

# The Effectiveness of Aerobic Exercise in Improving Peripheral Nerve Functions in Type 2 Diabetes Mellitus: An Evidence-based Case Report

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## ABSTRAK

**Latar belakang:** neuropati perifer merupakan salah satu komplikasi yang sering dijumpai pada penderita diabetes mellitus tipe 2. Timbulnya komplikasi ini dilatarbelakangi oleh kondisi kadar gula darah tidak terkontrol dalam waktu yang lama. Aktivitas fisik rutin dengan intensitas sedang sampai tinggi bermanfaat dalam pengelolaan diabetes mellitus. Telaah ini bertujuan untuk mengetahui efektivitas latihan aerobik dalam memperbaiki fungsi perifer yang lebih baik pada diabetes melitus tipe 2. **Metode:** pencarian literatur menggunakan beberapa kata kunci yang terkait di perpustakaan elektronik Medline®, Pubmed®, dan Cochrane library, mengikuti kriteria inklusi dan eksklusi. **Hasil:** studi Dixit et al menunjukkan bahwa 40-60% intensitas denyut jantung latihan aerobik dengan durasi 30-45 menit per sesi selama delapan minggu menunjukkan adanya dampak penting dalam mengontrol diabetes neuropati perifer. Kluding PM et al menunjukkan perbaikan secara signifikan dari pengukuran terpilih fungsi nervus perifer (tingkat keparahan “terburuk” dan skor MNSI), kontrol glikemik (HbA1c), dan denyut jantung istirahat. **Kesimpulan:** penelitian ini menunjukkan manfaat latihan aerobik yang signifikan, meski menggunakan latihan singkat sebagai intervensi terhadap perbaikan fungsi saraf perifer. Namun, diperlukan penelitian lebih lanjut dengan sampel besar dan durasi intervensi yang lebih lama untuk mengonfirmasi temuan tersebut.

**Kata kunci:** diabetes melitus, neuropati, latihan aerobik, HbA1c, evidence-based case report.

## ABSTRACT

**Background:** peripheral neuropathy is known as one of most common complication in diabetes mellitus type 2 patient. This complication is caused by uncontrolled condition of blood glucose level in long periode. Regular physical activity in moderate to high intensity is beneficial in management of diabetes mellitus. This report aimed to know the effectiveness of aerobic exercise in causing improved peripheral functions in type 2 diabetes mellitus. **Methods:** literature searching using several related keywords in Medline®, Pubmed®, and Cochrane library, following inclusion and exclusion criteria. **Results:** Dixit et al suggested that a heart rate intensity of 40-60% aerobic exercise of 30–45 min duration per session for eight weeks suggest an important impact in controlling diabetic peripheral neuropathy. Kluding PM et al suggested that significantly improved selected measures of peripheral nerve function (“worst” pain levels and MNSI score), glycemic control (HbA1c), and resting heart rate. **Conclusion:** the studies showed significant benefit of aerobic exercise, despite the short duration of exercise being used as intervention towards improvement in peripheral nerve function. However, further studies with large samples and longer duration of intervention are needed to confirm the finding.

**Keywords:** diabetes mellitus, neuropathy, aerobic exercise, HbA1c, evidence-based case report.

## INTRODUCTION

As one of the most common metabolic disease, diabetic mellitus prevalence has increased worldwide.<sup>1</sup> The complications that arise are the challenge of treating the patients. If blood glucose level is left untreated, mortality and morbidity are expected to arise.<sup>2</sup> One of the most common complication is peripheral neuropathy. Foot region are especially more prone to this phenomenon. If left untreated, the risk of diabetic ulcer can increase. Aside from diabetic neuropathy, risk factors such as peripheral vascular disease, duration of diabetes, foot deformity, previous foot ulceration, and long-term hyperglycemia are the known factors affecting worsened diabetic foot ulcers.<sup>3</sup>

The most common form of diabetic neuropathy is symmetrical distal degeneration of peripheral nerves. Aside from that, it is sometimes combined with impaired nerve degeneration that involved small and large nerve fibers leading to symptoms that are commonly felt by patient, which are pain and sensory loss.<sup>4</sup> There are several managements that can be done, one of which that has been proven to show benefit is increasing regimen of physical activity to the patients.

