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Prolonged plasma glucose elevation on oral glucose tolerance test in young healthy Japanese individuals

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Abstract

Aims: This study aims to assess insulin secretion and resistance through oral glucose tolerance test (OGTT) among young Japanese individuals.

Subjects and methods: We enrolled 595 young healthy Japanese individuals aged 22-29 years. They underwent an OGTT, and their results were divided into 4 groups (I-IV), according to the time at which their plasma glucose concentration declined below the fasting glucose concentration (30, 60 or 120 minutes or never as groups I, II, III and IV, respectively).

Results: We classified 575 normal glucose-tolerant subjects into 4 groups (I-IV) with I: 28 (4.9%), II: 120 (20.9%), III: 143 (24.9%) and IV: 284 (49.4%) individuals. The Matsuda, insulinogenic and disposition indices were decreased from groups I to IV. ROC curves of disposition index reflecting the composition of insulin secretion and sensitivity classified the prolonged glucose elevation group (group III + IV) from the rapid glucose lowering group (group II; AUC = 0.847).

Conclusions: Even in a young and healthy Japanese individual within the physiological range of glycaemic control, there is a sequential decrease in insulin sensitivity and secretion.

KEYWORDS

disposition index, high-density lipoprotein cholesterol, insulin secretion, oral glucose tolerance test, young Japanese

1 | INTRODUCTION

The majority of deaths in patients with type 2 diabetes mellitus (T2DM) result from accelerated cardiovascular arteriosclerosis.[1] The mortality attributable to cardiovascular disease (CVD) is increased 3.2-fold in men and 8.5-fold in women with T2DM compared to that in people not affected by the disease.[1] Macrovascular disease is associated with lower degrees of hyperglycaemia than microvascular disease.[2] The heightened risk for CVD extends to individuals with impaired glucose tolerance (IGT).[3] Both IGT and impaired fasting glucose (IFG) are intermediate states in glucose metabolism and associated with increased CVD risk.[4]

Abdul-Ghani et al showed conversion rates to T2DM at 2.4%, 5.1%, 11.5% and 13.5% for individuals with normal glucose tolerance (NGT), IFG, IGT or combined glucose tolerance (CGI), respectively, over a 7- to 8-year follow-up period.[5] Moreover, they divided NGT

and IFG subjects into four groups (I-IV), based upon the time (30, 60, or 120 minutes or never) at which their plasma glucose concentrations declined below the fasting glucose concentration after the oral glucose load. In NGT subjects, the incidence rate for the development of T2DM was 0% in group I and increased progressively to 1.8%, 2.1% and 2.9% in groups II, III and IV, respectively.[5]

Analyses from the DECODE data set have demonstrated that the hazard ratios for all-cause mortality in patients with IFG and IGT compared with those with normal fasting and 2-h glucose tolerance were 1.20 and 1.50, respectively.[6] A number of studies comparing IGT to IFG seem to point to IGT as being the better predictor of future T2DM development.[7-9] However, one study demonstrated both of them are equivalent.[10]

Reliable models for the identification of individuals at high-risk of T2DM are essential to improve strategies for the prevention of the disease. The oral glucose tolerance test (OGTT) is commonly used to identify high-risk individuals.[11] The OGTT is a useful examination tool, not only for diagnosis of T2DM, but also for estimation of insulin secretion. However, due to the need for frequent blood samplings, few studies have been done in young subjects who are commonly healthy.

In this study, we obtained OGTT results from university students, analysed their glucose curves and insulin secretion, and divided the subjects into four groups, according to a published protocol.[5] We also studied lipid profiles and compared with the indices of insulin sensitivity and insulin secretion, since glucose intolerance is associated with dyslipidaemia.[12]

2 | SUBJECTS AND METHODS

2.1 | Study population

All the participants signed informed consent forms, and the Gunma University Ethical Review Board for Medical Research Involving Human Subjects approved the study protocol. Participants were volunteers purely.

The participants were 595 medical candidates who practised at the Gunma University Hospital between May 2010 and July 2016. No subjects were diagnosed as having T2DM or received any medication. As part of their medical practice, they all underwent a comprehensive medical examination, including an OGTT (75 g dextrose monohydrate in 250 mL water) after an overnight fast.

