Myocardial Glucose Metabolism in Noninsulin-Dependent Diabetes Mellitus Patients Evaluated by FDG-PET

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Diabetes mellitus (DM) is one of several factors influencing the assessment of myocardial viability using fluorine-18 fluorodeoxyglucose (FDG) PET. **Methods:** To compare the myocardial glucose metabolism of normal subjects to patients with DM, we performed a quantitative FDG study during insulin clamp, oral glucose loading and fasting in nine normal volunteers and eight patients with noninsulin-dependent DM (NIDDM). **Results:** During oral glucose loading, myocardium-to-background (MB) ratio remarkably deteriorated in NIDDM patients compared with normals because of high plasma glucose and low serum insulin. Myocardial glucose utilization (MGU) rates in NIDDM patients were also lower than those in normal volunteers. MB ratio of FDG remarkably improved with insulin clamp in NIDDM patients compared with oral glucose loading. MGU rates during insulin clamp were still slightly lower than in the normal volunteers despite low plasma glucose and adequate plasma insulin. **Conclusion:** The insulin clamp method may be very useful in NIDDM patients for improved myocardial FDG uptake compared to oral glucose loading or fasting, but slight decreases in MGU rates during insulin clamp in NIDDM patients may be because of insulin resistance (GluT4 abnormality).

Key Words: heart; FDG-PET; diabetes mellitus; glucose

J Nucl Med 1995; 36:456–463

Fluorine-18-fluorodeoxyglucose (FDG) was first used in PET imaging of the myocardium by Phelps et al. (*1*). Myocardial PET studies were then later used to detect viable ischemic myocardium in infarct during qualitative evaluation of regional FDG uptake and its relation to flow (*2–7*). Diabetes mellitus (DM) complicates the evaluation for myocardial viability by deteriorating image quality during fasting or oral glucose loading (*8,9*). Although the insulin clamp and insulin injection methods are recommended (*9–11*), quantitative analysis of myocardial glucose metabolism in patients with DM has been performed in only two studies (*12,13*): one on patients with insulin-dependent diabetes mellitus (IDDM) without coronary artery disease (CAD) and with normal volunteers as controls, and the other on patients with CAD with and without noninsulin-dependent DM (NIDDM) during insulin clamp only. We quantified the myocardial glucose metabolism of normal subjects and patients with NIDDM without CAD during insulin clamp, oral glucose loading and fasting.

Received Feb. 15, 1994; revision accepted Sept. 1, 1994.

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METHODS

Subjects

Seventeen patients—nine nondiabetic, normal male volunteers (age 41.0 ± 19.5 yr, body mass index (BMI) 21.4 ± 2.0 kg/m) and eight patients with DM (age 50.6 ± 13.4 yr, BMI 21.5 ± 3.8 kg/m) but without a history of CAD and without wall motion abnormality evaluated by echocardiography—participated in this study.

The nine volunteers satisfied the criteria of having a fasting glucose level lower than 120 mg/dl (89.9 ± 9.0 mg/dl) and a normal pattern of glucose tolerance. The eight diabetic patients satisfied the criteria of having a fasting glucose level at admission (within a few weeks before the study) greater than 120 mg/dl (195 ± 50 mg/dl) and glucose tolerance with a DM pattern and hemoglobin A1c (HbA1c) greater than 7.0% (10.0% ± 2.5%, reference value 4.0%–6.0%).

Of the eight diabetic patients, five were male and three were female. Two had nephropathy, three had retinopathy and five had neuropathy. All eight patients had NIDDM. Before informed consent was obtained, each subject was informed of the investigative nature of the study and its potential risks and benefits. The study protocol was approved by the University of Tokyo's Human Subject Protection Committee.

Study Design

Three PET studies during fasting, oral glucose loading and insulin clamp were performed in random order within a week in nine nondiabetic, normal volunteers and eight NIDDM patients. Two intravenous catheters were inserted: one in an antecubital vein for a glucose and insulin infusion and FDG injection, and another in a contralateral hand vein for venous blood sampling. In the fasting study, FDG was injected 6–7 hr after breakfast. In the oral glucose loading study, subjects had a half lunch 1–3 hr before the study and drank 50 g of glucose solution (tolerane G) 1 hr before the injection of FDG. In the insulin clamp study, subjects had no lunch before the study. Plasma glucose was stabilized, and insulin and glucose infusion was started in the afternoon. At the beginning of the insulin clamp study, serum insulin was raised by

a primed, continuous infusion of short half-life insulin (4 mU/kg/min) for more than 10 min. In DM patients, this rate of insulin infusion was continued until plasma glucose decreased below 140 mg/min. In equilibrium, the infusion rate of insulin was more than 1 mU/kg/min. During hyperinsulinemia, normoglycemia (70–125 mg/dl) was maintained with 20% glucose infused at a rate of more than 6 mg/kg/min. Both rates were adjusted according to plasma glucose, which was measured every 5–10 min from venous blood. Blood samples were taken before FDG injection and at the end of the study to determine serum insulin and free fatty acid concentrations using a ^{125}I radioimmunoassay and a microfluorometric method. In the fasting and oral glucose loading studies, plasma-glucose determination was performed just before FDG injection, in the middle and at the end of the study using the glucose oxidase method.

