

1 **Resistance Training improves Nerve Conduction and Arterial Stiffness in Older Adults**
2 **with Diabetic Distal Symmetrical Polyneuropathy: A Randomized Controlled Trial**

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30 **Abstract**

31 Diabetes is the main cause of peripheral neuropathy where older patients are at increased risk
32 of diabetic distal symmetrical polyneuropathy (DSPN) due to age-related nerve degeneration
33 and vascular changes. The aim of the study was to investigate the effect of resistance training
34 on nerve conduction, measures of neuropathy and arterial stiffness in older patients with DSPN.
35 In a randomized controlled trial, thirty-four older adults with type-2 diabetes and peripheral
36 neuropathy were enrolled and randomly assigned to experimental and control groups. The
37 experimental group carried out circuit resistance training (1-3 rounds, 11 exercises, 10-15 reps,
38 50%-60% of 1RM, 3 times per week) for 12 weeks. Measurements were performed at baseline
39 and 48 h after the intervention. Measures of DSPN including Michigan neuropathy screening
40 instrument (MNSI), Michigan diabetic neuropathy score (MDNS), motor nerve action potential
41 amplitude (APA), sensory and motor nerve conduction velocity (NCV) improved following
42 intervention ($p < 0.001$, $p = 0.001$, $p = 0.034$, $p = 0.001$, and $p = 0.001$, respectively). Sensory
43 APA did not change after the intervention ($p = 0.139$). Cardio-ankle vascular index (CAVI)
44 and ankle-brachial index (ABI) improved in the experimental group compared with the control
45 group ($p = 0.014$ and $p = 0.033$, respectively). In addition, HbA1C decreased following the 12-
46 week resistance training program ($p = 0.002$). Older adults with DSPN respond positively to
47 resistance training by improved neuropathy symptoms, nerve conduction, arterial stiffness and
48 glucose regulation. Resistance training offers a positive intervention that can abate the
49 progression of DSPN in older adults.

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51 **Key words:** Type-2 diabetes mellitus; Nerve conduction; Polyneuropathy; Arterial stiffness;
52 Exercise training.

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61 **1. Introduction**

62 Type 2 diabetes mellitus is associated with progressive neurodegenerative complications.
63 Diabetic distal symmetrical polyneuropathy (DSPN) is a chronic microvascular complication
64 of diabetes that can cause symptoms of severe pain and numbness [1]. Metabolic and vascular
65 factors are known to be the major contributors of the pathogenesis and development of DSPN
66 [2]. Accordingly, elevated glucose concentration and impaired vascular function is associated
67 with severe neuropathy [2]. For instance, elevated femoral arterial stiffness has been reported
68 to be associated with ischemic symptoms in the lower extremity of patients with diabetes [3].
69 Increased arterial stiffness in the lower limbs is accompanied by elevated resistance against
70 blood flow that leads to decreased flow in the limbs arteries [3]. Diabetes related peripheral
71 neuropathy is especially troublesome in older patients as aging is an independent risk factor for
72 peripheral neuropathies [4]. Aging is associated with structural and functional changes in the
73 central and peripheral nervous system [5]. It has been indicated that aging can increase nerve
74 lipid peroxidation, Schwann cell apoptosis [6], nerve demyelination and axonal degeneration
75 [7]. Hence, older patients with DSPN are at increased risk of nerve degeneration and related
76 complications [4]. These changes have a negative impact on activities of daily living and
77 quality of life and increase the risk of morbidity and mortality in this population [4, 8]. DSPN
78 is the major cause of foot ulceration and non-traumatic lower limb amputation in diabetes [9].
79 Thus, any measures that can lessen the signs and symptoms of the disease would be a welcome
80 adjuvant intervention.

81 Currently, there is no definitive treatment for DSPN and the majority of therapies focus
82 on pain abatement [10]. However, addressing the underlying mechanisms of DSPN including
83 hyperglycemia and vascular dysfunction can influence the development of the disease [10].
84 Optimizing glucose control has been shown to be crucial for preventing and delaying the
85 development of peripheral nerve damage in type 2 diabetes [11]. In addition, restoring blood

86 flow to the lower extremity improves nerve conduction in patients with DSPN [12]. Exercise
87 training offers a wide range of benefits to patients with type 2 diabetes including optimal
88 glycemic control, improved vascular function and arterial stiffness [13-15]. Additionally,
89 physical activity and exercise training are known to have benefits on central and peripheral
90 nerves function. For example, aerobic training protects peripheral nerves from pathological
91 changes related to aging [6] and strength training has been shown to increase the thickness of
92 myelin sheath and delay age-related progressive changes in peripheral nerves [16].

