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Factors responsible for deteriorating glucose tolerance in newly diagnosed type 2 diabetes in Japanese men

Rie Mitsui[a], Mitsuo Fukushima[a,b,*], Yuichi Nishi[a], Naoya Ueda[a], Haruhiko Suzuki[a], Ataru Taniguchi[c], Yoshikatsu Nakai[d], Toshiko Kawakita[e], Takeshi Kurose[a], Yuichiro Yamada[a], Nobuya Inagaki[a], Yutaka Seino[a,c]

[a]*Department of Diabetes and Clinical Nutrition, Graduate School of Medicine, Kyoto University, Kyoto 606-8507, Japan*
[b]*Department of Health Informatics Research, Translational Research Informatics Center, Foundation for Biomedical Research and Innovation, Kobe 650-0047, Japan*
[c]*Division of Diabetes and Clinical Nutrition, Kansai-Denryoku Hospital, Osaka 553-0003, Japan*
[d]*Faculty of Medicine, School of Health Sciences, Kyoto University, Kyoto 606-8507, Japan*
[e]*Department of Internal Medicine, Kyoto Preventive Medical Center, Kyoto 604-8491, Japan*

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Abstract

Hyperglycemia frequently continues to worsen even after the diagnosis of overt diabetes. The aim of this study is to evaluate the factors contributing to increasing glucose intolerance after onset of type 2 diabetes in Japanese subjects. Five hundred fifty newly diagnosed type 2 diabetic patients were classified into 3 degrees of hyperglycemia based on plasma glucose levels estimated by 75-g oral glucose tolerance test: diabetes mellitus with isolated fasting hyperglycemia (DM/IFH), DM with isolated postchallenge hyperglycemia (DM/IPH), and DM with fasting and postchallenge hyperglycemia (DM/FPH). In addition, the DM/IFH and DM/IPH groups were subdivided to clarify the determinants of fasting and postchallenge hyperglycemia. Insulin secretion was evaluated by insulinogenic index, and insulin sensitivity was evaluated by composite index of insulin sensitivity (ISI composite). The insulinogenic index in DM/IFH was highest of the 3 groups ($P < .0001$). The insulinogenic index in DM/IPH was higher than in DM/FPH ($P < .0001$). The international sensitivity index composite in DM/IPH was highest of the 3 groups ($P < .05$). Although impaired early-phase insulin secretion plays the crucial role in deterioration from DM/IFH to DM/FPH in Japanese subjects, impaired early-phase insulin secretion and decreased insulin sensitivity both are factors in deterioration from DM/IPH to DM/FPH. In addition, comparison of subgroups of DM/IFH and DM/IPH shows that although decreased early-phase insulin secretion plays the more significant role in postchallenge hyperglycemia in Japanese subjects, insulin sensitivity is the more important factor in fasting hyperglycemia.

1. Introduction

Type 2 diabetes is a heterogeneous disorder characterized by progressive elevation of plasma glucose (PG) levels. Although the occurrence of diabetes in Japan is increasing as in other countries, the hyperglycemia of Japanese subjects is typically because of factors that differ somewhat from those of other ethnic groups [1-5], impaired insulin secretion, and sensitivity most notably being differently involved. In previous studies, we found that impaired early-phase insulin secretion plays the more important role in deterioration from normal glucose tolerance (NGT) via impaired glucose tolerance (IGT) to type 2 diabetes in Japanese subjects [6]. This agrees with reports on the importance of impaired early-phase insulin secretion in type 2 diabetes in Japanese subjects [7,8]. These findings differ from those in Pima Indians, Mexican Americans, and Caucasian populations, in which increasing insulin resistance is clearly the more important factor in developing glucose intolerance [9,10]. In the present study, we investigated the factors responsible for decreased glucose tolerance after onset of diabetes and evaluated the contribution of these factors in fasting and postchallenge hyperglycemia.

We classified 550 Japanese men with newly diagnosed diabetes mellitus (DM) into 3 subgroups of glucose intolerance based on 75-g oral glucose tolerance test

* Corresponding author. Tel.: +81 78 304 5988; fax: +81 78 304 5989.
E-mail address: fukum@tri-kobe.org (M. Fukushima).