According to Indonesian Endocrinologist Association (PERKENI) and American Diabetes Association (ADA), there are four recommendations for managing diabetes mellitus that are reported.<sup>5,6</sup> One of the recommendations that is proposed is to perform physical activity in form of routine exercises. Regular physical activity in moderate to high intensity is beneficial in management of diabetes mellitus. It is further recommended that Studies have shown several benefits of exercise with diabetes mellitus prevention. Specifically, aerobic exercise is shown to have an effect in increasing cardiorespiratory fitness, as well as decreased morbidity and mortality.<sup>7</sup> Cohort study showed that there was a lower mortality rate in 7 years follow up to half in patients exercising for about 7 hours per week of brisk walking.<sup>8</sup> Studies also suggested that there were benefits in reducing risk of peripheral neuropathy. This report will analyze the effectiveness of aerobic exercise in improving peripheral nerve functions in diabetic patients.

## CLINICAL QUESTION

A female, 50 years old came to a clinic with chief complaint of worsening pain in lower leg region for 3 days prior to admission. Previously, there has been wound on the left plantar region and untreated for 2 months. There was reddish and bulging area surrounding the wound, and warm upon palpation. Patient has been diagnosed with 8 months and consumed metformin and glimepiride but the blood glucose level is still uncontrolled. Upon physical examination, pedis examination revealed good pulsation of dorsalis pedis artery and tibialis posterior artery, there was wound upon size of 2x2x0.5 cm, the depth of the wound is up until muscle sheet and there were signs of infection such as warmth, reddish, and bulging region, the sensation was decreased on lower extremities. Supporting examinations revealed fasting blood glucose was 202 and radiologic examination showed osteomyelitis on the affected area. Patient was referred to the hospital for surgical management to be performed.

From the case illustration, a clinical question arises: "How effective is aerobic exercise in improving peripheral nerve functions in patients with type 2 diabetes mellitus?"

## METHODS

The search strategy that is used in this report is using several related keywords and search in Medline®, Pubmed®, and Cochrane library. In March 10, 2016, searching was done using the following keywords (diabetes mellitus OR diabetes mellitus type 2 OR T2DM OR non-insulin dependent diabetes mellitus OR NIDDM) AND (aerobic exercise OR aerobic activity) AND (peripheral neuropathy OR diabetic neuropathy OR peripheral nerve functions).

Upon searching in Medline®, Pubmed® with MESH terms, and Cochrane library respectively 6, 3 and 0 articles were found. Further inclusion,

**Table 1.** PICO question

Patient	Intervention	Control	Outcome
Patients with type 2 diabetes mellitus	Aerobic exercise	-	Peripheral nerve functions

