

Prolonged use of statins and peripheral neuropathy: A systematic review

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Abstract

Peripheral neuropathy is one of the most common neurological disorder. Traditionally, diabetes mellitus is the most common aetiology of peripheral neuropathy. However, there are many other aetiologies of peripheral neuropathy, such as drug-induced, spinal trauma, alcoholism, vitamin B12 deficiency, and many more. In previous studies, long-term statin use was also associated with peripheral neuropathy.

We conducted a systematic search through PubMed and Embase using the protocol following the PRISMA statement in making a systematic review. We included article that published in the last 10 years (from 2011 until July 2020). Two reviewers extracted data from the articles that have been selected. We extracted the study population, study design, type of intervention, control variable, p-value, and the outcome of the study

We found 250 journals in our search strategy, and at the end, 4 journals included. Some studies revealed that peripheral neuropathy was observed during the long-term treatment of statin. However, some studies also revealed that statin does not increase the risk of peripheral neuropathy.

The possible mechanism of statin-induced peripheral neuropathy in humans are disturbing the function and integrity of cell membrane, the role of alfa-tocopherol or Vitamin E, and the role of ubiquinone (Coenzyme Q10). In contrast, it is believed that statins lowering the risk of peripheral neuropathy through the anti-inflammatory effects of statins. Different result from each study can be caused by various factors. Besides the peripheral neuropathy side effect that described in the literature, statins are well tolerated. Awareness the side effects would lead to better treatment. Future study about association between statins and peripheral neuropathy is needed.

Keywords: Peripheral neuropathy; prolonged use; statins

INTRODUCTION

Peripheral neuropathy is one of the most common neurological disorder. Symptoms of peripheral neuropathy such as tingling sensation, pain, numbness, and also weakness. The symptoms usually first affect the legs, then hands, and the other part of body. Sometimes, it is called stocking-gloves patterns because the boundaries of the symptoms are clear like we wear the stocking-gloves (1). Peripheral neuropathy happens at any age, but most common found over 55 years of age (2). Traditionally, diabetes mellitus is the most common aetiology of peripheral neuropathy. However, there are many other aetiologies of peripheral neuropathy, such as drug-induced, spinal trauma, alcoholism, vitamin B12 deficiency, and many more. About 26% of people over 65 years of age, develop peripheral neuropathy without any aetiology and predisposing factors (3).

Drug-induced neuropathy is one of the main causes of peripheral neuropathy. The prevalence of drug-induced neuropathy is about 2-4% (4,5). Chemotherapy drugs, metronidazole, allopurinol, phenytoin, and colchicine may develop peripheral neuropathy. In previous studies, long-term statin use was also associated with peripheral neuropathy. Several statin patients report that they experienced neuropathic pain, thus creating the question of whether statins cause peripheral neuropathy or not (6). Statins are the drugs most common used to lower blood cholesterol. Statin is a Hydroxymethyl-glutaryl-CoA (HMG-CoA) reductase inhibitor, that lowering plasma cholesterol, especially Low-density Lipoprotein (LDL) (7). Due to role of statin that lowering cholesterol production, it may disturb the function and integrity of cell membrane. (8) Statins also inhibit ubiquinone (Coenzyme Q10), an important enzyme for mitochondrial respiration. Inhibiting

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ubiquinone may reduce the produce of energy that is required for nerve cells. Therefore, statins may have side effects such as central nervous system disorders and peripheral neuropathy (9,10).

Since statin is the most widely used lipid-lowering drugs, awareness the side effects would lead to better treatment. The purpose of this review is to perform a systematic review to identify association between prolonged use of statins and peripheral neuropathy.

Searching and Screening

We conducted a systematic search through PubMed and Embase using the protocol following the PRISMA statement in making a systematic review. We included article that published in the last 10 years (from 2011 until July 2020). We used specific keywords 1. "STATIN"; AND 2. "PERIPHERAL NEUROPATHY" on search database.

Inclusion and Exclusion Criteria

We included original and published articles with a cohort, cross-sectional, experimental, randomized-controlled

trial, and case-control study designs. We exclude articles that are descriptive studies, case reports, or qualitative studies. Table 1 presents the eligibility criteria in the PICOS model. First, the title and abstract were screened by two-reviewer, then full-text screening was performed based on the eligibility criteria.

Data Extraction

Two reviewers extracted data from the articles that have been selected. We extracted the study population, study design, type of intervention, control variable, p-value, and the outcome of the study. The disagreement of data that have been extracted by two reviewers will be resolved by the third reviewer

Quality Assessment

Fourteen criteria will be identified in each of the included journals. See Table 2 for more info about methodological quality assessment.

