Insulin Action on Heart and Skeletal Muscle FDG Uptake in Patients with Hypertriglyceridemia

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Abnormal heart and skeletal muscle ^{18}F-fluorodeoxyglucose (FDG) uptake in patients with insulin resistance has been demonstrated. Although the existence of whole-body insulin resistance has been reported in hypertriglyceridemics, its specific role in heart and skeletal muscle FDG uptake in hypertriglyceridemics has not been clarified. **Methods:** We compared heart and skeletal muscle FDG uptake using PET and the whole-body glucose disposal rate (GDR) during insulin clamping in 17 hypertriglyceridemics and 12 age-matched control subjects to increase our knowledge of whole-body insulin resistance and its relationship to heart and skeletal muscle FDG uptake in hypertriglyceridemics. **Results:** GDR was significantly reduced in hypertriglyceridemics compared with control subjects (4.50 ± 1.37 mg/min/kg versus 10.0 ± 2.97 mg/min/kg, $P = 0.00001$), as were the skeletal muscle FDG $K_i = (k_1 \times k_3)/(k_2 + k_3)$ (SFK_i: 0.007 ± 0.003 mL/min/g versus 0.018 ± 0.01 mL/min/g, $P = 0.0001$) and skeletal muscle FDG uptake ([SMFU] 0.725 ± 0.282 mg/min/100 g versus 1.86 ± 1.06 mg/min/100 g, $P = 0.00023$). However, myocardial FDG K_i (MFK_i) tended to be reduced in hypertriglyceridemics compared with that in control subjects (0.062 ± 0.017 mL/min/g versus 0.068 ± 0.015 mL/min/g), but the difference was statistically insignificant ($P = 0.3532$). Moreover, myocardial FDG uptake (MFU) in hypertriglyceridemics (6.47 ± 1.72 mg/min/100 g) tended to be reduced compared with that in control subjects (6.97 ± 1.73 mg/min/100 g), but the difference was statistically insignificant ($P = 0.4485$). GDR was significantly correlated with SFK_i ($r = 0.69$, $P = 0.0022$), SMFU ($r = 0.612$, $P = 0.009$), MFK_i ($r = 0.57$, $P = 0.0174$) and MFU ($r = 0.505$, $P = 0.0385$) in hypertriglyceridemics. **Conclusion:** Both heart and skeletal muscle glucose utilization were related to insulin resistance in hypertriglyceridemics. However, the less severe reduction in MFU (compared with SMFU) suggests that myocardium may have a mechanism to oppose insulin resistance in hypertriglyceridemics.

Key Words: insulin resistance; hypertriglyceridemia; fluorodeoxyglucose; PET; heart and skeletal muscle glucose metabolism

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The importance of insulin resistance in the development of coronary artery disease has been reported (*1–4*). Because insulin resistance can be present in several coronary risk factors, such as essential hypertension (*5*), type II diabetes (non–insulin-dependent diabetes mellitus [NIDDM]) (*6*), obesity (*7*) and hypertriglyceridemia (*8–13*), an investigation of the details of insulin resistance in these diseases is warranted. Translocation of insulin-sensitive glucose transporters in heart and skeletal muscle has been found to initiate glucose uptake in response to insulin (*14–16*). However, results of studies on the regulation of heart and skeletal muscle glucose metabolism have been conflicting. For example, increased myocardial glucose uptake (MGU) and decreased free fatty acid (FFA) uptake in response to insulin clamping was shown in normal dogs (*17–20*). Acutely elevated FFA by means of soybean emulsion infusion did not inhibit increases in MGU by insulin clamping, but skeletal muscle glucose uptake was reduced by such an acute elevation of FFA (*21*). Furthermore, another study reported that in chronic insulin-deficient diabetic dogs, the administration of insulin did not increase MGU but it reduced myocardial FFA uptake (*22*). Kim and Youn (*23*) also reported the inhibitory effect of plasma FFA on skeletal muscle and whole-body glucose uptake in the normal rat.

