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Original Research Article

Correlation between cholesterol levels and the severity of Parkinson disease

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ABSTRACT

Background: Parkinson disease is the second most common neurodegenerative disease after dementia Alzheimer. In neurodegenerative disease such as PD, there is a disturbance of cholesterol metabolism in the brain that could affect plasma cholesterol level. Laboratory test of cholesterol level could be used as an alternative parameter in assessing the severity degree of PD. Our objectives in this study are to analyze the correlation between cholesterol level and the severity of PD.
Methods: This study is a cross sectional study. The sample is collected from patients with PD that came too neurology clinic in Prof Dr. R. D. Kandou Manado Hospital. Patients will then be assessed whether they meet the inclusion criteria which is examined using unified Parkinson disease rating scale (UPDRS) questionnaire and Hoehn and Yahr (H and Y). If the inclusion criteria are met, subject will be tested for total cholesterol, high density lipoprotein (HDL), and low density lipoprotein (LDL) levels in plasma.
Results: There are 60 subjects of PD patients with mean age 64.37±8.26 years old. Male subjects were more dominant (53.3%) than female. Total cholesterol level and LDL have moderate negative correlation with UPDRS I, UPDRS II, UPDRS III, and UPDRS total score. Total cholesterol and LDL level also has moderate negative correlation with H and Y severity.
Conclusions: There is a moderate negative correlation between total cholesterol level and LDL with PD severity degree based on H&Y degree and UPDRS I, II, III, and UPDRS total score.

Keywords: Cholesterol level, *UPDRS*, H and Y, Parkinson disease

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease after dementia Alzheimer.[1]PD usually begins at the age of 40-70 years and reaches its peak in the sixth decade. The number of patients suffering from PD worldwide reached 6.1 million within the population with a death rate of 211,296 in 2016.[2] The burden of PD is likely to increase in the years to come among other countries, particularly those in Asia, especially in patients within aged population.[3] In 2030, the PD patients is estimated to reach 8.7 million people around the world or double the current number of 4.1 million people.[3,4] The cause of Parkinson's disease (PD) remains unknown. PD is part of parkinsonism syndrome which is pathologically characterized by degeneration of the basal ganglia, especially in the substantia nigra pars compacta accompanied by eosinophilic cytoplasmic inclusions (Lewy bodies).[4] Stages of PD can be graded according to Hoehn and Yahr into five stages and its severity can be graded using unified Parkinson's disease rating scale (UPDRS) questionnaire.[5]

Cholesterol is an amphipathic lipid and is a component of cell membranes that plays a role in maintaining membrane permeability and fluidity.[6]

Cholesterol presents in tissues and in plasma as free cholesterol or in correlation with long-chain fatty acids as cholesterol esters. In plasma, both forms of cholesterol are transported in the form of lipoproteins.[7] Plasma low density lipoprotein (LDL) transports free cholesterol and cholesterol esters to the tissues, while free cholesterol is cleared from the tissues by plasma high density lipoprotein (HDL) which will then be taken to the liver to be converted into bile.[7] The brain has the highest cholesterol content in the body; about 20% of our total body cholesterol. In normal physiological state, cholesterol contents in the brain highly depends on cholesterol synthesis in the brain due to blood brain barrier, but in pathological conditions such as neurodegenerative diseases like PD there will be a disturbance of cholesterol metabolism in the brain so it can affect plasma cholesterol levels.[8-10]

METHODS

This research is a cross-sectional survey of PD patient who came to the outpatient neurology clinic in Prof. Dr. R. D. Kandou Manado general hospital on January-April 2021. We included patients with PD who meet the criteria of Hughes or Koller, compos mentis, age >40 years and willing to be included in the study. We excluded patients with history of diabetes mellitus , BMI >25, history of thyroid disease, have a routine of heavy physical activity, on treatment for schizophrenia, affective disorders, depression and other psychiatric diseases , as well as regular consumption of statin drugs.

