Exercise-Facilitated Neurorehabilitation in Diabetic Neuropathy

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PI: Evan B. Stubbs, Jr.
Co-PI: Morris A. Fisher
Diabetes mellitus (diabetes, type 1 or type 2) and its triad of common complications (neuropathy, nephropathy, retinopathy) affect approximately 20.8 million Americans, or greater than 7% of the population (all ages, 2005; NIDDK). Diabetes is now considered at epidemic proportions in the Western world. United States Veterans are no exception, with approximately 500,000 currently receiving treatment at Veterans Affairs Medical Centers for type 2 diabetes mellitus (diabetes).\(^{(1)}\)

The morbidity and mortality of diabetes among our aging patient population is due, in part, to the development of both macrovascular and microvascular complications, and clearly represent a major health care concern for the Department of Veterans Affairs.\(^{(2)}\) Uncontrolled diabetes accelerates atherogenesis, resulting in large vessel peripheral vascular disease common among diabetics. Microvascular complications, however, eventually debilitate nearly all individuals with diabetes. Diabetes-associated retinopathy is the most common cause of adult blindness in the United States.\(^{(3)}\) Diabetes is also the leading cause of renal failure in the United States.\(^{(4)}\) Equally alarming, greater than half of all patients with diabetes develop neuropathy, a debilitating progressive deterioration of peripheral and autonomic nerves and affecting the central nervous system.\(^{(5; 6)}\)

Microvascular complications of diabetes share a common pathophysiology. Chronic hyperglycemia leads to glucose metabolic derangements including increased polyol and hexosamine metabolism, altered NAD(P)H redox homeostasis, nonenzymatic glycation of proteins producing advanced glycation end products, aberrant activation of signal transduction pathways. Oxidation is proposed to be a key initiator of microvascular and metabolic alterations.\(^{(7; 8)}\)

Currently, diabetic neuropathy is untreatable in humans. Maintenance of euglycemia as an indirect means of delaying development of diabetic complications is the recommended therapeutic approach. Several pharmacologic strategies, although successfully applied in experimental animals, have proven disappointing in clinical trials of diabetic neuropathy. The therapeutic benefits of acetyl-carnitine, aldose reductase inhibitors, or nerve growth factor have not been forthcoming.\(^{(9)}\) Innovative treatment strategies designed to address pre-existing nerve injury in the aged diabetic patient are critically needed.

It is now well established that exercise is a safe and integral approach to the management of patients with diabetes.\(^{(10-12)}\) Aerobic exercise significantly decreases peripheral nerve microvascular complications in the diabetic patient.\(^{(13)}\) Therapeutic interventions that improve blood flow to peripheral nerves, such as exercise, are expected to slow or perhaps reverse the progression of neuropathy in the diabetic patient.\(^{(14)}\) Recently, we reported improved measures of peripheral nerve function in diabetic patients following a 24-week program of moderate aerobic exercise.\(^{(15)}\) These findings support the thesis that aerobic exercise intervention can be helpful in the therapeutic management of patients with diabetic neuropathies.

A single-site, randomized, blinded, prospective clinical trial is proposed to determine the significance of an isokinetic strength and aerobic exercise training program on recovery of peripheral nerve function in type 2 diabetic Veterans with neuropathy. Recent findings from within our group demonstrate that exercise improves peripheral nerve function while remaining a safe adjunctive management strategy for the treatment of the type 2 diabetic veteran with neuropathy.\(^{(15)}\) A 24-week program of aerobic exercise produced measurable improvement in some neurologic outcome measures. Vibratory sensation threshold levels in exercised individuals, compared with non-exercised control subjects, were modestly but significantly lowered (p=0.006), suggesting improved large-fiber function. Significant (p=0.042) increases in distal motor nerve conduction amplitudes were observed in subjects receiving exercise. Our preliminary data demonstrate that aerobic exercise improves distal motor peripheral nerve function in diabetic neuropathic Veterans. Recent studies support a beneficial effect of exercise on CNS neural adaptive responses.\(^{(14)}\) We argue that an exercise program utilizing strength and aerobic training, as proposed in this application, will produce enhanced therapeutic benefits to the diabetic veteran with neuropathy.

**Study Protocol**

Diabetes mellitus (diabetes, type 1 or type 2) and its triad of common complications (neuropathy, nephropathy, retinopathy) affect approximately 20.8 million Americans, or greater than 7% of the population (all ages, 2005; NIDDK). Diabetes is now considered at epidemic proportions in the Western world. United States Veterans are no exception, with approximately 500,000 currently receiving treatment at Veterans Affairs Medical Centers for type 2 diabetes mellitus (diabetes).\(^{(1)}\)

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Statement of Hypothesis

A combined isokinetic strength and aerobic exercise training program will enhance recovery of peripheral nerve function in Veterans with diabetic neuropathy by a mechanism of neural adaption.

Specific Objectives

The primary outcome measure of this study is recovery of peripheral nerve function in type 2 diabetic Veterans. Secondary outcome measures of exercise intervention include changes in aerobic capacity, peak torque, pain perception and health care use. Exercise-induced rehabilitation of diabetic veterans with neuropathy is an overdue concept that remains poorly studied and merits a prospective clinical investigation. Edward Hines, Jr. VA hospital will serve as a readily available resource for completing these studies.

The hypothesis of this study will be tested with the following two Specific Objectives:

a. We will determine the effect of aerobic training, isokinetic strength training, or the combination of aerobic plus isokinetic strength training compared with non-exercise intervention on recovery of peripheral nerve function in age-matched type 2 diabetic Veterans with neuropathy.

i. Type 2 diabetic Veterans with established staged length-dependent sensorimotor polyneuropathy will be randomized to a 12 week program of exercise (aerobic, isokinetic, or the combination) or control (non-exercise) intervention. Isokinetic strength promoting leg extensions will be performed on a calibrated Biodex System 3 dynamometer. Aerobic exercise will consist of walking. Sustainability of intervention will be evaluated by repeated testing at 24 weeks. All subject groups will participate in identical biweekly diabetes-related Health Promotion Educational seminars designed to normalize participation.

ii. The effects of aerobic training, isokinetic strength training, or the combination of aerobic and isokinetic strength training compared with non-exercise intervention on recovery of peripheral nerve function will be statistically determined from baseline and follow-up testing using a battery of qualitative and quantitative assessments that include clinical history, physical and neurological examination, electrodiagnostic primary outcome measures, Quantitative Sensory Testing, completion of Total Neuropathy Score, visual analogue pain scale, quality of life (SF-36V Health Survey), peak torque (Biodex), peak oxygen uptake (incremental symptom-limited treadmill test) and everyday physical activity (Actical accelerometer physical activity counts).

b. We will determine the effect of aerobic training, isokinetic strength training, or the combination of aerobic plus isokinetic strength training compared with non-exercise intervention on muscle tissue oxygenation in age-matched type 2 diabetic Veterans with neuropathy.

The effect of these individual interventions on muscle tissue oxygenation will be determined from baseline and follow-up by measuring limb oxygenation of the quadricep and tibialis anterior muscle groups as quantified by non-invasive infrared spectroscopy using an InSpectra™ Tissue Spectrometer.

The immediate goal of this applied study is to quantify the effects of aerobic training, isokinetic strength training, or the combination of aerobic and isokinetic strength training compared with non-exercise intervention on recovery of peripheral nerve function in the type 2 diabetic Veteran with neuropathy. Defining neural adaptive responses to individual and combined exercise interventions will allow for immediate institution of applied exercise therapy. The benefits of exercise on recovery of peripheral nerve function in diabetic patients have not been established. Exercise intervention would provide a safe achievable therapeutic option to millions of Americans affected by this disorder. A Long-term benefit of this study that extends beyond its present scope includes the application of guided exercise protocols in the prophylactic treatment of type 2 diabetic subjects with neuropathy. This single-site clinical study will provide the critical evidence required to objectively and critically define the functional significance of exercise as a rehabilitative option for the neuro-compromised diabetic Veteran.
BACKGROUND AND SIGNIFICANCE
Diabetes Mellitus and Exercise

Diabetes mellitus (diabetes) is the most common cause of blindness, end-stage renal disease, and non-traumatic lower extremity limb amputations in adults.\(^{(6)}\) Whether insulin-dependent (type 1) or non-insulin dependent (type 2), diabetes is defined as a metabolic disorder complicated by long-term microvascular, neurologic, and macrovascular complications.\(^{(16)}\) Type 2 diabetes has reached epidemic proportions in the United States.\(^{(17)}\) Obesity secondary to physical inactivity is cited as a major factor in the increasing rates of type 2 diabetes and associated complications. The increased incidence of diabetes and obesity is not restricted to adults, and is rising among American children.

Regular physical activity, in combination with pharmacologic intervention, is now recognized as a cornerstone of treatment for type 2 diabetes. The benefits of moderate physical exercise are well established with pronounced effects on substrate utilization and insulin sensitivity resulting in reductions in blood pressure, body weight, body fat, improved lipid profiles and increased muscle strength. The application of moderate exercise for the treatment of type 2 diabetes has been shown to improve maintenance of blood glucose levels and, in some cases, decreases the need for pharmacologic intervention.\(^{(18-20)}\) Patients with type 2 diabetes without known complications are less fit (reduced VO\(_{2}\)\(_{\text{peak}}\) measurements) when compared to age, body mass, and activity-matched control subjects.\(^{(21)}\) Low cardiorespiratory fitness is an independent predictor of long-term cardiac mortality in individuals with diabetes.\(^{(22)}\) In a meta-analysis of the effect of exercise on cardiorespiratory fitness in type 2 diabetes, Boulé \textit{et al.}\(^{(23)}\) reported that moderate intensity exercise intervention of 8 weeks or more statistically improved VO\(_{2}\)\(_{\text{peak}}\). Thus cardiorespiratory fitness may be an independent modifiable risk factor in subjects with type 2 diabetes. Enhancing cardiorespiratory fitness is expected to improve quality of life and promote an active lifestyle in the type 2 diabetic patient.

