are associated with increased insulin resistance, diabetes and coronary artery disease[9]. In terms of biological action of adiponectin, adiponectin knockout mice have impaired insulin sensitivity and administration of adiponectin resulted in improved insulin sensitivity[10,11] and lower glucose levels in animals[12]. These data support that adiponectin probably play a significant part in the link between obesity and insulin resistance. However, the contribution of adiponectin in the protection of diabetes in obese individuals is unclear.

Ghrelin is a peptide hormone synthesized predominantly in the fundus of the stomach. Ghrelin receptors are present in the hypothalamus and pituitary[13]. Besides stimulating growth hormone release, ghrelin stimulates food intake in humans and regulates energy homeostasis. Obesity is associated with low ghrelin level[14], whereas conditions of negative energy balance such as weight loss is associated with higher ghrelin level[15]. There is also recent evidence that ghrelin may also involve in insulin resistance and diabetes[16-18]. Nevertheless, the role of ghrelin in the pathogenesis of diabetes related to obesity is less clear. It is, therefore, the purpose of the present study to assess the relative role of insulin resistance and beta cell secretory function in obese subjects without diabetes. The differences in adiponectin and ghrelin levels in relation to diabetic status were also explored.

Material and Method

Ninety-nine women aged 40 years or older without a previous history of diabetes and took no medications that might effect glucose or insulin participated in this study. Subjects were recruited by advertisement to have oral glucose tolerance tests performed at Ramathibodi Hospital, Bangkok, Thailand. All subjects had anthropometric measurements. Body mass index (BMI) cutoff value of above 25 kg/m^2 was used to define obesity. The present study protocol was approved by the Ethical Committee of Ramathibodi Hospital, Mahidol University and signed informed consent was obtained from each subject prior to the present study.

Oral glucose tolerance test

After an overnight fast, subjects were given 75 gm of glucose dissolved in 250 ml of water orally. Blood samples were drawn at baseline and 2 hours after the administration of glucose. Plasma glucose levels were measured by glucose oxidase method. Subjects were classified as having diabetes when the plasma glucose at 2 hours was at least 200 mg/dl and normal when plasma glucose levels were less than 140 mg/dl.

Assessment of insulin sensitivity, beta cell function and adiponectin

Insulin levels were measured by chemiluminescence assay (DPC, USA). Homeostasis model assessment of insulin sensitivity (HOMA-S) and beta cell function (HOMA-B) were used. The indexes were calculated using the computer program HOMA2 calculator version 2.2 (Diabetes Trials Unit, University of Oxford). Fasting blood samples were also obtained for measurement of adiponectin and ghrelin by radioimmunoassay (Linco Research Inc., USA).

Statistical analysis

Differences between groups were analyzed using unpaired-t test. P value less than 0.05 was considered statistically significant. Data were expressed as mean $\pm$ Standard error of mean (SEM).

Results

Oral glucose tolerance test results revealed 66 non-diabetic subjects (ND) and 33 diabetic subjects (D). Data of age and anthropometric measurements of the two groups are shown in Table 1. The mean ages were similar in the ND and D group, 62.7 $\pm$ 1.1 vs. 64.5 $\pm$ 1.4 years, respectively. Comparing the anthropometric data of the two groups, there was no difference in body weight, height, and BMI. However, higher waist circumference and waist/hip ratio (WHR) were noted in the D group: waist circumference 87.4 + 0.8 cm in ND vs. 92.0 $\pm$ 1.4 cm in D ($p < 0.01$), WHR 0.83 in ND vs. 0.86 in D ($p < 0.05$). With regard to insulin sensitivity and beta-cell function, obese non-diabetic subjects had near 100% insulin sensitivity as well as beta cell function, whereas the obese subjects with diabetes had significantly lower insulin sensitivity (105.7 $\pm$ 6.4% in ND vs. 62.3 $\pm$ 5.9% in D, $p < 0.001$), beta cell function (95.4 $\pm$ 3.0% in ND vs. 79.0 $\pm$ 6.1%, $p < 0.01$) as well as beta cell function after correcting for the degree of insulin resistance (91.8 $\pm$ 3.1% in ND vs. 46.3 $\pm$ 4.0% in D, $p < 0.001$).