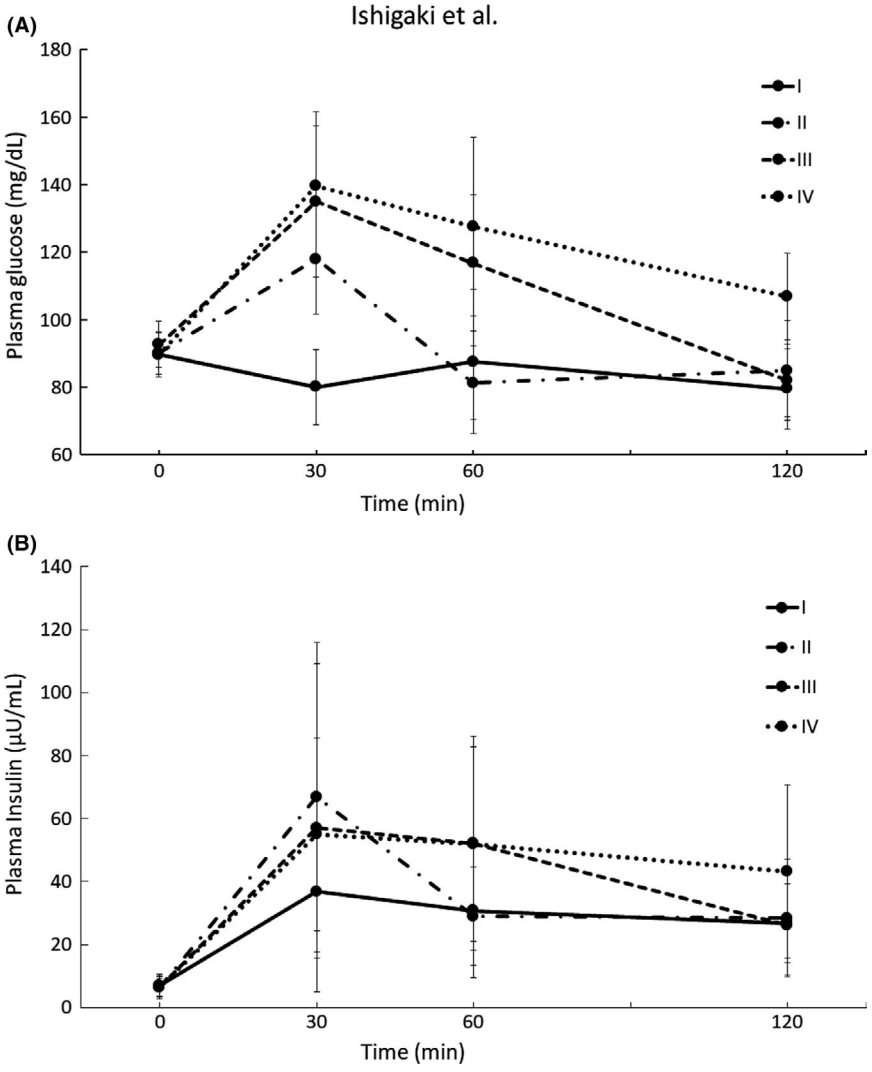

FIGURE 1 Grouping based on plasma glucose (A) and insulin (B) concentrations in subjects with normal glucose tolerance (NGT) according to the study by Abdul-Ghani et al[5]

TABLE 1 Clinical characteristics of the NGT subjects

Gender	Male, 359; Female, 216
Age	23.7 ± 1.7 y
Height	167.7 ± 8.3 cm
Weight	59.6 ± 10.4 kg
BMI	21.1 ± 2.5
FPG	90.5 ± 6.7 mg/dL (5.03 ± 0.37 mmol/L)
FPI	6.5 ± 3.4 IU/L
HbA1c (NGSP)	5.29 ± 0.2%
GA	13.4 ± 1.1%
CPR	1.42 ± 0.76 ng/mL

Data presented as mean ± SD. Abbreviations: CPR, C-peptide immunoreactivity; FPG, fasting plasma glucose; FPI, fasting plasma insulin; GA, glycoalbumin.

