Beta-cell function and insulin sensitivity contribute to the shape of plasma glucose curve during an oral glucose tolerance test in non-diabetic individuals

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SUMMARY
To clarify whether beta-cell function and/or insulin resistance contributes to the shape of plasma glucose curve during an oral glucose tolerance test (OGTT), we investigated 583 Japanese subjects with normal glucose tolerance (NGT, n = 306) or impaired glucose tolerance (IGT, n = 277). Each subject was subdivided into three shapes of plasma glucose curve as follows: monophasic pattern (M type), biphasic pattern (B type) and two peaks (T type). Homeostasis model assessment of insulin resistance, quantitative insulin sensitivity check index and insulinogenic index were assessed by plasma glucose and insulin concentrations obtained at fasting or during an OGTT. There was a greater proportion of M type in the IGT group (M = 80.9%, B = 15.5% and T = 3.6%), whereas the prevalence of B and T types was much higher in the NGT group (M = 66.6%, B = 26.5% and T = 6.9%). There were significant differences in the proportions of shape types between the NGT and IGT groups (p = 0.0006). Among the NGT category, insulin sensitivity was significantly higher in the B type than in the M type, and beta-cell function adjusted for insulin resistance was significantly higher in the B and T types than in the M type. Among the IGT category, no significant differences were seen among the three shape types with respect to insulin sensitivity, but the beta-cell function adjusted for insulin resistance was significantly lower in the M type than in the B and T types. In conclusion, both impaired insulin secretion and insulin resistance may contribute to the underlying mechanisms of the shape of plasma glucose curve in Japanese subjects.

Keywords: Oral glucose tolerance test; insulin secretion; insulin sensitivity; homeostasis model assessment of insulin resistance; beta-cell function

INTRODUCTION
Some investigators have attempted to extract the metabolic characteristics from the time course of plasma glucose appearance during an oral glucose tolerance test (OGTT) (1). Recently, Tschritter et al. (2) developed a simple index to classify the shape of glucose curve into a monophasic type or a biphasic type. It is interesting to note that the biphasic type is strongly associated with higher insulin sensitivity and higher insulin secretion. Indeed, the authors demonstrated the shape index is a useful parameter in epidemiological studies. However, their shape index was based on the plasma glucose concentrations at two specific time-points during the OGTT (at 90 and 120 min). In this context, we speculate that the shape of plasma glucose curve represent more diverse patterns even in the same status of glucose tolerance when the peak time and the peak value of plasma glucose levels are considered. More importantly, it has been known that Japanese individuals with glucose intolerance are characterised by a decrease in insulin response to a glucose load (3–5). In this study, we examine insulin sensitivity and insulin secretion in relation to the shape of plasma glucose curve during an OGTT in relatively lean Japanese.

SUBJECTS AND METHODS
Subjects
We studied consecutive 792 Japanese subjects who underwent a diagnostic 75-g OGTT as a part of an evaluation for glucose intolerance attending our division at Nara Medical University Hospital between January 2000 and October 2003. Of these, 144 subjects with overt diabetes (fasting plasma glucose ≥7.0 mmol/l) or postchallenge hyperglycaemia (fasting plasma glucose < 7.0 mmol/l and 2-h plasma glucose ≥11.1 mmol/l) were excluded from analysis. Furthermore, 35 subjects with signs of congestive heart failure, chronic infectious diseases, renal failure, liver disease, cancer, marked
bowl disease or gastrectomy were excluded. Remaining 613 subjects were classified into three types of plasma glucose curve as monophasic pattern (M type), biphasic pattern (B type) or two peaks (T type), except for 30 subjects with unclassified pattern (i.e. upward-form with a continuous increase during the 120 min). As shown in Figure 1, the M and B patterns were divided into six subtypes as follows: M1 (a peak at 30 min after glucose load), M2 (a peak at 60 min), M3 (a peak at 90 min), B1 (a peak at 30 min and a nadir at 90 min), B2 (a peak at 30 min and a nadir at 90 min) and B3 (a peak at 60 min and a nadir at 90 min). The T type represents two complete peaks at 30 and 90 min: T1 (a higher peak at 30 min) and T2 (a higher peak at 90 min). Finally, this study included 306 subjects with normal glucose tolerance (NGT) and 277 subjects with impaired glucose tolerance (IGT). This study was performed in accordance with the Helsinki Declaration, and written informed consent was obtained from each participant.

