Turk Kardiyol Dern Ars 2019;47(7):554-563 doi: 10.5543/tkda.2019.78379

ORIGINAL ARTICLE

Peripheral polyneuropathy in patients receiving long-term statin therapy

Uzun dönem statin kullanan hastalarda periferik polinöropati gelişimi

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ABSTRACT

Objective: Peripheral neuropathy is an important potential side effect of statin use. This study was an investigation of the incidence of peripheral neuropathy in patients taking atorvastatin or rosuvastatin for hypercholesterolemia and the relationship to the dose and duration of the treatment.

Methods: In all, 50 patients using a statin treatment and 50 healthy controls matched for age and gender who had never taken a statin were included in the study. Polyneuropathy was assessed with a neurological examination and electroneuromyography (ENMG).

Results: While no polyneuropathy was detected in the control group, polyneuropathy was seen in 33 (66%) of the patients in the statin group (p<0.01). There was no significant difference between the 2 statin groups in the results of the neurological examination or the ENMG findings regarding the incidence of polyneuropathy (p=0.288 and p=0.720, respectively). Neuropathy was observed in a neurological examination performed within the first year in 50% of the rosuvastatin users and 18% of those taking atorvastatin. The severity of the polyneuropathy increased with the duration of the treatment in the atorvastatin group (p=0.030).

Conclusion: This study revealed an increased risk of peripheral neuropathy with long-term statin use (>1 year). Electrodiagnostic changes have been detected in motor and sensory nerves in nerve conduction studies of patients on long-term statin treatment. The assessment of neurological symptoms, like tingling, numbness, pain and tremor in the hands and feet, and unsteadiness during walking associated with peripheral neuropathy may be useful in the follow-up of the patients on long-term statin treatment. Early detection of peripheral neuropathy and changing hypercholesterolemia treatment may prevent permanent nerve damage.

ÖZET

Amaç: Periferik nöropati, statinlerin önemli bir yan etkisidir. Çalışmamızda hiperkolesterolemi nedenli atorvastatin veya rosuvastatin kullanan hastalarda perferik polinöropati insidansını ve bunun tedavi dozu ve süresi ile ilişkisini araştırdık.

Yöntemler: Statin kullanan 50 hasta ve hiçbir zaman statin kullanmamış olan cinsiyet ve yaş ile eşleştirilmiş 50 sağlıklı kontrol grubu alındı. Polinöropati, nörolojik muayene ve elektronöromiyografi (ENMG) ile değerlendirildi.

Bulgular: Kontrol grubunda polinöropati saptanmazken, statin grubunda 33 (%66) hastada (p<0.01) polinöropati saptandı. Statin grupları arasında nörolojik muayene, ENMG bulguları ve polinöropati insidansı arasında anlamlı fark yoktu (sırasıyla, p=0.288 ve p=0.720). Nörolojik muayenede ilk yıl içinde nöropati gözlendi (rosuvastatin %50, atorvastatin %18). Polinöropatinin şiddeti atorvastatin grubunda tedavi süresi ile arttı (p=0.030).

Sonuç: Çalışmamız uzun süreli statin kullanımı ile periferik nöropati riskinin arttığını ortaya koymuştur (bir yıldan fazla). Kontrol grubundaki bireylere göre uzun süreli statin tedavisi alan hastalarda sinir iletim çalışmalarında motor ve duyusal sinirlerde elektrodiyagnostik değişiklikler saptanmıştır. Periferik nöropati ile ilişkili olarak yürüme sırasında ellerde ve ayaklarda karıncalanma, uyuşma, ağrı ve titreme gibi nörolojik semptomların değerlendirilmesi uzun süreli statin tedavisi alan hastaların takibinde yararlı olabilir. Periferik nöropatinin erken saptanması ile hiperkolesterolemi tedavisi değiştirilerek kalıcı sinir hasarı önlenebilir.

