Impaired Free Fatty Acid Uptake in Skeletal Muscle But Not in Myocardium in Patients With Impaired Glucose Tolerance

Studies With PET and 14(R, S)-[^{18}F]Fluoro-6-Thia-Heptadecanoic Acid

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Free fatty acids (FFAs) are an important substrate for myocardial and skeletal muscle metabolism, and increased availability and oxidation of FFA are suggested to be associated with insulin resistance. This study was undertaken to assess whether myocardial or muscle uptake of FFA is altered in patients with impaired glucose tolerance (IGT). Eight healthy men (control group; age 48 ± 1 years, BMI 25 ± 1 kg/m^2, mean ± SE) and eight men with IGT (glucose-intolerant group; age 49 ± 1 years, BMI 29 ± 1 kg/m^2) were studied in the fasting state. Myocardial oxygen consumption and blood flow and myocardial and femoral muscle FFA uptake rates were measured with positron emission tomography (PET) and [^{15}O]O_2, [^{15}O]H_2O, [^{15}O]CO, and 14(R, S)-[^{18}F]fluoro-6-thia-heptadecanoic acid ([^{18}F]FTHA), a fatty acid tracer trapped into the cell after undergoing initial steps of β-oxidation. Serum glucose and insulin concentrations were higher in the glucose-intolerant group during the PET study, but FFA concentrations were comparable between the groups. No differences between the groups were observed in the myocardial blood flow, oxygen consumption, fractional FTHA uptake rates, or FFA uptake indices (5.6 ± 0.4 vs. 5.2 ± 0.4 μmol · 100 g^{-1} · min^{-1}, glucose-intolerant versus control, NS). In the femoral muscle, fractional FTHA uptake (0.0062 ± 0.0003 vs. 0.0072 ± 0.0003 min^{-1}, P = 0.044) and FFA uptake indices (0.30 ± 0.02 vs. 0.43 ± 0.04 min^{-1}, P = 0.020) were significantly lower in the glucose-intolerant group than in the control group. In conclusion, when studied at the fasting state and normal serum FFA concentrations, subjects with IGT have similar myocardial but lowered femoral muscle FFA uptake. This finding argues against the hypothesis that an increased oxidation of serum FFA, via the competition of glucose and FFA as fuel sources, is the primary cause for impaired peripheral glucose utilization and insulin resistance commonly observed in IGT.
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Free fatty acid (FFA) is the major oxidative fuel for some body tissues, particularly the heart and the skeletal muscle. The competition between glucose and fatty acids as oxidative fuel sources in these tissues, i.e., the glucose-fatty acid cycle, was originally described by Randle et al. in 1963 (1). They postulated that increased availability and oxidation of FFAs, via the competition between glucose and FFAs as fuel sources, lead to impaired insulin-mediated glucose uptake and at least partly cause insulin resistance in type 2 diabetes (1). Thereafter, studies have shown repeatedly that high plasma FFA levels inhibit insulin-stimulated glucose uptake both in human skeletal muscle and in the heart (2,3). Basal serum FFA concentrations are usually increased in type 2 diabetic patients (4) because of the enhanced rate of lipolysis (5), impaired suppression of lipolysis by insulin, and defective FFA clearance (6). A long-term exposure to FFAs may also interfere with pancreatic β-cell function and insulin secretion (7) and increase hepatic gluconeogenesis (2).

Elevated rates of lipid oxidation at the whole-body level are shown to be associated with impaired oxidative glucose disposal in nonobese type 2 diabetic patients in some (6,8) but not all studies (9). Uptake and oxidation of plasma FFA occur in the liver, skeletal muscle, and heart, as well as in other tissues. Skeletal muscle is the largest tissue in the body and responsible for the majority of lipid oxidation and insulin-stimulated glucose uptake. Previous investigations of muscle FFA uptake and oxidation in subjects with impaired glucose tolerance (IGT) are few, and their results are controversial. Moreover, muscle FFA metabolism has been estimated using leg balance technique (10–12) or forearm perfusion techniques (13). Similar uptake rates were found in mild type 2 diabetic and control subjects (13). In recent

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FFA, free fatty acid; [^{18}F]FTHA, 14(R, S)-[^{18}F]fluoro-6-thia-heptadecanoic acid; HDA, ^{123}I-heptadecanoic acid; IGT, impaired glucose tolerance; PET, positron emission tomography.

years, there has been evidence suggesting that FFA utilization in the skeletal muscle could even be impaired in type 2 diabetes (10,11) and in women with visceral obesity (12). Plasma FFA concentration, the main determinant of FFA transport (13), has been either increased (10,11) or comparable (12) between glucose-intolerant and control subjects during the studies.

