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Association between plasma PCSK9 levels and lipid profile in patients with Parkinson's disease and comparison with healthy subjects

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Keywords
Triglycerides; Low Density Lipoprotein; High Density Lipoprotein; Proprotein Convertase Subtilisin Kexin; Parkinson Disease

Abstract

Background: Up to know, limited and contradictory results have been published about the role of prognostic values of lipid profile and proprotein convertase subtilisin/kexin type 9 (PCSK9) in Parkinson's disease (PD). The aim of the present study is to investigate the role of lipid profile and PCSK9 in patients with PD and compare it with healthy individuals.

Methods: In this case-control study, 31 individuals diagnosed with PD were compared with 31 healthy individuals. The lipid profile and PCSK9 of research participants were measured and the resulting data were analyzed using SPSS software. The P-values smaller than 0.05 were considered significant.

Results: The mean age of participants in the PD and control group was 56.9 ± 8.8 and 53.7 ± 10.1 years, respectively (P > 0.050). 27 individuals (87.1%) in the PD group and 13 individuals (41.9%) in the control group were men. Low-density lipoprotein (LDL) level (84.2 ± 24.9 ml/dl vs. 105.5 ± 16.8, P < 0.001), high-density lipoprotein (HDL) level (45.5 ± 8.7 ml/dl vs. 51.1 ± 9.5 ml/dl, P < 0.001), and total cholesterol (155.3 ± 31.2 ml/dl vs. 192.8 ± 32.5 ml/dl, P < 0.001) were lower and triglyceride (TG) level was higher in the PD group (133.3 ± 79.3 ml/dl vs. 131.2 ± 58.6 ml/dl, P = 0.900) compared with the control group.

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PCSK9 level was higher in the PD group, but no significant difference was found (141.6 ± 70.0 vs. 129.7 ± 51.0 ng/ml, P = 0.500) compared to healthy subjects. Moreover, there was no relation between PCSK9 and severity of PD.

Conclusion: Our findings showed that individuals with PD had lower levels of HDL, LDL, and total cholesterol compared with the control group. However, higher concentrations of PCSK9 were observed in patients with PD compared with healthy volunteers.

Introduction

Parkinson's disease (PD) has a prevalence of less than 1 percent in societies, and nowadays, it is considered a therapeutic problem by physicians. At the present, physicians can just treat the symptoms of the disease not its pathology.[1,2] Therefore, identification of the effective factors underlying the pathology and clinical progress of the disease can contribute to early diagnosis of PD and finding more effective therapies.

It is well documented that high levels of cholesterol can increase the risk of diseases.[3] In the past two decades, some evidence has been found on the relation between lipid serum level and neurodegenerative diseases such as Alzheimer's disease, Huntington's disease, and Niemann-Pick type C.[3] Nevertheless, fewer studies have addressed the relation between serum cholesterol or hypercholesterolemia history and the risk of being affected by PD.[4,5] The recent reports have indicated the relation between high cholesterol level and lower occurrence of PD, and they also showed the positive role of high serum cholesterol level. However, the findings are controversial and more investigations are necessary.[6-8] Moreover, administration of statins, especially if it is done for a long time, can have a protective effect on PD.[9-11]

Proprotein convertase subtilisin/kexin type 9 (PCSK9) was recently discovered as a protein secreted by liver cells which involved a key regulator in low-density lipoprotein (LDL) receptor (LDLR) processing.[12,13] Both cholesterol and statin have direct effect on PCSK9 level, and if they increase in the serum, the PCSK9 level will increase.[14-18] PSCK9 reduces the number of LDLRs and results in increased level of LDL in the serum. Lipid-lowering drugs (e.g., statins) decrease hepatic intracellular cholesterol resulting in increased LDLR and also they have been observed to have an increasing effect on circulating PCSK9 concentration in higher doses.[14,15,19-22]

Higher level of PCSK9 is related to neurodegenerative diseases such as Alzheimer's disease.[23,24] A study showed that low LDL cholesterol (LDL-C) due to PCSK9 and 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) variants was not associated with Alzheimer's dementia, vascular dementia, and PD, and also there was no causal role for low LDL-C in these diseases.[25] In order to reach a better conclusion on the relation between PCSK9 level and neurodegenerative diseases, more investigations are needed. Before the present research, the evaluation of PCSK9 had not been studied in patients with PD. Therefore, this led the researchers in this study to investigate the lipid profile and PCSK9 in patients with PD and healthy individuals. Our findings can shed some light on the extant evidence in the relation between lipid level and severity of PD with PCSK9.

