Recent Glycemia Is a Major Determinant of β-Cell Function in Type 2 Diabetes Mellitus

Ji Yoon Kim, Jiyoon Lee, Sin Gon Kim, Nam Hoon Kim

Diabetes Metab J Published online Jun 17, 2024 | https://doi.org/10.4093/dmj.2023.0359

**Highlights**

- We assessed the impact of clinical factors on β-cell function in T2DM.
- Recent HbA1c was the key factor affecting β-cell function.
- β-cell function was flexible and dependent on recent HbA1c.
- Recent glycemia, rather than other factors, primarily determines β-cell function in T2DM.

**Conclusion**

β-cell function declines over time; however, it is flexible and largely affected by recent glycemia in patients with T2DM.
Recent Glycemia Is a Major Determinant of β-Cell Function in Type 2 Diabetes Mellitus

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Background: Progressive deterioration of β-cell function is a characteristic of type 2 diabetes mellitus (T2DM). We aimed to investigate the relative contributions of clinical factors to β-cell function in T2DM.

Methods: In a T2DM cohort of 470 adults (disease duration 0 to 41 years), β-cell function was estimated using insulinogenic index (IGI), disposition index (DI), oral disposition index (DIO), and homeostasis model assessment of β-cell function (HOMA-B) derived from a 75 g oral glucose tolerance test (OGTT). The relative contributions of age, sex, disease duration, body mass index, glycosylated hemoglobin (HbA1c) levels (at the time of the OGTT), area under the curve of HbA1c over time (HbA1c AUC), coefficient of variation in HbA1c (HbA1c CV), and antidiabetic agents use were compared by standardized regression coefficients. Longitudinal analyses of these indices were also performed.

Results: IGI, DI, DIO, and HOMA-B declined over time (P<0.001 for all). Notably, HbA1c was the most significant factor affecting IGI, DI, DIO, and HOMA-B in the multivariable regression analysis. Compared with HbA1c ≥9%, DI was 1.9-, 2.5-, 3.7-, and 5.5-fold higher in HbA1c of 8%–<9%, 7%–<8%, 6%–<7%, and <6%, respectively, after adjusting for confounding factors (P<0.001). Conversely, β-cell function was not affected by the type or duration of antidiabetic agents, HbA1c AUC, or HbA1c CV. The trajectories of the IGI, DI, DIO, and HOMA-B mirrored those of HbA1c.

Conclusion: β-Cell function declines over time; however, it is flexible, being largely affected by recent glycemia in T2DM.

Keywords: Diabetes mellitus, type 2; Glycemic control; Insulin secretion

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance and a progressive decline in pancreatic β-cell function [1]. The pathophysiology and progressive nature of T2DM have been well described in terms of the interplay between insulin resistance and β-cell dysfunction. Once insulin resistance develops, pancreatic β-cells increase insulin secretion to offset insulin resistance. However, when pancreatic β-cells fail to compensate for increased insulin resistance, T2DM develops [2]. Notably, β-cell dysfunction worsens over time, determines the rate of T2DM progression, and results in the loss of glycemic control [3,4].

Multiple factors have been implicated in impairing β-cell function [3,5]. Specifically, age and genetic predisposition are associated with β-cell dysfunction [3,5]. Evidence for the detrimental effect of hyperglycemia on β-cell function, has been supported by in vivo, in vitro, and epidemiologic studies [6-10]. Additionally, the critical role of lipotoxicity, chronic elevation of the plasma free fatty acid concentration, and lipid accumulation in β-cells in the impairment of insulin secretion have been described [11-14]. Insulin resistance and consequently increased islet amyloid polypeptide are involved in β-cell dysfunction [15]. Randomized controlled trials have confirmed that specific types of antidiabetic agents also affect β-cell function [16].
However, the relative contribution of these factors to β-cell dysfunction is not well understood. The identification of the dominant factors affecting β-cell dysfunction will be helpful in understanding the pathogenesis of diabetes and β-cell dysfunction. Therefore, we aimed to examine the progressive decline in β-cell function in a cohort of patients with T2DM and compare the relative importance of factors affecting insulin secretion and pancreatic β-cell function among these patients.

