Long-Term Statin Use and the Risk of Parkinson's Disease

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Background: Recent studies have suggested a relation between statin use and the risk of Parkinson's disease (PD). However, the conclusions are inconsistent. Some studies found an increased incidence of PD among statin users; others found a decreased incidence. Others showed that PD incidence was related to baseline cholesterol levels.

Objectives: To examine the association between baseline levels of low-density lipoprotein cholesterol (LDL-C), long-term statin use, and the incidence of PD.

Methods: The study group consisted of a historical cohort of 94,308 men and women in Israel aged 45 years or more without PD or statin use at baseline, between 2000 and 2007. PD incidence among long-term statin users was compared with that among nonusers. The cohort was divided into 4 groups according to baseline LDL-C levels, and their relative risks of developing PD were calculated with adjustment for potential confounders (sex, age, socioeconomic status, history of ischemic heart disease, hypertension, stroke, and smoking). The association between different variables was analyzed with a Cox proportional hazards model.

Results: During the study period, 1035 incident cases of PD were identified. Statin use was associated with a significant decrease in the incidence of PD (odds ratio, 0.73, 95% confidence interval, 0.60-0.88; $P = .001$). No association was found between baseline LDL-C levels and PD risk.

Conclusions: Our results provide additional evidence regarding the lower incidence of PD among statin users. These findings warrant further research regarding the possible neuroprotective role of statins in PD and other neurodegenerative diseases.

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Parkinson's disease (PD) is the second-most common neurodegenerative disorder after Alzheimer's disease, and it causes much disability and suffering for patients and their families. It is a progressive disease with no known cure and becomes more common as people get older; thus, it will become an even greater and more frequent burden as the worldwide population ages.[1] It is imperative that every effort should be made to identify possible preventable causes and risk factors for this disease.

Recent studies have suggested that cardiovascular factors—hypertension, diabetes, hypercholesterolemia, and smoking—play a role in the etiology of PD. A few researchers examined the association between diabetes,[2,3] body mass index,[4,5] hypertension,[6] and PD, and some found a positive correlation. By contrast, however, there is evidence that smoking is a protective factor for PD.[7,8]

Some studies have also shown an inverse correlation between low-density lipoprotein cholesterol (LDL-C) levels and PD incidence, with lower PD incidence rates in people with higher LDL-C levels.[9-11] These findings have prompted further investigations on the influence of cholesterol and cholesterol-lowering medications on PD risk.[12-16]

CHOLESTEROL, STATINS, AND PARKINSON'S DISEASE

Statins (ie, HMG-CoA reductase inhibitors) have been widely used as cholesterol-lowering drugs for more than 15 years. They have been proved to be both effective and safe for preventive treatment of cardiovascular morbidity and mortality. The most common adverse effects associated with statin use are elevation of liver function tests and myopathy.[17,18]

Investigating the possible influence of statins on PD risk is of great importance not only for improving our understanding of PD etiology, but also for identifying additional potential effects of this widely used medication.

A number of the hypothesized mechanisms in the pathogenesis of PD may be influenced by blood cholesterol levels or by use of statins. Over the past few years, the biologic actions of statins have been a subject of extensive research. A recent review by Roy and Pahan[19] summarizes

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some of the proposed mechanisms by which statins may affect the pathogenesis and progression of PD. Statins have an anti-inflammatory effect and have been shown to attenuate glial activation, inhibit oxidative stress, and protect dopaminergic neurons in animal models of PD.[20] They also suppress the aggregation of α-synuclein protein, an important component in PD, as demonstrated in in vitro models.[21]

Take-Away Points

Statins are widely used in the prevention of cardiovascular morbidity. In this study, statin use was associated with a significant decrease in the incidence of Parkinson's disease (PD).

- This finding adds to our knowledge about the beneficial effects of statins and strengthens the benefit-risk ratio of these medications.
- The findings warrant further research regarding the possible neuroprotective role of statins in PD and other neurodegenerative diseases.
- These results also raise the possibility of statin use for prevention of PD progression, especially as statins are known to be safe, inexpensive, and widely available.