Materials and Methods

Study design and population: In the present research, a case-control study was conducted on 31 patients with PD and 31 healthy volunteers of the same age and sex as PD group between September 2017 and March 2018. The groups were divided as PD group (case group) and healthy group (control group). The PD group was randomly selected from patients referring to neurology clinic in Rasoul Akram Hospital, which is affiliated to Iran University of Medical Sciences, Tehran, Iran. The control group was selected from the companions of non-PD patients referring to the above-mentioned clinic. Inclusion criteria included being 20-75 years old and suffering from PD for at least more than 1 year. Exclusion criteria included participants' dissatisfaction, the presence of family history for PD in the control group, using sedative medicines, metoclopramide, and anti-hyperlipidemia, as well as having been diagnosed with other diseases of central and peripheral neural system.

Ethical approval: The study complied with the Declaration of Iran University of Medical Sciences and was approved by the Ethics Committee of Rasoul Akram Hospital and School of Pharmacy, Tehran. Informed written consent was obtained from all patients and volunteers enrolling in the present study.

Blood sampling and PCSK9 enzyme-linked immunosorbent assay (ELISA): First, patients diagnosed with PD were called based on their records in the archives of the clinic, and were asked to participate in a free-of-charge examination and the project. Similarly, the companions of non-PD

patients referring to the clinic were asked to participate in the project. The project executive was present in the mentioned clinic on some determined days and interviewed the individuals and selected those who met the criteria for participating in the project.

Venous blood samples of each participant were obtained after an overnight fasting. In the lab, the serum of blood samples was separated using a centrifuge (4000 rpm for 6 minutes). The enzymatic method was used for evaluating the lipid and PCSK9. The serum PCSK9 was measured using ELISA method and Abcam's Human PCSK9 SimpleStep Elisa Kit. Then, PCSK9 level was reported in ng/ml using the obtained amount from standard curve. Plasma concentrations of lipids were measured using commercial enzymatic reagents[26] as follows: total cholesterol was analyzed by human-based kits, high-density lipoprotein (HDL) was analyzed by Zist Shimi kits (Zist Shimi Company, Iran), and LDL and triglyceride (TG) were analyzed by Pars Azmoon kits (Pars Azmoon Company, Iran), and all were reported in mg/dl. Moreover, the demographic characteristics of patients including their age, sex, background illnesses other than PD, the period of being affected by PD, anti-PD medicines, and severity of PD were collected from participants through a standard questionnaire named "Unified Parkinson's Disease Rating Scale" (UPDRS).[27,28] UPDRS includes 42 items evaluating through interview and clinical observation, and its scores range from 0 to 147. Higher scores show more severe disease and more complications.

Study endpoints: The primary endpoint was comparison of serum level of PCSK9 and lipid profile in PD group and healthy volunteers (control group). The secondary endpoint of the study was association between PCSK9 with severity of PD as well as association of lipid profile with PCSK9 in both groups.

Data were analyzed using SPSS software (version 20, IBM Corporation, Armonk, NY) and chi-square test, Fisher's exact test, and t-test. The quantitative findings were shown as mean ± standard deviation (SD), and the qualitative findings were shown as percentage. Linear regression was used to examine the association between LDL-C and PCSK9 plasma levels. The P-values smaller than 0.05 were considered significant. One-way analysis of variance (ANOVA) and Scheffe post-hoc test were used to compare the mean of different factors between studied groups.

