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Retrospective analysis of treatment modalities in diabetic muscle infarction

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¹Department of Medicine, ²Allergy/ Immunology Rheumatology Division, University of Medicine and Dentistry of New Jersey, Newark, NJ, USA **Background:** Diabetic muscle infarction (DMI) is a spontaneous necrosis of skeletal muscle of unknown etiology. The major risk factor is longstanding uncontrolled diabetes mellitus (DM). Optimal treatment for DMI is not known. The purpose of this study was to analyze the outcome of surgical treatment, physiotherapy, and bed rest in DMI.

Methods: We searched Medline from its inception to April 2013. We selected cases that provided sufficient data on recovery duration, recurrences, and non-recurrences. Baseline characteristics, including age, sex, microvascular complications, lesion size estimated on magnetic resonance imaging, type of diabetes, and duration of diabetes were assessed. The primary outcome was mean time to recovery from initial treatment and secondary outcomes were mean time to recurrence and recurrence rate.

Results: Mean time to recovery was 149 (95% confidence interval [CI] 113–186), 71 (95% CI 47–96), and 43 (95% CI 30–57) days for surgery, physiotherapy and bed rest, respectively. These figures were statistically significant only for surgery versus physiotherapy and surgery versus bed rest (P<0.01). Mean time to recurrence was 30, 107, and 297 days for surgery, physiotherapy, and bed rest, respectively. The recurrence rate was 57%, 44%, and 24% for surgery, physiotherapy, and bed rest, respectively.

Conclusion: Our results show a similar outcome for physiotherapy as compared with bed rest. It also confirms nonsurgical treatment as a better therapeutic option compared with surgical treatment

Keywords: therapy, infarction, diabetes, complications, comparison

Introduction

Diabetic muscle infarction (DMI) refers to spontaneous ischemic necrosis of skeletal muscle that is not related to major arterial thromboembolism. DMI was first described in 1965 by Angervall and Stener, who demonstrated that this condition is ischemic in nature and may be secondary to diabetic microangiopathy and arteriosclerosis. DMI occurs in patients with longstanding uncontrolled diabetes mellitus (DM), who have underlying microvascular complications. ²⁻⁶ The average age at onset is approximately 44 (range 19–81) years, with both sexes equally affected. ⁷

The pathogenesis of DMI is not fully understood, and numerous theories have been suggested, including coagulation-fibrinolysis abnormalities, hypoxia-reperfusion events, and diabetic microangiopathy with arteriosclerosis. ^{1,8–11} Fibrosis and apoptosis have been shown to be features of long-term myocardial damage in experimental type 1 DM. ¹² Patients present with an acute onset of painful swelling of the affected muscle with subsequent appearance of a palpable painful mass. ^{7,13} Systemic signs are often

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absent, and laboratory findings are varied and nonspecific. The thigh muscles are the most commonly involved muscle group.²⁻⁵ Typical magnetic resonance imaging (MRI) findings on T2-weighted imaging include high signal intensity in the infarcted muscle with subcutaneous and subfascial edema. 3,10,14-20 Histologic findings are nonspecific, and usually show large areas of muscle necrosis with varying degrees of edema, regenerating muscle fibers, polymorphonuclear leukocyte cells, and hemorrhage.21 The diagnosis is established based on the overall clinical picture and MRI findings. Biopsy is generally not recommended and is reserved for atypical cases. The short-term prognosis of DMI is good, but the long-term prognosis is poor due to underlying advanced microvascular disease in patients with this condition.^{8,9,22,23}

The management modalities for DMI that are widely reported in the literature are bed rest and physiotherapy. The treatment outcome and favorability of these are based on limited evidence and expert opinion, and the outcomes reported for physiotherapy are inconsistent. Therefore, in order to better elucidate the data on this topic, we analyzed and compared treatment outcomes for surgery, physiotherapy, and bed rest in DMI. Physiotherapy and bed rest are general descriptive terms used for all forms of immobility and physical therapy. Surgery denotes that a muscle or part of a muscle is excised.

