The Relation between Parameters from Homeostasis Model Assessment and Glycemic Control in Type 2 Diabetes

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Objective: To determine the association of insulin sensitivity and pancreatic beta-cell function parameters assessed by the homeostasis model assessment (HOMA) and glycemic control, and their potential utilization in the clinical care of patients with type 2 diabetes mellitus.

Material and Method: The HOMA indices were assessed in 204 (62 males, 142 females) type 2 diabetic outpatients aged 60.7 ± 10.9 years. All patients were non-insulin treated for their diabetes. The correlation between variables including logarithmically transformed HOMA-%S and HOMA-%B, body mass index (BMI) and duration of diabetes to glycemic control were assessed. The value of the disposition index (HOMA-%SxHOMA-%B) that best discriminated patients with good glycemic control (HbA1C < 7%) from those without (HbA1C > 7%) was determined.

Results: Both log (HOMA-%S) and log (HOMA-%B) were inversely related to HbA1C with comparable degrees of association (beta = -0.62, p < 0.001 and beta = -0.61, p < 0.001, respectively). The log-transformed disposition index of at least 3.57 had a sensitivity of 74.2% and a specificity of 67.6% in classifying patients as having HbA1C < 7%. The result suggested that in order to achieve acceptable glycemic control, oral hypoglycemic agents should be adjusted to maximize the likelihood of the log-transformed disposition index reaching 3.57.

Conclusions: Glycemic control in diabetic patients partially depends on both insulin sensitivity and pancreatic beta-cell function. Assessing both parameters with the HOMA model is likely to result in a more rational approach for achieving better glycemic control in type 2 diabetic patients.

Keywords: Homeostasis model assessment (HOMA), Glycemic control, T2DM


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Diabetic complications can be prevented or delayed by tight glycemic control. The American Diabetes Association (ADA) recommended HbA1C less than 7% as the glycemic goal for non-pregnant diabetic patients(1). Even in individuals who cannot achieve the goal, improved glycemic control is still associated with decreased rates of microvascular complications(2-4). Glycemic control depends mainly on the degree of residual pancreatic beta-cell function, insulin sensitivity and other factors such as compliance to treatment and glycemic loads. In order to manage diabetic patients effectively, such data should be readily available to physicians. However, choosing and adjusting glucose-lowering agents in the routine care of diabetic patients are largely empirical. A decision of insulin secretagogue, insulin sensitizing agents’s prescription and doses-modifications depend mainly on the patients’ clinical features without the precise
knowledge of the underlying insulin sensitivity and pancreatic beta-cell function, which may lead to suboptimal results in some circumstances.

A number of clinical features are associated with pancreatic beta-cell function or insulin sensitivity. With the exceptions of the duration of diabetes, which is related to the deterioration of pancreatic beta cells, and body mass index (BMI), waist circumference, plasma triglyceride as well as HDL-cholesterol which are related to insulin resistance, the performances of other clinical predictors are rather inconsistent(5-10). Largely because of the fact that the standard methods for assessing beta-cell function and insulin sensitivity, the hyperglycemic and euglycemic glucose clamps, are complex and costly to perform, there have been several studies conducted to determine simpler and more applicable assessments including the homeostasis model assessment (HOMA). However, it is unclear how to incorporate the information in the clinical decision making for the routine care of diabetic patients. They were therefore, the purposes of the present study to examine whether indices assessed by HOMA are associated with glycemic outcome and to evaluate the contribution of these parameters to HbA1C levels in outpatients with type 2 diabetes. Moreover, the authors also investigated to see if a cutoff value based on the HOMA indices could assist in the management of glycemic control in clinical practice.

Material and Method

The present study population comprised 204 patients (62 men and 142 women) with type 2 diabetes attending the diabetes clinic of Ramathibodi Hospital, Bangkok, Thailand. Patients on insulin treatment, as well as those with liver or kidney disease were excluded. Informed consents were obtained from all subjects before the beginning of the present study.

Blood samples were drawn in the morning after an overnight fast. Glycated hemoglobin (HbA1C) was measured by high performance liquid chromatography. Fasting insulin concentrations were measured by a solid-phase, two-site chemiluminescent immunometric commercial kit (Immulate 1000, CA, USA). HOMA-%S for insulin sensitivity and HOMA-%B for pancreatic beta cell function were computed using fasting insulin and glucose levels by a HOMA2 calculator program(11).