Researcher took identity data in the form of name, gender, age, education, address, and registration number of patients diagnosed with PD who meet the inclusion criteria. Patients were checked for blood pressure, peripheral blood sugar, weight, and height. Patients who met the inclusion criteria were given information and an explanation about the research conducted, then asked about their willingness to be a research sample and documented in writing by signing a statement of willingness to be in the research sample. The researcher gave an explanation of how to fill out the UPDRS questionnaire and the H and Y stage. Subjects filled out the UPDRS I-IV questionnaire and stage H and Y. The blood was taken from the vein about 5cc to be checked for total cholesterol, LDL and HDL. Statistical analysis data was processed with R version 3.5.2 software. The data obtained were tested for the normality of the data distribution using the Kolmogorov Smirnov test. Bivariate analysis to assess the correlation between total cholesterol levels, HDL, and LDL with the severity of Parkinson's disease (UPDRS score) using the Pearson correlation test if the distribution is normal or Spearman's if the distribution is not normal.

RESULTS

Sixty patients with Parkinson's disease (PD) were involved in this study. The study subjects had almost the same sex ratio between men and women (32 vs. 28 people), their mean age was 64.37 with a standard deviation of 8.26 years. Most patients have the onset of symptoms ≤5 years (66.7%, n=40) whereas the education level is junior high school with 31.7% (n=19). Most patients with Parkinson use combination of more than two types of drugs, with 53.3% (n=32).

The severity of PD patients was assessed using the UPDRS questionnaire and the H and Y classification. The UPDRS questionnaire consists of 4 major components, which are UPDRS 1 (thinking, behaviour, and mood), UPDRS II (ADL), UPDRS III (motor), and UPDRS IV (medication complications). The total UPDRS I, II, III, IV, and UPDRS values were found to be abnormally distributed with the median value being UPDRS I=3.0, UPDRS II=9.5, UPDRS III=18.0, UPDRS IV=1, and UPDRS total=34.5. The H and Y classification is dominated by grade II, which is 40% (n=24). In terms of disease history and habits, patients who had a history of hypertension were 45% (n=27), history of smoking were 8.3% (n=8), and history of alcohol consumption were 5% (n=3) (Table1). The laboratory results of the subjects, and their total cholesterol, LDL and HDL are presented in (Table 2). Total cholesterol was not normally distributed with a median total cholesterol value of 197 with a Q1-Q3 value of 180.5-212. The mean LDL value was 128.63 with a standard deviation of 35.25, and HDL was 47.65 with a standard deviation of 10.997. Correlation between blood cholesterol levels and UPDRS values was analyzed using Spearman's test (abnormal distribution). Total cholesterol levels have a negative correlation (p=0.000) with the value of UPDRS I, UPDRS II, UPDRS III, and total UPDRS with correlation coefficients (-0.397), (-0.469), (-0.489), and (-0.492). LDL levels were also negatively correlated with the values of UPDRS I, UPDRS II, UPDRS III, and total UPDRS with correlation coefficients (-0.366), (-0.469), (-0.480), and (-0.476). Therefore, it can be concluded that total cholesterol and LDL levels have a negative correlation with a moderately strong correlation with scores of UPDRS I, UPDRS II, UPDRS III, total UPDRS. However, there was no correlation between total cholesterol levels (p=0.084) and LDL (p=0.223) with the UPDRS IV value. Blood HDL levels did not show a correlation with UPDRS I (p=0.418), UPDRS II (p=0.876), UPDRS III (p=0.944), UPDRS IV (p=0.877), and total UPDRS (p=0.879). These results can be seen in (Table 3). The correlation between cholesterol levels and the severity of PD based on the degree of H and Y was analyzed using the Spearman correlation test. Total and LDL cholesterol levels also had negative correlation (p=0.000) with H and Y degree with correlation coefficient of -0.474, and LDL with the H and Y degree of -0.489. So it can be concluded that total and LDL cholesterol levels also have a negative correlation

direction with a strong moderate correlation with the degree of H&Y. There was no correlation (p=0.625) of HDL levels with the degree of H and Y which was statistically significant in this study. These results can be seen in (Table 4).

Table 1: Characteristics of PD patients.

