

NARRATIVE REVIEW

Statins an oft-prescribed drug is implicated in peripheral neuropathy: The time to know more

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Abstract

Statins are hydroxymethylglutaryl-coenzyme A reductase inhibitors inhibit denovo cholesterol synthesis leading to reduction of serum cholesterol and low density lipoprotein as well as elevation of high density lipoprotein level. Statins are used in the treatment of dyslipidaemia, prevention of major cardiovascular events and complications. The potential role of statins in the induction of peripheral neuropathy has not been verified as most of statins induced-peripheral neuropathy had been reported as case reports. Also, statins therapy leads to noteworthy reduction of Coenzyme Q10, causing impairment of neuronal energy. The incidence of polyneuropathy was high with atorvastatin (65%) which is lipophilic, and relatively less with fluvastatin (54%) which is hydrophilic. Long-term statins therapy, mainly with atorvastatin and simvastatin, is linked with the development of peripheral neuropathy.

Keywords: Statins, Peripheral neuropathy, Dyslipidaemia.

Introduction

Peripheral neuropathy (PN) is a term used to describe dysfunctions and disorders of the peripheral nervous system. PN leads to impairment of movements and/or sensations depending on the affected neurons. Single nerve neuropathy is called mono-neuropathy, while two or more affected neurons in different body areas are called mononeuritis multiplex.¹ PN may be acute or chronic, depending on the time of its onset. PN is more precisely classified into motor, sensory and autonomic neuropathies.² Sensory symptoms comprise numbness, tingling and prickling sensations as well as positive sensory symptoms such as freezing, burning and throbbing sensations which are common in acquired neuropathy and rare in hereditary PN.³ Motor neuropathy leads to muscle weakness, cramping, paresis and wasting. Autonomic neuropathy is characterised by constipation and/or diarrhoea, urinary

retention, erectile dysfunction, dry eye, dry mouth, excessive sweating, postural hypotension and tachycardia.⁴ Electro-diagnostic investigations, including needle electromyography and nerve conduction studies, are recommended for accurate and precise diagnosis of PN.

Drug-induced PN is one of the chief causes after diabetes mellitus, and it is of immense value in early diagnosis since; stopping the relevant drugs leads to significant recovery. Drugs that are implicated in the induction of PN including allopurinol, amiodarone, metronidazole, hydralazine, enalapril, colchicines and phenytoin.⁵

Statins Family

Statins are hydroxymethylglutaryl-coenzyme A (HMG-CoA) inhibitors that inhibit denovo cholesterol synthesis leading to reduction of serum cholesterol and low density lipoprotein (LDL) with an increase in high density lipoprotein (HDL) level. The statins family comprises synthetic statins, like atorvastatin, rosuvastatin, fluvastatin and cerivastatin, and natural statins, like mevastatin, lovastatin, pravastatin and simvastatin, which differ in their half-life, potency and lipophilicity. Regardless of their differences in the chemical structure, all bind HMG-CoA, leading to competitive inhibition of natural substrate of this enzyme. Therefore, conversion of mevalonic acid into cholesterol is reduced that activates expression of LDL receptor gene which helps in the reduction of circulating LDL and cholesterol.⁶

Statins are used in the treatment of dyslipidaemia and the prevention of major cardiovascular events and complications.⁷ Moreover; statins inhibit endothelial dysfunction and plaque-associated inflammatory reactions independent of its cholesterol-reducing effect, suggesting that statins have potential pleiotropic effects.⁸

Pleiotropic effects including; improvement of endothelial function, preserve plaque stability, prevention of blood clot formation and modulation of inflammatory responses.⁹ Recently, statins have been found to have significant anti-bacterial activity and have illustrated synergistic effects with different antibiotics.¹⁰