It has been well established that diabetic patients have increased risk for myocardial infarction (14,15). The results of recent studies with positron emission tomography (PET) suggest that myocardial glucose uptake during euglycemic hyperinsulinemia is not changed in type 2 diabetic patients (16,17). Myocardial fatty acid metabolism in diabetic patients was measured with single-photon emission tomography and ^{123}I-heptadecanoic acid in our previous study (18). We found that myocardial fatty acid uptake and β-oxidation indices were not different in type 2 diabetic patients but were reduced in subjects in IGT (18).

In the present study, we used PET and a newly introduced tracer for fatty acid metabolism, 14(R, S)- [18F]fluoro-6-thia-heptadecanoic acid ([^{18}F]FTHA) (19–23). [^{18}F]FTHA has a high first-pass uptake in the heart and muscles. After transport into the mitochondria, it undergoes initial steps of β-oxidation and is thereafter trapped in the cell. Then the tracer uptake can be quantitated. According to the original hypothesis of Randle et al. (1), this study was undertaken to directly test whether skeletal muscle or myocardial FFA uptake is increased in the basal state in subjects with IGT compared with healthy control subjects. The findings indicate that there is impaired uptake of FFA by skeletal muscle in subjects with IGT, whereas myocardial FFA uptake is not altered.

RESEARCH DESIGN AND METHODS

Subjects. Eight men with IGT according to the World Health Organization criteria (24) were recruited from the ongoing studies in the Social Insurance Institution, Research and Development Centre, Turku, and from the Department of Clinical Nutrition, University of Kuopio, Finland. None of them had a history of any cardiac illness or was taking any medication. Eight healthy normal-weight men without any family history of diabetes served as control subjects. None of them was taking any medication. The control and glucose-intolerant groups were comparable in age, whereas the latter group was significantly more obese as determined with BMI, but their fat percent and maximal oxygen uptake capacity was not significantly different (Table 1). All subjects gave their informed consent for the study, and the study was approved by the Commission Ethics of Turku University Central Hospital and Kuopio University Hospital.

Study design. Before the PET study, all subjects had been fasting for 12–15 h to achieve high FFA levels and enhance FFA utilization. Two catheters were inserted, one in the left antecubital vein for the injection of tracers and the other in the radial vein of the contralateral arm that was warmed (air temperature 70°C) for the collection of the blood samples. Myocardial blood volume, blood flow, and oxygen consumption were determined with [^{15}O]CO, [^{15}O]H_2O, and [^{15}O]O_2. PET scans were started at 0, 15, and 30 min, respectively. [^{18}F]FTHA was injected at 60 min, and a dynamic scan of the thoracic region was performed for 32 min. Thereafter, the femoral region was scanned over 15 min. The mean doses of [^{15}O]CO, [^{15}O]H_2O, [^{15}O]O_2, and [^{18}F]FTHA were 3,280 ± 72 Mbq, 1,570 ± 24 MBq, 2,960 ± 110 MBq, and 171 ± 5 MBq, respectively. Myocardial oxygen consumption of one control subject and one IGT subject were not measured because of technical problems. Blood glucose, insulin, FFA, and lactate concentrations were determined every 60 min, and the mean of the three values was used in the analyses. Electrocardiogram, heart rate, and blood pressure were monitored throughout the study.

Exercise echocardiography was performed before the PET study to exclude patients with asymptomatic coronary heart disease; cardiac dimensions and systolic function were also measured. In two patients, coronary heart disease was excluded with myocardial perfusion scintigraphy. Maximal exercise capacity was measured with a bicycle ergometer within 2 weeks after the PET study.