Received: April 10, 2018 *Accepted:* March 12, 2019

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Statins are the drugs most widely prescribed to lower blood cholesterol.[1] They block cholesterol synthesis through the inhibition of the hydroxymethylglutaryl-CoA (HMG-CoA) reductase enzyme. Recent studies have indicated statin inhibition of the synthesis of ubiquinone, an enzyme present in all respiring eukaryotic cells, primarily in the mitochondria. It is a component of the electron transport chain and participates in aerobic cellular respiration, which generates energy in the form of adenosine triphosphate, providing 95% of the human body's energy. Coenzyme Q_{10} (CoQ_{10}) shares a biosynthetic pathway with cholesterol. The synthesis of an intermediary precursor of CoQ_{10}, mevalonate, is inhibited by some beta blockers and statins. Statins can reduce serum levels of CoQ_{10} by up to 40%.[2]

This inhibitory effect may reduce the production of energy required for striated muscle fibers and nerve cells.[3] Statins may have other side effects as well, including gastrointestinal disorders, headache, skin rash, sleep disturbances, central nervous system disorders, drug interactions, peripheral neuropathy, myopathy, and increased levels of liver enzymes.

Peripheral neuropathy refers to disorders of the peripheral nervous system affecting sensory, motor, and/or autonomic nerves. There are numerous causes and diverse presentations. Sensory symptoms such as prickling, tingling, numbness, and a sensation of limbs locking in place have been reported. Motor symptoms usually manifest as paresis. Autonomic neuropathy occurs when the nerves that control involuntary bodily functions are damaged. The symptoms can include diarrhea, syncope, light-headedness, urinary problems, early satiety, constipation, dry mouth, dry eyes, diminished or excessive perspiration, and erectile dysfunction.[4] These symptoms may also be related to diabetes, alcoholism, toxin exposure, metabolic disorders, vitamin B12 deficiency, or may be a side effect of other drugs.[5] The prevalence of peripheral neuropathy is approximately 2.4%, but increases up to 8% over the age of 55.[6] Electrodiagnostic tests are used in the differential diagnosis of peripheral neuropathy.[7]

Electrodiagnostic tests help to document the extent of sensory motor deficits, any involvement of axons or myelin or both, as well as to classify the neuropathy as sensory, motor, or sensorimotor, determine the location of the nerve injury and reveal the severity of peripheral nerve involvement.[4,8] Observational studies have reported isolated peripheral neuropathy of the lower limbs related to statin use. Observational data from 1 study of patients on long-term statin treatment compared with healthy controls who did not use a statin revealed a possible link between long-term statin exposure and the risk of peripheral neuropathy based on electroneuromyography (ENMG) and neurological examinations.[9]

Abbreviations:

CoQ_{10}	*Coenzyme Q10*
DTR	*Deep tendon reflex*
ENMG	*Electroneuromyography*
HMG-CoA	*Hydroxymethylglutaryl-CoA*
SSR	*Sympathetic skin response*

METHODS

Study design

This research protocol complied with the Declaration of Helsinki and was approved by the Celal Bayar University Faculty of Medicine Non-Interventional Clinical Trials Ethics Committee (Decision no.: 20478486-41/31.01.2013). Every patient/legal representative provided written, informed consent and accepted that their personal data would be used for scientific purposes.

The study and control groups were chosen from patients who were referred to an outpatient clinic between 2013 and 2015. Patients with hypercholesterolemia who had been taking atorvastatin or rosuvastatin for at least 1 year were selected as the patient group. A complete blood count, and the levels of fasting blood glucose, creatine kinase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, thyroid stimulating hormone, and vitamin B12 were measured. In addition, the rheumatoid factor value and the level of anti-nuclear, anti-neutrophil, anti-cytoplasmic, anti-Ro, and anti-La antibodies was assessed to exclude vasculitis or degenerative connective tissue disease. Patients on steroids, immunosuppressive medications, or with a family history of polyneuropathy were not included in the study. Those with a known chronic systemic disease that could initiate polyneuropathy (diabetes mellitus, thyroid disorder, collagen tissue disease, chronic liver disease, uremia, vitamin B12 deficiency, cancer) and those who consumed alcohol or were exposed to toxic substances were also excluded.

All of the electroneurophysiological examinations were performed by a single researcher using the Keypoint XP 2 Channel Portable ENMG device (Alpine

Biomed ApS, Skovlunde, Denmark). Sensory and motor wave features (amplitude, latency, and nerve conduction velocity) of the peripheral nerves (medianus, ulnaris, radialis, peroneous profundus, suralis, tibialis posterior) were evaluated.

