ORIGINAL ARTICLE

Decreased Serum Lipid Levels and Ratios Correlate with Low Prevalence of Coronary Heart Disease in Patients with Parkinson’s Disease

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SUMMARY

Background: Patients with Parkinson's disease (PD) are at a lower risk of suffering cardiovascular events, but the underlying factors for this decreased risk remain unclear. Serum triglycerides (TG) and total cholesterol (TC), and their expression relative to high-density lipoprotein cholesterol (TG/HDL-C and TC/HDL-C), are independent predictors of cardiovascular events. This study aimed to determine if PD patients have decreased lipid levels and lipid ratios, which may underlie the decreased risk of coronary heart disease (CHD).

Methods: This retrospective study included 92 PD patients (PD group), 450 control subjects with no CHD (OD group), and 450 CHD patients (CHD group). We analyzed serum lipid levels and lipid ratios in each group.

Results: There were significant differences in TC (F = 10.459, p < 0.0001), TG (F = 46.856, p < 0.0001), low density lipoprotein cholesterol (LDL-C) (F = 6.910, p = 0.001), high density lipoprotein cholesterol HDL-C (F = 30.694, p < 0.0001), TC/HDL-C (F = 32.675, p < 0.0001), and TG/HDL-C (F = 45.554, p < 0.0001) between all three groups; TC/LDL-C (F = 2.518, p = 0.081) was not significantly different between groups. Compared to the CHD group, PD patients had lower TC (p < 0.0001), TG (p < 0.0001), LDL-C (p = 0.001), TG/HDL-C (p < 0.0001), and TC/HDL-C (p < 0.0001); TC/LDL-C (p = 0.563) and HDL-C (p = 0.196) were not significantly different. TC and LDL-C levels were positively correlated within individual groups (all p < 0.0001). In addition, TG and HDL-C were negatively correlated in the OD and CHD groups (p < 0.0001); no significant negative association was observed in the PD group (p = 0.077). TG/HDL and LDL-C levels were inversely correlated in the CHD group (p < 0.0001) and weakly positively correlated in the PD (p = 0.159) and OD (p = 0.199) groups.

Conclusions: TC/HDL and TG/HDL ratios were significantly lower in PD patients compared to CHD patients, suggesting there is a strong correlation between lipid ratios and incidence of CHD in PD patients.


KEY WORDS
coronary heart disease, Parkinson’s disease, triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol

INTRODUCTION

Parkinson's disease (PD) is a chronic, age-related neurodegenerative disease that is typically characterized by extrapyramidal symptoms (tremor, rigidity, bradykine-
PD cardiometabolic risk compared to the general population. Epidemiological studies have demonstrated that low levels of low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and total cholesterol (TC) were associated with a higher prevalence of PD, suggesting that low lipid levels are associated with PD pathogenesis [1-6]. In contrast, increased levels of LDL-C, TG, and TC and low levels of high-density lipoprotein cholesterol (HDL-C) have been shown to be tightly associated with the pathogenesis of atherosclerosis and are important risk factors for coronary artery heart disease (CHD) and stroke [7-11]. Therefore, lowering LDL-C levels has been a primary goal for CHD prevention [12,13]; however, residual CHD risk still persists in those patients who have achieved targeted LDL-C levels [14,15]. Furthermore, CHD risk has been associated with atherogenic dyslipidemia (AD), characterized by an increased ratio of TG to HDL-C (TG/HDL-C) [16]. Increasing HDL-C levels has been utilized as a therapy to reduce cardiovascular risk, but this therapeutic approach has failed. For example, the AIM HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health) trial was prematurely terminated because increasing HDL-C levels with niacin treatment did not effectively reduce residual CHD risk [17]. In addition, epidemiological studies confirmed that lipid particle size is a key determinant of a lipid’s anti- or pro-atherogenic properties, and increased content of small HDL particles and small LDL particles was significantly associated with CHD risk [18-21]. High TC/HDL-C and TG/HDL-C ratios were significantly correlated with smaller HDL and LDL particles [19,22,23], suggesting that a high lipid ratio may be a good indicator of abnormal cholesterol metabolism. TG/HDL-C and TC/HDL-C ratios have also been shown to be better indicators of coronary atherosclerosis compared to individual lipid levels [24]. Therefore, lipid ratios may be powerful independent predictors of cardiovascular events. Previous studies have shown that PD patients have decreased occurrences of CHD [25,26], but the underlying associations between PD and CHD remain unclear. However, there is evidence that PD patients have a lower cardiometabolic risk compared to the general population. PD patients have lower TC, TG, and LDL-C levels [3,27,28], which suggests that decreased lipid levels correlate with a lower risk of CHD. However, the associations between TC/HDL-C and TG/HDL-C ratios with CHD risk in PD patients have not been well researched. In this retrospective study, we examined the associations of TC/HDL-C and TG/HDL-C ratios among non-CHD, CHD, and PD patients.

