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

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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\textsubscript{comp}) and disposition index (DI). In multiple regression models, BMI had independent positive associations with HOMA-IR, ISI\textsubscript{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...
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 (m²). 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) = (I₃₀ - I₀) / (G₃₀ - G₀)

Homeostasis model assessment of β-cell function (HOMA-β) = 20 × I₀ / (G₀ - 3.5)

Homeostasis model assessment of insulin resistance (HOMA-IR) = I₀ × G₀ / 22.5

Insulin sensitivity index composite (ISIcomp) = 10,000 / (G₀·I₀·Gₘ·Iₘ)½

Disposition index (DI) = IGI / HOMA-IR

where I₀ is fasting plasma insulin, G₀ is fasting plasma glucose, Iₚ₀ is insulin 30 minutes after glucose load, Gₚ₀ is plasma glucose 30 minutes after glucose load, Gₘ is the mean glucose during the OGTT, and Iₘ is the mean insulin during the OGTT.

Glycated hemoglobin (HbA₁c) (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/m². 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 ISIcomp 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 ISIcomp as well as higher levels of HOMA-β and IGI. However, the DI values decreased as BMI increased.
When multiple regression modeling was performed to determine the associations among BMI, insulin resistance, and \( \beta \)-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-\( \beta \). 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-\( \beta \) 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 \( \beta \)-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 assessed by the euglycemic clamp [10]. HOMA-\( \beta \) provides good \( \beta \)-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, \( \beta \)-cells compensate by

| 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, mmol/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-\( \beta \) | 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-\( \beta \), homeostasis model assessment of \( \beta \)-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

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

| BMI, kg/m² | Tertile 1 (BMI ≤ 23.7) | Tertile 2 (23.7 < BMI ≤ 25.7) | Tertile 3 (25.7 < BMI) | p for trend |
|------------|-------------------------|-------------------------------|------------------------|-------------|
| No.        | 43                      | 45                            | 44                     | 0.312       |
| Age, yr    | 56.9 ± 9.7              | 54.2 ± 9.4                    | 53.5 ± 10.1            | 0.920       |
| Male, n (%)| 23 (53.4)               | 23 (51.1)                     | 24 (54.5)              | < 0.001     |
| BMI, kg/m² | 22.0 ± 1.0              | 24.7 ± 0.6                    | 28.3 ± 2.1             | 0.901       |
| Systolic BP, mmHg | 132.7 ± 22.6  | 131.0 ± 14.7                  | 132.7 ± 17.5           | 0.232       |
| Diastolic BP, mmHg | 77.1 ± 13.9 | 81.0 ± 10.4                   | 80.0 ± 11.2            | 0.534       |
| Total cholesterol, mmol/L | 5.06 ± 1.0 | 5.66 ± 1.2                     | 5.24 ± 1.1             | 0.026       |
| Triglyceride, mmol/L (%) | 1.30 (0.98) | 1.41 (1.18)                   | 2.30 (1.28)            | 0.086       |
| HDL-cholesterol, mmol/L | 1.31 ± 0.34 | 1.31 ± 0.28                    | 1.17 ± 0.30            | 0.012       |
| Free fatty acid, nmol/L (%) | 631.5 (596.2) | 709.5 (512.5)                  | 767.0 (729.0)          | 0.127       |
| HbA₁c, %  | 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           | 0.012       |
| 2-hr insulin, pmol/L | 214.6 (141.6) | 215.9 (186.8)                  | 348.6 (391.0)          | 0.242       |
| 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; HbA₁c, 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 | R² (adjusted R²) | 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, HbA₁c, 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.

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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.

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