Polyneuropathy was graded according to clinical findings: superficial tactile sensation, deep sensation, deep tendon reflex (DTR), and muscle strength assessment. In the deep sensory examination, vibration sense, Romberg sign, and joint position sense were tested using a 128-Hz tuning fork. Muscle strength was graded on a scale of 0–5, in which 5 indicated full-strength and 0 indicated plegia. The diagnosis of mild polyneuropathy was considered if 1 or 2 of the measures of superficial tactile sensation, deep sensation, or DTR were affected, and moderate polyneuropathy if all 3 parameters were affected. The addition of motor deficits in distal muscles to these parameters indicated a diagnosis of severe polyneuropathy.

The ENMG protocol was determined according to the literature.[10] Nerve conduction velocity was eva-luated in at least 3 extremities. Assessment was performed in the median, ulnar, and radial nerves in an upper extremity, and in the peroneal, tibial, and sural nerves in a lower extremity. Neurotransmission studi-es were performed at room temperature (25–28°C) with stimulating and recording electrodes. The sweep speed of the ENMG was 2 milliseconds and the gain was 10 microvolts with a filter width of 20 Hz-3 kHz for sensory processing and 2 Hz-3 kHz for motor processing. The presence of polyneuropathy was confirmed with the involvement of more than 1 of the examined nerves and the presence of at least 1 pathological finding in the involved nerve (a decrease in sensory nerve action potential amplitude, a decrease in sensory conduction velocity, prolonged distal motor latency, a decrease in compound muscle action potential amplitude, a decrease in motor conduction velocity).[10] Motor conduction velocity was measured in the bilateral median and ulnar nerves in the upper extremity and in the right peroneal and tibial nerves in the lower extremity. Distal motor latency was measured as the time elapsed from the moment the stimulus was given to the time the compound muscle action potential deflected from the isoelectric line. The amplitude of the motor action potential was measured in millivolts between the positive and negative peak potentials. Sensory conduction studies were performed with the antidromic technique in the bilateral median, ulnar, and radial nerves in the upper extremity (using a ring electrode for recording) and in the sural nerve in the right lower extremity. Sensory conduction studies were performed to record distal sensory latency, sensory conduction velocity, and sensory nerve action potential amplitudes. Latency and velocity measurements were performed at the first negative peak and amplitude measurements were performed as peak-to-peak. The Celal Bayar University Faculty of Medicine Physical Therapy and Rehabilitation Department laboratory values were used as the reference for ENMG normal values (Table 1).

Table 1. Electroneuromyography normal range values

	Upper/ lower limit
Median motor amplitude (mv)	>9
Median motor latency (ms)	≤4.0
Median conduction velocity(motor) (m/s)	>50
Median sensory amplitude (μv)	29
Median sensory latency (ms)	≤3.5
Median conduction velocity (sensory) (m/s)	>40
Ulnar motor amplitude (mv)	>8
Ulnar motor latency (ms)	≤3.0
Ulnar conduction velocity (motor) (m/s)	>50
Ulnar sensory amplitude (μv)	>20
Ulnar sensory latency (ms)	≤3.1
Ulnar conduction velocity (sensory) (m/s)	>40
Tibial motor amplitude (mv)	≥6
Tibial motor latency (ms)	≤5.8
Tibial conduction velocity (motor) (m/s)	>40
Sural sensory amplitude (μv)	>9
Sural sensory latency (ms)	≤3.8
Sural conduction velocity (sensory) (m/s)	≥37
Radial sensory amplitude (μv)	≤2.5
Radial sensory latency (ms)	<18
Radial conduction velocity (sensory) (m/s)	>40
Peroneous profundus motor amplitude (mv)	≤5.5
Peroneous profundus motor latency (ms)	>4.5
Peroneous profundus conduction velocity (motor) (m/s)	>40

Study population

Fifty patients on statins and 50 healthy subjects of matched for age and gender were included in the study.

Statistical analysis

SPSS for Windows, Version 15.0 (SPSS Inc., Chicago, IL, USA) was used to perform the statistical analysis of all of the study data. A chi-square test was performed to analyze categorical variables and the Student's t-test and the Mann-Whitney U test were used for the analysis of continuous variables. Analysis of variance was used in comparisons of 3 or more. A p value <0.05 was considered statistically significant.

RESULTS

The statin treatment group was divided into 2 arms: 34 patients on atorvastatin and 16 patients on rosuvastatin. The entire statin group comprised 14 female and 36 male patients. There were 10 women and 24 men enrolled in the atorvastatin arm and 4 women and 12 men in the rosuvastatin arm. The control group consisted of 30 women and 20 men. The treatment and control groups were comparable in age and gender (Table 2).