**METHODS**

**Data source and study participants**

Adults aged ≥19 years undergoing a 75 g oral glucose tolerance test (OGTT) from two separate cohorts of prediabetes and T2DM were included in the study. The first cohort was a single-center, prospective, observational cohort of people with glucose intolerance (Anam Diabetes Observational Study [ADIOS]), comprising participants aged ≥19 years who were newly diagnosed with prediabetes and T2DM between March 2017 and June 2022. The participants regularly visited the Korea University Anam Hospital and completed questionnaires, anthropometric and blood pressure measurements, and blood tests, including a 75 g OGTT annually for 5 years. The questionnaires included information on age, sex, concurrent drug use, and comorbidities, such as hypertension, dyslipidemia, and cardiovascular diseases. Anthropometric measurements included height and weight, while blood tests included glycosylated hemoglobin (HbA1c) levels, creatinine levels, and OGTT with insulin levels. During the OGTT, serum glucose and insulin levels were measured at 0 (fasting), 30, and 120 minutes after 75 g glucose loading.

The second cohort was a retrospectively constructed T2DM cohort with diabetes duration ranging from 6 months to 41 years, who completed the OGTT between December 2020 to June 2022. At the time of the OGTT, the participants completed questionnaires on the duration of diabetes, anthropometric measurements, and blood tests as described above. Furthermore, past records of HbA1c levels and the use of antidiabetic agents until the date of the 75 g OGTT were identified using a common data model database from January 2002.

Supplementary Fig. 1 illustrates the flow diagram of the study subject selection. We excluded individuals using insulin at the time of the OGTT or those with an estimated glomerular filtration rate <60 mL/min/1.73 m², as circulating insulin levels could be affected by insulin administration or impaired kidney function. Subjects without T2DM (n=55) were compared with patients with T2DM in scatter plot analyses of β-cell function measures and were subsequently excluded from the other analyses. Finally, 470 patients with T2DM were included in this study.

This study was approved by the Institutional Review Board of Korea University Anam Hospital (IRB number 2017AN00050). Written informed consent was obtained from participants.

**Assessment of insulin secretion and β-cell function**

As insulin secretion is dependent on blood glucose level, we selected indices considering both the blood glucose levels and circulating insulin levels to estimate β-cell function. β-Cell function was estimated using 75 g OGTT-derived indices, including the insulingenic index (IGI), disposition index (DI), oral disposition index (DIO), and homeostasis model assessment of β-cell function (HOMA-B). IGI, which represents an early insulin response, was calculated as (insulin 30 min−insulin 0 min [μIU/mL]/(glucose 30 min−glucose 0 min [mg/dL]) [17]. Insulin sensitivity was estimated by the Matsuda insulin sensitivity index (ISI), calculated as 10,000/(fasting glucose [mg/dL]×fasting insulin [μIU/mL]×mean glucose [mg/dL]×mean insulin [μIU/mL])1/2 [18]. DI, which reflects β-cell function relative to insulin sensitivity, was calculated as IGI×ISI [19]. DIO, which provides a measure of β-cell function adjusted for insulin sensitivity, was calculated as IGI×(1/fasting insulin [μIU/mL]) [20]. HOMA-B was calculated as (360×fasting insulin [μIU/mL]/(fasting glucose [mg/dL]−63) [21]. Additionally, homeostasis model assessment for insulin resistance (HOMA-IR) was calculated as (fasting glucose [mg/dL]×fasting insulin [μIU/mL]/405) [21].

Plasma glucose was measured by the glucose oxidase method using a Beckman Coulter chemistry analyzer AU5800 (Beckman Coulter, Brea, CA, USA), and plasma insulin was measured by radioimmunoassay.

**Clinical and glycemic variables associated with β-cell function**

Potential variables considered to affect insulin secretion and β-cell function included age, sex, duration of diabetes, body mass index (BMI), type and duration of antidiabetic agents, HbA1c level (at the time of OGTT), area under the curve of HbA1c over time (HbA1c AUC), and coefficient of variation in HbA1c (HbA1c CV). Antidiabetic agents included metformin, sulfonylurea, glinide, glucagon-like peptide-1 receptor agonist
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Diabetes Metab J 2024 Forthcoming. Posted online 2024 https://e-dmj.org

(GLP-1RA), dipeptidyl peptidase-4 (DPP-4) inhibitor, thiazolidinedione (TZD), sodium-glucose cotransporter 2 (SGLT2) inhibitor, alpha-glucosidase inhibitor, and insulin. The duration of antidiabetic agent use was determined by adding the length of the prescription, and the HbA1c AUC was calculated using all HbA1c values during the study period (from January 2002 to the time of the measurement of the OGTT). The HbA1c CV was calculated as 100×(standard deviation [SD] of HbA1c values during the study period/mean HbA1c values during the study period). Additionally, we estimated the association between insulin indices and systolic blood pressure, diastolic blood pressure, hypertension, dyslipidemia, and cardiovascular disease to identify whether these variables also affected β-cell function.

