Impaired Skeletal Muscle Glucose Uptake by \[^{18}\text{F}]\text{Fluorodeoxyglucose–Positron Emission Tomography in Patients With Peripheral Artery Disease and Intermittent Claudication}

Reena L. Pande, Mi-Ae Park, Todd S. Perlstein, Akshay S. Desai, Jeanne Doyle, Nicole Navarrete, Robert S. Copeland-Halperin, Whitney Redline, Marcelo F. Di Carli, Mark A. Creager

Objective—Reduced limb perfusion from arterial stenosis does not adequately account for intermittent claudication symptoms in peripheral artery disease (PAD). Insulin resistance is associated with PAD and may contribute to claudication by impairing skeletal muscle metabolism. We aimed to determine whether skeletal muscle glucose uptake, assessed by \[^{18}\text{F}]\text{fluorodeoxyglucose positron emission tomography}, is reduced in patients with claudication.

Methods and Results—Thirty-seven subjects with PAD and claudication and 11 healthy controls underwent \[^{18}\text{F}]\text{fluorodeoxyglucose–positron emission tomography imaging of the legs during hyperinsulinemic-euglycemic clamp. Calf glucose uptake was quantified by graphical Patlak analysis, and whole-body insulin sensitivity was assessed as the glucose disposal rate (M) from the insulin clamp. Compared with healthy controls, PAD subjects were insulin resistant (M = 3.4 mg/kg per minute [interquartile range, 2.7 to 4.8] versus 5.0 [3.7 to 6.6], \(P = 0.019\)). Calf muscle glucose uptake was significantly lower in PAD compared with healthy subjects (48.6 ± 2.6 mol/kg per minute versus 62.9 ± 6.5 mol/kg per minute, \(P = 0.009\)) and correlated with systemic insulin sensitivity (\(r = 0.37, P = 0.03\)) in PAD subjects. These abnormalities persisted even after exclusion of PAD subjects with diabetes.

Conclusion—Patients with claudication have impaired calf muscle glucose uptake. Future studies are required to assess whether calf muscle insulin resistance contributes to exercise limitation in patients with intermittent claudication.

Key Words: insulin resistance • peripheral arterial disease • intermittent claudication

Intermittent claudication is a cardinal symptom of peripheral artery disease (PAD), arising when the supply of oxygen and nutrients is inadequate to meet the metabolic demands of the exercising skeletal muscle. Claudication commonly manifests as exertional leg discomfort with disabling symptoms that can affect functional capacity and quality of life.1

Although the presence of atherosclerotic stenosis is necessary for the diagnosis of PAD, the severity of intermittent claudication symptoms does not correlate well with hemodynamic measures of lower extremity perfusion pressure, such as the ankle brachial index (ABI).2 Furthermore, established therapies known to improve walking distance, such as supervised exercise training, do so without measurable change in the ABI.3,4 This lack of correlation with abnormalities of supply implies that non-hemodynamic factors related to abnormal skeletal muscle metabolic demand may play a role in the underlying pathophysiology of claudication.

Indeed, prior work has demonstrated that patients with PAD and claudication have abnormal skeletal muscle metabolic function, as evidenced by abnormal accumulation of intermediates of oxidative phosphorylation, reduced levels of mitochondrial enzymes, propensity to shift earlier to anaerobic metabolism, and slower restoration of energy stores after exercise.5–8 Impaired nutrient uptake into skeletal muscle cells, as might occur in insulin-resistant states, could limit nutrient availability in skeletal muscle and contribute to exercise limitation in patients with PAD. Using data from the National Health and Nutrition Examination Survey, we have indeed previously established that insulin resistance is associated with PAD.9 There is evidence of skeletal muscle mitochondrial dysfunction and reduced ATP generation in insulin-resistant states.10,11 In this context, it has also been shown that individuals with insulin resistance have reduced expression of a series of genes that are critical for mitochondrial function and oxidative metabolism.12,13 Furthermore,
Gardner and Montgomery have shown that PAD patients with features of the metabolic syndrome have reduced walking times.\textsuperscript{14}