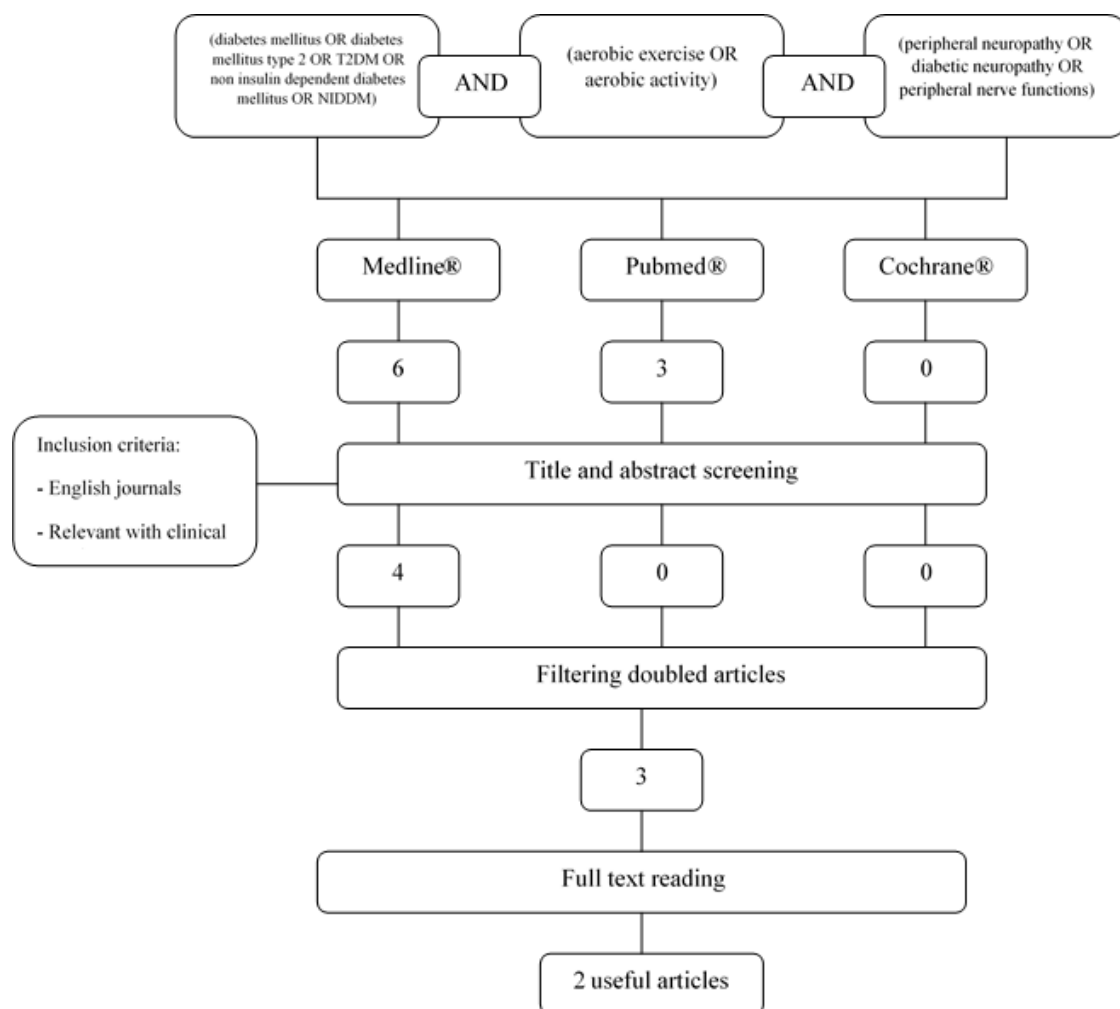
which are those with English written journals and relevant to clinical questions, 4 and 3 articles were obtained from Medline® and Pubmed®. After filtering doubled articles and further excluding some articles according to exclusion criteria, 2 useful articles were used to be appraised according to Center of Evidence-Based Medicine, University of Oxford. (**Figure 1**)

## RESULTS

After several selections of articles using inclusion and exclusion criteria, 2 full text articles were appraised and considered to match criteria of good validity and relevance according to Centre of Evidence Medicine University of Oxford. The following table summed up the critical appraisal of studies about the effectiveness of aerobic exercise in improving

peripheral nerve functions in type 2 diabetes mellitus.

Based on the validity appraisal, both journals were considered to have good level of evidence based on Center of Evidence Medicine University of Oxford. Both journals clearly state its study design and number of participants. Both studies have clear explanation of randomization, also the treatment were comparable and there was clear measurement of outcome. Based on the importance critical appraise, due to distinct difference in number of samples, the relative risk cannot show the impact on all population (small power). Kluding PM et al<sup>10</sup> has no control group, different with Dixit S et al that used no intervention group as control. Both studies are applicable to be implemented. Similar population of those with type 2 diabetes mellitus were used



**Figure 1.** Searching strategy flow chart

**Table 1.** Validity, important, applicability critical appraisal for 2 useful articles based on criterias by Centre of Evidence Medicine University of Oxford

	Dixit S, et al <sup>9</sup>	Kluding PM, et al <sup>10</sup>
<b>Validity</b>		
Study design	Stated clearly in the article	Stated clearly in the article
Number of participants	87	17
Randomization	Stated clearly in the article	Stated clearly in the article
Similarity treatment and control	Stated clearly in the article	Stated clearly in the article
Blinding	Stated clearly in the article	Not stated clearly
Comparable treatment	Stated clearly in the article	Stated clearly in the article
Intention to treat	Not being done	Not being done
Domain	Not stated clearly	Not stated clearly
Determinant	Not stated clearly	Not stated clearly
Measurement of outcome	Stated clearly in the article	Stated clearly in the article
Level of evidence	1B	2B
<b>Important</b>		
RRR	0.079	1.765
ARR	0.062	0,177083333
NNT	16	4
<b>Applicability</b>		
Similar population	Yes	Yes
Realistic	Yes	Yes
Harm, cost, and benefit	The benefit of both studies is greater than of harm and cost	The benefit of both studies is greater than of harm and cost
Patient preference	No studies were done in Indonesia yet	No studies were done in Indonesia yet
Other alternatives	Other alternatives were not yet found affective	Other alternatives were not yet found affective