93 Evidence shows that exercise has benefits on growth of damaged nerves that is suggested
94 to be dependent on the type of injury, exercise modality, duration and intensity [17, 18].
95 However, there is little consensus on the benefits of different exercise modalities on diabetes-
96 related peripheral nerve damage due to the paucity of research. Aerobic and balance exercises
97 are frequently studied and suggested modes of exercise for patients with DSPN [19]. Reviews
98 of literature indicated that resistance training has been recommended for clinical purposes as it
99 brings about various benefits [14, 15]. For instance, some studies suggested that resistance
100 training can be more effective than aerobic training for glucose regulation in patients with type
101 2 diabetes [13]. These benefits can have unique clinical implications in type 2 diabetes and the
102 related complications. However, to date, no study has evaluated the effect of resistance training
103 on DSPN in older adults, which might be related to the concerns regarding feasibility and safety
104 of exercise in this population. Physicians seem to be reluctant to encourage patients with DSPN
105 to engage in resistance-type exercise, possibly because of fears of adverse outcomes such as
106 increased pain or foot ulceration. This may have been arisen from preliminary research that
107 suggested DSPN might be a contraindication for weight-bearing exercise [20]. However, recent
108 studies indicated that weight-bearing exercise in the form of aerobic and balance exercise do
109 not increase foot pain and ulcers in individuals with DSPN [21]. Accordingly, the aim of this
110 investigation was to investigate the effect of supervised low-to-moderate intensity resistance-

111 type exercise program on neuropathy symptoms, nerve conduction and arterial stiffness in older
112 adults with DSPN. We hypothesized that engaging in resistance training would have a positive
113 influence on neuropathic symptoms in older adults with DSPN.

114

115 **2. Materials and Methods**

116 A randomized-controlled trial was conducted to assess the effect of a 12-week resistance
117 training on neuropathy symptoms, nerve conduction and arterial stiffness. The study complied
118 with the codes of *Declaration of Helsinki* for human research and approved by the Human
119 Research Ethics Committee of Shahrood University of Medical Sciences
120 (IR.SHMU.REC.1398.087, 09.30.2019) and the trial was registered at Iranian Clinical Trial
121 Registry (Trial No: IRCT20170120032066N4); although the trial appears to be registered
122 retrospectively, all authors can attest that the trial was registered prior to participant enrolment.

123

124 **2.1. Participants**

125 Community-dwelling male patients registered in diabetes clinics and aged > 60 years were
126 invited to participate and screened for eligibility. The patients were included if they had history
127 of diabetes > 5 years, HbA1c > 6.6%, inactive lifestyle, and if they were diagnosed with mild
128 to moderate stage of DSPN. Participants were excluded if they were not permitted to participate
129 in exercise programs, if they had orthopedic issues, foot deformity and ulcers, and if they had
130 absent nerve action potential amplitude. The diagnosis of type 2 diabetes was based on the
131 criteria by American Diabetes Association and the presence of DSPN was confirmed by a
132 neurologist based on Michigan Diabetic Neuropathy Score (MDNS) and Michigan Neuropathy
133 Screening Instrument (MNSI) with signs and symptoms of DSPN [22, 23]. Physical activity
134 level was assessed by The International Physical Activity Questionnaire (IPAQ) and all the

135 participants were leading inactive lifestyle. Eligibility was confirmed in 34 volunteers (Figure
136 1), they were informed about the study procedure and provided written consent.

137

138 **2.2. Randomization**

139 The randomization was carried out by a person independent of the trial team to ensure
140 concealment of the allocation. The participants were assigned to the groups using a blocked/
141 stratified randomization method in a 1:1 ratio. Stratification was applied based on the stage of
142 DSPN at two levels including mild and medium neuropathy. A distinct block randomization
143 with the block size of 4-6 was implemented for each stratum. The participants were randomly
144 assigned to each group using random number tables generated by computer.

145

146 **2.3. Exercise Training**

147 According to exercise guidelines, type 2 diabetic patients have been recommended to engage
148 in resistance training programs with moderate intensity of $\geq 50\%$ of 1RM at least 2 times a
149 week on non-consecutive days [24]. Given this and previous pilot studies in this population,
150 the resistance training protocol began at the least recommended exercise intensity and preceded
151 by a familiarization period. The experimental group was familiarized with the exercise protocol
152 over two weeks. One-repetition maximum (1RM) was estimated by each participant
153 performing 10-RM for each exercise. This was re-assessed every month to adjust the resistance
154 for each exercise in order to ensure progressive overload. The resistance exercise program was
155 performed 3 times per week, for 12 weeks that lasted ~90 minutes per session and consisted of
156 11 dynamic exercises on large muscle groups with free weights and machines including squat,
157 bench press, shoulder press, knee extension, knee flexion, calf rise, elbow extension and
158 flexion, sit ups, lat pulldown and back extension. The resistance training consisted of 1-3
159 circuits with 10-15 reps for each exercise at between 50-60% of 1RM. Rest intervals of 30-60

160 s between each exercise and 3-5 min between each round were allowed. A 15-minute warm up
161 and 10-minute cool down consisting of brisk walking/ jogging, stretching of major muscle
162 groups and the main exercises with lighter weights were included at each session.

163 All exercise sessions were carried out under the supervision of an exercise physiologist.
164 To avoid any possible hyper/hypoglycemia induced by exercise, blood glucose levels were
165 checked prior to each exercise session to ensure participants were in a safe range (not to be <
166 100 mg/dl or > 250 mg/dl). If glucose testing revealed hyperglycemia, exercise training was
167 postponed and if hypoglycemic, a carbohydrate snack was provided and glucose was re-
168 checked. Furthermore, to avoid DSPN-related adverse events such as pain aggravation and foot
169 ulceration, the participants were asked to be wearing comfortable and dry socks and shoes
170 while exercising.

