ORIGINAL ARTICLE
Korean J Intern Med 2012;27:66-71
http://dx.doi.org/10.3904/kjim.2012.27.1.66

pISSN 1226-3303 eISSN 2005-6648
http://www.kjim.or.kr

Associations among Body Mass Index, Insulin Resistance, and Pancreatic ß-Cell Function in Korean Patients with New-Onset Type 2 Diabetes

Jin Ook Chung, Dong Hyeok Cho, Dong Jin Chung, and Min Young Chung

Division of Endocrinology and Metabolism, Department of Internal Medicine, Chonnam National University Medical School, Gwangju, Korea

Background/Aims: We investigated the associations among body mass index (BMI), insulin resistance, and β-cell function in Korean patients newly presenting with type 2 diabetes.
Methods: In total, 132 patients with new-onset type 2 diabetes mellitus were investigated. A standard 75-g oral glucose tolerance test was performed, and the indices of insulin secretion and insulin resistance were calculated.
Results: A higher BMI was associated with higher homeostasis model assessment values for insulin resistance (HOMA-IR), homeostasis model assessment of β-cell function (HOMA-β), and insulinogenic index as well as lower levels of insulin sensitivity index composite (ISI_{comp}) and disposition index (DI). In multiple regression models, BMI had independent positive associations with HOMA-IR, ISI_{comp}, and HOMA-β and inverse associations with the DI.
Conclusions: Our results showed that BMI had independent positive associations with indices of insulin resistance and an inverse association with β-cell function adjusted for insulin resistance in Korean patients newly presenting with type 2 diabetes.

Keywords: Body mass index; Insulin resistance; Secretion; Diabetes mellitus, type 2

INTRODUCTION

Type 2 diabetes, a heterogeneous disorder characterized by impaired insulin secretion and insulin resistance [1], is closely related to obesity. Insulin resistance is a constant finding in patients with type 2 diabetes, and insulin resistance is present years before the onset of the disease [2]. Thus, when pancreatic β-cells fail to compensate for insulin resistance, hyperglycemia develops. However, an ethnic difference underlying the pathogenesis of type 2 diabetes mellitus appears to exist. Patients with type 2 diabetes in Korea are characteristically nonobese [3], and Korean patients may show different clinical characteristics compared to Western patients with type 2 diabetes. Mounting evidence indicates that insulin secretory defects may be predominant properties in Korean patients with type 2 diabetes [4,5]. Although several factors that lead to β-cell dysfunction have been suggested, the relationship between body mass index (BMI) and insulin secretion may be complicated by the impact of the associated insulin resistance on β-cell function. Several studies have reported that BMI was positively associated with endogenous

Received : July 1, 2011
Revised : July 20, 2011
Accepted: August 11, 2011

Correspondence to Min Young Chung, M.D.
Division of Endocrinology and Metabolism, Department of Internal Medicine, Chonnam National University Medical School, 8 Hak-dong, Dong-gu, Gwangju 501-757, Korea
Tel: 82-62-220-6500, Fax: 82-62-225-8578, E-mail: mychung@chonnam.ac.kr

insulin secretion as assessed by serum C-peptide response in type 2 diabetes [6,7]. In addition, BMI has been suggested to be positively associated with the decreased insulin sensitivity in type 2 diabetes mellitus [8]. Thus, because BMI is directly related to insulin resistance and type 2 diabetes mellitus, the association between BMI and insulin secretion may be a concern in Korean patients with type 2 diabetes [8]. However, few analyses have been conducted to assess the changes in insulin secretion depending on BMI in Koreans. In the present study, we investigated the associations among BMI, insulin resistance, and β-cell function in Korean patients with new-onset type 2 diabetes.

METHODS

This study, conducted from February 2009 to January 2011, was approved by the local ethics committee, and all participants gave informed consent. In total, 132 patients with new-onset type 2 diabetes mellitus were investigated. Diabetes was diagnosed based on the criteria of the American Diabetes Association [9]. To avoid severe β-cell dysfunction and to exclude any change in insulin secretion or resistance due to medication, subjects were confined to having a < 3-month history of hyperglycemia and no history of taking medication that affected glucose metabolism. Subjects with a family history of diabetes in first-degree relatives or with positive glutamic acid decarboxylase (GAD) antibodies were also excluded. BMI was calculated as weight (kg) divided by the square of height (m^2). A standard 75-g oral glucose tolerance test (OGTT) was performed after a 10-hour overnight fast. Plasma samples were obtained at -10, -5, 0, 30, 60, 90, and 120 minutes to measure glucose (Hitachi 7600-110, Hitachi Co., Tokyo, Japan) and insulin (IRMA kit, Dainabot, Tokyo, Japan) concentrations. The indices of insulin secretion and insulin resistance were calculated as follows [10-13]:

