Comparison of energy metabolism in Insulin-Dependent and Non-Insulin-Dependent diabetes mellitus

Kazumi Takata*, Noriko Chiba*, Mariko Tawara*, Hisami Yamanaka* Emi Syuto*,

Ken-ichi Miyamoto*, Ichiro Yokota†, Junko Matsuda†, Yasuhiro Kuroda†and Eiji Takeda*

*Department of Clinical Nutrition ; and †Department of Pediatrics, The University of Tokushima School of Medicine, Tokushima, Japan

Abstract : To compare the metabolic consequences of insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM), glycemic control and energy metabolism were evaluated in 18 children displaying IDDM and 19 NIDDM adult patients. With rising concentrations of fasting blood glucose (FBG), hemoglobin A_{1C} and free fatty acid, the percentage of the ratio of resting energy expenditure (REE) to predicted REE expressed as %REE increased and the respiratory quotient (RQ) decreased. The linear regression between RQ and FBG showed the same gradient in IDDM and NIDDM although the RQ in IDDM was always 0.07 lower than that in NIDDM given various FBG concentrations. Those patients whose RQ values were less than 0.7, indicating ketone body production, included 8 (44%) IDDM and 2 (11%) NIDDM patients. These results may explain the relatively greater manifestation of ketoacidosis in IDDM. J. Med. Invest. 44 : 67-71, 1997

INTRODUCTION

Insulin stimulates the cellular uptake of glucose and subsequent glucose oxidation by suppressing free fatty acid (FFA) levels and fat oxidation (1). Insulin also activates pyruvate dehydrogenase (2, 3), which controls the entry of carbohydrates into the tricarboxylic acid cycle. Insulin-mediated glucose utilization is diminished in the presence of elevated plasma FFA concentration in patients with diabetes mellitus (4, 5). Fatty acid and its oxidation stimulate gluconeogenesis, which inhibits glucose uptake and glycolysis in liver (6, 7). In addition, a positive correlation has been reported between plasma FFA concentration or lipid oxidation and hepatic glucose production in non-insulin-dependent diabetes mellitus (NIDDM) patients (8, 9).

Elevated concentrations and the increased oxidation of plasma FFA have been shown to induce insulin resistance (10-12). Insulin resistance is a characteristic feature of NIDDM (8, 13, 14). In contrast, insulin resistance has not been demonstrated to be significant in treated insulin-dependent diabetes mellitus (IDDM) (15). However, it has been demonstrated that the cellular effect of insulin is reduced in IDDM (16-18). In addition, adolescents with poorly controlled IDDM have a significant degree of hepatic insulin resistance (19).

In this study, the relationship between glycemic control and indices of energy metabolism such as resting energy expenditure (REE) and respiratory quotient (RQ) was evaluated to compare the pattern of energy metabolism in IDDM and NIDDM patients.

PATIENTS AND METHODS

Patients

The study population consisted of 18 IDDM children who attended a summer camp for diabetic children and 19 NIDDM adult patients admitted to Tokushima University Hospital for dietary education and glycemic control. The physical characteristics of the subjects are shown in Table 1. Body mass index tended to be higher in NIDDM patients. IDDM patients underwent dietary therapy and received insulin. NIDDM patients were treated with either diet alone or oral hypoglycemic agents or both. Four NIDDM patients were re-studied after treatment for one month. Informed consent in this study was obtained from all subjects.

Energy metabolism studies

The REE was studied using open-circuit indirect calorimetry (Calorie Scale, Chest MI, Tokyo) employing a transparent ventilated hood system while the IDDM children attended camp or on the second day of admission

Table 1. Physical and metabolic parameters in IDDM and NIDDM patients

	IDDM[1] (n=18)	NIDDM[1] (n=19)
Age (y)	11.9±2.7[2]	54.4±12.9
BMI (kg/m²)	18.9±2.9	24.1±4.8
FBG (mg/dl)	175±99	186±84
HbA₁c (%)	8.64±1.6	9.29±2.2
FFA (μEq/l)	928±421	628±418[3]
% REE (%)	133±25	115±14[4]
RQ	0.707±0.06	0.768±0.06[5]

1. IDDM, insulin-dependent diabetes mellitus ; NIDDM, non-insulin-dependent diabetes mellitus ; BMI, body mass index ; FBG, fasting blood glucose ; HbA₁c, glycohemoglobin ; FFA, free fatty acid ; % REE, resting energy expenditure(REE)/predicted energy expenditure (BEE)x 100 ; RQ, respiratory quotient.
2. x±standard deviation (SD).
3-5. Significant difference between IDDM and NIDDM, 3, p<0.02 ; 4, p<0.001 ; 5, p<0.005.

for NIDDM patients. The system was calibrated before each test with a reference gas mixture (95% O_2 and 5% CO_2). The REE was measured for 15 min between 7 : 00 and 8 : 00 after a 12-h overnight fast. Energy expenditure was calculated from the respiratory gas exchange using a standard equation (20). The RQ and protein oxidation rate were calculated from measurements of daily urinary nitrogen excretion. Urinary nitrogen production was calculated from measured daily urinary urea elimination (21). Fat and carbohydrate utilizations were calculated from the nonprotein RQ (20). Percentages of the ratio of REE to predicted REE which was obtained from recommended dietary allowances for the Japanese (22), were expressed as % REE.