171 Participants were required to follow their habitual diet throughout the study. During the
172 familiarization period and during the last week of training, the calorie intake was recorded by
173 a 3-day dietary recall. Dietary data were recorded in the case of significant difference between
174 groups and/ or between pre and post-test and hence requiring the application of a covariate of
175 analysis. In addition, food intake before baseline measurements was recorded using a 24-hour
176 recall and participants were asked to replicate the same diet before the final measurements to
177 the best of their ability.

178

179 ***2.4. Measurements***

180 In line with our hypothesis the primary outcomes were MDNS, Sural sensory and Peroneal
181 motor NCV and action potential amplitude, CAVI and ABI. All measurements were carried
182 out at baseline and were replicated 48 h following last exercise session. The participants were
183 asked to abstain from vigorous physical activity and caffeine for 24 h before the measurements.
184 Body composition was analyzed by a bioelectrical impedance analyzer (Inbody230, Korea)

185 after an overnight fast. Fasting blood samples were taken from the antecubital vein and used to
186 assess HbA1c content by liquid chromatography (Pishtaz, Tehran, Iran). Arterial stiffness was
187 measured by oscillometric method using VaSera VS-2000 (Fukuda Denshi, Tokyo, Japan) that
188 captures pulse waves in 4 limbs non-invasively. Before measurements, participants
189 comfortably rested supine for 10 minutes. The measurements were carried out according to the
190 manufacturer's instruction. Blood pressure cuffs with sensors were applied to all limbs to
191 generate plethysmograms. Phonocardiogram (PCG) was also placed at sternal angel and ECG
192 leads were attached to the arm. The measurements of brachial and ankles systolic pressure and
193 calculations of CAVI and ABI were automatically carried out by the Vasera-2000 system [25].
194 Nerve conduction studies and neuropathy assessments were performed by a neurologist blinded
195 to group allocations using an EMG/NCV system (Viking Quest, USA). For sural sensory nerve
196 the recording point was behind the lateral malleolus and stimulation point was 14 cm from the
197 active electrode up to the posterior aspect of the calf. For peroneal motor nerve recording point
198 was at extensor digitorum brevis muscle and stimulation points were at anterior ankle and
199 lateral popliteal fossa immediately below the head of fibula. For both nerves studied nerve
200 action potential amplitude (APA) and nerve conduction velocity (NCV) have been reported.
201 The measurements were performed in a quiet room with constant temperature 25 ± 2 °C.
202 Michigan Diabetic Neuropathy Instrument (MNSI) consists of 15 questions with yes/no
203 responses on foot sensation that indicates the presence and severity of symptoms of neuropathy
204 [22]. Michigan Diabetic Neuropathy Score (MDNS) consists of 46-point score of clinical
205 neurological examination [22].

206

207 ***2.5. Statistical analysis***

208 The sample size was determined through a priori power analysis for repeated measures
209 ANOVA using G*power (version 3.1.9.2). The calculation was based on a medium effect size

210 (= 0.06) for interaction between time and group, $\alpha = 0.05$, and power of 80% [26]. Based on a
211 previous study, the correlation between repeated measures was assumed to be 0.6 for nerve
212 conduction velocity [27]. According to these assumptions a sample size of 28 was required.
213 Considering a drop-out rate of 20%, the initial number of participants included in this study
214 was 34.

215 Data were expressed as mean \pm SD. The Shapiro-Wilk test was used to confirm the
216 normal distribution of the data. The effects of exercise training on variables were determined
217 by repeated measures of ANOVA (Time x Group) and main effects of time were also reported.
218 For follow-up comparisons, Bonferroni's *post-hoc* analysis was carried out. An independent
219 samples *t*-test was also used to examine the change scores between groups over time (pre to
220 post-test). Effect sizes of the differences was indicated by partial *eta* squared. Pearson's
221 correlation coefficient was used to determine the association between variables. The
222 significance level was $P < 0.05$. Data were analyzed using SPSS for windows version 25 (SPSS
223 Inc, Chicago, III).

224

225 **3. Results**

226 A total of 34 participants were recruited to start the study and were randomized to two groups
227 (Figure 1). In total, 29 participants completed the study; 2 participants in the experimental
228 group and 3 participants in the control group failed to complete the study (Figure 1). The
229 participants' attendance to exercise sessions in the experimental group was 91-100%. The mean
230 and standard deviation for age, weight, fat percentage, and daily calorie intake are presented in
231 Table 1. There were no significant differences between groups at baseline ($p > 0.05$). Mean
232 and standard deviation for other variables are presented in Table 2. The baseline values were
233 similar in both groups ($P > 0.05$).

234 The supervised resistance training program was well tolerated with no adverse events
235 related to exercise program other than the expected transient muscle soreness during first few
236 sessions. The main intervention commenced with a familiarization period at lower intensity
237 and glucose level was strictly checked prior to exercise sessions, as previously described. As a
238 result, no adverse event including exercise-induced hypoglycemia/ hyperglycemia was
239 observed and the participants were able to deal with the procedure. Moreover, no adverse
240 events related to DSPN such as aggravated pain and foot ulceration were reported throughout
241 the study.