Direct quantification of insulin-mediated glucose uptake in skeletal muscle can be achieved with dynamic positron emission tomography (PET) imaging with the radioisotope \textsuperscript{18}F-fluorodeoxyglucose (FDG). Prior studies in subjects with diabetes and coronary artery disease have demonstrated decreased skeletal muscle FDG uptake, as would occur with insulin resistance, in the myocardium and skeletal muscles of the upper extremities,\textsuperscript{15,16} but no prior studies have evaluated glucose uptake in subjects with PAD. Given the known association of insulin resistance with PAD, we used this application of FDG-PET imaging to test the hypothesis that skeletal muscle glucose uptake is impaired in the legs of patients with symptomatic PAD.

**Methods**

**Patient Population**

We recruited subjects with PAD and stable intermittent claudication and healthy control subjects. A diagnosis of PAD was based on a resting ABI of ≤0.90. ABI was calculated by dividing the higher of the ankle pressures of each leg by the higher of the brachial artery pressures. PAD patients were eligible only if they had stable symptoms of intermittent claudication confirmed by physician history and using the San Diego claudication questionnaire. Subjects were excluded if they had recent peripheral vascular surgery or percutaneous endovascular intervention within the previous 6 months; if they had unstable angina, myocardial infarction, or cerebrovascular accident within the previous 3 months; if they had renal insufficiency (serum creatinine >220 \(\mu\text{mol}/\text{L}\) [2.5 mg/dL]); or if they were taking insulin or insulin-sensitizing medications, such as thiazolidinediones. Healthy subjects had no known medical problems, a normal cardiovascular examination, and normal ECG. Healthy controls were ineligible if they were current smokers or had smoked within the past year. Subjects were recruited from clinical practices at Brigham and Women’s Hospital, the VA Boston Healthcare Service, and by advertisement. The study was approved by the institutional review committees at both institutions, and all subjects gave written informed consent.

**FDG-PET Imaging and Glucose Uptake Analysis**

Skeletal muscle glucose uptake was evaluated using FDG-PET imaging. Imaging was performed using a whole-body PET scanner (GE Discovery LS PET/CT Imaging System, Milwaukee, Wis) that acquires 47 contiguous transaxial planes with an image resolution of 5.4 mm at full-width–half-maximum in-plane and 5.4 mm at full-width–half-maximum in the axial direction. The images were acquired in two-dimensional mode and reconstructed with iterative ordered-subset expectation maximization. Post processing was performed using a Hanning filter with a cutoff frequency of 1.10 cycles/cm. Subjects were positioned in the PET scanner with the midcalf region corresponding to the center of the axial field of view. A transmission scan was taken to allow for attenuation correction during reconstruction of images. Subjects were given an intravenous bolus of FDG (approximately 10 to 15 mCi), and dynamic imaging over the calf region was performed over 60 minutes. The imaging protocol consisted of 6 frames of 20 seconds each, 3 frames of 60 seconds each, 3 frames of 300 seconds each, and 4 frames of 600 seconds each. Sampling of arterialized whole blood to measure plasma FDG radioactivity was performed at 30 seconds and 1, 2, 4, 6, 8, 10, 20, 30, 40, 50, and 60 minutes after FDG injection. Two milliliters of blood were withdrawn at each time point and centrifuged for 4 minutes at 12,000 rpm, and 0.2 mL of plasma was reserved to measure FDG radioactivity with a Gamma Well Counter (Packard COBRA II, Auto-Gamma Counting Systems, Meriden, Conn). Reconstructed images were displayed as transaxial slices, and using the fused computed tomography and PET images for localization, predefined regions of interest were drawn to encompass each of the primary muscle groups in the lower leg (gastrocnemius, soleus, and tibialis anterior muscles) (Figure 1). Corresponding regions of interest were then applied to the 16 serially acquired FDG-PET frames, and tissue FDG uptake curves were generated.