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(OGTT): DM with isolated fasting hyperglycemia (DM/IFH), DM with isolated postchallenge hyperglycemia (DM/IPH), and DM with fasting and postchallenge hyperglycemia (DM/FPH) (Fig. 1A). Insulin secretion and insulin sensitivity measurements were compared to evaluate the factors involved in the deterioration of glucose tolerance in newly diagnosed type 2 diabetic Japanese subjects. The insulinogenic index (30 minutes) was used as the parameter of early-phase insulin secretion [11,12]; the composite index of insulin sensitivity (ISI composite) was used as the parameter of insulin sensitivity [13]. Subcategories of DM/IFH and DM/IPH were compared to evaluate the contributions of these factors in fasting and postchallenge hyperglycemia.

2. Materials and methods

2.1. Subjects

We recruited for closer evaluation 550 Japanese men undergoing 75-g OGTT who had positive urine glucose test, greater than 5.6 mmol/L fasting PG (FPG), greater than 5.0% HbA_{1c}, or family history of diabetes at initial examination for regular medical check-up at Kyoto University Hospital, Ikeda Hospital, Kansai-Denryoku Hospital, Kansai Health Management Center, and Kyoto Preventive Medical Center between 1993 and 2004. OGTT was performed within 3 months of the initial examination. All subjects were Japanese males with no signs of hypertension, hepatic, renal, endocrine, or malignant diseases. No subject had engaged in heavy exercise, had taken gastrectomy, or had taken any medication known to affect glucose metabolism before the study. The study was designed in compliance with the ethics regulations set out by the Helsinki Declaration.

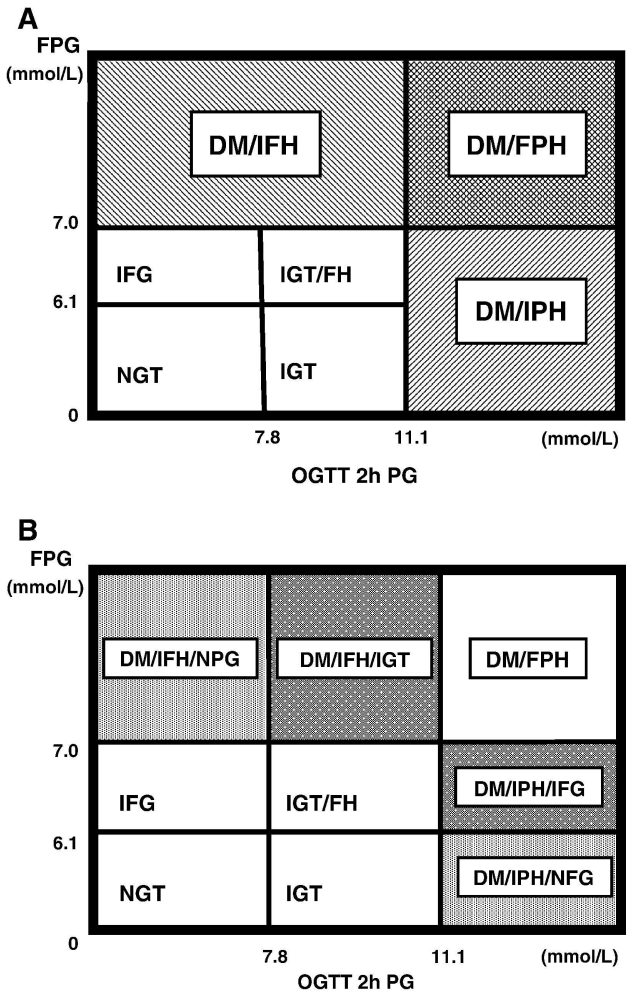

Fig. 1. A, Degrees of glucose intolerance: DM/IFH, DM/FPH, and DM/IPH. B, DM/IFH subdivided into 2 groups: DM/IFH/NPG and DM/IFH/IGT. DM/IPH subdivided into 2 groups: DM/IPH/NFG and DM/IPH/IFG.

Standard OGTT was administered according to the National Diabetes Data Group recommendations [14], which require the subjects to fast overnight for 10 to 16 hours. We obtained fasting, 0.5-, 1-, 1.5-, and 2-hour blood samples for measurement of PG, and fasting, 0.5-, 1-, and 2-hour samples for measurement of serum insulin after oral administration of 75-g glucose. Blood samples for measurements of HbA_{1c}, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglyceride levels were collected after an overnight fast.