Analysis

The plasma glucose concentration was measured by the glucose oxidase method using a Beckman glucose analyzer II (Beckman Instrument, Fullerton, CA). FFA level was assayed by a fluorometric method (23). Hemoglobin A₁c (HbA₁c) concentration in blood was measured by high-pressure liquid chromatography and its reference level for the assay was 5-7%. Body composition including lean body mass was assessed by a bioelectric impedance analysis. All data are presented as means±SD. Statistical analyses were performed using Student's t test for unpaired data and the Wilcoxon matched pairs test for nonparametric data.

RESULTS

1) Physical and metabolic parameters in IDDM and NIDDM patients (Table 1)

Fasting blood glucose (FBG) and HbA₁c concentrations in NIDDM individuals were not significantly different from those of IDDM patients. In contrast, % REE and FFA concentrations were higher while the RQ was lower in IDDM patients than those of NIDDM. These results indicated that the rates of energy expenditure and lipid oxidation in IDDM were significantly elevated than those

of NIDDM patients. However glycemic control as estimated by FBG and HbA₁c concentrations were the same in both IDDM and NIDDM patients.

2) Relationship between FBG or HbA₁c and % REE or RQ in IDDM and NIDDM patients

% REE demonstrated a positive correlation with both FBG (r=0.490, p<0.05) and HbA₁c (r=0.477, p<0.05) in IDDM individuals. These parameters also showed same values in NIDDM patients although they were not significant (Figure 1 A and 1 B). RQ was found to have an inverse correlation with HbA₁c in NIDDM (r=-0.652, p<0.01) but was not remarkable in IDDM (Figure 2 A). Moreover, RQ had an inverse correlation with the FBG in both IDDM (r=-0.718, p<0.001) and NIDDM (r=-0.580, p<0.01) (Figure 2 B). The linear regression was similar for both IDDM and NIDDM patients. However, RQ values in IDDM individuals were always 0.07 lower than those in NIDDM, indicating a 17% higher lipid oxidation rate in IDDM than in NIDDM patients at various FBG concentrations.

3) Relationship between FFA and FBG in IDDM and NIDDM patients (Figure 3)
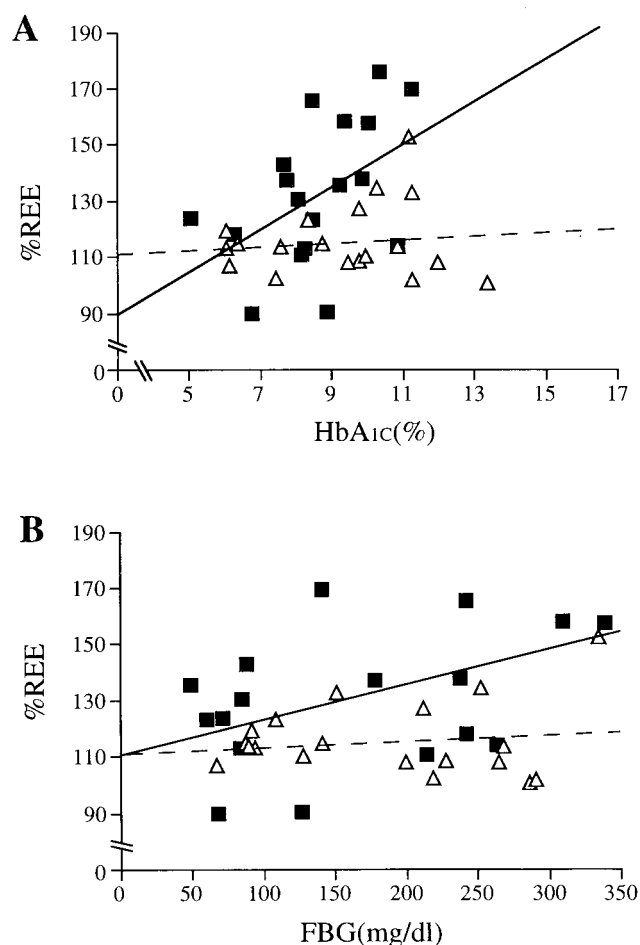
FFA concentrations in IDDM were more widely

Fig. 1. Relationship between A) HbA₁c (IDDM : r=0.477, p<0.05, NIDDM : ns.) and B) FBG (IDDM : r=0.490, p<0.05, NIDDM : ns.) and % REE in IDDM (■ - - - - and) and NIDDM (△ and – – –) patients.

distributed than those in NIDDM. FFA concentrations were positively related with FBG (r=0.655, p<0.01) in IDDM, although this relationship was not significant in NIDDM.

