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Enhanced Platelet Aggregation, High Homocysteine Level, and Microvascular Disease in Diabetic Muscle Infarctions

Implications for Therapy

Venkatraman Rajkumar,[1] Paul Ragatzki,[1] Anders Sima,[2] and Joseph Levy[1]

[1]*Department of Medicine* [2]*Department of Pathology, Wayne State University School of Medicine, Detriot, MI*

Muscle infarction is a rare complication in patients with diabetes mellitus, probably because of the rich vascular supply of this tissue. We describe a patient with type 1 diabetes who had infarction of the muscles in her right thigh. We report, for the first time, that the patient, in addition to an advanced microvascular disease in the muscle, had increased plasma total homocysteine levels and increased platelet aggregation. These pathologies might have a synergistic effect on the development of this rare complication and should be treated aggressively to prevent further episodes.

Key Words: Diabetes; homocysteine; muscle infarction; folic acid; aspirin.

Introduction

Muscle infarction is a rare vascular complication in patients with diabetes mellitus. It was first described in 1965 as "tumoriform focal muscular degeneration" *(1)*, and since then an additional 33 cases have been reported *(2–5)*. Because the underlying pathology for this rare complication remains unknown, the management of diabetic patients with muscle infarction consists mainly of pain relief and glycemic control, with spontaneous resolution occurring in most patients. However, recurrent episodes occur in up to 50% of patients *(3)*. Although an early accurate diagnosis of this condition is essential to spare repeated extensive workup and hospitalizations, it remains unclear whether these recurrences might be prevented. We report here about a patient with type 1 diabetes mellitus who after 8 mo of intermittent right thigh and gluteal pain was diagnosed as having muscle infarction. Further workup revealed hyperhomocysteinemia and increased platelet aggregability, in addition to marked basement membrane thickening and endothelial cell swelling in the muscle capillaries, suggesting extensive muscle microvascular disease. Treatment with aspirin and folic acid was initiated with an intent to prevent further episodes. No such episodes occurred during a 16 mo follow-up period.

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Author to whom all correspondence and reprint requests should be addressed: Joseph Levy, University Health Center—4H, Division of Endocrinology, 4201 St. Antoine, Detriot, MI 48201. E-mail: jlevy@intmed.wayne.edu

Case Report

A 25-yr-old woman with type 1 diabetes mellitus for 11 yr, presented with a history of intermittent, right lower extremity pain and swelling for approx 8 mo, becoming more severe 2 mo prior to her admission. On admission, the patient described a sudden onset of extreme pain in the area of her right midcalf reaching to the upper thigh and gluteal area associated with increased swelling. There was no history of trauma. The pain was aggravated by movement and bearing of weight. There was no relief of the pain with the use of codeine-containing analgesics. In her prior repeated hospitalizations for similar episodes, she was evaluated with multiple investigations, including computerized tomography (CT) and ultrasound imaging of the pelvis and thigh as well as muscle biopsy of the right thigh on two occasions. The only abnormalities reported were in her imaging studies. The CT scan showed low-density areas in the right semitendinosus and right gluteus maximus muscles with enlargement of the muscles. These abnormalities became more extensive 1 mo prior to her admission, when an ultrasound scan revealed hypoechoic muscles but with no discrete fluid collection. The patient was not treated with either aspirin or anticoagulant therapy prior to her admission.

The patient's medical history was significant for nephropathy, hypertension, and severe retinopathy leading to blindness. She was a nonsmoker and had no history of alcohol or illicit drug use.

On examination the patient was afebrile (97.6°F [36.4°C]) and blind with periorbital edema and generalized anasarca. Blood pressure was 160/102 mmHg. Heart sounds were normal and lungs were clear. The right leg was swollen, and she had limited range of motion owing to pain and tenderness of the right thigh. There were two healed incision scars in the thigh. Pedal arterial pulses were normal bilaterally, and monofilament testing for peripheral neuropathy showed no sensory deficits.