Ethical Approval

Ethical approval for this review was not required.

Table 1. Eligibility criteria in PICOS model

	Inclusion	Exclusion
Population	Human, adults (>18 years) with history of statin use	Non-human
Intervention	long-term statins use	Do not observed patients with long term statin use (only with a short-term statin or use other agent of lipid-lowering drugs)
Control	Healthy patients who do not take statins	
Outcomes	peripheral neuropathy as measured by certain method and assessment	besides peripheral neuropathy
Study Design	Cohort Case-control Cross-sectional Randomized-Controlled Trial	Case Report Case Series Descriptive Studies Qualitative studies
Language	English	Non-English
Statistics	An adequate method of statistics that explain the association between 2 variables (p value)	Just only descriptive studies

Study Selection

We found 250 journals in our search strategy. At the first screening, we excluded 50 duplicated journals. Second, the title and abstract were reviewed based on the eligibility criteria, as many as 158 were excluded, 42 remained. At the third screening, full-text was reviewed, as many as 38 journals were excluded. Finally, 4 studies met the eligibility criteria and were included in this review. The flow diagram of systematic searching strategy is showed on Figure 1.

Quality Assessment

Methodological quality of the studies was high. All of the studies described the eligibility criteria, study population, and population characteristic. For the quality of statistical

analysis, all of the studies described statistical model appropriately. All of other item score were 4, except the participation rate, frequencies of most important determinants, and controlled for confounding or effect modification, the score were 3. The quality assessment is presented in the Table 2.

Study Report Characteristics

The studies were conducted in Malaysia, Iran, Turkey, and Czech Republic. There were 2 experimental studies, 1 cohort study, and 1 case-control study. The number of study subjects ranged from 39 to 757. Otruba et al revealed that of the 42 patients who used statins for a long time for more than 2 years, they did not have symptoms of

peripheral neuropathy. But, in the ENMG examination, there was a prolongation of F-waves. So, Otruba et al. concluded that prolonged use of statins can cause silent neuropathy, because there are no symptoms, but found abnormalities on ENMG examination. Ozdemir et al revealed that of the 50 study subjects who used statins for a long time period, 33 out of 50 experienced peripheral neuropathy symptoms. Study results from Mohammad Reza are different from the other 3. Mohammadreza revealed that there was no significant difference between the intervention and control groups ($p=0.055$), but there was a difference between the amplitude of the sural and peroneal nerves which showed that there was peripheral neuropathy. This might be due to the small sample size, which is only 39. In contrast, a study from Warendorf revealed that statin do not increase the risk of polyneuropathy. Whereas, statin use decreased the odds ratio of polyneuropathy as duration of statin exposure increased ($p=0,03$, OR 0,5 95%; CI 0,34-0,9). More info about study characteristic is presented in Table 3.

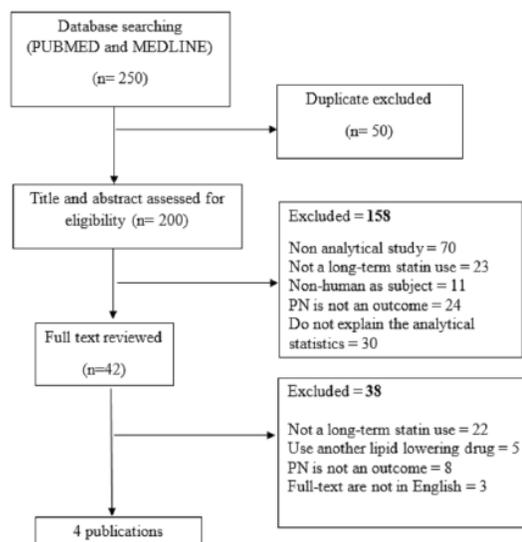


Figure 1. Flow diagram. The search strategy for systematic review

Table 2. Methodological quality assessment					
	Otruba, 2011	Ozdemir, 2019	Warendorf, 2019	Mohammadreza, 2018	Total per item
Study design and object					
1. objective of the study was clear	1	1	1	1	4
Study population					
2. Description of eligibility criteria.	1	1	1	1	4
3. Description of selection of study population	1	1	1	1	4
4. Description of population characteristics	1	1	1	1	4
5. Case-control: definition of cases and control were mentioned	-	-	1	1	2
6. Participation rate is more than 80%	0	0	0	0	0
Measure of instruments					
7. Appropriate definition and assessment of outcome	1	1	1	1	4
8. Appropriate definition and assessment of determinants	1	1	1	1	4
Data					
9. The measurements of most important outcome	1	1	1	1	4
10. Frequencies of most important determinants	1	1	0	1	3
11. Measures of association presented	1	1	1	1	4
Analysis					
12. Appropriate statistical model	1	1	1	1	4
13. Controlled for confounding or effect modification	0	1	1	1	3
Other					
14. No identification of funding sources and conflicts of interest	1	1	1	1	4
15. Other sources of bias (that not mention)	0	0	0	0	0
Total score for each study and/or well performed	11	12	12	13	
1, and/or well performed; 0, has not been reported, has not been well performed or unclear; -, not have been applicable yet					