Deoxyglucose has been reported to be taken up by heart and skeletal muscle cells in response to insulin (*17,20,24,25*). The linear relationship between deoxyglucose uptake and glucose uptake has suggested that deoxyglucose is a glucose analog (*17,20,24,25*). Clinically, ^{18}F-fluorodeoxyglucose (FDG) has been used for the diagnosis of viability of myocardium as well as the detection of tumor tissue or evaluation of brain function with PET. Moreover, PET technique with FDG to quantitatively measure tissue glucose metabolism is available for both animal and human studies (*23–32*). Traditionally, it is well recognized that increased FDG uptake is a marker of viability, whereas reduced tissue FDG uptake is a marker of necrotic tissue (*33,34*). However, investigations have shown that heart and skeletal muscle FDG uptake may be altered in patients with insulin resistance. For example, studies have demonstrated significantly reduced myocardial FDG uptake (MFU) in NIDDM patients (*35,36*), increased MFU but reduced skeletal muscle FDG uptake (SMFU) in young patients with mild hypertension (*37*) or preserved MFU but reduced

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SMFU in hypertensive NIDDM patients (*38*) despite the existence of whole-body insulin resistance. Although impaired skeletal muscle glucose uptake has been thought to be most likely related to whole-body insulin resistance (*6,16*), the specific role of insulin resistance on heart and skeletal muscle FDG uptake in hypertriglyceridemics has not been investigated. In this study, we investigated differences in the action of insulin on FDG uptake between heart and skeletal muscle in hypertriglyceridemics to increase our knowledge of tissue-specific insulin resistance in hypertriglyceridemia.

MATERIALS AND METHODS

Subjects

We studied 17 hypertriglyceridemics and 12 asymptomatic age-matched healthy control subjects. None of the patients was being treated with triglyceride-lowering drugs, but all were on diet therapy. Patients with non-diabetic glucose intolerance were excluded. None of the patients or controls had any history of heart disease or any other serious or chronic disease. Patients with hypertension were excluded because the kinetics of myocardial glucose metabolism can be altered by hypertension (*33,34*). Characteristics of the participants are shown in Table 1. Before the study, we informed all participants of the nature of the study, after which they agreed to participate in the protocol that was approved by the ethics committee of the University of Tokyo.

PET

Preparation of FDG. ^{18}F was synthesized using the Cypris Model 370 cyclotron (Sumitomo JYUKI Industries, Ltd., Tokyo, Japan), and FDG was synthesized with an automated system based on the method reported by Ehrenkaufer et al. (*39*). Radiochemical purity was greater than 95%.

Acquisition of Myocardial Metabolic Images. Myocardial FDG images were obtained using a Headtome IV PET scanner (Shimadzu Corp., Kyoto, Japan). This PET scanner has seven imaging planes; in-plane resolution is 4.5 mm at full width at half maximum (FWHM) and the z-axial resolution is 9.5 mm at FWHM. Effective in-plane resolution was 7 mm after using a smoothing filter. The sensitivity of the Headtome IV scanner is 14 and 24 kct/s for direct and cross planes, respectively.

TABLE 1
General Characteristics of Participants

Characteristic	Controls	Hypertriglyceridemics
Number (men/women)	12 (10/2)	17 (12/5)
Age (y)	48.9 ± 10.1	51.5 ± 11.0
Body weight (kg)	60.1 ± 11.9	64.9 ± 9.44
Height (cm)	161.7 ± 8.34	161.0 ± 9.91
Body mass index	23.1 ± 2.51	25.1 ± 1.37
BPS (mm Hg)	124.0 ± 20.2	134.0 ± 19.2
BPD (mm Hg)	72.6 ± 12.8	82.1 ± 12.8
Heart rate (beats/min)	69.0 ± 8.90	65.4 ± 6.84
HbA1c (%)	5.37 ± 0.23	5.41 ± 0.55
FBS (mg/dL)	97.9 ± 10.9	106.0 ± 13.1
Total cholesterol (mg/dL)	188.0 ± 18.5	191.0 ± 21.3
HDL (mg/dL)	55.8 ± 26.7	38.6 ± 8.48*
TG (mg/dL)	112.0 ± 27.7	448.0 ± 283.0*
LDL (mg/dL)	121.0 ± 17.4	113.0 ± 63.1

*$P = 0.01$.