DM was defined by the 1998 World Health Organization diagnostic criteria [15]. Diabetic subjects were classified into 3 groups based on the results of OGTT: DM/IFH, FPG $\geq$7 mmol/L and 2-hour PG level <11.1 mmol/L (n = 66); DM/IPH, FPG <7 mmol/L and 2-hour PG level $\geq$11.1 mmol/L (n = 148); and DM/FPH, FPG $\geq$7 mmol/L and 2-hour PG level $\geq$11.1 mmol/L (n = 336) (Fig. 1A).

To evaluate the factors involved in fasting and postchallenge hyperglycemia, we subdivided DM/IFH and DM/IPH into DM/IFH with normal postchallenge glucose levels (DM/IFH/NPG), FPG $\geq$7 mmol/L and 2-hour PG level <7.8 mmol/L (n = 17); DM/IFH with IGT (DM/IFH/IGT), FPG $\geq$7 and 7.8 mmol/L $\leq$ 2-hour PG level <11.1 mmol/L (n = 49); DM/IPH with normal fasting glucose levels (DM/IPH/NFG), FPG <6.1 mmol/L and 2-hour PG level $\geq$11.1 mmol/L (n = 50); and DM/IPH with impaired fasting glucose (DM/IPH/IFG), 6. mmol/L $\leq$ FPG <7 mmol/L $\leq$ 2-hour PG level $\geq$11.1 mmol/L (n = 98). As shown in Fig. 1B, DM/IFH/NPG is characterized by increasingly impaired fasting glucose and 2-hour PG within normal limits, whereas DM/IPH/NFG is characterized by increasingly impaired 2-hour PG and fasting glucose within normal limits.

2.2. Measurements

PG level was measured by glucose oxidase method using Hitachi Automatic Clinical Analyzer 7170 (Hitachi, Tokyo, Japan). Serum insulin level was measured by 2-site radioimmunoassay (Insulin Riabead II, Dainabot, Tokyo, Japan), as reported previously [6]. Serum total cholesterol, HDL-C, and triglyceride levels were measured as reported previously [16].

Table 1
Clinical characteristics of DM/IFH, DM/IPH, and DM/FPH

	DM/IFH	DM/IPH	DM/FPH
n	66	148	336
Age (y)	52.3 ± 1.2*	55.7 ± 0.8**	52 ± 0.5
BMI (kg/m2)	24.4 ± 0.5	24.5 ± 0.2	24.8 ± 0.2
FPG (mmol/L)	7.5 ± 0.1*,**	6.4 ± 0.0	8.9 ± 0.1
2-h PG (mmol/L)	8.8 ± 0.2*,**	13.1 ± 0.1**	17.2 ± 0.2
Fasting insulin (pmol/L)	50 ± 4	46 ± 2	50 ± 1
HbA_{1c} (%)	6.2 ± 0.1**	6.1 ± 0.1**	7.5 ± 0.1
Triglycerides (mmol/L)	1.72 ± 0.16	2.35 ± 0.26	2.15 ± 0.15
Total cholesterol (mmol/L)	5.43 ± 0.13	5.51 ± 0.12	5.46 ± 0.06
HDL-C (mmol/L)	1.44 ± 0.07	1.36 ± 0.04	1.36 ± 0.02

Data are mean ± SE.
* $P < .05$ (vs DM/IPH).
** $P < .005$ (vs DM/FPH).

Insulinogenic index was used to measure the capacity of early-phase insulin secretion [11,12], and ISI composite was used to measure systemic insulin sensitivity [13], according to the following formulas:

$$\text{Insulinogenic index} = [30\text{-minute serum insulin} - \text{fasting serum insulin (FI) (pmol/L)}] / [30\text{-minute plasma glucose} - \text{FPG (mmol/L)}] \quad [11, 12]$$

$$\text{ISI composite} = 10000 / [\text{FPG (mg/dL)} \times \text{FI}(\mu\text{U/mL})] \times [\text{mean OGTT PG (mg/dL)} \times \text{mean OGTT serum insulin } (\mu\text{U/mL})]^{0.5} \quad [13]$$