According to previously established methods,\textsuperscript{17,18} the overall rate of FDG uptake (\(K_1\)) was quantified for each muscle group in each leg using the graphical Patlak analysis. The individual kinetic parameter \(k_1\) was determined using the PMOD kinetic modeling tool (PMOD Technologies Ltd) for a 3-compartment model, corresponding to extracellular FDG (ie, within blood), intracellular FDG, and intracellular phosphorylated FDG. The rate constant \(k_1\) represents inward transport of FDG from the blood into the intracellular space and correlates with leg blood flow.\textsuperscript{19,20} Net glucose uptake can be determined from the overall rate of FDG uptake multiplied by the average arterial glucose level during the scan and correcting for relative metabolism of FDG versus true glucose (using a constant, termed the lumped constant, that is equal to 1.2).\textsuperscript{21} The resulting rate of glucose uptake for each muscle group is expressed in \(\mu\text{mol} / \text{min} / \text{kg} / \text{tissue} \). In our subjects, inter- and intraobserver variability using this technique was low (coefficient of variation, \(\approx 4\%\)).

**Hyperinsulinemic-Euglycemic Clamp**

A hyperinsulinemic-euglycemic clamp was performed before and during FDG-PET imaging to measure insulin sensitivity and to standardize metabolic conditions.\textsuperscript{22} Under fasting conditions, subjects were given a primed weight-based insulin infusion (2 mU/kg per minute). Serum glucose measurements were made at 5-minute intervals from an arterialized venous sample achieved by placing the hand in a warming box at 50°C. Dextrose infusion (20%) was adjusted to maintain a serum glucose level of approximately 4.4 mmol/L (80 mg/dL). Steady state was achieved when the dextrose infusion rate varied by no more than 5%. Whole-body insulin sensitivity was assessed as the glucose disposal rate (M) from the insulin clamp during steady state, calculated from the average of
the glucose infusion rates over the last 20 minutes of the clamp. Space correction was applied to account for any changes in serum glucose levels during that time period.22

**Covariates**

Age, gender, and race/ethnicity were self-reported. Race and ethnicity are reported as non-Hispanic white or other. Subjects were considered to have hypertension or hyperlipidemia if they reported a prior physician diagnosis of these conditions or took antihypertensive or cholesterol-lowering prescription medications. A diagnosis of diabetes was assigned if subjects had a prior diagnosis of diabetes or diabetes was assigned if subjects had a prior diagnosis of diabetes or if the fasting plasma glucose was ≥7 mmol/L (126 mg/dL). Prior history of coronary artery disease, myocardial infarction, stroke/transient ischemic attack, or family history of diabetes or PAD was self-reported. Smoking status was self-reported as never, former, or current smoking. Body mass index was calculated as weight (kg) divided by height (m²).

**Statistical Analysis**

Subject characteristics are reported as the mean and standard deviation (SD) for normally distributed continuous variables, median and interquartile range for nonnormally distributed variables, and percentiles for categorical variables. Continuous variables were compared using either the t test or the Wilcoxon rank sum test. The χ² test was used to compare categorical variables. Correlations and univariate analyses for continuous variables were achieved by linear regression with log transformation of nonnormally distributed variables. Glucose uptake values were generated for individual muscle groups (soleus, gastrocnemius, and tibialis anterior muscles). The primary measure was the average calf muscle glucose uptake of all muscle groups in both legs. For the correlation of leg glucose uptake with ABI, we used average skeletal muscle glucose uptake from each leg separately to correlate with individual leg ABI data. Comparisons were repeated excluding subjects with diabetes to address potential confounding by diabetes status. Probability values of <0.05 were considered statistically significant. All statistical analyses were performed with SAS, version 9.1 (SAS Institute Inc). The authors had full access to the data and take full responsibility for the integrity of the data. All authors have read and agree to the article as written.