2.2 | Study design

The OGTTs were performed after 10-hour fasts with 0-, 30-, 60- and 120-minute samplings to establish plasma glucose and insulin levels, and at the preload time, serum high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), haemoglobin A1c (HbA1c) and glycoalbumin (GA) were measured. Excluded from this study were subjects who were over 30 years of age.

We classified 575 subjects into the NGT group, 19 into the IGT group, and 1 into the IFG group. We removed the subjects with IGT and IFG from further analyses in this analysis. We found no subjects with apparent T2DM.

We measured height and weight and calculated BMIs (weight [kg]/height [m^2]). We used enzymatic methods to measure serum HDL-C, LDL-C, TG and GA concentrations, with an automatic analyser (LABOSPECT 008; Hitachi). Serum insulin concentrations were measured by chemiluminescence immunoassay using an automatic analyser (AIA-2000 LA; Tosoh). Plasma glucose concentrations were measured using a hexokinase method, and HbA1c levels were measured by high-performance liquid chromatography, using automatic analysers (ADAMS Glucose GA-1170 and ADAMS A1c HA8180, respectively; Arkray).

2.3 | Grouping

We divided the subjects with NGT into four groups (I-IV), based upon the time (30, 60, or 120 minutes or never) and showed the sequential changes in plasma glucose (Figure 1A) and insulin (Figure 1B) at which their plasma glucose concentration during the OGTT declined below the fasting glucose concentration, following a published protocol.[5] Groups I, II and III included subjects whose plasma glucose concentration fell below the PG0 at 30, 60 and 120 minutes, respectively. Subjects whose plasma glucose never fell below the PG0 at any time during OGTT were defined as group IV.

2.4 | Statistical methods

We calculated areas under the glucose or insulin curves (AUCg and AUCi) based on the trapezoid rule. We also calculated the homeostasis model assessment of insulin resistance (HOMA-IR, fasting plasma glucose [PG0] (mg/dL) × IRI0 (μU/mL)/405),[13] β-cell function (HOMA-β, IRI0 (μU/mL) × 360/[PG0 (mg/dL) − 63])[13] and Matsuda index of insulin sensitivity (10,000/square root of [fasting glucose (mg/dL) × fasting insulin (μU/mL)] × [mean glucose (mg/dL) × mean insulin (μU/mL) during OGTT]),[14] as reported. We calculated the insulinogenic index by dividing the increment in serum insulin (μU/mL) by the increment in plasma glucose (mg/dL) during the 0- to 30-minutes time periods of the OGTT.[15] The insulin secretion/insulin resistance (disposition) index was calculated as insulinogenic index x Matsuda index.[16]

The SPSS version 25 statistical software package was used to perform the statistical analyses. The data were expressed as the mean ± standard deviation. We compared the continuous variables across the glucose tolerance groups using one-way ANOVA followed by Tukey's post hoc tests. We used ROC curves to discriminate between group II and group III + IV by some indices.

3 | RESULTS

3.1 | Clinical characteristics

The average age of the 575 NGT subjects was 23.7 ± 1.7 years, and the average BMI was 21.2 kg/m^2 (Table 1). Of these, 28 subjects (4.9%), 120 subjects (20.9%), 143 subjects (24.9%), and 284 subjects (49.4%) were classified into groups I, II, III and IV, respectively (Table 2).

3.2 | Sequential changes in plasma glucose and insulin

Figure 1 and Table 2 show the sequential changes in plasma glucose and insulin for each group during OGTT. We observed significant differences among the groups, especially in the plasma glucose values. The 30-minute postload plasma glucose (PG30) in group II was significantly higher than that in group I, and that in groups III and group IV was significantly higher than that in groups I and II. Regarding the 60-minute postload plasma glucose (PG60), the values in groups III and IV were significantly higher than those in groups I and II. The mean level of the 120-minute postload plasma glucose (PG120) in group IV was significantly higher than that in the other groups.