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Adverse Effects of Statins

Muscle Damage

Long-term statins therapy increases the risk of muscle damage which accounts for 10-15% of the users. Rhabdomyolysis, which is destruction of muscle cells, may occur rarely during statins therapy. Statins-induced-muscle damage occurs more in old age, in people with hypothyroidism and concomitant use of fibrates. It has been reported that hydrophilic statins are less toxic than lipophilic statins as lovastatin increases expression of atrogen-1 gene which is linked with the induction of skeletal muscle fibre destruction.¹¹

Cognitive Deficits

Statins therapy might cause reversible cognitive deficits as reported by the Food and Drug Administration (FDA).¹² However, meta-analysis studies have concluded that the present evidences does not support the link between statins and cognitive deficits. Some studies have illustrated that statins therapy improves cognitive function and reduces the risk of dementia in patients with cardiovascular complications.¹³

Type 2 Diabetes Mellitus (T2DM)

Prolonged use of statins increase the risk of type 2 diabetes mellitus (T2DM) due to the inhibition of peripheral glucose uptake through down-regulation of glucose uptake transporter-1 (GLT1) whose activity depends on cholesterol. Also, statins are thought to decrease insulin sensitivity and to inhibit insulin secretion due to damaged β -cells of islet of Langerhan.¹⁴

Drug-drug Interactions

High doses of statins, or when combined with niacin or fibrates, increase the risk of rhabdomyolysis. Bitter orange and grape fruit juice inhibits metabolism of certain statins. Besides, protease inhibitors inhibit statins metabolism and increase the risk of myopathy.¹⁵

Consequently, extensive and broad usage of statins necessitates research into the significant side effects, such as PN.

Statins Induced-peripheral Neuropathy

These drugs may cause distal axonal damage, degeneration of the myelin sheath and nerve roots deterioration. Nevertheless, the potential role of statins in the induction of PN has not been verified as most of statins-induced PN cases have been reported as case reports. The main mechanisms of statins induced-PN are linked to the reduction of cholesterol which is necessary

for the myelin sheath of peripheral neurons.¹⁶ Also, statin therapy leads to significant reduction of coenzyme Q10 (CoQ10) which causes impairment of neuronal energy. CoQ10 is an endogenous anti-oxidant essential for the mitochondrial transport chain found in all cell membranes that participate in the regulation and prevention of lipid and protein peroxidation.¹⁷ In rare circumstances, one case for every 2200 statin users developed large fibre neuropathy which might be due to neuronal mitochondrial dysfunction caused by the inhibition of ubiquinone and/or depletion of neuronal membrane cholesterol.¹⁸ The link between small fibre neuropathy and statins therapy is limited. Previously, a study confirmed the association between statins and painful PN.¹⁹ On the contrary, another study reported significant ameliorative effects of statins on diabetic PN.²⁰

Moreover, statins induced-PN is never fibre length independent as statins lead to thigh sensory and autonomic neuropathy with sparing of distal axons in the feet. The reason behind this phenomenon is statin induced-ganglionopathy as statins may cause degeneration of sensory and autonomic ganglions. This type of ganglionopathy may be sub-acute or chronic, leading to neuropathic dysfunction due to the reduction of nerve fibre density.²¹

The probable mechanisms of statins induced-ganglionopathy and/or neuropathy are due to induction of neuronal apoptosis and necrosis as well as myelin sheath degeneration due to inhibiting the conversion of HMG-CoA into mevalonate which is essential for neuronal cholesterol. Besides, mevalonate is necessary for neuronal ubiquinone and adenosine triphosphate (ATP) production. Consequently, the reduction of mevalonate leads to the reduction of farnesyl-pyrophosphate which is involved in the production of geranyl-geranyl pyrophosphate which is responsible for the production of anti-apoptotic proteins that inhibit neuronal apoptosis.^{22,23}

Additionally, epidemiological studies illustrated equivocal results in the association between statins and risk of PN, but remain indistinct whether hyper-cholesterolaemia or statins is the main cause of PN.²⁴