Materials and methods

Data selection

We searched Medline from its inception to April 2013 using the key terms "diabetic muscle infarction" and all synonyms and associated words; bibliographies in the reports obtained were reviewed. From the search results, we selected cases that provided sufficient data on recovery duration, recurrences, and non-recurrences. Cases were included in the final analysis if the clinical presentation was sufficiently described, MRI or computed tomographic images of the lesion were documented, and the patient underwent only a single therapy (ie, surgery alone, physiotherapy alone, or bed rest alone). We excluded cases that had not adequately eliminated trauma, infection, tumor, myositis, and deep vein thrombosis as possible causes. The clinical data used to establish baseline characteristics were age, sex, microvascular complications (nephropathy, retinopathy, and neuropathy), number of muscles involved, type of diabetes, and duration of diabetes. Laboratory findings, including glycosylated hemoglobin (HbA_{1c}), creatine kinase level, erythrocyte sedimentation rate, and white cell count, were documented when available. HbA_{1c}, erythrocyte sedimentation rate, and creatine kinase values obtained were those provided during the initial evaluation. Baseline characteristics and laboratory parameters are summarized in Table 1.

Data analysis

The outcomes in the three treatment modality groups are presented as mean time to recovery, mean time to recurrence, and one-year recurrence rate. Mean time to recovery is defined as the average time interval between initiation of treatment and complete recuperation (near or complete resolution of symptoms). Mean time to recurrence is the average time interval between complete recuperation and

Table I Baseline characteristics^{2,3,7–9,13,15,16,18–22,24–56}

Items	Surgery	Physiotherapy	Bed rest	P-values
Percent female	6/8 (75.0%)	12/25 (48.0%)	19/32 (59.4%)	0.52
Mean age (years)	41 (n=8)	42 (n=25)	43 (n=32)	NS^a
Mean duration of DM (years)	18.3 (n=6)	13.7 (n=21)	14.3 (n=27)	NS^a
Percent type I DM	4/7 (57.1%)	8/15 (53.3%)	17/32 (53.1%)	0.99
MV complication: nephropathy	6/7 (85.7%)	10/15 (66.7%)	25/29 (86.2%)	0.87
MV complication: neuropathy	5/7 (71.4%)	10/14 (69.2%)	15/26 (57.7%)	0.90
MV complication: retinopathy	6/7 (85.7%)	6/14 (38.5%)	20/26 (76.9%)	0.54
Number of muscles ^b involved				
1	1/8 (12.5%)	1/12 (8.3%)	11/31 (35.5%)	0.33
2	3/8 (37.5%)	4/12 (33.3%)	5/31 (16.1%)	
≥3	4/8 (50.0%)	7/12 (58.3%)	15/31 (48.4%)	
HbA _{1c} >6.5%	1/1	2/4	13/17	
ESR >20 mm/hour	5/5	6/6	19/21	
CK >200 IU/L	2/6	3/10	9/24	
WBC $>$ 12 \times 10 9 cells/L	1/6	2/10	6/23	

Notes: aNS, not statistically significant (surgery versus bed rest, P>0.05; surgery versus physiotherapy, P>0.05; physiotherapy versus bed rest, P>0.05); anumber of muscles involved was obtained from MRI.

Abbreviations: DM, diabetes mellitus; CK, creatine kinase; MV, microvascular; MRI, magnetic resonance imaging; ESR, erythrocyte sedimentation rate; WBC, white blood cell count; HbA12, glycosylated hemoglobin; NS, not statistically significant.

first episode of recurrence. Recurrence rate is defined as first episode of recurrence within one year. The categorical statistical variables are first episode of recurrence, no recurrence, lesion size, sex, microvascular complications, and type of DM; continuous variables are recovery duration, recurrence-free duration, patient age, and duration of DM. We assessed for differences between baseline characteristics using the chi-square test, Fisher's exact test, Student's *t*-test, and Tukey's test as appropriate. We performed pairwise comparisons of mean time to recovery between the three treatment modality groups using Tukey's test post analysis of variance with adjusted *P*-values for multiple comparisons; a similar analysis was done for mean time to recurrence. Pairwise comparison of recurrence rate was performed using Fisher's exact test. All reported *P*-values are two-sided.