BPS = systolic blood pressure; BPD = diastolic blood pressure; HbA1c = hemoglobin A1c; FBS = fasting plasma blood glucose concentration; HDL = high-density lipoprotein cholesterol; TG = triglyceride; LDL = low-density lipoprotein cholesterol.

After acquisition of transmission data to correct photon attenuation and after the plasma glucose concentration became steady state by insulin clamping, we injected 185–370 MBq (5–10 mCi) FDG and collected dynamic PET data for the thoracic region for 1 h and 45 s to obtain input function. During the interval of PET scanning of the thoracic region, we obtained 19 dynamic scans using the following protocol: five 15-s, three 30-s, four 120-s, four 300-s and three 600-s scans.

Quantification of Heart and Skeletal Muscle FDG Uptake. The amount of glucose metabolized by various organs was determined by calculating the tissue glucose utilization rate. Data were reconstructed to a 1×1 mm^2 pixel size. Following the method previously reported by Ohtake et al. (*30*), we obtained input function from the time-activity curve of the descending aorta corrected by seven venous blood samplings. Using the input function, we determined $(k_1 \times k_3)/(k_2 + k_3)$ by least-squares nonlinear regression analysis and calculated the tissue glucose utilization rate by substituting $(k_1 \times k_3)/(k_2 + k_3)$ (K_i) in the following equation:

$$\text{Tissue FDG uptake rate} = [K_i] \times (BG1 + BG2 + BG3)/3,$$

where BG1, BG2 and BG3 were serum glucose concentrations during the dynamic PET scan using FDG.

k_1, k_2 and k_3 were rate constants of the following chemical reaction:

$$\text{FDG (serum)} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{FDG (tissue)} \underset{k_4}{\overset{k_3}{\rightleftharpoons}} \text{FDG-6 phosphate (tissue)}.$$

k_4 is assumed to be zero in the myocardium and skeletal muscle.

All data were corrected for dead-time effects to reduce error to less than 1%. To avoid the influence of the partial volume effect associated with the object's size, recovery coefficients (RCs) obtained from experimental phantom studies in our laboratory were used. The RC was 0.8 when the myocardial wall thickness was 10 mm. For correction of the partial volume effect, wall thickness was measured with two-dimensional echocardiography by specialists in our hospital. The RC was taken into consideration in our program to measure the tissue glucose utilization rate.

We obtained MFU from the transaxial images. To obtain regional MFU, region-of-interest (ROI) analysis was undertaken on 256 × 256 PET reconstructions. ROIs were placed at each segment on each of the reconstructed transaxial images (upper, middle and lower) within an inner edge of the myocardium by visual observation. MFU was determined by averaging the values listed above. We also obtained the SMFU from back muscle using transaxial dynamic data of seven planes. SMFU was determined by averaging these values. To determine the orientation of the back muscle, MRI was performed. To place the ROI on the back muscle, we traced the edge of the MR images of the back muscle and then fused them to the PET images.

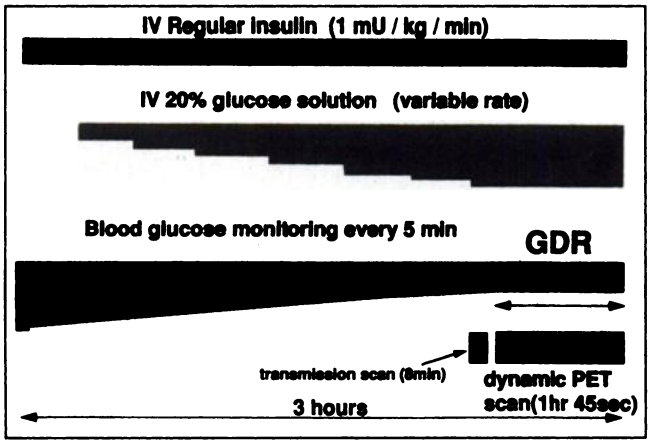

FIGURE 1. Diagram of study procedure. Hyperinsulinemic euglycemic clamping was introduced. Blood glucose sampling was done every 5 min. When blood glucose concentration reached steady state at level of 100 mg/dL, transmission scan over 8 min was undertaken, and then FDG was injected intravenously and dynamic PET scan over 1 h and 45 s was undertaken. IV = intravenous infusion.