Measurement of Myocardial Glucose Utilization Rates

FDG Injection and Blood Sampling. Five to 10 mCi of FDG were intravenously injected over a 30–60 sec period at rest. Blood samples were withdrawn from a venous line seven times (13 min 15 sec; 18 min 15 sec; 23 min 15 sec; 28 min 15 sec; 35 min 45 sec; 45 min 45 sec and 55 min 45 sec after FDG injection). Fluorine-18 activity in whole blood and plasma was measured by a well counter and corrected for radioactive decay (*14*).

Image Acquisition. Patients were studied using a HEADTOME IV PET scanner (Shimadzu Corp., Kyoto, Japan) with seven imaging planes at 13-mm intervals, each 10 mm thick. In-plane resolution was 4.5 mm FWHM. Axial resolution was 9.5 mm FWHM and the sensitivities were 14 and 24 kcps/(μCi/ml), respectively, for direct and cross planes (*15*). Effective in-plane resolution was 7 mm after using a smoothing filter. In all studies, transmission images were acquired for 10 min in order to correct for photon attenuation prior to obtaining the PET images. Nineteen dynamic scans were obtained during a 60-min 45-sec period (*14*).

Image Processing. Cross-sectional images were reconstructed and corrected for the physical decay of ^{18}F relative to the FDG injection time.

Input function was obtained by correcting the time-activity curves of the descending aorta for the partial volume effect, and by correcting the difference between plasma and whole-blood counts using the whole blood and plasma counts of venous blood sampled seven times (*14*). The venous whole-blood count at each time was raised to arterial whole-blood count so that the decay ratio of corrected venous count and the time-activity curve of the descending aorta became the same. The average ratio of the corrected venous whole-blood count and the count of the descending aorta at each time was used to correct partial-volume effect. The average ratio of the plasma and whole-blood count was used to correct the whole-blood count with the plasma count (*14*).

Echocardiography. Echocardiograms obtained within 2 wk of the PET study were interpreted by a cardiologist without knowledge of the PET data. The thicknesses of the septum and posterior wall were measured by M-mode echocardiography. When the thickness was variable in each myocardial wall, the thicknesses of the anterior and lateral walls were measured by short-axis tomography.

Corrections. All data were corrected for scanner deadtime effects to reduce the error to less than 1%. To correct for partial volume effects associated with object size, recovery coefficients (RC) experimentally obtained from phantom studies were used. The RC was changed according to myocardial wall thickness measured by echocardiography (*16*). The RC was 0.8 when myocardial thickness was 10 mm.

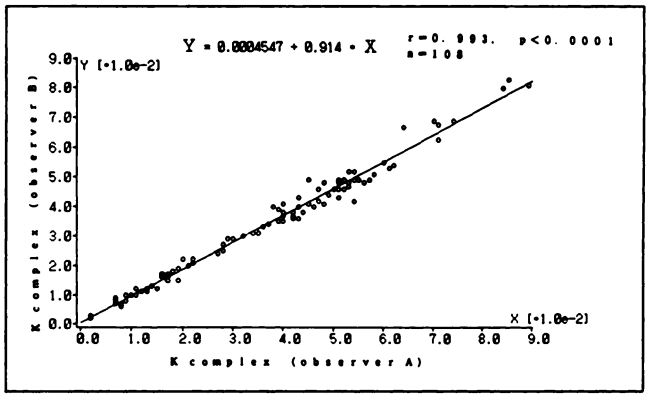

FIGURE 1. Interobserver difference of K complex of each wall in setting ROI on transaxial and sagital long axial tomograms of K complex functional images.

Calculation of Regional Myocardial Glucose Utilization Rates

A three-compartment FDG tracer-kinetic model (*17*) was used in the present study. The regional myocardial glucose utilization rate (rMGU) can be calculated as rMGU = (Cp/LC)k1k3/(k2 + k3), where Cp is the plasma concentration of glucose, and LC is the lumped constant that accounts for differences in the transport and phosphorylation of FDG and glucose (*17,18*). In this study, LC was assumed to be a constant equal to 0.67 in myocardium (*19*). The dephosphorylation rate constant (k4) of FDG was assumed to be zero, and k1k3/(k2 + k3) was calculated by using Patlak graphic analysis (*14,20,21*).