Characteristics	Mean±SD; Median (Q1-Q3)			N (%)
Gender	Male	-	-	32 (53.33)
	Female	-	-	28 (46.67)
Age (years)	64.37±8.26			
	≤50	-	-	2(3.33)
	55-70	-	-	40 (66.67)
	>70	-	-	18 (30)
Onset (years)	3.5; (2-6.75)			-
	≤5	-	-	45 (75,00)
	>5	-	-	15 (25,00)
Education	Elementary	-	-	16 (26,70)
	Junior high	-	-	24(31,60)
	Senior high	-	-	16 (26.70)
	Bachelor	-	-	9 (15.00)
Number of Parkinson drugs	1 type of drug	-	-	1 (1,67)
	2 types of drugs	-	-	27 (45,00)
	>2 types of drugs	-	-	32 (53.33)
History of hypertension	Yes	-	-	27 (45,50)
	No	-	-	33 (55.50)
History of smoking	Yes	-	-	5 (8,30)
	No	-	-	55 (91.70)
History of alcohol	Yes	-	-	3 (5.00)
	No	-	-	57 (95.00)
PD degree	Stage I	-	-	12 (20.00)
	Stage II	-	-	24 (40.00)
	Stage III	-	-	19 (31.60)
	Stage IV	-	-	4 (6.70)
	Stage V	-	-	1 (1.70)
UPDRS score	UPDRS I	-	3 (1-4)	-
	UPDRS II	-	9.5 (5-15.75)	-
	UPDRS III	-	18 (10.25-18)	-
	UPDRS IV	-	1 (1-2)	-
	UPDRS total	-	34.5(19.25-51.25)	-

DISCUSSION

The results of this study showed that the demographics of Parkinson's patients at Kandou general hospital is dominantly males (53.33%) than females (46.66%). The same results were also obtained in other research studies conducted in Indonesia with the same population and the same sampling method as those conducted by Agustin et al in Yogyakarta in 2017 which has more males (57.5%) than females (42.5%) among the population, as well as study conducted by Sari et al in Jakarta in 2010 which shows predominant population of males (54.05%) than females (45.95%).[11,12] Research from outside Indonesia conducted by Huang et al in 2007 in the United States also reported the same results of male predominance (55.65%) than female (44.35%).[13] Another study whose results were quite different from the characteristics of PD patients was obtained in a study by Oktariza et al in 2019 in Bandung, female were more dominant (51.52%) than male (48.48%) and Larasanti et al in Denpasar in 2019 (male 72.3% compared with female 27.7 %).[14,15] The majority of patients with PD are men due to the influence of the female hormone estrogen which is neuroprotective and the risk of head trauma, which is one of the risk factors for PD is greater in men than women.[15] The majority of PD patients in this study were 55-70 years old (66.7%) with a mean age of 64.37±8.26. This is consistent with studies which state that PD reaches its peak in the 6th decade and the results of previous studies with the same target population as Agustin et al in Yogyakarta in 2017 (mean age 62.80±9.96), Larasanti et al in Denpasar (mean age 63.87±8.67), Oktariza et al in

Bandung in 2019 (mean age 61.03±9.12) and Huang et al in the United States in 2007 (mean age 63.7±11.4).[11,13-15]

Table 2: Cholesterol profile in PD patients.

Cholesterol profile	Mean±SD	Median (Q1-Q3)
Total cholesterol	-	197 (180.5-212)
LDL	128.63±35.25	-
HDL	47.65±10.997	-

This study also found that more than half of the study subjects had onset of symptoms within 5 years (75%). This may be explained by the tendency of patients that seek medical help after motor symptoms that interfere with daily activities began to appear. The theory by Hawkes and Braak states that patients usually complain of symptoms such as hyposmia, indigestion, sleep disturbances, or decreased cognitive function. Progression of symptoms from unilateral to bilateral usually occurs 5 years from the onset of motor symptoms, and postural instability usually occurs within 10 years. Non-motor symptoms were initially ignored or at first the symptoms were not suspected as a symptom of PD so that the patient came for general check-up after the motor symptoms appeared and began to interfere with daily activities, which may takes 1-5 years from the appearance of motor symptoms.[16]

Table 3: Correlation between total cholesterol, LDL, and HDL levels with severity of Parkinson's disease based on UPDRS.

Cholesterol level (mg/dl)	UPDRS I		UPDRS II		UPDRS III		UPDRS IV		Total UPDRS	
	R value	P value	R value	P value	R value	P value	R value	P value	R value	P value
Total cholesterol	-0.397	0.002	-0.464	0.000	-0.489	0.000	-0.225	0.084	-0.492	0.000
LDL	-0.366	0.004	-0.469	0.000	-0.480	0.000	-0.160	0.223	-0.476	0.000
HDL	-0.106	0.418	-0.21	0.876	-0.09	0.944	-0.02	0.877	-0.02	0.879

P value is from Spearmen test and R=correlation coefficient.