**Results**

**Baseline Characteristics and Laboratory Values**

We studied 37 subjects with PAD and intermittent claudication and 11 healthy control subjects. Baseline characteristics of the 2 groups are presented in the Table. PAD subjects had an average ABI of 0.66±0.19, were slightly older (66±8.7 versus 60.5±6 years, P=0.06) and had higher systolic blood...
pressure than healthy subjects (152.8±19.5 versus 127±9.3 mm Hg, P<0.0001). Diabetes was present in 9 of 37 PAD subjects (24%). Coexisting coronary artery disease was reported in 43% of PAD subjects, and 29% had a prior history of stroke or transient ischemic attack. Nearly all PAD subjects (97%) were either current (30%) or former (67%) smokers, whereas 55% of healthy subjects reported having smoked in the past (P=0.0003). There were greater abnormalities of lipid parameters in the PAD group, with higher triglycerides (131 [107 to 244] versus 90 [75 to 188] mg/dL, P=0.003) and lower HDL (42.1±3.5 versus 56.3±12 mg/dL, P=0.001).

Whole-Body Insulin Sensitivity

PAD subjects were insulin resistant, with significantly lower whole-body insulin sensitivity measurements from the hyperinsulinemic-euglycemic clamp (M=3.4 [interquartile range, 2.7 to 4.8] versus 5.0 mg/kg per minute [3.7 to 6.6] in healthy controls, P=0.019) (Figure 2). Baseline glucose values were higher in PAD subjects (91 [interquartile range, 79 to 101] versus 77 mg/dL [72 to 83] in healthy subjects, P=0.003), as were baseline insulin values (8.51±4.7 versus 5.1±3.5 µU/mL in healthy subjects, P=0.03). Glucose levels at steady-state during the insulin clamp were similar in the 2 groups (80.1±11.9 mg/dL in PAD subjects versus 78.0±14.6 mg/dL in healthy subjects, P=0.7). There was a nonsignificant trend toward higher steady-state insulin levels measured in PAD subjects (157.9±33.5) compared with healthy subjects (131.2±37.2, P=0.06).

Lower Extremity Skeletal Muscle Glucose Uptake

In patients with PAD, net calf skeletal muscle glucose uptake determined by Patlak modeling was significantly lower in each individual muscle group (Figure 3), including the soleus muscle (median, 47.2 [38 to 69] per minute versus 62.2 µmol/kg [47 to 90] in healthy subjects, P=0.01), gastrocnemius muscle (33.1 [22.3 to 45] versus 60.9 [41 to 79], P<0.0001), and tibialis anterior muscle (42.9 [31.3 to 59] versus 54.8 [42 to 72], P=0.02). Accordingly, average calf muscle glucose uptake was significantly lower in PAD subjects (48.6±15 µmol/kg per minute) compared with healthy subjects (62.9±21 µmol/kg per minute, P=0.009) (Figure 4). These differences remained statistically significant even after adjusting for age and gender (P=0.018), with PAD subjects demonstrating 16.1 µmol/kg per minute lower glucose uptake compared with healthy control subjects.

Univariate linear regression analyses demonstrated that only whole-body insulin sensitivity correlated with overall lower extremity glucose uptake, though insulin sensitivity explained only 14% of the variability in local calf glucose uptake (r=0.37, R²=0.14, P=0.03) (Figure 5A). There was no significant correlation between calf muscle glucose uptake and ABI (r=0.10, R²=0.01 P=0.40) (Figure 5B), nor between calf muscle glucose uptake and age, gender, systolic blood pressure, baseline glucose, baseline insulin, or smoking status.
To further evaluate whether overall calf muscle glucose uptake was affected by differences in local delivery of glucose, we used full 3-compartment modeling to determine the specific rate constant $k_1$, which represents inward transport of FDG from the plasma compartment into the intracellular compartment, one component of overall glucose uptake. Prior studies have demonstrated that $k_1$ correlates strongly with leg blood flow.\textsuperscript{19,20} We found no significant difference in $k_1$ values between the 2 groups (0.028±0.007 in healthy subjects versus 0.024±0.009 in PAD subjects, $P=0.17$), suggesting no difference in delivery of glucose to the skeletal muscle during insulin stimulation.