Results

Of the 87 subjects who enrolled in the present investigation, 42 patients were randomly assigned to the case group and 45 healthy volunteers to the control group (Figure 1). Finally, 31 patients in case group and 31 subjects in control group were analyzed. Table 1 demonstrates patients' baseline demographic and clinical characteristics based on the study groups. The PD group (case group) lacked background diseases. In addition, in the control group, 12 individuals (38.7%) lacked any background diseases. Hypothyroidism and high blood pressure were the most prevalent background diseases, respectively. Fisher's exact test showed that there was a significant difference between the two groups in terms of background diseases other than PD.

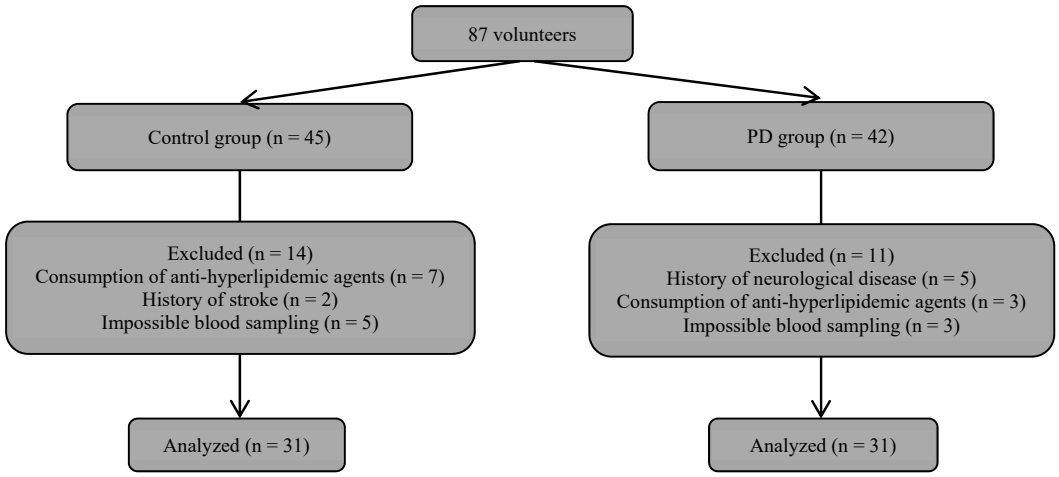

Figure 1. Study flow diagram

Table 1. Participants' basic demographic information

Variable	PD group	Control group	P
Age (year)	56.9 ± 10.1	53.7 ± 8.8	0.20
Sex			
Women	4 (12.9)	18 (58.1)	< 0.01
Men	27 (81.7)	13 (41.9)	
Background illness			
High blood pressure		6 (19.4)	
Cardiovascular disease		8 (25.8)	
Diabetes		2 (6.5)	
Hyperlipidemia		2 (6.5)	
Others		2 (6.5)	
Duration of illness (year)	7.9 ± 5.0		
Diagnosis time (year)	49.0 ± 8.0		
Levodopa monotherapy versus combination therapy			
Levodopa-C	12 (36.7)		
Levodopa + benserazide	1 (3.2)		
Amantadine	4 (14.8)		
Combination therapy	14 (45.2)		
Severity of PD	24.3 ± 9.1		

Data are presented as mean ± standard deviation (SD) or number and percentage
PD: Parkinson's disease

The mean score of UPDRS was 24.3 ± 9.1 and its median was 23. Moreover, we showed the relation between UPDRS with PCSK9, HDL, LDL, cholesterol, and TG levels in PD group in figure 2. Meanwhile, the results showed that there were no significant differences between lipid profiles of patients with PD with severity of PD measured by UPDRS.

As shown in table 2 and figure 2, the mean levels of LDL, HDL, and total cholesterol were significantly lower in the PD group compared with the control group.