This study found that 40% of patients were in stage H&Y II followed by 31.7% at stage III. This result is similar to the patient characteristics of the study conducted by Larasanti et al in Denpasar in 2019 which found 44.7% of patients were in stage II and 34% at stage III and Agustin et al in 2017 in Yogyakarta (45% were in stage II H and Y).[11,15] Different results were obtained in the study by Oktariza et al in Bandung in 2019, with 69.69% were in stage III H and Y.[14]

Table 4: Correlation between total cholesterol, LDL, and HDL levels with the severity of Parkinson's disease based on H and Y degrees.

Cholesterol level (mg/dl)	H&Y Degree	
	R value	P value
Total cholesterol	-0.474	0.000
LDL	-0.489	0.000
HDL	-0.064	0.625

P value is from Spearmen test and R=correlation coefficient.

The majority of PD patients were at H and Y II-III stages according to the previous explanation, whereas in this study more than half of patients had an onset of <5 years and according to staging by Braak, the symptoms that appeared correlated with H and Y II-III stages. Only 6.7% of patients came with stage H and Y IV and 1.7% H and Y V, this may be explained by limited patient mobility so that patients do not come routinely to the clinic for control.[15,16] Some PD patients in this study used more than two drugs (53.33%). Several previous studies obtained almost have the same results by Oktariza et al in Bandung whereas patients usually consume more than two types of drugs (54.54%) and Agustin et al in 2017 in Yogyakarta the majority of patients used two types of Parkinson's drugs (60%).[11,14] This may be in accordance with PD therapy guidelines using combination therapy to avoid side effects of long-term levodopa use such as wearing off or on off phenomena.[4] In this study, it was also found that some PD patients had no history of hypertension (55.5%) and the majority did not have a history of smoking (91.70%). The results were almost the same by Agustin et al in 2017 in Yogyakarta, which has no history of hypertension (65%) and no history of smoking (72.5%).[11] Another study conducted by Pariama et al in 2016 in Semarang also found that there was no history of hypertension (75%) among the patients.[17] This is consistent with a study conducted by Miyake et al in 2010 that hypertension is one of the factors that can actually reduce the risk of PD.[18]

The results of the correlation test between serum LDL cholesterol levels with the severity of PD revealed a negative correlation with a moderate strong correlation between total and LDL cholesterol levels and the severity of PD based on UPDRS scores and H and Y degrees. It can be explained that cholesterol and LDL levels have an inverse correlation with the severity of Parkinson's disease so that lower levels of total cholesterol and LDL are associated with more severe Parkinson's disease. This is in line with research conducted by Huang et al in the United States in 2007 which stated that high serum total cholesterol levels were associated with slower progression of PD as seen from changes in UPDRS

values and low LDL levels were associated with an increased risk of PD.[13] The results of this study also did not show a correlation between HDL and PD.[13-19] However, the results of this study are different from the results of research conducted by Agustin et al in Yogyakarta in 2017 which showed no significant difference in LDL levels to the severity of PD based on the H and Y scale.[11]

The difference in the results of this study is due to the fact that there are many factors that can changes the mechanism and pathophysiology of dopaminergic cells in patients with PD that affect disease progression and the differences in the statistical test methods of this study with those of Agustin et al. The effect of cholesterol levels on the biologic progression of PD is unknown, but it has been suggested that cholesterol may facilitate the repair of injured neuronal pathways in Parkinson's disease.[20] It was also studied that cholesterol also plays a role in synaptogenesis.[6] Under normal physiological state, cholesterol load in the CNS does not depend on dietary intake or hepatic synthesis but only depends on synthesis by astrocytes in the brain. Therefore, in progressive degenerative diseases, the theory supports that plasma cholesterol can cross the blood-brain barrier to facilitate repair of neuronal pathways and synaptogenesis.[8-10]

CONCLUSION

From this study, we conclude that majority of patient with PD were male with mean age of 64.37±8.26 years old. Mean total cholesterol level, LDL, HDL among PD patient were within normal range. There is a moderate negative correlation between total cholesterol level and LDL with PD severity degree based on H and Y degree and UPDRS I, II, III, and UPDRS total score. However, this study has several limitations, such as that it is difficult to determine cause and effect because risk and effect data collection is carried out at the same time. In conclusion, since this study has a non-randomized sample collection technique with a predominance of more samples at mild-moderate grades of PD, there might be a large possibility of bias, as well as short study duration, confounding factors that are not controlled by randomization, stratification mechanisms or multivariate analysis.

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