Regarding plasma insulin, we observed no significant differences in the fasting plasma insulin (IRI0) among groups. For the mean 30-minute postload plasma insulin (IRI30), those in groups II, III and IV were significantly higher than the average in group I. The mean 60-minute postload plasma insulin (IRI60) was significantly higher in groups III and IV than in groups I and II. The mean 120-minute postload plasma insulin (IRI120) of group IV was significantly higher than that in the other groups. Although we divided subjects according

TABLE 2 Baseline and metabolic characteristics of the NGT subjects

	I	II	III	IV
n	28 (4.9%)	120 (20.9%)	143 (24.9%)	284 (49.4%)
Male:female	10:18	64:56	102:41**	185:99**
BMI (kg/m^2)	20.2 ± 2.1	20.5 ± 2.1	21.1 ± 2.3	21.3 ± 2.8
PG0 (mg/dL)	89.6 ± 6.7	90.2 ± 6.1	92.5 ± 6.8	89.6 ± 6.5§§
IRI0 (μU/mL)	7.0 ± 3.7	6.5 ± 2.8	6.5 ± 3.3	6.4 ± 3.6
HbA1c (%) (NGSP)	5.29 ± 0.14	5.29 ± 0.19	5.30 ± 0.20	5.28 ± 0.22
GA (%)	13.5 ± 1.1	13.4 ± 0.89	13.3 ± 1.2	13.4 ± 1.0
PG30 (mg/dL)	80.1 ± 11.16	117.9 ± 16.4**	135 ± 22.5**,++	139.5 ± 22.0**,++
PG60 (mg/dL)	87.6 ± 21.4	81.3 ± 10.9	116.8 ± 20.1**,++	127.6 ± 26.5**,++,§
PG120 (mg/dL)	79.6 ± 11.9	85.0 ± 14.8	82.1 ± 10.8	106.7 ± 12.8**,++,§§
IRI30 (μU/mL)	36.8 ± 21.0	66.8 ± 49.2**	57.1 ± 52.0**	55.0 ± 30.5*
IRI60 (μU/mL)	30.7 ± 21.1	29.0 ± 15.6	52.1 ± 34.0**,++	51.9 ± 30.8**,++
IRI120 (μU/mL)	26.8 ± 12.6	28.4 ± 18.7	26.2 ± 15.8	43.1 ± 27.5**,++,§§
HDL-C (mg/dL)	68.1 ± 10.8	66.5 ± 12.8	62.6 ± 14.7+	62.3 ± 10.1++
LDL-C (mg/dL)	93.6 ± 22.4	95.5 ± 21.3	95.1 ± 24.4	102.5 ± 27.1§
TG (mg/dL)	67.3 ± 23.9	67.3 ± 29.2	74.4 ± 36.3	77.1 ± 41.6
AUCg	10 080 ± 1460	11 100 ± 1120	13 150 ± 1580**,++	14 470 ± 1870**,++,§§
AUCi	3450 ± 1510	4270 ± 2160	5330 ± 3110**,+	5500 ± 2780**,++
AUCi/AUCg	0.342 ± 0.137	0.385 ± 0.195	0.402 ± 0.217	0.380 ± 0.182
HOMA-IR	1.54 ± 0.89	1.53 ± 1.03	1.50 ± 0.82	1.42 ± 0.93
HOMA-β	95.7 ± 40.6	87.4 ± 34.9	80.5 ± 39.3	88.1 ± 43.9
Insulinogenic index	−3.34 ± 3.19	2.17 ± 2.17**	1.43 ± 3.38**,++	0.84 ± 1.27**,++
Matsuda index	8.18 ± 3.34	6.94 ± 2.78	6.28 ± 2.90*	5.86 ± 2.98**,++
Disposition index	−28.14 ± 27.28	15.68 ± 16.35**	7.97 ± 15.70**,++	4.92 ± 9.03**,++,§§

Data presented as mean ± SD. Abbreviations: BMI, body mass index; GA, glycoalbumin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of beta cell function; IRI0, fasting plasma insulin; IRI30, 30-min postload plasmas insulin; IRI60, 60-min postload plasmas insulin; IRI120, 120-min postload plasma insulin; PG0, fasting plasma glucose; PG30, 30-min postload plasma glucose; LDL-C = low-density lipoprotein cholesterol; PG60, 60-min postload plasma glucose; PG120, 120-min postload plasma glucose; TG, triglyceride.

*P < .05 vs group I.

+P < .05 vs group II.

§P < .05 vs group III.

**P < .01 vs group I.

++P < .01 vs group II.