In the treatment group, the ENMG results revealed polyneuropathy in 33 of the 50 patients. No polyneuropathy was detected in the control group. There was a significant difference between the 2 primary groups in terms of the ENMG polyneuropathy detected with ENMG (p<0.01), but there was no significant difference between the atorvastatin and the rosuvastatin groups based on the ENMG findings (p=0.720) or the neurological examination (p=0.288).

The effect of the statin dose on the incidence of polyneuropathy

The atorvastatin group was subdivided into 3 groups based on a dose of 10, 20, or and 40 mg. Of a total of 12 patients in the 10-mg group, polyneuropathy was detected with ENMG in 9. In the 20-mg group, 13 patients among 18 had polyneuropathy, and in the 40-mg group, 1 patient of a total of 3. There was no significant difference in the incidence of polyneuropathy detected with ENMG between groups based on the dose of atorvastatin (p=0.406).

Neurological examination findings indicated that in the atorvastatin 10-mg group, 7 patients had mild polyneuropathy, 1 had moderate polyneuropathy, and 5 patients had no pathology. In the 20-mg group, 13 patients had mild polyneuropathy while no pathology was detected in the remaining 5 patients. Of the patients in the 40-mg group, 1 was found to have mild polyneuropathy and 2 had no polyneuropathy. No significant difference in the incidence of polyneuropathy assessed by neurological exam was found between groups according to the dose of atorvastatin (p=0.460).

The patients taking rosuvastatin were also divided into 3 groups based on a dose of a 5, 10, or 20 mg. One patient in the 5-mg had ENMG polyneuropathy findings. In the 10-mg, polyneuropathy was detected in 5 patients with ENMG but not in the remaining 4. Among patients taking 20 mg, polyneuropathy was detected with ENMG in 7 of 14 patients. No significant difference was observed in the incidence of polyneuropathy as assessed by ENMG among patients with different doses of rosuvastatin (p=0.660).

Neurological examinations in the rosuvastatin group revealed 1 patient with mild polyneuropathy in the 5-mg group. In the 10-mg group, 4 patients had mild polyneuropathy, 1 had moderate polyneuropathy, and no pathology was observed in 4. Among patients with a 20-mg dose, 7 had mild polyneuropathy,

Table 2. Demographic data

	Atorvastatin			Rosuvastatin			Control			*p*
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	
Gender										
Male	24	37.5		12	18.8		28	43.8		0.238
Female	10	27.8		4	11.1		22	61.1		
Age (years)			62.3±8.25			60.1±9.25			58.08±7.93	0.073

Statistical test: Student's t-test. SD: Standard deviation.

2 had moderate polyneuropathy, and no pathology was observed in 7. Similarly, the dose of rosuvastatin as assessed by neurological examination had no effect on the incidence of polyneuropathy (p=0.811) (Table 3).

The effect of the duration of statin treatment on the incidence of polyneuropathy

The patients taking statins were divided into 3 groups according to the duration of treatment: 1 year, 1–5

Table 3. Detection of polyneuropathy with electroneuromyography and neurological examination according to the dose of atorvastatin and rosuvastatin

	Drug use (+) (n=50)			Drug use (-) (n=50)		p
Polyneuropathy by ENMG (+), (%)	33 (66.0)			0 (0)		<0.01
Polyneuropathy by ENMG (-), (%)	17 (34.0)			50 (100)		
	Dose of atorvastatin			Total		p
	10 mg	20 mg	40 mg			
Polyneuropathy (+), (%)	9 (69.2)	13 (72.2)	1 (33.3)	23 (100)		0.436
Polyneuropathy (-), (%)	4 (30.8)	5 (27.8)	2 (66.7)	11 (100)		
Normal neurological examination (%)	5 (38.5)	5 (27.8)	2 (66.7)	12 (35.3)		0.460
Mild polyneuropathy (%)	7 (53.8)	13 (72.2)	1 (33.3)	21 (61.8)		
Moderate polyneuropathy (%)	1 (7.7)	0 (0)	0 (0)	1 (2.9)		
Total	13 (100)	18 (100)	3 (100)	34 (100)		
	Dose of rosuvastatin			Total		p
	5 mg	10 mg	20 mg			
Polyneuropathy (+), (%)	1 (100)	5 (55.6)	4 (66.7)	10 (100)		0.660
Polyneuropathy (-), (%)	0 (0)	4 (44.4)	2 (33.3)	6 (100)		
Normal neurological examination (%)	0 (0)	4 (44.43)	3 (50)	7 (43.8)		0.811
Mild polyneuropathy (%)	1 (100)	4 (44.43)	2 (33.3)	7 (43.8)		
Moderate polyneuropathy (%)	0 (0)	1 (11.13)	1 (16.7)	2 (12.5)		
Total	1 (100)	9 (100)	6 (100)	16 (100)		