Diabetic Polyneuropathy (DP)

DP is the most common and troublesome complication of diabetes and is a leading cause of peripheral neuropathy in the United States.\(^{(24)}\) DP is not a single disorder, but rather a number of different syndromes that accounts for more admissions to hospitals than all other diabetic complications combined. DP is responsible for 50-75\% of non-traumatic amputations.\(^{(25)}\) As a heterogeneous disorder, DP affects distinct regions of the nervous system including proximal and distal peripheral sensory and motor nerves as well as the autonomic nervous system. The reported prevalence of DP varies, but may be as high as 90\%.\(^{(26)}\) The major morbidity associated with DP is foot ulceration, the precursor of gangrene and limb amputation. Neuropathy is considered the major (87\%) contributor of limb amputations.

DP can be separated into two distinctive entities: (i) sensorimotor and autonomic neuropathies that gradually progress with increasing duration of diabetes and (ii) mononeuropathies, radiculopathies, and acute painful neuropathies that are short lived and remit usually completely.\(^{(27)}\) Progression of DP is inversely related to glycemic control and is often present at diagnosis in subjects with type 2 diabetes. In a long-term follow-up study of type 2 diabetic patients, Partanen \textit{et al.}\(^{(28)}\) demonstrated progressive electro-physiologic abnormalities in lower limb sensory and motor nerve conduction amplitudes, suggestive of axonal injury. Slowing of nerve conduction velocity in diabetes generally progresses at a steady rate (1 m/s/yr) and correlates with duration of disease. DP is a disorder in which the prevailing pathology is axonal loss, although loss of conduction velocity is seen over extended durations.

Similar to microvascular complications, multiple etiologies including metabolic, vascular, immune-mediated, oxidative stress and growth factor deficiencies have been proposed to explain the pathogenesis of DP.\(^{(29)}\) It is likely that the pathological diversity associated with DP is related to microvascular disease heterogeneity. Clinical neuropathic syndromes in diabetes include nearly every segment of the peripheral and autonomic nervous system. The most common form of DP is distal symmetrical polyneuropathy (DSP). This disorder is characterized clinically by insidious onset (occasionally rapid) that usually follows stress or initiation of therapy for diabetes. Small nerve fibers, large nerve fibers or both can be affected and sensorimotor findings are common.\(^{(30)}\) Small fiber injury may occur early in disease development and is manifested by lower limb symptoms of pain and hyperalgesia, thermal sensitivity and reduced light touch and pinprick sensation with impaired neurovascular blood flow.\(^{(31)}\) Large fiber injury can involve sensory and/or motor nerves and are usually neuropathies of signs.
(motor function, vibration, position sense, cold thermal perception) than symptoms. Most patients with DSP have a mixture of both large and small fiber injury.

Management of DP is primarily through glycemic control. In a longitudinal study by Pirat(5), 4,400 diabetic patients followed over 25 years demonstrated significant increases in the prevalence of DP with poor blood glucose control. The Diabetes Control and Complications Trial research group has shown that progression of DP is significantly slowed with improved glycemic control.(32; 33) However, the effect of intensive glycemic control on neuropathy in diabetic Veterans remains equivocal.(29) Various pharmacologic intervention measures have failed in clinical trials to show improvement of DP in patients with type 1 or type 2 diabetes. (9) In a one-year study of lifestyle (diet and exercise) intervention in 32 subjects with impaired glucose tolerance (pre diabetic), Smith et al.(34) observed a modest improvement in intraepidermal nerve fiber density with decreased neuropathic pain and improved sural sensory responses. Improved clinical measures of peripheral nerve function in the diabetic patient following exercise is suggested.(14; 15) With the exception of our own,(15) no studies to date have examined exercise as a therapeutic intervention on recovery of peripheral nerve function in type 2 diabetics.

**Diabetic Neuropathy and Exercise**

Exercise training also has beneficial effects on cardiac autonomic regulation.(35) Nearly half of diabetic patients develop autonomic neuropathy, a potentially fatal complication resulting in an increased 5-year mortality.(36) Tonic and reflexory cardiovascular neural regulation are reduced in type 2 diabetic subjects,(37) resulting in a higher risk for cardiac death in affected individuals. In a recent study by Loimaala et al.(38), long-term endurance training was shown to increase baroreflex sensitivity, a measure of reflexory autonomic regulation associated with improved prognosis. Improved autonomic function observed in the Loimaala study was attributed to improved glucose control rather than to changes in central hemodynamics. While the course of large vessel disease in type 2 diabetes may not be altered by exercise intervention, HbA1c content is inversely correlated with forearm blood flow and impaired endothelium-dependent vasodilation.(39) Mechanisms by which exercise intervention increases autonomic function may involve improved endothelial function and enhanced endoneurial blood flow. (40) It is clear that physical training can reduce the risk for cardiac autonomic events in diabetes.

In addition to improved blood glucose control, diabetic patients with increased exercise capacity have decreased peripheral nerve microvascular complications.(13) Therapeutic interventions that improve blood flow to peripheral nerves, such as moderate exercise, is expected to slow or perhaps reverse the progression of peripheral nerve disease in the aged diabetic patient. Improved clinical measures of peripheral nerve function in the diabetic patient following exercise is suggested.(14; 15)

**Diabetes Neuropathy and Endoneurial Vasculature**

Pathological changes in endoneurial blood vessels have long been recognized as a characteristic feature of diabetic neuropathy.(41) The lumen of endoneurial vessels in diabetes is decreased due to reduplicated basement membranes and pericyte degeneration,(42) a finding that has been associated with the severity of polyneuropathy.(43) Capillary alterations and platelet thrombi in the lumen of microvessel have also been reported in human diabetic neuropathy.(44) Endoneurial blood flow, along with oxygen diffusing capacity and tension, are decreased in the diabetic nerve,(44; 45) supporting a hypoxic/ischemic thesis of nerve injury. Improved nerve conduction in diabetic patients has been correlated with improved transcutaneous oxygen tension.(46) Interestingly, experimental hypoxia produces peripheral nerve injury with pathological changes similar to that observed in diabetes.(47) Interventions which improve endothelial function and enhance endoneurial blood flow (angiogenesis, vascular endothelial growth factor) is anticipated to facilitate recovery of or preserve peripheral nerve function in the diabetic patient.(48)

Microvascular complications of diabetes share a common pathophysiology. Four major pathways of glucose metabolism in the development of diabetic microvascular complications have been implicated. (8; 49) Nitric oxide, a potent vasodilator, is also decreased in experimental diabetes.(50) The formation of reactive oxygen species is considered penultimate in the initiation and progression of microvascular complications seen in diabetes.
Animal Models of Diabetic Neuropathy

In humans, long-standing hyperglycemia results in altered nerve conduction velocity, axonal degeneration, and segmental demyelination. (53) Experimental animals with spontaneous or induced hyperglycemia represent imperfect models of neuropathic changes seen in human diabetics. Systemic administration of alloxan or streptozotocin, pancreatic □ cell toxins, induces a diabetic condition similar to that of type 1 (insulin-dependent) diabetes mellitus. (54) A large number of genetic rodent models have been used in diabetes-related studies, including models that represent type 1 diabetes mellitus (NOD, NOR and C57BL/6-Ins2akita murine strains; BioBreeding (BB) Wistar rat) or type 2 diabetes (obese Zucker ZDF (fatty, fa/fa) rat, Goto Kakizaki (GK) rats). With the onset of hyperglycemia, many of these models develop diabetic complications that are observed in diabetic patients, including nerve function deficits and morphologic changes suggestive of axonal atrophy and paranodal swelling. (53) However, other pathologic hallmarks of DP, such as loss of nerve fibers and demyelination, are not as marked in experimental models. Despite these limitations, experimental studies strongly support the thesis that reduced nerve blood flow resulting from microangiopathy of the endoneurial microvessels is an important contributor toward development of DP. (51) To our knowledge, we are the only group to study the effect of exercise on the development and progression of experimental diabetic neuropathy. (54)

Benefits of Isokinetic Strength Training on PNS Rehabilitation

While exercise intervention is firmly established as an effective strategy for the management of the diabetic patient, there remains a pause in the current literature regarding the effectiveness of exercise of any type for the management of established diabetic neuropathy. A beneficial effect of aerobic exercise on neural adaptive responses has been reported. (14) Improved vascular blood flow to the peripheral nerves is expected to promote recovery of nerve function by enhancing neural adaptive responses. To our knowledge, we are the only group to have examined the effect of exercise on neural adaptive responses in peripheral nerves of diabetics. (15, 55) We have found that moderate-intensity aerobic exercise improves some measures of peripheral nerve function in diabetic subjects. Muscle strength in symptomatic diabetic neuropathic patients, however, is markedly reduced when compared to control subjects and non-neuropathic diabetic patients. (56) This may represent a ceiling to the effectiveness of aerobic exercise one may observe among diabetic subjects. To address this concern, we considered different forms of exercise, such as isokinetic in comparison to isotonic, as a way to maximize the amount of muscle activation per unit of work. (57)

As such, isokinetic exercise is known to produce significant muscle strength recovery. Isokinetic resistance training of 39 patients with chronic heart failure significantly improved forearm blood flow, peak VO2, skeletal muscle strength, and endurance. (58) Isokinetic training also improves muscle strength in some neuropathic patients. Six neuropathic patients undergoing dynamometric isokinetic training demonstrated significant strength improvement within six months of rehabilitation. (59) Ischemic environments resulting from microvascular disease often occur in distal limbs of diabetic subjects and are thought to contribute greatly to peripheral nerve injury. Lower leg vascular conductance measured in 10 subjects following a period of passive arterial occlusion or ischemic exercise was found to be enhanced by isokinetic dynamometry, suggesting improved blood flow. (60) Moreover, isokinetic dynamometry has been safely used to quantitate and grade muscle weakness in diabetic neuropathic patients. (61)

Isokinetic resistance is proven to be a safe rehabilitative alternative to other exercise modalities (e.g., isotonic, isometric). By maintaining a preset velocity throughout a joint's entire range of motion, isokinetic exercise facilitates maximum performance of muscle groups. Even at extremes of joint motion, where a muscle is at physiological and mechanical disadvantage, the preset velocity is maintained by the dynamometer by reducing force thereby facilitating maximum voluntary force exerted by the muscle. This resistance mechanism disengages when a subject experiences pain or discomfort, providing pain-free protocols with total available joint motion.

