# ORIGINAL

# Nateglinide with glibenclamide examination using the respiratory quotient (RQ)

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**Abstract : *Purpose*: The respiratory quotient (RQ) is useful for evaluating glucose and lipid metabolism *in vivo*. We previously reported that the RQ value, even after fasting, was high in diabetics being treated with sulphonylurea (SU), which might explain the accumulation of fat, leading to weight gain in such individuals. In the present study, we measured the RQ in type II diabetic patients who were being treated with a rapid-onset/short-duration insulinotropic agent, nateglinide, and compared it with those being treated with SU. *Methods*: A glucose tolerance test was performed in 20 patients with type II diabetes mellitus treated with nateglinide and in 14 patients treated with SU, and the RQ was simultaneously measured. *Results*: The RQ values in the patients treated with nateglinide, were similar to those in healthy adults, but was lower than in those treated with SU. No weight gain was observed in patients treated with nateglinide. *Conclusion*: A significant weight gain was reported in subjects treated with SU, accompanied by an increase in RQ. However, weight gain was less frequent in diabetics treated with nateglinide. J. Med. Invest. 53:303-309, August, 2006**

## INTRODUCTION

In the treatment of diabetes, strict glycemic plasma glucose control increases the incidence of hypoglycemia, and fat accumulation-related obesity frequently occurs according to DCCT (1) and UKPDS 33 (2). The respiratory quotient (RQ) is a noninvasive and simple test for evaluating both glucose and fat metabolism and can provide different information from serum levels of glucose and hemoglobin A1c. The measurement of RQ facili-

tates the combustion of glucose and lipid metabolic states as well as synthesis of fat from glucose. When lipids are synthesized from surplus glucose, the RQ increases to 1.0 or more (3).

With respect to the relationship between RQ and diabetes, it has been reported that a reduced glucose utilization decreased the RQ in untreated diabetics (4). However, our knowledge of the influence of treatment on RQ is incomplete, especially for newly developed drugs. In our previous studies, we found that well-controlled diabetic patients with insulin and SU showed significantly higher RQ values compared to normal subjects. Those with RQ values >1.0 gained more weight after they started drug treatment. Nateglinide, a rapid insulin secretagogue, facilitates the early phase of insulin se-

cretion and has been used in the treatment of type 2 diabetic patients with postprandial hyperglycemia. However, the duration of its action is much shorter than classic SUs. Therefore, a lower RQ and less fat accumulation would be expected in subjects being treated with nateglinide.

In the present study, we compared the effect of nateglinide on RQ and weight gain and the results were compared with those for a standard SU agent, glibenclamide.

## PATIENTS AND METHODS

### 1) Patients

The subjects were 20 patients being treated with nateglinide and 14 patients being treated with glibenclamide (Table 1). They were diagnosed as having non-insulin-dependent diabetes mellitus according to the criteria established by the Japanese Society of Diabetes (1999) : a morning fasting plasma glucose (FPG) level of 126 mg/dl or more, or a casual plasma glucose level of 200 mg/dl or more. In the nateglinide group, 90 mg of nateglinide was administered before each meal for a period of 6 months, and the mean HbA1c level was 6.7± 0.78% (mean± SD). In the glibenclamide group, 2.5 mg of glibenclamide was administered before breakfast for a period of 6 months, and the mean HbA1c level was 7.0± 0.64 % Furthermore, there were no major diabetic complications in either group. There were no significant differences in gender, age, body mass index (BMI), or FPG between the two groups. As complications, hypertension and hyperlipidemia were observed in 12 and 10 patients in the nateglinide group and in 8 and 6 patients in the glibenclamide group, respectively, without significant differences between the two groups (the subjects with hypertension and smokers were excluded in the present study).

The present study was approved by the directors of the medical office, and informed consent was given to the patients or their family after full explanation of the purpose of this study.

### 2) Measurement of plasma glucose and RQ (Fig.1)

The protocol of this study is outlined in Fig. 1. The RQ was measured for 10 minutes using a TEEM-100 device (Aero Sport Inc. Ann Arbor Michigan, USA) or an AE-300S device (MINATO Inc. Osaka, Japan). The subjects were rested in a sitting position 10 minutes prior to the examination until the end of the examination, and the nose and mouth was covered with a mask. After confirming the absence of leakage in the measurement circuit, the RQ was measured only on spontaneous respiration. To eliminate measurement errors related to residual air in the circuit immediately after the start of the examination and the influence of hyperventilation, the mean over the latter 5 minutes was taken as the RQ value.