Insulinogenic index (IGI) = $(I_{30} - I_0) / (G_{30} - G_0)$
Homeostasis model assessment of β-cell function (HOMA-β) = $20 \times I_0 / (G_0 - 3.5)$
Homeostasis model assessment of insulin resistance (HOMA-IR) = $I_0 \times G_0 / 22.5$
Insulin sensitivity index composite (ISI_{comp}) = $10{,}000 / (G_0 \cdot I_0 \cdot G_m \cdot I_m)^{1/2}$
Disposition index (DI) = IGI / HOMA-IR

where I_0 is fasting plasma insulin, G_0 is fasting plasma glucose, I_{30} is insulin 30 minutes after glucose load, G_{30} is plasma glucose 30 minutes after glucose load, G_m is the mean glucose during the OGTT, and I_m is the mean insulin during the OGTT.

Glycated hemoglobin (HbA_{1C}) (HLC-723-GHbV, Tosoh, Tokyo, Japan), total cholesterol, high-density lipoprotein cholesterol, triglycerides (AU5400, Olympus, Tokyo, Japan), and free fatty acids (NEFA-HR kit, Wako, Osaka, Japan) were also measured.

Statistical analysis

Statistical analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Data are expressed as the mean ± SD unless otherwise stated. Variables not normally distributed were log-transformed before analysis. Linear trends were tested for BMI in the regression models. Using the logistic regression model, multivariate analyses were performed to analyze the associations among BMI, insulin resistance, and β-cell function. A p value of < 0.05 was considered statistically significant.

RESULTS

Table 1 shows the characteristics of the patients with type 2 diabetes in this study. The mean age of the subjects was 54.8 ± 9.7 years, and the mean BMI was 25.0 ± 1.1 kg/m^2. The mean concentration of fasting plasma glucose was 7.26 ± 1.32 mmol/L, and the median value of fasting plasma insulin was 43.0 pmol/L. The median values of HOMA-IR and ISI_{comp} were 1.85 and 4.85, respectively. The respective median values of HOMA-β, IGI, and DI were 34.17, 2.70, and 1.41. Table 2 shows the characteristics of the patients with type 2 diabetes according to the tertiles of BMI. As BMI increased, the patients had higher concentrations of triglycerides, fasting plasma insulin, and plasma insulin 2 hours after the glucose load. In addition, the patients exhibited higher values of HOMA-IR and lower levels of ISI_{comp} as well as higher levels of HOMA-β and IGI. However, the DI values decreased as BMI increased.

Table 1. Clinical and metabolic characteristics of the subjects

Variables	Values
Total	132
Age, yr	54.8 ± 9.7
Male, n (%)	70 (53.0)
BMI, kg/m^2	25.0 ± 1.1
Systolic BP, mmHg	132.5 ± 18.1
Diastolic BP, mmHg	79.7 ± 11.7
Total cholesterol, mmol/L	5.35 ± 1.12
Triglyceride, mmol/L	1.70 (1.33)
HDL-cholesterol, mmol/L	1.27 ± 0.30
Free fatty acid, nmol/L	720.0 (441.0)
HbA_{1C}, %	7.2 ± 0.9
Fasting glucose, mmol/L	7.26 ± 1.32
Fasting insulin, pmol/L	43.0 (48.6)
2-hr glucose, mmol/L	14.14 ± 3.28
2-hr insulin, pmol/L	234.0 (256.2)
HOMA-IR	1.85 (2.66)
ISI_{comp}	4.85 (4.96)
HOMA-β	34.17 (46.51)
IGI	2.70 (3.05)
DI	1.41 (1.91)

Values are presented as mean ± SD or median (interquartile range).

BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; HbA_{1c}, hemoglobin glycation; HOMA-IR, homeostasis model assessment of insulin resistance; ISI_{comp}, insulin sensitivity index composite; HOMA-β, homeostasis model assessment of β-cell function; IGI, insulinogenic index; DI, disposition index.

When multiple regression modeling was performed to determine the associations among BMI, insulin resistance, and β-cell function, BMI was a positive correlate of log-transformed HOMA-IR and a negative correlate of log-transformed ISI_{comp} (Table 3). In addition, BMI was positively associated with log-transformed HOMA-β. However, BMI was a negative correlate of log-transformed DI.