Overall statistical analysis

Data are presented as mean and SD or median and interquartile range (IQR) for continuous variables. Categorical data are presented as numbers and percentages (%). Variables with a right-skewed distribution were logarithmically transformed and presented as geometric mean and SD. As patients from ADIOS cohort received OGTT repetitively, a linear mixed-effects model was used to handle repeated outcomes.

Cross-sectional analyses

Both the scatter plot of β-cell function according to the duration of diabetes and regression analysis for the association of clinical and glycemic factors with β-cell function measures were performed using the cross-sectional data of the two separate cohorts (n=470). Log-transformed IGI, DI, DIo, and HOMA-B according to the duration of diabetes were graphically presented as scatter plots to investigate the association between β-cell function and diabetes duration. Annual changes in these indices were calculated using simple linear regression analysis.

To identify the associations of β-cell function with glycemic and clinical factors, univariable and multivariable regression analyses in a linear mixed model were conducted. The dependent variables were the log-transformed IGI, DI, DIo, and HOMA-B values, while the predefined independent variables were age, sex (male as a reference group), duration of diabetes, BMI, duration of antidiabetic agent use by class, HbA1c level at the time of OGTT, HbA1c AUC, and HbA1c CV. The relative contributions of these factors to β-cell function measures were compared by estimating standardized regression coefficient (β). Moreover, we evaluated the association between β-cell function measures and HbA1c levels at the time of the OGTT using multivariable regression analyses after categorizing HbA1c levels into groups. As a reference for HbA1c ≥9%, the adjusted rate ratio of IGI, DI, DIo, and HOMA-B was calculated based on HbA1c levels of 8%–<9%, 7%–<8%, 6%–<7%, and <6%. The analyses were adjusted for age per 1 year, sex (male as a reference group), duration of diabetes per 1 year, and BMI per 1 kg/m².

Longitudinal analyses

Further analyses were performed on patients newly diagnosed with T2DM who underwent repetitive OGTT annually (from the ADIOS cohort, n=151). First, annual changes in these indices were calculated using a linear mixed model. Next, HbA1c was categorized into groups (≥8%, 7%–<8%, 6%–<7%, and <6%) at each visit. The means of the log-transformed IGI, DI, DIo, and HOMA-B according to these HbA1c categories were estimated by regression analysis.

Among patients who had records of HbA1c, glucose, and insulin levels at 0, 30, and 120 minutes after 75 g of glucose loading without missing data for 3 consecutive years (n=25), the trajectories of mean IGI, DI, DIo, and HOMA-B were drawn according to the HbA1c trajectory pattern. The trajectory of HbA1c was classified into three groups: improvement in HbA1c (n=8), rebound in HbA1c (n=4), and no significant change in HbA1c (n=13). A linear mixed-effects model was used to identify whether the trajectory of insulin indices differed by HbA1c trajectory groups.

All statistical analyses were performed using the SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical significance was set at a two-sided P<0.05.

RESULTS

Characteristics of study participants

Table 1 presents the participant characteristics at the OGTT measurement (n=470). Their mean age was 59±12 years, and 38.5% were female. The median duration of T2DM was 8 years (IQR, 0 to 14), and the mean HbA1c level and BMI were 7.2%±1.2% and 26.0±3.8 kg/m², respectively.

Supplementary Table 1 presents the previous use of antidiabetic agents. Metformin was the most commonly used drug (73.2%), with the median duration of use of 74.3 months (IQR, 34.8 to 111.6), followed by sulfonylureas (47.2%), DPP-4 inhibitors (43.2%), TZD (28.9%), and SGLT2 inhibitors (28.7%).
β-Cell insulin secretory function according to diabetes duration

Fig. 1 displays a scatter plot of the log-transformed IGI, DI, DIO, and HOMA-B values according to the duration of T2DM. Patients without T2DM in the ADIOS cohort were compared. The ADIOS cohort was for patients with newly diagnosed diabetes or prediabetes. However, upon OGTT and HbA1c testing at baseline, four individuals were classified as having normal glucose tolerance (NGT). These four NGT subjects, along with 51 patients of prediabetes, were compared with 470 patients with T2DM.

Patients with T2DM had lower β-cell function than did those with prediabetes or NGT. Among patients with T2DM, β-cell function decreased with disease duration, with annual
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Clinial and glycemic factors and their associations with β-cell function

To assess the relative contribution of clinical and glycemic factors on β-cell function, univariable and multivariable analyses were performed. In the univariable analyses (Supplementary Table 2), HbA1c level (at the time of the OGTT), duration of diabetes, HbA1c AUC, HOMA-IR, ISI, and duration of use of several classes of antidiabetic agents were significantly associated with log(IGI), log(DI), log(DIO), and log(HOMA-B). Factors associated with glycemic burden were generally negatively associated with β-cell function measures. Systolic blood pressure, diastolic blood pressure, hypertension, dyslipidemia, or cardiovascular disease did not significantly affect the measures of β-cell function.