242 Data analysis indicated time x group interaction ($F = 4.996$, $p = 0.034$, $\eta_p^2 = 0.156$) and
243 main effect of time ($F = 8.725$, $p = 0.006$, $\eta_p^2 = 0.244$) for motor nerve action potential
244 amplitude (APA). Analysis of change scores between groups using independent samples *t*-test
245 also revealed a significant difference ($p = 0.034$). Follow-up comparison indicated an increase
246 of motor nerve APA in the experimental group (6% increase, $p = 0.048$). However, the time x
247 group interaction for sensory APA was not significant ($F = 2.329$, $p = 0.139$, $\eta_p^2 = 0.079$) and
248 analysis of change scores between groups using independent samples *t*-test also indicated no
249 significant difference ($p = 0.139$). A difference in motor NCV was observed with the time x
250 group interaction ($F = 13.456$, $p = 0.001$, $\eta_p^2 = 0.333$) and main effect of time ($F = 11.153$, $p =$
251 0.002 , $\eta_p^2 = 0.292$), (Figure 2). Analysis of change scores between groups using independent
252 samples *t*-test also indicated a significant difference ($p = 0.001$). Follow-up comparison
253 indicated an increase of motor NCV in the experimental group (7% increase, $p = 0.016$). For
254 sensory NCV, there was also a time x group interaction ($F = 14.242$, $p = 0.001$, $\eta_p^2 = 0.345$)
255 and main effect of time ($F = 26.217$, $p = 0.0001$, $\eta_p^2 = 0.493$). Analysis of change scores
256 between groups using independent samples *t*-test also revealed a significant difference ($p =$
257 0.001). Follow-up comparison indicated an improvement of sensory NCV in the experimental
258 group (8% increase, $p = 0.002$). Furthermore, time x group interaction ($F = 12.541$, $p = 0.001$,

259 $\eta_p^2 = 0.317$) and main effect of time ($F = 8.893$, $p = 0.006$, $\eta_p^2 = 0.248$) were observed for
260 MDNS and analysis of change scores between groups using independent samples *t*-test also
261 revealed a significant difference ($p = 0.001$). Follow-up comparison revealed a reduction for
262 MDNS in the experimental group (10% reduction, $p = 0.019$). We also observed a time x group
263 interaction ($F = 26.350$, $p = 0.0001$, $\eta_p^2 = 0.494$) and main effect of time ($F = 7.640$, $p = 0.010$,
264 $\eta_p^2 = 0.221$) for MNSI (Figure 2). Analysis of change scores between groups using independent
265 samples *t*-test also revealed a significant difference ($p = 0.0001$) Follow-up comparison
266 indicated a marked reduction of MNSI in the experimental group (20% improvement, $p =$
267 0.003). Pearson's correlation coefficient analysis indicated the changes in MNSI score was
268 associated with the changes in HbA1C ($r = 0.589$, $p = 0.021$). The correlation of MNSI with
269 ABI and sensory nerve conduction did not reach significance ($r = -0.447$, $p = 0.095$ and $r = -$
270 0.473 , $p = 0.075$, respectively).

271 A difference in CAVI was observed with the time x group interaction ($F = 6.904$, $p =$
272 0.014 , $\eta_p^2 = 0.204$) and main effect of time ($F = 12.703$, $p = 0.001$, $\eta_p^2 = 0.320$), (Figure 2).
273 Analysis of change scores between groups using independent samples *t*-test also revealed a
274 significant difference ($p = 0.001$). Follow-up comparison revealed a reduction in the
275 experimental group (6.6% reduction, $p = 0.039$). For ABI, there was a time x group interaction
276 ($F = 5.077$, $p = 0.033$, $\eta_p^2 = 0.158$) but the main effect of time was not significant ($F = 2.683$,
277 $p = 0.113$, $\eta_p^2 = 0.090$). Analysis of change scores between groups using independent samples
278 *t*-test also revealed a significant difference ($p = 0.033$). Follow-up comparison did not show
279 significant alterations in the experimental group (4% increase, $p = 0.123$). A difference in ankle
280 systolic pressure was observed with the time x group interaction ($F = 8.670$, $p = 0.007$, $\eta_p^2 =$
281 0.243) and main effect of time ($F = 4.258$, $p = 0.049$, $\eta_p^2 = 0.136$). Analysis of change scores
282 between groups using independent samples *t*-test also revealed a significant difference ($p =$
283 0.007). Follow-up comparison revealed an increase in the experimental group (3.4% increase,

284 $p = 0.001$). For brachial systolic pressure, there was neither significant time x group interaction
285 ($F = 0.867$, $p = 0.360$, $\eta_p^2 = 0.031$) nor the main effect of time ($F = 1.000$, $p = 0.326$, $\eta_p^2 =$
286 0.036).

287 We also observed a time x group interaction ($F = 11.240$, $p = 0.002$, $\eta_p^2 = 0.294$) and
288 main effect of time ($F = 5.712$, $p = 0.024$, $\eta_p^2 = 0.175$) for HbA1C (Figure 2). Analysis of
289 change scores between groups using independent samples t -test also revealed a significant
290 difference ($p = 0.002$). Follow-up comparison revealed a reduction in HbA1C in the
291 experimental group (10% reduction, $p = 0.025$).

292

293 **4. Discussion**

294 The aim of the study was to investigate the effect of resistance training on symptoms of
295 neuropathy, nerve conduction and arterial stiffness in older adults with DSPN. For the first
296 time, we observed that low-to-moderate intensity resistance training improved measurements
297 of DSPN including neuropathic symptoms, nerve conduction velocity, nerve action potential
298 amplitude, measurements of arterial stiffness including CAVI and ABI, and HbA1c levels in
299 older adults with DSPN. Besides, no major complications and adverse events directly related
300 to exercise training were reported throughout the intervention. Accordingly, low-to-moderate
301 intensity resistance training can be an effective and safe therapeutic intervention for this group
302 of patients.