Tissue activities at seven different times (from 13 min 15 sec to 55 min 45 sec) were used to estimate the slope [k1k3/(k2 + k3)] in Patlak analysis in all pixels of seven image planes. We obtained a functional transaxial (13-mm interval and 10-mm thick) image of the slope. Sagittal images (10-mm thick) of k1k3/(k2 + k3) were reconstructed from interpolated transaxial images. Using a central three slice, we obtained the slope of the septum and lateral wall from transaxial functional images and the slope of the anterior and posteroinferior wall from sagittal long-axis functional images. The average k1k3/(k2 + k3) value of all pixels within a region of interest (ROI) of each wall was used. MGU of each wall was obtained by multiplying k1k3/(k2 + k3) of each wall and Cp/LC × RC. Interobserver difference of k1k3/(k2 + k3) in setting ROI is shown in Figure 1 (r = 0.99). Each observer was blinded to the studies and to each other's results.

Statistical Analysis. Results are presented as mean ± 1 s.d. For statistical analysis, comparisons between the two groups were made using an unpaired t-test. The comparison of the insulin clamp method, glucose loading and fasting studies, or the comparison of each wall, was subjected to analysis of variance followed by t-tests corrected for the number of comparisons by the Bonferroni method. Probability values of < 0.05 were considered statistically significant.

RESULTS

Plasma insulin, glucose and free fatty acid levels in normal and NIDDM groups during fasting, insulin clamp and

TABLE 1
Serum Levels of Insulin, Glucose and Free Fatty Acids During Insulin Clamp, Oral Glucose Loading and Fasting

Serum level	Test condition	Normal (n = 9)		NIDDM (n = 8)
insulin	IC	89.9 ± 40.9	ns	182.9 ± 111.3
		($p < 0.01$ vs. OG)		$p < 0.0001$ vs. OG, FS
(mU/l)	OG	45.4 ± 19.1	†	16.1 ± 7.5
	FS	4.0 ± 1.3	†	7.5 ± 2.3
		$p < 0.0001$ vs. IC, $p < 0.01$ vs. OG		
glucose	IC	98.1 ± 17.3	ns	100.3 ± 12.6
(mg/dl)	OG	125.9 ± 22.6		282.6 ± 95.1†
		$p < 0.01$ vs. IC, $p < 0.001$ vs. FS		$p < 0.0001$ vs. IC, FS
	FS	89.9 ± 9.0	‡	126.0 ± 15.4
FFA	IC	0.34 ± 0.17	ns	0.39 ± 0.30
(mEq/liter)	OG	0.31 ± 0.20	*	0.56 ± 0.30
	FS	1.07 ± 0.46	ns	1.31 ± 0.47
		$p < 0.0001$ vs. IC, OG		$p < 0.0001$ vs. IC $p < 0.001$ vs. OG

*$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$ unpaired t-test between normal and NIDDM group.
IC = insulin clamp; OG = oral glucose loading; FS = fasting results of IC, OG and FS were compared by analysis of variance; FFA = free fatty acid; NIDDM = noninsulin dependent diabetes mellitus; ns = not significant compared with normal; mean ± s.d. is shown.

oral glucose loading are shown in Tables 1 and 2. The serum-insulin value was the average of the values just before FDG injection and at the end of the study. Serum insulin was lower during oral glucose loading ($p < 0.01$) and higher, on average, during fasting and insulin clamp in the NIDDM group than in the normal group ($p < 0.01$, not significant). Plasma glucose was the average of the values at three times during fasting, oral glucose loading and at ten to twelve times during the insulin clamp method. Plasma glucose was about the same in two groups during the insulin clamp method, while it was significantly higher during oral glucose loading ($p < 0.01$) and slightly higher during fasting ($p < 0.001$) in NIDDM groups compared to the normal groups. In the NIDDM group, plasma glucose during oral glucose loading was significantly higher than in the insulin clamp method and fasting ($p < 0.0001$). Serum free fatty acid was within normal range during the insulin clamp method and oral glucose loading in each group (normal range 0.1–0.9 mEq/l). Serum free fatty acids during oral glucose loading and fasting in the NIDDM group were slightly higher, on average, than in the normal group ($p < 0.05$, not significant). It was higher during fasting than during the insulin clamp method or oral glucose loading in both groups ($p < 0.001$ to $p < 0.0001$).

