Heart and Skeletal Muscle Glucose Disposal in Type 2 Diabetic Patients as Determined by Positron Emission Tomography

Liisa-Maria Voipio-Pulkki, Pirjo Nuutila, M. Juhani Knuuti, Ulla Ruotsalainen, Merja Haaparanta, Mika Teräs, Uno Wegelius and Veikko A. Koivisto

Department of Medicine, University of Turku and Turku Medical Cyclotron-PET Center; Turku University Central Hospital, Turku; and Second Department of Medicine, University of Helsinki, Helsinki, Finland

Myocardial and skeletal muscle glucose uptake was examined in 9 type 2 diabetic patients and 13 control subjects using PET and the insulin clamp technique. All subjects had clinically stable coronary heart disease. To simulate the clinical situation, diabetic patients were kept slightly hyperglycemic during the clamp study. Consequently, there were no differences in skeletal muscle or total body glucose disposal between the two groups. With PET, myocardial glucose uptake was 12–20-fold greater than that in skeletal muscle in both groups. However, in the diabetic patients, myocardial glucose uptake was 39% lower ($p < 0.05$) than in the control subjects. These data suggest a defect in myocardial glucose utilization in type 2 diabetes and emphasize the need for standardized metabolic conditions in diabetic patients during ^{18}FDG PET imaging.

J Nucl Med 1993; 34:2064–2067

Patients with type 2 diabetes are characterized by abnormalities in glucose metabolism in several organs: skeletal muscle glucose disposal is reduced, hepatic glucose production is increased and insulin-independent glucose uptake into the lens and neural tissue are increased (*1,2*). Although the actual mechanisms of insulin resistance in type 2 diabetes remain unknown, several steps in the uptake and intracellular handling of glucose are probably affected (*3,4*).

There is evidence of a specific diabetic cardiomyopathy—possibly of metabolic origin (*5*)—in the absence of hypertension or coronary heart disease (*6,7*). Glucose serves as an important fuel for the myocardium (*8*). We have recently shown that during euglycemic hyperinsulinemic clamp, young subjects with type 1 diabetes have normal rates of myocardial glucose uptake despite insulin resistance in skeletal muscle (*9*). Whether there are any abnormalities in the myocardial glucose uptake in type 2 diabetes, a disease of older age and commonly associated with coronary artery disease (CAD), is not known. In the present study, we determined myocardial and skeletal muscle glucose uptake in patients with type 2 diabetes noninvasively with the use of an insulin clamp, ^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}FDG) and PET.

Received Jan. 21, 1993; revision accepted Aug. 15, 1993.
For correspondence or reprints contact: Liisa-Maria Voipio-Pulkki, MD, Turku University, Department of Medicine, FIN-20520 Turku, Finland.

METHODS

Subjects

We studied 9 male type 2 diabetic patients (58 ± 2 yr (mean ± s.e.m.), body mass index (BMI) 27 ± 1 kg/m^2, HbA_{1c} 8.2% ± 1.2%, reference value 4.0%–6.0%), and 13 nondiabetic control subjects (10 men, 3 women, 53 ± 2 yr, BMI 24 ± 1 kg/m^2). All patients had clinically stable CAD and preserved global left ventricular systolic function documented by cineangiography. All antianginal medications except nitrates were withdrawn at least 24 hr before the study. Seven subjects in both groups were on long-acting nitrates. However, only one diabetic patient had taken this medication within 24 hr prior to the study. The protocol was approved by the Ethical Committee of the Turku University Central Hospital and written informed consent was obtained from all subjects.

Design

The study was started after an overnight fast at 9 a.m. Three intravenous catheters were inserted: one in an antecubital vein for the infusion of glucose and insulin, one in a contralateral antecubital vein for the injection of ^{18}FDG and the third into a heated (70°C) hand vein for sampling of arterialized venous blood. Serum insulin was acutely raised and maintained for 120 min with the constant rate of insulin infusion (15 pmole/kg · min^{-1}) (*10,11*). Plasma glucose was determined at 10-min intervals, and glucose was infused to maintain fasting glycemia in all subjects. This resulted in slightly, although not significantly, higher mean steady-state plasma glucose concentrations in diabetic than control subjects (7.0 ± 0.7 versus 5.5 ± 0.6 mmol/l, N.S.). Serum insulin and free fatty acids (FFAs) were measured at 30-min intervals.