It has also been suggested that statins could affect PD via inhibition of HMG-CoA reductase.[22] This pathway is shared by coenzyme Q10, known as ubiquinone, which is an important antioxidant and may play a role in PD. An unintended consequence of statins is lowering of coenzyme Q10 levels, thus potentially increasing the risk and worsening the course of PD.[23] Another possible link between statins and cholesterol and PD is the apolipoprotein E e2 allele, which is associated with increased incidence of cases of sporadic PD[24] and also related to lower levels of LDL-C in the serum.[25]

According to these various biologic theories, statins may either have a protective or a deleterious effect regarding PD. Empirical evidence is needed to determine their actual effect.

Recently, a number of epidemiologic studies have examined the association between cholesterol levels, statin use, and PD incidence.[9-16,26] However, these studies have revealed conflicting results with no clear conclusion.

While some studies found a decrease in PD incidence related to statin use,[9,12,13,15] others have shown that differences in PD incidence were related to baseline cholesterol levels (ie, cholesterol metabolism playing a role in PD pathogenesis).[9,10,11,26] Most of the latter found an inverse association between serum cholesterol levels and PD incidence; however, one study showed opposite results.[26]

The conclusions regarding statins varied, with some studies suggesting they have a protective role in PD,[9,10,12,13,15] and others not finding any significant association between statin use and PD.[11,14,16] These inconsistent results are perhaps due to the diverse methods used and the different populations studied. Many of the studies mentioned the need for a large epidemiologic study to verify their results.

As statins are known to be very safe, cheap, and widely available, we believe that it is important to determine their effect on PD, because this might have practical implications for prevention of this debilitating disease. We set out to study the association between baseline LDL-C level, long-term statin use, and the incidence of PD using our large patient database.

METHODS

This population-based historical cohort study was based on the computerized clinical database of Clalit Health Services, the largest health service in Israel. The database includes laboratory results, a central register of medical diagnoses (smoking, diabetes, hypertension, ischemic heart disease, cerebrovascular accidents [CVAs]), information on medication purchase, and sociodemographic details.[27]

The study population included all eligible people over the age of 45 years living in 1 administrative region in central Israel, between the years of 2000 and 2007.

According to Israeli guidelines, LDL-C measurements are taken routinely as a standard screening for all males over the age of 35 years and all females over the age of 45 years.[28]

The date of entry into the study was defined as the date of the first measurement of LDL-C as documented in the patient's file, between January 1, 2001, and December 31, 2005. This date was personal for each participant. Exclusion criteria were (1) existing PD as indicated by use of anti-parkinsonian medication prior to the study period (**Table 1**); (2) statin use before the commencement of the study; (3) neuroleptic drug use, a frequent cause of secondary parkinsonism (**Table 2**); (4) change of health insurance during the study; and (5) subjects with no recorded LDL-C value during the study period.

We applied these exclusion criteria to the study population during the year prior to study commencement (ie, January 1, 2000, to December 31, 2000) to ensure that participants had not been exposed to statins or diagnosed with PD before the study period.

Exposure was defined as statin purchase as recorded in the computerized database between the years of 2001 and 2005. Statins purchased were simvastatin (93%), pravastatin, atorvastatin, and rosuvastatin. The level of exposure was calculated as the number of months of statin use before the diagnosis of PD. Statin use was considered chronic if at least 6 monthly prescriptions were dispensed over a period of 9 consecutive months. Purchase of fewer than 6 monthly prescriptions was not considered as exposure.