§§P < .01 vs group III.

to the shape of glucose concentration curve,[5] insulin concentration curve showed a similar shape.

3.3 | Lipid profiles

In the analyses of lipid profiles, the HDL-C levels in groups III and IV were significantly lower than those in group II. The LDL-C levels in group IV were significantly higher than those in group III, and we found no significant differences in the TG levels among the groups (Table 2).

3.4 | AUC of glucose and insulin

The incremental areas under both the glucose and insulin curves (AUCg and AUCi) increased progressively from groups II to IV (Table 2). In contrast, we found no significant differences in the ratio of AUCi/AUCg among the groups.

3.5 | Glucose metabolism indices

We found no significant differences in the HbA1c levels among groups. Likewise, the mean insulin resistance index, HOMA-IR showed no significant group differences. Similarly, there were no significant differences in mean HOMA-β and indicator of insulin secretion potential. However, the Matsuda index, an indicator of whole-body insulin sensitivity, declined progressively from group I to IV, and the insulinogenic index, calculated by (IRI30-IRI0)/(PG30-PG0), was less than 0 in group I, a higher value in group II, a lower value in group III and an even lower value in group IV. The

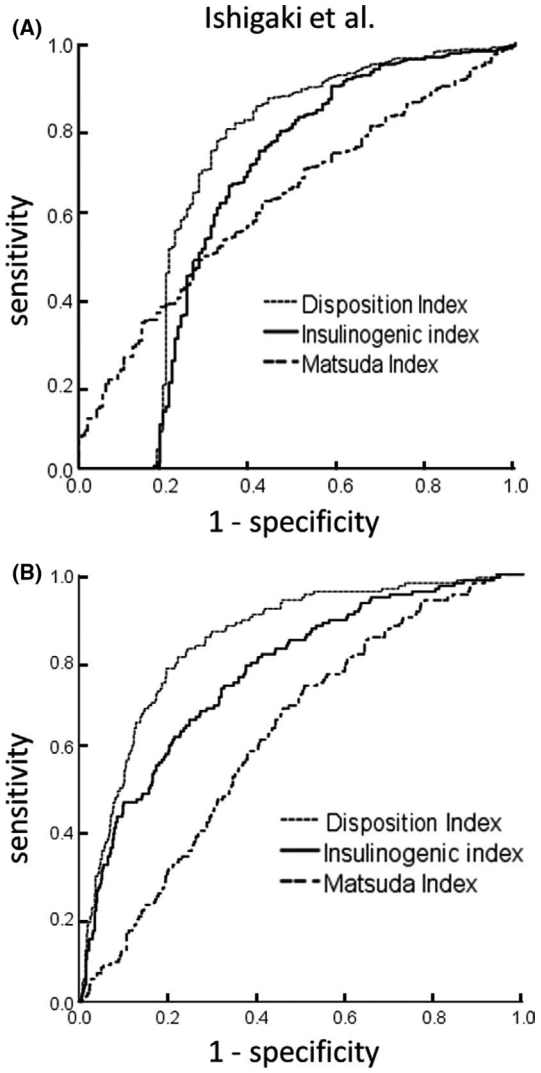

FIGURE 2 Summary of ROC curve analysis for disposition index, insulinogenic index and Matsuda index for groups I + II and III + IV (A) and groups II and III + IV (B). A, Disposition index: AUC, 0.706; CI, 0.645-0.768. Insulinogenic index: AUC, 0.652; CI, 0.590-0.714. Matsuda index: AUC, 0.629; CI, 0.579-0.679. (B) Disposition index: AUC, 0.847; CI, 0.814-0.881. Insulinogenic index: AUC, 0.786; CI, 0.738-0.834. Matsuda index: AUC, 0.616; CI, 0.562-0.669

disposition index (the product of Matsuda index and insulinogenic index), reflected the combination of insulin secretion and insulin sensitivity, also showed a similar trend (less than 0 in group I, the highest value in group II, and progressively lower values in groups III and IV).