In multivariable analyses (Fig. 2, Supplementary Fig. 2), HbA1c level was consistently the most significant factor affecting log(IGI), log(DI), log(DIO), and log(HOMA-B), demon-

Fig. 1. Scatter plot of log-transformed (A) insulinogenic index (IGI), (B) disposition index (DI), (C) oral disposition index (DIO), and (D) homeostasis model assessment of β-cell function (HOMA-B) according to diabetes duration. Four subjects with normal glucose tolerance (NGT) and 51 subjects with prediabetes mellitus (PreDM) were compared with 470 subjects with type 2 diabetes mellitus (T2DM). Among the subjects with T2DM, annual changes in log-transformed indices were calculated using simple linear regression analysis.
strating a negative association ($\beta = -0.348, -0.441, -0.359, \text{ and } -0.478$, respectively; $P < 0.001$ for all). Notably, the HbA1c level was the only significant factor affecting log(DI) and log(DIO). BMI and female sex were positively associated with log(IGI) and log(HOMA-B), but not with log(DI) or log(DIO). Conversely, age, HbA1c AUC, HbA1c CV, and use of antidiabetic agents showed no significant association with log(IGI), log(DI), log(DIO), or log(HOMA-B).

**\(\beta\)-Cell function according to HbA1c level at the time of measurement**

Since HbA1c level at the time of the OGTT was the most significant factor affecting \(\beta\)-cell function in the multivariable analysis, we estimated IGI, DI, DIO, and HOMA-B according to HbA1c levels (Fig. 3). All of these indices gradually increased as the HbA1c level decreased. Compared with that of patients with HbA1c level $\geq 9\%$, IGI was $1.81\text{-}, 2.51\text{-}, 3.52\text{-},$

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**Fig. 2.** Multivariable analysis between metabolic parameters and log-transformed (A) insulinogenic index (IGI) and (B) disposition index (DI) ($n=470$). Standardized regression coefficients ($\beta$) and $P$ values were obtained using a linear mixed model for repeated outcomes in the clustered data. SD, standard deviation; CI, confidence interval; HbA1c, glycosylated hemoglobin; BMI, body mass index; HbA1c AUC, area under the curve of HbA1c over time; HbA1c CV, coefficient of variation in HbA1c; DM, diabetes mellitus; GLP-1R, glucagon-like peptide-1 receptor; DPP-4, dipeptidyl peptidase-4; TZD, thiazolidinedione; SGLT2, sodium-glucose cotransporter 2; AGI, alpha-glucosidase inhibitor.
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**Fig. 3.** (A) Insulinogenic index (IGI), (B) disposition index (DI), (C) oral disposition index (DIO), and (D) homeostasis model assessment of β-cell function (HOMA-B) according to the glycosylated hemoglobin (HbA1c) level at the time of measurement (n=470). The analyses were adjusted for age per 1 year, sex, duration of diabetes per 1 year, and body mass index per 1 kg/m² (P for trend <0.001 for all). CI, confidence interval.
Fig. 4. Log-transformed (A) insulinogenic index (IGI) and (B) disposition index (DI) according to the glycosylated hemoglobin (HbA1c) level among patients receiving oral glucose tolerance tests repetitively \((n=151)\). HbA1c groups were categorized at each respective visit, and \(P\) values for trends regarding log-transformed indices corresponding to these HbA1c groups were calculated. The group exhibited a significant difference \((P<0.05)\) in log-transformed indices compared to the HbA1c <6% group.

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>Visit</th>
<th>No. of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6%</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>6%–7%</td>
<td>2</td>
<td>62</td>
</tr>
<tr>
<td>7%–8%</td>
<td>3</td>
<td>31</td>
</tr>
<tr>
<td>≥8%</td>
<td>4</td>
<td>42</td>
</tr>
</tbody>
</table>

Fig. 5. Trajectory of disposition index (DI) according to change patterns of the glycosylated hemoglobin (HbA1c) trajectory \((n=25)\). (A) Improvement in HbA1c, (B) rebound in HbA1c, and (C) no significant chang in HbA1c. The mean DI (red line) and HbA1c (black line) are shown. The trajectory of DI significantly differed by HbA1c trajectory groups \((P<0.001;\) calculated using a linear mixed model).
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and 5.55-fold higher in those with HbA1c levels of 8%–<9%, 7%–<8%, 6%–<7%, and <6%, respectively, after adjusting for age, sex, diabetes duration, and BMI (P for trend <0.001). DI was 1.91-, 2.46-, 3.67-, and 5.49-fold higher in those with HbA1c levels of 8%–<9%, 7%–<8%, 6%–<7%, and <6%, respectively, compared with that of patients with HbA1c level ≥9% (P for trend <0.001). Similar associations were observed in the analyses of DI0 and HOMA-B.