Table 1. Anti-Parkinsonian Medications

Amantadine sulphate (A-Parkin, Paritrel, PK-Merz)
Apomorphine (Apo-go)
Biperiden (Dekinet)
Bromocriptine (Dostinex, Parlodel, Parilac)[a]
Cabergoline (Cabaser)
Entacopone (Comtan)
Levodopa + benserazide (Levopar plus)
Levodopa + carbidopa (Dopicar)
Levodopa + carbidopa (Sinemet)
Levodopa + carbidopa + entacapone (Stalevo)
Pergolide (Pergolide Teva)
Procyclidine (Kemadrin)
Rasagiline (Azilect)
Ropinorole (Requip)
Selegiline (Selegiline, Selegiline Teva)
Trihexyphenidyl (Partane, Rodenal)

[a]While manually reviewing patient files, we found that bromocriptine was more frequently indicated for treatment of endocrinologic disorders. Therefore, it was excluded from the list of anti-parkinsonian medications.

Table 2. Antipsychotic Medications

Amisulpride (Solian)
Chlorpromazine (Taroctyl)
Clotiapine (Entumin)
Clozapine (Leponex, Lozapine)
Flupentixol (Fluanxol)
Fluphenazine (Fludecate)
Haloperidol (Haldol, Pericate, Peridor)
Olanzapine (Zyprexa)
Penfluridol (Semap)
Perphenazine (Perphenan)
Quetiapine (Seroquel)
Risperidone (Risperdal, Risperidex, Rispond)
Sulpiride (Modal)
Thioridazine (Mellaril, Ridazin)
Ziprasidone (Geodon)
Zuclopenthixol dihydrochloride (Clopixol)

Outcome was defined as incident of PD as indicated by a record of at least 2 monthly prescriptions for anti-parkinsonian drugs. These drugs are used specifically for parkinsonian symptoms, primary or secondary, while the medical diagnoses in computerized patient files are not always as reliable as the central register.

In order to validate the diagnosis, we reviewed manually 500 medical files of patients identified from the computerized database as having newly diagnosed PD according to the criteria mentioned above. Diagnosis of PD was validated if a clinical diagnosis of PD was recorded in the file at the time that anti-parkinsonian medication was

instituted. The diagnosis was validated in more than 90% of the files.

A number of independent confounding variables were included in the statistical analysis, based on previous studies linking them to PD: (1) patient sex; (2) low socioeconomic status (defined as exempted by social security from copayments); (3) history of diabetes, ischemic heart disease, hypertension, or previous CVA; and (4) smoking status as regularly recorded in the electronic files. Due to a high rate of missing data, body mass index was not included in the statistical analysis.

The analysis was conducted in 2 stages. In the first stage, we used the Adult Treatment Panel III classification of cholesterol levels to divide the whole cohort into 4 groups according to baseline LDL-C levels.[29] We determined the incidence of PD in the different groups and compared relative risks, adjusting for the potential confounders. In the second stage, we compared the PD incidence among statin users with that among nonusers, adjusting for confounders and for baseline LDL-C levels. The association between the different variables was analyzed by using Cox proportional hazards models.[30]

The study was approved by the Meir Hospital Medical Ethics Committee.

RESULTS

The cohort consisted of 94,308 subjects over the age of 45 years, of whom 52.8% were female and 22.3% were defined as having low socioeconomic status (**Table 3**). The mean age at the end of the study period was 66.90 years (standard deviation, 10.85 years).

A total of 29,714 participants (31.5% of the cohort) started use of statins for a minimum of 6 months during the study period. During the study period, 1035 patients were diagnosed with PD. The incidence was 1.1% (1035/94,308), or 15.7 cases per 100,000 person-years. The mean age of individuals with newly diagnosed PD was 73.69 years (standard deviation, 9.0 years) at end of the study period.We compared PD incidence at different baseline LDL-C levels. The cohort at this stage included 87,971 subjects (**Table 4**), after omitting 6205 cases (6.6% of the cohort) where LDL-C was first recorded after initiation of statin treatment. The number of subjects with newly diagnosed PD was 824.

There was no statistically significant difference in PD incidence among the different LDL-C quartiles (**Table 5**). A number of variables were found to be associated with an increase in PD incidence: Male sex (odds ratio [OR],1.57; 95% confidence interval [CI], 1.36-1.81; P <.001), previous CVA (OR, 1.97; 95% CI, 1.68-2.29; P <.001) and low socioeconomic status (OR, 1.33; 95% CI, 1.14-1.54; P <.001). Smoking was not associated with a change in PD incidence (OR, 0.93; 95% CI, 0.75-1.14; P = .4).