Statistical test: One way analysis of variance (ANOVA). ENMG: Electroneuromyography.

Table 4. Comparison of polyneuropathy detected by ENMG and with neurological examination in the patients taking statins

ENMG	Normal neurological findings	Mild polyneuropathy	Moderate polyneuropathy	Total	p
Atorvastatin					
Polyneuropathy (+), (%)	6 (26.1)	17 (73.9)	0 (0)	23 (100)	0.073
Polyneuropathy (-), (%)	6 (54.5)	4 (36.4)	1 (9.1)	11 (100)	
Total (%)	12 (35.3)	21 (61.8)	1 (2.9)	34 (100)	
Rosuvastatin					
Polyneuropathy (+), (%)	3 (30.0)	5 (50.0)	2 (20.0)	10 (100)	0.274
Polyneuropathy (-), (%)	4 (66.7)	2 (33.3)	0 (0)	6 (100)	
Total (%)	7 (43.8)	7 (43.8)	2 (12.5)	16 (100)	

Statistical test: One way analysis of variance. ENMG: Electroneuromyography.

years, and 5 years or more. No significant effect on the polyneuropathy incidence detected by ENMG was seen based on the duration of treatment with atorvastatin (p=0.534) but a significant difference was observed in the neurological evaluation of polyneuropathy in these groups (p=0.03). The length of use of rosuvastatin had no effect on the incidence of polyneuropathy as assessed by ENMG (p=0.587) or neurological examination (p=0.950).

Comparison of ENMG with neurological examination for detecting polyneuropathy

Among the patients on atorvastatin diagnosed with polyneuropathy by ENMG, the neurological examination revealed mild polyneuropathy in 17 patients. Among the atorvastatin patients without polyneuropathy findings on ENMG, 6 had a normal neurological examination, 4 had mild polyneuropathy, and 1 had moderate polyneuropathy (p=0.073) based on the neurological examination.

In the rosuvastatin group, among the patients diagnosed with polyneuropathy by ENMG, 3 had no neuropathology, 5 had mild polyneuropathy, and 2 had moderate polyneuropathy according to the neurological examination. Among rosuvastatin patients without polyneuropathy as assessed by ENMG, 4 had normal findings and 2 had mild polyneuropathy results in the neurological examination (p=0.274) (Table 4).

The statin patients had a lower nerve conduction velocity in the median nerve motor test, the ulnar sensory, the tibial motor, the peroneous profundus mo-

Table 5. Electroneuromyography data

	Drug use (+) (50 patient)	Drug use (-) (50 patient)	*p*
	Mean±SD	Mean±SD	
Median motor amplitude (mv)	12.43±4.73	14.01±4.53	0.091
Median motor latency (ms)	3.75±0.54	3.18±0.47	<0.001
Median conduction velocity (motor) (m/s)	51.09±6.10	56.3±5.14	<0.001
Median sensory amplitude (μv)	21.04±11.05	24.56±9.21	0.087
Median sensory latency (ms)	2.55±0.41	2.48±0.28	0.344
Median conduction velocity (sensory) (m/s)	44.41±6.18	55.01±7.91	<0.001
Ulnar motor amplitude (mv)	11.28±3.57	12.23±3.22	0.164
Ulnar motor latency (ms)	2.62±0.59	2.57±0.61	0.710
Ulnar conduction velocity (motor) (m/s)	55.90±6.66	61.08±6.81	<0.001
Ulnar sensory amplitude (μv)	20.63±9.72	22.82±11.09	0.297
Ulnar sensory latency (ms)	2.09±0.38	2.28±0.38	0.017
Ulnar conduction velocity (sensory) (m/s)	43.98±5.04	51.90±7.38	<0.001
Tibial motor amplitude (mv)	9.43±4.69	10.36±4.52	0.314
Tibial motor latency (ms)	3.88±0.99	3.54±1.51	0.196
Tibial conduction velocity (motor) (m/s)	43.69±4.99	48.41±7.24	<0.001
Sural sensory amplitude (μv)	10.61±6.44	11.82±10.35	0.482
Sural sensory latency (ms)	2.87±0.95	3.04±0.66	0.316
Sural conduction velocity (sensory) (m/s)	38.08±4.66	47.25±8.20	<0.001
Radial sensory amplitude (μv)	1.88±0.39	1.64±0.21	0.017
Radial sensory latency (ms)	13.85±8.40	11.46±6.98	0.295
Radial conduction velocity (sensory) (m/s)	39.27±5.36	41.88±4.23	0.167
Peroneous profundus motor amplitude (mv)	4.93±1.29	4.01±1.28	0.001
Peroneous profundus motor latency (ms)	3.85±2.49	4.24±1.89	0.381
Peroneous profundus conduction velocity (motor) (m/s)	45.26±5.95	51.67±6.56	<0.001