Whole-body glucose disposal was calculated based on the insulin clamp technique (*10,12*). Since the insulin infusion rate employed totally suppresses hepatic glucose production (*12*), the glucose infusion rate, corrected with minor changes in plasma glucose, equals the rate of total body glucose disposal.

Cardiac and skeletal muscle glucose uptake rates were determined using PET. Sixty minutes after the start of the insulin clamp, 170–300 MBq of ^{18}FDG were injected and dynamic 60-min

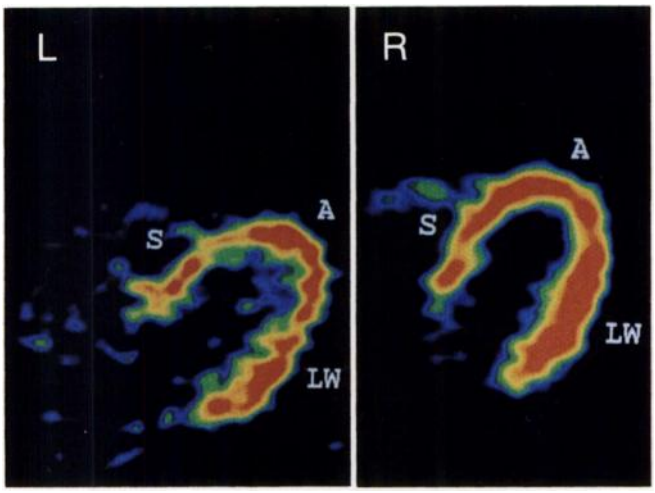

FIGURE 1. Fluorine-18-FDG PET images of the heart in a diabetic subject (left, heart glucose uptake 48 μmole · min^{-1}) and a control subject (right, heart glucose uptake 61 μmole/100 g · min^{-1}) as determined during insulin clamp. Both images are scaled to the same maximum. S = septum, A = apex, LW = lateral wall of the left ventricle.

PET emission scanning started simultaneously. Twenty-five arterialized plasma samples were obtained for the input function as previously described (*13*). Mean heart rate and systolic blood pressure were recorded during the PET study to calculate the double product.

PET Imaging

The patient was positioned in an eight-ring ECAT 931/08-12 tomograph (CTI Inc., Knoxville, TN) with his arms at his sides. Transmission scanning was performed as previously described (*13*) with total counts of 15–30 × 10^6 per plane followed by the 60-min dynamic emission imaging. The data were corrected for deadtime, randoms and measured photon attenuation. Transaxial images of the heart were reconstructed in a 256 × 256 matrix (Fig. 1). Four to six elliptical regions of interest (ROIs; 40–120 pixels/ROI) were drawn on at least three representative midventricular slices avoiding myocardial borders. The regions were carefully selected to represent normal myocardium as identified by the following criteria: <50% diameter stenosis in the corresponding epicardial coronary artery, normal wall motion by cineventriculography and echocardiography and no historical evidence of myocardial infarction in the corresponding territory. Myocardial time-activity curves obtained in the normal segments were corrected for partial volume according to wall thickness and left ventricular diameter (from two-dimensional echocardiography) and phantom studies as previously described (*13*). The magnitude of correction did not exceed 15%.

Correspondingly, at least three spherical ROIs (80–120 pixels/ROI) were placed in the anterior and posterior muscular compartments of the arm contralateral to the ^{18}FDG injection (*9,11*). The localization of the ROIs was verified by comparison with the position in the transmission images. During the later half of the emission study, the average counts obtained in the arm muscles were 60–80 × 10^{-4} cts/pixel per sec and in the myocardium 200–400 × 10^{-4} cts/pixel per sec.

Regional glucose uptake was calculated with graphic analysis of plasma and tissue time-activity curves according to Patlak et al. (*14*). After the initial period of ^{18}FDG uptake, the slope of the plot is equal to the transfer constant (K_i), representing the fractional phosphorylation rate of ^{18}FDG. The rate of glucose utilization is calculated as K_i × plasma glucose concentration/lumped constant (LC). LC accounts for the differences in the transport and phosphorylation of ^{18}FDG and glucose. LC was assumed to be 0.67 for myocardium (*15*) and 1.0 for skeletal muscle (*9,11*).