Table 3. Sociodemographic Features and Cardiovascular Risk Factors of the Cohort (N = 94,308)

Characteristics	No. (%)
Female	49,755 (52.8)
Low socioeconomic status	21,005 (22.3)
Smoker	18,526 (19.6)
Diabetes	20,521(21.8)
Hypertension	48,326 (51.2)
Ischemic heart disease	18,252 (19.4)
Past history of cerebrovascular accident	7762 (8.2)

Table 4. Baseline LDL-C Levels

Frequency (N = 87,971)	LDL-C Category, mg/dL
15,760	<100
30,189	100-130
26,773	130-160
15,247	>160

LDL-C indicates low-density lipoprotein cholesterol.

Next, we added statin use as a variable in the regression model (Table 5). Statin use was found to be associated with a significant decrease in the incidence of PD (OR, 0.73; 95% CI, 0.60-0.88; P = .001). The association of the other variables with PD incidence was not affected.

After finding a significant association between the exposure (statin use) and the outcome (PD incidence), we looked for a dose-related effect.

We defined 4 categories of statin use according to number of treatment years: none, up to 2.5 years, 2.5 to 4 years, and more than 4 years. After adding these variables to the regression model, we observed a continuing trend of decreased PD incidence associated with statin use. However, the association was not statistically significant beyond 2.5 years of treatment (Table 5).

DISCUSSION

The wide use of statins in prevention of cardiovascular morbidity warrants a continuous search for possible adverse effects associated with this group of medications.

A few studies over the past years have examined the possible association between statin use and PD. However, their findings vary widely, as discussed in the introduction. Our historical prospective cohort study was designed to overcome some of the weaknesses of previous studies. One

Table 5. Logistic Regression Model for the Incidence of Parkinson's Disease Among Patients With Known LDL-C Baseline With and Without Statin Treatment Characteristics

	Model With LDL Baseline			Model With LDL-C Baseline and Statin Treatment		
Characteristics	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
LDL-C category, mg/dL						
<100	1.00	.	.36	1.00		.42
100-130	1.06	0.88-1.28	.50	1.10	0.90-1.32	.33
130-160	1.08	0.88-1.31	.45	1.15	0.94-1.40	.17
>160	0.89	0.70-1.13	.37	0.99	0.77-1.27	.96
Male	1.57	1.36-1.81	<.001	1.58	1.36-1.82	<.001
Low socioeconomic status	1.33	1.14-1.54	<.001	1.36	1.16-1.58	<.001
Smoking	0.93	0.75-1.14	.4	0.94	0.76-1.15	.57
Diabetes	1.08	0.92-1.26	.3	1.13	0.96-1.32	.12
Ischemic heart disease	0.91	0.78-1.05	.22	0.93	0.80-1.08	.38
Hypertension	1.06	0.90-1.25	.43	1.1	0.93-1.29	.25
Past history of cerebrovascular accident	1.97	1.68-2.29	<.001	1.95	1.66-2.28	<.001
Statin treatment				**0.73**	**0.60-0.88**	**.001**
Years of statin use						.008
None (n = 64,593)				1.00		
Up to 2.5 (n = 15,394)				0.69	0.55-0.86	.001
2.5-4 (n = 5152)				0.74	0.53-1.04	.08
>4 (n = 2830)				0.88	0.59-1.29	.50

CI indicates confidence interval; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio.

advantage was that it enabled us to show a temporal association between the exposure (cholesterol level and statin use) and the outcome (a new diagnosis of PD). Another advantage of choosing a cohort design was reduction of selection bias. A population-based study based on data from unselected medical files from primary care clinics reflects the epidemiology of the disease more accurately than case-control studies.