Further analyses were performed among patients who were newly diagnosed with T2DM and received repetitive 75 g OGTT at 1 year intervals (n = 151). There was a significant change in IGI, DI, DI0, and HOMA-B with the progression of diabetes over time, estimated by linear mixed model analyses (P<0.001 for all). Next, we have estimated IGI, DI, DI0, and HOMA-B according to the HbA1c category at each visit (Fig. 4, Supplementary Fig. 3). There was a trend that patients with higher HbA1c levels exhibited lower β-cell function at each visit.

Trajectory of β-cell function according to the trajectory of HbA1c
To further examine whether β-cell function is largely dependent on recent glycemia, we estimated the trajectory of β-cell function measures according to the trajectory of HbA1c. The analyses were performed in newly diagnosed patients with T2DM who had records of HbA1c, glucose, and insulin levels at 0, 30, and 120 minutes after 75 g of glucose loading without missing data for 3 consecutive years (n = 25). We classified patients into three groups according to their HbA1c trajectory patterns: improvement in HbA1c (n = 8), rebound in HbA1c (n = 4), and no significant change in HbA1c (n = 13). The trajectory of DI was a mirror image of that of HbA1c (Fig. 5), demonstrating a significant difference according to HbA1c trajectory groups (P<0.001). The trajectories of IGI, DI0, and HOMA-B also mirrored those of HbA1c (Supplementary Fig. 4), indicating that HbA1c level largely determined β-cell function at the time of measurement in individuals.

DISCUSSION
In this cohort study, we found that β-cell function in patients with T2DM was largely affected by recent glycemia. Various indices of insulin secretory β-cell function, including IGI, DI, DI0, and HOMA-B, have shown consistent results. Overall, β-cell function declined steadily over time; however, large differences in β-cell function between individuals have been reported. Our findings suggest that β-cell function is flexible, depending on the glycemic status at the time of measurement. The amount of accumulated HbA1c, variability in HbA1c levels, and type of treatment were not significantly associated with β-cell function in the current study.

Physiologically, glucose stimulation is important for maintaining β-cell function; however, exposure to supraphysiologic levels of glucose impairs β-cell function. Notably, glucotoxicity, which is the impaired insulin secretion induced by prolonged exposure to hyperglycemia, has been well described in animal and human studies. β-Cell apoptosis has been observed after exposure to hyperglycemia for a few weeks or even a few days in animal models of T2DM [22-24], while experimental hyperglycemia for 24 hours decreased arginine-stimulated insulin secretion in normal glucose-tolerant subjects [25,26]. The proposed mechanisms of glucotoxicity include impairment of insulin gene expression, activation of oxidative stress by reactive oxygen species (ROS), endoplasmic reticulum stress, inflammation, loss of β-cell differentiation, and increased rate of β-cell apoptosis [22].

In general, glucotoxicity refers to the progressive and irreversible effects of chronic hyperglycemia on pancreatic β-cell dysfunction [27]. Thus, we anticipated that chronic hyperglycemia burden, represented by the duration of diabetes or HbA1c AUC, would be a dominant factor associated with β-cell function. The duration of diabetes or HbA1c AUC was negatively associated with log(IGI), log(DI), log(DI0), and log(HOMA-B) in univariable analyses; however, the associations were attenuated after adjusting for other factors. Conversely, the HbA1c level at the time of measurement, which represents recent glycemia, was consistently and highly negatively correlated with β-cell function. In the logistic regression analysis, the DI of patients with HbA1c levels <6% was 5.5 times higher than that of patients with HbA1c ≥9%. These results suggested that the current glycemic burden might be more important in determining β-cell function than the previous long-term glycemic burden in patients with T2DM.

In a longitudinal analysis of patients who repeatedly completed OGTT, we found that β-cell function measures were flexible and largely dependent on HbA1c level at the time of measurement. In the current study, the trajectories of IGI, DI, DI0, and HOMA-B showed a mirror image of HbA1c in various patterns of HbA1c trajectories. Importantly, because this analysis was performed only for newly diagnosed patients with T2DM who were followed up for several years, the flexible na-
ture of β-cell function dependent on recent HbA1c levels may be limited to those with a recent onset of T2DM. Nonetheless, along with the cross-sectional analyses of patients with a longer duration of diabetes, the strong association between β-cell function and recent glycemia seemed consistent.