Oral Glucose Tolerance Test
A 75-g OGTT was performed after a 10-h overnight fast. Plasma glucose was determined using a glucose oxidase auto-analyzer, and plasma insulin was measured using an electrochemiluminescence immunoassay (Roche-Diagnostic, Basel, Switzerland). The trapezoidal rule was used to calculate the area under the response curve for plasma glucose and insulin (AUC-G and AUC-I).

Evaluation for Insulin Sensitivity
Homeostasis model assessment of insulin resistance (HOMA-R) was used to calculate an index from the product of the fasting concentrations of plasma insulin (mU/l) and plasma glucose (mg/dl) divided by 405 (6). The quantitative insulin sensitivity check index (QUICKI) proposed by Katz et al. (7) was defined as follows: \(1 / (\log \text{fasting plasma insulin} + \log \text{fasting plasma glucose})\).

Evaluation for Pancreatic Beta-Cell Function
The insulinogenic index, a widely used index of early-phase insulin response, was defined as the ratio of the increment of plasma insulin to that of plasma glucose at 30 min after glucose loading (8). Beta-cell function adjusted for insulin resistance was calculated from insulinogenic index and HOMA-R as described by Jensen et al. (9).

Statistical Analysis
Data are presented as the mean ± standard deviation. Comparisons between groups were performed using analysis of variance followed by post hoc testing with Scheffe’s test. The proportion of shape type was analysed by a chi-square test with Yate’s correction. A value of p < 0.05 was considered significant.

RESULTS
The characteristics of subjects were summarised in Table 1. No significant differences were seen between NGT and IGT groups with respect to mean age or gender. As expected, body mass index (BMI), fasting glucose and insulin, 2-h glucose and insulin, AUC-G and AUC-I were significantly higher in IGT than in NGT.

The actual data for glucose responses during an OGTT were illustrated in Figure 2. On the pooled data from all subjects with NGT or IGT, plasma glucose curve in both groups represented monophasic pattern. But when each
subject was subdivided on the basis of shape type, the NGT group consisted of 204 cases (66.6%) with M type, 81 (26.5%) with B type and 21 (6.9%) with T type. The IGT group consisted of 224 cases (80.9%) with M type, 43 (15.5%) with B type and 10 (3.6%) with T type. As summarised in Table 2, there was a greater proportion of M type in IGT compared to NGT, and there was a significant difference in the proportions of three shape types between NGT and IGT (p = 0.0006). The distributions of shape subtypes are given in Table 3. There were significant differences in the distributions of their shape subtypes between NGT and IGT groups (p < 0.0001 between M subtypes, p = 0.0032 between B subtypes and p = 0.0192 between T subtypes).

The metabolic parameters of the study subjects subdivided on the basis of their shapes are listed in Table 4. In NGT, no significant differences were seen among the three shape types with respect to mean age, BMI, fasting glucose, fasting insulin or 2-h glucose. The total insulin secretion assessed by AUC-I decreased in the B type compared to the M type. HOMA-R was slightly but significantly lower in the B type than in the M type and tended to be lower (but not significant) in the T type compared to the M type. QUICKI was slightly but significantly higher in the B type than in the M type and tended to be higher between M and T shapes. The data are given as mean ± standard deviation.