### Insulin Sensitivity and Calf Muscle Glucose Uptake in PAD Subjects Without Diabetes

To ensure that these findings were not driven by the subgroup of PAD subjects who had diabetes ($n=9$), we repeated these analyses including only the subset of nondiabetic PAD subjects ($n=28$). PAD subjects without diabetes had baseline characteristics similar to those of the PAD group as a whole (Table). Even after excluding diabetic patients, we demonstrated that PAD subjects with claudication have systemic insulin resistance ($M=3.4$ [2.7 to 4.6] versus $5.0$ [3.7 to 6.6] in healthy subjects, $P=0.02$), with $M$ values that were comparable to those in the PAD population including diabetic patients (Figure 2). Calf muscle glucose uptake was also significantly lower in PAD subjects without diabetes (49.5±3.1 μmol/kg per minute) compared with healthy subjects (62.9±6.5 μmol/kg per minute, $P=0.04$ versus healthy controls) (Figure 4). Univariate analyses in nondiabetic PAD subjects demonstrated that calf glucose uptake remained significantly correlated with systemic insulin resistance ($r=0.40$, $P=0.04$), but there was no association between calf muscle glucose uptake and ABI ($r=0.06$, $P=0.68$). There was a positive correlation between average calf glucose uptake and baseline serum glucose levels ($r=0.48$, $P=0.008$) but no associations with other baseline variables.

### Discussion

We examined the presence of local insulin resistance in patients with PAD and intermittent claudication by examining calf skeletal muscle glucose uptake by FDG-PET imaging. Our data not only extend our previous report of insulin resistance in patients with PAD using a formal measurement of whole-body insulin sensitivity but also highlight the presence of local calf muscle insulin resistance in individuals with PAD and intermittent claudication. Specifically, we demonstrate that (1) symptomatic PAD subjects have impaired calf skeletal muscle glucose uptake and (2) impaired calf muscle glucose uptake in PAD subjects with claudication is associated with systemic insulin resistance. Finally, we establish a novel role for FDG-PET imaging in the assessment of skeletal muscle metabolism specifically in the PAD population. These findings support the underlying hypothesis that skeletal muscle glucose uptake is impaired in the legs of patients with claudication and extend our understanding of skeletal muscle metabolic abnormalities in PAD.

Despite the unambiguous contribution of hemodynamic stenosis in the peripheral arteries to symptoms of intermittent claudication, hemodynamic abnormalities do not adequately explain the degree of functional impairment. Several lines of evidence suggest that abnormalities of skeletal muscle metabolism may contribute to the functional limitations in PAD patients. During exercise, patients with PAD shift earlier to anaerobic metabolism, a less efficient means of energy production, and have elevated lactate levels even at rest.\textsuperscript{23} Direct evidence of ineffective oxidative phosphorylation in PAD is provided by studies of calf muscle biopsy specimens showing accumulation of lactate and intermediates of oxidative metabolism such as acylcarnitines.\textsuperscript{6} Moreover, subjects with the greatest degree of acylcarnitine accumulation in skeletal muscle have the most exercise limitation, and improvement in exercise performance (as with exercise training) is associated with improved intermediary metabolism in skeletal muscle.\textsuperscript{3} More recent studies using magnetic resonance spectroscopy have shown delayed restoration of phosphocreatine stores after calf muscle exercise in PAD subjects, changes that do not correlate well with measures of tissue perfusion.\textsuperscript{8} Lastly, subjects with PAD have decreased levels of mitochondrial enzymes involved in the electron transport chain, such as NADH dehydrogenase (complex I) and ubiquinol–cytochrome c oxidoreductase (complex III).\textsuperscript{7}
Whether insulin resistance contributes to the pathophysiology of intermittent claudication symptoms is unknown. Although not previously explored specifically in patients with PAD, existing evidence supports a relationship between insulin resistance and skeletal muscle metabolic dysfunction, which may link insulin resistance with exercise limitation in PAD. Insulin resistance is associated with impaired mitochondrial substrate oxidation and reduced activity of the tricarboxylic acid cycle, resulting in reduced ATP synthesis. In addition, insulin resistance is associated with decreased expression of sets of genes essential for normal mitochondrial function and oxidative phosphorylation. Thus, local insulin resistance may affect not only uptake of glucose into the myocyte but also downstream metabolic processes critical for ATP generation. Whether these metabolic abnormalities contribute to exercise limitation in symptomatic PAD patients has not been studied, but recent evidence that claudicants with metabolic syndrome have reduced maximal and pain-free walking times compared with PAD subjects without features of the metabolic syndrome supports this hypothesis. However, given the cross-sectional nature of our findings and the data in the existing literature, we do not know whether insulin resistance is a contributor to claudication symptoms or arises secondarily as a result of reduced physical activity. Future studies will be necessary to explore whether improving insulin sensitivity can increase functional capacity in patients with PAD.