2.3. Statistical analysis

All data are expressed mean ± SE. All statistical analyses were performed using STATVIEW 5 system (Abacus Concepts, Berkeley, CA). Age, body mass index (BMI), FPG, 2-hour PG, HbA_{1c}, triglycerides, total cholesterol, HDL-C, insulinogenic index, and ISI composite were compared among DM/IFH (DM/IFH/NPG, DM/IFH/IGT), DM/IPH (DM/IPH/NFG, DM/IPH/IFG), and DM/FPH groups by general analysis of variance. For comparison between 2 groups, unpaired Student *t* test was performed as post hoc analysis. $P < .05$ was considered statistically significant.

3. Results

3.1. Clinical characteristics

Table 1 shows the clinical and metabolic characteristics of the 550 Japanese men classified with DM/IFH, DM/IPH, and DM/FPH. The age and BMI (mean ± SE) were 53.0 ± 0.4 years and 24.7 ± 0.2, respectively. The mean age of the DM/IPH group was significantly higher than that of the other 2 groups ($P < .005$). There was no significant difference in BMI, triglycerides, total cholesterol, or HDL-C among the 3 groups. HbA_{1c} and the area under the curve of glucose (DM/IFH, 25 056; DM/IPH, 26 284; and DM/FPH, 33 509) were significantly higher in the DM/FPH group than in the other groups ($P < .0001$, respectively).

3.2. Insulin secretion

The insulinogenic indices of the 3 groups are shown in Fig. 2A. The insulinogenic index in the DM/IFH group was significantly higher than in the other groups ($P < .0001$). There was a significant difference in the insulinogenic index between the DM/IPH and DM/FPH groups ($P < .0001$).

3.3. Insulin sensitivity

Fig. 2B shows the ISI composite of the 3 groups. ISI composite in the DM/IPH group was significantly higher than in the other groups ($P < .05$). There was no significant difference in ISI composite between DM/IFH and DM/FPH.

3.4. Comparison of DM/IFH/NPG and DM/IPH/NFG

Seventeen subjects were classified DM/IFH/NPG and 50 subjects were classified DM/IPH/NFG. Table 2 shows a comparison of the DM/IFH/NPG and DM/IPH/NFG groups. There was no significant difference in mean age, BMI, or HbA_{1c} between the 2 groups. As shown in Fig. 1B, DM/IFH/NPG was characterized by increasingly impaired

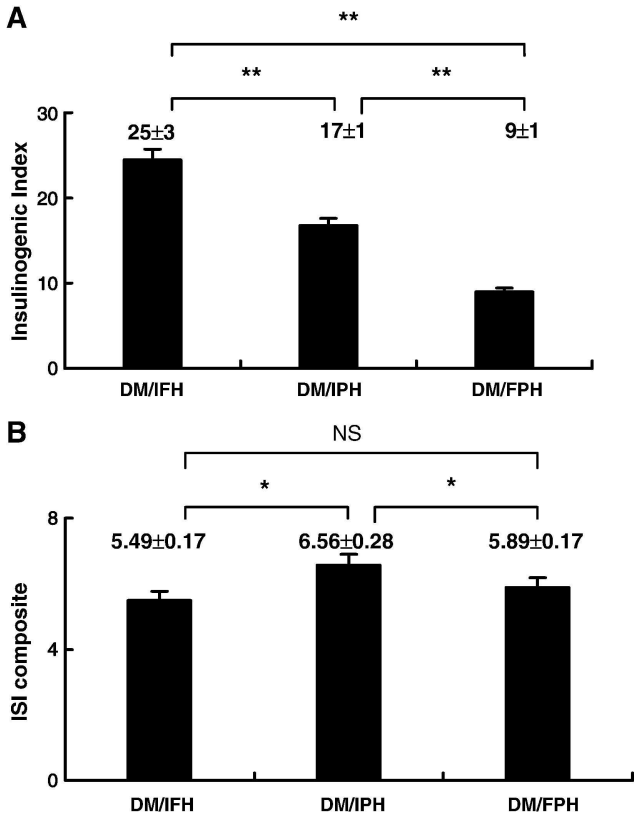

Fig. 2. Indexes of insulin secretion and sensitivity. A, Early-phase insulin secretion. Insulinogenic index in DM/IFH is highest. Insulinogenic index in DM/IPH is significantly higher than in DM/FPH. B, Insulin sensitivity. ISI composite in DM/IPH is significantly higher. *$P < .05$; **$P < .0001$; NS, not significant.