Table 1 Clinical characteristics of study subjects

|                       | Normal glucose tolerance | Impaired glucose tolerance | p     |
|-----------------------|--------------------------|-----------------------------|-------|
| Number                | 306                      | 277                         | 0.6768|
| Age (years)           | 61.8 ± 11.2              | 62.1 ± 10.4                 |       |
| Female (%)            | 32.0                     | 31.8                        | 0.9471|
| BMI (kg/m²)           | 23.3 ± 3.2               | 24.6 ± 3.8                  | <0.001|
| Fasting glucose (mmol/l) | 5.12 ± 0.47         | 5.44 ± 0.59                 | <0.001|
| Fasting insulin (pmol/l) | 39.6 ± 21.9           | 45.9 ± 26.2                 | 0.0016|
| 2-h glucose (mmol/l)  | 6.32 ± 0.98              | 9.10 ± 0.91                 | <0.001|
| 2-h insulin (pmol/l)  | 256.7 ± 162.0            | 422.6 ± 286.5               | <0.001|
| AUC-G (mmol h/l)      | 10.62 ± 1.39             | 13.39 ± 1.61                | <0.001|
| AUC-I (pmol h/l)      | 554.8 ± 296.5            | 602.5 ± 337.9               | 0.0201|

AUC-G, area under the curve of plasma glucose; AUC-I, area under the curve of plasma insulin; BMI, body mass index.

Figure 2 Plasma glucose concentration during a 75-g oral glucose tolerance test in subjects with normal glucose tolerance (circle) or impaired glucose tolerance (closed square)

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in the T type compared to the M type. Insulinogenic index was significantly higher in the B and T types than in the M type. Beta-cell function adjusted for insulin resistance was also significantly higher in the B and T types than in the M type and was highest in the T type. In IGT, no significant differences were seen among the three shape types with respect to gender, BMI, fasting glucose, fasting insulin, 2-h insulin or AUC-I, whereas mean age was significantly higher in the T type than in the M type. No significant differences were seen among the three shape types with respect to HOMA-R and QUICKI. Insulinogenic index was significantly lower in the M type than in the B type and tended to be lower (but not statistically significant) in the M type than in the T type. Beta-cell function adjusted for insulin resistance was also significantly lower in the M type than in the B and T types.

The actual data for insulin responses during an OGTT were illustrated in Figure 3. In NGT, the 30 min increment in plasma insulin was most prominent in the T type, followed by the B type. By contrast, plasma insulin values at 60 min decreased significantly in the T type compared to both M and B types, and those at 90 min decreased significantly in the B type compared to the M type. Plasma insulin values at 120 min returned to similar levels among the three shape types. In IGT, plasma insulin values at 60 min decreased significantly in the T type compared to both M and B types, and those at 90 min decreased significantly in the M type compared to the B type. Plasma insulin curve in the M type represented a continuous increase during 120 min, whereas those in the B and T types had formed a biphasic and a two-peak pattern, respectively.

DISCUSSION

In the present study, we found that one-third subjects with NGT do not show a monophasic pattern of plasma glucose curve during an OGTT. Tschritter et al. (2) reported that a biphasic pattern is seen in 35.7% of NGT subjects and 30.3% of IGT subjects. The authors also reported that individuals with the biphasic pattern are characterised by younger age, more women, lower BMI and a better estimated insulin sensitivity and secretion compared to those with a monophasic pattern. But it is unclear whether insulin sensitivity and beta-cell function differ between the monophasic and the biphasic types at different stages of glucose intolerance. In our NGT subjects, no significant differences were seen between the monophasic and the biphasic types with respect to gender, mean age or BMI. However, we found that subjects with biphasic shape have increased early insulin responses but reduced total insulin secretions compared to those with monophasic pattern. Several factors may explain the different OGTT curves between the monophasic and the biphasic types. We speculate that one determination of biphasic pattern in the NGT group may be an exaggerated response of early-phase insulin secretion associated with insulin hypersensitivity. When insulin secretion was analysed in relation to the degree of insulin resistance, the value of (delta I/G)/HOMA-R was also significantly higher in the biphasic type compared to the monophasic type. In this biphasic type, it seems possible that a reactive hypoglycaemia at 60 min or at 90 min after a glucose load is induced by those abnormalities.