MGU rates and k1k3/(k2 + k3) values from Patlak analysis during fasting, the insulin clamp method and oral glucose loading in each group are shown in Tables 2 and 3. The range of MGU rates were 0.39–0.68 μmole/min/g during the insulin clamp method and oral glucose loading in the normal group and these rates are about the same. The range of MGU rates was 0.02–0.30 μmole/min/g during fasting, with more interindividual variance compared with variations in serum insulin. During oral glucose loading, k1k3/(k2 + k3) was lower than that during the insulin clamp method ($p < 0.01$), and k1k3/(k2 + k3) during fasting was lower than that during oral glucose loading or the insulin clamp method ($p < 0.0001$).

In the NIDDM group, the MGU rate during the insulin clamp method was slightly lower than that in the normal group ($p < 0.05$). The MGU rate during oral glucose loading was lower than that in the normal group ($p < 0.01$) and lower than that during the insulin clamp method in the NIDDM group ($p < 0.05$). The MGU rate during fasting was slightly lower, on average, than that in normal group (not significant). The double product during all three studies was about the same in the normal and NIDDM groups (9024 ± 1831, 9267 ± 2665, the insulin clamp method; 8927 ± 1590, 9170 ± 2561, oral glucose loading; 8932 ± 1665, 9110 ± 2474, fasting). During the insulin clamp method, k1k3/(k2 + k3) in the NIDDM group was slightly lower than that in the normal group ($p < 0.05$), while k1k3/(k2 + k3) during oral glucose loading in the NIDDM group was remarkably lower than that in the normal group ($p < 0.001$) and lower than that during the insulin clamp method in the NIDDM group ($p < 0.001$). During fasting, k1k3/(k2 + k3) was slightly lower in the NIDDM group than in the normal group.

The MB ratio is shown in Tables 2 and 3. This was obtained by dividing the average myocardial count by the plasma-venous count at the middle of the image acquisition (55 min in FDG study). The MB ratio of the FDG image during the insulin clamp method was very high in the normal and the NIDDM groups. Although the MB ratio during the insulin clamp method in the NIDDM group was slightly lower than that in normal group (not significant), it was about as high as the MB ratio during oral glucose loading in the normal group; however, the MB ratio during oral glucose loading in the NIDDM group was significantly lower than that in the normal group ($p < 0.01$). The MB ratio during fasting was low in both groups.

TABLE 2
Subject Data

Subject no.	Age	Sex	MGUIC	MGUOG	MGUFS	KCIC	KCOG	KCFS	MBIC	MBOG	MBFS	DPIC	DPOG
d1	41	M	0.39	0.09	0.04	0.029	0.002	0.002	5.1	0.6	0.5	8736	9006
d2	54	M	0.29	0.16	0.05	0.024	0.007	0.003	7.7	1.5	0.7	5888	5808
d3	69	F	0.44	0.53	0.16	0.051	0.031	0.017	12.3	4.5	2.2	11200	10764
d4	29	M	0.34	0.30	0.08	0.030	0.011	0.007	5.8	2.2	1.1	8208	8056
d5	50	F	0.61	0.39	0.10	0.051	0.009	0.007	11.9	1.7	1.1	7980	8239
d6	66	F	0.34	0.08	0.02	0.041	0.002	0.002	6.6	0.5	0.5	12720	12717
d7	55	F	0.61	0.44	0.13	0.051	0.016	0.009	11.6	2.6	1.3	12800	12324
d8	41	M	0.36	0.20	0.05	0.046	0.010	0.004	13.5	1.9	0.8	6615	6448
n1	21	M	0.51	0.52	0.30	0.050	0.036	0.029	13.5	6.7	3.5	6600	6633
n2	21	M	0.39	0.49	0.20	0.038	0.040	0.018	9.4	8.8	2.3	6528	7276
n3	21	M	0.65	0.46	0.02	0.045	0.039	0.003	9.8	9.1	0.7	9000	8280
n4	20	M	0.67	0.63	0.11	0.067	0.055	0.012	16.3	12.5	1.7	9360	8970
n5	52	M	0.59	0.49	0.09	0.069	0.037	0.009	14.0	6.0	1.3	10800	9804
n6	63	M	0.68	0.56	0.05	0.061	0.038	0.005	12.0	6.2	0.9	10296	9324
n7	62	M	0.47	0.48	0.19	0.070	0.037	0.022	14.3	6.0	2.8	11900	12212
n8	53	M	0.51	0.51	0.04	0.061	0.038	0.004	12.0	6.2	0.8	8954	9150
n9	56	M	0.42	0.55	0.14	0.031	0.032	0.016	4.5	4.7	2.1	7777	8692