The mechanism by which isokinetic exercise enhances muscle performance is not known. Early gains in performance cannot be simply attributed to muscle hypertrophy. Neural adaptation such as increased synchronous discharge of motor units, lower threshold of activation, dampened inhibitory influence, or a
combination have been suggested.\textsuperscript{(62)} Compared to either exercise modality alone, a combination of aerobic exercise and strength training significantly increases glutathione antioxidant capacity beneficial to disease prevention.\textsuperscript{(63)}

While there are no published data demonstrating effectiveness of isokinetic training on recovery of peripheral nerve function in diabetic subjects, we argue that an exercise program utilizing strength and aerobic training, as proposed in this application, is strongly anticipated to produce measurable and meaningful therapeutic benefits to the diabetic veteran with neuropathy.

**Significance of Research**

Diabetes mellitus afflicts more than 20 million Americans and is the main cause of kidney failure, new onset blindness, and neuropathy-associated limb amputations in adults.\textsuperscript{(7)} Type 2 diabetes accounts for up to 95% of all diabetic cases and affects 7% of the U.S. population age 20 and older. Type 2 diabetes and its associated complications is strongly associated with obesity, secondary to physical inactivity and over-nutrition. The prevalence of type 2 diabetes has conservatively tripled in the last 30 years. Individuals with a body mass index (BMI) of 30 or more have a 5-fold greater risk of diabetes compared to subjects with BMI of 25 or less. In a major clinical trial conducted by the Diabetes Prevention Program (DPP), exercise reduced the risk of getting type 2 diabetes by 58\%.\textsuperscript{(12)} It is well established that moderate exercise is a safe and integral approach to the management of patients with diabetes.\textsuperscript{(10-12)} However, the management of neuropathy in type 2 diabetic patients remains palliative. Exercise significantly decreases peripheral nerve microvascular complications in the diabetic patient.\textsuperscript{(13)} Therapeutic interventions that improve blood flow to peripheral nerves, such as exercise, are expected to slow or perhaps reverse the progression of neuropathy in the diabetic patient.\textsuperscript{(14)} In a one-year study of lifestyle (diet and exercise) intervention, Smith et al.\textsuperscript{(34)} observed a modest improvement in intraepidermal nerve fiber density with decreased neuropathic pain and improved sural sensory responses. Recently, we reported improved measures of peripheral nerve function in diabetic patients following a 24-week program of moderate aerobic exercise.\textsuperscript{(15)} Muscle strength in symptomatic diabetic neuropathic patients, however, is markedly reduced when compared to control subjects and non-neuropathic diabetic patients.\textsuperscript{(56)} This may represent a ceiling to the effectiveness of aerobic exercise one may observe among diabetic subjects. To address this concern, we considered different forms of exercise, such as isokinetic in comparison to isotonic, as a way to maximize the amount of muscle activation per unit of work.\textsuperscript{(57)}

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**Relevance of Proposed Work to the VA Patient Care Mission**

Approximately 16\% of U.S. Veterans are treated for diabetes.\textsuperscript{(1)} At least 8-10\% of the treated VA population now suffers with diabetic neuropathy. For these patients, improved treatment is expected to produce an improved quality of life, a decrease in the disabling burden of diabetic nerve dysfunction, and a diminished need for medical care. Although specific costs for treating diabetic neuropathies are not available, the potential savings with better management of diabetic neuropathies is evident given the large number of such patients cared for by the VA. With an aging Veteran population, the number of diabetic neuropathic patients in need of VA medical services is expected to increase considerably.

**RESEARCH DESIGN AND METHODS**

General Design: This single-site clinical trial will utilize a prospective, randomized blinded design to determine the effects of aerobic, isokinetic strength, or the combination of aerobic plus isokinetic strength training compared with non-exercise intervention on recovery of peripheral nerve function in age-matched type 2 diabetic Veterans with length dependent sensorimotor polyneuropathy (stage N2a) as diagramed below. One hundred (100) subjects will be recruited with written informed consent in compliance with the Hines Human Studies Subcommittee. Currently there are over 450 Hines VA patients with clinically documented type 2 diabetes...
mellitus and neuropathy available for study. Annual educational seminars on blood glucose management and monitoring are anticipated to provide > 1000 new subjects for study.

**Subject randomization** will be computer generated with permuted blocks. In our experience, permuted blocks preserve balance in the randomization over the course of the study. At any point in time, there will be approximately equal numbers of patients randomized into each of the four groups. All consented and enrolled subjects will complete baseline testing prior to being randomized to exercise/non-exercise interventions that includes a clinical history, physical (including blood pressure monitoring), neurological examination, laboratory studies (including fasting blood glucose, HbA1c, lipid profile), electrodiagnostic studies, Quantitative Sensory Testing (QST) as well as completion of the Total Neuropathy Score, visual analogue pain score, the SF-36V Health Survey, and incremental symptom-limited treadmill test (see below). To avoid inter-examiner variability and maximize neurophysiologic test/retest reliability, the same neurologist (Morris Fisher, M.D.) will conduct all clinical examinations and electrodiagnostic studies. Dr. Fisher will be blinded to subject group assignment and all subjects will be instructed not to discuss their group assignment with Dr. Fisher. If the baseline incremental symptom-limited treadmill test is positive (i.e., any factors are identified that point to undiagnosed or untreated heart disease) the subject will be withdrawn from the study.

After baseline testing, eligible individuals will be randomized to one of four groups of 25 subjects each: aerobic, isokinetic strength, combined aerobic plus isokinetic exercise or control non-exercise intervention. All subjects will be enrolled in the study for 24 weeks and will complete the battery of tests three times, i.e., baseline, 12, and 24 weeks. To control for effects of blood glucose management, subjects will have stable blood glucose control as demonstrated by a fluctuation in the glycosylated hemoglobin of no greater than 1% during the previous six months. Clinical records, including HbA1c levels, of all potential subjects are reviewed by the Nurse clinical coordinator during the screening process prior to enrollment. Candidates with HbA1c levels that vary greater than 1% during the previous six months are excluded from enrollment. As HbA1c levels represent the current standard measure of glucose control in diabetics, and therefore for monitoring the patient's diabetic medications, HbA1c levels are closely monitored (ideally at baseline, 12 weeks, and 24 weeks).

**Data Collection, blinding, and Security:** Ms. Corzine, R.N. is the clinical coordinator of this study and will maintain a hard-copy registry of all enrolled study subjects, including subject randomization and blinded identification. Study subjects will be instructed and frequently reminded NOT to discuss intervention assignments with Drs. Fisher or Stubbs. Results of the electrodiagnostic primary outcome testing will be recorded on coded study data collection forms. After each session, the form will be given to Ms. Corzine to file in subject study binders. This information will remain in the sole possession of Ms. Corzine as hard data, locked in her Research Service office (Bldg 1, room D326). No other participants will have access to this information until the completion of the study, at which time the code will be broken and the findings evaluated by Drs. Stubbs, Collins and Fisher. In compliance with VA Directive 6500, all electronic study data will be stored on a fire-wall secured password-protected IT-managed VA-approved server to prevent loss or corruption of data. At no time will patient study information be stored on computerized mobile storage devices. To maintain blinded assessment, no one but Mrs. Corzine will have access to this information. At the conclusion of the study, the code will be broken and findings evaluated.

**Medical Management:** We realize that subjects within the exercise intervention groups may need to have their diabetic medications adjusted. We hypothesize that exercise intervention will improve peripheral nerve function by enhancing tissue oxygenation in addition to improved blood glucose control. Because physical activity lowers insulin resistance, hypoglycemia may occur during treadmill testing or exercise interventions and up to 48 h afterwards. **Blood glucose will be monitored** before and after each exercise training session. Subjects will not begin treadmill testing or exercise interventions until their blood glucose levels are between 100 and 250 mg/dL. All enrolled subjects will be asked to perform and record daily blood glucose during the study. Forms for recording the daily blood glucose level will be given to the subjects. If needed, the equipment required for blood glucose measurement will be provided. Blood glucose will be measured each time subjects are seen in the Physical Performance Research Laboratory (see below). Adjusting a subject’s medication to better manage blood glucose control is a priority health care issue and not contra-indicated. As previously conducted, immediate management...
concerns are addressed by our collaborator endocrinologist Dr. Emanuele. The subject’s primary care physician is consulted and kept informed to oversee comprehensive clinical management of the study subjects’ diabetes throughout the duration of this project. **A staff cardiologist (Dr. Edwards, Co-Investigator, Staff Physician and Director of Cardiographics) will review all treadmill exercise test electrocardiograms (ECG).** In the event the treadmill ECG is positive, patients will be referred for appropriate follow-up. If the patient has coronary artery disease, unstable angina or other findings that would make it unsafe for he/she to engage in an exercise program, they will be withdrawn from the study. If needed, a cardiologist at the Hines VA Hospital will interpret these tests immediately; a cardiologist is readily available to the Physical Performance Research Laboratory. The subjects’ primary care physician will be aware that their patients are enrolled in the study. A summary of the subject’s response to each exercise training session and incremental treadmill test will be entered in the subjects’ medical record (via computer). When requested more detailed summaries will be provided to the subjects’ physician. In the event that baseline, 12 or 24 week follow-up assessment demonstrates ischemic disease, study staff will work closely with the Hines Cardiology Service and the patient’s primary care physician. Drs. Emanuele and Edwards will not be blinded to this study and will not participate in the data analysis and interpretation of the proposed clinical trial. **Foot problems constitute the primary cause of hospitalization of individuals with diabetes.** All subjects will undergo a detailed foot exam during pre-screening prior to entry into this study as part of our enrollment process. All enrolled subjects will undergo routine foot exams prior to intervention regardless of group assignment and are strongly encouraged to perform daily self foot-exams as part of their educational awareness training. To encourage proper foot care, the subject, a family member, or a caregiver will perform regular foot examinations which includes checking the dorsal and plantar surfaces and between the toes for red or warm spots, swelling, pain, breaks in the skin and blisters. All enrolled subjects will be required to wear well-fitting athletic shoes. Foot examinations will also be performed during intervention training; three times per week during the exercise portion of the protocol. All Physical Performance Research Laboratory staff have attended the podiatry foot clinic and received training in foot examination by the podiatrists at Hines and mechanisms for referral. At the earliest sign of foot problems, the subject will be referred to the Hines Podiatry Section for follow-up.