Production of [^{15}O]CO, [^{15}O]H_2O, [^{15}O]O_2, and [^{18}F]FTHA. For production of ^{15}O, a low-energy deuteron accelerator Cyclone 3 was used (Ion Beam Application, Louvain-la-Neuve, Belgium). A natural nitrogen gas target containing 1% oxygen was used, and the radiochemical purity of [^{15}O]O_2 was 97%. [^{15}O]CO was produced in a conventional way (25). ^{15}O-labeled water was produced using dialysis techniques in a continuously working water module (25). Sterility and pyrogenity tests for water and chromatographic analysis for gases were performed to verify the purity of the products. [^{18}F]FTHA was produced as previously described (22), and the radiochemical purity of the final product was >98%.

Image acquisition, processing, and corrections. The patients were positioned supine in a 15-slice ECAT 931/08-12 tomograph (Siemens/CTI, Knoxville, TN) with a technical in-plane resolution of 6.5 mm and an axial resolution of 6.7 mm. To correct for photon attenuation, transmission scanning was performed for 10 min for femoral regions and 20 min for thoracic regions prior to the emission scans. For the thoracic region, transmission scanning was repeated before the FTHA study. Two reconstruction methods were applied: *1*) median root prior (26) in [^{15}O]CO, [^{15}O]H_2O, and [^{15}O]O_2 studies (FWHM 8.0 mm) and *2*) filtered back projection in [^{18}F]FTHA studies (FWHM 9.5 mm).

Definition of regions of interest in PET studies. Transaxial PET slices were visually aligned, and the left ventricular myocardium was assigned to eight segments with the help of a heart map phantom (3). A total of 30–34 elliptical regions of interest were placed on an average of 9 transaxial ventricular slices in each [^{18}F]FTHA study, with care taken to avoid myocardial borders. For the femoral regions, regions of interest were drawn on the anteromedial, anterolateral, and posterior muscle compartments in four adjacent planes (3). Large vessels were avoided when outlining the muscle areas.

Calculation of the myocardial blood flow and oxygen consumption. Regional myocardial blood flow, oxygen extraction fraction, and oxygen consumption ($MMRO_2$) were quantitated using previously published methods (27,28) and an image analysis package (Dr. View, Asahi-Kasei, Tokyo) with special dedicated software.

Calculation of the regional [^{18}F]FTHA fractional uptake constant and FFA uptake index. The nonmetabolized fraction of [^{18}F]FTHA was determined with high-performance liquid chromatography from nine blood samples (2, 5, 10, 15, 20, 25, 30, 40, and 50 min from the beginning of FTHA injection, Fig. 1), and the metabolite corrected plasma curve was calculated by linear interpolation and used to correct the plasma input function, as previously described (22). Thereafter, the time-activity curves of plasma, myocardial, and femoral tissue were analyzed graphically (29). The slope of the plot in the graphical analysis is equal to the fractional uptake constant of [^{18}F]FTHA, K_i. The last seven time points (6–29.5 min) were used to determine the slope by linear regression in the myocardium, and all seven time points were used in the femoral regions. The regional myocardial and skeletal muscle FFA uptake indices were calculated by multiplying myocardial and skeletal muscle K_i with the mean serum FFA concentration during PET imaging.

Rest and exercise echocardiography. To rule out cardiomyopathy and coronary heart disease, the study subjects underwent a rest and exercise echocardiographic examination. All patients had a normal exercise capacity and were asymptomatic during an incremental maximal-cycle ergometry test, and they had no diagnostic ST-segment changes in the electrocardiogram during exercise. All subjects had a normal left ventricular function at rest and had no wall motion disturbances either at rest or immediately after the exercise test.