DISCUSSION

We found that in addition to a higher degree of insulin resistance, a higher BMI was associated with higher values of HOMA-β and IGI in patients with type 2 diabetes. However, the higher BMI was associated with a lower DI. Thus, our results demonstrated that BMI had independent inverse associations with β-cell function adjusted for insulin resistance as well as independent positive associations with indices of insulin resistance in Korean patients newly presenting with type 2 diabetes.

Various methods have been proposed for estimating insulin sensitivity and insulin secretion *in vivo*. The hyperinsulinemic euglycemic clamp is a standard tool for estimating insulin sensitivity, but the procedure is complex in clinical practice [14,15]. The insulin sensitivity index, an ISI_{comp}, obtained from the OGTT is a good surrogate measure of whole-body insulin sensitivity compared to the euglycemic clamp study [11]. The insulinogenic index, calculated as the ratio of the increment of plasma insulin to plasma glucose concentration 30 minutes after the OGTT, provides a parameter of early insulin response during the test [12]. The indices from OGTT data yield measures of dynamic insulin secretion and insulin sensitivity, whereas HOMA offers steady-state measures of insulin secretion and insulin sensitivity in the basal states. HOMA-IR is a tool to estimate insulin sensitivity, which is closely correlated with the insulin resistance index as assessed by the euglycemic clamp [10]. HOMA-β provides good β-cell function estimation to prevailing glucose levels compared to the frequent sampling in the intravenous glucose tolerance test or the hyperglycemic clamp [10,16].

With changes to modern lifestyles in recent years, the prevalence of type 2 diabetes has increased in Korea. An increasing BMI is known to be a contributing factor for the development of type 2 diabetes mellitus in Korea as well as in other countries [17,18]. Sung et al. [19] reported that obesity is a risk factor for type 2 diabetes mellitus, and that the relative risks for diabetes mellitus in subjects with a BMI of > 27 kg/m^2 were significantly higher than those with a BMI of < 23 kg/m^2. Campbell and Carlson [20] demonstrated that BMI was negatively correlated with glucose disposal and positively associated with glucose production in type 2 diabetes mellitus. Chang et al. [8] also reported that BMI was the most important determinant of insulin resistance, even in nonobese patients with type 2 diabetes mellitus. In the present study, a higher BMI was associated with decreased insulin sensitivity, which supports the positive relationship between BMI and insulin resistance in type 2 diabetes mellitus [8].

As insulin resistance increases, β-cells compensate by

Table 2. Clinical and metabolic characteristics of the patients with type 2 diabetes according to body mass index

BMI, kg/m^2	Tertile 1 (BMI ≤ 23.7)	Tertile 2 (23.7 < BMI ≤ 25.7)	Tertile 3 (25.7 < BMI)	*p* for trend
No.	43	45	44	
Age, yr	56.9 ± 9.7	54.2 ± 9.4	53.5 ± 10.1	0.312
Male, n (%)	23 (53.4)	23 (51.1)	24 (54.5)	0.920
BMI, kg/m^2	22.0 ± 1.0	24.7 ± 0.6	28.3 ± 2.1	< 0.001
Systolic BP, mmHg	132.7 ± 22.6	131.0 ± 14.7	132.7 ± 17.5	0.901
Diastolic BP, mmHg	77.1 ± 13.9	81.0 ± 10.4	80.0 ± 11.2	0.232
Total cholesterol, mmol/L	5.06 ± 1.02	5.66 ± 1.20	5.24 ± 1.12	0.534
Triglyceride, mmol/L (%)	1.30 (0.98)	1.41 (1.18)	2.30 (1.28)	0.026
HDL-cholesterol, mmol/L	1.31 ± 0.34	1.31 ± 0.28	1.17 ± 0.30	0.086
Free fatty acid, nmol/L (%)	631.5 (596.2)	709.5 (512.5)	767.0 (729.0)	0.127
HbA_{1C}, %	7.1 ± 0.9	7.1 ± 0.8	7.3 ± 1.2	0.606
Fasting glucose, mmol/L	7.16 ± 1.35	7.19 ± 1.18	7.50 ± 1.22	0.108
Fasting insulin, pmol/L	29.8 (27.0)	42.3 (48.6)	63.1 (76.0)	< 0.001
2-hr glucose, mmol/L	14.61 ± 3.28	13.75 ± 2.91	14.52 ± 3.38	0.909
2-hr insulin, pmol/L	214.6 (141.6)	215.9 (186.8)	348.6 (391.0)	0.024
HOMA-IR	1.38 (1.32)	1.90 (2.71)	3.06 (3.03)	< 0.001
ISI_{comp}	6.23 (5.12)	4.51 (5.00)	3.02 (3.31)	< 0.001
HOMA-β	23.87 (28.40)	34.17 (40.12)	43.3 (74.98)	0.002
IGI	2.10 (2.45)	2.60 (2.10)	3.40 (4.07)	0.036
DI	1.94 (2.44)	1.43 (1.97)	1.11 (1.54)	0.022

Values are presented as mean ± SD or median (interquartile range).

BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; HbA_{1c}, hemoglobin glycation; HOMA-IR, homeostasis model assessment of insulin resistance; ISI_{comp}, insulin sensitivity index composite; HOMA-β, homeostasis model assessment of β-cell function; IGI, insulinogenic index; DI, disposition index.

Table 3. Associations among body mass index, insulin resistance, and β-cell function in subjects with type 2 diabetes as assessed using multivariate linear regression models

	Standard regression coefficient	R^2 (adjusted R^2)	F value	*p* value
HOMA-IR BMI	0.574	0.329 (0.275)	6.116	< 0.001
ISI_{comp} BMI	-0.539	0.320 (0.265)	5.875	< 0.001
HOMA-β BMI	0.378	0.191 (0.126)	2.954	0.001
IGI BMI	0.212	0.213 (0.150)	3.383	0.060
DI BMI	-0.314	0.260 (0.200)	4.285	0.005

Log-transformed variables were used for analysis.

All values were adjusted for age, gender, systolic blood pressure, HbA_{1C}, triglycerides, and free fatty acids.

HOMA-IR, homeostasis model assessment of insulin resistance; BMI, body mass index; ISI_{comp}, insulin sensitivity index composite; HOMA-β, homeostasis model assessment of β-cell function; IGI, insulinogenic index; DI, disposition index.

increasing insulin secretion, resulting in compensatory hyperinsulinemia and the maintenance of normal glucose tolerance [1]. In an autopsy-based study of individuals with normal glucose tolerance, a greater β-cell volume was found in obese individuals [21]. Yoon et al. [22] reported that type 2 diabetes was associated with reduced β-cell mass compared to BMI-matched normal subjects, but BMI was also positively correlated with relative β-cell volume in Korean patients with type 2 diabetes. These results suggest that increased BMI may be related to

increased β-cell mass, but the impact of BMI on β-cell function is not fully understood in patients with type 2 diabetes. Several previous studies have suggested that the contribution of insulin resistance and insulin secretory dysfunction might differ in nonobese and obese subjects. Pontiroli et al. [23] reported that patients with type 2 diabetes who had a relatively normal body weight had lower plasma insulin or C-peptide levels in the postprandial state or after a glucagon stimulatory test compared to obese subjects with diabetes. Arner et al. [24] reported that nonobese Swedes with type 2 diabetes had impairment in insulin secretion rather than decreased insulin sensitivity, whereas obese patients with diabetes had both impaired insulin action and secretion. Park et al. [3] reported that nonobese Korean patients with type 2 diabetes had lower levels of fasting serum C-peptide compared to obese subjects. Chang et al. [8] also reported that insulin-sensitive patients with diabetes were associated with low HOMA-β. In the present study, patients with type 2 diabetes who had higher BMI also had increased values of HOMA-β and IGI. In addition, in the multivariate analysis and for indices of insulin resistance, BMI was a positive association for HOMA-β or IGI, similar to previous studies [6,7,22,25]. However, as reported by Kahn et al. [13], evaluation of β-cell function may require adjustment for insulin sensitivity. The DI, the composite measure of β-cell function, may reflect the true underlying cellular function. In the present study, as BMI increased, the DI decreased. In the multivariate analysis, BMI had an independent inverse association with the DI. Thus, our results showed that when insulin sensitivity was also considered, BMI might be inversely associated with β-cell function, although BMI had a positive association with relative β-cell volume in Korean patients with type 2 diabetes as reported by Yoon et al. [22]. Thus, our findings may suggest that increasing BMI possibly contributes to further deterioration of β-cell function with associated increasing insulin resistance regardless of the presence of obesity in Korean patients with type 2 diabetes. However, further investigations are required to evaluate the direct relationship between β-cell function and mass with increasing BMI in such patients.