Statistical test: Student's t-test. SD: Standard deviation.

tor, and the sural sensory assessment compared with the control group (p<0.001). The patients also had lower conduction velocity measurements in the radial sensory testing compared with the control group (p=0.167). The amplitude of action potential in sensory and motor nerves was comparable between the patient group and the controls. There was a tendency for the latency period to be greater in some nerves (Table 5).

DISCUSSION

Several clinical studies have investigated the potential risk of peripheral neuropathy development with statin exposure. Neuropathy may occur months or years after the beginning of statin treatment and the risk has been reported to increase after long-term exposure.[11] Investigators often used electromyography for the assessment of polyneuropathy.[7] A significant decrease in nerve conduction velocity may suggest axonal neuropathy.[12] West[2] noted that patients using statins have been reported to be 4–14 times more likely to develop peripheral neuropathy compared with control groups. Patients on statins are 2.5 times more susceptible to polyneuropathy compared with normal populations, according to Gaist et al.[13] In a prospective study investigating peripheral neuropathy, significant nerve damage was detected with ENMG without clinical polyneuropathy (after 3 years of exposure to 20 mg of simvastatin).[14] Among 166 patients with a first time diagnosis of idiopathic peripheral neuropathy, 35 were considered definite, 55 probable, and 77 possible cases. Nine patients had used statins. The odds ratio linking idiopathic polyneuropathy with statin use was 3.7 (95% confidence interval) for all cases and 14.2 for definitive cases. After 2 years of use, the odds ratio for developing peripheral neuropathy was 16.1 for the patients with definite neuropathy and 26.4 for the patients with probable neuropathy.[15] Other cohort studies have also reported an association between statin exposure and peripheral neuropathy. Corrao et al.[16] compared 2040 Italian neuropathy patients with a control group of 36,041 people who were matched for age and sex. They concluded that exposure to simvastatin, pravastatin, and fluvastatin was associated with a significant risk of peripheral neuropathy.

Phan et al.[17] reported the development of mixed sensorimotor neuropathy in 4 patients who used simvastatin and who had complete or partial resolution of clinical abnormalities after withdrawal of treatment.

Chong et al.[18] evaluated a possible link between statins and peripheral neuropathy using the databases of MEDLINE (January 1993-November 2003) and International Pharmaceutical Abstracts (January 1970-June 2002). They reported a significant risk of peripheral neuropathy associated with statins and suggested that they should be considered as a cause of peripheral neuropathy when other etiologies have been excluded.

The Fremantle Diabetes Study (FDS) assessed a cross-sectional sample comprising 1237 participants with type 2 diabetes mellitus and a longitudinal subgroup of 531 individuals who had attended 6 consecutive annual assessments. Neuropathy was identified using the clinical portion of the Michigan Neuropathy Screening Instrument. Fibrate and statin exposure were qualified as significant determinants of neuropathy with time-dependent Cox proportional hazards modelling (p≤0.042).[19]

Tierney et al.[20] evaluated a relationship between statin use and peripheral neuropathy using data from the lower extremity examination supplement of the US National Health and Nutrition Examination Survey 1999–2004. The overall prevalence of statin use was 15% and the prevalence of peripheral neuropathy was 14.9%. The prevalence of peripheral neuropathy was significantly higher among those who used statins compared with those who did not (23.5% *vs*. 13.5%, respectively; p<0.01). They reported a modest association between peripheral neuropathy and statin use.