				DPFS	INSIC	INSOG	INSFS	GLUIC	GLUOG	GLUFS	FFAIC	FFAOG	FFAFS
d1	41	M		8880	323	4	5	119	380	155	0.38	1.02	1.44
d2	54	M		5963	276	9.5	6	92	172	126	0.11	0.33	2.29
d3	69	F		10472	244	21	12	98	196	114	0.20	0.30	0.65
d4	29	M		8085	68	23	9	108	259	115	0.27	0.40	1.28
d5	50	F		8685	47.5	11.5	7	93	336	108	0.47	0.69	1.22
d6	66	F		12480	86.5	13.5	7.5	95	441	124	0.56	0.90	1.24
d7	55	F		12403	130	25	8.5	115	268	141	0.11	0.22	1.01
d8	41	M		6510	288	21.5	5	82	209	125	1.01	0.63	1.35
n1	21	M		6664	65	33	3	99	139	90	0.37	0.30	0.66
n2	21	M		6760	54.5	24	4	90	107	93	0.28	0.11	0.65
n3	21	M		8584	68.5	58	3	125	102	71	0.42	0.16	1.20
n4	20	M		8932	126	85	3	104	130	95	0.72	0.10	0.58
n5	52	M		10374	42.5	36	4.5	83	84	99	0.18	0.28	1.31
n6	63	M		10010	162.5	44.5	3	107	144	92	0.29	0.34	0.80
n7	62	M		11844	73	32.5	7	70	137	86	0.34	0.78	1.23
n8	53	M		8979	83.5	60	4	88	141	100	0.12	0.37	2.02
n9	56	M		8240	134	35.5	4.5	117	149	83	0.37	0.36	1.18

d = noninsulin-dependent diabetes mellitus, n = normal volunteer, IC = insulin clamp, OG = oral glucose loading, FS = fasting, MGU = myocardial glucose utilization rates μmole/min/g, KC = k1k3/(k2 + k3) calculated by Patlak analysis, MB = myocardium-to-blood ratio, DP = double product, INS = plasma insulin mU/liter, GLU = plasma glucose mg/dl, FFA = plasma free fatty acid mEq/1.

Insulin infusion rates in the NIDDM group were slightly higher, on average, than in the normal group (1.59 ± 0.58, 1.35 ± 0.31 mU/kg/min, not significant). Glucose infusion rates in the NIDDM group were about the same in both groups (7.50 ± 1.38, 7.47 ± 1.02 mg/kg/min, not significant). The time from the start of insulin injection to equilibrium during the insulin clamp method in the NIDDM group was longer than in normal group (77.7 ± 13.4 min, 59.0 ± 10.3 min, $p < 0.01$).

Regional analysis of FDG uptake in Table 4 confirmed the previously reported heterogeneous tracer uptake (*23,24*). During fasting in the normal group, and during fasting in oral glucose loading in the NIDDM group, the MGU rate in the lateral wall was higher than the other wall ($p < 0.05$). During the insulin clamp method and oral glucose loading in the normal group, and during the insulin clamp method in the NIDDM group, there was no significant regional difference in MGU rates.

MGU functional images of FDG studies during the insulin clamp method and oral glucose loading of a 21-yr-old normal male and a 45-yr-old male NIDDM patient are shown in Figures 2 and 3.

DISCUSSION

This study demonstrates that MGU rates and the MB ratio in NIDDM patients decreases with low serum insulin and high plasma glucose during oral glucose loading, but remarkably improves and is slightly lower than normal during the insulin clamp method.

TABLE 3
Myocardial Glucose Utilization Rates, k1k3/(k2 + k3) (KC) Value and Myocardium-to-Background Ratio During Insulin Clamp, Oral Glucose Loading and Fasting

		Normal (n = 9)		NIDDM (n = 8)
MGU	IC (μmole/min/g)	0.54 ± 0.11	*	0.42 ± 0.12 p < 0.05 vs. OG
	OG	0.52 ± 0.05	†	0.27 ± 0.17
	FS	0.13 ± 0.09 p < 0.0001 vs. IC, OG	ns	0.08 ± 0.05 p < 0.0001 vs. IC, p < 0.01 vs. OG
KC	IC	0.055 ± 0.014 p < 0.01 vs. OG	*	0.040 ± 0.011 p < 0.0001 vs. OG, FS
	OG	0.039 ± 0.006	†	0.011 ± 0.009
	FS	0.013 ± 0.009 p < 0.0001 vs. IC, OG	ns	0.006 ± 0.005
MB	IC	11.8 ± 3.5 p < 0.01 vs. OG	ns	9.3 ± 3.3 p < 0.0001 vs. OG, FS
	OG	7.4 ± 2.4	†	1.9 ± 1.3
	FS	1.8 ± 1.0 p < 0.0001 vs. IC, OG	ns	1.0 ± 0.6