Comparing the difference of adiponectin levels, The authors found that non-diabetic subjects had higher serum adiponectin levels compared to diabetic subjects despite similar BMI (8.3 $\pm$ 0.4 mg/ml in ND vs. 6.3 $\pm$ 0.4 mg/ml in D, $p < 0.01$) (Table 2).

Table 1. Age, anthropometric measurements, pancreatic beta cell function and insulin sensitivity of obese subjects without diabetes (ND) and those with diabetes (D)

	ND (n = 66)	D (n = 33)	p-value
Age (year)	62.7±1.1	64.5±1.4	NS
BW (kg)	64.5±0.9	67.4±0.9	NS
Height (cm)	152.0±0.65	152.0±0.94	NS
BMI (kg/m^2)	27.9±0.3	29.0±0.59	NS
Waist (cm)	87.4±0.8	92.0±1.4	<0.01
WHR	0.83	0.86	<0.05
HOMA-B (%)	95.4±3.0	79.0±6.1	<0.001
HOMA-S (%)	105.0±6.4	62.3±5.9	<0.001
Insulin resistance adjusted HOMA-B (%)	91.8±3.1	46.3±4.0	<0.001

Data are shown as mean ± SEM
BW = Body weight, WHR = Waist-Hip-Ratio, HOMA-B = Homeostasis model assessment of beta cell function, HOMA-S = Homeostasis model assessment of insulin sensitivity

Table 2. Comparisons of adiponectin and ghrelin levels in obese non-diabetic (ND) and diabetic (D) groups

	ND (n = 66)	D (n = 33)	p-value
Adiponectin levels (mg/ml)	8.3±0.4	6.3±0.4	<0.01
Ghrelin (pg/ml)	1027.2±32.0	875.1±34.6	<0.05

Data are shown as mean ± SEM

Furthermore, after adjusting for the difference in waist circumference by analysis of covariance, serum adiponectin remained significantly higher in obese subjects without diabetes ($p < 0.05$). With regard to serum ghrelin levels, obese subjects with diabetes had lower serum ghrelin levels than obese non-diabetic subjects (875.1 ± 34.6 pg/ml in D vs. 1027.2 ± 32.0 pg/ml in ND, $p < 0.05$). Since glucose has been demonstrated to suppress ghrelin levels, the difference in serum ghrelin levels were also assessed after being adjusted for fasting plasma glucose and waist circumference. The difference in serum ghrelin levels was still significant after taking into account fasting plasma glucose and waist circumference ($p < 0.05$).

Discussion

Obesity is one of the well-known risk factors for diabetes through increased insulin resistance[19]. However, not all obese individuals develop diabetes and the explanation is unclear. These individuals may have relatively normal insulin resistance or more efficient insulin secretion. Although there is a correlation of increased insulin resistance and increased body weight, there is also variability in the degree of insulin resistance in obese individuals[20]. Moreover, some obese individuals have normal insulin sensitivity while some individuals with insulin resistance are not obese. It is likely that obesity-related metabolic changes may not affect each individual similarly, depending not only on genetic and life style factors but also on how obesity is defined. The available data indicates that the BMI cutoff value for defining obesity based on the risk of metabolic derangements is different across ethnicities[21-23]. Furthermore, the regional distribution of adiposity also influences insulin resistance and metabolic effects[24]. The presented data, which comprises postmenopausal women, suggest difference in insulin resistance between obese subjects with and without diabetes despite similar BMI. The relatively normal insulin resistance and more efficient beta cell function, as demonstrated by HOMA-B, likely protect the development of diabetes in the non-diabetic group.