TABLE 1
Physiological and metabolic characteristics

	Control subjects	IGT subjects
n	8	8
Age (years)	48 ± 1	49 ± 1
BMI (kg/m^2)	25 ± 1	29 ± 1*
Fat percent	18 ± 2	22 ± 2
Vo_{2max} (ml · kg^{-1} · min^{-1})	40 ± 2	34 ± 3
Systolic blood pressure (mmHg)	127 ± 4	136 ± 4
Heart rate (1/min)	60 ± 2	64 ± 2
Double product (mmHg/min)	7,566 ± 310	8,711 ± 400†
Wall stress (kPa/cm)	5.8 ± 0.3	6.8 ± 0.4
Ejection fraction (%)	67 ± 2	66 ± 1
LV mass (g)	209 ± 10	226 ± 8
LV mass index (g/m^2)	108 ± 4	110 ± 4
Glucose (mmol/l)	4.9 ± 0.2	6.1 ± 0.3‡
Insulin (pmol/l)	24 ± 2	56 ± 5‡
Lactate (mmol/l)	0.76 ± 0.06	1.15 ± 0.14†
FFAs (mmol/l)	0.54 ± 0.06	0.51 ± 0.05

Results are means ± SE. *P < 0.01, †P < 0.05, and ‡P < 0.001 between the groups. LV, left ventricular.

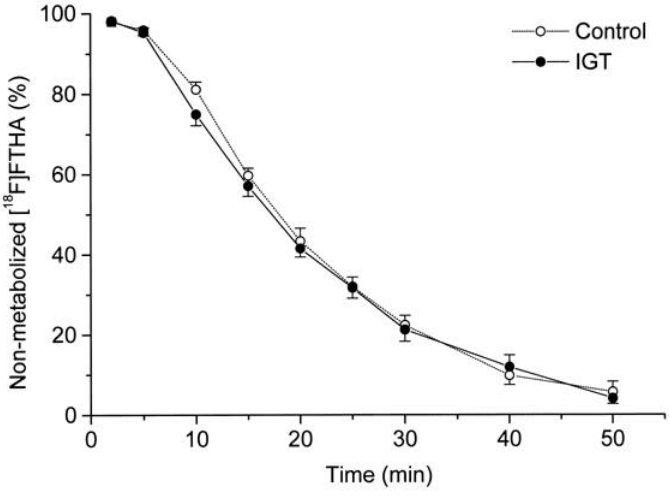

FIG. 1. The results of high-performance liquid chromatography studies of metabolites express the fraction of the mean nonmetabolized [^{18}F]FTHA as a function of time in the IGT and control subjects.

Maximal exercise test. Maximal aerobic power (Vo_{2max}) was determined using oxygen detectors and a cycle ergometer (Model 800 S; Ergoline, Mijnhardt, Netherlands) with a continuous incremental protocol. Body fat content was estimated from four skinfolds (subscapular, triceps brachii, biceps brachii, and crista iliaca) as measured with caliper.

Analytical procedures. Serum FFAs were determined by an enzymatic method (ACS-ACOD Method; Wako Chemicals, Neuss, Germany). Plasma glucose was measured using the glucose oxidase method (Analox GM7 Analyser; Analox Instruments, Hammersmith, London). Serum free insulin concentrations were measured using a double antibody radioimmunoassay (Pharmacia Insulin RIA Kit; Pharmacia, Uppsala, Sweden) after precipitation with polyethylene glycol. Lactate was measured by enzymatic analysis (22). Glycosylated hemoglobin in blood was measured with fast protein liquid chromatography (MonoS; Pharmacia). Serum total cholesterol, HDL cholesterol, and triglyceride concentrations were measured using standard enzymatic methods (Boehringer Mannheim, Mannheim, Germany) with a fully automated analyzer (Hitachi 704; Hitachi, Tokyo, Japan). HDL cholesterol was measured after polyethylenglycol (mw 6000, final concentration 10%) precipitation (30).

Statistical analysis. Data were analyzed using the SPSS for Windows statistical package (version 6.0; SPSS, Chicago). After the normal distribution of the variables had been checked with the Kolmogorov-Smirnov test, a two-tailed Student's *t* test and analyses of variance and covariance were performed to study the differences between the groups. Pearson's correlation coefficients were used in analyzing linear correlations between the variables. All results are expressed as means ± SE.