4) Relationship between % REE and RQ in IDDM and NIDDM patients (Figure 4)

A remarkable inverse relationship between % REE and RQ was observed in both IDDM (r=-0.670, p<0.01) and NIDDM patients (r=-0.520, p<0.05) (Figure 4). However,

the slope between those parameters was steeper in IDDM than in NIDDM. The lines corresponding to IDDM and NIDDM values crossed at 122 of % REE and 0.740 of RQ. In marked contrast, RQ values were found to be less than 0.7, which indicated the production of ketone bodies (24), in 8 (44%) of 19 IDDM patients and 2 (11%) of 19 NIDDM patients, respectively.

5) Effects of treatment on % REE and RQ in NIDDM patients

As shown in Table 2, a one-month period of treatment of 4 NIDDM patients resulted in improvement of FBG, HbA1c and FFA values. Likewise, % REE decreased remarkably while RQ slightly increased. Thus, all the biochemical and metabolic parameters improved with treatment.
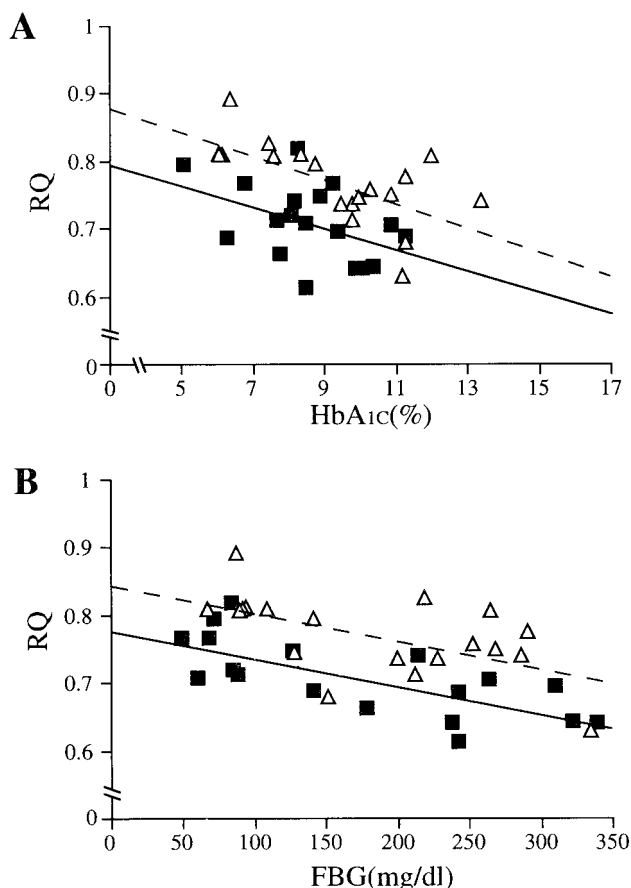

Fig. 2. Relationship between A) HbA1c (IDDM : ns, NIDDM : r= -0.652, p<0.01) and B) FBG (IDDM : r= -0.718, p<0.001, NIDDM : r=-0.580, p<0.01) and RQ in IDDM (■ - - - - and) and NIDDM (△ and – – –) patients.
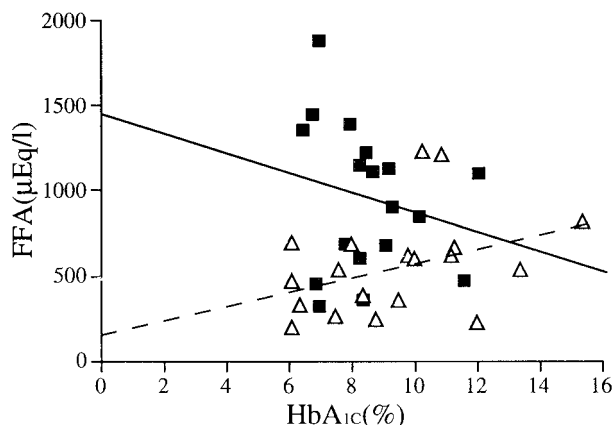