However, a recent study reported dose-independent effect of statins in the induction PN, so there is no apparent dose-response pattern between statins and risk of PN which may give a clue for the negative association between statins and risk of PN.²⁵ Besides, a study reported that risk of statins induced-neuropathy is typically developed after long-term therapy and, therefore, statins-induced neuropathy is cumulatively dose-dependent.²⁶ A

study illustrated that statins induced-neuropathy sets in after two years of therapy and neuropathic manifestations are reduced and relieved by statins discontinuation. These symptoms reappear after resumption of the statins therapy.²⁷

Previously, in vitro studies have shown that fluvastatin led to neuritic degeneration for cultured spinal motor neurons. Simvastatin and pravastatin might cause neuritic degeneration only at a higher concentration. Besides, peripheral neurons are less susceptible to the toxic effect of statins compared to spinal neurons, suggesting different mechanism of neuronal toxicity. Hydrophilic statins, like pravastatin and rosuvastatin, demonstrated less peripheral neuronal damage compared with lipophilic statins, like simvastatin and rosuvastatin, due to the difference in the compartmental pharmacokinetics.²⁸

Tall et al's animal model study confirmed that statins have a potential effect on mitochondrial membrane through inhibition of carnitine palmitoyl transferase leading to the reduction of the attachment of Ras-family protein (Rab5) which is involved in neuronal endocytosis.²⁹

Accumulating evidence supports a key role for extracellular signal-regulated kinase 1/2 (ERK1/2) signaling in the development of the central nervous system (CNS) and in the regulation of peripheral neuron functions. ERK1/2, is one of the most well characterized members of the mitogen-activated protein kinase family, regulates a range of processes, from metabolism, motility and inflammation, to cell death and survival. In the nervous system, ERK1/2 regulates synaptic plasticity, brain development and repair of neuronal damage. ERK1/2 is also has a potent effect on of neuronal death and neuroinflammation in PN.³⁰ Akt is one of the central kinases that perform a pivotal function in mediating survival signaling in a wide range of neuronal cell types in response to growth factor stimulation, it prohibits neuronal death.³¹

Yanae et al illustrated that, statins provoke glioma cell line apoptosis and induce membrane damage through modulation of AKT and ERK1/2 pathways in the peripheral neurons, signifying different molecular pathways in normal and abnormal neuronal cells.³²

Moreover, a recent study confirmed the usefulness of rosuvastatin in the PN management through the reduction of pro-inflammatory biomarkers.³³ In contrast, Carrillo-Ibarra et al reported that both simvastatin and rosuvastatin did not reduce the biomarkers of deoxyribonucleic acid (DNA) oxidative damage in

patients with diabetic PN.³⁴ Furthermore, a previous double-blind, placebo-controlled clinical trial demonstrated that statins were not superior to placebo in the attenuation of diabetic PN after 16 weeks of intervention in spite of reduction of oxidative stress by statins.³⁵

Dyslipidaemia and the Risk of Statins induced-peripheral Neuropathy

Dyslipidemia may be a risk factor in the development of PN regardless of the statins therapy. Oxidised LDL (oxLDL) serum levels are linked with the incidence and progression of PN. It has been reported that oxLDL is responsible for neuronal damage through the induction of apoptotic injury, including activation of caspase-3 and cytochrome-c with the reduction of anti-apoptotic pathway. Besides, oxLDL reduces native protective neuronal LDL receptors.³⁶ Therefore, rosuvastatin but not atorvastatin improves symptoms and severity of PN due to reduction of oxLDL, lipid peroxidation and oxidative stress sera levels after three months of therapy, indicating that hydrophilic but not lipophilic statins are less associated with risk of PN.³⁷

Likewise, dyslipidaemia may be considered as an independent risk factor in the progression and development of PN. Animal model study confirmed that high-fat diet (HFD) in mice with leptin deficiency leads to dyslipidaemia and decreases nerve conduction velocity with potential sensory deficit.³⁸ Nevertheless, Vincent et al illustrated that apolipoprotein-knockout mice with dyslipidaemia did not develop PN.³⁹