303 Nerve conduction velocity and nerve APA improved following 12-week resistance
304 exercise regimen in older adults with DSPN. This finding is partly in accordance with some
305 previous studies that reported enhanced NCV of sensory and motor nerves following aerobic
306 exercise training [26, 27]. The evidence showed that the neural system responds positively to
307 physical activity through morphological and functional adaptations to the training stimulus [6,
308 28-30]. Exercise training has been shown to decrease apoptosis of Schwann cells and increase

309 myelin thickening [6], increase Schwann cell proliferation [28], enhance axonal regeneration
310 of the peroneal nerve [30] and improve axon transport and electrophysiological properties [29].
311 Resistance training also enhances neural activation and neuroplasticity that occurs at earlier
312 stages of training program. These changes likely explain the initial functional adaptations and
313 subsequent strength gains following resistance training program [31]. Moreover, resistance
314 exercise can activate the effects of neurotrophin because it can increase brain-derived
315 neurotrophic factor (BDNF) expression and its receptor tropomyosin receptor kinase B (trkB)
316 [32]. BDNF and its receptor seem to be substantial modulator for axon regeneration as the
317 continuous presence of BDNF enhanced axon regeneration after nerve damage [33].

318 The improvements in the measurements of nerve conduction in the current study might
319 be partly explained by local and direct impact of resistance training on peripheral nerves.
320 Morphological changes in peripheral nerves are not the only factor to explain nerve conduction
321 improvements [34]; functional alterations are also essential so that improved neural function
322 can be attributed to the reinforcement of existing sensory-motor pathways rather than
323 generating additional pathways [35]. In the present study, the changes in NCV and APA were
324 coupled with improved neuropathy symptoms. Another established effect of exercise,
325 irrespective of type, is hypoalgesia induced by exercise [34]. Groover et al, (2013) indicated
326 that exercise can regulate cutaneous sensation and nociceptive threshold related to prediabetes
327 [36]. It may be explained by cutaneous regeneration as exercise training has been shown to
328 increase distal leg intraepidermal nerve fiber density (IENFD) in diabetic patients with [37]
329 and without neuropathy [38]. Although IENDF is a measure of integrity of small diameter
330 axons and evaluates unmyelinated axons, it is correlated with large myelinated fiber surrogates
331 such as nerve conduction studies [38]. Singleton et al, (2014) indicated that development of
332 abnormal neurological examinations was remarkably reduced in patients receiving exercise
333 intervention [38]. Additionally, exercise training increased the endogenous opioid production

334 which might play a role in neuropathic pain reversal induced by exercise [39]. These alterations
335 suggest that exercise training provides benefits to both central and peripheral nervous system.
336 These exercise effects are valuable for this population and we contend that the low-to-moderate
337 intensity resistance exercise program in this study also has the potential to improve neural
338 function in older adults with DSPN, which is manifested by reduced neuropathy symptoms.

339 Besides neural alterations, glucose regulation and vascular function are essential
340 contributors of nerve function in DSPN. Hyperglycemia is the principal determinant of the
341 development of DSPN. It has been suggested that 1% increase in HbA1C is associated with
342 almost 10-15% increase in frequency of DSPN [40]. Constant or fluctuating hyperglycemia
343 can induce sorbitol accumulation in nerves, oxidative stress, chronic inflammation and
344 endothelial dysfunction [2] and lead to peripheral nerve damage in type 2 diabetes. Hence,
345 aggressive control of glucose is crucial for type 2 diabetes and related complications, especially
346 DSPN. Optimized glucose control reduces nerve conduction abnormalities and is important in
347 the prevention and treatment of DSPN [41]. We observed a marked reduction in HbA1C from
348 9.09% to 8.11% following a 12 week resistance exercise program that was correlated with
349 alterations in neuropathy symptoms, which supported previous work showing that
350 improvement in signs of DSPN were coupled with a reduction of HbA1C [37]. The effect of
351 different modes of exercise on glucose regulation is well documented [15] and resistance
352 training has been suggested to be as effective as aerobic training to reduce levels of HbA1C
353 [15]. One study has shown that resistance training was superior at reducing HbA1C level to
354 aerobic training [13]. Hence, the application of resistance training can be clinically significant
355 because of the HbA1C lowering effects, the potential to lower the prevalence and progression
356 of DSPN [31].