**Stopping Intervention & Intent-to-Treat Principle:** Subjects are carefully screened at the start of the study in an effort to minimize the need for medical withdrawal. As noted above, the subject’s primary care physician is kept informed throughout the study, and if it is the primary care physician’s judgment that the subject should not continue in the study, the subject is withdrawn. We have withdrawn patients in the past for worsening joint arthritis, new cancer diagnosis necessitating treatment, diagnosis of coronary artery disease at the mid-testing period (as patients become capable of more work, previously undiagnosed coronary artery disease may surface), or unexpected injuries (e.g., car accidents). If a subject is unable to complete the full intervention protocol, the last available electrodiagnostic primary outcome measurement will be used for the analysis. In these cases, the primary analyses will be based on intention-to-treat principles (i.e., all randomized subjects will be included in the analyses). Protocol adherence will be treated as a co-variate to control for subject compliance. The primary analyses will be repeated, restricted to subjects who complete the intervention protocol. Analysis of covariance (see above) will be used to compare the responses between the intervention groups. Regression will then be used to determine whether the observed intervention persists using adjustment for baseline covariates and measures of treatment compliance.

**Incremental Symptom-Limited Treadmill Test:** At baseline, 12 weeks, and 24 weeks, all 100 enrolled subjects will complete a symptom-limited incremental treadmill test to provide the data for the secondary outcome measure of aerobic capacity. The symptom-limited treadmill test will be performed last, after all other study measurements have been completed to ensure that the acute effects of exercise dose not affect the results of these measures. The **treadmill protocol used in this study was developed for individuals with peripheral vascular disease and osteoarthritis.** The initial ramp characteristics (5% grade, 2 mph for the first six minutes) allow for subject acclimation and baseline measurements. Small increases in percent grade (2.5%) and speed (0.3 mph) occur thereafter every two minutes until the subject terminates the test. Metabolic measurements (gas exchange; MedGraphics CPX/D system, St. Paul, MN) will be taken breath-by-breath beginning two minutes before and ending five minutes after exercise. Dr. Collins will supervise the treadmill testing.
A Case system monitor (General Electric) will be used for continuous visual monitoring (Leads II, V1, and V5) and recording ECG. A 12-lead ECG will be taken every minute during all exercise tests. Blood pressure will be determined by the auscultatory technique using a sphygmomanometer, a pregauged adult cuff, and a stethoscope. The first and last Korotkoff sounds will be recorded. Blood pressure will be taken pre-exercise, every two minutes while the subject is exercising, and every minute post exercise until the patient's BP approaches baseline values. Ratings of perceived breathlessness, exertion, and right/left foot pain will be obtained using Borg's ratio scale. Ratings will be taken during the last 30s of each stage of exercise. Prior to each testing period, subjects will be asked to look over the Borg scale. After the subject has indicated that he/she is familiar with the scale, a technician will read aloud the instructions for the determination of perceived breathlessness and exertion while the subject follows on a second copy.

Subject Selection Criteria: Randomized subjects will meet the World Health Organization criteria for diabetes: fasting plasma glucose concentration \( \geq 126 \text{ mg/dL} \) or a plasma glucose concentration \( \geq 200 \text{ mg/dL} \) 2 hr after an oral glucose challenge. \(^{(70)}\) To control for effects of blood glucose management, subjects will have stable blood glucose control as demonstrated by a fluctuation in the glycosylated hemoglobin of no greater than 1% during the previous six months. Subjects will also have clinical findings consistent with length-dependent sensorimotor polyneuropathy, stage N2a \(^{(71)}\) as defined by positive or negative distal sensory symptoms, less than 50% weakness of ankle dorsiflexion, and nerve conduction abnormalities in at least 2 distal nerves. Positive sensory symptoms include aching, burning, and tingling while negative symptoms include loss of feeling with diminished ability to distinguish heat from cold in the feet. Recruitment of eligible subjects will include minorities as well as females whenever possible. Based on previous experience, we anticipate recruitment of approximately 2% female and 30% minorities.

Control or test subjects will be excluded if they present with foot ulceration, unstable heart disease, or co-morbid conditions limiting exercise. Subjects will also be excluded if they have disorders of the central nervous system causing weakness or sensory loss determined by clinical history and neurological examination (Dr. Fisher), have received treatment with medications known to have neuropathy as a prominent side effect including vincristine, vinblastine, cis-platin, and paclitaxel, or have medical conditions that may be associated with neuropathies such as alcoholism (ongoing heavy alcohol use by history), liver disease (abnormal liver function tests), kidney disease (elevated creatinine), toxic exposure (by history), vitamin deficiency (by history as well as clinical signs and symptoms), autoimmune disorders (immunoglobulin abnormalities, studies for collagen diseases), cancer (by history and review of medical record, laboratory studies), or hypothyroidism (increased thyroid stimulating hormone [TSH]).

As part of the evaluation for such conditions, if not done within the previous six months, all subjects will have a CBC, ESR, CRP, ANA, BUN, creatinine, electrolytes, calcium, phosphorus, AST, bilirubin, alkaline phosphatase, B12, TSH, quantitative immunoglobulins, serum protein electrophoresis, and immunofixation. These studies will be performed by the Hines VA Hospital Chemical Laboratories.

Specific Objective A: We will determine the effect of aerobic training, isokinetic strength training, or the combination of aerobic plus isokinetic strength training compared with non-exercise intervention on recovery of peripheral nerve function in age-matched type 2 diabetic Veterans with neuropathy. Exercise intervention is firmly established as an effective strategy for the co-management of the diabetic patient. Exercise has been shown to improve maintenance of blood glucose levels and, in some cases, decreases the need for pharmacologic intervention in subjects with type 2 diabetes.\(^{(18-20)}\) Exercise intervention of 8 weeks or more statistically improves VO\(_{2}\)max in diabetic patients.\(^{(23)}\) Despite a clear benefit of exercise as a co-therapy for the management of diabetes, there remains a pause in the current literature regarding the effectiveness of exercise of any type for the management of established diabetic neuropathy.

Our rationale for anticipating that exercise will improve peripheral nerve function in type 2 diabetics with established neuropathy is based on the following published clinical data: (i) in a one-year study of lifestyle (diet and exercise) intervention, Smith \textit{et al.}\(^{(34)}\) observed a modest improvement in intraepidermal nerve fiber density with decreased neuropathic pain and improved sural sensory responses (ii) improved vascular blood
flow to the peripheral nerves is expected to promote recovery of nerve function by enhancing neural adaptive responses; a beneficial effect of aerobic exercise on neural adaptive responses has been reported (14). (iii) exercise attenuates the development and progression of peripheral neuropathies (72) and (iv) our own preliminary studies suggest that moderate-intensity aerobic exercise modestly improves some measures of peripheral nerve function in type 2 diabetics Veterans. (15; 55) While there remains an uncomfortable pause of clinical studies evaluating the impact of exercise training on recovery of nerve function in diabetic subjects, there is an overwhelming amount of experimental evidence to support a positive effect of exercise on recovery of peripheral nerve function: (v) exercise promotes neuroplasticity by increasing neurotrophins (73-76) and very recently (vi) treadmill and resistance exercise training has been shown to increase axonal regeneration and sprouting after peripheral nerve injury. (77; 78)

It remains possible that the type of exercise is of critical importance to promoting recovery of peripheral nerve function. Muscle strength in symptomatic diabetic neuropathic patients is markedly reduced compared to control subjects and non-neuropathic diabetic patients. (56) This may represent a ceiling to the effectiveness of aerobic exercise one may observe among diabetic subjects. To address this concern, we considered different forms of exercise, such as isokinetic in comparison to isotonic, as a way to maximize the amount of muscle activation per unit of work. (57) As such, isokinetic exercise is known to produce significant muscle strength recovery. Isokinetic resistance training of 39 patients with chronic heart failure significantly improved forearm blood flow, peak VO₂, skeletal muscle strength, and endurance. (58) Isokinetic training also improves muscle strength in some neuropathic patients. Six neuropathic patients undergoing dynamometric isokinetic training demonstrated significant strength improvement within six months of rehabilitation. (59) Ischemic environments resulting from microvascular disease often occur in distal limbs of diabetic subjects and are thought to contribute greatly to peripheral nerve injury. Lower leg vascular conductance measured in 10 subjects following a period of passive arterial occlusion or ischemic exercise was found to be enhanced by isokinetic dynamometry, suggesting improved blood flow. (60) Moreover, isokinetic dynamometry has been safely used to quantitate and grade muscle weakness in diabetic neuropathic patients. (61)

While there are no published data demonstrating effectiveness of isokinetic training on recovery of peripheral nerve function in diabetic subjects, we argue that an exercise program utilizing strength and aerobic training, as proposed in this application, is strongly anticipated to produce measurable and meaningful therapeutic benefits to the diabetic veteran with neuropathy.

i. Type 2 diabetic Veterans with established staged length-dependent sensorimotor polyneuropathy will be randomized to a 12 week program of exercise (aerobic, isokinetic, or the combination) or control (non-exercise) intervention.