Table 3. Study Characteristics						
Author	Design	Subject	Intervention	Control	p	Result
Otruba (2011) (11)	RCT	42 patients	Long-term statin (simvastatin 20mg) use (>2 years)	-	<0.001	In this study, there were no peripheral neuropathy symptoms found on neurological examination. However, the Electroneuromyography (ENMG) examination found prolongation of F-wave mean latency on peroneal and tibial nerves. The study confirmed that long-term treatment with statins caused a clinically silent but still definite damage to peripheral nerves when the treatment lasts longer than 2 years
Mohammadreza, 2018(4)	Case-control	78 aged 35-55 years	39 patients who received statin for 6 months	39 healthy controls	0.055	No significant difference between two groups (statin and control group), but there was a significant difference between the amplitude of sural nerve and peroneal nerve, indicates peripheral neuropathy
Ozdemir (2019) (9)	RCT	100 patients	50 patients with long term statin use (>1 year)	50 healthy people who do not take a statin that match for age and gender	<0.01	In the group using long-term statins, the ENMG results revealed polyneuropathy in 33 out of 50 patients (34 on atorvastatin, 16 on rosuvastatin). No polyneuropathy was revealed in control group. There was a significant difference between intervention and control group (p<0.01), but not between atorvastatin and rosuvastatin group (p=0.720). This study showed that long-term use of statin (>1 year) could induced peripheral neuropathy based on ENMG examination
Warendorf, 2019 (12)	Case-control	616 patients	333 with cryptogenic axonal polyneuropathy	283 healthy controls	P=0.03; OR 0.5 95% CI 0.34-0.95	Statin use decreased the odds ratio of polyneuropathy as duration of statin exposure increased

In this systematic review, we tried to identify the association between prolonged use of statins and peripheral neuropathy. The most common neurological manifestation of prolonged use of statin is muscular disorder, from mild to severe like rhabdomyolysis and myoglobinuria. The second neurological manifestation is peripheral neuropathy. Some studies revealed that peripheral neuropathy was observed during the long-term treatment of statin (13). However, some studies also revealed that statin does not increase the risk of peripheral neuropathy (12). In human studies, statins may induce peripheral neuropathy. But in animal studies, statins reduced the risk of peripheral neuropathy.

The possible mechanism of statin-induced peripheral neuropathy in humans are disturbing the function and

integrity of cell membrane, the role of alfa-tocopherol or Vitamin E, and the role of ubiquinone (Coenzyme Q10). Vitamin E or alfa-tocopherol is a fat-soluble vitamin and has a function in maintaining nerve health. It is transported to tissue by LDL.(4) Thus, lowering LDL means lowering the transport of alfa-tocopherol, and may play a role in peripheral neuropathy (14). The association between ubiquinone, statin, and peripheral neuropathy is not well explained. Ubiquinone is an enzyme for mitochondrial respiration, and statins inhibit this enzyme. Inhibiting ubiquinone may reduce the production of energy that is required for nerve cells. Therefore, statins may have side effects such as central nervous system disorders and peripheral neuropathy.

While peripheral neuropathy is associated indirectly with poor glycaemic control in diabetes, peripheral neuropathy is also found in people who do not have diabetes, but hyperlipidemia (15). Association between hyperlipidemia and peripheral neuropathy has been discussed. People with hyperlipidemia have high amounts of LDLs and oxysterols, that promotes the proliferation of pro-inflammatory cytokines. Thus, it may cause local inflammatory lesions on the peripheral neuron (16). In animal studies, it is believed that statins lowering the risk of peripheral neuropathy through the anti-inflammatory effects of statins. In in-vitro study, statins decrease the proliferation of monocyte and pro-inflammatory cytokines such as interleukin-2, interleukin-4, interleukin-6, and interferon- γ (17).

Different result from each study can be caused by various factors. One of which is the methods and tools for diagnosing peripheral neuropathy. Some study uses ENMG for diagnosing PN, while some study only uses a questionnaire to diagnose PN. It is known that the gold standard to diagnose PN is using ENMG, because the symptoms may be silent. It is proven by the study of Otruba. There were no peripheral neuropathy symptoms found on neurological examination but found the prolongation of F-wave in ENMG examination. (11) Comorbid factors like cardiovascular disease and metabolic syndrome could lead to over-diagnose statin-induced peripheral neuropathy since these conditions are also associated with cryptogenic axonal polyneuropathy (18).