3.6 | ROC curves of identifying the prolonged glucose elevation group

In the past study, Abdul-Ghani et al defined group I + II as low-risk group for T2DM, and group III + IV as high-risk group for T2DM.[5] Low-risk group showed rapid glucose lowering, and high-risk group showed prolonged glucose elevation. Therefore, we described ROC curves of indices between groups identifying the high-risk group (group III + IV) from the low-risk group (group I + II). The Matsuda, insulinogenic and disposition indices were compared. Between groups I + II and III + IV, the AUCs of ROC of the disposition, the insulinogenic and Matsuda indices were not good (AUC = 0.706, 0.652 and 0.629, respectively) (Figure 2A). Since PG30 is smaller than PG0 in group I, insulinogenic and disposition indices were calculated into negative value in group I. Negative value misled to be poor insulin secretion potential. Therefore, we excluded the group I from ROC analysis. As a result, good AUCs were obtained in disposition index (AUC = 0.847) better than the insulinogenic and Matsuda indices (AUC = 0.786, 0.616, respectively; Figure 2B).

4 | DISCUSSION

In this cross-sectional study, we found that healthy young Japanese individuals within physiological range of glycaemic control accompanied the sequential decreases in insulin sensitivity and secretion. We showed the differences in the OGTT-derived indices of insulin sensitivity and insulin secretion among 4 groups, according to a previous study.[5] The insulin sensitivity, calculated using the Matsuda index, decreased progressively in subjects from groups I to IV as with the study.[5] In addition, the insulin secretion assessed using the insulinogenic index decreased in the subjects from groups II to IV (the value of this index in group I was less than zero by definition) along with the study.[5]

Although we tried to classify participants by insulin secretion pattern according to the previous study,[17] we could not find a significant difference among groups. We also tried to apply other indices such as the QUICKI (quantitative insulin sensitivity check index),[18] the McAuley (an index of insulin resistance)[19] and the fasting Belfiore (fasting insulin resistance index)[20]; however, we found no significant differences between the groups (data not shown).

In terms of glucose tolerance, our results showed similar insulin sensitivities or secretion levels to the levels in the above-mentioned study.[11] Even though the mean age of subjects in our study at 23.7 was 30 years younger than the mean age of subjects in the prior study at 54.1,[5] our results suggest that Japanese young individuals and Finnish middle-aged individuals share similar glucose metabolism. This is similar to a publication, suggesting that the insulin response in Asian Americans was lower than that in other ethnic groups such as Hispanic American, Caucasians and African Americans.[21]

Among the Japanese population, a study on OGTTs among 2157 middle-aged Japanese individuals showed that only 1125 (52.1%) had NGT, while the others had IFG (525 [24.3%]), IGT (159 [7.3%]), IFG + IGT (263 [12.2%]) and diabetes (85 [3.9%]).[22] The mean age of that study was 52.6 years, which was similar to that in the study by Abdul-Ghani et al[5,22] Young normoglycaemic children of Indian parents with diabetes mellitus showed higher plasma insulin levels, and lower insulin sensitivity and β-cell compensation than subjects without parents with T2DM.[23] The difference may have been caused by the different ethnicities, dietary habits or family histories.

The IRI0, an index that can identify the future risk for T2DM, has been associated with insulin resistance. A comparison between the OGTT and the euglycaemic hyperinsulinaemic clamp technique suggested that the fasting insulin level should be a marker of insulin resistance.[24] In addition, an insulin suppression test study concluded that fasting plasma insulin and HOMA-IR were highly correlated in nondiabetic individuals.[25] However, in the present study, we found no significant difference in IRI0 among the study groups.

Some subjects showed lower glucose values at PG30 than at PG0. In addition, about 5% of the subjects in group I had negative insulinogenic index values, a percentage close to that in the literature, where the majority of individuals with low glucose and increased insulin values belonged to the NGT group.[26] In the present study, all the subjects in group I showed similar changes in glucose and insulin. Although we tried to draw the ROC curves classifying the prolonged glucose elevation group (group III + IV) from the rapid glucose lowering group (group I + II), the specificities of insulinogenic and disposition indices were poor (Figure 2A). These results were explained as follows: they were calculated into negative value in group I. In general, a higher insulinogenic index shows better insulin secretion. Although subjects in group I were thought to have good insulin secretion potential, negative value misled to be poor insulin secretion potential. Therefore, we excluded the group I from ROC analysis. As a result, good AUCs were obtained in disposition index (Figure 2B).