357 DSPN has been shown to be significantly associated with blood flow to the peripheral
358 nerves and arterial stiffness [3, 42]. Increased arterial stiffness in the lower extremity can

359 compromise blood flow to foot arteries [3]; this has been shown with femoral arterial stiffness
360 in diabetes patients being closely related with ischemic symptoms of the lower extremity.
361 Reduced endoneural blood flow causes hypoxia in the peripheral nerves that can influence
362 nerve conduction [2]. For instance, NCV is shown to be sensitive to blood supply, and so the
363 restoration of blood flow to the lower extremity can enhance conduction velocity of peroneal
364 nerve in patients with type 2 diabetes [12]. This study showed a reduction in the mean values
365 of CAVI and an increase in ABI following the 12-week resistance training intervention. A
366 recent systematic review concluded that resistance training at lower intensities could bring
367 about cardiovascular health benefits and may improve measures of arterial stiffness [42]. CAVI
368 reflects heart-to-ankle stiffness of arterial walls and ABI is the ankle-brachial pressure index
369 reflecting the degree of arterial blockage in the lower limbs that is reduced in peripheral arterial
370 diseases. Despite the non-significant alterations in brachial systolic pressure, ankle pressure
371 did improve following resistance training. Thus, improvements in ABI are thought to be driven
372 by an improvement in ankle systolic pressure rather than changes in brachial systolic pressure.
373 A potential explanation for improved ankle pressure and ABI by resistance training might be
374 improved blood flow in the lower extremities [43]. Exercise training enhances endothelium-
375 dependent and independent vasodilation, nitric oxide synthesis and bioavailability and
376 expression of growth factors that can lead to improved blood flow to the limbs [44]. Even
377 though leg vascular function can be precisely assessed via ultrasound or femoral-ankle pulse
378 wave velocity, ABI has also a well-supported prognostic value that reflects improved leg
379 vascular function following resistance training in this study. Regarding this, Fahs et al. (2011)
380 reported that acute resistance exercise increased arterial compliance and calf blood flow. They
381 found that high-intensity resistance exercise at 70% of 1RM caused greater elevation of calf
382 vascular conductance, elasticity of large artery and small artery compared to low intensity
383 exercise at 20% of 1RM [14]. Hence, high-intensity resistance exercise could be more effective

384 than low-intensity exercise to improve large and small artery blood flow. The exercise intensity
385 in our study roughly corresponded to the high-intensity protocol implemented by Fahs et al.
386 (2011). Muscle contraction during resistance exercise causes hyperemia that can immediately
387 increase arterial compliance and blood perfusion to the active sites. Over time, with repeated
388 exposure, exercise-induced elevation of blood flow can increase blood supply to the vasa
389 nervorum and therefore contribute to restoring nerve function [46]. Besides, resistance exercise
390 reduces systemic vascular resistance indicating relaxation of vascular smooth muscle. This can
391 further explain improved arterial compliance and blood flow by resistance exercise training
392 [14]. Hence, improved measurements of nerve conduction in this study could also be attributed
393 to factors other than glucose regulation alone i.e., restoration of blood flow and oxygen supply
394 to peripheral nerves as a result of resistance training. However, due to little understandings in
395 this area it needs to be clarified in future studies.

396 In contrast, some previous studies did not report the effectiveness of an aerobic exercise
397 program on some measurements of nerve conduction in DSPN [25, 37]. Dixit et al, (2014)
398 reported that aerobic training over 8 weeks had no significant effect on nerve APA of the
399 peroneal nerve in patients with DSPN [26]. This discrepancy might be explained by the
400 exercise type (aerobic versus resistant-type training), the intensity and duration and hence
401 determine nerve response to training. Exercise has been suggested to be an effective treatment
402 for nerve functional recovery, yet the effects depend on the type, duration and intensity of the
403 protocol [17]. Another possible mediator in the response to exercise is sex; where a previous
404 animal study reported that the effect of different exercises on axon regeneration after peripheral
405 nerve injury is sex-dependent [47]. This study showed that male animals were more responsive
406 to continuous exercise while female animals responded well to interval exercise [47]. This
407 observation might go some way to explaining the differences in studies where a male-only
408 cohort was used. Based on the contribution of sex on nerve responsiveness to exercise [47], the

409 mediatory effects of resistance training to this intervention could be explored in future studies
410 can extend the understandings in this area.

411

412 **5. Limitations and Future Directions**

413 The study includes some strength and limitations to be acknowledged. In spite of several
414 medical concerns with this group of patients, the adherence to exercise intervention was very
415 good and drop-out rate was trivial. Furthermore, walking and jogging is the frequently used
416 and prescribed form of exercise in this population. This is the first randomized trial that
417 indicates feasibility of resistance-type exercise program for older adults with DSPN. The
418 homogenous group of male participants show the benefits of resistance training for this cohort.
419 However, the data might be limited to this cohort and further studies on female participants
420 should be conducted to increase our understanding regarding effect of sex on exercise-induced
421 neural changes in DSPN and extend the generalizability of the findings.

422 We observed benefits of resistance training on neuropathic symptoms in older male
423 adults with DSPN. Since diabetes-related nerve damage is associated with impaired balance
424 and increased risk of falling [48], further research is required to determined how the effects of
425 resistance training can translate into functional measures such as daily physical activities and
426 quality of life. A greater understanding of the effects of resistance-type exercise on functional
427 measurements can provide further implications for exercise recommendations to this
428 population. One might assume that improved nerve conduction measurements and symptoms
429 of neuropathy can be resulted from the concurrent effect of resistance training on metabolic
430 and vascular measures in addition to direct local effects on peripheral nerves. However, due to
431 the lack of understandings in this area, this should be explored in more detail with mechanistic
432 studies.