RESULTS

Substrate concentrations during the study and echocardiographic findings. Fasting plasma glucose and lactate and serum insulin concentrations were significantly higher in the glucose-intolerant group than in the control group, but no differences could be observed in the FFA concentrations during the study (Table 1). The glucose-intolerant group showed a decreased HDL cholesterol level (1.02 ± 0.13 vs. 1.42 ± 0.13 mmol/l, $P = 0.048$) and increased triglyceride concentration (1.64 ± 0.19 vs. 0.59 ± 0.06 mmol/l, $P < 0.0001$) when compared with the control group. Serum total cholesterol was not significantly different between the glucose-intolerant and control groups (4.66 ± 0.34 vs. 5.38 ± 0.31 mmol/l, $P = 0.15$), nor was HbA_{1c} (6.0 ± 0.3 vs. 5.4 ± 0.1%, $P = 0.09$).

Systolic blood pressure and heart rate tended to be higher in the glucose-intolerant group, and myocardial workload as estimated by rate-pressure product was slightly but significantly higher in the glucose-intolerant group than in the control group. Left ventricular mass, wall stress, and ejection fraction were comparable between the groups.

Myocardial oxygen consumption and blood flow. Myocardial oxygen consumption (10.7 ± 1.3 vs. 9.9 ± 1.0 ml · 100 g^{-1} · min^{-1}, IGT vs. control), oxygen extraction fraction (0.65 ± 0.04 vs. 0.64 ± 0.03), and blood flow (90 ± 9 vs. 84 ± 10 ml · 100 g^{-1} · min^{-1}) were comparable between the glucose-intolerant group and the control group. Total left ventricular oxygen consumption (24 ± 3 vs. 20 ± 2 ml/min) and blood flow (205 ± 24 vs. 174 ± 20 ml/min) were also comparable between the groups. Total left ventricular oxygen consumption ($r = 0.55$, $P = 0.044$) and blood flow ($r = 0.56$, $P = 0.024$) correlated positively with the double product in pooled data.

Myocardial [^{18}F]FTHA kinetics and FFA uptake indices. Rapid tracer uptake in the myocardium was observed within 2–3 min after [^{18}F]FTHA injection, which

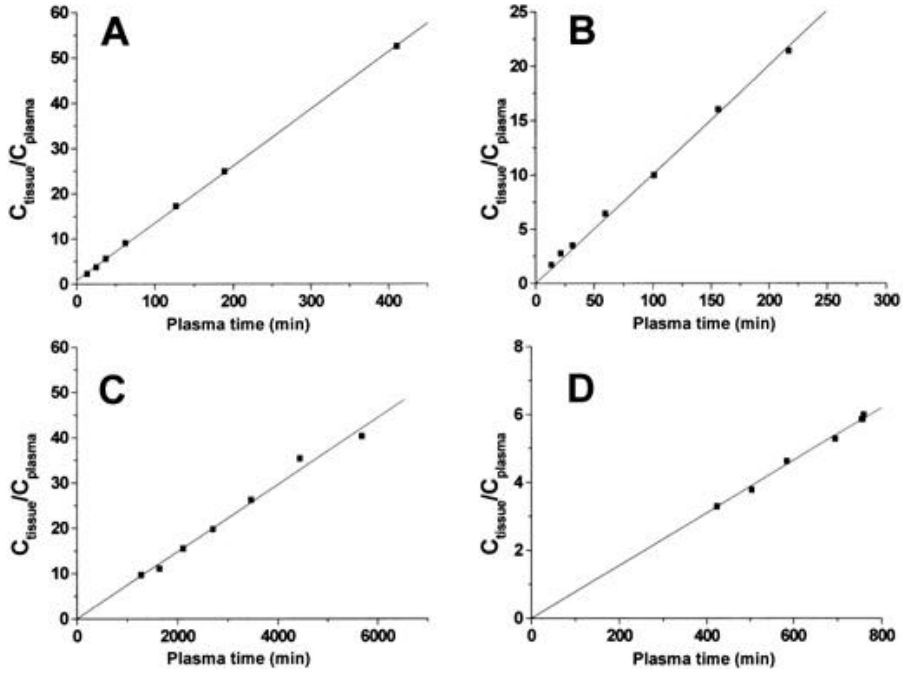

FIG. 2. Patlak plots of myocardial (*A*: IGT; *B*: control) and femoral (*C*: IGT; *D*: control) muscle of one IGT subject and one control subject. The plots are linear, indicating metabolic trapping. Please note the different scales in each graph.