To calculate the heart and skeletal muscle glucose utilization rate, we used the TAITAN high-speed image processing system (Asahi Kasei Information System Co., Ltd., Tokyo, Japan) with "Dr. View" software (Asahi Kasei Information System Co., Ltd.).

Estimation of Whole-Body Insulin Resistance. Quantitative estimation of whole-body insulin resistance was made by obtaining the glucose disposal rate (GDR; μmol/min/kg) during hyperinsulinemic euglycemic clamping 2 h after the beginning of insulin infusion, as reported previously (*38,40*). Hyperinsulinemic euglycemic clamping was undertaken by simultaneous infusion of regular insulin at a fixed rate (1 mU/kg/min) and of 20% glucose at a variable rate to maintain plasma glucose concentration at an equilibrium of approximately 100 mg/dL. Infusion rate of 20% glucose was changed every 5 min during the insulin clamping until the GDR achieved a steady state. Because it usually takes 2–3 h after the initiation of insulin clamping for the GDR to become constant, the average GDR at 2 h after the initiation of insulin clamping was used as an indicator of insulin resistance. Precisely at this time, FDG was injected and the dynamic scan over a period of 1 h and 45 s was started. For all participants, FDG PET was undertaken under the same conditions of hyperinsulinemic euglycemic clamping. A diagram of what the participants underwent was added to Figure 1.

Statistical Analysis

Data consisting of two parameters were analyzed by the two-tailed Student t test. $P < 0.05$ was considered statistically significant. Values were expressed as mean ± SD.

RESULTS

Glucose Metabolism During Hyperinsulinemic Euglycemic Clamping in Hypertriglyceridemics

GDR was significantly reduced in hypertriglyceridemics compared with control subjects (4.50 ± 1.37 mg/min/kg versus 10.0 ± 2.97 mg/min/kg, $P = 0.0001$), as were the skeletal muscle FDG K_i (SFK_i; 0.007 ± 0.003 mL/min/g versus 0.018 ± 0.01 mL/min/g, $P = 0.0001$) and SMFU (0.725 ± 0.282 mg/min/100 g versus 1.86 ± 1.06 mg/min/100 g, $P = 0.00023$). Whereas, myocardial FDG K_i (MFK_i) tended to be reduced in hypertriglyceridemics compared with control subjects (0.062 ± 0.017 mL/min/g versus 0.068 ± 0.015 mL/min/g), but the difference was statistically insignificant ($P = 0.3532$). Moreover, MFU in hypertriglyceridemics (6.47 ± 1.72 mg/min/100 g) also tended to be decreased compared with control subjects (6.97 ± 1.73 mg/min/100 g), but the difference was statistically insignificant ($P = 0.4485$).

In hypertriglyceridemics, there were significant relationships between GDR and SFK_i ($SFK_i = 0.001$ GDR + 0.0001, $r = 0.69$, $P = 0.0022$; Fig. 2A), SMFU (SMFU = 0.126 GDR + 0.16, $r = 0.612$, $P = 0.009$; Fig. 2B), MFK_i ($MFK_i = 0.007$ GDR + 0.031, $r = 0.568$, $P = 0.0174$; Fig. 3A) and MFU (MFU = 0.631 GDR + 3.632, $r = 0.505$, $P = 0.0385$; Fig. 3B). However, there was no significant relationship between GDR and MFK_i in control subjects ($r = 0.223$, $P = 0.4856$; Fig. 4A). There was also no significant relationship between GDR and MFU in control subjects ($r = 0.151$, $P = 0.639$; Fig. 4B).

Serum Glucose Concentration

During hyperinsulinemic euglycemic clamping, the average serum glucose concentration in hypertriglyceridemics (102 ± 4.32 mg/dL) was the same as that in control participants (103 ± 13.0 mg/dL).