Table 2
Comparison of DM/IFH/NPG and DM/IPH/NFG

	DM/IFH/NPG	DM/IPH/NFG	*P*
n	17	50	
Age (y)	51.3 ± 2.7	54.8 ± 1.4	NS
BMI (kg/m^2)	23.6 ± 0.8	23.9 ± 0.3	NS
HbA_{1c} (%)	6.0 ± 0.2	5.9 ± 0.1	NS
Insulinogenic index	34 ± 8	17 ± 3	<.05
ISI composite	5.9 ± 0.82	8.33 ± 0.56	<.05

Data are mean ± SE. NS indicates not significant.

fasting glucose and 2-hour PG within normal limits, whereas DM/IPH/NFG was characterized by increasingly impaired 2-hour PG and fasting glucose within normal limits. The insulinogenic index in DM/IFH/NPG was significantly higher than in DM/IPH/NFG ($P < .05$). The ISI composite in DM/IPH/NFG was significantly higher than in DM/IFH/NPG ($P < .05$).

4. Discussion

In the present study, we evaluated the factors contributing to deterioration of glucose tolerance after the onset of type 2 diabetes in Japanese subjects. We previously reported that impaired early-phase insulin secretion plays an important role in the development from NGT via IGT to DM/IPH in Japanese subjects [6,17]. The present study reveals a reduction in the insulinogenic index, a measure of early-phase insulin secretion, in DM/FPH compared with DM/IPH (Fig. 2A). The ISI composite, an index of systemic insulin sensitivity, is also decreased in the deterioration from DM/IPH to DM/FPH (Fig. 2B). Although both impaired insulin secretion and insulin sensitivity are important factors in the deterioration from DM/IPH to DM/FPH, impaired early-phase insulin secretion is the more important factor in deterioration from DM/IFH to DM/FPH in Japanese subjects (Fig. 2A and B). We also classified the subjects into 3 groups based on American Diabetes Association classification: NGT, IFG, and DM. Thirty-two subjects were NGT, 117 were IFG, and 401 were DM. Of the 550 diabetic subjects judged only by the FPG level, 149 (27%) were NGT or IFG. Thus, FPG measurement as well as 2-hour PG measurement is important at the diagnosis of diabetes in Japanese subjects.

To clarify the factors involved in fasting and postchallenge hyperglycemia, we compared 2 subgroups of DM/IFH and DM/IPH: DM/IFH/NPG, DM/IFH/IGT, DM/IPH/NFG, and DM/IPH/IFG (Fig. 1B). DM/IFH/NPG is characterized by increasingly impaired fasting glucose and 2-hour PG within normal limits; DM/IPH/NFG is characterized by increasingly impaired 2-hour PG and fasting glucose within normal limits. In the present study, DM/IFH/NPG was associated with lower insulin sensitivity, and DM/IPH/NFG was associated with impaired early-phase insulin secretion as shown in Table 2. There was no significant difference in mean age, BMI, or HbA_{1c} between these 2 groups. Thus, although decreased insulin sensitivity plays the more important role in increasing FPG, reduced early-phase insulin secretion plays the more important role in increasing 2-hour PG in newly diagnosed Japanese type 2 diabetic subjects.

Glucotoxicity is induced by chronic hyperglycemia; a short time exposure to elevated glucose induces reversible glucose desensitization [18,19], whereas longer exposure causes irreversible beta-cell dysfunction, decreasing beta-cell mass by inducing apoptosis [20]. Immunohistochemical examination in autopsy cases of Japanese type 2 diabetes found that beta-cell mass was decreased because of oxidative stress [21]. Short-term glucotoxicity acts to reduce both glucose-induced insulin secretion and glucose uptake in skeletal muscle [19]. Both DM/IFH and DM/IPH showed normal PG levels in the postchallenge and the fasting state, respectively, suggesting that the subjects had been exposed to elevated glucose for a relatively short period. The simultaneously declining insulin secretion and the decreasing insulin sensitivity also implicate glucose desensitization in deterioration to DM/FPH in both groups. Deranged glucose metabolism induced by hyperglycemia per se was found in type 2 diabetic patients with a FPG level greater than 6.4 mmol/L in previous studies [22]. The mean fasting glucose level in DM/IPH of 6.4 mmol/L found in this study also suggests a role of glucotoxicity in the deteriorating glucose tolerance seen after onset of type 2 diabetes.