Analytical Procedures

Plasma glucose was determined with the glucose oxidase method (Beckman Glucose Analyzer II, Beckman Instruments, Fullerton, CA) and serum insulin by radioimmunoassay after precipitation with polyethylene glycol (*16*), and serum FFA with a microfluorometric method (*17*).

Statistical Analysis

Statistical comparisons between the groups were performed using the unpaired t-test. The results are given as mean ± s.e.m.

RESULTS

During the steady-state (60–120 min) that coincided with ^{18}FDG emission imaging, the mean plasma glucose concentration was slightly higher in diabetics than in control subjects (7.0 ± 0.7 versus 5.5 ± 0.6 mmol/liter, ns). Serum insulin (1198 ± 100 versus 1255 ± 230 pmole/liter) and FFA concentrations (264 ± 54 versus 289 ± 84 μmole/liter), and double products (9356 ± 1901 versus 8468 ± 2140 mmHg/sec) were similar in the diabetic and control groups, respectively.

Glucose disposal rates were similar in the diabetic and control subjects, respectively, in the whole body (3.0 ± 0.3 versus 3.4 ± 0.5 μmole/100 g · min^{-1}) and in the skeletal muscle (5.6 ± 0.6 versus 5.8 ± 0.5 μmole/100 g · min^{-1}, Fig. 2). However, myocardial glucose uptake was 39% lower in the diabetic (60.3 ± 8.2 μmole/100 g · min^{-1}) than in the nondiabetic subjects (97.1 ± 12.8 μmole/100 g · min^{-1}, $p < 0.05$, Fig. 2). Compared to the uptake in the skeletal muscle, the glucose uptake rate in the myocardium was 11.7 ± 1.7-fold greater in the diabetic group ($p < 0.01$) and 19.7 ± 4.4-fold greater in the control subjects ($p < 0.01$). The ratio was not significantly different between the two groups.

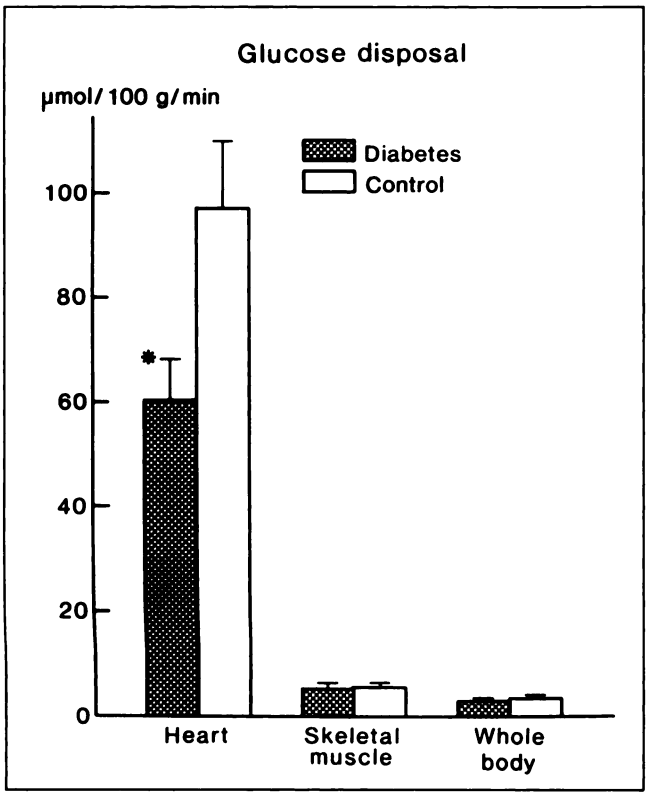

FIGURE 2. Insulin-stimulated glucose uptake by the heart, skeletal muscle and whole body in type 2 diabetic patients (shaded bars) and control subjects (open bars). *$p < 0.05$ as compared to control subjects.

DISCUSSION

PET is a unique tracer technique which allows noninvasive, quantitative determination of glucose transport and phosphorylation (*18*). When this is combined with high physiologic steady-state hyperinsulinemia, our previous studies (*9,11*) and the current one indicate that sufficient tracer uptake is achieved both in the myocardium and skeletal muscle to examine glucose uptake in these tissues.

In the present study, myocardial glucose uptake during insulin stimulus was found to be reduced by 39% in patients with type 2 diabetes. As reported previously in healthy subjects (*11*) and type 1 diabetic patients (*9*), in type 2 diabetes glucose uptake was also several-fold faster in myocardial than skeletal muscle. However, in contrast to type 1 diabetic subjects (*9*), myocardial glucose uptake was reduced as compared to a nondiabetic group.