Exercise Interventions: Aerobic exercise will consist of treadmill walking. Isokinetic strength promoting leg extensions will be performed on a calibrated Biodex System 3 dynamometer. The use of Biodex machine is proposed as an experimental means of determining the impact isokinetic strength training has on recovery of peripheral nerve function in diabetic neuropathic veteran. Demonstrating effect with isokinetic strength training, or in combination with aerobic training, will be used as a strong rationale for implementing interventions of this type into clinical rehabilitative practice. Subjects randomized to the combined aerobic plus isokinetic strength training will receive isokinetic strength training followed by aerobic treadmill training so that maximal benefits can be gained from the strength program. Patients will be allowed to rest 15-30 minutes between strength and aerobic training with each session ending with a 10 minute cool-down period. Based on prior experience with exercise intervention studies, we anticipate an 80% retention rate within this intervention group. Our sample size for this group includes a 20% attrition rate to compensate for subjects unable or unwilling to complete the 24-week intervention program. Sustainability of interventions will be evaluated by repeated testing at 24 weeks. All subject groups will participate in identical biweekly diabetes-related Health Promotion Educational seminars designed to normalize participation.

Subjects randomized to aerobic, isokinetic, or the combination of aerobic plus isokinetic exercise group will be trained in the Physical Performance Laboratory three times weekly. A 10 minute warm-up consisting of stretching...
and flexibility exercises will precede all training sessions. Exercised training duration and intensity will progress as listed in the following table:

<table>
<thead>
<tr>
<th>Weeks 1-2</th>
<th>Strength Training</th>
<th>Aerobic Training</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 sets, 10 repetitions, 1 min rest between sets</td>
<td>25 min at 60-70% VO₂ peak; 5 min 71-80% VO₂ peak</td>
</tr>
<tr>
<td>Weeks 3-4</td>
<td>4 sets, 10 repetitions, 1 min rest between sets</td>
<td>25 min at 60-70% VO₂ peak; 10 min 71-80% VO₂ peak</td>
</tr>
<tr>
<td>Weeks 5-6</td>
<td>5 sets, 10 repetitions, 1 min rest between sets</td>
<td>25 min at 60-70% VO₂ peak; 15 min 71-80% VO₂ peak</td>
</tr>
<tr>
<td>Weeks 7-8</td>
<td>6 sets, 10 repetitions, 1 min rest between sets</td>
<td>25 min at 60-70% VO₂ peak; 17 min 71-80% VO₂ peak</td>
</tr>
<tr>
<td>Weeks 9-10</td>
<td>6 sets, 10 repetitions, 1 min rest between sets</td>
<td>20 min at 60-70% VO₂ peak; 20 min 71-80% VO₂ peak</td>
</tr>
<tr>
<td>Weeks 11-12</td>
<td>6 sets, 10 repetitions, 1 min rest between sets</td>
<td>17 min at 60-70% VO₂ peak; 20 min 71-80% VO₂ peak</td>
</tr>
</tbody>
</table>

Subjects randomized to the exercised intervention groups will be given Digiwalker pedometers to serve as a motivational tool and to monitor daily physical activity. **Changes in fitness will be quantitated by peak oxygen uptake and exercise tolerance during the incremental treadmill exercise tests performed at 12 & 24 weeks.** The repeated exercise tests will also serve as an indicator of the sustainability of exercise volume.

During each strength, aerobic, or combined training session pre-exercise and post-exercise heart rate (HR), blood pressure (BP), ratings for perceived discomfort/pain for right (RPPR) and left (RPPL) legs and effort (RPE) will be recorded. Frequent measures of HR and RPE will serve as indicators of exercise strain. Body weight will be measured every other week.

The rehabilitation (clinical) objective of the training program will be to increase participants’ aerobic capacity to ≥ 6 METs, a level sufficient to afford the cardiorespiratory reserve (fitness) for performing normal activities of daily living.\(^{(79, 80)}\)

**Conventional Care (Health Promotion Education) Intervention:** The conventional care and Health Promotion Education intervention will consist of 12 clinical visits over 24 weeks. The clinical nurse coordinator (Mrs. Corzine, R.N.) will conduct the educational clinical visits. During these visits, subjects’ blood glucose for the previous two weeks will be retrieved from home glucometers. Their current blood sugar will be checked with POC glucometer and vital signs at rest determined. **ALL subjects will participate in a series** of twelve 45-minute skill building sessions. Initial assessments of personal lifestyle habits will be completed. These include nutrition (logs of food intake, nutritional value, shopping patterns, cooking/restaurant habits and food budget), body hygiene, especially foot care and podiatry needs) and consultations needs. Food lab ‘hands-on’ preparation sessions will be conducted. Classes will also incorporate the importance of medication management, blood sugar monitoring, graphing patients glycated hemoglobin values over time and the interaction of these with food/fluid intake and daily activities. Patients will also access the internet and obtain current best source information on Diabetes and other topics of interest. The clinic/educational visits should not affect the patients’ neuropathies. The non-exercised control intervention group receiving conventional care will be compared with the exercised intervention groups receiving conventional care plus strength, aerobic, or combined training. Actical accelerometers will be used on all study participants to monitor variations that might occur in the exercised patterns of the control subjects, and any change in fitness will be assessed by peak oxygen uptake and exercise tolerance during the incremental treadmill exercise tests performed at 12 & 24 weeks.
The effects of aerobic training, isokinetic strength training, or the combination of aerobic plus isokinetic strength training compared with non-exercise intervention on recovery of peripheral nerve function will be statistically determined from baseline and follow-up testing using a battery of qualitative and quantitative assessments that include clinical history, physical and neurological examination, electrodiagnostic primary outcome measures, Quantitative Sensory Testing, completion of Total Neuropathy Score, visual analogue pain scale, quality of life (SF-36V Health Survey), peak torque (Biodex), peak oxygen uptake (incremental symptom-limited treadmill test). Actical accelerometers will be used to quantitate differences in everyday physical activity between exercised and non-exercise interventions.

Initial Evaluation: Consented and enrolled subjects will complete baseline evaluation prior to exercise/non-exercise interventions that includes a clinical history, physical (including blood pressure monitoring) and neurological examination, laboratory studies (including fasting blood glucose, HbA1c, lipid profile), electrodiagnostic studies, Quantitative Sensory Testing (QST) as well as completion of the Total Neuropathy Score, visual analogue pain score, the SF-36V Health Survey, and an incremental symptom-limited treadmill test (as described above). To avoid inter-examiner variability and maximize neurophysiologic test/retest reliability, the same neurologist (Morris Fisher, M.D.) will conduct all clinical and neurological examinations and electrodiagnostic studies. Dr. Fisher will be blinded to the subjects exercise status and subjects will be instructed not to discuss their group assignment with Dr. Fisher. If the baseline incremental symptom-limited treadmill test is positive (i.e., any factors are identified that point to undiagnosed or untreated heart disease) the subject will be withdrawn from the study. A complete history will be obtained concentrating on medical conditions associated with neuropathies, altered sensations (hypesthesias, paresthesias, dysesthesias), and weakness. The physical examination will screen for associated medical conditions as well as for coexistent neurological problems. Careful evaluation will be made of the findings for a peripheral neuropathy; namely strength and muscle bulk, the presence or absence of reflex, and sensory loss (position, vibration, light touch, pain, and temperature).

Whereas electrodiagnostic findings constitute the primary outcome measure of this study (see below), secondary outcome measures of exercise intervention include changes in aerobic capacity, peak torque, quality of life measures including pain perception and health care use (medications (type and dosage), number of diabetes-related clinical visits, number of diabetes-related hospital admissions and length of stay, number of diabetes-related ER visits). Changes in primary outcome findings will be statistically compared (correlations) with the various secondary measures to determine effect of exercise intervention on quality of life. Our previous experience suggests that improved peripheral nerve function significantly enhances quality of life measures in diabetic subjects. Identifying a correlative statistical relationship between primary and secondary outcome measures, as proposed, will be used as a strong rationale for supporting exercise intervention in the management of diabetic neuropathy in affected Veterans. The clinical history and secondary neurologic findings will be quantitated using previously established and validated measures. Relative neurologic deficits will be quantitated using the Total Neuropathy Score, TNS and NSS. Disability will be graded on a scale of 0 to 5 using a modified Rankin Scale. (82) The specifics of the scoring are shown in Appendix A & B. Health related quality of life will be measured using a SF-36V Health Survey. (83) Pain perception will be evaluated using a validated analogue visual pain scale. (84) Level of chronic physical activity will be quantitated using activity counts from Actical accelerometers. Biceps, triceps, brachioradialis, patellar and Achilles’ phasic myotatic (“deep tendon”) reflexes will be tested bilaterally in every patient. Diminished reflexes will only be considered abnormal if asymmetric or if different from a previous examination. The subject will be scored 1 point for each diminished reflex and 2 points for an absent reflex for a maximum possible score of 20. This scoring is similar for both the TNS and NSS scores. Vibration, proprioception, pinprick and light touch will be evaluated in every subject. For the NSS, each modality will be given a numerical score of 0 to 5 depending on the degree of sensory deficit. The scores will be added so that a patient could have a maximum score of 20. This is similar to the Sensory Function Score in the TNS. The TNS scale is, however, skewed somewhat distally but also records changes in temperature sensation. Sensory perception will also be assessed by the ability to feel 1 and 10-gram filaments applied to the left large toe and index finger (Sensory Testing Systems, Dallas).
**Electrodiagnostic Primary Outcome Measures:** Electrodiagnostic findings constitute the primary outcome measures of this study and will be used to define the recovery of peripheral nerve function. Limb temperature will be standardized in this study by using a surface temperature probe integrated with the EMG equipment. Consistent with accepted recommendations, correction factors will NOT be used. The limb surface temperature will be continuously displayed to allow for moment-by-moment monitoring and minimization of variations in limb temperature within and between subjects. Surface temperatures in a limb will be maintained at the same temperature during a subject's sequential nerve conduction studies. For this study, the temperature probe will be placed distally on the leg at the dorsal surface of the ankle and distally on the volar surface of the forearm at the wrist crease. Prior to neurophysiologic evaluation, limbs will be warmed (heating lamp) if the surface temperature is less than 32°C in the leg or less than 33°C at the wrist. If needed, continuous moist heat will be applied to the limb to maintain limb temperature using a hydrocollator heating unit with 4 standard size (10x12 inches) moist heat steam packs. We will measure the following: (i) sensory nerve action potential (SNAP) conduction velocity and amplitude in at least one sural and one median and ulnar nerve; (ii) compound muscle action potential (CMAP) conduction velocity, distal motor latency, and amplitude in at least one tibial, peroneal, median and ulnar nerve; and (iii) F-waves from at least one tibial and ulnar nerve. CMAP amplitudes will be measured from baseline to the negative peak, and conduction velocities in the forearm or leg will be calculated by dividing the measured distances (millimeters) between proximal and distal stimulation sites by the difference between proximal and distal onset latencies (milliseconds). F-wave latencies will be recorded as minimal and mean values following 20 stimuli. F-wave recordings will also be obtained from the abductor hallucis muscle stimulating the tibial nerve at the ankle using a prefabricated stimulating and recording array (NC-stat). These recordings will include correction for age, temperature, and height and will be analyzed using a centralized database containing approximately 130,000 validated electrodiagnostic studies providing an unparallel degree of statistical power with the intent to standardize and enhance the sensitivity of these primary outcome measures. SNAP amplitudes will be measured from the start of the initial negative deflection to the negative peak. Sensory nerve conduction velocities will be calculated by dividing the distance between the stimulating and recording electrodes by the onset latencies. Electrodiagnostic measures of autonomic function will not be evaluated. Normative data appropriate for age range of subjects enrolled in this study are available (Appendix C). F-wave norms are based on regression equations that include variables for both age and limb length.