There are some limitations to this review. First, the small number of studies included in this review (only 4 studies). Second, there were different diagnostic criteria, modality, and another comorbid factor in each included study. Third, not all study explained the dosage and type of statin that used for intervention. So, there might be under or over-diagnose. Hopefully, this systematic review could give update information about the related topic.

CONCLUSIONS

Statin is the most widely used lipid-lowering drugs and often used for a long time period. Their efficacy and effectiveness for treating hypercholesterolemia were well established. Besides the peripheral neuropathy side effect that described in the literature, statins are well tolerated. The benefits and disadvantages must be considered. Awareness the side effects would lead to better treatment. Future study about association between statins and peripheral neuropathy is needed.

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REFERENCES

- Mohamed A Hammad, Syed Azhar Syed Sulaiman, Saleh Alghamdi, et al. Statins-related Peripheral Neuropathy Among Diabetic Patients. *Diabetes & Metabolic Syndrome: Clinical Research and Reviews*. Elsevier,2020;14:341-6.
- St Charles JL, Bell JA, Gadsden BJ, et al. Guillain Barré Syndrome is induced in Non-Obese Diabetic (NOD) mice following *Campylobacter jejuni* infection and is exacerbated by antibiotics. *J Autoimmun* 2017;77:11-38.
- West B. The implications of statin induced peripheral neuropathy. *J Foot Ankle Res* 2011;4:57.
- Emad M, Arjmand H, Farpour HR, Kardeh B. Lipid-lowering drugs (statins) and peripheral neuropathy. *Electron Physician* 2018;10:6527-33.
- de Langen JJ, van Puijenbroek EP. HMG-CoA-reductase inhibitors and neuropathy: Reports to the Netherlands Pharmacovigilance Centre. *Neth J Med* 2006;64:334-8.
- McCarberg B, D'Arcy Y, Parsons B, et al. Neuropathic pain: a narrative review of etiology, assessment, diagnosis, and treatment for primary care providers. *Current Medical Research and Opinion*. 2017;33:1361-9.
- Svendson T de K, Nørregaard Hansen P, García Rodríguez LA, et al. Statins and polyneuropathy revisited: case-control study in Denmark, 1999–2013. *Br J Clin Pharmacol* 2017;83:2087-95.
- Bosomworth NJ. Statin therapy as primary prevention in exercising adults: Best evidence for avoiding Myalgia. *J Am Board Fam Med* 2016;29:727-40.
- Ozdemir IH, Copkiran O, Tikiz H, et al. Peripheral polyneuropathy in patients receiving long-term statin therapy. *Turk Kardiyol Dern Ars* 2019;47:554-63.
- Apostolopoulou M, Corsini A, Roden M. The role of mitochondria in statin-induced myopathy. *Eur J Clin Invest* 2015;45:745-54.
- Otruba P, Kanovsky P, Hlustik P. Treatment with statins and peripheral neuropathy: Results of 36-months a prospective clinical and neurophysiological follow-up. *Neuroendocrinol Lett* 2011;32:688-90.
- Warendorf JK, Vrancken AFJE, Van Eijk RPA, et al. Statins do not increase risk of polyneuropathy A case-control study and literature review. *Neurology*. 2019;92:2136-44.
- Golomb BA, Evans MA. Statin adverse effects: A review of the literature and evidence for a mitochondrial mechanism. *American Journal of Cardiovascular Drugs* 2008;8:373-418.
- Muller DPR. Vitamin E and neurological function. *Molecular Nutrition and Food Research* 2010;62:107-12.
- Rajabally YA. Neuropathy and impaired glucose tolerance: An updated review of the evidence. *Acta Neurologica Scandinavica* 2011;124:1-8.
- Vincent AM, Hinder LM, Pop-Busui R, et al. Hyperlipidemia: A new therapeutic target for diabetic neuropathy. *Journal of the Peripheral Nervous System*. 2009;14:257-67.
- Gustavsson C, Agardh CD, Zetterqvist A V., et al. Vascular cellular adhesion molecule-1 (VCAM-1) expression in mice retinal vessels is affected by both hyperglycemia and hyperlipidemia. *PLoS One*. 2010; 5:12699.

18. Visser NA, Vrancken AFJE, Van Der Schouw YT, et al. Chronic idiopathic axonal polyneuropathy is associated with the metabolic syndrome. *Diabetes Care* 2013;36:817-22.