

## The Effect of Glucagon on FDG Uptake in Skeletal Muscle

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Glucagon is used as an anti-motility agent during gastrointestinal tract examinations. We experienced subjects with enhanced <sup>18</sup>F-fluorodeoxyglucose (FDG) uptake in whole-body skeletal muscle when conducting positron emission tomography (PET). The subjects had been administered glucagon during gastroscopy just prior to PET. This observation prompted us to perform the present retrospective study to determine whether or not glucagon enhances FDG uptake in skeletal muscle. We randomly selected 30 cases, including subjects who had undergone PET and gastroscopy on the same day as cancer screening procedures, and classified them into three groups. In the NO group (n = 10), no medications were used prior to PET. In the SC group (n = 10), scopolamine butylbromide (10 mg) was intravenously administered during endoscopy. In the GL group (n = 10), glucagon (0.5 mg) was intravenously administered during endoscopy. Both drugs were administered 45-60 min prior to FDG administration. The mean standardized uptake value (SUV) for gluteal muscle was  $0.7 \pm 0.14$ ,  $0.69 \pm 0.15$ , and  $0.99 \pm 0.7$  in the NO, SC, and GL groups, respectively. The SUV in the GL group was highest, but the difference was not statistically significant. In the subject with the highest SUV (3.04; GL group), the quality of the oncologic PET image was impaired, perhaps because of a relative decrease of FDG distribution in the chest and abdomen. Because previous literature showed that via hyperglycemia and hyperinsulinemia glucagon has the effect of increasing FDG uptake in skeletal muscle, the use of glucagon should be avoided just prior to FDG PET, although in our subjects, no statistical proof that glucagon enhances FDG uptake in skeletal muscle was obtained.

**Key words:** Glucagon, glucose metabolism, skeletal muscle, <sup>18</sup>F-fluorodeoxyglucose (FDG), positron emission tomography (PET)

### INTRODUCTION

Positron Emission Tomography/Computed Tomography (PET/CT) with <sup>18</sup>F-fluorodeoxyglucose (FDG) is used in clinical practice. Here we experienced subjects with enhanced FDG uptake in whole-body skeletal muscle. The subjects had been administered glucagon as a premedication for gastroscopy performed just prior to PET on the same day. Glucagon is routinely used as a substitute for scopolamine butylbromide (Buscopan<sup>TM</sup>) as an endoscopic premedication. We suspected that administration of glucagon is responsible for the increased FDG uptake in skeletal muscles. Therefore, this study was conducted to determine whether or not glucagon indeed enhances FDG uptake in skeletal muscles.

### SUBJECTS AND METHODS

We retrospectively reviewed PET/CT records at a PET center (Yotsuya Medical Cube, Tokyo, Japan). From January to April 2006, 272 asymptomatic subjects, including 174 who underwent PET/CT after gastroscopy on the same day, underwent PET/CT for cancer screening. We randomly selected 30 cases with no history of diabetes mellitus and classified them into three groups. In the NO group (n = 10, 5 males and 5

females), no endoscopy was performed, and therefore, no medications were used prior to PET. In the SC group (n = 10, 4 males and 6 females), scopolamine butylbromide (10 mg) was administered intravenously during endoscopy (1/2 ampoule). In the GL group (n = 10, 8 males and 2 females), glucagon (0.5 mg; 1/2 vial) was administered intravenously during endoscopy. These gastroscopy premedications were administered 45-60 min prior to FDG administration.

At around 60 min after injection of 140-200 MBq of FDG, image data were acquired (Discovery ST, GE Healthcare, Milwaukee, WI). On PET images, several regions of interests were selected to calculate the mean standardized uptake value (SUV) of gluteal muscle (as a representative of skeletal muscle), the myocardium, liver, and intraperitoneal fat tissue. SUVs were then compared between groups.

Statistical analysis was performed using the two-sided Mann-Whitney U test, and  $p < 0.05$  was considered significant.

### RESULTS

The mean SUV for gluteal muscle was  $0.7 \pm 0.14$ ,  $0.69 \pm 0.15$ ,  $0.99 \pm 0.7$  in the NO, SC, and GL groups, respectively (Table). Although the SUV in the GL group was highest, the difference was not statisti-

**Table** Mean SUVs of each group and statistical *p*-values

		Age	Gluteal muscle	Myocardium	Liver	Fat
Groups	NO	57.5 ± 10.5	0.7 ± 0.14	4.25 ± 3.16	2.41 ± 0.3	0.72 ± 0.23
	SC	54.5 ± 8.87	0.69 ± 0.15	4.35 ± 2.75	2.47 ± 0.45	0.8 ± 0.33
	GL	57.9 ± 8.84	0.99 ± 0.7	5.25 ± 2.76	2.16 ± 0.29	0.62 ± 0.18
Results	NO vs SC	0.819*	0.909	0.762	0.909	0.65
	NO vs GL	0.849	0.289	0.256	0.041	0.289
	SC vs GL	0.705	0.289	0.307	0.096	0.403

NO: no premedication, SC: scopolamine butylbromide, GL: glucagon.