The Statin Use and Peripheral Sensory Perception pilot study compared the sensory perception tests of long-term statin treatment patients with healthy controls. The results suggested a potential association between long-term statin use and a decrease in peripheral sensory perception.[21] McKenney et al.[22] assessed sensory and motor wave features (amplitude, latency and nerve conduction velocity) of the peripheral nerves (median, ulnar, tibial, sural, and peroneal) in 39 patients who had been taking statins for at least 6 months and 39 healthy matched controls. Significant differences were observed in the amplitude of the peroneal motor nerve and sural sensory nerve. An expert panel has suggested termination of statin treatment and monitoring for resolution of symptoms when peripheral neuropathy occurs. If the symptoms

resolve, the resumption of therapy with another statin should be considered.[23]

In our study, the comparison of the treatment group using an HMG-CoA reductase inhibitor with the control group revealed a significant difference in pathological findings related to polyneuropathy assessed with a neurological examination and electrodiagnostic studies ($p<0.01$). These results support previous studies reporting on statin-induced peripheral neuropathy.

We evaluated the effects of atorvastatin and rosuvastatin, the most commonly used statins.[3] We compared the incidence of polyneuropathy in patients using statins with healthy controls not taking drugs and assessed the effects of the atorvastatin and rosuvastatin dose and duration of use on the incidence of polyneuropathy development. A neurological examination and electrophysiological evaluation were used to identify the type of nerve bundle affected. To the best of our knowledge, our study is the first prospective clinical investigation comparing small and large fiber neuropathies after atorvastatin and rosuvastatin exposure. The patient history and physical examination findings are still considered the gold standard for the diagnosis of small fiber neuropathy. A detailed review of the symptoms, rate of progression, and complaints suggestive of autonomic fiber involvement is advised. In a patient with a compelling history for small fiber neuropathy and an appropriate clinical exam, further testing to confirm the diagnosis may not be necessary. This scenario is particularly likely in the context of an associated disease, such as diabetes. However, in many cases, the diagnosis may be less clear and ancillary testing may provide additional guidance. Patients should always be screened for other treatable causes of small fiber neuropathy. Recently, new scoring examinations have been reported that may be helpful in the diagnosis of small fiber neuropathies.[24]

In the atorvastatin group, neuropathology was detected with the neurological examination but not with ENMG. As thin myelinated fibers cannot be evaluated with ENMG, one may speculate about more damage to the thin myelinated fibers with atorvastatin use than rosuvastatin. Future studies with larger sample sizes may better evaluate the selective involvement of large and small fibers according to the dose and duration of exposure to different statins.

The incidence of polyneuropathy was similar in the atorvastatin and rosuvastatin groups as assessed by neurological examination and electrophysiological evaluation. The patients' superficial tactile sensation, deep sensation, deep tendon reflex, and muscle strength were evaluated with a neurological examination. When the doses and durations of treatment were compared, there was no difference between the 2 statins in the incidence of electrophysiological polyneuropathy findings. Patients on atorvastatin were divided into 3 groups according to the duration of exposure: 1 year, 1–5 years, and 5 years or more. A significant difference was found between the incidence of polyneuropathy assessed in the neurological examination of the patients using atorvastatin for 1 year compared with the other groups ($p=0.030$). This supports previous reports on the effect of the duration of exposure on the incidence of polyneuropathy.

One can roughly divide polyneuropathies into small and large fiber neuropathies. The degree of involvement of different fiber types determines the characteristics of clinical findings. The deep senses of vibration, position sense, and the afferent fibers of the deep tendon reflex arc are conducted with thick myelinated fibers. The information from thermoreceptors on pain and temperature sensation is carried via thinly myelinated fibers. When the thick myelinated fibers are damaged, loss of the sensations of position and vibration, areflexia, sensory ataxia, and pseudo athetosis are observed in patients. Routine electrophysiological nerve conduction studies assess the conduction of thick myelinated fibers but do not reveal the involvement of the thin myelinated fibers. Ziajka[25] reported the occurrence of peripheral neuropathy in thin fibers with statin exposure and recovery of tests to normal values after drug cessation using the sympathetic skin response (SSR) testing. In our study, we used conventional techniques to evaluate nerve conduction of the large nerve fibers only, but the SSR test may be used to evaluate thin fibers. The presence of significant neuropathy detected by neurological examination, but not with ENMG in the assessment of the duration of atorvastatin exposure, may be related to the involvement of different sized fibers.