By contrast, there was a greater proportion of monophasic type in the IGT group, but insulin sensitivity was similar between the monophasic and the biphasic types. It has been known that IGT is characterised by a blunted insulin response to an oral glucose load and an abnormal ability of the beta cell to detect plasma glucose (10). In the present study, IGT subjects with monophasic shape represent significant lower values of insulinogenic index and (delta I/G)/HOMA-R compared to those with biphasic pattern. In addition, IGT

### Table 2

| Shape      | Normal glucose tolerance | Impaired glucose tolerance | p    |
|------------|--------------------------|----------------------------|------|
| Monophasic form | 204 (66.6)               | 224 (80.9)                 | 0.0006 |
| Biphasic form   | 81 (26.5)                | 43 (15.5)                  |      |
| Two peaks      | 21 (6.9)                 | 10 (3.6)                   |      |

The data are given as n (%).

### Table 3

| Shape      | Subtype | Normal glucose tolerance | Impaired glucose tolerance | p    |
|------------|---------|--------------------------|----------------------------|------|
| Monophasic form | M1      | 4                        | 4                          | <0.0001 |
|              | M2      | 131                      | 132                        |      |
|              | M3      | 28                       | 88                         |      |
| Biphasic form  | B1      | 37                       | 7                          | 0.0032 |
|              | B2      | 10                       | 9                          |      |
|              | B3      | 34                       | 27                         |      |
| Two peaks      | T1      | 13                       | 1                          | 0.0192 |
|              | T2      | 8                        | 9                          |      |

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subjects may have an apparent failure to appropriately reduce the rate of insulin secretion when glucose concentrations are declining (1). Indeed in our study, plasma insulin curve in IGT subjects with monophasic pattern represented a continuous increase during 120 min.

Furthermore, we assessed the third category of two peaks of plasma glucose curve. Overall, the number of subjects with this pattern was relatively small (6.9% in NGT and 3.6% in IGT). Insulinogenic index and (delta I/G)/HOMA-R were highest in this group. It seems possible that the accelerated beta-cell response at 30 min after a glucose load induces a falling glucose concentration at 60 min, but we cannot satisfactorily explain the mechanism for the second peak.

This study has several limitations. First, plasma glucose appearance equals the sum of the rate of appearance of the ingested glucose and hepatic glucose production. It has been known that an endogenous glucose production is promptly inhibited following glucose ingestion and that postprandial hyperglycaemia in diabetes results from both excessive hepatic glucose release and lack of an appropriate increase in peripheral glucose uptake (11). It has been also reported that the excessive glycaemic response during an OGTT was related to a reduced suppression of hepatic glucose output (12). But the endogenous glucose production during an OGTT was not measured in our study. Secondly, plasma glucose curve during an OGTT may be influenced by gastric emptying and/or bowel absorption rates (13). Indeed in the present study, marked bowel diseases or gastroenteropathy due to overt diabetes were excluded from analysis. We believe that these factors are unlikely to be the main cause of the different shape patterns. Furthermore, we must consider a role of intestinal

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**Table 4** Metabolic characteristics of subjects studied