Fig. 3. Relationship between FBG and FFA in IDDM (■ - - - - and, r= -0.655, p<0.01) and NIDDM (△ and – – –, ns.) patients.
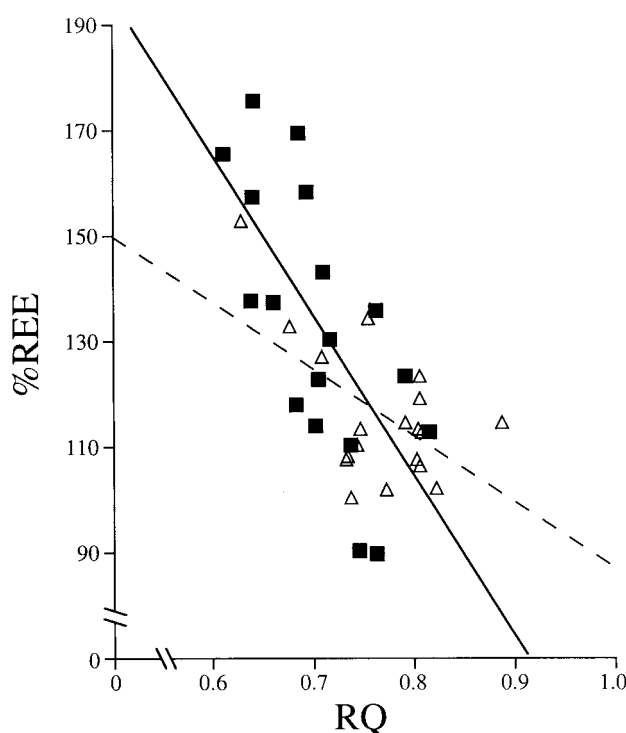
Fig. 4. Relationship between % REE and RQ in IDDM (■ - - - - and, r= -0.670, p<0.01) and NIDDM (△ and – – – , r= -0.520, p<0.05) patients.

Table 2. Effects of glycemic control on % REE and RQ in NIDDM patients

	Before (n=4)	After (n=4)
FBG (mg/dl)[1]	183±91[2]	153±73.
HbA1c (%)[1]	10.1±2.8	8.7±1.7
FFA (μEq/l)[1]	667±309	593±236
% REE (%)[1]	119±15	108±9[3]
RQ[1]	0.753±0.05	0.779±0.05

1. FBG, fasting blood glucose ; HbA1c, glycohemoglobin ; FFA, free fatty acid ; REE, resting energy expenditure ; RQ, respiratory quotient.
2. x±standard deviation (SD).
3. Significantly different than before treatment, p<0.05.

DISCUSSION

The negative correlation between FBG or FFA and RQ suggests that low insulin levels exert their regulatory effect on intracellular glucose and fat metabolism by controlling the availability of FFA substrate for fat oxidation, which in turn inhibits glucose oxidation. In diabetic patients, FFA oxidation consumes nicotinamide adenine dinucleotide, thereby resulting in an accumulation of acetyl CoA, a powerful allosteric inhibitor of pyruvate dehydrogenenase (25, 26). A prolonged effect of decreased glucose oxidation is an increase in pyruvate dehydrogenase kinase activity, which in turn leads to enhanced phosphorylation and inactivation of the pyruvate dehydrogenase complex (27). On the other hand, the accumulation of acetyl CoA activates pyruvate carboxylase, the first enzymatic step in the gluconeogenesis pathway (25), thus making more pyruvate available for gluconeogenesis (28). Furthermore, oxidation of FFA provides energy for gluconeogenesis and stimulates it in an FFA concentration dependent manner (29). It is conceivable that increased FFA concentration contributes to the excessive rates of gluconeogenesis in IDDM and NIDDM patients. Therefore, increased REE is associated with a degree of glucose intolerance in both IDDM and NIDDM (30). The reduction in REE after improved glycemic control was also observed in association with an increase in RQ, reflecting reductions of lipid oxidation and hepatic glucose production (31).
RQ in IDDM was 0.07 lower than that of NIDDM patients at various FBG concentrations. These results indicate that the lipid oxidation rate was 17% higher in IDDM than NIDDM. Since the RQ of ketogenesis is zero, a measured nonprotein RQ of less than 0.70 is conceivable when a net synthesis of ketone bodies occurs without further oxidation but with subsequent retention and/or excretion (24). Thus, ketone bodies appear in plasma as products of increased FFA oxidation in poorly controlled diabetic patients. IDDM patients have a greater tendency to manifest ketoacidosis than NIDDM because % REE is inversely correlated with RQ to a much greater degree in IDDM than NIDDM. Thus, the pattern of energy metabolism in IDDM patients is quite different from that in NIDDM patients. This may result from a propensity by IDDM patients to synthesize ketone bodies.

Skutches et. al. have demonstrated a reduced responsiveness of adipose tissue to insulin-stimulated glucose oxidation in the presence of acetone, acetol, and 1,2-propanediol which was not readily reversible after the withdrawal of acetone from drinking water (32). These results indicate that time is required in order to return to maximum insulin sensitivity after the onset of diabetic ketoacidosis. Therefore, our study suggests that more intensive treatment is required to adequately control blood glucose levels in IDDM.

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