RRR = Relative risk reduction, ARR = Absolute risk reduction, NNT = Number needed to treat

**Table 2.** Summary of study result

No	Author	Pts Number	Follow-up	Type of aerobic exercise	Control	Result
1	Dixit S <sup>9</sup>	87	8 week intervention	moderate intensity aerobic exercise and standard care	standard care	There was a significant difference in two groups at eight weeks ( $p < 0.05$ ) for distal peroneal nerve's conduction velocity, Degrees of freedom (Df)=1, 62, $F=5.14$ , and $p=0.03$ . Sural sensory nerve at eight weeks showed a significant difference in two groups for conduction velocity, Df =1, 60, $F=10.16$ , and $p=0.00$ . Significant differences in mean scores of MDNS were also observed in the two groups at eight weeks ( $p$ value significant $< 0.05$ )
2	Kluding PM <sup>10</sup>	17	10 week intervention	stretching to warm up followed by aerobic or strengthening exercise by a variety of cardiovascular training equipment; body recumbent steppers (Nustep), upright cycle, recumbent cycle, elliptical trainer, and treadmill	result of pre-test	Significant reductions in pain ( $-18.1 \pm 35.5$ mm on a 100 mm scale, $p=0.05$ ), neuropathic symptoms ( $-1.24 \pm 1.8$ on MNSI, $p=0.01$ ), and increased intraepidermal nerve fiber branching ( $+0.11 \pm 0.15$ branch nodes/fiber, $p=-.008$ ) from a proximal skin biopsy were noted following the intervention

as study population. Also, the intervention being used in these studies are realistic. The benefit of both studies is greater than of harm and cost. However, there has been no studies yet about how is the patient preference in Indonesia.

## DISCUSSION

A study by Dixit S et al.<sup>9</sup> involved 87 individuals with diabetic peripheral neuropathy. 47 participants were set in the control and 40 participants in the experimental group. After given intervention of recommended guidelines for supervised physical activity according to American Heart Association (AHA). The result suggested that a heart rate intensity of 40-60% aerobic exercise of 30-45 min duration per session for eight weeks suggest an important impact in controlling diabetic peripheral neuropathy.

As a randomized control trial study with valid measurement of nerve conduction, this study showed a very promising result. Aside from seeing the impact on peripheral neuropathy itself, this study also found significant result despite of short duration of studies on the dosage of OHA (oral hyperglycemic agent) and insulin. The study suggested that in the management of diabetic neuropathy, aerobic exercise should be prescribed before starting insulin therapy or should be considered in combination with OHA and insulin therapy to prevent, halt or slow down the progression of neuropathy. However, due to small number of samples and large drop outs by the end of the trial, the result may be bias.

This finding is also supported by Kluding PM et al.<sup>10</sup> The study analyzed the effect of exercise on neuropathic symptoms, nerve function, and cutaneous innervation in people with diabetic peripheral neuropathy. With smaller sample size (17 participants), the study used (visual analog scale), Michigan Neuropathy Screening Instrument (MNSI) questionnaire of neuropathic symptoms, nerve function measures, and intraepidermal nerve fiber (IENF) density and branching in distal and proximal lower extremity skin biopsies. What we can compare to study by Dixit S et al is the nerve function measures, and intraepidermal nerve fiber (IENF) density and branching in distal and proximal lower extremity skin biopsies.

The result suggested that significantly improved selected measures of peripheral nerve function ("worst" pain levels and MNSI score), glycemic control (HbA1c), and resting heart rate. Also, there is a significant improvement in the number of branches per fiber in proximal biopsy site. Even though nerve function measures were found insignificant, but there is marked improvement observed. This may happen due to low sample that involved and short duration of intervention. Also, the study has no control group, and limited knowledge of potential mechanisms that can influence the improvements in neuropathic symptoms and cutaneous innervation.

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## CONCLUSION

Both of these studies showed significant benefit of aerobic exercise, despite the short duration of exercise being used as intervention towards improvement in peripheral nerve function. This finding can be applied to the patient and easily implemented to the daily life because there is no harm and cost that can limit the applicability. However, further studies with large samples and longer duration of intervention are needed to confirm the finding.

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