Results

In total, 80 citations were obtained and fully reviewed; 34 of these were rejected for analysis based on our inclusion/exclusion criteria. A total of 46 references, describing 65 patients, were selected. 2,3,7-9,13,15,16,18-22,24-56 Overall, 32 patients were treated with bed rest, 25 received physiotherapy, and eight underwent surgical excision of the infarcted muscle. Nearly all patients were placed on a rigorous glycemic control regime following diagnosis of DMI. Baseline characteristics were similar between the three groups (Table 1). The types of DM were in an approximately 1:1 ratio between the three groups; the mean patient age was 41, 42, and 44 years for surgery, physiotherapy, and bed rest, respectively; more than 60% of patients in each treatment group had involvement of two or more muscles. Approximately 67% and 29% of the muscle groups involved the thigh and calf, respectively. The rest comprised foot, lower back, and proximal upper limb muscles.

The primary outcome, ie, mean time to recovery, was 149 (95% confidence interval [CI] 113–186), 71 (95% CI 47–96), and 43 (95% CI 30–57) days for surgery, physiotherapy, and bed rest, respectively. These were only statistically significant for surgical treatment compared with physiotherapy (P<0.01) and surgical treatment compared with bed rest (P<0.01, Figure 1). The secondary outcome, ie, mean time to recurrence, was 30, 107, and 297 days for surgery, physiotherapy, and bed rest, respectively; a cross group pairwise comparison was not statistically significant (P>0.05, Figure 2). The recurrence rate within one year was 57% (4/7) for surgery, 44% (4/9) for physiotherapy, and 24% (4/17) for bed rest (P=0.52, Figure 3). A subgroup analysis of patients in the bed rest group comparing mean time to

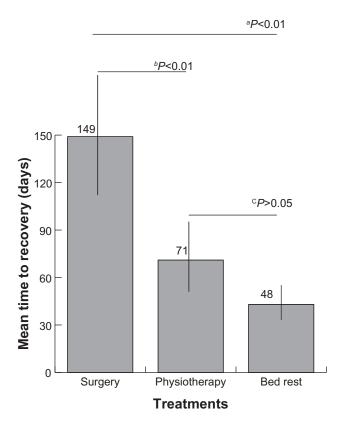


Figure I Mean time to recovery.

Notes: Mean time to recovery following surgery, physiotherapy, and bed rest in days. Bed rest has the shortest time to recovery followed by physiotherapy, then surgery. "Surgery versus bed rest; "surgery versus physiotherapy; "physiotherapy versus bed rest. P is adjusted for multiple comparisons.

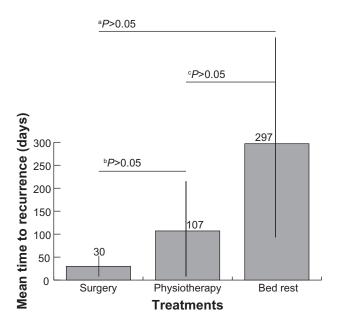


Figure 2 Mean time to recurrence.

Notes: Mean time to recurrence after surgery, physiotherapy, and bed rest in days.

Bed rest has the longest duration of well interval followed by physiotherapy, then surgery. *Surgery versus bed rest; *bsurgery versus physiotherapy; *physiotherapy versus bed rest. *P is adjusted for multiple comparisons.

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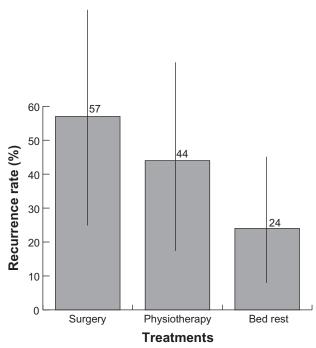


Figure 3 Recurrence rate within one year. **Notes:** Recurrence rate within one year for surgery, physiotherapy, and bed rest. Bed rest has the lowest recurrence rate followed by physiotherapy, then surgery (*P*=0.52). Vertical bars represent confidence intervals.

recovery between those who underwent incision biopsy versus no biopsy showed a trend toward faster recovery in patients without biopsy (49 days versus 40 days, *P*=0.54).