In conclusion, our results show that BMI had positive associations with indices of insulin resistance and inverse associations with β-cell function adjusted for insulin resistance in Korean patients newly presenting with type 2 diabetes. Thus, in clinical practice, managing body weight may be important even in nonobese patients with type 2 diabetes. Further studies are necessary to investigate the direct associations between β-cell function and β-cell mass with increasing BMI in nonobese and obese patients with type 2 diabetes.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Ferrannini E. Insulin resistance versus insulin deficiency in non-insulin-dependent diabetes mellitus: problems and prospects. Endocr Rev 1998;19:477-490.
2. DeFronzo RA. Lilly lecture 1987. The triumvirate: beta-cell, muscle, liver. A collusion responsible for NIDDM. Diabetes 1988;37:667-687.
3. Park JY, Lee KU, Kim CH, et al. Past and current obesity in Koreans with non-insulin-dependent diabetes mellitus. Diabetes Res Clin Pract 1997;35:49-56.
4. Rhee SY, Kim JY, Chon S, et al. The changes in early phase insulin secretion in newly diagnosed, drug naive Korean prediabetes subjects. Korean Diabetes J 2010;34:157-165.
5. Kim DJ, Lee MS, Kim KW, Lee MK. Insulin secretory dysfunction and insulin resistance in the pathogenesis of Korean type 2 diabetes mellitus. Metabolism 2001;50:590-593.
6. Funakoshi S, Fujimoto S, Hamasaki A, et al. Analysis of factors influencing pancreatic beta-cell function in Japanese patients with type 2 diabetes: association with body mass index and duration of diabetic exposure. Diabetes Res Clin Pract 2008;82:353-358.
7. Juang JH, Huang HS, Huang MJ. C-peptide response to glucagon in patients with non-insulin-dependent diabetes mellitus. J Formos Med Assoc 1992;91:491-496.
8. Chang SA, Kim HS, Yoon KH, et al. Body mass index is the most important determining factor for the degree of insulin resistance in non-obese type 2 diabetic patients in Korea. Metabolism 2004;53:142-146.
9. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2008;31 Suppl 1:S55-S60.
10. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-419.
11. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the eugly-

cemic insulin clamp. Diabetes Care 1999;22:1462-1470.
12. Seltzer HS, Allen EW, Herron AL Jr, Brennan MT. Insulin secretion in response to glycemic stimulus: relation of delayed initial release to carbohydrate intolerance in mild diabetes mellitus. J Clin Invest 1967;46:323-335.
13. Kahn SE, Prigeon RL, McCulloch DK, et al. Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects: evidence for a hyperbolic function. Diabetes 1993;42:1663-1672.
14. Bergman RN, Phillips LS, Cobelli C. Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and beta-cell glucose sensitivity from the response to intravenous glucose. J Clin Invest 1981;68:1456-1467.
15. Finegood DT, Hramiak IM, Dupre J. A modified protocol for estimation of insulin sensitivity with the minimal model of glucose kinetics in patients with insulin-dependent diabetes. J Clin Endocrinol Metab 1990;70:1538-1549.
16. Hermans MP, Levy JC, Morris RJ, Turner RC. Comparison of tests of beta-cell function across a range of glucose tolerance from normal to diabetes. Diabetes 1999;48:1779-1786.
17. Kim SM, Lee JS, Lee J, et al. Prevalence of diabetes and impaired fasting glucose in Korea: Korean National Health and Nutrition Survey 2001. Diabetes Care 2006;29:226-231.
18. Qiao Q, Nyamdorj R. Is the association of type II diabetes with waist circumference or waist-to-hip ratio stronger than that with body mass index? Eur J Clin Nutr 2010;64:30-34.
19. Sung EJ, Sunwoo S, Kim SW, Kim YS. Obesity as a risk factor for non-insulin-dependent diabetes mellitus in Korea. J Korean Med Sci 2001;16:391-396.
20. Campbell PJ, Carlson MG. Impact of obesity on insulin action in NIDDM. Diabetes 1993;42:405-410.
21. Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. Diabetes 2003;52:102-110.
22. Yoon KH, Ko SH, Cho JH, et al. Selective beta-cell loss and alpha-cell expansion in patients with type 2 diabetes mellitus in Korea. J Clin Endocrinol Metab 2003;88:2300-2308.
23. Pontiroli AE, Calderara A, Maffi P, et al. Secondary failure to oral hypoglycaemic agents in non-obese patients with non-insulin-dependent diabetes is related to reduced insulin release. Diabete Metab 1989;15:79-84.
24. Arner P, Pollare T, Lithell H. Different aetiologies of type 2 (non-insulin-dependent) diabetes mellitus in obese and non-obese subjects. Diabetologia 1991;34:483-487.
25. Roy MN, Biswas KB, Siddiqua N, Arslan MI, Ali L. Determinants of insulin secretion and sensitivity in Bangladeshi type 2 diabetic subjects. Metab Syndr Relat Disord 2007;5:275-281.