It has been reported that statins might affect autonomic neurons since; atorvastatin but not rosuvastatin reduces sympathetic nerve activity due to the lipophilic property of atorvastatin.⁴⁰ This finding gives evidence that hydrophilic statins do not penetrate the neuronal membrane and do not produce an effect on neuronal metabolism and function. As well, the association between statins and risk of PN was high with atorvastatin (65%), which is lipophilic, and relatively less with fluvastatin (54%), which is hydrophilic.⁴¹ Hence, hyperlipidaemia and statins are inter-related as causative factors in the induction of PN, but statins are still used in patients with major cardiovascular events like myocardial infarction and ischaemic stroke.⁴² Consequently, statins are mainly blamed for peripheral neuronal damage and PN.

Therefore, large-scale studies are recommended to explore the effect of individual statins on nerve electrophysiology in normal healthy volunteers to precisely

elucidate the effect of statins on nerve physiology.

Conclusion

Long-term statins therapy, mainly with atorvastatin and simvastatin, are associated with the development of peripheral neuropathy.

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References

1. Watson JC, Dyck PJ. Peripheral neuropathy: a practical approach to diagnosis and symptom management. *Mayo Clin Proc* 2015;90:940-51.
2. Pan Q, Li Q, Deng W, Zhao D, Qi L, Huang W, et al. Prevalence of and risk factors for peripheral neuropathy in chinese patients with diabetes: a multicenter cross-sectional study. *Front Endocrinol (Lausanne)* 2018;9:617.
3. Jember G, Melsew YA, Fisseha B, Sany K, Gelaw AY, Janakiraman B. Peripheral sensory neuropathy and associated factors among adult diabetes mellitus patients in Bahr Dar, Ethiopia. *J Diabetes MetabDisord*2017;16:16.
4. Vill K, Müller-Felber W, Gläser D, Kuhn M, Teusch V, Schreiber H, et al. SACS variants are a relevant cause of autosomal recessive hereditary motor and sensory neuropathy. *Hum Genet* 2018;137:911-19.
5. Vilholm OJ, Christensen AA, Zedan AH, Itani M. Drug-induced peripheral neuropathy. *Basic Clin PharmacolToxicol*2014;115:185-92.
6. Navarese EP, Buffon A, Andreotti F, Kozinski M, Welton N, Fabiszak T, et al. Meta-analysis of impact of different types and doses of statins on new-onset diabetes mellitus. *Am J Cardiol*2013;111:1123-30.
7. Alkuraishy HM, Al-Gareeb AI, Waheed HJ. Lipoprotein-associated phospholipase A2 is linked with poor cardio-metabolic profile in patients with ischemic stroke: a study of effects of statins. *J Neurosci Rural Pract*2018;9:496-503.
8. Byrne P, Cullinan J, Murphy C, Smith SM. Cross-sectional analysis of the prevalence and predictors of statin utilisation in Ireland with a focus on primary prevention of cardiovascular disease. *BMJ Open* 2018;8:e018524.
9. Labos C, Brophy JM, Smith GD, Sniderman AD, Thanassoulis G. Evaluation of the pleiotropic effects of statins: a reanalysis of the randomized trial evidence using egger regression-brief report. *ArteriosclerThrombVasc Biol* 2018;38:262-65.
10. Al-Kuraishy HM, Al-Gareeb AI, Al-Buhadily AK. Rosuvastatin as forthcoming antibiotic or as adjuvant additive agent: In vitro novel antibacterial study. *J Lab Physicians* 2018;10:271-75.
11. Newman CB, Tobert JA. Statin-Related Myopathy and Rhabdomyolysis. In: Matfin G. *Endocrine and Metabolic Medical Emergencies: A Clinician's Guide* 2nd ed. Hoboken, NJ: Endocrine Society and Wiley Blackwell Press, 2018; pp 760-74.