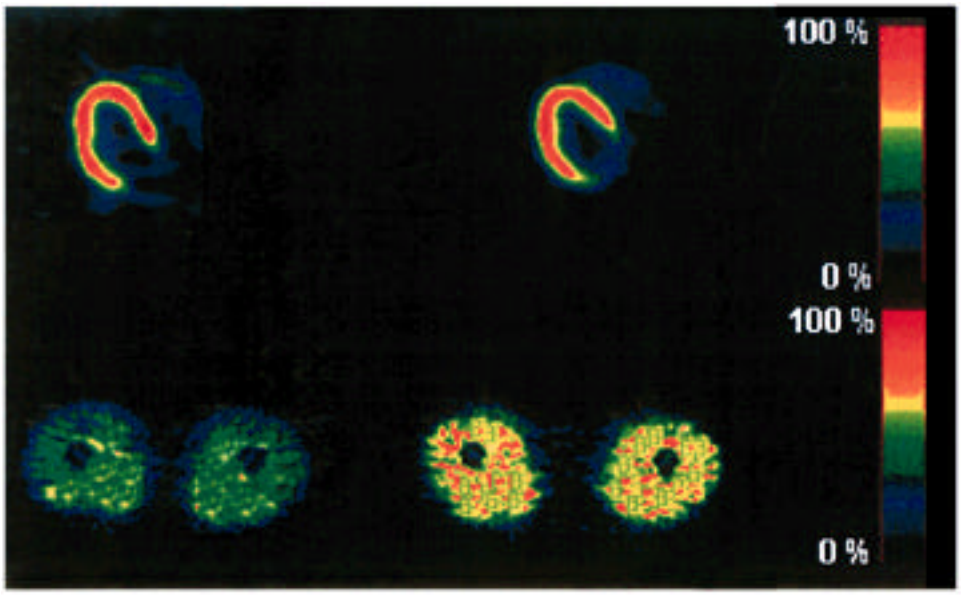

FIG. 3. Example of [^{18}F]FTHA uptake in the heart (*upper row*) and femoral (*lower row*) muscle in the IGT subject (*left*) and control subject (*right*).

remained nearly constant during the study. Patlak plots of FTHA were linear, indicating metabolic trapping (Fig. 2). The residuals of the regressions were stocastically scattered. Fractional uptake of FTHA in the myocardium (K_i) was similar in both groups (glucose-intolerant group 0.11 ± 0.01 min^{-1}, control group 0.10 ± 0.01 min^{-1}, NS); and myocardial FFA uptake indices were also comparable in glucose-intolerant and control subjects (5.6 ± 0.4 vs. 5.2 ± 0.4 µmol · 100 g^{-1} · min^{-1}, NS) (Figs. 3 and 4). Further, total left ventricular FFA uptake indices, obtained by multiplying the FFA uptake index with left ventricular mass, were comparable between the groups (12.5 ± 0.8 vs. 10.8 ± 0.7 µmol/min, NS). Total left ventricular FFA uptake index correlated with the double product in the pooled data (r = 0.63, P = 0.013).

Skeletal muscle [^{18}F]FTHA kinetics and FFA uptake indices. The average femoral muscle fractional [^{18}F]FTHA uptake was 14% lower in the glucose-intolerant group (0.0062 ± 0.0003) than in the control group (0.0072 ± 0.0003 min^{-1}, P = 0.044). The FFA uptake in the femoral muscle was 30% lower in the glucose-intolerant group compared with the control group (0.30 ± 0.02 vs. 0.43 ± 0.04 µmol · 100 g^{-1} · min^{-1}, P = 0.020) (Figs. 3 and 4). This difference remained statistically significant even after adjustment for BMI (P = 0.043).