Among the glucose and insulin indices, the most significant differences were observed in the AUCg among the groups. However, this was an inevitable result given that we divided the subjects into four groups according to their glucose values.

The definition of the disposition index varies among the researchers. While Weiss et al determined it as the product of the insulinogenic index and the Matsuda index,[16] Asano et al calculated it as the quotient of the insulinogenic index divided by the HOMA-IR,[27] and Retnakaran et al calculated it as the product of the Matsuda index and the AUCi/AUCg.[28] We used the product of the insulinogenic index and the Matsuda index because we found no significant differences in HOMA-IR and AUCi/AUCg, among the study groups. Our analyses with the AUCi/AUCg x Matsuda index showed differences among groups similar to those of the Matsuda index alone (data not shown). For the product of the insulinogenic index and the Matsuda index, we found more significant differences among groups than insulinogenic index as with the study by Abdul-Ghani et al.[5]

We compared the ROC curves of indices between groups distinguishing the prolonged glucose elevation group (group III + IV) from the rapid glucose lowering group (group II). Between group II and group III + IV, disposition index showed good AUC of ROC compared to insulinogenic and Matsuda indices (Figure 2B). The Matsuda index is a good indicator of whole-body insulin sensitivity.[14] On the other hand, in Japanese, IGT is associated with reduction of insulin secretion.[29] These data suggested low early secretion of insulin has larger impact on glucose intolerance of Japanese than low peripheral insulin sensitivity. Further, disposition index, an index that indicates the composition of insulin secretion and sensitivity, may be a good indicator of glucose tolerance.

T2DM and its complications account for more than 2 million deaths every year, and they impose substantial economic costs on patients, on their families and on health systems.[30] The direct annual cost of diabetes in the world is estimated at $825 billion, with China ($170 billion), the USA ($105 billion), India ($73 billion) and Japan ($37 billion) having the largest costs.[30] In the present study, about three fourths of young Japanese subjects within physiological range of glycaemic control accompanied sequential decreases in insulin sensitivity and secretion. Previous report showed that Japanese have lower insulin secretion potential than Caucasians.[31] Furthermore, prevalence of T2DM among Asian Americans is higher than Caucasians.[32] The National Health and Nutrition Survey by Ministry of Health, Labour and Welfare reported that fat intake of Japanese is increasing. The insulin resistance is expected to increase as previous study stated.[33] To reduce the economic burden of T2DM, it seems important to identify those at high-risk and to promote lifestyle habit improvements for the prevention of macrovascular diseases. Although this study showed no significant difference in HOMA-IR and HOMA-β among young healthy Japanese individuals, subjects with decreased insulin sensitivity and secretion could be found by 75gOGTT and disposition index.

There are some limitations in our study. First, we did not take familial T2DM history into consideration, and individuals with affected parents should not have participated in the study. Second, we did not account for food intake and exercise habits, especially the behaviour of previous day, and these may affect insulin sensitivity or secretion. Third, the omission of the 90-min value might have also compromised the accuracy of our estimates of the Matsuda index, the AUCg and the AUCi. Real glucose shape (monophasic or biphasic) was not assessed either. Fourth, this study is a pure cross-sectional study and only provides indirect evidence of an increased risk for the development of type 2 diabetes mellitus. Fifth, participants took OGTT only one time. Therefore, intraindividual variability was not assessed.

In conclusion, even in a young and healthy Japanese individual within the physiological range of glucose control, there is a sequential decrease in insulin sensitivity and secretion. So that, the promotion of lifestyle habit improvements for prevention of T2DM is needed for young Japanese. Further study is needed to investigate the familial history, food and exercise habit, activity former to the study and 90-minute value, and follow-up study will make clear the glucose metabolism and future risk of T2DM among young Japanese.

CONFLICT OF INTEREST

There are no conflicts of interest to declare.

AUTHORS' CONTRIBUTIONS

TK and MM designed the study. OA, TO, KT, YS, HI and MN have contributed to data collection. AY contributed to data interpretation and wrote the initial draft of the manuscript. TK contributed to analysis and interpretation of data, and assisted in the preparation of the manuscript. MM critically reviewed the manuscript and finally approved of the article. All authors approved the final version of the

manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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