Laboratory tests revealed blood glucose levels ranging between 12 and 16 mmol/L (216–288 mg/dL), serum creatinine phosphokinase (CPK) was 351 IU/L (n = 25–240 IU/L)

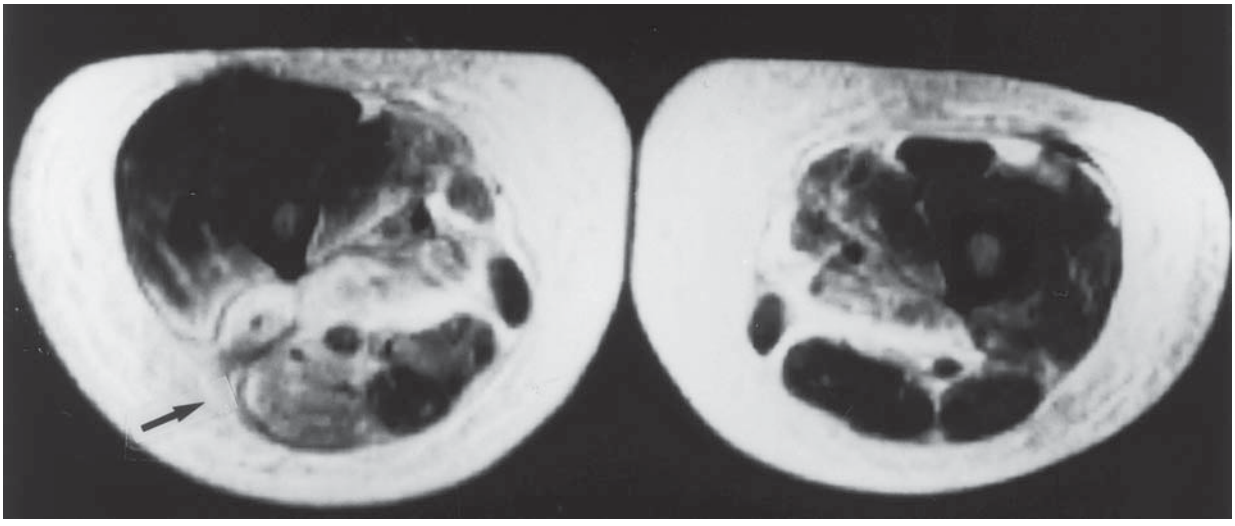

Fig. 1. MRI showing T2 weighted images of the right thigh **(left)** and left thigh **(right)**. Diffusely increased signal is seen involving the muscles of the posterior and medial compartments of the right thigh, biceps femoris, and semimembranosous (left, *see* arrow) compared with the left normal thigh **(right)**.

25–240), white blood cell count was 10,000/μL, hematocrit was 32.8%, prothrombin time was 10.3 s (n = 11–13 s), and activated partial thromboplastine time was 22.0 s (n = 21–35 s). Urinalysis revealed 3+ proteinuria and 4+ glycosuria. Serum creatinine was 150.3 μmol/L (1.7 mg/dL), and serum electrolytes were normal. Blood cultures were negative. Venous Doppler studies of both lower extremities excluded deep vein thrombosis. A magnetic resonance imaging (MRI) of her right thigh (Fig. 1) showed marked sc edema of the gluteal area and thigh. There was diffusely increased signal in the posterior and medial compartments. The adductors and biceps femoris muscles were edematous; the mid and distal portions of the latter were completely replaced by fluid, indicating muscle necrosis to the level of the knee. Surgical exploration of her right thigh revealed no purulent pockets. The biceps femoris muscle was grossly boggy and gray. Microscopy of the muscle biopsy showed recent and remote muscle infarctions (Fig. 2) and small vessel thrombi (Fig. 3) without any inflammation. Electron microscopy (Fig. 4) revealed basement membrane thickening of the small vessels and endothelial cell swelling. Cultures were taken at the time of biopsy for bacteria and fungi and were found to be negative. The pathological finding of skeletal muscle infarction in this patient prompted a search for a hypercoagulable state.