This study was designed to reflect the usual clinical situation in type 2 diabetes: plasma glucose was clamped on a fasting level and consequently it was slightly higher in diabetic patients than in control subjects. In this respect, the present study differs from the euglycemic hyperinsulinemic design (*9–13*). Under the conditions of the present study, peripheral glucose disposal is increased due to the mass action of glucose (*19*). Mild hyperglycemia may have overcome insulin resistance often reported in type 2 diabetic patients (*1*), and insulin-stimulated total body and skeletal muscle glucose uptake were similar in diabetic and nondiabetic subjects.

Myocardial glucose utilization during normoxia is mainly determined by cardiac work load (*20,21*) and the availability of preferred substrates such as fatty acids (*11*), lactate and ketone bodies (*20,21*). Thus, insulin as well as glucose per se appear to be less prominent regulators of glucose uptake in the heart than in skeletal muscle. The observed lower myocardial glucose uptake in type 2 diabetic patients probably cannot be accounted for by a greater myocardial fatty acid utilization by the glucose-FFA cycle (*11,22*) since steady-state serum FFA concentrations were not elevated in diabetic patients. However, we cannot exclude substrate competition as a possible explanation of this finding since type 2 diabetic patients have recently been shown to have higher plasma lactate levels during insulin clamp (*4*).

Fluorine-18-FDG is transported and phosphorylated but not further metabolized (*18*). The LC accounts for differences in the transport and phosphorylation of ^{18}FDG and glucose. There are no directly measured data of the ^{18}FDG LC in humans. We assumed the LC to be unaltered in type 2 diabetes. Recent whole-body studies (*3,4*) have suggested that glucose handling in type 2 diabetes is probably disturbed on multiple intracellular levels far beyond the first two steps (*18,23,24*) that govern the LC of ^{18}FDG. In the heart, experimental studies have shown that physiological glucose levels are unlikely to affect the LC (*23*), but insulin may do so (*24*). Serum insulin levels were comparable in the diabetic and nondiabetic subjects during this study. Thus, although it is possible that type 2 diabetes affects the LC, we suggest that differential LC in the diabetic versus nondiabetic heart is an unlikely explanation of our observations in the myocardium of type 2 diabetic patients.

Whether the reduced myocardial glucose uptake in type 2 diabetes is a metabolic defect alone, or whether alterations in myocardial microcirculation or other factors also contribute to it, is not known. Regardless of the mechanisms, it is possible that reduced glucose uptake contributes to the myocardial dysfunction observed in patients with type 2 diabetes (*5–7*).

CONCLUSION

Our data suggest a defect in myocardial glucose uptake during insulin stimulus in type 2 diabetes. Reduced glucose uptake may contribute to the development of myocardial dysfunction in these patients. It also explains in part the poor ^{18}FDG image quality often seen diabetic subjects (*25*) and emphasizes the need for careful metabolic standardization in PET imaging of patients with type 2 diabetes and coronary artery disease.

ACKNOWLEDGMENTS

This work was supported by grants from the Academy of Finland, the Yrjö Jahnsson Foundation, the Sigrid Juselius Foundation, the Jenny and Antti Wihuri Foundation, the Research and

Science Foundation of Farmos, the Turku City Council and the Finnish Diabetes Research Foundation.