Discussion

DMI is a seemingly rare complication of DM, but is probably underdiagnosed. This analysis is unique because it is the first to analyze outcomes of physiotherapy compared with other modalities. Our results show that physiotherapy has a treatment outcome comparable with that of bed rest, based on our primary and secondary outcomes. The outcome of surgery, on the other hand, was a more prolonged recovery duration that was statistically significant compared with the recovery duration with physiotherapy and bed rest. The latter finding confirms the report by Kapur and McKendry.⁵⁷ In general, there is a trend toward better outcomes with bed rest than with physiotherapy and surgery in regard to both primary and secondary outcomes (Figures 1–3).

A subgroup analysis of the bed rest group that compared outcomes in patients who underwent incision biopsy with those in patients with no biopsy showed a trend toward reduced recovery duration for the no biopsy group, although this result was not statistically significant. Excision biopsy is commonly associated with worsening symptoms and prolonged recovery duration, so is generally

discouraged. 19,58,59 If a confirmatory biopsy is warranted, needle biopsy is recommended because it has been observed to be well tolerated. 9,59

The optimal treatment for DMI is still unknown, and current treatment practices are based on limited evidence. Prolonged bed rest leads to deconditioning, joint contractures, and thromboembolic disease; 40,60 on the other hand, a vigorous exercise regime prescribed during the acute or postoperative period will perpetuate inflammation, disrupt the healing process, and ultimately result in a prolonged recovery. 9,42,59 When a judicious exercise regime is undertaken at the appropriate time, deconditioning can be prevented and muscle tissue regeneration is promoted. Therefore, the optimal therapy for DMI may be a period of bed rest during the acute phase followed by gentle physiotherapy as tolerated.

Other treatment modalities that have been tried include antibiotics, corticosteroids, and anticoagulants. Data on each of these are limited, but when reported, these treatment modalities are usually used in combination^{5,11,42,58,61-63} or for a specific primary clinical purpose (eg, deep vein thrombosis, infection) in the setting of DMI. 40,42,63,64 The rationale behind use of anticoagulation for DMI is the hypothesis that DMI is caused by an acquired hypercoagulable state; 40,42,63 autopsy studies in reported cases have not shown thromboembolus, but have shown diffuse arteriosclerosis and microangiopathy.^{1,9} The hypercoagulable state hypothesis alone does not sufficiently account for the pathogenesis of DMI, given that the condition is rare. Nearly all patients with DMI have uncontrolled DM; in this setting, systemic steroid therapy will exacerbate hyperglycemia. This risk in diabetic patients with multiple microvascular complications will likely exceed any unproven benefit. Platelet hyperaggregability, as demonstrated by Rajkumar et al, is the primary rationale for use of antiplatelet agents as potential therapy for reducing the rate of recurrence of DMI.63 Although data are few, reduction in recurrence has been documented in cases that involved bed rest. 6,61,63,65 Lastly, there were limited data on crossover therapy in the treatment modality groups.

The primary limitation of this study is its retrospective nature and strict inclusion/exclusion criteria, which introduces bias in data gathering and reporting. Further, this study is underpowered due to its small sample size; as a result, some effects of practical significance may not have been identified. It could be that the trend towards a better outcome with bed rest is real but statistically insignificant due to the small sample size. Scarce and poorly reported data on antiplatelet therapy and crossover studies resulted in a

limited analysis on these topics. Confounding variables that have been inconsistently reported (eg, other chronic medical conditions) may have played a significant role in the overall outcome in ways that are not readily quantified. With the data available, the baseline characteristics that were reported are similar between the three groups.

In summary, the optimal treatment for DMI is still unclear, and the current practice is based on limited evidence and expert opinion. Our results show a similar treatment outcome with physiotherapy compared with bed rest. They also confirm that nonsurgical treatment is a better therapeutic option than surgical treatment. This information serves to clarify the data on this topic.

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Disclosure

The authors report no conflict of interest in this work.

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