The toxic effects of statins on thin, myelinated fibers have been demonstrated with a skin biopsy. However, these effects cannot be precisely assessed

using ENMG.[14] Thin, myelinated fibers transmit sensation of cold, heat, and pain, while autonomic fibers control sweating and vascular responses. Painful paraesthesias and loss of temperature sensation can be observed in distal lower extremities with the involvement of thin myelinated fibers. When the autonomic fibers are also affected, autonomic dysfunction related symptoms as orthostatic dizziness, sweating disorders, bladder, and bowel dysfunction may be observed. Hypoesthesia was also detected in our study. Though it did not reach the level of statistical significance, a relationship was observed between polyneuropathy detected by ENMG and loss of sense of vibration on neurological examination. However, based on these results one may only speculate about the involvement of thick myelinated fibers in such patients.

There was no increase in the number of patients developing neuropathy in the first year among those on rosuvastatin. There was an increase in the number of patients developing neuropathy in the first year among those using atorvastatin. Decreased nerve conduction velocity and prolongation of distal latency may suggest demyelinating disorders. On the other hand, a decreased compound nerve action potential with a relatively conserved distal latency and conduction velocity may suggest a pathology associated with axonal loss.[8] We found decreased motor conduction velocities or prolonged distal latencies at different levels in the median, ulnar, tibial, and peroneal nerves in our patients with polyneuropathy. Similarly, we found decreased sensory conduction velocities in the median, ulnar, and sural sensory nerves. Sensorimotor demyelinating polyneuropathy was mild or moderate in those with pathology observed in sensory and motor conduction studies among our patients on statins.

In this study, the superiority of the neurological examination to ENMG to identify statin-induced polyneuropathy may suggest a more important involvement of thin myelinated fibers. We suggest routine use of a neurological examination in the follow-up of patients on long-term statin treatment in order to identify peripheral neuropathy and switch to other statins to prevent further nerve damage, as suggested by the National Lipid Association Statin Safety Assessment Task Force.[23]

Study limitations

In our study, there was no significant difference in the incidence of ENMG-assessed polyneuropathy between the patient groups on different doses and for different durations of rosuvastatin treatment. This may be related to the smaller number of patients in the rosuvastatin group compared with the atorvastatin group. Further prospective comparative studies enrolling larger populations may reveal potential differences.

Another limitation of the present study is the lack of assessment of the involvement of thin myelinated fibers. SSR test and R-R interval analysis indicating autonomic fiber involvement were not included in the study protocol.

Conclusion

Our study supports previous observations about increased risk of peripheral neuropathy with long-term (>1 year) statin exposure. Nerve conduction studies revealed electrodiagnostic changes in motor and sensory nerves in long-term statin treatment patients. These changes were associated with specific findings observed on clinical examination. The results may suggest that doctors should be aware of the risk of peripheral neuropathy in patients on statins for over a year. Neurological symptoms, such as tingling, numbness, pain, and tremor in the hands and feet, and unsteadiness during walking should be investigated in such patients on follow-up visits. A neurological examination can be performed for patients with suspected polyneuropathy, and further investigation with ENMG may be carried out if necessary. When statin-induced peripheral neuropathy is suspected, one may suggest to discontinuing the treatment, monitoring for the resolution of symptoms, and switching to another statin after recovery to prevent further nerve damage. Additional prospective studies are needed for more precise and rational data.

Ethics Committee Approval: The study protocol was approved by the Celal Bayar University Faculty of Medicine Non-Interventional Clinical Trials Ethics Committee (Decision no.: 20478486-41/31.01.2013).

Peer-review: Externally peer-reviewed.

Conflict-of-interest: None.

Authorship contributions: Concept: H.T.; Design: H.T.; Supervision: H.T.; Materials: Ö.C.; Data: İ.H.Ö.; Analysis: C.T.; Literature Search: Ö.C.; Writing: İ.H.Ö.; Critical Revision: İ.H.Ö.

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Keywords: Atorvastatin; peripheral neuropathy; rosuvastatin; statin.

Anahtar sözcükler: Atorvastatin; periferik nöropati; rosuvastatin; statin.