Adiponectin has been shown to play a role in modifying insulin sensitivity. Many studies have demonstrated negative correlation between adiponectin and obesity and the degree of hypoadiponectin was more closely related to the degree of insulin resistance, as calculated by insulin clamp, and hyperinsulinemia than the degree of adiposity[9,25,26]. There is also marked variations in adiponectin levels among obese subjects[7]. These findings are in agreement with the presented results that adiponectin levels are lower in the diabetic group, which has lower insulin sensitivity as shown by HOMA-S, than the non-diabetic group. The higher adiponectin level, which can possibly reflex the difference in activity or stage of adipocytes differentiation, is likely to protect some obese subjects from developing diabetes. A study in animals demonstrated that administration of adiponectin can improve insulin resistance[12]. Yet, there is no evidence of the direct effect of adiponectin on insulin resistance in humans but PPAR-g agonist, thiazolidinedione, increases adiponectin and improves insulin resistance[27]. These data imply the causal relationship between higher adiponectin and lower insulin resistance in humans. Elucidation of the causal pathways leading to higher adiponectin in obese non-diabetic subjects should prove to be helpful in the prevention of diabetes and probably other metabolic derangements associated with obesity.

Ghrelin has been demonstrated to play an important role in appetite control and energy homeostasis. Ghrelin stimulates food intake and is associated with negative energy balance[28] and obesity has been associated with low ghrelin levels[29]. The significance of ghrelin in insulin resistance and development of diabetes has received more attention recently. A study in women with polycystic ovary syndrome (PCOS) has found that serum ghrelin was significantly lower in insulin resistant woman with PCOS than lean and obese controls and was highly correlated with the degree of insulin resistance[18]. It has also been found that ghrelin levels were negatively associated with fasting insulin, elevated blood pressure and prevalence of diabetes[17]. The presented finding also showed lower ghrelin levels in obese diabetic subjects compared to those without diabetes. Although glucose and uncontrolled diabetes have been shown to lower plasma ghrelin[30], it is of note that the lower ghrelin in obese diabetic subjects was also apparent after plasma glucose and waist circumference was taken into account. To the authors' knowledge, the present study is the first to show higher ghrelin levels in obese non-diabetic subjects. Whether there is a causal relationship between higher ghrelin and the lack of diabetes in some obese subjects remain to be determined. A study by Tassone et al showed that acute administration of ghrelin in human obesity leads to increased glucose and reduced insulin levels, whereas the responses in the non-obese group showed increased glucose but no reduction of insulin level [31]. This finding implied that effect of ghrelin is altered in obese subjects and, ghrelin possibly play a role in metabolic consequence of obesity. There is also no physiologic or pharmacologic study of direct ghrelin effect on diabetes or insulin resistance, but it is possible that influence of ghrelin may be directly through adipogenic property or indirectly via the central nervous system.

Conclusion

There are significant differences of both insulin sensitivity and beta cell function between obese non-diabetic and diabetic women. Interestingly, obese non-diabetic women still have near normal insulin sensitivity suggesting there may be other factors influencing insulin sensitivity other than increased adiposity. The higher adiponectin levels found in the obese non-diabetic group may be one of protective factors in the development of diabetes. The authors also found significantly lower ghrelin levels in the obese diabetic group, but the physiological significance remains to be further investigated.

References

1. Kahn SE. The importance of the beta-cell in the pathogenesis of type 2 diabetes mellitus. Am J Med 2000; 108(Suppl 6a): 2S-8S.
2. Porte D Jr. Banting lecture 1990. Beta-cells in type II diabetes mellitus. Diabetes 1991; 40: 166-80.
3. Nesher R, Della CL, Litvin Y, Sinai J, Del Rio G, Pevsner B, et al. Insulin deficiency and insulin resistance in type 2 (non-insulin-dependent) diabetes: quantitative contributions of pancreatic and peripheral responses to glucose homeostasis. Eur J Clin Invest 1987; 17: 266-74.
4. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. J Clin Endocrinol Metab 2004; 89: 2548-56.
5. Rajala MW, Scherer PE. Minireview: The adipocyte - at the crossroads of energy homeostasis, inflammation, and atherosclerosis. Endocrinology 2003; 144: 3765-73.
6. Fasshauer M, Paschke R. Regulation of adipocytokines and insulin resistance. Diabetologia 2003; 46: 1594-603.
7. Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun 1999; 257: 79-83.
8. Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, et al. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab 2001; 86: 1930-5.
9. Diez JJ, Iglesias P. The role of the novel adipocytederived hormone adiponectin in human disease. Eur J Endocrinol 2003; 148: 293-300.
10. Maeda N, Shimomura I, Kishida K, Nishizawa H, Matsuda M, Nagaretani H, et al. Diet-induced insulin resistance in mice lacking adiponectin/ ACRP30. Nat Med 2002; 8: 731-7.
11. Kubota N, Terauchi Y, Yamauchi T, Kubota T, Moroi M, Matsui J, et al. Disruption of adiponectin causes insulin resistance and neointimal formation. J Biol Chem 2002; 277: 25863-6.
12. Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med 2001; 7: 941-6.
13. Meier U, Gressner AM. Endocrine regulation of energy metabolism: review of pathobiochemical and clinical chemical aspects of leptin, ghrelin,