Type 2 diabetes is a disease of progressing glucose intolerance that frequently becomes more severe after onset. Previous large-scale studies comparing diet therapy to intensive therapy revealed that glucose tolerance continues to deteriorate even after treatment of diabetes has begun. For example, the United Kingdom Prospective Diabetes Study found that HbA_{1c} increased from 7.2% to 7.6% after 3 years and from 6.9% to 8.0% after 6 years among patients with type 2 diabetes on diet therapy [23,24]. In these studies, fasting glucose levels were increased from 8.3 to 9.0 mmol/L and 8.0 to 9.5 mmol/L. The Kissingen Diabetes Intervention Study found that both basal and reactive C-peptide levels continued to decrease 15 to 20 years after the diagnosis of type 2 diabetes and suggested a relationship between the decrease in C-peptide levels and the increase in HbA_1 levels [25]. Although there are few studies regarding deteriorating function after the development of type 2 diabetes, it is well known that decreasing beta-cell activity and increasing insulin resistance both play important roles in the increasing glucose intolerance [26]. Indeed, several studies have identified ethnic factors involved in the deteriorating glucose tolerance characteristic of the onset of type 2 diabetes. For example, increasing insulin resistance is the more important factor in Pima Indians, Mexican Americans, and Caucasians [9,10], whereas impaired insulin secretion is the more important factor in Japanese subjects, as reported previously [6,27,28].

We examined insulin sensitivity, glucose effectiveness, and endogenous glucose production using the stable-labeled minimal model approach in our previous study [29]. Despite the impairment in both glucose turnover rate and insulin secretion, the magnitude of the derangement in insulin secre-

tion is greater than in the glucose turnover rate in Japanese subjects. In addition, we have reported that the validity of the ISI composite and insulinogenic index is confirmed by insulin sensitivity index and insulin secretion capacity (acute insulin response) obtained from minimal model analysis, respectively [30]. Thus, similar conclusions were reached in different Japanese populations by different methods.

The reason for the increasing prevalence of type 2 diabetes in Japan is, at least in part, related to an increased prevalence of obesity due to lifestyle changes. However, obesity in Japan is less extreme, the average BMI of Japanese diabetic subjects having increased only slightly to 23 to 25 according to typical epidemiological study. It is also difficult to establish insulin resistance as the cause because the mean BMI of Japanese diabetic patients is less than 25 and the ISI composite is more than 5. In addition, glucose intolerance in Japanese subjects is well known to be dependent on poor reserve capacity of insulin secretion rather than insulin resistance [6,7,27,31]. Thus, Japanese subjects may develop glucose intolerance and diabetes because of only slight impairment of insulin sensitivity. Another factor may be that Japanese subjects are more readily susceptible to glucotoxicity and lipotoxicity due to slight impairments of carbohydrate and lipid metabolism [21,32,33].

In conclusion, although impaired early-phase insulin secretion plays a crucial role in the deterioration from DM/IFH to DM/FPH, impaired early-phase insulin secretion and decreased insulin sensitivity are both key factors in the deterioration from DM/IPH to DM/FPH. The simultaneous degradation of the various factors involved in the maintenance of PG after the development of type 2 diabetes suggests glucotoxicity. In addition, although decreased early-phase insulin secretion plays an important role in postchallenge hyperglycemia, decreased insulin sensitivity contributes to elevated FPG levels. The distinct pathophysiologies of type 2 diabetes could provide a basis for patient management. Treatment for DM/IFH might be targeted to impaired insulin secretion or to decreased insulin sensitivity, and treatment of DM/IPH might be targeted to impaired early-phase insulin secretion. These findings should be helpful clinically in stabilizing glucose levels in Japanese type 2 diabetic patients at onset of type 2 diabetes.

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