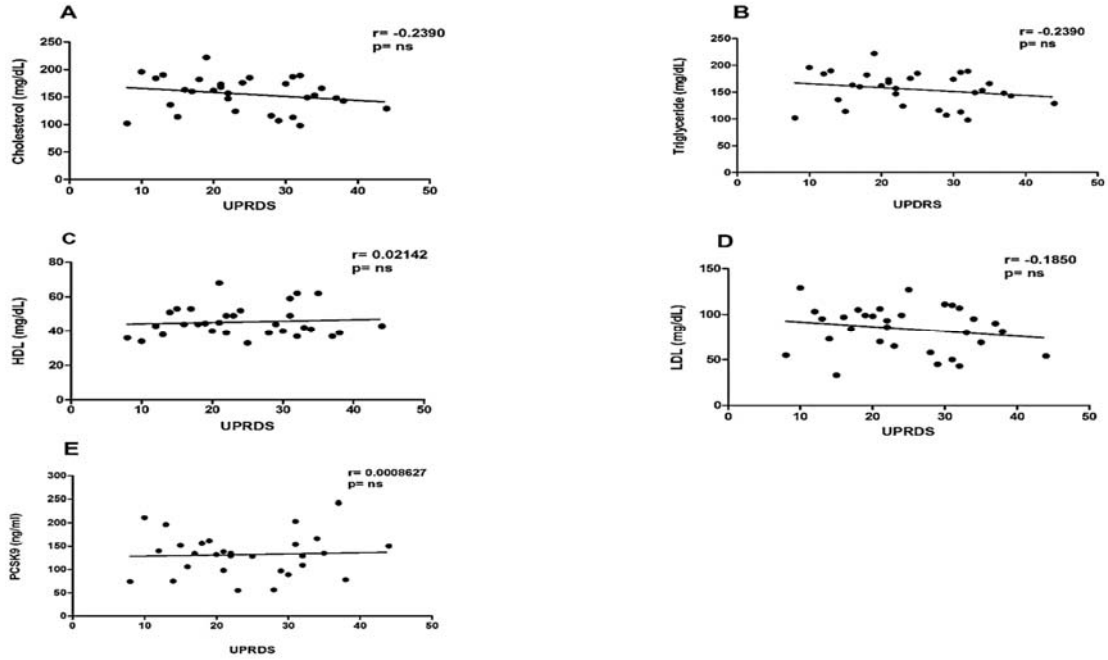

Figure 2. Relationship between cholesterol and Unified Parkinson's Disease Rating Scale (UPDRS) (A), triglyceride and UPDRS (B), high-density lipoprotein (HDL) and UPDRS (C), low-density lipoprotein (LDL) and UPDRS (D), proprotein convertase subtilisin/kexin type 9 (PCSK9) and UPDRS (E) in serum from patients without Parkinson's disease (PD) (n = 31) and patients with PD (n = 31). Analysis was performed by nonparametric correlation and Spearman r was reported.

Table 2. Lipid profile level and proprotein convertase subtilisin/kexin type 9 (PCSK9) in participants

Variable	Mean ± SEM	P
LDL (mg/dl)		< 0.01
Control	105.5 ± 16.8	
PD	84.2 ± 24.9	
HDL (mg/dl)		0.02
Control	51.1 ± 9.5	
PD	45.5 ± 8.7	
TG (mg/dl)		
Control	131.2 ± 58.6	0.90
PD	133.3 ± 79.3	
Total cholesterol		
Control	12.8 ± 32.5	< 0.01
PD	155.3 ± 31.2	
PCSK9 (ng/dl)		
Control	129.7 ± 51.0	0.45
PD	141.6 ± 70.0	

SEM: Standard error of the mean; PD: Parkinson's disease; LDL: Low-density lipoprotein; TG: Triglyceride; HDL: High-density lipoprotein; PCSK9: Proprotein convertase subtilisin/kexin type 9

Moreover, TG level was a little higher (without significant difference) in the PD group (133.3 vs. 131.2 ml/dl). PCSK9 level was higher in the PD group compared to control group (without significant difference). There were no significant differences between levodopa monotherapy or combination therapy with HDL, LDL, TG, and PCSK9 (Table 3). As shown in table 3, there was a significant difference between levodopa monotherapy or combination therapy with total cholesterol. Post-hoc analysis showed that this significant difference of total cholesterol was between without treatment and combination therapy (Table 4). As shown in figure 3, association between lipid profile with duration of disease showed that there was an inverse relation between LDL-C and cholesterol ($r = -0.398$, $P < 0.001$ and $r = -0.410$, $P < 0.001$, respectively). Besides, association between PCSK9 with duration of disease has been shown in figure 4.