After administering nateglinide at 90 mg or glibenclamide at 2.5 mg, a Trelan-G (75 g glucose) tolerance test was performed. The plasma glucose level and RQ were measured before loading and at 30, 60, 90, 150, and 180 minutes after loading. To avoid the influence of motion, the subjects were rested in a sitting position before and after measurement.
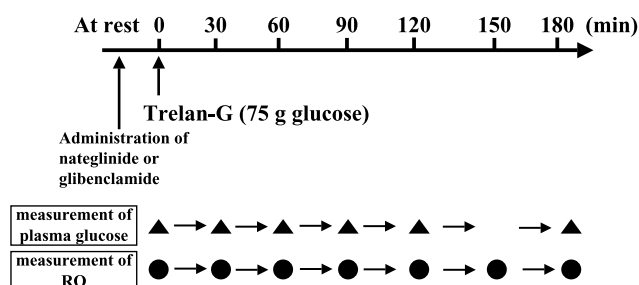


Fig. 1. Protocol for this study.
RQ, respiratory quotient.

### 3) Ratio of immunoreactive insulin change to plasma glucose change (ΔIRI /ΔPG) and homeostasis model assessment-insulin resistance (HOMA-IR)

When the plasma glucose level and RQ were measured, $\Delta IRI/\Delta PG$ was calculated by dividing IRI 30 minutes after the ingestion of Trelan-G by plasma glucose changes after 30 minutes to investigate insulin secretion. Furthermore, we compared insulin resistance between the two groups by HOMA-IR measurements.

### 4) Measurement of body weight

In the two groups, the daily calorie intake was

Table 1 Patient characteristics

|  | Nateglinide (n=20) | Glibenclamide (n=14) | p value |
|---|---|---|---|
| Sex(men/women) | 9/11 | 6/8 | ns |
| Age (years) | 67.7± 8.5 | 70.4± 8.9 | ns |
| Body height (cm) | 156.8± 9.4 | 154.1± 12.1 | ns |
| Body weight (kg) | 57.1± 10.6 | 61.3± 6.8 | ns |
| BMI (kg/m²) | 23.4± 4.9 | 25.8± 2.8 | ns |
| FPG (mg/dl) | 135.1± 21.2 | 132.4± 40.0 | ns |

BMI, body mass index ; FPG, fast plasma glucose. (mean± SD)

established as the standard body weight× 25 kcal/ day for diet therapy. The mean body weight was measured 6, 3, and 1 month before the examination and on the day of examination to compare changes in body weight.

## RESULTS

### 1) Case presentation in the nateglinide and gliben- clamide groups

The plasma glucose levels and RQ for a 62-year- old female (HbA1c : 6.4%) in the nateglinide group are shown in Fig. 2. The FPG levels were 101 mg/dl, and 180 mg/dl after 2 hours. The RQ values before 75 g OGTT loading and 60, 120, and 180 minutes after loading were 0.791, 0.834, 0.861, and 0.804, respectively, similar to the RQ pattern in healthy adults.

The plasma glucose levels and RQ in a 65-year- old male (HbA1c : 6.7%) in the glibenclamide group are shown in Fig. 3. FPG levels were 102 mg/dl, and 176 mg/dl after 2 hours. The RQ values before 75 g OGTT loading and 60, 120, and 180 minutes after loading were 0.906, 0.944, 0.988, and 0.978, respectively, higher than the values in the repre- sentative patient in the nateglinide group and in healthy adults.
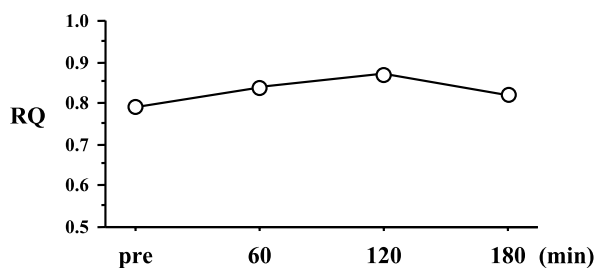


Fig. 2. Plasma glucose levels and RQ in a 62-year-old female (HbA1c : 6.4%) in the nateglinide group.
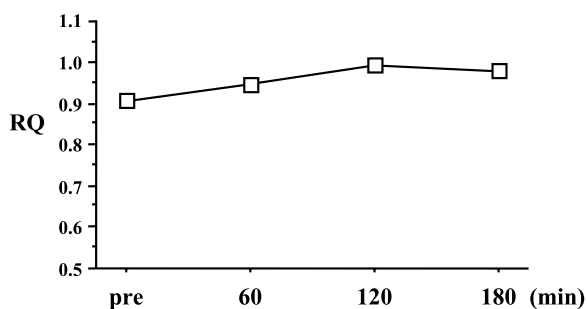RQ, respiratory quotient ; Pre, before 75 g OGTT loading.