**Quantitative Sensory Testing (QST):** QST (Computer Assisted Sensory Evaluator [CASE IV System], WR Medical Electronics, Stillwater MN) is a sensitive quantifiable method for evaluating sensory nerve function. These data will supplement information obtained from clinical and electrodiagnostic examination. We will quantify vibration (large fiber) as well as cold and heat-pain (small fiber) thresholds. The same technician will conduct all QST studies. The technician will be blinded to the subjects’ exercise and clinical/electrodiagnostic status and subjects will be instructed not to discuss their group assignment with the technician. A 4-2-1 methodology will be used. Alternatively, a forced choice paradigm will be employed. Abnormal findings will be defined as outside the 95th percentile of normal limits for gender and age. **Total Neuropathy Score, TNS:** The total neuropathy score is a validated measure of peripheral nerve function and is used as an end point for clinical trials of peripheral neuropathy. The modified Rankin scale is a validated measure of disability used as a primary endpoint in clinical trials of acute stroke. The modified Rankin scale describes six grades (0-5) of disability (grade 5, severe disability and bedridden; grade 0, no symptoms). Interrater reliability meets criteria for satisfactory clinical assessment (weighted kappa (with quadratic disagreement weights) is 0.91). **SF-36V Health Survey:** Modified from the SF-36, this survey is tailored and validated for the veteran population. The SF-36V is comprised of 8 subscales, all of which have demonstrated high levels of internal consistency and discriminate validity when administered to groups of medically stable individuals. The eight subscales are: physical function, general health, role physical, role emotional, mental health, body pain, vitality and social functioning. The survey will enable monitoring of the subjects’ sense of their own well-being, critical for determining whether exercise in Veterans with diabetic neuropathy can produce a meaningful

*Stubbs, 14*
improvement in a patient’s perception of his/her own health. **Visual Pain Scale**: Although we do not anticipate exercise intervention to be painful, subjects will be continuously evaluated using a validated visual analogue pain scale as previously described.\(^{(64)}\) **Peak Torque**: All subjects will receive strength testing at baseline, 12 weeks, and again at 24 weeks for determination of isokinetic leg extension peak torque of both legs at a velocity of 90°/s on a calibrated Biodex System 3 dynamometer as previously described.\(^{(68)}\) Subjects will be in a seated position with a restraining strap over the pelvis and trunk, and the contralateral leg free of the stabilization bar. Three sub-maximal warm-up trials will precede three maximal muscle actions with the highest non-gravity-corrected peak torque scored. This method has been reported to yield an intra-class reliability correlation for isokinetic leg extension peak torque ranging from 0.84 to 0.97; \(p>0.05\) between test-retest values at muscle action velocities ranging from 60-360°/s.\(^{(88)}\)** Peak VO\(_2\):** Oxygen uptake (VO\(_{2peak}\)) will be determined using the open circuit method. Subjects will breathe through a low resistance MedGraphics preVent pneumotachometer inhaling ambient air and exhaling directly into the collection device. Expired gases will be routed through a permapure line to a MedGraphics CPX/Max/D™ System for breath-by-breath analysis. Expired gases will be analyzed for concentrations of CO\(_2\) using a nondispersive infrared technique and for concentrations of oxygen using a Zirconium analyzer. Prior to and after each test, the analyzers will be calibrated with reference gases and room air. **Daily Physical Activity:** Daily physical activity is defined as the totality of voluntary movement produced by skeletal muscles during everyday functioning.\(^{(89)}\) Daily physical activity can include activities performed through the course of the day, such as making a bed or gardening. It also includes exercise (planned, structured, and repetitive body movement to maintain or improve physical fitness).\(^{(89)}\) Physical activity will be objectively monitored using accelerometer at the waist (Mini Mitter Co., Inc., Bend, OR, Actical). The accelerometer will reflect whole body activity. The Actical is small (28 x 27 x 10 mm) lightweight (1.5 oz) accelerometer that contains a single vertical axis piezoelectric bender element that generates an electrical signal proportional to the force acting on it. Acceleration detection ranges in magnitude from 0.05 to 3.2 Gs, and the frequency response ranges from 0.25 to 2.5 Hz. Motion outside normal human movements is rejected by a bandpass filter. The acceleration/deceleration signal is digitized by an analog to digital converter and numerically integrated over a pre-programmed epoch interval. At the end of each data collection interval, the integrator is reset. The monitor is programmed for start time and data collection interval, and data are retrieved for analysis via a PC interface and software provided with the accelerometer. It is capable of recording up to 45 days of continuous data in one-minute epochs. Since physical activity is known to vary based on the day of the week due to differences in work and leisure activity profiles,\(^{(90)}\) subjects will wear the accelerometers for 7 consecutive days at baseline (before training), 12 weeks (after training), and 24 weeks (sustainability measure).

**Specific Objective B:** We will determine the effect of aerobic training, isokinetic strength training, or the combination of aerobic plus isokinetic strength training compared with non-exercise intervention on muscle tissue oxygenation in age-matched type 2 diabetic Veterans with neuropathy. The short-term goal of this study addressed in **Specific Objective A** is to determine whether an isokinetic strength, aerobic, or combined strength plus aerobic training program can improve recovery of peripheral nerve function in type 2 diabetic Veterans with neuropathy. An intermediate goal is to determine how individual or combined exercise interventions actually improve peripheral nerve recovery. We hypothesize that recovery of peripheral nerve function occurs by neural adaptation secondary to exercise-improved muscle tissue oxygenation.

In our previous work with type 2 diabetic Veterans with neuropathy, we found that aerobic exercise produced measurable, and in some cases significant \((p<0.03)\), improvement over baseline in motor and sensory nerve conduction electrodiagnostic studies.\(^{(15)}\) A 24-week program of structured aerobic exercise produced measurable improvement in some neurologic outcome measures. Vibratory sensation threshold levels in exercised individuals, compared with non-exercised sedentary subjects, were modestly but significantly lowered \((p=0.006)\), suggesting improved large-fiber function. Significant \((p=0.042)\) increases in distal motor nerve conduction amplitudes were observed in subjects receiving exercise. These findings provide for the first time quantitative evidence that exercise training improves peripheral nerve function in type 2 diabetic veterans.
Pathological changes in endoneurial blood vessels have long been recognized as a characteristic feature of diabetic neuropathy. Endoneurial blood flow, along with oxygen diffusing capacity and tension, are decreased in the diabetic nerve, supporting an hypoxic/ischemic thesis of nerve injury. Interventions which improve endothelial function and enhance endoneurial blood flow (exercise intervention) are anticipated to facilitate recovery of or preserve peripheral nerve function in the diabetic patient.

The effect of the three exercise interventions on muscle tissue oxygenation will be determined from baseline and at 12 week and 24 week follow-up by measuring limb oxygenation of the quadricep (during leg extensions) and tibialis anterior muscle (during treadmill testing) of all study groups as quantitated by non-invasive infrared spectroscopy using an InSpectra Tissue Spectrometer.

Exercise-facilitated recovery of peripheral nerve function in previous subjects is postulated to have occurred due to a decrease in tissue hypoxia. We will directly test this thesis by quantitating tissue oxygenation of our subject population by measuring muscle tissue oxygenation levels. In our hands, the InSpectra Tissue Spectrometer successfully quantitated tissue oxygenation from pre-exercise ($\text{StO}_2 = 92\%$), to peak exercise ($\text{StO}_2 = 49\%$), and recovery ($\text{StO}_2 = 91\%$). Interestingly, in some subjects $\text{StO}_2$ levels at peak of exercise are non-responsive and remain at baseline saturation (>90%). These subjects may be experiencing indolent autonomic neuropathy. Conversely, other subjects peak $\text{StO}_2$ levels drop below 5% saturation, possibly reflecting previously undetected large vessel disease.