The values of HOMA-%S and HOMA-%B were logarithmically transformed to normal distributions before analyses. Linear regression and stepwise multiple regression analyses were performed to evaluate the relationship among HbA1C, HOMA indices, body mass index (BMI), and the duration of diabetes. A p-value less than 0.05 were considered statistically significant. Receiver-operating characteristic (ROC) curve analysis was used to define the cutoff values differentiating glycemic control based on the HbA1C < 7% as the definition of good glycemic control(12,13). Data were expressed as mean ± SD.

Results

The clinical and biochemical features of the present study population are summarized in Table 1. Most of the subjects were treated with oral hypoglycemic agents (Table 2). The subjects were characterized with regard to glycemic control as good (HbA1C < 7%, n = 62), fair (HbA1C 7-8%, n = 78), and poor (HbA1C > 8, n = 74).

Both log (HOMA-%S) and log (HOMA-%B), BMI and duration of diabetes were chosen as independent variables in the regression analysis while blood

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Sex (M/F)</td>
<td>62 /142</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.7 ± 10.9</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>8.9 ± 6.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.9 ± 4.4</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>141.5 ± 20.8</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>79.4 ± 13.3</td>
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<tr>
<td>HbA1C (%)</td>
<td>7.8 ± 1.4</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg%)</td>
<td>147.8 ± 45.6</td>
</tr>
<tr>
<td>Fasting serum insulin (mU/L)</td>
<td>15.1 ± 14.0</td>
</tr>
<tr>
<td>HOMA%S</td>
<td>70.1 ± 46.3</td>
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<tr>
<td>HOMA%B</td>
<td>65.4 ± 40.8</td>
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<tr>
<td>Serum total cholesterol (mg/dL)</td>
<td>189.47 ± 47.82</td>
</tr>
<tr>
<td>Serum triglyceride (mg/dL)</td>
<td>140.22 ± 83.55</td>
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<tr>
<td>Serum LDL-cholesterol (mg/dL)</td>
<td>112.11 ± 34.24</td>
</tr>
<tr>
<td>Serum HDL-cholesterol (mg/dL)</td>
<td>51.24 ± 6.14</td>
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</tbody>
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Table 2. Diabetic treatment and antidiabetic agents used in the subjects

<table>
<thead>
<tr>
<th>Treatment</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet control alone</td>
<td>9.8</td>
</tr>
<tr>
<td>Oral hypoglycemic agents used</td>
<td></td>
</tr>
<tr>
<td>Sulfonylurea alone</td>
<td>12.25</td>
</tr>
<tr>
<td>Metformin alone</td>
<td>11.76</td>
</tr>
<tr>
<td>Sulfonylurea+metformin</td>
<td>55.88</td>
</tr>
<tr>
<td>Sulfonylurea+metformin+thiazolidenedione</td>
<td>4.9</td>
</tr>
<tr>
<td>Thiazolidenedione or acarbose alone</td>
<td>5.41</td>
</tr>
</tbody>
</table>
pressure and lipid profiles were not included due to its weak association with glycemic control in previous reports and because many patients were on antihypertensive and lipid lowering drugs (data not shown). From stepwise multiple regression analysis, both log (HOMA-%S) and log (HOMA-%B) were inversely and significantly correlated with HbA1C, beta = -0.62, p < 0.001 for log (HOMA-%S) and beta = -0.61, p < 0.001 for log (HOMA-%B), respectively. The degrees of association were comparable since the corresponding beta values were similar. No significant correlation was observed between BMI (p = 0.058), duration of diabetes (p = 0.132) and HbA1C. The regression equation obtained from the model was HbA1C = 18.994 - 3.218 log (HOMA-%S) - 3.178 log (HOMA-%B). Overall the regression of log (HOMA-%S) and log (HOMA-%B) on HbA1C showed an r² value of 0.36 indicating that this model explain about 36% of HbA1C variability and 64% was likely to be accounted for by other factors.

Since the coefficients of HOMA-%S and HOMA-%B in the regression equation is comparable, factoring out the coefficients yielded the sum of log (HOMA-%S) and log (HOMA-%B), which is the logarithm of the mathematical product of HOMA-%S and HOMA-%B, the so-called disposition index that reflects the pancreatic beta-cell function adjusted for the degree of insulin resistance. Regression of the disposition index on HbA1C yielded the equation HbA1C = 18.994 - 3.198 log (disposition index), which was also significantly related to HbA1C (r = 0.60, p < 0.001) (Fig. 1).