adiponectin, and resistin. Clin Chem 2004; 50: 1511-25.
14. Shiiya T, Nakazato M, Mizuta M, Date Y, Mondal MS, Tanaka M, et al. Plasma ghrelin levels in lean and obese humans and the effect of glucose on ghrelin secretion. J Clin Endocrinol Metab 2002; 87: 240-4.
15. Leidy HJ, Gardner JK, Frye BR, Snook ML, Schuchert MK, Richard EL, et al. Circulating ghrelin is sensitive to changes in body weight during a diet and exercise program in normal-weight young women. J Clin Endocrinol Metab 2004; 89: 2659-64.
16. Choi KM, Lee J, Lee KW, Seo JA, Oh JH, Kim SG, et al. The associations between plasma adiponectin, ghrelin levels and cardiovascular risk factors. Eur J Endocrinol 2004; 150: 715-8.
17. Poykko SM, Kellokoski E, Horkko S, Kauma H, Kesaniemi YA, Ukkola O. Low plasma ghrelin is associated with insulin resistance, hypertension, and the prevalence of type 2 diabetes. Diabetes 2003; 52: 2546-53.
18. Schofl C, Horn R, Schill T, Schlosser HW, Muller MJ, Brabant G. Circulating ghrelin levels in patients with polycystic ovary syndrome. J Clin Endocrinol Metab 2002; 87: 4607-10.
19. Gerich JE. Is insulin resistance the principal cause of type 2 diabetes? Diabetes Obes Metab 1999; 1: 257-63.
20. Ferrannini E, Natali A, Bell P, Cavallo-Perin P, Lalic N, Mingrone G. Insulin resistance and hypersecretion in obesity. European Group for the Study of Insulin Resistance (EGIR). J Clin Invest 1997; 100: 1166-73.
21. Ko GT, Chan JC, Cockram CS, Woo J. Prediction of hypertension, diabetes, dyslipidaemia or albuminuria using simple anthropometric indexes in Hong Kong Chinese. Int J Obes Relat Metab Disord 1999; 23: 1136-42.
22. Deurenberg-Yap M, Chew SK, Lin VF, Tan BY, van Staveren WA, Deurenberg P. Relationships between indices of obesity and its co-morbidities in multi-ethnic Singapore. Int J Obes Relat Metab Disord 2001; 25: 1554-62.
23. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies Lancet 2004; 363: 157-63.
24. Garg A. Regional adiposity and insulin resistance. J Clin Endocrinol Metab 2004; 89: 4206-10.
25. Abbasi F, Chu JW, Lamendola C, McLaughlin T, Hayden J, Reaven GM, et al. Discrimination between obesity and insulin resistance in the relationship with adiponectin. Diabetes 2004; 53: 585-90.
26. Hotta K, Funahashi T, Bodkin NL, Ortmeyer HK, Arita Y, Hansen BC, et al. Circulating concentrations of the adipocyte protein adiponectin are decreased in parallel with reduced insulin sensitivity during the progression to type 2 diabetes in rhesus monkeys. Diabetes 2001; 50: 1126-33.
27. Yang WS, Jeng CY, Wu TJ, Tanaka S, Funahashi T, Matsuzawa Y, et al. Synthetic peroxisome proliferator-activated receptor-gamma agonist, rosiglitazone, increases plasma levels of adiponectin in type 2 diabetic patients. Diabetes Care 2002; 25: 376-80.
28. Zigman JM, Elmquist JK. Minireview: From anorexia to obesity - the yin and yang of body weight control. Endocrinology 2003; 144: 3749-56.
29. Tschop M, Weyer C, Tataranni PA, Devanarayan V, Ravussin E, Heiman ML. Circulating ghrelin levels are decreased in human obesity. Diabetes 2001; 50: 707-9.
30. Gelling RW, Overduin J, Morrison CD, Morton GJ, Frayo RS, Cummings DE, et al. Effect of uncontrolled diabetes on plasma ghrelin concentrations and ghrelin-induced feeding. Endocrinology 2004; 145: 4575-82.
31. Tassone F, Broglio F, Destefanis S, Rovere S, Benso A, Gottero C, et al. Neuroendocrine and metabolic effects of acute ghrelin administration in human obesity. J Clin Endocrinol Metab 2003; 88: 5478-83.