**Muscle tissue oxygenation** (oxygen saturation of hemoglobin; %StO$_2$) and aerobic power ($\text{VO}_2 \text{ mL kg}^{-1} \text{ min}^{-1}$) will be measured in the quadricep (during leg extensions) and the tibialis anterior (during walking) muscle groups of all subjects using near infrared spectroscopy (InSpectra Tissue Spectrometer, Hutchinson Technology, Hutchinson, MN). These studies will be performed throughout each incremental symptom-limited treadmill test. The InSpectra Tissue Spectrometer is a non-invasive monitoring system that measures an approximated value of percent hemoglobin oxidation in tissue (%StO$_2$) based on spectrophotometric principles. The spectrometer measures tissue absorbance values at wavelengths between 650-900 nanometers. The volume of tissue measured by the InSpectra Tissue Spectrometer is directly related to the distance between the illumination and the detection fibers. The sensor probe will be placed on the quadricep or the anterior tibialis muscle of the same limb used for determining peripheral nerve function. This product is routinely used by this laboratory and has proven to be a reliable measure of $\text{StO}_2$. The spectrometer successfully tracks minute-by-minute tissue oxygenation from pre-exercise, to peak exercise, and recovery. $\text{StO}_2$ measures will be taken before, during and post exercise until measures approach the pre exercise values.

**Statistical Analysis Plan**

In response to reviewer’s concerns, we addressed statistical concerns with this program by recruiting the services of James Sinacore, Ph.D. (Associate Professor of Preventative Medicine and Epidemiology and biostatistician, Loyola University Chicago). Dr. Sinacore has generously agreed to serve as lead statistician of this study. He will be responsible for the statistical analyses of all collected study data. The statistical analytical sections of this revised application, including determination of subject sample size, have been substantially revised per the advice of Dr. Sinacore.

All data will be entered in SPSS 15 for Windows (SPSS, Inc., Chicago, IL). Results will be expressed as mean ± SEM of (n) observations. To directly test the hypothesis that a combined influence of aerobic and isokinetic strength training will enhance recovery of peripheral nerve function, measures of conduction velocity and amplitude will be analyzed by way of a 2 x 2 factorial analysis of covariance followed by a Bonferroni’s multiple comparison post-hoc analysis according to the following scheme:
Data collected at 12 weeks will be analyzed, using baseline measurements as a covariate. This will be repeated with the data that are collected at 24 weeks. In both analyses, primary interest will be in the combined aerobic training plus isokinetic strength training interaction. We hypothesize that patients with the combined exercise program will experience the best outcome. Although data will be collected across three time periods (baseline, 12 weeks, and 24 weeks), we have chosen to not employ a repeated measures design. There are two reasons for this: (i) the proposed study is designed to determine the combined influence of aerobic and isokinetic training on recovery of peripheral nerve function, which we believe is best achieved with a factorial design and (ii) our previous experience identified baseline differences among groups of diabetic neuropathy subjects. These group differences will go uncontrolled using a repeated measures design, but can be controlled statistically with analysis of covariance. Therefore, the aerobic plus isokinetic strength training interaction for our primary electrodiagnostic measures will be observed at 12 weeks, controlling for baseline values. This will be done again for the data collected at 24 weeks. A 2 x 2 factorial analysis of covariance also will be conducted with secondary outcome measures such as changes in aerobic capacity, peak torque, pain perception and health care use. Again, data collected both at 12 and 24 weeks will be analyzed using baseline measurements as a covariate. These analyzes will allow us to observe the extent to which the secondary measures dovetail with the primary electrodiagnostic measures. In addition, primary outcomes will be correlated with secondary outcomes in order to assess the association of recovery of peripheral nerve function and quality of life. Partial correlation coefficients will be computed at 12 weeks, controlling for baseline values. This will be repeated for the data collected at 24 weeks.

**Sample Size Estimate:** The requisite sample size for the proposed study has been based upon the primary outcome measure endpoints of conduction velocity and amplitude. In our preliminary studies (see Table 2), we present data from peroneal nerve conduction velocity and amplitude for sedentary and aerobic (PoleStriding) exercise study groups. We use this information for the proposed study. However, we have not conducted strength training studies and, as such, have had to estimate values that we believe are realistic outcomes. The table below is an estimate of the conduction velocity findings for the proposed study.

<table>
<thead>
<tr>
<th>Isokinetic Strength Training</th>
<th>No</th>
<th>Yes</th>
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<tbody>
<tr>
<td>Aerobic Training</td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>38 m/s</td>
<td>39 m/s</td>
</tr>
<tr>
<td>Yes</td>
<td>39 m/s</td>
<td>43 m/s</td>
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Using these estimates we have computed that the effect size for the aerobic plus isokinetic strength training interaction is 0.36. From this, computations indicate that 17 subjects per group will provide 80% power with analysis of covariance to detect an effect size of that magnitude using a 0.05 alpha level. In terms of conduction amplitude, the following table is an estimate of the findings for the proposed study. Again, data from our preliminary studies are incorporated.

<table>
<thead>
<tr>
<th>Isokinetic Strength Training</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobic Training</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.9 mV</td>
<td>1.9 mV</td>
</tr>
<tr>
<td>Yes</td>
<td>2.4 mV</td>
<td>4 mV</td>
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</table>
Using these estimates we have calculated the effect size for the aerobic training-by-isokinetic strength training interaction to be 0.25. Subsequently, computations indicate that greater than 20 subjects per group will needed to provide 80% power with analysis of covariance to detect an effect size of that magnitude using a 0.05 alpha level. Given the variability in electrodiagnostic findings between our elderly study subjects, inherent limitations in statistical Power are unavoidable. Smaller sample sizes are calculable using within person changes. However, experience gained from our previous funding cycle clearly demonstrates that some electrodiagnostic measures, such as peroneal motor amplitude responses, markedly and significantly increase with aerobic training in diabetic subjects (Table 2, Preliminary Studies). We hypothesize a larger effect size with the addition of isokinetic strength training which will yield more Power to these analyses using a subject group size of 20. During our previous funding cycle, four of twenty-one (19%) subjects randomized to longitudinal exercise withdrew from study participation. In anticipation of a similar attrition rate, five additional subjects per group will be enrolled, totaling 100 subjects randomized to the four groups. Delays in recruiting during the last funding period have been addressed and resolved. Using the large established pool of recruits, we respectfully argue that our ability to recruit 100 subjects into this 24-week study over a 4-year period is realistic largely because: (i) the proposed time commitment is considerably less than our previously funded application (6 months vs. 18 months) and (ii) we have established a unique data base of study-qualified subjects from which to recruit.
DESCRIPTION OF RESEARCH BY INVESTIGATOR

PRINCIPLES CONCERNING RESEARCH: You are being asked to take part in a research project. It is important that you read and understand these principles that apply to all individuals who agree to participate in the research project below:

1. Taking part in the research is entirely voluntary.

2. You may not personally benefit from taking part in the research but the knowledge obtained may help the health professionals caring for you better understand the disease/condition and how to treat it.

3. You may withdraw from the study at any time without anyone objecting and without penalty or loss of any benefits to which you are otherwise entitled.

4. If, during your participation in the research project, new information becomes available concerning your condition (disease) or concerning better therapies which would affect your being in the research project, your doctor will discuss this new information with you and will help you make a decision about continuing in the research.

5. The purpose of the research, how it will be done, and what your part in the research will be, is described below. Also described are the risks, inconveniences, discomforts, and other important information, which you need to make a decision about whether or not you wish to participate. You are urged to discuss any questions you have about this research with the staff members.

PURPOSE:
You have been asked to participate in this Research Project because you have diabetes mellitus. The purpose of this research study is to investigate whether exercise will be beneficial as a treatment for nerve dysfunction in diabetes. Illness of the peripheral nerves (a neuropathy) is common in diabetes and may be present even if you do not have symptoms of a neuropathy. The disorder of nerves in diabetes may produce numbness, pain, or weakness. As such, preventing or stopping the progress of a neuropathy is important in the management of diabetes. You will not be entered into the study if you have unstable heart disease or other medical conditions limiting exercise including a severe pain in the calf muscles (leg claudication) nor if you have factors predisposing you to foot ulcers. This study is sponsored by the Department of Veterans Affairs and the Edward Hines, Jr. VA Hospital. A total of 100 patients will participate in this study at Hines.

The duration of this study is 4 years. Your participation in this study will be limited to 24-weeks (one-half year).

PROCEDURES:
When entered into this study, a sample of your blood will be drawn by the Hines VA Hospital Chemical Laboratories and you have a standard clinical examination and electrodiagnostic evaluation performed as part of routine medical care. You will be asked to complete questionnaires relating to any symptoms and disability due to a neuropathy. Your general health and well-being and your level of physical activity will be assessed. You will also be asked to look at a chart to define the level of any pain. Electrodiagnostic examinations are routine medical procedures that evaluate the normality or abnormality of the nerves in the...
arms or legs. These studies involve placement of metal recording electrodes on your skin and stimulating your nerves with low levels of electric current. You will also have a quantitative sensory examination performed which evaluates your ability to sense vibration, cooling, and heat-pain. This examination involves placement of a vibratory station or cooling/heating block on your foot and stimulating your nerves with low levels of vibration or small decreases/increases in temperature. You will also have the oxygen tension in one of your legs measured as part of this research project using equipment that is about the size of an electrode which will be placed on your shin or thigh of one leg. All these procedures will be repeated at 12 weeks and again at 24 weeks during the study.

If you qualify and are randomized into this study, you will be asked to voluntarily undergo a biopsy procedure on your lower leg. A small sample of your tissue the size of a pencil erasure will be sent for analysis (Therapath Neuropathology, New York, New York) to determine the presence of small fiber neuropathy. This minor surgical procedure will be performed by an experienced skilled Neurologist and involves aseptic removal of a small (3 mm) amount of skin the size of a small pencil eraser. This procedure will be repeated once more at 12 weeks. Your sample will be destroyed after analysis.

If you are suspected of having autonomic neuropathy, you may also have a separate test that determines how well you sweat. This test involves placement of a plastic chamber on your forearm, leg, or foot. The chamber contains a drug that will make you sweat. A low level of electric current will be applied to your skin to start the test. This test will be performed at the time you are randomized and again repeated at 12 weeks.

As part of the research project, you will be entered into an educational program. In addition, you may be assigned to a carefully monitored 12-week program of walking or strength-training exercise or a combination of both.