Discussion

This project is probably a unique one to evaluate PCSK9 concentration in patients with PD compared with healthy subjects. Further, our study was the first one conducted to find the relationship between severity of PD with PCSK9 and lipid profile.

Our findings showed that LDL, HDL, and total cholesterol levels were significantly lower in patients with PD, while there was not any significant difference between two groups in terms of PCSK9 level. Moreover, it was observed that there was no relation between the severity of PD using UPDRS with lipid profile in patients with PD.

So far, few studies have been done evaluating and comparing lipid profiles in patients with PD and healthy individuals. The previous studies have shown that patients with PD have mainly lower lipid profile level, and a reverse relation has been found between lipid profile and PD occurrence, which corresponds to our findings.

Guo et al. conducted a case-evidence study and showed that total cholesterol, LDL, HDL, and TG levels were lower in patients with PD, which corresponds to our findings except for TG. Their findings also showed that higher LDL and total cholesterol correlated to lower occurrence of PD.[29] The analyses of the data here showed a similar relation with total cholesterol, LDL, and HDL in PD. Huang et al. reported that PD occurrence was significantly related to lower LDL level just in patients with 71-75 years of age, so that the occurrence of PD in individuals with LDL > 80 ml/dl was 38.5 individuals per 10000 people, while in individuals with LDL > 140 ml/dl, the PD occurrence was 9 individuals per 1000 people.[30] In the study of Huang et al., the chance ratio of being diagnosed with PD at LDL = 115-138 ml/dl was 2.3, and the chance ratio for those with LDL = 93-114 ml/dl was 3.5, and also the chance ratio for those with LDL < 92 ml/dl was 2.6,[6] which indicates the protective effect of higher LDL on PD occurrence. Contrary to our findings, Ikeda et al. compared 119 patients with PD and 120 healthy individuals in terms of lipid profile level and found that total cholesterol and LDL level were higher in patients with PD compared with healthy people.

Table 3. Comparison between different treatment groups

	N	Mean ± SD	SE	95% CI for mean		P
				Lower bound	Upper bound	
Monotherapy	37	173.73 ± 34.79	5.71	162.13	185.33	0.001
Without treatment	10	205.10 ± 36.42	11.51	179.04	231.15	
Combination therapy	14	149.35 ± 23.24	6.21	135.93	162.77	
Total	61	173.27 ± 36.67	4.69	163.88	182.67	

CI: Confidence interval; SD: Standard deviation; SE: Standard error

Table 4. Post-hoc analysis of between different treatment groups

Multiple comparisons						
(I) Drug	**(J) Drug**	**Mean difference (I-J)**	**SE**	**P**	**95% CI**	
					Lower bound	**Upper bound**
Monotherapy	Without treatment	-31.37*	11.70	0.034	-60.77	-1.96
	Combination therapy	24.37	10.30	0.069	-1.51	50.25
Without treatment	Monotherapy	31.37*	11.70	0.034	1.96	60.77
	Combination therapy	55.74*	13.59	0.001	21.58	89.90
Combination therapy	Monotherapy	-24.37	10.30	0.069	-50.25	1.51
	Without treatment	-55.74*	13.59	0.001	-89.90	-21.58

*The mean difference is significant at the 0.05 level. Post-hoc analysis was done by Scheffe test.
CI: Confidence interval; SE: Standard error

They found that such variations in lipid in their sub-group analysis were related to more advanced stages of the disease and duration of suffering from PD.[31] Hu et al. found that in ages lower than 55 years, higher cholesterol might double the chance of being diagnosed with PD.[32]