433

434 **6. Conclusions/ Implications**

435 This study provide new data that older patients with DSPN respond positively to low-to-
436 moderate intensity resistance training by improved neuropathy symptoms, nerve conduction,
437 arterial stiffness and glucose regulation. What is important to note is that resistance-type
438 training is a safe and feasible intervention to improve the signs and symptoms associated with
439 the progression of DSPN and hence can be used as an effective intervention to improve these
440 variables. These new data can be used as a platform for the exploration of other benefits of this
441 type of intervention, but critically, can be applied in patients with type 2 diabetes and
442 specifically to the growing population of older adults with diabetic peripheral neuropathy.

443

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446

447 **8. Authors' Contribution**

448 The study was conceptualized and designed by FG; data were collected by FG, RK and BM;
449 data were interpreted by FG and GH; and manuscript preparation was undertaken by FG and
450 GH. The final version of the manuscript was approved by all authors.

451

452 **9. Competing interests**

453 The authors have no conflict of interest to declare.

454

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601 **Table 1.** Mean \pm SD values for age, height, weight, fat percentage, calorie intake, and selected lower and upper-
 602 body strength.

Group Variable	Experimental (n=15)		Control (n=14)	
	Pre	Post	Pre	Post
Age (years)	63 \pm 3	-	64 \pm 3	-
Height (cm)	170.2 \pm 5.1	-	168.7 \pm 4.0	-
Weight (kg)	74.9 \pm 9.0	73.5 \pm 9.0	72.6 \pm 8.9	73.2 \pm 8.6
Fat (%)	27.7 \pm 4.4	26.6 \pm 4.5	26.6 \pm 5.1	27.0 \pm 4.8
Calorie intake (Kcal)	2199 \pm 267	2216 \pm 255	2272 \pm 263	2308 \pm 221
Squat 1RM (kg)	56.7 \pm 11.0	65.4 \pm 9.7	-	-
Bench press 1RM (kg)	43.0 \pm 8.3	49.4 \pm 7.4	-	-

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Table 2. Description of the changes in mean and standard deviation for variables at baseline and following 12 weeks in groups.

Group	Experimental (Mean ± SD, 95% CI) (n=15)		Control (Mean ± SD, 95% CI) (n=14)		P	EF
	Pre	Post	Pre	Post		
HbA1C (%)	9.09±1.82 (8.08–10.10)	8.11±1.45 (7.31–8.33)	9.97±1.82 (8.91–11.02)	10.13±1.50 (9.26–11.00)	0.002	0.294
HbA1C (mmol/ mol)	75.86±19.79(64.90-86.82)	65.13±15.72(56.42-73.4)	85.28±19.61(73.95-96.61)	87.29±16.55(77.72-96.84)	0.002	0.309
CAVI	8.51±0.73 (8.10–8.92)	7.94±0.69 (7.56–8.34)	8.30±0.52 (7.99–8.60)	8.21±0.48 (7.93–8.49)	0.014	0.204
ABI	0.94±0.12 (0.87–1.01)	0.98±0.10 (0.92–1.04)	0.95±0.08 (0.90–0.99)	0.94±0.08 (0.89–0.99)	0.033	0.158
BSP	137.60±10.90(131.55–143.64)	135.80±8.28(131.21–140.28)	138.35±9.06(133.12–143.59)	138.28±6.46(134.55–142.01)	0.360	0.031
ASP	128.86±9.90(123.38–134.35)	133.33±9.64(127.99–138.67)	131.57±9.04(126.34–136.79)	130.78±9.25(125.44–136.13)	0.007	0.243
Sensory APA (µV)	4.54±2.06 (3.49–5.69)	4.63±2.05 (3.50–5.77)	4.67±2.01 (3.51–5.83)	4.64±1.99 (3.48–5.79)	0.139	0.079
Motor APA (mV)	2.92±1.16 (2.27–3.57)	3.12±1.15 (2.48–3.76)	2.95±1.33 (2.18–3.72)	2.98±1.29 (2.23–3.73)	0.034	0.156
Sensory NCV (m/s)	27.62±8.75 (22.77–32.47)	30.06±8.56 (25.31–34.80)	28.56±8.92 (23.41–33.71)	28.93±8.69 (23.91–33.95)	0.001	0.345
Motor NCV (m/s)	33.01±8.88 (28.09–37.92)	35.38±8.72 (30.55–40.21)	36.02±9.41 (30.58–41.45)	35.90±8.97 (30.72–41.09)	0.001	0.333
MDNS	16.53±6.18 (13.11–19.96)	14.87±5.95 (11.57–18.16)	15.36±5.73 (12.05–18.67)	15.50±5.58 (12.28–18.72)	0.001	0.317
MNSI	8.26±1.94 (7.18 – 9.34)	6.60±1.40 (5.82-7.37)	7.50±2.06 (6.30-8.69)	8.00±1.79 (7.01-8.98)	0.0001	0.494

636 Abbreviations: EF, Effect size; CAVI, Cardio-ankle vascular index; ABI, Ankle-brachial index; BSP, Brachial
637 systolic pressure; ASP, Ankle systolic pressure; APA, Action potential amplitude; NCV, Nerve conduction
638 velocity; MDNS, Michigan diabetic neuropathy score; MNSI, Michigan neuropathy screening instrument.
639 P values are presented for Time x Group interactions.