\*: *p*-value (Mann-Whitney *U* test, two-sided)

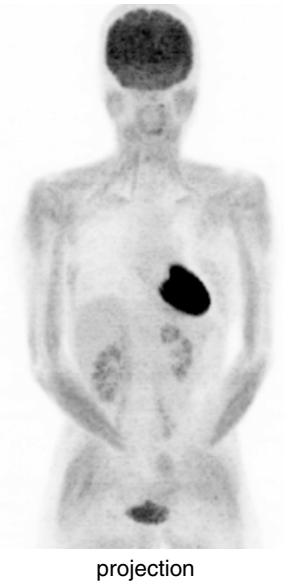
cally significant. Similarly, the SUV of the myocardium was highest in the GL group, but the difference was not significant. The SUV for the liver was significantly lower in the GL group than in the NO group ( $p = 0.041$ ). The SUV of the fat was lowest in the GL group, but the difference was not significant.

In the subject with the highest SUV (3.04; GL group) for gluteal muscle, the quality of the oncologic PET image was impaired (Figure).

Fasting blood glucose level was as follows. In the NO group, the blood glucose level was 75 – 105 mg/dl ( $91 \pm 8.4$  mg/dl) at the time of PET, as measured by a blood glucose meter to quickly determine the whole blood glucose level. In the SC and GL groups, the blood glucose level was not measured at the time of PET; instead, fasting plasma glucose level and HbA1c level were measured one day before PET and found to be 82–128 mg/dl ( $102 \pm 12.0$  mg/dl) and 4.8–5.5% ( $4.9 \pm 0.24\%$ ) in the SC group and 89–118 mg/dl ( $103 \pm 7.9$  mg/dl) and 4.6–5.6% ( $5.0 \pm 0.27\%$ ) in the GL group, respectively.

## DISCUSSION

This retrospective study was prompted after we experienced subjects with increased FDG uptake in whole-body skeletal muscle. The subjects had been administered glucagon just prior to FDG PET. At the beginning of this study, we simply suspected that hyperglycemia caused by glucagon was attributed to the increased FDG uptake. In our analysis, gluteal muscle was selected as a representative whole-body skeletal muscle, and SUV values were estimated. It has been reported that SUV is a reliable indicator for estimating skeletal muscle glucose utilization as dephosphorylation of FDG-6-phosphate is negligible in skeletal muscle [1]. As a result, the mean SUV for gluteal muscle was higher in the GL group than in the NO and SC groups. The difference, however, was not statistically significant, although the existence of a type II error due to the small sample size is a possibility. At least in our subjects, to whom 0.5 mg of glucagon was intravenously administered 45–60 min prior to FDG administration, a significant increase of FDG uptake in skeletal muscle was not statistically proven.



**Figure** Enhanced FDG uptake was observed in whole-body skeletal muscle in a subject who had been administered glucagon just prior to PET study.

In the subject (50-year-old male) with exceptionally high gluteal muscle SUV (3.04), the quality of the oncologic PET image was impaired probably because of the relative decrease of FDG distribution in the chest and abdomen. In this patient, blood glucose level was not measured at the time of PET, but the day before, and fasting plasma glucose was 104 mg/dl ( $N < 110$  mg/dl) and HbA1c was 4.9 % ( $N \leq 5.8$  %). When this case was excluded from analysis, the mean SUV of the other nine subjects was  $0.77 \pm 0.21$ , which is similar to  $0.7 \pm 0.14$  in the NO group and  $0.69 \pm 0.15$  in the SC group.

The SUV for the liver was significantly lower in the GL group than in the NO group ( $p = 0.041$ ). We considered that the increased FDG uptake in whole-body skeletal muscle could be attributed to the relative decrease in hepatic FDG uptake, although the precise mechanism is unknown.

Glucagon has the following physiological and pharmacological effects [2]: 1) It acts on cyclic AMP in hepatocytes that activate hepatic glycogen breakdown and

increase blood glucose concentration. Administration of glucagon pharmacologically leads to a rapid rise in blood glucose and is clinically used for emergency treatment of hypoglycemia in diabetic patients. 2) Glucagon is used to treat acute cardiac failure precipitated by  $\beta$ -adrenoceptor antagonists. 3) Glucagon has an anti-motility effect on the gastrointestinal (GI) tract and is used to relax smooth muscle activity during GI examinations. The inhibitory effect of glucagon is thought to be due to adrenergic stimulation, which is possibly a vagal effect [3].

The physiological regulation of skeletal muscle glucose uptake is complex. Muscle glucose uptake is mediated by multiple distributed processes that control glucose delivery to, membrane transport into, and phosphorylation within muscle [4]. An increase in blood glucose concentration causes glucose delivery to increase. Insulin stimulation results in increased Glut-4 translocation and leads to membrane transportation of glucose into myocytes. Glucose phosphorylation into glucose-6-phosphate is irreversible, therefore, FDG-6-phosphate becomes trapped in myocytes.

Here we considered that intravenous glucagon injection results in immediate and sustained hyperglycemia, with an immediate and brief rise in insulin level [3, 5]. A rise in blood glucose level *per se* increases the level of FDG uptake in muscle [6], and simultaneously occurring hyperinsulinemia seems to be largely attributed to the increase of muscle glucose uptake (insulin-stimulated glucose uptake) [3, 4].

To our knowledge, this is the first report to observe the effect of glucagon on skeletal muscle glucose uptake with FDG PET. From the oncological FDG PET perspective, medicines directly related to glucose metabolism should be avoided prior to FDG PET.

## CONCLUSION

In our subjects, no statistical evidence was obtained to show that glucagon significantly enhances FDG uptake in skeletal muscle. Based on the results of previous studies, however, glucagon promotes increased FDG uptake in skeletal muscle via hyperglycemia and hyperinsulinemia. Medicines that act on glucose metabolism, including glucagon, should thus be avoided just prior to FDG PET.

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