การคงสภาวะของความไวต่ออินซูลินในผู้หญิงอ้วนที่ไม่มีเบาหวาน

ฉัตรประอร งามอุโฆษ, สุวรรณี ชั้นประเสริฐโยธิน, กอบชัย พัววิไล, บุญส่ง องค์พิพัฒนกุล

วัตถุประสงค์: *เพื่อประเมินความไวต่ออินซูลิน การทำงานของบีตาเซลล์ของตับอ่อน และเปรียบเทียบระดับ adiponectin และ ghrelin ในเลือด ในผู้หญิงอ้วนที่มีและไม่มีเบาหวาน*

วัสดุและวิธีการ: *กลุ่มศึกษาประกอบด้วยผู้หญิงจำนวน 99 คนที่มี ดัชนีมวลกาย มากกว่า 25 กก./ม^2 และอายุมากกว่า 40 ปีและไม่เคยมีประวัติเบาหวานมาก่อน ผู้เข้าร่วมโครงการได้รับการทดสอบความทนทานน้ำตาล (oral glucose tolerance) และตรวจระดับน้ำตาล อินซูลิน adiponectin และ ghrelin ในเลือด ค่าผลการศึกษาแสดงเป็นค่าเฉลี่ย $\pm$ SEM*

ผลการศึกษา: *จากผลทดสอบความทนทานน้ำตาลพบว่า มีผู้ที่ไม่มีเบาหวาน (ND) 66 คน และมีเบาหวาน (D) 33 คน แม้ว่าระดับความอ้วนเท่ากันในทั้ง 2 กลุ่ม ผลการประเมินโดยวิธี HOMA (Homeostasis model assessment) แสดงว่ากลุ่มที่ไม่มีเบาหวานมีความไวต่ออินซูลิน (ND, 105.7 $\pm$ 6.4%; D, 62.3 $\pm$ 5.9%; $p < 0.001$) และการทำงานของบีตาเซลล์ (ND, 95.4 $\pm$ 3.0%; D, 79.0 $\pm$ 6.1%; $p < 0.01$) ที่ใกล้เคียงปกติ นอกจากนี้ กลุ่ม ND มีระดับ adiponectin ในเลือดสูงกว่า (ND, 8.3 $\pm$ 0.4 mg/ml; D, 6.3 $\pm$ 0.4 mg/ml; $p < 0.01$). ผู้เข้าร่วมโครงการที่มีเบาหวาน (ND, 1027.2 $\pm$ 32.0 pg/ml; D, 875.1 $\pm$ 34.6 pg/ml; $p < 0.05$)*

สรุป: *ผู้หญิงอ้วนที่ไม่มีเบาหวานนอกจากมีความผิดปกติของการทำงานของบีตาเซลล์น้อยกว่าและมีความไวต่ออินซูลินมากกว่าเมื่อเปรียบเทียบกับผู้หญิงอ้วนที่มีเบาหวาน ระดับ adiponectin ในเลือดที่สูงกว่าอาจจะมีบทบาทในการป้องกันเบาหวานในกลุ่มนี้ ส่วนความสำคัญของระดับghrelin ควรต้องทำการศึกษาเพิ่มเติม*