Fig. 3. Plasma glucose levels and RQ in a 65-year-old male (HbA1c : 6.7%) in the glibenclamide group.
RQ, respiratory quotient ; Pre, before 75 g OGTT loading.

### 2) Changes in plasma glucose in the nateglinide and glibenclamide groups (Fig. 4)

As shown in Fig. 4, we compared the changes in plasma glucose levels between the two groups. The plasma glucose levels 180 minutes after a 75 g OGTT loading in the glibenclamide group was significantly higher than that in the nateglinide group. However, there were no significant differences at any other time points ; thus glycemic control was similar be- tween the two groups.
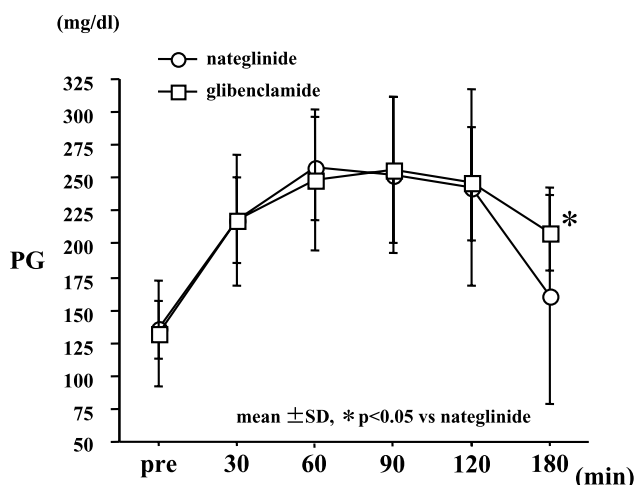


Fig. 4. Changes in plasma glucose levels between the two groups. PG, plasma glucose level.

### 3) Changes in RQ in the nateglinide and gliben- clamide groups (Fig. 5)

As shown in Fig. 5, we compared the changes in RQ between the two groups. The RQ values before and after loading in the nateglinide group were lower than those in the glibenclamide group; in
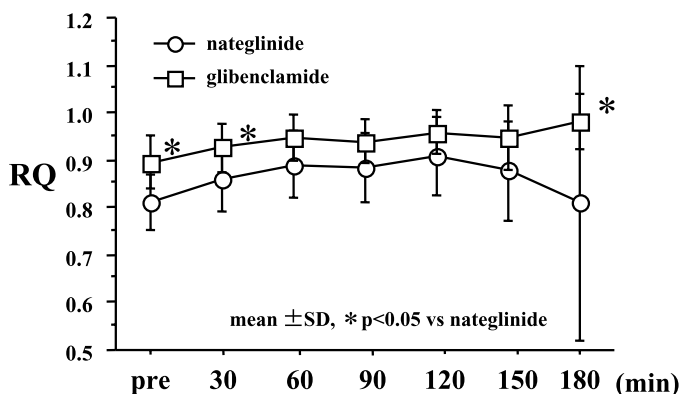


Fig. 5. Changes in RQ between the two groups. RQ, respiratory quotient.

particular, the values were significantly lower before loading and 30 and 60 minutes after loading (p<0.05).

### 4) *ΔIRI/ΔPG in the nateglinide and glibenclamide groups (Fig. 6)*

As shown in Fig. 6, we compared the ΔIRI/ΔPG ratio between the two groups. The ΔIRI/ΔPG values in the nateglinide and glibenclamide groups were 0.227± 0.048 and 0.136± 0.031, respectively. In the nateglinide group, initial insulin secretion was slightly higher, although there was no significant difference.