Serum Insulin Concentration

Serum insulin concentration in patients with hypertriglyceridemia (60.4 ± 14.2 μU/mL) was comparable with that in controls (60.9 ± 21.5 μU/mL). There were no significant

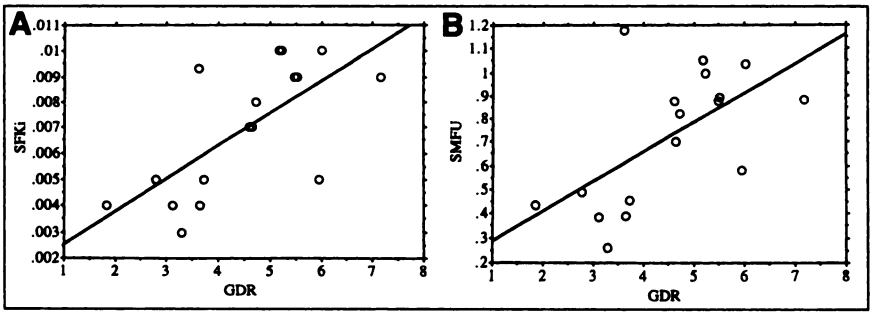

FIGURE 2. (A) Scatter plot of relationship between skeletal muscle FDG K_i (SFK_i) and glucose disposal rate (GDR) in hypertriglyceridemics. There was significant relationship between SFK_i and GDR. (B) Scatter plot of relationship between skeletal muscle FDG uptake (SMFU) and GDR in hypertriglyceridemics. There was significant relationship between SMFU and GDR.

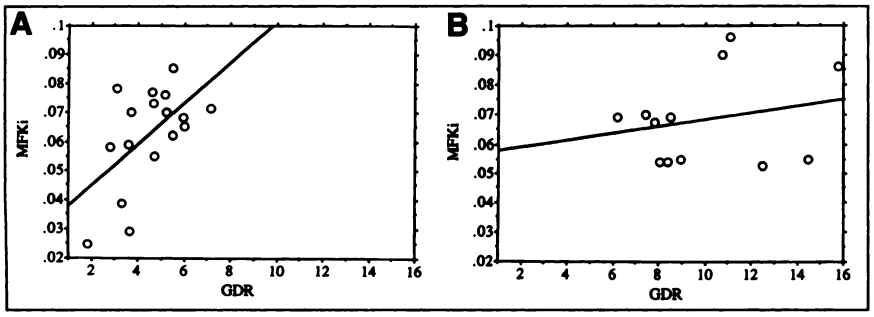

FIGURE 3. (A) Scatter plot of relationship between glucose disposal rate (GDR) and myocardial FDG K_i (MFK_i) in hypertriglyceridemics. There was significant relationship between GDR and MFK_i in hypertriglyceridemics. (B) Scatter plot of relationship between GDR and MFK_i in control subjects. There was no significant relationship between GDR and MFK_i in control subjects.

differences between the serum insulin concentration at the beginning and at the end of the dynamic PET scan in either patients or control subjects.

Serum Free Fatty Acid Concentration

Serum FFA concentration during hyperinsulinemic euglycemic clamping in hypertriglyceridemics (1.33 ± 0.79 mEq/L) was significantly higher compared with that of control subjects (0.47 ± 0.20 mEq/L, $P = 0.001$). There was no significant relationship between plasma FFA concentration and MFK_i in both hypertriglyceridemics ($r = 0.193$, $P = 0.457$; Fig. 5A) and control subjects ($r = 0.007$, $P = 0.984$; Fig. 5B). There was no significant relationship between plasma FFA concentration and MFU in both hypertriglyceridemics ($r = 0.007$, $P = 0.984$; Fig. 6A) and control subjects ($r = 0.151$, $P = 0.639$; Fig. 6B).

DISCUSSION

Insulin Resistance and Its Relationship to Skeletal Muscle FDG Uptake and Myocardial FDG Uptake in Hypertriglyceridemics