|                      | Normal glucose tolerance | Impaired glucose tolerance |
|----------------------|--------------------------|---------------------------|
|                      | Monophasic | Biphasic | Two peaks | Monophasic | Biphasic | Two peaks |
| Number               | 204        | 81       | 21        | 224        | 43       | 10        |
| Age (years)          | 61.9 ± 10.8 | 61.6 ± 12.1 | 61.3 ± 11.1 | 61.8 ± 10.4 | 62.4 ± 10.9 | 68.5 ± 6.1* |
| Female (%)           | 28.4       | 35.8     | 52.4*     | 31.7       | 27.9     | 50.0      |
| BMI (kg/m²)          | 23.6 ± 3.2 | 23.1 ± 3.2 | 22.4 ± 2.3 | 24.9 ± 3.7 | 23.4 ± 3.8 | 23.1 ± 3.2 |
| Fasting glucose (mmol/l) | 5.15      | 5.06 ± 0.45 | 4.98 ± 0.35 | 5.47 ± 0.61 | 5.28 ± 0.51 | 5.48 ± 0.48 |
| Fasting insulin (pmol/l) | 41.2      | 36.1 ± 22.8 | 37.5 ± 16.3 | 45.4 ± 25.6 | 49.6 ± 28.9 | 42.0 ± 27.4 |
| 2-h glucose (mmol/l) | 6.30 ± 1.04 | 6.44 ± 0.82 | 6.06 ± 1.00 | 9.17 ± 0.91† | 8.80 ± 0.85 | 8.84 ± 0.96 |
| 2-h insulin (pmol/l) | 268.3 ± 157.4 | 232.2 ± 173.7 | 238.6 ± 155.2 | 431.2 ± 299.4 | 403.4 ± 234.7 | 312.0 ± 145.2 |
| AUC-G (mmol h/l)     | 11.02 ± 1.33‡ | 9.64 ± 1.05 | 10.48 ± 1.16‡ | 13.7 ± 1.5‡ | 11.8 ± 1.2 | 13.3 ± 1.8‡ |
| AUC-I (pmol h/l)     | 585 ± 311   | 490 ± 270*  | 511 ± 187   | 613 ± 357   | 572 ± 238 | 505 ± 237  |
| HOMA-R               | 1.59 ± 0.89 | 1.36 ± 0.88* | 1.38 ± 0.61 | 1.86 ± 1.09 | 1.96 ± 1.17 | 1.77 ± 1.30 |
| QUICKI               | 0.369 ± 0.037 | 0.380 ± 0.041* | 0.373 ± 0.036 | 0.361 ± 0.038 | 0.360 ± 0.039 | 0.365 ± 0.038 |
| Insulinogenic index  | 0.71 ± 0.56 | 1.01 ± 0.81§ | 1.21 ± 0.69§ | 0.47 ± 0.36‡ | 0.65 ± 0.41 | 0.67 ± 0.37 |
| (delta I/G)/HOMA-R   | 10.0 ± 8.9  | 16.9 ± 12.6§ | 20.7 ± 16.2§ | 5.9 ± 5.2¶  | 8.7 ± 7.5 | 9.9 ± 8.1  |

AUC-G, area under the curve of plasma glucose; AUC-I, area under the curve of plasma insulin; BMI, body mass index; HOMA-R, homeostasis model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index.

The data are given as mean ± standard deviation.

* p < 0.05 vs. monophasic form.

† p < 0.05 vs. biphasic form.

‡ p < 0.01 vs. biphasic form.

§ p < 0.01 vs. monophasic form.

¶ p < 0.05 vs. two peaks.
hormones, because insulin secretion is accelerated by incretin when glucose is ingested orally (14). But we have no data for those intestinal hormones. Finally, the general concept has evolved that hyperglycaemia in postglucose load was caused by a mixture of insulin resistance and insulin deficiency. But many previous studies have based conclusions on the measurement of plasma insulin concentrations rather than true insulin secretion rates from pancreas. Recently, Ferrannini et al. (15) have shown that the beta-cell sensitivity to glucose is reduced in subjects with IGT compared to those with NGT. We must consider this mechanism to form the different shapes of OGTT curve.

In conclusion, the present study is first to demonstrate a large number of non-diabetic subjects who had different shapes of plasma glucose curve during an OGTT. Our data strongly suggest that a balance between beta-cell function and insulin sensitivity seems to be important in determining the shape of plasma glucose curve.

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