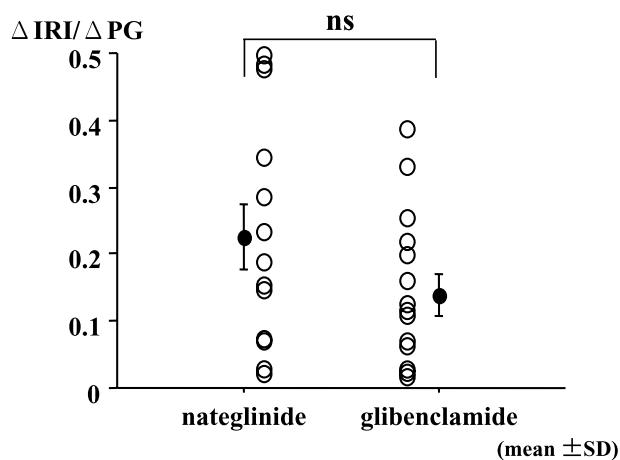Fig. 6. Comparison of ΔIRI/ΔPG between the two groups. ΔIRI /ΔPG, ratio of immunoreactive insulin change to plasma glucose change.

### 5) *HOMA-IR in the nateglinide and glibenclamide groups (Fig. 7)*

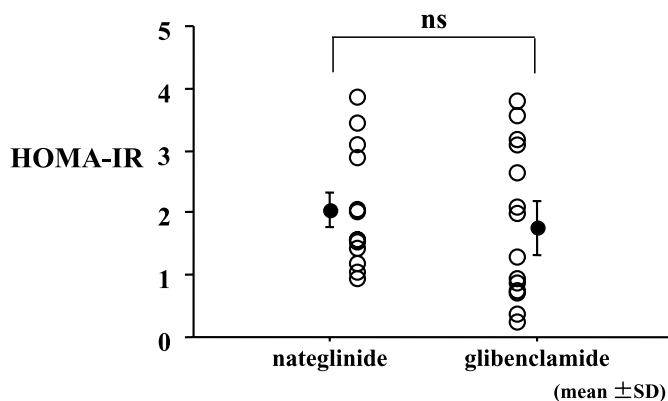As shown in Fig. 7, the HOMA-IR values in the nateglinide and glibenclamide groups were 2.05±



Fig. 7. HOMA-IR values in the nateglinide and glibenclamide groups.
HOMA-IR, homeostasis model assessment-insulin resistance.

0.27 and 1.87± 0.45, respectively. No marked difference in insulin resistance was found between the two groups.

### 6) *Changes in mean body weight in the nateglinide and glibenclamide groups (Fig. 8)*

Fig. 8 shows the changes in mean body weight for the two groups. In the nateglinide group, the mean body weight values 6 and 3 months prior to the examination and at the time of the examination were 59.3± 2.8 kg, 58.8± 2.7 kg, and 58.2± 2.7 kg, respectively, showing slight weight loss. On the other hand, in the glibenclamide group, the values were 59.4± 3.2 kg, 59.8± 3.2 kg, and 61.3± 3.1 kg, respectively, showing weight gain. There was a significant difference in the influence of the agent on body weight changes between the two groups (p=0.0004)
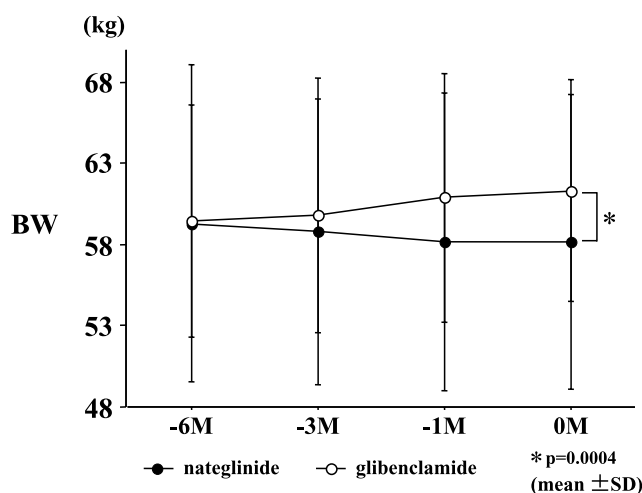


Fig. 8. Changes in mean body weight in the nateglinide and glibenclamide groups.
BW, body weight; M, month.