ns = not significant compared to normal; *p < 0.05, †p < 0.01, ‡p < 0.001 unpaired t-test between normal and NIDDM group; IC = insulin clamp; OG = oral glucose loading; FS = fasting; results of IC, OG and FS were compared by analysis of variance; MGU = myocardial glucose utilization rates; KC = k1k3/(k2 + k3) by Patlak analysis; MB = myocardium-to-background ratio; NIDDM = noninsulin-dependent diabetes mellitus; mean ± s.d. is shown.

Myocardial Glucose Uptake in Normal Subjects

In normal subjects, myocardial metabolism depends on various substrates such as free fatty acids, glucose, lactate, pyruvate, amino acids and ketones. Although the hormonal factors that regulate myocardial substrate utilization are complex, insulin is the main factor that regulates myocardial glucose metabolism.

During fasting, free fatty acids are the main fuel for myocardial oxidative metabolism, and glucose metabolism is relatively low. Under postprandial conditions, serum insulin levels increase. Myocardial glucose utilization increases, and glucose uptake is stimulated in adipocytes and skeletal muscle, where glucose is stored as glycogen.

MGU rates in normal subjects during oral glucose loading and the insulin clamp method in our study are almost the same as in a previous report (22), although there is interindividual variation. Serum free fatty acid was just as low during the insulin clamp method and oral glucose load-

TABLE 4
Regional Myocardial Glucose Utilization Rates (μmole/min/g) in Normal and Diabetic Subjects

	Normal (n = 9)	NIDDM (n = 8)
Fasting		
Septum	0.088 ± 0.11	0.075 ± 0.052
Anterior	0.086 ± 0.13	0.076 ± 0.046
Lateral	0.101 ± 0.14*	0.086 ± 0.056†
Posterior	0.089 ± 0.12	0.077 ± 0.049
Oral glucose		
Septum	0.52 ± 0.054	0.27 ± 0.18
Anterior	0.52 ± 0.048	0.25 ± 0.14
Lateral	0.53 ± 0.062	0.31 ± 0.19‡
Posterior	0.51 ± 0.053	0.26 ± 0.16
Insulin clamp		
Septum	0.54 ± 0.12	0.42 ± 0.13
Anterior	0.53 ± 0.12	0.41 ± 0.12
Lateral	0.56 ± 0.10	0.43 ± 0.16
Posterior	0.53 ± 0.14	0.42 ± 0.11

*p < 0.05 vs. septum and anterior wall.
†p < 0.05 vs. septum.
‡p < 0.05 vs. anterior wall and posterior wall.
mean ± s.d. is shown.

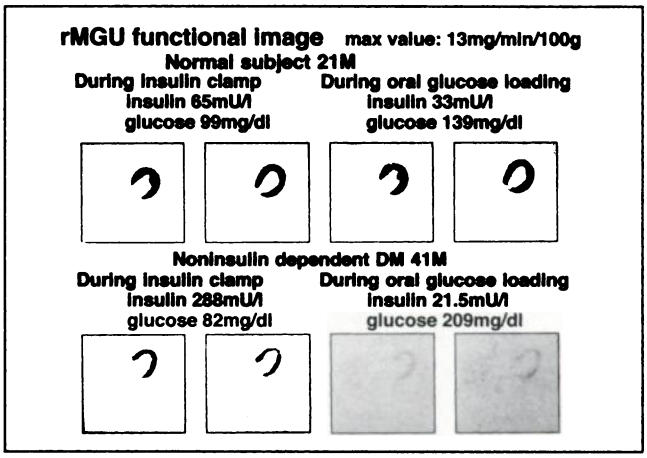

FIGURE 2. rMGU functional transaxial images of an FDG study during insulin clamp and oral glucose loading of a 21-yr-old normal male subject and 41-yr-old male patient with NIDDM (Case 3) are shown. In each set of two transaxial images, the left image is more cephalic and the right image is more caudal. In normal subject, rMGU during insulin clamp and oral glucose loading was about the same. But in this NIDDM patient, rMGU during insulin clamp was slightly lower than normal but relatively high, while rMGU during oral glucose loading was apparently low.