The patient was found to have a fasting plasma total homocysteine level of 18.1 μmol/L (n = 6–10) and increased platelet responsiveness to epinephrine (type III sticky platelet syndrome). To ensure accurate measurement for plasma total homocysteine level, a blood sample was obtained by venipuncture after a 12-h fasting period. Blood was collected in tubes containing EDTA on ice, and separated plasma was stored at –70°C. Total homocysteine was measured by high-performance liquid chromatography *(6)*. The remainder of the hypercoagulability work-up including antithrombin III level, protein C, protein S, factor VII, and plasminogen activities was normal. The patient was treated with opiate analgesics for her pain management, and her blood glucose was intensively controlled.

The patient's condition improved with this supportive therapy, and she was also started on 325 mg/d of aspirin and 2 mg/d of flic acid and subsequently was discharged from the hospital. After 4 m of treatment, her plasma total homocysteine level decreased to 13.5 μmol/L. No recurrence of these episodes occurred in 16-mo follow-up.

Discussion

The cause of diabetic muscle infarction is unknown but is believed to be primarily microvascular *(1–3)*. In support of this belief are the findings that most of the diabetic patients reported have also had retinopathy (80%), nephropathy (80%), and peripheral neuropathy (72%) *(3)*. Our patient had no demonstrable clinical peripheral neuropathy on monofilament testing, however, subtle evidence of neuropathy could not be ruled out in the absence of electrophysiological studies, which were difficult to conduct in her acute condition. Nevertheless, she had nephropathy and severe retinopathy. In the previously reported cases, there were no instances of large vessel occlusion *(1–5,7)*, and we also found our patient to have intact peripheral arterial pulses. A rich collateral blood supply in the skeletal muscle makes infarction in this tissue a rare phenomenon *(8)*. However, the presence of extensive small vessel disease was reported to be the principal finding in patients with diabetic muscle infarction *(1–5,7)*. Our findings of basement membrane thickening, endothelial cell swelling, and intraluminal thrombi of the muscular microvasculature