REFERENCES

1. DeFronzo RA. The triumvirate: beta cell, muscle, liver: a collusion responsible for NIDDM. *Diabetes* 1988;37:667–687.
2. Greene DA, Lattimer SA, Sima AAF. Sorbitol, phosphoinositides and sodium-potassium ATPase in the pathogenesis of diabetic complications. *N Engl J Med* 1987;316:599–606.
3. Eriksson J, Koranyi L, Bourey R, et al. Insulin resistance in type 2 (non-insulin-dependent) diabetic patients and their relatives is not associated with a defect in the expression of the insulin-responsive glucose transporter (GLUT-4) gene in human skeletal muscle. *Diabetologia* 1992;35:143–147.
4. Del Prato S, Bonadonna RC, Bonora E, et al. Characterization of cellular defects of insulin action in type 2 (noninsulin-dependent) diabetes mellitus. *J Clin Invest* 1993;91:484–494.
5. Uusitupa M, Siitonen M, Aro A, Korhonen T, Pyörälä K. Effect of correction of hyperglycemia on left ventricular function in noninsulin-dependent (type 2) diabetics. *Acta Med Scand* 1983;213:363–368.
6. Ledet T, Neubauer B, Christensen NJ, Lundbaek K. Diabetic cardiomyopathy. *Diabetologia* 1979;16:207–209.
7. Shapiro LM. Specific heart disease in diabetes mellitus. *Br Med J* 1982;1: 140–141.
8. Neely JR, Rovetto MJ, Oram JF. Myocardial utilization of carbohydrate and lipids. *Prog Cardiovasc Dis* 1972;15:289–329.
9. Nuutila P, Knuuti J, Ruotsalainen U, et al. Insulin resistance is localized to skeletal but not heart muscle in type 1 diabetes. *Am J Physiol* 1993;264: E765–E762.
10. DeFronzo RA, Tobin JD, Andres R. The glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 1979; 237:E214–E223.
11. Nuutila P, Koivisto VA, Knuuti J, et al. The glucose-free fatty acid cycle operates in human heart and skeletal muscle in vivo. *J Clin Invest* 1992;89: 1767–1744.
12. Koivisto VA, Yki-Järvinen H, Puhakainen I, et al. No evidence of isotope discrimination of tritiated glucose tracers in measurements of glucose turnover rates in man. *Diabetologia* 1990;33:168–173.
13. Knuuti MJ, Nuutila P, Ruotsalainen U, et al. Euglycemic hyperinsulinemic clamp and oral glucose load in stimulating myocardial glucose utilization during positron emission tomography. *J Nucl Med* 1992;33:1255–1262.
14. Patlak CS, Blasberg RG, Fenstermacher JD. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. *J Cereb Blood Flow Metab* 1983;3:1–7.
15. Krivokapich J, Huang S-C, Selin CE, Phelps ME. Fluoride-oxyglucose rate constants, lumped constant, and glucose metabolic rate in rabbit heart. *Am J Physiol* 1987;252:H777–H787.
16. Desbuquoise B, Aurbach GD. Use of polyethylene glycol to separate free and antibody-bound peptide hormones in radioimmunoassays. *J Clin Endocrinol Metab* 1971;33:732–738.
17. Miles J, Glassock R, Aikens J, Gerich J, Haymond MA. A microfluorometric method for the determination of free fatty acids in plasma. *J Lipid Res* 1983;24:96–99.
18. Gambhir SS, Schwaiger M, Huang S-C, et al. Simple noninvasive quantification method for measuring myocardial glucose utilization in humans employing positron emission tomography and fluorine-18 deoxyglucose. *J Nucl Med* 1989;30:359–366.
19. DeFronzo RA, Ferrannini E, Hendler R, Felig P, Wahren J. Regulation of splanchnic and peripheral glucose uptake by insulin and hyperglycemia in man. *Diabetes* 1983;32:35–45.
20. Camici P, Marraccini P, Marzilli M, et al. Coronary hemodynamics and myocardial metabolism during and after pacing in normal humans. *Am J Physiol* 1989;257:E309–E317.
21. Taegtmeyer H. Principles of fuel metabolism in heart muscle. In: de Jong JW, ed. *Myocardial energy metabolism.* Dordrecht: Martinus Nijhoff Publishers; 1988:17–34.
22. Randle PJ, Garland PB, Hales CN, Newsholme EA. The glucose fatty acid cycle: its role in insulin sensitivity and metabolic disturbances of diabetes mellitus. *Lancet* 1963;1:785–789.
23. Ng CK, Holden JE, DeGrado TR, Raffel DM, Kornguth ML, Gatley SJ. Sensitivity of myocardial fluorodeoxyglucose lumped constant to glucose and insulin. *Am J Physiol* 1991;260:H593–H603.
24. Russel RR, Mrus JM, Mommessin JI, Taegtmeyer H. Compartmentation of hexokinase in rat heart. A critical factor for tracer kinetic analysis of myocardial glucose metabolism. *J Clin Invest* 1992;90:1972–1977.
25. Bonow RO, Berman DS, Gibbons RJ, et al. Cardiac positron emission tomography. A report for health professionals from the committee on advanced cardiac imaging and technology of the council on clinical cardiology, American Heart Association. *Circulation* 1991;84:447–454.