12. US Food and Drug Administration. FDA Drug Safety Communication: Important safety label changes to cholesterol-lowering statin drugs. Rockville, MD: US Food and Drug Administration, 2012.
13. Chan AK, Fornazzari L, Golas AC, Barfett J, Munoz DG, Schweizer TA, et al. Lipophilic statin use associated with deficits in memory and cognition. *Alzheimers Dement* 2018;14:960-1.
14. Feng Q, Wei WQ, Chung CP, Levinson RT, Sundermann AC, Mosley JD, et al. Relationship between very low low-density lipoprotein cholesterol concentrations not due to statin therapy and risk of type 2 diabetes: A US-based cross-sectional observational study using electronic health records. *PLoS Med* 2018;15:e1002642.
15. Bellosta S, Corsini A. Statin drug interactions and related adverse reactions: an update. *Expert Opin Drug Saf*2018;17:25-37.
16. Emad M, Arjmand H, Farpour HR, Kardeh B. Lipid-lowering drugs (statins) and peripheral neuropathy. *Electron Physician* 2018;10:6527-33.
17. Montano SJ, Grünler J, Nair D, Tekle M, Fernandes AP, Hua X, et al. Glutaredoxin mediated redox effects of coenzyme Q10 treatment in type 1 and type 2 diabetes patients. *BBA Clin* 2015;4:14-20.
18. Kiortsis DN, Filippatos TD, Mikhailidis DP, Elisaf MS, Liberopoulos EN. Statin-associated adverse effects beyond muscle and liver toxicity. *Atherosclerosis* 2007;195:7-16.
19. Lo YL, Leoh TH, Loh LM, Tan CE. Statin therapy and small fibre neuropathy: a serial electrophysiological study. *J Neurol Sci* 2003;208:105-8.
20. Hernández-Ojeda J, Román-Pintos LM, Rodríguez-Carrizalez AD, Troyo-Sanromán R, Cardona-Muñoz EG, Alatorre-Carranza Mdel P, et al. Effect of rosuvastatin on diabetic polyneuropathy: a randomized, double-blind, placebo-controlled Phase IIa study. *Diabetes MetabSyndrObes*2014;7:401-7.
21. Gemignani F, Giovanelli M, Vitetta F, Santilli D, Bellanova MF, Brindani F, et al. Non-length dependent small fiber neuropathy: a prospective case series. *J PeripherNerv Syst* 2010;15:57-62.
22. Prospective Studies Collaboration, Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet* 2007;370:1829-39.
23. Al-Kuraishy HM, Al-Gareeb AI. Aclylation-stimulating protein is a surrogate biomarker for acute myocardial infarction: role of statins. *J Lab Physicians* 2017;9:163-69.
24. Teunissen LL, Franssen H, Wokke JH, Van Der Graaf Y, Linsen WH, Banga JD, et al. Is cardiovascular disease a risk factor in the development of axonal polyneuropathy? *J Neurol Neurosurg Psychiatry* 2002;72:590-5.
25. Wallach-Kildemoes H, Stovring H, Holme Hansen E, Howse K, Pétursson H. Statin prescribing according to gender, age and indication: what about the benefit-risk balance? *J Eval Clin Pract*2016;22:235-46.
26. Grover HS, Luthra S, Maroo S. Are statins really wonder drugs? *J Formos Med Assoc* 2014;113:892-8.
27. Otruba P, Kanovsky P, Hlustik P. Treatment with statins and peripheral neuropathy: results of 36-months a prospective clinical and neurophysiological follow-up. *Neuro Endocrinol Lett* 2011;32:688-90.
28. Murinson BB, Haughey NJ, Maragakis NJ. Selected statins produce rapid spinal motor neuron loss in vitro. *BMC MusculoskeletDisord*2012;13:100.
29. Tall GG, Barbieri MA, Stahl PD, Horazdovsky BF. Ras-activated endocytosis is mediated by the Rab5 guanine nucleotide exchange activity of RIN1. *Dev Cell* 2001;1:73-82.
30. Sun J, Nan G. The extracellular signal-regulated kinase 1/2 pathway in neurological diseases: a potential therapeutic target (Review). *Int J Mol Med* 2017;39:1338-46.
31. Ahn JY. Neuroprotection signaling of nuclear akt in neuronal cells.