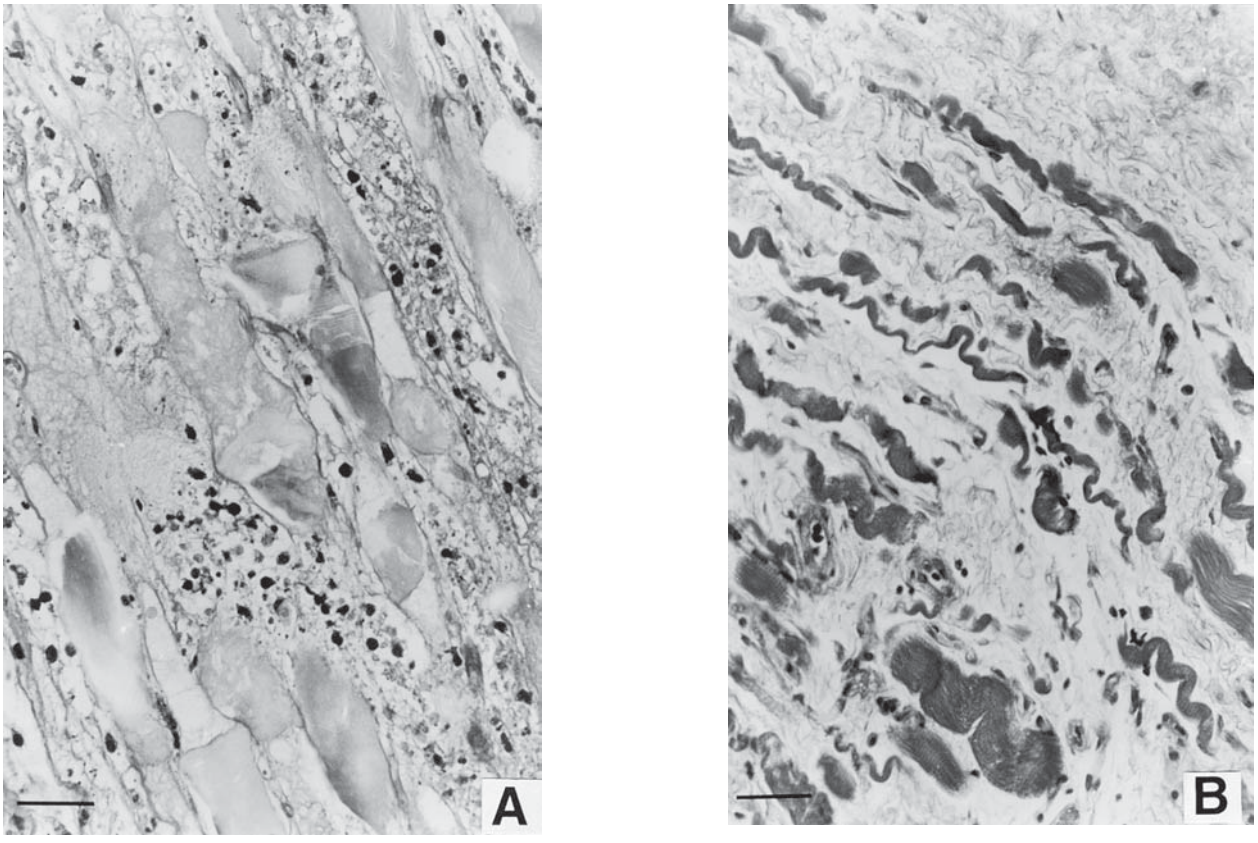

Fig. 2. **(A)** Acute coagulation necrosis or recently infarcted muscle and discrete polymorphonuclear infiltration (magnification × 320). Bar = 30 μm **(B)** Marked endomysial fibrosis and muscle fiber atrophy indicative of remote ischemic injury. Hematoxylin-eosin stain (magnification × 80). Bar = 125 μm.

support this observation. Recurrence of muscle infarction occurs in up to 50% of patients *(3)*, suggesting that conventional management of this condition is only partially satisfactory. It has been reported that the fibrinolytic activity in patients with diabetic muscle infarction is impaired, and abnormalities have been found in the levels of thrombomodulin, tissue plasminogen activator, plasminogen activator inhibitor, and factor VII *(8)*. *Consequently, long-term anticoagulation therapy as a strategy to prevent recurrence was suggested.* Treatment with Coumadin showed encouraging results *(8)*.

The observations in our patient extend these findings by demonstrating hyperhomocysteinemia and increased platelet aggregability as additional abnormalities to be considered for therapeutic interventions. It has been shown that plasma homocysteine levels are mildly elevated in patients with both type 1 and type 2 diabetes mellitus *(9–11)* even in the absence of chronic renal disease *(12)*. Recently it was found that up to 39.3% of patients with diabetes mellitus and coronary artery disease have high plasma total homocysteine levels *(13)*. However, it is not clear whether there is a direct cause-and-effect relation between the increased homocysteine levels and the diabetes or the coronary disease. Elevated homocysteine levels may exert their deleterious effects through alterations in endothelial and platelet function, which are already impaired in diabetes *(14–16)*. We feel that this combination of abnormalities may have a synergistic effect in contributing to the clinical outcome of diabetic skeletal muscle infarction. Although the levels of plasma total homocysteine in our patient did not return to normal with treatment, they were markedly improved. It has been suggested that increased risk of cardiovascular disease starts with plasma total homocysteine levels above 14 μmol/L. Thus, it is possible that in our patient the decrease in total homocysteine levels to a level of 13.5 μmol/L could be sufficient to contribute to a favorable outcome *(13)*.

