Effect of a single bout of moderate exercise on glucose uptake in type 2 diabetes mellitus

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Summary
Background and purpose: Hypoglycemia during exercise is a serious problem in diabetic patients during cardiac rehabilitation, whereas normal subjects rarely experience hypoglycemia. Inappropriate glucose uptake by working muscles may be responsible. However, the precise characteristics of glucose uptake during exercise have not been fully studied. We have investigated the effect of acute exercise on glucose uptake in diabetic patients.

Methods: Nine type 2 diabetic patients (age, 57 ± 6 years; HbA1c, 7.7 ± 1.3%) performed exercise at an intensity of anaerobic threshold for 15 min. Glucose utility was determined using euglycemic hyperinsulinemic clamp technique. Glucose infusion rate (GIR) was calculated throughout the exercise and recovery session.

Results: Average GIR at rest was 3.4 ± 1.6 mg/(kgBW min). Fifteen minutes after starting exercise, it increased significantly (6.6 ± 2.4, \textit{p} < 0.001). Thirty minutes after cessation of exercise, GIR decreased significantly (4.8 ± 1.9, \textit{p} < 0.05) compared with peak value. Increase in GIR was greater as BMI or body fat ratio became greater (\textit{r} = 0.608 and 0.475). There was a weak correlation (\textit{r} = 0.344) between HbA1c and GIR improving ratio (GIR during exercise × 100/GIR at rest).

Conclusions: Glucose uptake was revealed to augment significantly within 15 min after the commencement of exercise. This improvement was more obvious in patients with greater body weight, fat accumulation, and poorer diabetic control.

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Introduction

Favorable effects of exercise training in diabetes mellitus are widely established. It stabilizes the glycemic control and insulin resistance (IR) resulting in the diminishment of both microvessel and macrovessel complications. These effects can be obtained by mild to moderate intensity of exercise training. The safety of moderate exercise has been confirmed even if it is performed on the day after percutaneous coronary intervention or 1–2 weeks after acute phase of myocardial infarction. However, exercise is also widely known to induce hypoglycemia.

Hypoglycemia during exercise is induced by disproportionately accelerated glucose uptake by working skeletal muscles. There are three mechanisms of regulation of skeletal muscle glucose uptake: glucose delivery to the skeletal muscle cells; glucose transport through the cell surface membrane; and flux through intracellular metabolism. Especially, acceleration of glucose transport through the cell surface membrane during exercise is one of the important mechanisms to increase glucose uptake. However, it is not well studied how much glucose uptake is augmented during exercise and the characteristics of subjects whose improvement of IR is extreme.

Euglycemic hyperinsulinemic clamp procedure enables us to evaluate glucose uptake during exercise continuously during exercise. We hereby investigated the effect of acute exercise on glucose uptake and the concerning factors with accelerated glucose uptake using euglycemic hyperinsulinemic clamp procedure.

Methods

Subjects

Nine patients with type 2 diabetes mellitus attending the cardiac rehabilitation program in our hospital were enrolled. Their anthropometric data were almost normal. The range of body mass index was from 28.7 to 18.0. Their exercise tolerance was slightly impaired compared with that of normal subjects (peak VO₂, 18.9 ± 4.2 mL/(min kg), 77.6 ± 18.9%). They had no characteristic heart disease or pulmonary problems and all of the subjects had no exercise habit. Therefore, impaired exercise tolerance might be mainly attributed to their sedentary lifestyle.

Five subjects were taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and five were taking beta-blocking agents. These medications were not changed during this study. Two patients were treated with insulin, and five were treated with sulfonylurea derivatives.

Body fat ratio was evaluated using bioimpedance assay technique.

Study protocol

The study design is shown in Fig. 1. After 10 h fast, glucose uptake was measured on an upright cycle ergometer. After taking data of glucose uptake at rest, subjects started exercise session at an intensity of anaerobic threshold for 15 min. Then data of glucose uptake was taken again. After the evaluation of glucose uptake, subjects stopped pedaling and stayed sedentary for 15 min to take the data of recovery.

We measured glucose infusion rate (GIR) during exercise after 15 min. As is shown in Fig. 2 (A, B, and C), GIR increases relatively abruptly after starting exercise. Then 15 min after exercise, GIR looks to reach plateau. This is the reason why we have taken the data of 15 min after exercise.