In this study, both MFU and SMFU in hypertriglyceridemics were significantly correlated with whole-body insulin resistance. Certainly, skeletal muscle glucose utilization plays a central role in the development of whole-body insulin resistance (*6,16*). However, the results of studies on the relationship between whole-body insulin resistance and MFU are conflicting. The significant positive relationships between GDR and both SMFU and MFU suggest that in hypertriglyceridemia the mechanisms by which deoxyglucose is incorporated into myocytes and skeletal muscle are similar. It is unclear why MFU in hypertriglyceridemics was correlated with whole-body insulin resistance but was insignificantly reduced compared with control subjects. In hypertriglyceridemics, the slope of the linear regression line between GDR and MFU was steeper than that between GDR and SMFU. In addition, there was no significant relationship between MFU and GDR in control subjects. Therefore, our results suggest that insulin resistance in the myocardium exists in severe hypertriglyceridemics. It is speculated that in hypertriglyceridemics with severe insulin resistance, MFU may be altered. However, because the scatter of MFU was very wide, the degree of the decrease in MFU in hypertriglyceridemics compared with control subjects was insignificant and the relationship between whole-body insulin resistance was less robust for MFU than for SMFU, the influence of insulin resistance on MFU is less than that on SMFU in hypertriglyceridemics. Thus, the myocardium may have a mechanism to oppose insulin resistance, as indicated in patients with hypertension (*37,38*). There was no significant relationship between MFU and GDR in control subjects. This result suggests that MFU can be saturated when GDR is within normal range, and this result is consistent with recent results of Bøtker et al. (*24*), who showed that both MGU and MFU in healthy humans were saturated when insulin concentration was more than approximately 40 mU/L.

Influence of Insulin Resistance, Free Fatty Acid and Randle's Mechanism on Myocardial FDG Uptake

That there was no significant relationship between MFU and plasma FFA in hypertriglyceridemics suggests that the myocardial Randle's cycle does not operate in hypertriglyceridemics because it is altered by whole-body insulin resistance. It is well acknowledged that FFA is a predominant source of energy for the myocardium under fasting.

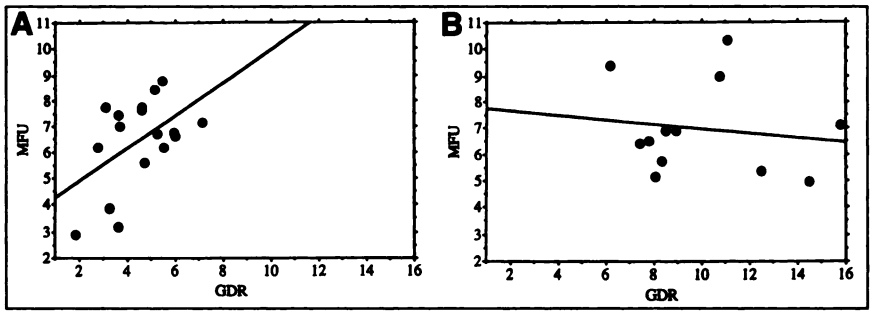

FIGURE 4. (A) Scatter plot of relationship between glucose disposal rate (GDR) and myocardial FDG uptake (MFU) in hypertriglyceridemics. There was significant relationship between GDR and MFU in hypertriglyceridemics. (B) Scatter plot of relationship between GDR and MFU in control subjects. There was no significant relationship between GDR and MFU in control subjects.

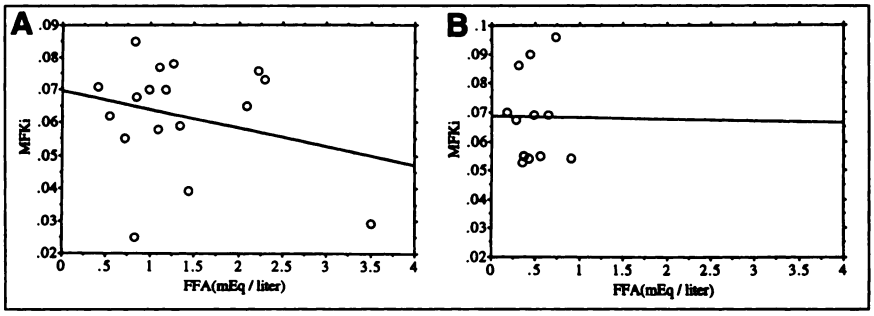

FIGURE 5. Scatter plot of relationship between myocardial FDG K_i (MFK_i) and free fatty acid (FFA) in both hypertriglyceridemics (A) and normal participants (B). There were no significant relationships between MFK_i and FFA in both hypertriglyceridemics and control subjects.