Hyperhomocysteinemia and hyperaggregability of platelets are potentially amenable to simple therapeutic interventions with folic acid, vitamins B6 and B12, and aspirin, respectively *(16,17)* and these should be considered as preventive measures. It is not clear whether treatment with aspirin alone could be sufficient to prevent the recurrence of muscle infarction episodes. However, in the absence of a large series that would prove aspirin's efficacy when used alone, because of the rarity of this condition, we feel that aggressive treatment aimed to both decrease homocysteine levels and improve platelet function is preferable. Because of the findings in our patient and findings previously described in diabetic patients with muscle

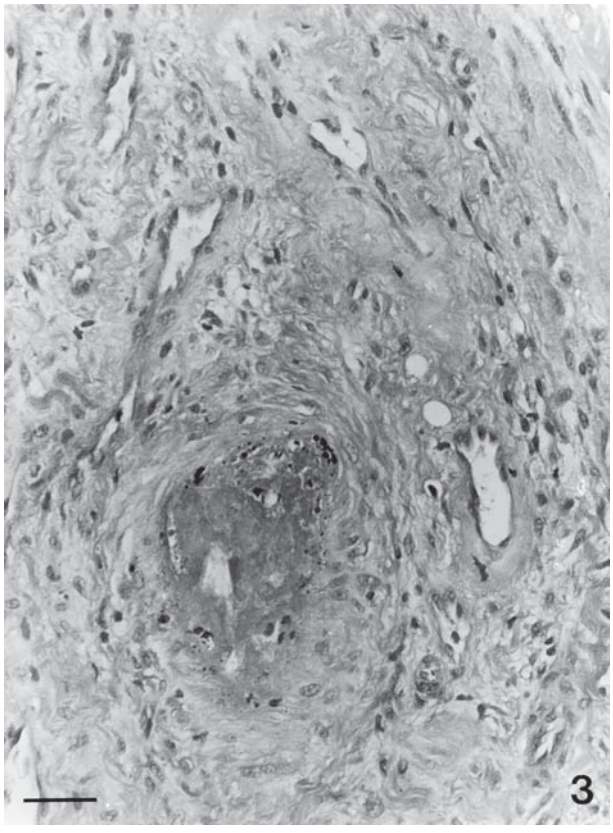

Fig. 3. Perimysial small artery showing recent thrombosis (magnification × 320). Bar = 30 μm.

infarction, we suggest that investigation for heritable and acquired causes of hypercoagulability and measurement of plasma homocysteine levels should be performed in all patients with diabetic muscle infraction.

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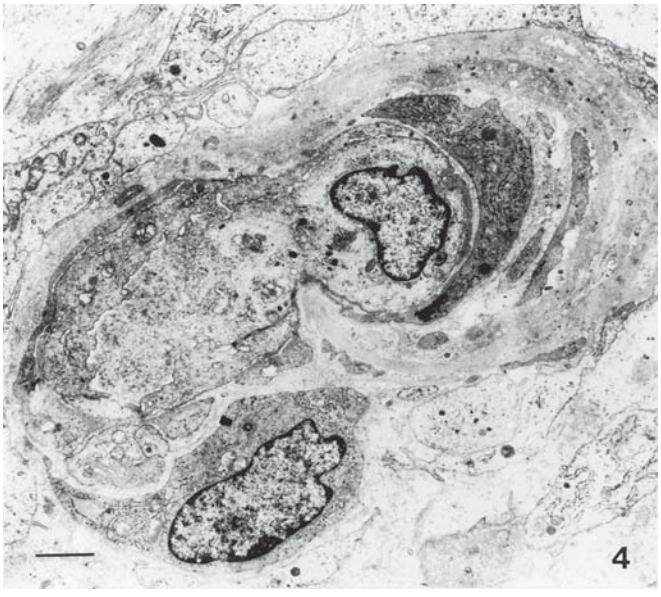

Fig. 4. Electron micrograph of perimysial vessel showing endothelial cell swelling and marked basement membrane thickening consistent with diabetic microvascular disease (magnification × 3,000). Bar = 3.3 μm.

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