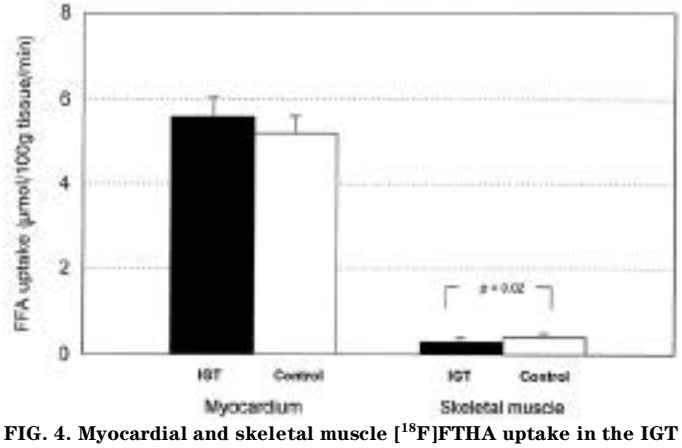

FIG. 4. Myocardial and skeletal muscle [^{18}F]FTHA uptake in the IGT and control groups expressed by tissue weight.

DISCUSSION

The present study demonstrated that FFA uptake in the femoral muscle was decreased by 30% in the glucose-intolerant subjects with IGT, whereas no differences could be observed in the myocardial FFA uptake between the two groups. To our knowledge, this is the first study in which skeletal and myocardial FFA uptake has been directly quantitated applying the PET technique in subjects with IGT.

Skeletal muscle FFA uptake. The femoral muscle FFA uptake rates in this study in the fasting state (0.43 vs. 0.30 µmol · 100 g^{-1} · min^{-1}, control vs. IGT subjects) are comparable with those measured previously with FTHA and PET in patients with stable coronary heart disease (0.38 µmol · 100 g^{-1} · min^{-1}) (22) and to those measured with leg balance technique (0.39 µmol · 100 g^{-1} · min^{-1}) (31). Our results are also comparable with those measured by forearm technique in healthy subjects (0.25 µmol · 100 g^{-1} · min^{-1}), taking into account that in the latter study, serum FFA concentration was ~40% lower (13). The present finding that skeletal muscle FFA uptake was decreased is in accord with previous reports of Kelley and Mandarino (10), who demonstrated that during fasting hyperglycemia, leg respiratory quotient was increased in type 2 diabetic subjects, suggesting that skeletal muscle FFA utilization could be impaired during these conditions. Later, it was found that in patients with type 2 diabetes (11) and in women with visceral obesity (12), muscle FFA utilization was indeed decreased. The former study demonstrated that skeletal muscle FFA uptake in type 2 diabetes is reduced during fasting, with lipid oxidation being reduced during both fasting and postprandial conditions (11). In a study by Capaldo et al. (13), forearm FFA uptake rates in the basal state were found to be comparable in patients with type 2 diabetes and control subjects, but plasma FFA concentration, the main determinant of FFA uptake, tended to be higher in insulin-treated type 2 diabetic patients. In our study, serum FFA concentrations were comparable between the groups, although subjects with IGT usually have higher FFA concentrations (4). However, the similar serum FFA concentration between the study groups enables a demonstration of the possible differences in FFA uptake by excluding increments

in uptake caused by substrate levels (13). Our result on impaired muscle FFA uptake in the insulin-resistant subjects argues against the hypothesis that excessive FFA utilization per se is the key explanation for impaired peripheral glucose utilization via the glucose–fatty acid competition. However, this does not exclude that in the conditions where circulating FFA concentrations are increased, the FFA utilization could be enhanced, further inhibiting glucose metabolism.