Although some irreversible alterations in β-cell function and gene expression after chronic hyperglycemia have been suggested [22,28], blood glucose normalization with intensive treatment has been reported to reverse β-cell dysfunction in patients with T2DM [29,30]. Blood glucose normalization may have beneficial effects on β-cell function, including restocking the cellular insulin pool, reducing ROS, anti-inflammatory effects, and inducing the redifferentiation of dedifferentiated β-cells into mature β-cells [30-32].

In contrast, specific antidiabetic agents were not associated with β-cell function in our study. Evidence indicated that several types of antidiabetic agents, including TZDs, GLP-1RAs, and SGLT2 inhibitors were associated with the preservation of β-cell function, either directly or indirectly, by reducing glucotoxicity [16,33-35]. However, the long-term effects of these drugs on β-cell function have not been well elucidated. Importantly, the duration of specific antidiabetic drug use did not significantly affect β-cell function in our study, probably because various treatment methods can have similar ameliorative effects on glucotoxicity and β-cell function [30,36,37].

Glycemic variability may be associated with impaired insulin secretion [38]. However, here, HbA1c variability was not significantly associated with β-cell function. One possible explanation is that patients with a high HbA1c CV were mostly those with a shorter diabetes duration who experienced a rapid reduction in HbA1c levels after initial treatment following the diagnosis of T2DM.

The association between sex and β-cell function was not consistent; female sex was positively associated with IGI and HOMA-B, but not with DI or DIO. Previous studies have suggested sex differences regarding insulin secretion in individuals with NGT due to protective effects of endogenous estrogens on islets [39,40]. However, it has also been reported that these sex differences disappear when glucose tolerance deteriorates towards the development of diabetes [41]. Therefore, the sex differences in insulin secretory β-cell function remains to be elucidated. Higher BMI was positively associated with IGI but negatively associated with ISI (data not shown), consequently showing no significant effects on DI. Age was negatively associated with insulin secretion, as reported in previous studies [42,43]; however, this association was not statistically significant.

This study had several limitations. First, the results of the earlier part of the current study were based on cross-sectional analyses; thus, we could not prove a causal relationship between potential factors and β-cell function measures. Moreover, this study could not rule out the possibility that glycemia is determined by β-cell function—that improvement in HbA1c is a result of an improvement in β-cell function. Considering that hyperglycemia occurs when β-cell function is impaired, improvement in β-cell function would likely contribute to the improvement in HbA1c. Second, the accumulated burden of glycemia, which the HbA1c AUC represented, was estimated since 2002. Therefore, the hyperglycemic burden of patients with long-standing T2DM of a duration longer than 20 years is limited by the current data. Finally, we did not estimate the effect of lipotoxicity and genetic predisposition on β-cell function, owing to a lack of relevant data. Further investigation is required to consider the effects of unmeasured factors.

In conclusion, this study suggests that recent glycemia is a major determinant of β-cell function to a greater degree than other clinical factors, including the duration of diabetes or types of antidiabetic agents in patients with T2DM. At least in newly diagnosed patients with T2DM, β-cell function changed depending on HbA1c levels at the time of measurement, suggesting the reversible nature of β-cell function in the early stages of T2DM.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2023.0359.

CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

Conception or design: J.Y.K., J.L., N.H.K.
Acquisition, analysis, or interpretation of data: all authors.
Drafting the work or revising: J.Y.K., N.H.K.
Final approval of the manuscript: J.Y.K., N.H.K.
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FUNDING

This study was supported by the grant from the Korean Diabetes Association (Ji Yoon Kim, 2023F-8). The funders played no role in the design and conduct of the study, analysis, interpretation of the data, or review or approval of the manuscript.

ACKNOWLEDGMENTS

The authors thank the volunteers who participated in this study.