Multiple factors may have contributed to the finding of impaired skeletal muscle glucose uptake in PAD subjects. In our study, local glucose uptake correlated modestly with systemic insulin sensitivity \( r = 0.37 \), suggesting that systemic insulin resistance contributes to the impaired glucose uptake at the cellular level in the local calf musculature. Although we did not directly measure blood flow or local tissue perfusion in this study, we did determine the rate constant \( k_1 \), which represents the rate of initial glucose transport from the plasma into the intracellular compartment. In prior studies, \( k_1 \) strongly correlated with leg blood flow, measured either by venous occlusion strain-gauge plethysmography or by PET imaging with radioisotopes that measure flow, such as \( ^{15}O \)H\(_2\)O. We found no difference in \( k_1 \), the rate of glucose transport, between the 2 groups, suggesting no difference in local blood flow or delivery of glucose. This finding is consistent with prior studies demonstrating that resting calf blood flow, as assessed by plethysmography, is similar in individuals with intermittent claudication and healthy subjects. Future studies will be needed to explore whether restoration of blood flow in patients with PAD can ameliorate the metabolic abnormalities demonstrated here.

New diagnostic modalities to assess skeletal muscle metabolic function in PAD will be critical to allowing improved understanding of the underlying pathophysiology of claudication. To that end, we used FDG-PET imaging to directly quantify skeletal muscle glucose uptake in PAD patients with claudication. FDG-PET imaging provides an ideal physiological assessment of skeletal muscle metabolism and has been used to explore cardiac muscle insulin resistance in patients with coronary heart disease, diabetes, and hypertriglyceride-mia. However, to our knowledge, this is the first application of this imaging modality to patients with PAD. This modality not only might provide insight into underlying pathophysiology of claudication but might provide a novel method for measuring responses to therapies targeting metabolic function in PAD.

This study must be evaluated in the context of its limitations. First, despite attempts to match our 2 groups by age and gender, PAD subjects were slightly, but not significantly, older and were more likely to be male. After adjustment for these baseline differences, we nonetheless demonstrated that symptomatic PAD subjects have significantly impaired calf muscle glucose uptake. Second, it is important to note that all studies were performed at rest. Because impaired glucose uptake was evident in PAD subjects compared with healthy controls even at rest, we might anticipate that studies during exercise would unearth even greater impairment in substrate utilization. Finally, whether impaired skeletal muscle glucose uptake in subjects with PAD and intermittent claudication correlates with walking performance remains unknown. Future studies are under way to evaluate whether these metabolic abnormalities predict exercise limitation in claudication.

Conclusions

With FDG-PET imaging, we demonstrate that symptomatic PAD patients with intermittent claudication are insulin resistant and have impaired skeletal muscle glucose uptake in the calf. Future studies will be required to explore whether these intrinsic defects in skeletal muscle metabolism in PAD contribute to exercise limitation and whether therapies targeting these metabolic disturbances can improve symptoms in patients with PAD and intermittent claudication.

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Disclosures

Dr Creager serves as a consultant for Genzyme and NormOxys.

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