Myocardial FFA uptake. Quantitation of myocardial FFA uptake has been previously based on determination of arteriovenous differences and myocardial blood flow measurements. The FTHA-derived myocardial FFA uptake rate in the fasting state in the present study (5.2 and 5.6 μmol · 100 g^{-1} · min^{-1}, control vs. IGT group) is in accord with previous animal and human studies in which myocardial FFA uptake in the fasting state could be estimated to be 5.7–13 μmol · 100 g^{-1} · min^{-1} (22,32,33). The unaltered myocardial FFA uptake and decreased muscle FFA uptake resembles that of glucose metabolism, because myocardial insulin-stimulated glucose uptake is not impaired in patients with type 2 diabetes (16,17) despite insulin resistance in skeletal muscles. We have previously studied myocardial FFA kinetics with single-photon emission tomography and ^{123}I-heptadecanoic acid (HDA) in both type 1 and type 2 diabetic patients and in subjects with IGT (18). It was found that myocardial HDA uptake and β-oxidation indices were reduced in subjects with IGT, but not significantly reduced in type 2 or type 1 diabetic patients (18). This discrepancy could be explained by the increased left ventricular mass of subjects with IGT, because the total myocardial HDA uptake was comparable between all groups (18). Myocardial substrate uptake depends on energy demand. The double product was slightly greater in the IGT group, but myocardial blood flow and oxygen consumption were similar between the groups, which indicates similar energy requirements in the IGT and control subjects.

[^{18}F]FTHA as a tracer for FFA uptake and β-oxidation. [^{18}F]FTHA has been developed for the investigation of FFA metabolism (19,20), and it has been found to be a feasible tracer for the investigation of human myocardial and skeletal muscle FFA uptake (21,22). After transport into the mitochondria, it undergoes initial steps of β-oxidation and is thereafter trapped in the cell. In the mouse heart, the inhibition of β-oxidation with the carnitine palmitoyltransferase I inhibitor decreased myocardial FTHA uptake by 81% within 1 min and by 87% within 60 min (19). In a recent comparison with β-oxidation rates by tritiated palmitate in the extracorporeally perfused pig heart model, myocardial FTHA uptake was found to correlate with fatty acid β-oxidation rate (23). These findings in the heart suggest that the accumulation of FTHA is mainly related to FFA β-oxidation, and only 5–10% is esterified (19,23). The results of FTHA uptake measurements are in concordance with findings of Wisneski et al. (33) that in the human heart, 80% of extracted FFAs are immediately β-oxidized (33). Whether there is an intracellular lipid storage that could produce significant amounts of FFAs for the energy needs of the human heart is unknown.

In isolated working rat hearts, endogenous fatty acid accounted for from 12 to 20% of total fatty acid oxidation, depending on the availability of FFA in the perfusate (34). In the hearts of acutely diabetic rats, myocardial triglyceride content was significantly higher than in control rats, but endogenous palmitate oxidation rates were similar to control hearts and contributed 10% of overall ATP production (35), suggesting that differences in myocardial intracellular triglyceride metabolism between glucose-intolerant and control groups are unlikely to markedly affect myocardial FFA uptake results. Of note, the fraction of FTHA esterified to triglycerides is almost the same as the fraction of endogenous fatty acids (triglycerides) of total fatty acid oxidation, which further confirms that myocardial FTHA uptake is mainly associated with FFA β-oxidation. In the skeletal muscle, however, there seems to be a large intracellular lipid pool (36), and intramuscular lipolysis may account for a significant amount of energy production (37).

Moderate obesity is a very characteristic feature of the insulin resistance syndrome, and it may be difficult to distinguish the separate contributions of obesity and disturbed glucose metabolism to the impaired FFA uptake in the IGT muscle. In the present study, the patient group consisted of moderately obese patients with recently diagnosed IGT. Because our aim was to study myocardial and skeletal muscle FFA metabolism in insulin-resistant glucose-intolerant patients, one could argue that obesity per se, not disturbed glucose metabolism, could have an effect on our findings. Because femoral muscle FTHA uptake was significantly lower in the glucose-intolerant group even after adjustment for BMI, it is obvious that obesity does not influence the interpretation of the results.

In conclusion, our data indicate that skeletal muscle FFA uptake is reduced in patients with IGT, whereas myocardial FFA uptake appears normal in this condition. Mechanisms other than increased FFA oxidation are responsible for the lowered peripheral glucose uptake and insulin resistance in IGT.

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