- Exp Neurobiol 2014;23:200-6.
32. Yanae M, Tsubaki M, Satou T, Itoh T, Imano M, Yamazoe Y, et al. Statin-induced apoptosis via the suppression of ERK1/2 and Akt activation by inhibition of the geranylgeranyl-pyrophosphate biosynthesis in glioblastoma. *J Exp Clin Cancer Res* 2011;30:74.
 33. Miranda HF, Sierralta F, Aranda N, Poblete P, Castillo RL, Noriega V, et al. Antinociception induced by rosuvastatin in murine neuropathic pain. *Pharmacol Rep* 2018;70:503-08.
 34. Carrillo-Ibarra S, Miranda-Díaz AG, Sifuentes-Franco S, Cardona-Muñoz EG, Rodríguez-Carrizalez AD, Villegas-Rivera G, et al. Effect of statins on oxidative DNA damage in diabetic polyneuropathy. *J Circ Biomark* 2018;7:e1849454418804099.
 35. Villegas-Rivera G, Román-Pintos LM, Cardona-Muñoz EG, Arias-Carvajal O, Rodríguez-Carrizalez AD, Troyo-Sanromán R, et al. Effects of ezetimibe/simvastatin and rosuvastatin on oxidative stress in diabetic neuropathy: a randomized, double-blind, placebo-controlled clinical trial. *Oxid Med Cell Longev* 2015;2015:e756294.
 36. Vincent AM, Hinder LM, Pop-Busui R, Feldman EL. Hyperlipidemia: a new therapeutic target for diabetic neuropathy. *J Peripher Nerv Syst* 2009;14:257-67.
 37. Hernández-Ojeda J, Román-Pintos LM, Rodríguez-Carrizalez AD, Troyo-Sanromán R, Cardona-Muñoz EG, Alatorre-Carranza Mdel P, et al. Effect of rosuvastatin on diabetic polyneuropathy: a randomized, double-blind, placebo-controlled Phase IIa study. *Diabetes Metab Syndr Obes* 2014;7:401-7.
 38. Wiggins TD, Sullivan KA, Pop-Busui R, Amato A, Sima AA, Feldman EL. Elevated triglycerides correlate with progression of diabetic neuropathy. *Diabetes* 2009;58:1634-40.
 39. Vincent AM, Hayes JM, McLean LL, Vivekanandan-Giri A, Pennathur S, Feldman EL. Dyslipidemia-induced neuropathy in mice: the role of oxLDL/LOX-1. *Diabetes* 2009;58:2376-85.
 40. Tokuhisa H, Murai H, Okabe Y, Hamaoka T, Sugimoto H, Mukai Y, et al. Differential effects of lipophilic and hydrophilic statins on muscle sympathetic nerve activity in heart failure with preserved left ventricular ejection fraction. *Auton Neurosci* 2018;213:8-14.
 41. Gaist D, Jeppesen U, Andersen M, García Rodríguez LA, Hallas J, Sindrup SH. Statins and risk of polyneuropathy: a case-control study. *Neurology* 2002;58:1333-7.
 42. Al-Kuraishy HM, Al-Gareeb AI. Effects of rosuvastatin alone or in combination with omega-3 fatty acid on adiponectin levels and cardiometabolic profile. *J Basic Clin Pharm* 2016;8:8-14.
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