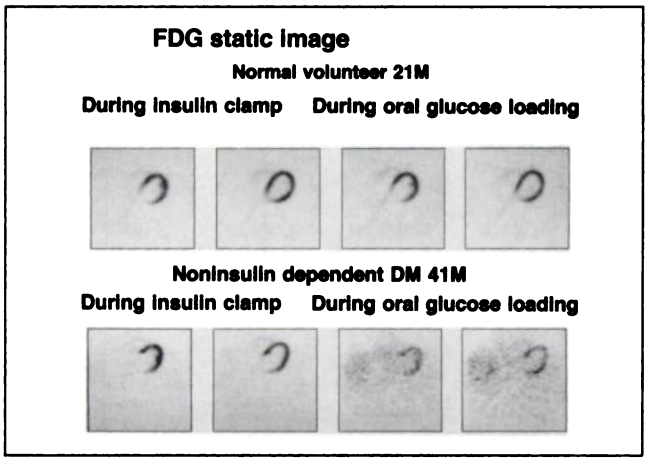

FIGURE 3. The images in Figure 2 normalized by maximal count of each image. The image of the NIDDM patient during oral glucose loading shows the most background noise.

ing, suggesting low fatty acid myocardial metabolism. There was little regional difference in MGU rates during both oral glucose loading and the insulin clamp method, as previously reported (*12,23*).

MGU rates in normal subjects during fasting were lower than that in oral glucose loading or the insulin clamp method and interindividual variation was large although there was only a small interindividual variation in serum-insulin level. Serum free fatty acid levels were high during fasting compared with that during oral glucose loading or the insulin clamp method. Regional difference in MGU rates was more remarkable than that during oral glucose loading or the insulin clamp method as previously reported (*23,24*).

The MGU rate during the insulin clamp method was 0.74 ± 0.029 μmole/min/g as reported by Knuuti et al. (*22*), 0.44 ± 0.12 μmole/min/g as reported by vom Dahl et al. (*12*) and 0.97 ± 0.13 μmole/min/g as reported by Voipio-Pulkki et al. (*13*). Our result (0.54 ± 0.11 μmole/min/g) was slightly higher than the results reported by vom Dahl et al., and lower than that of Knuuti et al. or Voipio-Pulkki et al. in average value. Interindividual variability (s.d.) of our result was about the same as the results reported by vom Dahl et al. or Voipio-Pulkki et al. and larger than the results reported by Knuuti et al. Myocardial metabolic rate of oxygen was reported to be 0.11 ± 0.02 ml/min/g (4.9 ± 0.9 μmole/min/g) by Bol et al. (*25*). Considering that one mole of glucose is metabolized aerobically by 6 moles of oxygen, MGU rates may be 0.82 μmole/min/g (4.9/6) in the state when only glucose is utilized as energy substrate. Interindividual variability may result from the variability in the total amount of energy metabolism and in the utilization of other substrates (free fatty acids, lactate etc.) during insulin clamp. We think 0.5–0.7 μmole/min/g of MGU during the insulin clamp method may be reasonable. Although we did not measure plasma lactate, the MGU rate during the insulin clamp method might decrease in some volunteers in our study because of low-energy metabolism or relatively high lactate or free fatty acid metabolism during the insulin clamp method.

Myocardial Glucose Uptake in NIDDM Patients

Three major metabolic abnormalities in NIDDM include defective glucose-induced insulin secretion, elevated rates of hepatic glucose output and insulin's impaired ability to stimulate glucose uptake in peripheral target tissues (insulin resistance) (*26*). Peripheral insulin resistance is associated with decreased glucose transport activity, the likely rate-limiting step for glucose uptake in fat and muscle. In recent studies, pretranslational suppression of insulin-responsive glucose transporter (GluT4) appears to be the key mechanism of insulin resistance in adipocytes (*27,28*); however, levels of GluT4 protein and mRNA are normal in skeletal muscle, implying that defects in GluT4 functional activity or insulin-mediated translocation cause insulin resistance in muscle (*26,29*).

During oral glucose loading, myocardial FDG uptake (k1k3/(k2 + k3) value and MB ratio) in NIDDM patients was remarkably suppressed because of low serum insulin, high plasma glucose and insulin resistance. The MGU rate was also lower than normal, and the regional difference was larger than normal. Further, the serum free fatty acid level was rather high during oral glucose loading in NIDDM patients.

During the insulin clamp method, myocardial FDG uptake in NIDDM patients was remarkably improved although k1k3/(k2 + k3) and MGU was slightly lower than normal. Considering the insulin resistance in NIDDM, we feel that the decrease of MGU during the insulin clamp method in NIDDM patients compared with the normal group in a previous report (*13*) may be reasonable.