Exercise Program: If entered into one of the treadmill exercise programs, well fitting athletic shoes will be provided. Your feet will be frequently examined for the presence of foot ulcers. You will also be instructed on how to properly examine your own feet for such problems. The exercise training consists of either vigorous walking on a treadmill, leg extension strength training, or both. The treadmill walking program will consist of supervised training three times per week lasting 30-45 min for a total of 12 consecutive weeks. The strength training program will consist of supervised training for a total of 12 consecutive weeks and involve three to six sets of 10 repetitions each of leg extension exercises performed on a special machine called a dynamometer that controls the speed at which you can extend your leg. If you are assigned to the combined program, you will first undergo leg extension strength training followed by a 15-30 minute rest period before treadmill walking. Each session ends with a 10 minute cool-down period.

You should continue taking all your medications as advised by your primary care provider currently caring for you. In addition, you will be asked to complete two treadmill exercise tests at entry and one treadmill exercise test each at 12 weeks and again at 24 weeks to evaluate your heart. During the treadmill test, you will begin walking at 1.8 miles per hour with no incline. Every 30 seconds there will be a slight increase in speed or incline making it harder for you to walk. You will be expected to walk until you feel that you cannot continue or the investigator stops you.

During all exercise tests your heart’s response to exercise, blood pressure, rating of perceived leg pain and effort (how hard you are working) will be measured. The amount of oxygen your body is using while you are exercising will also be measured. Measuring how much oxygen you are using requires that you breathe through a special mouthpiece or facemask while exercising. Although somewhat bulky and unnatural, the mouthpiece will not restrict your ability to breathe. Ten electrodes will be attached firmly to your body using adhesive discs and tape to monitor your heart rate. During all testing, staff will be present to monitor and answer your questions.

Your regular primary care provider will continue to manage your diabetes. You will be requested to perform and record point of care blood sugar tests. If not done as part of your regular diabetic management, your glycosylated hemoglobin will be checked at entry and every 3 months while you are in the study.
primary care provider will receive regular reports about your condition, and the physicians and exercise physiologists in the study will monitor you frequently. The exercise physiologists will also examine your feet at each laboratory visit. During the exercise portion of the study, you, a family member, or your caregiver will also be asked to examine your feet weekly.

Educational Program: You will also be asked to complete 12 educational visits over 24 weeks. During these visits, you will have your blood glucose and vital signs measured at rest. You will be expected to participate in a series of twelve 45-minute skill building discussion seminars addressing a variety of health promotion topics including the impact of stress on diabetic health, stress management in the diabetic, diabetes and smoking, healthy eating, vaccination against the flu, current topics and using the internet to access accurate health information. To monitor your level of physical activity, you will be required on three separate occasions (at the start of the study, at 12 weeks, and again at 24 weeks) to wear, for a period of one week at a time, a small unobtrusive device on your ankle that is a microprocessor-controlled step counter.

You may choose to withdraw from the study at any time. The researchers may also require that you withdraw if after screening studies, it is found that you do not qualify or a medical condition arises or is discovered that would make it dangerous for you to continue. If you choose to withdraw, or are required to withdraw, the researchers will discuss alternate treatment of your condition.

RISKS:
The risks associated with participation in this study follow.

1) Finger stick testing of blood glucose is standard procedure for managing blood glucose. There is temporary discomfort with insertion of the lancet.

2) Electrodiagnostic and sweat studies involve electrical stimulation of nerves. Although there is an electric-like sensation and may be some discomfort, the studies are well tolerated. The only known effects are temporary discomfort.

3) When testing your ability to feel heat, you may feel a brief moment of discomfort.

4) A skin punch biopsy is a standard procedure which has been performed a great many times without known ill effects. There may be slight temporary discomfort associated with the skin removal. As with any such procedure, there is always the risk, even if remote, of bleeding and/or infection.

5) Patients with diabetes have an increased risk of foot ulcers. This type of aerobic exercise, the availability of well fitting shoes and frequent foot examinations are used to reduce this risk of foot ulcers. If at any time during the study there is a question of foot ulceration, you will be asked to stop exercising and will be referred for appropriate care.

6) Preparation for electrode placement for the ECG involves rubbing the skin with alcohol or fine sandpaper and acetone. This may produce a mild skin irritation. It may be necessary to shave a small amount of hair from the areas where the electrodes are placed which may also cause skin irritation or discomfort.

7) An exercise test requires you to work hard. Occasionally, a person may experience abnormal high blood pressure, nausea, muscle soreness/injury, fainting, changes in the heart rhythm and, in very rare instances, heart attack, stroke, or death. A cardiologist and emergency services are immediately available where the exercise testing is performed. Your exercise testing when entering the study will
include evaluation for heart problems that might pose a risk for your participating in this project. In the event a problem is identified, you will be referred for appropriate follow-up. Your physician will be informed as to your enrollment into this study.

8) During the treadmill test, you will be required to breathe through a special mouthpiece while exercising. The mouthpiece will not restrict your ability to breathe, but may feel somewhat bulky, restrictive, and unnatural. Your mouth will become very dry and you may develop a sore throat. If you have sensitive gums or other dental concerns, the mouth piece may be discomforting.

9) During treadmill walking there is the possibility of falling, muscle injury, and fracture. Testing and training will be stopped at the first sign of any serious symptoms.

10) Exercise should improve your glucose control. With this, your blood glucose may decrease. Although rare, hypoglycemia (low blood sugar) with symptoms such as dizziness and sweating may develop. Particularly, at the start of the exercise program, you may experience muscle aches and pains. Hypoglycemia may be treated by eating and may require adjustment of your diabetic medication. The muscle discomfort should usually be temporary and helped by mild pain relievers. If there should be any questions about these issues or any others related to your exercise, the physicians involved in the study will be available to answer your concerns.

11) There are no psychological, financial, social risks associated with this study. There is a possible risk of loss of confidentiality or privacy. However, any information obtained about you will be treated as confidential and will be safeguarded in accordance with the Privacy Act of 1974. Information published or presented about you will be in a form that does not identify you.

If any significant new findings develop during the course of the research regarding the treatment of your condition or which may impact on your decision to continue to participate, the investigator will discuss them with you.

**BENEFITS:**
There are no direct benefits to you from your participation in this research study. However, the knowledge gained from this study may provide new knowledge that may benefit people with Diabetes and illness of the peripheral nerves.

**ALTERNATIVES:**
There are no known alternatives for evaluating the effects of exercise in the neuropathy of diabetes. You may choose not to participate in this study.

**STUDY WITHDRAWAL:**
You do not have to take part in this study and refusal to participate will involve no penalty or loss of rights to which you are entitled. You may withdraw from this study at any time without consequences or loss of VA benefits. You may be withdrawn from this study at any time at the discretion of the Principal Investigator (i.e. health issues, unwilling or unable to follow study procedures). In the event a medical concern prevents you from continuing in this study, you will be referred for appropriate follow-up. Your primary care provider will be informed as to the medical concern preventing your continuation in this study.

**CONFIDENTIALITY:**
Any information obtained about you in this study will be treated as confidential and will be safeguarded in accordance with the Privacy Act of 1974. Information published or presented about the results of the study will be in a form that does not identify any particular participant. In order to comply with federal
regulations, records identifying you may be reviewed by the members of the research team, the Department of Veterans Affairs, authorized representatives of the institutional review board, the Food and Drug Administration, the Office for Human Research Protection or the Government Accounting Office. By signing this document, you consent to such inspection.

FINANCIAL COMPENSATION:
If entered into the study, you will be paid in cash at the completion of each session: $10 for each supervised training or educational session as well as $50 for each clinical evaluation (i.e., at the beginning of the study and at 12 weeks and 24 weeks). Maximum compensation is $630 if all study requirements are completed. You will receive IRS Form 1099 documenting this compensation. Please note, total payments of $600.00 or more per calendar year (from January 1st through December 31st) from any one source requires to have an IRS Form 1099-MISC issued, and you will need to report this on your income tax return.

RESEARCH SUBJECT COSTS: You will not be required to pay for medical care or services received as a participant in a VA research project except as follows: some veterans are required to pay co-payments for medical care and services provided by VA. These co-payment requirements will continue to apply to medical care and services provided by VA that are not part of this study.

RESEARCH-RELATED INJURIES:
According to the federal regulations, (Title 38 Code of Federal Regulations (CFR) 17.85), the VA will provide necessary medical treatment to you as a research subject if you are injured by participation in this research project. Except in limited circumstances, this care will be provided at this VA facility. This requirement does not apply to treatment for injuries that result from non-compliance by you with study procedures. The Department of Veterans Affairs does not normally provide any other form of compensation for injury. You have not released this institution from liability for negligence.

RESEARCH SUBJECT’S RIGHTS:
You have read or have had read to you all the above information. _________________________ has explained the study to you and has answered all your questions. The risks or discomforts and possible benefits and the alternatives of the study have been explained to you.

The results of this study may be published but your identity and records will not be revealed unless required by law.

In case there are any medical problems, complaints, or if you have questions about the research, you can call Dr. XX at 708-202-XXXX during and day and Dr. YY at 708-202-ZZZZ after hours. Additionally, if you have any questions about the research, your rights as a research subject or other concerns, you can contact the Chair of the Institutional Review Board or Research Staff at 708-202-MMMM.

STATEMENT OF CONSENT:
I voluntarily consent to participate in this study. This research study and my rights as a research participant have been explained to me.

I will receive a copy of this consent form and a copy will be placed in my medical chart and additional copies will be filed in the Research Office.

_____________________________   _____________________________
Subject’s Signature      Subject’s Social Security Number
<table>
<thead>
<tr>
<th>Subject’s Telephone Number</th>
<th>Date</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>_________________________</td>
<td>______________</td>
<td>__________________________</td>
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<table>
<thead>
<tr>
<th>Signature of Investigator</th>
<th>Date</th>
<th>Signature of Person Obtaining Consent</th>
<th>Date</th>
</tr>
</thead>
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