One of the main advantages of this study is its use of objective data, without reliance on patient-reported information or even physician-reported diagnosis. All information—laboratory tests, medical diagnoses, and drug purchase—was obtained from a computerized database. In this way we minimized potential information bias.

The statistical power of this study is high due to the large size of the cohort and the number of patients with incident PD, which is the largest number reported in any prospective study to date. There have been studies with larger cohorts and longer periods of observation (eg, Simon and colleaues[14]); however, the number of incident cases of PD was smaller, probably due to the younger ages of subjects included and the larger proportion of women.

In our study we were able to show that long-term statin use was associated strongly with a significant decrease in PD incidence (OR, 0.73; $P = .001$). No association was found between baseline LDL-C levels and risk of PD.

These findings suggest that in addition to their effectiveness in reducing cardiovascular risk, statins may also have a beneficial role in reducing the risk of PD. Clinically, this strengthens the benefit-risk ratio of statins. Another important implication is the understanding of the etiology and pathophysiology of PD. The association between statins and PD strengthens theories suggesting an influence of vascular factors on neurodegenerative diseases.[31]

This approach is supported by another finding in the present study: the strong association found between past history of CVA and the risk of PD (relative risk 1.97; 95% CI, 1.68-2.29; $P < .001$). However, the association found between CVA and PD incidence may be due to the method of defining PD in our study. Despite manual review of medical files and the exclusion of cases of secondary parkinsonism from the study, it is possible that some of the subjects who were diagnosed with PD actually suffered from parkinsonism due to vascular causes. Vascular parkinsonism is a parkinsonian

syndrome caused by cerebrovascular disease. Its clinical and pathologic characteristics are different from those of PD, but it is probably underdiagnosed. The prevalence of vascular parkinsonism is estimated to be 4% to 12% of all parkinsonian syndromes.[32]

The main causes of secondary parkinsonism (as opposed to idiopathic PD) are medications and cerebrovascular disease. We defined our cohort as excluding patients treated with antipsychotic drugs, which may cause extrapyramidal symptoms. We did not exclude patients with a history of CVA. However, only a small minority of patients suffering from parkinsonian symptoms actually have vascular parkinsonism. It is more likely to find a common incidence of PD and cerebrovascular diseases, both of which present in the same age groups. It is not possible to suggest a pathophysiologic association between the 2 diseases solely on the basis of their chronological appearance.[33]

In this study, we were not able to show a dose-related association between statin use and PD incidence. Extent of exposure to statins was measured as years of statin use. The majority of subjects were exposed to statins for a period of up to 2.5 years due to the limited time of follow-up; the 2 other groups (2.5-4 years, >4 years) contained significantly fewer subjects. For example, the group that received statins for more than 4 years consisted of 2830 subjects, with an estimated incidence of fewer than 30 PD cases during the study period. The small size of these subgroups did not enable a statistically significant subgroup analysis, which is probably why we could not show a dose-related association between the exposure and the disease. Future studies would likely be able to test more patients who had protracted use of statins.

Several other variables were found to be associated with the incidence of PD. Male sex was related to an increased incidence of PD (OR, 1.58)—a finding consistent with previous studies.[34-36]

Socioeconomic status was found to be inversely related to PD risk, with low socioeconomic status associated with a higher rate of PD. However, the importance of this finding is limited in the context of the present study, due to a very narrow definition of socioeconomic status (ie, exemption from social security fees).

Interestingly, in a number of previous studies smoking was found to be a protective factor for PD.[7,8,34] In our study we did not find a significant association between these variables.

CONCLUSIONS

In this study we were able to show a clear association between exposure to statins and PD incidence. The statins were found to have a protective effect, and their use was associated with an important and significant decrease in the incidence of PD.

Our results provide evidence confirming the lower incidence of PD among statin users. These findings warrant further research regarding the possible neuroprotective role of statins in PD and other neurodegenerative diseases. These results may also raise the possibility of statin use for the prevention of PD, especially as statins are known to be safe, inexpensive, and widely available.

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