## DISCUSSION

Various metabolic disorders involving glucose and lipid metabolism occur in subjects with diabetes mellitus. The levels of plasma glucose and HbA1c, which are routinely used in the assessment of diabetes, are useful for evaluating only plasma glucose, that is, a portion of the metabolic state in diabetes. However, RQ is a noninvasive and simple test for evaluating not only glucose metabolism but lipid metabolism as well. The RQ value is calculated by dividing carbon dioxide output by oxygen intake. Thus, when glucose alone is utilized as an energy source, the value is 1.0. When lipids alone are

utilized, the value is 0.7. Therefore, this parameter reflects the ratio of glucose metabolism and lipid metabolism (5).

In a prospective UKPDS study involving patients with type II diabetes in England (6), obesity was frequent despite an increase in the incidence of hypoglycemia in the intensified therapy group in which stricter glycemic control was required. Yki-Jarvinen *et al.* indicated that routine treatment with SU agents may promote obesity (7). Carlson *et al.* also reported that intensified insulin therapy decreased the incidence of complications, but led to weight gain (8). Weight gain is mainly associated with an increase in fat, indicating that this finding causes further insulin resistance, disorders in lipid metabolism, and hypertension.

There are several studies of the relations between nateglinide and obesity (9-11). Ravussin *et al.* (12) and Nakaya *et al.* (13) reported that weight gain was frequent in patients with a high RQ value, suggesting that the RQ can be useful for predicting subsequent body weight changes.

In the present study, changes in the plasma glucose levels and ΔIRI/ΔPG and HOMA-IR values showed that glycemic control, balanced by insulin secretion and resistance, was similar between the nateglinide and glibenclamide groups. The difference in RQ in the present study may have been related to the difference in fat combustion or synthesis. When fat is metabolized, the RQ value decreases to approximately 0.7. In contrast, for fat synthesis, 1 mol of triglyceride is synthesized from glucose, and 23 mol of oxygen are produced. Thus, oxygen ingested via respiration is conserved, and the RQ increases to approximately 1 or greater. In some patients with diabetes being treated with insulin or SU, the RQ value exceeds 1 (13).

In the present study, in the nateglinide group, the RQ values before loading as well as 30 and 180 minutes after loading were significantly lower than those in the glibenclamide group, suggesting that the ratio of fat combustion was high in the nateglinide group, and that the ratio of fat synthesis was high in the glibenclamide group. High RQ values before glucose loading indicate that, even during the interdigestion period such as early morning or before meals, fat is still synthesized in these patients. This is consistent with the changes in body weight during the 6 months period before the examination, that is, weight loss in the nateglinide group and weight gain in the glibenclamide group.

The interval for the blood concentration of

glibenclamide to reached a maximum (Tmax) is 3 to 4 hours (14). However, for nateglinide, it is 30 minutes demonstrating that the latter would have a more immediate action (15). Therefore, nateglinide may not cause a rapid increase in plasma glucose, and may inhibit the elevation of postprandial plasma glucose levels, with a total insulin secretion than that in the glibenclamide group (16). In addition, nateglinide immediately dissociates from the sulfonylurea receptors of pancreatic βcells (17), and the action time of nateglinide is within 3 hour (18), shortening the duration of a high-insulin state, whereas the action time of glibenclamide is about 12 hours (19). Insulin promotes fat synthesis from glucose. Therefore, treatment with nateglinide may reduce the risk of hypoglycemia as well as weight gain.

Consistent with our results, Fukuda *et al.* (20) reported that nateglinide therapy for 6 months decreased plasma glucose levels without increasing BMI. In Americans, Horton *et al.* (21) reported that there were no significant changes in body weight (less than 1 kg) after single therapy with nateglinide for 6 months. Alternately, the difference in the actions on $K_{ATP}$ channels in the hypothalamus between nateglinide and glibenclamide may play a role in the less frequent weight gain related to nateglinide (22, 23).

There was no significant difference in HOMA-IR in both groups, but insulin secretion and resistance in response to a glucose stimulus was decreased in glibenclamide group because the plasma glucose levels 180 minutes after 75 g OGTT were significantly higher than the nateglinide group in the present study,. Therefore, we cannot deny that hyperglycemia after a food intake due to the severity of diabetes progression cause obesity besides pharmaceutical influence of diabetic drugs.

## CONCLUSION

RQ values in the nateglinide group was lower than those in the glibenclamide group. The RQ is useful for predicting weight gain. Nateglinide may not promote fat synthesis, and may not cause obesity. In the glibenclamide group, the RQ values after fasting as well as 30 and 180 minutes after loading were higher, suggesting that glibenclamide promotes fat synthesis immediately and for a period of 3 hours after an oral administration.

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