REFERENCES


https://e-dmj.org Diabetes Metab J 2024 Forthcoming. Posted online 2024


### Supplementary Table 1. Use of antidiabetic agents in participants from 2002 to the time of the examination (n = 470)

<table>
<thead>
<tr>
<th>Antidiabetic drug use</th>
<th>No. (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Duration, mo&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>344 (73.2)</td>
<td>74.3 (34.8–111.6)</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>222 (47.2)</td>
<td>55.8 (15.2–111.9)</td>
</tr>
<tr>
<td>Glinide</td>
<td>19 (4.0)</td>
<td>9.2 (2.1–62.9)</td>
</tr>
<tr>
<td>GLP-1R agonist</td>
<td>8 (1.7)</td>
<td>6.7 (1.8–25.8)</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>203 (43.2)</td>
<td>54.6 (17.0–74.6)</td>
</tr>
<tr>
<td>TZD</td>
<td>136 (28.9)</td>
<td>43.2 (14.7–61.9)</td>
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<tr>
<td>SGLT2 inhibitor</td>
<td>135 (28.7)</td>
<td>25.5 (9.1–47.3)</td>
</tr>
<tr>
<td>AGI</td>
<td>33 (7.0)</td>
<td>42.2 (5.3–61.1)</td>
</tr>
<tr>
<td>Insulin</td>
<td>5 (1.1)</td>
<td>4.0 (3.1–6.4)</td>
</tr>
</tbody>
</table>

GLP-1R, glucagon-like peptide-1 receptor; DPP-4, dipeptidyl peptidase-4; TZD, thiazolidinedione; SGLT2, sodium-glucose cotransporter 2; AGI, alpha-glucosidase inhibitor.

<sup>a</sup>Number of participants who received antidiabetic agents at least once.  
<sup>b</sup>Median duration (interquartile range) of antidiabetic drug use among participants receiving the drug.
Supplementary Table 2. Univariable analysis between metabolic parameters and log-transformed IGI, DI, DIO, and HOMA-B (n = 470)

<table>
<thead>
<tr>
<th>Per 1SD</th>
<th>Log(IGI)</th>
<th>Log(DI)</th>
<th>Log(DIO)</th>
<th>Log(HOMA-B)</th>
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<td>P value</td>
<td>β</td>
<td>P value</td>
</tr>
<tr>
<td>HbA1c</td>
<td>−0.386</td>
<td>&lt;0.001</td>
<td>−0.458</td>
<td>&lt;0.001</td>
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<tr>
<td>DM duration</td>
<td>−0.314</td>
<td>&lt;0.001</td>
<td>−0.199</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.202</td>
<td>0.030</td>
<td>0.119</td>
<td>0.196</td>
</tr>
<tr>
<td>HbA1c AUC</td>
<td>−0.224</td>
<td>&lt;0.001</td>
<td>−0.135</td>
<td>0.002</td>
</tr>
<tr>
<td>Age</td>
<td>−0.090</td>
<td>0.046</td>
<td>0.000</td>
<td>0.995</td>
</tr>
<tr>
<td>BMI</td>
<td>0.262</td>
<td>&lt;0.001</td>
<td>0.031</td>
<td>0.501</td>
</tr>
<tr>
<td>HbA1c AUC</td>
<td>0.059</td>
<td>0.240</td>
<td>0.028</td>
<td>0.575</td>
</tr>
<tr>
<td>SBP</td>
<td>0.005</td>
<td>0.897</td>
<td>−0.047</td>
<td>0.257</td>
</tr>
<tr>
<td>DBP</td>
<td>0.041</td>
<td>0.311</td>
<td>−0.023</td>
<td>0.587</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.154</td>
<td>0.084</td>
<td>0.100</td>
<td>0.261</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0.152</td>
<td>0.080</td>
<td>0.086</td>
<td>0.335</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>0.134</td>
<td>0.384</td>
<td>0.176</td>
<td>0.247</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.200</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ISI</td>
<td>−0.357</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DM medication duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>−0.227</td>
<td>&lt;0.001</td>
<td>−0.165</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>−0.236</td>
<td>&lt;0.001</td>
<td>−0.171</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glinide</td>
<td>−0.007</td>
<td>0.860</td>
<td>−0.009</td>
<td>0.814</td>
</tr>
<tr>
<td>GLP-1R agonist</td>
<td>0.036</td>
<td>0.374</td>
<td>−0.006</td>
<td>0.880</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>−0.177</td>
<td>&lt;0.001</td>
<td>−0.142</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TZD</td>
<td>−0.135</td>
<td>&lt;0.001</td>
<td>−0.076</td>
<td>0.065</td>
</tr>
<tr>
<td>SGLT2 inhibitor</td>
<td>−0.045</td>
<td>0.265</td>
<td>−0.026</td>
<td>0.523</td>
</tr>
<tr>
<td>AGI</td>
<td>−0.127</td>
<td>0.001</td>
<td>−0.041</td>
<td>0.311</td>
</tr>
<tr>
<td>Insulin</td>
<td>−0.041</td>
<td>0.308</td>
<td>−0.024</td>
<td>0.558</td>
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</tbody>
</table>