Fig. 2 demonstrates the ROC curve of using log (disposition index) to classify patients into those with good glycemic control (HbA1C < 7%) and without good glycemic control (HbA1C >= 7%). The ROC curve suggested that log (disposition index) was a significant classifier of glycemic control (area under the ROC curve 0.77, 95% CI 0.70-0.83). The ROC curve analysis revealed the log (disposition index) of 3.57 corresponding to the disposition index value of 3,715 as the cutoff with the highest sensitivity and specificity. The cutoff resulted in a sensitivity of 74.2% and a specificity of 67.6% with a positive predictive value of 50.0% and a negative predictive value of 85.7% in determining patients as having good glycemic control.

**Discussion**

Knowing the factors underlying glycemic control such as insulin sensitivity and pancreatic beta cell function should be helpful in the management of diabetic patients. However, the gold standard for assessing insulin resistance and beta-cell secretion function, the euglycemic and hyperglycemic clamps, is time-consuming, costly, and cumbersome to perform. Other methods including frequently sampled intravenous glucose tolerance test (FSIGTT) and minimal

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**Fig. 1** Correlation between HbA1C and log (disposition index), the log (disposition index) was significantly related to HbA1C (r = 0.60, p < 0.001)

**Fig. 2** ROC curve of log (disposition index) for the classification of patients as having good glycemic control (HbA1C < 7%), disposition index is a significant classifier with area under the ROC curve 0.77, 95% CI 0.70-0.83
modeling, continuous infusion glucose model assessment (CIGMA), intravenous glucose tolerance test (IVGTT), and oral glucose tolerance test (OGTT) are also not convenient enough to be performed in routine clinical practice. Homeostasis Model Assessment (HOMA) is a structural mathematical model which allows values for insulin sensitivity (HOMA-%S) and beta-cell function (HOMA-%B), expressed as a percentage of normal, to be obtained if simultaneous fasting plasma glucose and fasting plasma insulin or C-peptide concentrations are known. The method has been proposed as a simple test to measure insulin secretion and sensitivity in basal state in non insulin-treated subjects and is suitable for epidemiological studies. According to previous reports, estimation of insulin sensitivity and beta-cell function by HOMA showed strong correlation to values obtained from insulin clamps, CIGMA and IVGTT. HOMA can be used either in normal subjects or in those with varying degrees of glucose tolerance. It has been validated in diabetic patients treated with diet alone, or with oral hypoglycemic agents such as sulphonylureas, metformin or even thiazolidinediones. This test has been utilized in the UKPDS and the Belfast studies to demonstrate gradual loss of beta cell function in type 2 diabetes. It is also an appropriate method for assessing longitudinal change in insulin resistance and beta cell function with time and during treatment of diabetes. The present study was conducted in diabetic patients mostly on oral hypoglycemic agents. The authors found that both HOMA-%S and HOMA-%B were significantly associated with glycemic outcome. The similarity of beta values of both parameters in the regression equation suggested that they were equally influential on glycemic outcome. However, from the regression model, only 36% of the total variance of HbA1C could be explained by HOMA-%S and HOMA-%B. The reason is probably because HOMA itself estimates the basal states of insulin sensitivity and beta-cell function, but not at the stimulated state there; it does not cover the entire dynamic range of glycemic results. Moreover, glycemic load is also contributory to HbA1C, which cannot be captured in the HOMA model.

In clinical practice, adjusting glucose lowering agents to achieve acceptable glycemic control is often empirical. The authors’ findings in the present study demonstrate that the product of HOMA-%S and HOMA-%B, the so-called disposition index, was significantly related to glycemic control as assessed by HbA1C. This implies that assessing the disposition index is likely to be useful in clinical decision making for taking care of patients with diabetes. For a particular patient whose disposition index is lower than 3,715, effort should be made to enhance insulin sensitivity or beta cell function in order to raise the index above the threshold where acceptable glycemic control is more likely to be achievable. If the low disposition index is due mainly to low HOMA-%S, the underlying problem is predominantly insulin resistance and the addition or the increase in the doses of insulin sensitizer can be of benefit. Many studies reported that thiazolidinediones, using alone or in combination with other hypoglycemic agents, increase HOMA-%S by 9-37% and may increase HOMA-%B up to 28%, which suggests their beneficial effect on the pancreatic beta cells. On the other hand, if HOMA-%B is markedly reduced despite maximum doses of insulin secretagogue, secondary drug failure is likely and insulin therapy should be initiated. Taverna reported that in the subjects with HOMA-%B < 20, 86% did require insulin within one year. On the other hand, if poor glycemic control exists despite the index higher than 3,715, it suggests that factors besides insulin sensitivity and beta cell function are responsible and more attention should be paid to stricter dietary control and effort to lower glycemic load.