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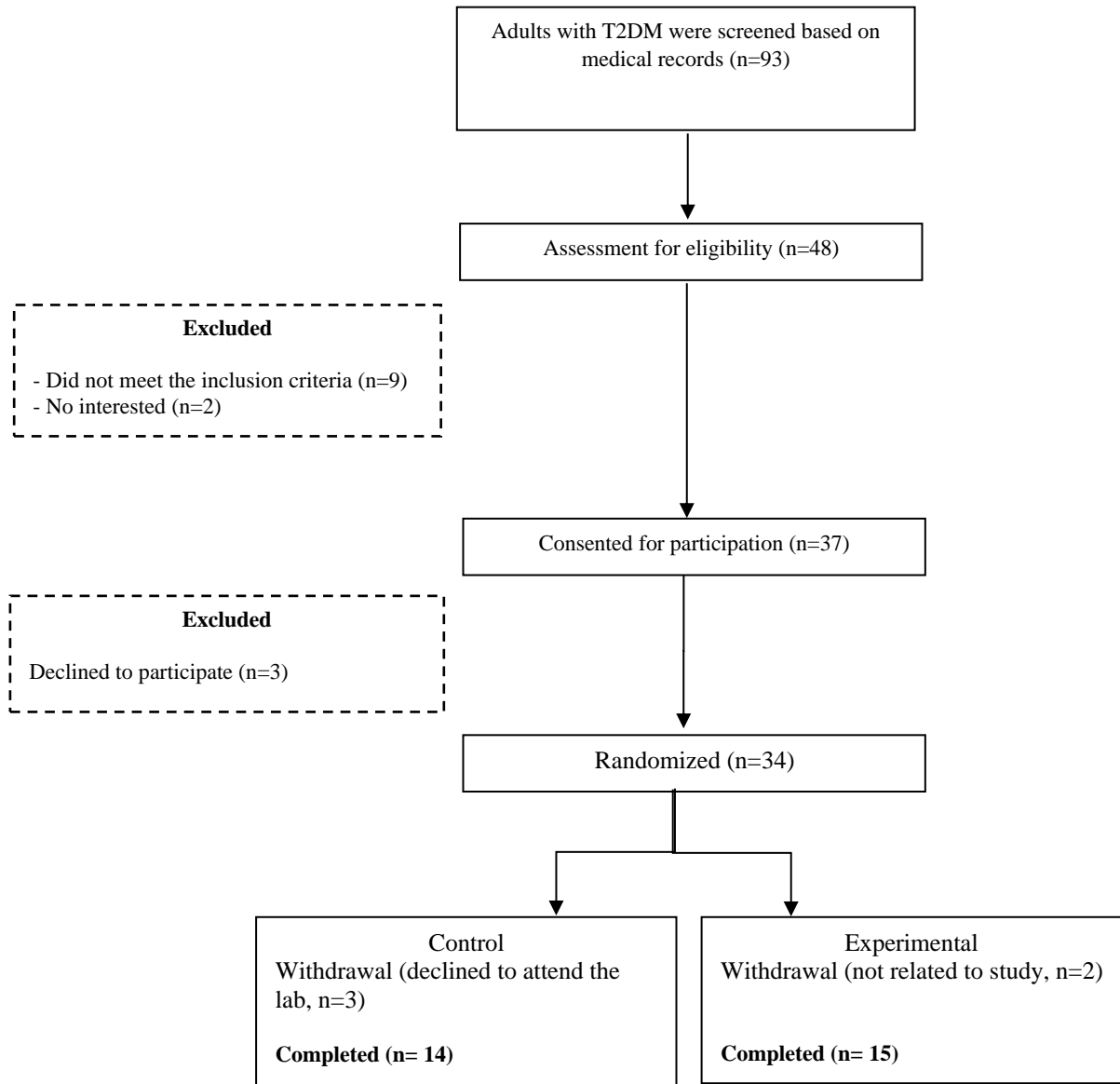
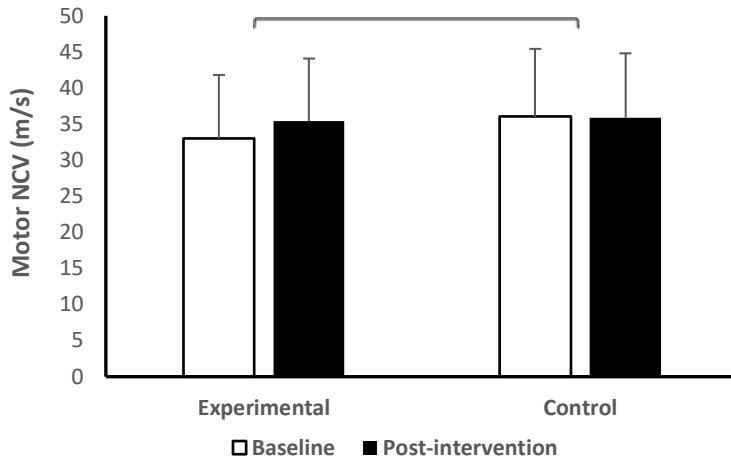



Figure 1. Consort flow chart of participant enrolment, randomization and analysis



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Figure 2. Changes in A) Motor Nerve Conduction Velocity (NCV); HbA1C; C) Cardio-Ankle Vascular Index (CAVI); and D) Michigan Diabetic Neuropathy Instrument (MNSI) score from pre to post-test. The data are presented as Mean \pm SD. * Significant difference with corresponding pre-test values $P < 0.05$. # Significant Time x Group interaction at $P < 0.05$. Experimental  Control 