The reason behind lipid profile level and PD occurrence is unknown. Epidemiologic findings have shown that higher cholesterol can have a protective effect on PD occurrence, but it is necessary to conduct more researches to reach a better conclusion and determine its mechanism.[33,34] PSCK9 is related to lower LDLR level.[35,36] This molecule may decrease LDLR at the surface of target tissue, and it may increase LDL level in circulation. The previous studies showed that PCSK9 was related to family hypercholesterolemia.[37] In the present analysis, no relation was found between PD and PCSK9 level, and it seemed that lower LDL in the PD group was not affected, hence rejecting the hypothesis of the study. Benn et al. reported that although lower LDL level might increase the risk of PD occurrence, lower LDL resulting from increased PCSK9 was not related to PD occurrence,[25] which agrees with our findings. One of the limitations of this study was its small scale which might affect the results.

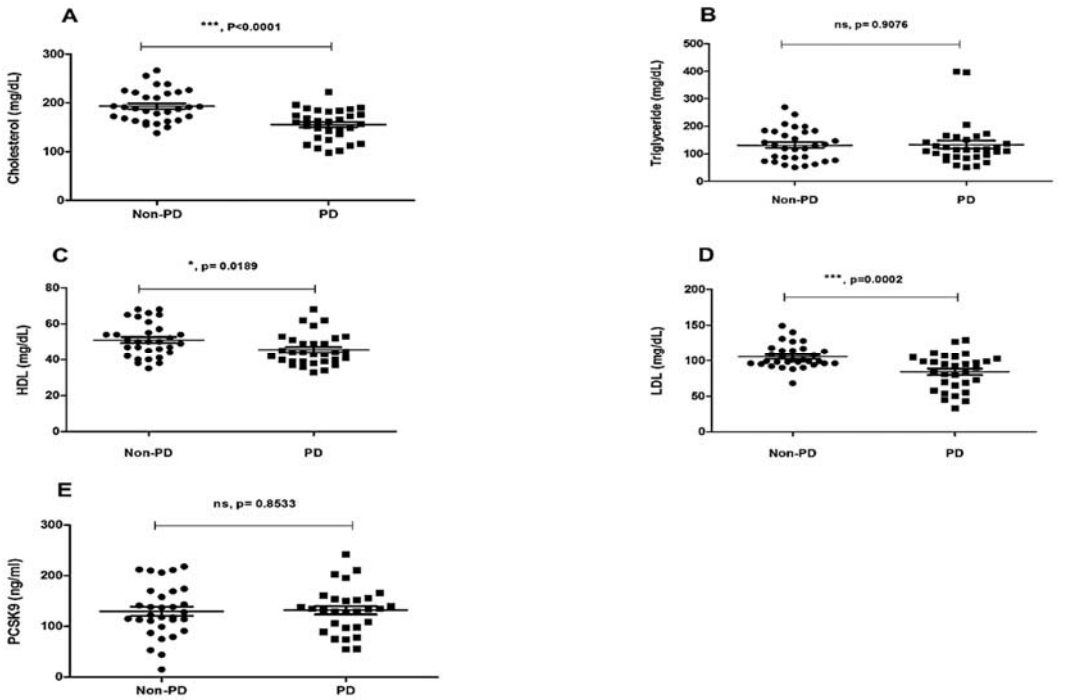

Figure 3. Cholesterol (A), triglyceride (B), high-density lipoprotein (HDL) (C), low-density lipoprotein (LDL) (D), proprotein convertase subtilisin/kexin type 9 (PCSK9) (E) from patients without Parkinson's disease (PD) (n = 31) and patients with PD (n = 31). Each sample was run in duplicate. Two-tailed unpaired t-test was applied to compare the two groups. Mean ± standard error of the mean (SEM) was reported.