Glucose uptake measurement

To evaluate the glucose uptake at rest and during exercise, all subjects underwent the euglycemic hyperinsulinemic clamp procedure during physiological hyperinsulinemia (100 U/mL) using STG-22 (Nikkiso, Tokyo, Japan) with short-acting insulin infusion (40 U/(m² min)). Hyperinsulinemia was maintained for 120 min during which time the euglycemia was achieved using a variable infusion of 16.6% glucose in water. Euglycemic target during the procedure was set at 100 mg/dL, and GIR was adjusted using the negative feedback equation of DeFronzo et al. This method is regarded as the
'gold standard' for measuring IR [12]. As for the glucose turnover during exercise, plasma glucose is transferred into muscle cells through cell surface membranes in an insulin-sensitive [13] and insulin-independent [14] manner. That is, the data obtained by euglycemic hyperinsulinemic clamp procedure during exercise indicates not only IR. Therefore, we used a term "glucose uptake" instead of "insulin resistance". We used GIR as an index of IR or glucose uptake in this study.

**Exercise prescription**

We used anaerobic threshold as an index of moderate exercise intensity. To determine the anaerobic threshold, cardiopulmonary exercise testing was performed to determine the anaerobic threshold (AT) as an index of moderate exercise intensity.

**Figure 1**  Study protocol. AT, anaerobic threshold.

**Figure 2**  Samples of euglycemic hyperinsulinemic clamp data. A, B, and C are samples of patients. Glucose infusion rate (GIR) showed relatively abrupt increase after starting the exercise. Figure D is a sample of normal subject. Exercise level was anaerobic threshold. Exercise lasts for more than 30 min. Data at the recovery are not shown.
Figure 3  Panel A: relationship between glucose infusion rate (GIR) at rest and during exercise. Panel B: relationship between improving ratio and GIR at rest. GIR improving ratio: GIR during exercise $\times$ 100/GIR at rest.

performed using a ramp protocol. Equipment used included a cycle ergometer (Lode, Groningen, The Netherlands), breath-by-breath gas analyzer (MINATO 3005, Minato Ikagaku, Osaka, Japan), and electrocardiograph recorder (ML6000, Fukuda Denshi, Tokyo, Japan). Anaerobic threshold was determined using the V-slope method [15]. Cardiopulmonary exercise test was performed within 1 week prior to the study.

Ethics

Ethical approval for the study was granted by the Gunma Prefectural Cardiovascular Center Subjects Committee. Written informed consent was given by all subjects.

Statistical analysis

Data are expressed as mean ± S.D. One way analysis of variance was used to determine the statistical significance and Bonferroni test was used for post hoc analysis. Linear regression analysis was performed to evaluate the relationship between GIR and other parameters. Values of $p < 0.05$ were considered significant.

Results

Average GIR was $3.4 \pm 1.6$ mg/(kgBW min) at resting stage. This value was a little lower than the normal value.

GIR at rest was positively correlated ($r = 0.586$) with that during exercise (Fig. 3A). Glucose utilization was improved significantly ($p < 0.01$) by 216.7% during exercise (GIR, $6.6 \pm 2.4$ mg/(kgBW min)) compared with that at rest ($3.4 \pm 1.6$ mg/(kgBW min)) as shown in Fig. 4. However, after cessation of exercise, GIR diminished significantly ($p < 0.05$) to $4.8 \pm 1.9$ mg/(kgBW min), although this value is still higher ($p < 0.01$) than that at rest.

Enhancement of glucose uptake was greater as glucose uptake at rest was more impaired. Consequently, as shown in Fig. 3B, GIR improving ratio (GIR during exercise $\times$ 100/GIR at rest (%)) was negatively ($r = -0.692$) correlated.

As for the effect of anthropometric parameters on improvement of glucose uptake, it was revealed

Figure 4  Alteration in glucose infusion rate during exercise and recovery.
that the greater body mass index or body fat ratio facilitates the improvement of glucose sensitivity. GIR ratio was negatively correlated both with BMI ($r = 0.608$, Fig. 5 left panel) and body fat ratio ($r = 0.475$, Fig. 5 right panel).

Improvement in glucose uptake was also affected by control status of diabetes mellitus. As the control status becomes poorer, glucose uptake improved greater. GIR improving ratio was significantly correlated with fasting plasma glucose ($r = 0.414$, Fig. 6 left panel) and HbA1c ($r = 0.344$, Fig. 6 right panel).