In conclusion, the present findings suggest that HOMA indices are partial determinants of glycemic control. Assessing HOMA indices can be helpful in a more rational approach to manage type 2 diabetes.

Acknowledgement

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ความสัมพันธ์ของตัวแปรใน Homeostasis Model และการควบคุมระดับน้ำตาลในผู้ป่วยเบาหวานชนิดที่ 2

บันทิศ มานสุนทร, สุวรรณี ชั้นประเสริฐโยธิน, วัศย จงเจริญประเสริฐ, ณัฐธิชัย งามอุโฆษ, พงศ์อมร บุนนาค, กอบชัย บุญส่ง องค์พิพัฒนกุล

วัตถุประสงค์: เพื่อศึกษาความสัมพันธ์ระหว่างค่าตัวแปรที่ได้จากการคำนวณด้วย Homeostasis Model Assessment (HOMA) ซึ่งบ่งชี้ภาวะดื้ออินสุลินและการหลั่งอินสุลินของเบาต์เซลล์จากเซลล์ตับอ่อนกับการควบคุมระดับน้ำตาลและประโยชน์ในการนำไปใช้ในทางคลินิกในการดูแลผู้ป่วยเบาหวานชนิดที่ 2

วัสดุและวิธีการ: เป็นการศึกษาในคนไข้เบาหวานชนิดที่ 2 จำนวน 204 คน (ชาย 62 คน หญิง 142 คน) อายุ 60.7 ± 10.9 ปี คนไข้ทุกคนได้รับการรักษาด้วยยาลดระดับน้ำตาล โดยนำค่าระดับน้ำตาลและระดับอินสุลินในเลือด ขณะอดอาหารมาคำนวณ HOMA หาค่า HOMA-%S และ HOMA-%B จากนั้นนำค่าคู่ของ log ของค่าดังกล่าวที่นั้นรวมกับวัดค่าดัชนีมวลกายและประวัติระยะเวลาของการเป็นโรคเบาหวาน และหาความสัมพันธ์กับค่า HbA1C และค่าดัชนี Disposition index ที่ได้จากการคูณ HOMA-%S และ HOMA-%B และใช้ค่านี้ในการหาจุดตัดของตัวแปรที่มีความในและความถูกต้องมากที่สุดที่จะทำนายการควบคุมระดับน้ำตาลให้มีค่า HbA1C < 7% โดยการคำนวณจาก ROC curve

ผลการศึกษา: ผลการศึกษาพบว่า log HOMA-%S และ log HOMA-%B มีความสัมพันธ์เชิงลบกับค่า HbA1C (B = -0.62, p < 0.001 และ B = -0.61, p < 0.001) ตามลำดับ พบว่า log ของ Disposition index อย่างน้อย 3.57 จำเป็นสำหรับการควบคุมระดับน้ำตาลให้อยู่ในเกณฑ์ (HbA1C < 7%) โดยมีค่า sensitivity 74.2% และ specificity 67.6% จากผลที่ได้แสดงให้เห็นว่า การควบคุมระดับน้ำตาลให้อยู่ในเกณฑ์ ยาที่ใช้ลดระดับน้ำตาลควรปรับปรุงขนาดให้ใกล้ค่าของ log ของ Disposition index เท่ากับ 3.57

สรุป: การควบคุมระดับน้ำตาลในคนไข้เบาหวานชนิดที่ 2 จำเป็นจะต้องใช้ HOMA model ในการคำนวณอาจช่วยเป็นแนวทางในการปรับยาเพื่อการควบคุมระดับน้ำตาลในคนไข้เบาหวานชนิดที่ 2 ได้ดียิ่งขึ้น