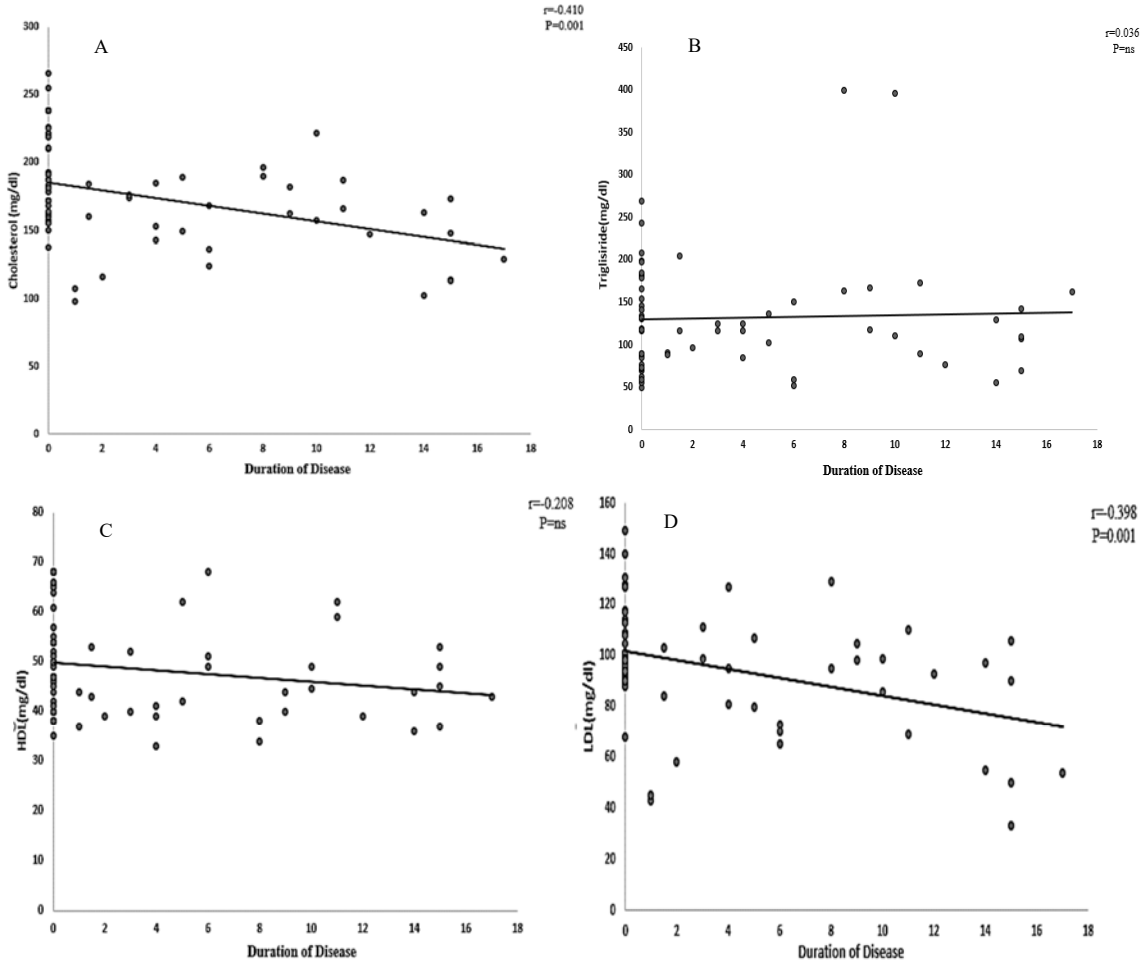

Figure 4. Relationship between cholesterol and duration of disease (A), triglyceride and duration of disease (B), high-density lipoprotein (HDL) and duration of disease (C), low-density lipoprotein (LDL) and duration of disease (D), proprotein convertase subtilisin/kexin type 9 (PCSK9) and duration of disease (E) in serum from patients without Parkinson's disease (PD) (n = 31) and patients with PD (n = 31). Analysis was performed by nonparametric correlation and Spearman r was reported.

Conclusion

The findings of this case-evidence study showed that patients with PD had lower level of HDL, LDL, and total cholesterol, which can be considered as risk factors for PD occurrence. Moreover, it was found that lipid variation was not related to PCSK9.

Conflict of Interests

The authors declare no conflict of interest in this study.

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