Some patients were taking antidiabetic agents. GIR improving ratio of patients with and without oral antidiabetic drugs was $224.2 \pm 85.8\%$ vs. $210.8 \pm 62.5\%$ (mean \& S.D.). There was no significant difference between them. As well, GIR improving ratio of patients with and without insulin therapy were $268.1 \pm 73.0\%$ vs. $202.0 \pm 65.8\%$ (mean \& S.D.). There was also no significant difference between them. These data indicate that medical therapeutics do not modify the results.

**Discussion**

This paper revealed the acute effect of moderate exercise on glucose uptake and its relevant factors. Glucose sensitivity improved dramatically within 15 min after the commencement of exercise. It lasts at least 15 min after cessation of exercise. This improvement was extreme in patients with greater body weight and fat accumulation, as well as poorer diabetes control.

GIR showed 216.7% increase in this study. All three factors to regulate the glucose uptake by skeletal muscle, which were previously described in this paper, would be involved. Blood flow to the working muscle increases 10-fold [16]. Glucose transporter (GLUT)-4 translocation to the cell surface increases more than 2-fold by exercise stimulus [17]. Of course, exercise needs greater ATP, which is produced by glycolysis. Although, we cannot determine which mechanism is the most determinant in this study, all of the mechanisms seem important.
In our study, although IR was relatively abnormal at rest, GIR during exercise improved to the normal range. This may be explained by the fact that there are two different manners to stimulate the GLUT-4 translocation. Experimentally, short duration of electrical muscle stimulation (EMS) facilitates GLUT-4 translocation [18]. The deformity of skeletal muscle cell structure due to muscle contraction is a key signal to stimulate the AMP-activated protein kinase (AMPK) which induces GLUT-4 translocation independently with insulin signaling pathway [19]. That is, there is another way to increase translocation of GLUT-4 independently with insulin receptor activation. Since exercise intervention causes skeletal muscle contraction, this may be one of the main mechanisms to induce the improvement of IR.

Our study revealed that improvement in glucose utilization occurs within 15 min after starting exercise. This time course matches the preceding experiment [20]. It is also reported that AMPK is activated in muscle of subjects with type 2 diabetes mellitus within 20 min after commencement of exercise [21]. Acute effect of exercise on up-regulating the GLUT-4 to the cell surface is not due to a protein and/or mRNA expression since it usually takes a few days, but due to a translocation from an intracellular storage to cell surface. Therefore, a rapid improvement of glucose uptake would be due to a translocation of GLUT-4 from vesicle to cell surface membrane.

The degree of IR is affected by the visceral fat volume [22]. In our study, GIR was negatively correlated with body mass index and body fat ratio. Our study also revealed that GIR improved greater in fatter subjects and with poorer diabetic control. This result is matched with the clinical findings that blood glucose declines greater in diabetic patients than normal subjects during exercise [23]. Skeletal muscle glycogen storage is reported to be diminished in diabetes mellitus [24]. Greater amount of glucose transfer would be necessary in diabetes mellitus whose intracellular glycogen pool is exhausted to retain them and fulfill the energy demand.

As for the effect of diabetes mellitus on GIR improvement during exercise, we cannot discuss whether GIR improvement is greater in diabetic subjects than in normal subjects. However, we have data from just one normal subject (Fig. 2D). From this panel, it is supposed that GIR increases during exercise in normal subjects too, and seemed that improving ratio of healthy subject is smaller than that in diabetic patients. Anyway, we must take more data from normal subjects to determine the effect of diabetes mellitus.

The relationship between exercise tolerance and GIR improving ratio is shown in Fig. 7. There were no significant relationships between them.

**Study limitations**

We tested only nine subjects. Although, there was no intentional selection for the enrollment into this study, there still leaves a possibility that when larger mass is studied, results are affected. It is desired to study using a greater number of subjects.

We measured neither plasma catecholamines nor sympathetic nerve response during and after exercise. They might affect the results of metabolic change. It is reported that obesity is related to the central nervous system [25]. Therefore, we must not decide that only anthropometric abnormalities and/or poor diabetic control affect the GIR improvement. These factors are just one of the mechanisms to enhance the glucose uptake during exercise.
Conclusions

In conclusion, glucose uptake is revealed to increase significantly within 15 min after commencement of moderate exercise, especially in patients with obese and poorer controlled diabetes mellitus. We must take care of the risk of hypoglycemia during exercise training in patients with diabetes mellitus especially with obese and poorly controlled diabetes mellitus.

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