However, several investigations have shown that insulin regulates myocardial deoxyglucose or glucose uptake during insulin clamping. Barrett et al. (*20*) reported that both insulin and FFA independently regulate MGU. They observed a significantly increased MGU during insulin clamping compared with the baseline level, even though plasma FFA remained elevated by additional infusions of soybean triglyceride emulsion. They also observed that the reduction of FFA by infusion of glucose and somatostatin failed to increase MGU (*20*). Nearly the same results were observed by Hicks et al. (*41*), who showed that an acute increase of FFA failed to inhibit MFU during insulin clamping in healthy human subjects. These results indicate that under insulin clamping MGU is regulated primarily by insulin rather than FFA and they also can explain why increased FFA due to hypertriglyceridemia failed to significantly reduce MFU during insulin clamping.

Quantitative Analysis of Skeletal Muscle FDG Uptake and Myocardial FDG Uptake with FDG PET

In this study, both MFU and SMFU were measured with the FDG tracer kinetic model because that method is well validated (*24–32*) and frequently used in clinical studies of tissue glucose utilization (*35–38,40–46*). Because an apparent linear relationship between FDG or deoxyglucose and glucose has been shown experimentally (*17,19,20*), it has been thought that FDG is a glucose analog. However, to obtain the net absolute value of MGU, but not MFU, using the FDG PET tracer kinetic method, a correction quotient called the lumped constant (LC) should be applied appropriately. Investigations have revealed that the LC can vary according to variations in conditions, including glucose concentration and insulin concentration (*17,23,24,47*). Comparisons of net MFU and net MGU in humans have shown that MGU in healthy humans can be measured when the LC is appropriately estimated by the biphasic relationship between plasma insulin concentration and LC (*24*) and that the LC can be estimated to be 1.0 in diabetic patients during insulin clamping with the usual dose of insulin that we used (*25*). It is not clear whether the LC would differ between hypertriglyceridemics and controls. Therefore, in this study, we used the term MFU rather than MGU because the relationship between MGU and insulin resistance or FFA may be elucidated by estimating the relationship between MFU and insulin resistance or FFA in hypertriglyceridemics. If insulin resistance or FFA can alter MFU, these findings might increase our ability to diagnose myocardial viability accurately and they might also indicate the clinical usefulness of FDG in diagnosing insulin resistance in patients with several coronary risk factors, including hypertriglyceridemia. Ng et al. (*25*) reported that the LC was 1.0 in diabetics with coronary artery disease during insulin clamping. Because diabetes is usually associated with hypertriglyceridemia or increased plasma FFA, it is expected that the LC in hypertriglyceridemics does not differ from that in diabetics. Accordingly, heart and skeletal muscle glucose utilization in reaction to insulin in hypertriglyceridemics would be expected to be the same as MFU and SMFU as determined in this study. We realize that catheterization would be required to answer the question completely, but for ethical reasons such invasive studies in asymptomatic patients cannot be done. Further study should address this point.

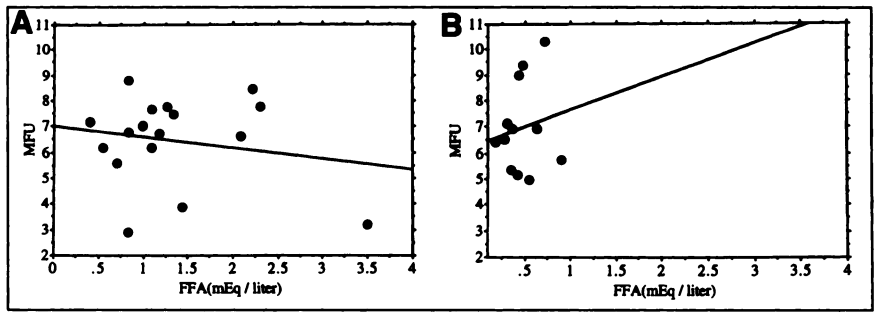

FIGURE 6. Scatter plot of relationship between myocardial FDG uptake (MFU) and free fatty acid (FFA) in both hypertriglyceridemics (A) and normal participants (B). There were no significant relationships between MFU and FFA in both hypertriglyceridemics and control subjects.

CONCLUSION

In patients with hypertriglyceridemia, SMFU was significantly reduced but MFU was insignificantly reduced. Whole-body insulin resistance was related to both heart and skeletal FDG uptake in hypertriglyceridemia.

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