Standardized regression coefficients (β) and P values were obtained using a linear mixed model for repeated outcomes in the clustered data. IGI, insulinogetic index; DI, disposition index; DIO, oral disposition index; HOMA-B, homeostasis model assessment of β-cell function; SD, standard deviation; HbA1c, glycosylated hemoglobin; DM, diabetes mellitus; HbA1c AUC, area under the curve of HbA1c over time; BMI, body mass index; HbA1c CV, coefficient of variation in HbA1c; SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMA-IR, homeostasis model assessment for insulin resistance; ISI, Matsuda insulin sensitivity index; GLP-1R, glucagon-like peptide-1 receptor; DPP-4, dipeptidyl peptidase-4; TZD, thiazolidinedione; SGLT2, sodium-glucose cotransporter 2; AGI, alpha-glucosidase inhibitor.
**Supplementary Fig. 1.** The flow diagram of the study subject selection. ADIOS, Anam Diabetes Observational Study; T2DM, type 2 diabetes mellitus; OGTT, oral glucose tolerance test; eGFR, estimated glomerular filtration rate; NGT, normal glucose tolerance.
**Supplementary Fig. 2.** Multivariable analysis between metabolic parameters and log-transformed (A) oral disposition index (DIO) and (B) homeostasis model assessment of β-cell function (HOMA-B) (n=470). Standardized regression coefficients (β) and P values were obtained using a linear mixed model for repeated outcomes in the clustered data. SD, standard deviation; CI, confidence interval; HbA1c, glycosylated hemoglobin; BMI, body mass index; DM, diabetes mellitus; HbA1c AUC, area under the curve of HbA1c over time; HbA1c CV, coefficient of variation in HbA1c; GLP-1R, glucagon-like peptide-1 receptor; DPP-4, dipeptidyl peptidase-4; TZD, thiazolidinedione; SGLT2, sodium-glucose cotransporter 2; AGI, alpha-glucosidase inhibitor.

### A. Outcome: log (DIO)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>β (per 1SD)</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>-0.359</td>
<td>(-0.476 to -0.242)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.011</td>
<td>(-0.117 to 0.095)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>0.103</td>
<td>(-0.091 to 0.296)</td>
<td>0.023</td>
</tr>
<tr>
<td>DM duration</td>
<td>-0.153</td>
<td>(-0.314 to 0.009)</td>
<td>0.035</td>
</tr>
<tr>
<td>HbA1c AUC</td>
<td>0.095</td>
<td>(-0.077 to 0.267)</td>
<td>0.138</td>
</tr>
<tr>
<td>HbA1c CV</td>
<td>-0.011</td>
<td>(-0.113 to 0.091)</td>
<td>0.824</td>
</tr>
<tr>
<td>Age</td>
<td>0.012</td>
<td>(-0.106 to 0.129)</td>
<td>0.837</td>
</tr>
</tbody>
</table>

### B. Outcome: log (HOMA-B)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>β (per 1SD)</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>-0.478</td>
<td>(-0.569 to -0.387)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>0.364</td>
<td>(0.271 to 0.456)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>0.388</td>
<td>(0.217 to 0.559)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DM duration</td>
<td>-0.051</td>
<td>(-0.192 to 0.090)</td>
<td>0.480</td>
</tr>
<tr>
<td>HbA1c AUC</td>
<td>0.118</td>
<td>(-0.029 to 0.266)</td>
<td>0.115</td>
</tr>
<tr>
<td>HbA1c CV</td>
<td>0.053</td>
<td>(-0.032 to 0.139)</td>
<td>0.222</td>
</tr>
<tr>
<td>Age</td>
<td>-0.031</td>
<td>(-0.134 to 0.072)</td>
<td>0.556</td>
</tr>
</tbody>
</table>

**Outcome: log (DIO)** and **Outcome: log (HOMA-B)**

**Outcome: log (DIO)** and **Outcome: log (HOMA-B)**
Supplementary Fig. 3. Log-transformed (A) oral disposition index (DiO) and (B) homeostasis model assessment of β-cell function (HOMA-B) according to the glycosylated hemoglobin (HbA1c) level among patients receiving oral glucose tolerance tests repetitively (n = 151). HbA1c groups were categorized at each respective visit, and P values for trends regarding log-transformed indices corresponding to these HbA1c groups were calculated. The group exhibited a significant difference (P < 0.05) in log-transformed indices compared to the HbA1c < 6% group.
Supplementary Fig. 4. Trajectories of (A) insulinogenic index (IGI), (B) oral disposition index (DIO), and (C) homeostasis model assessment of β-cell function (HOMA-B) according to change patterns of the glycosylated hemoglobin (HbA1c) trajectories (n=25). The mean IGI, DIO, or HOMA-B (red lines) and HbA1c (black lines) are shown.