During fasting, although the serum insulin level and the glucose level were slightly higher in NIDDM group than in normal patients, MGU rates and k1k3/(k2 + k3) were slightly lower. This may be because of insulin resistance in NIDDM patients.

Clinical Implication

What is the appropriate condition in NIDDM patients for an FDG study of myocardial viability? In non-DM patients, oral glucose loading or fasting are usually used. During fasting, FDG uptake in normal myocardium is suppressed. Then, enhanced tracer uptake represents viable myocardium.

Several problems with fasting are pointed out. It is reported that in 40%–60% of patient's, or normal volunteer's, FDG images were clinically uninterpretable due to reduced myocardial FDG uptake and slower clearance of FDG from the blood during fasting (*24,30*). In addition, a recent report suggested heterogeneity of FDG uptake in normal myocardium, particularly during fasting, reduces the specificity of the procedure (*23*). Tamaki et al. reported that by interpreting FDG images in a quantitative manner, accuracy may be improved during fasting (*31,32*). In DM patients, however, as myocardial FDG uptake decreases during fasting, the difficulty to interpret images increases.

Compared with fasting oral glucose loading is generally more preferred in non-DM patients because it yields diagnostically adequate images in the majority of patients and it minimizes the apparent heterogeneity in myocardial FDG uptake (*23*). In DM subjects, it is reported that 10%–30% of the FDG study during oral glucose loading become uninterpretable (*8,9*) because the MB ratio of FDG images decreases in DM patients when plasma glucose rises, as seen in our results. During the insulin clamp method, the MB ratio of FDG image was excellent in DM patients, as seen in our results.

Schelbert, however, reported that the maintenance of a regular diabetic regimen and, if necessary, administration of supplemental doses of regular insulin improve the MB ratio of FDG image without using the insulin clamp method (*11*). As several studies report, the MB ratio of FDG images appears to be inversely related to plasma-glucose concentration (*33*). To improve the MB ratio of FDG images in diabetic patients, the use of insulin to suppress plasma-glucose concentration may be a main factor.

As to the detection of flow-metabolism mismatch, there has been no data indicating a preference for the insulin clamp method.

In the FDG study of NIDDM patients, the use of insulin to increase myocardial FDG uptake by decreasing plasma glucose is important, but further studies are necessary to determine whether the insulin clamp method is effective in detecting flow-metabolism mismatch.

Limitation

During oral glucose loading, plasma glucose changed significantly during the study and its state was not the same as the steady-state condition defined by Sokoloff (17). By using the average value of plasma glucose during the beginning, the middle and at the end of the study, however, the approximate estimation of MGU may be possible during oral glucose loading as Knuuti et al. reported (*22*).

There are no directly measured data of the LC in humans. In a recent study by Ng et al. (*34*), the LC was found to respond to extreme changes in insulin and glucose concentration in an isolated rabbit heart preparation. Previous studies, performed during more physiological conditions, have shown that nutritional state does not affect LC (*35,36*). We have to investigate whether an LC value of 0.67 can be used in the state of high serum insulin during oral glucose loading or the insulin clamp method or in the state of high plasma glucose during oral glucose loading in NIDDM patients. We also have to investigate whether LC is the same between normal subjects and NIDDM patients; however, our result that MGU rates in NIDDM patients decreased during oral glucose loading and was slightly lower than normal during the insulin clamp method, may not be affected by LC.

The accuracy of our method in evaluating MGU, the accuracy of the input function, problems in Patlak analysis, partial volume effect in target tissue, cardiac movement and patient movement are discussed in our previous study (*14*). As for partial volume effect, our method may not be perfect, because the thickness of myocardial wall in transaxial wall or sagittal long-axis wall may not be the same as the thickness measured by echocardiography and its change by cardiac movement. Although recovery coefficients determined by echocardiography may not be accurate, we think the error may not be large.

CONCLUSION

During oral glucose loading, the MB ratio of FDG in NIDDM patients often deteriorates because of high plasma glucose and low plasma insulin. The MB ratio of FDG remarkably improves with the insulin clamp method in NIDDM patients. However, MGU rates during the insulin clamp method decreased slightly compared with normals in spite of low plasma glucose and adequate plasma insulin. This may be because of insulin resistance in NIDDM (GluT4 abnormality). FDG studies in NIDDM patients to detect viable ischemic myocardium during oral glucose loading or fasting were not good because the MB ratio and image quality decreased. Insulin infusion may be needed to increase myocardial FDG uptake by decreasing plasma glucose, but further study is needed to determine if flow-metabolism mismatch can be detected well in the FDG study during the insulin clamp method.

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