MATERIALS AND METHODS

PD patient selection
This retrospective study enrolled 92 PD patients (49 males and 43 females; mean age, 70.09 ± 7.08 years) who were diagnosed with PD according to the clinical criteria of the UK PD Society Brain Bank at the People's Hospital of Xuancheng City from May 2010 to January 2017. Each patient was evaluated according to the Hoehn and Yahr scale. Fourteen patients were in stage I, 27 in stage II, 34 in stage III, 14 in stage IV, and 3 in stage V. Patients who had any one of the following were excluded from our study: 1) atypical degenerative parkinsonisms, secondary parkinsonisms, severe liver disease, severe kidney disease, or cancer; 2) symptoms such as vomiting or anorexia; or 3) a history of using lipid medications or lack of lipid records.

Control patient selection
A total of 900 age- and gender-matched patients were selected from the same hospital as controls for this study. Patients who were taking lipid lowering medications or diagnosed with myocardial disease, diabetes, or lung, liver, kidney, and other serious diseases, were excluded from our study. Among the 900 patients, 450 subjects who did not have CHD but who had other diseases, such as anxiety disorders, vertigo, and traumatic fracture, were included in the non-CHD group (OD group: 240 males and 210 females; mean age, 68.48 ± 7.48 years). Another 450 subjects who were diagnosed with coronary atherosclerotic heart disease, including acute coronary syndrome, ST segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, and unstable angina, were included in the CHD group (CHD group: 240 males and 210 females; mean age, 69.40 ± 7.02 years).

Determination of biomarkers
All lipid levels, including TC and TG, were measured by an enzymatic colorimetric kit, and HDL-C was determined by an assay kit in combination with the Olympus automatic analyzer AU5400 (Olympus, America). LDL-C was calculated using the Friedewald formula. TG/HDL-C, TC/HDL-CL, and TC/LDL-C ratios were also calculated. All subjects enrolled in our study were from the city of Xuancheng, China, and had similar living habits and dietary structures. Our study was approved by The People's Hospital of Xuancheng Citing City Ethics Committee, and written informed consent was obtained from every patient. Anonymous data were used for statistical analyses, and information on pharmacological treatment was also collected.

Statistical analysis
All statistical analyses were performed with IBM SPSS Statistics for Windows, Version 19.0. (IBM Corp; Armonk, NY, USA). The results are reported using two-tailed significance, which was set at p < 0.05. All variables were examined for normality with histograms and
the one-sample Kolmogorov-Smirnov test. Measurement data were presented as the mean ± standard deviation (SD). Enumeration data were compared with the chi-square test, while continuous variables were compared with one-way analysis of variance (ANOVA) among groups. The LSD (least significant difference) analysis was used for post-hoc comparisons following ANOVA analysis. The relationships between lipid profiles were determined using Pearson’s correlation analysis for the three groups.

RESULTS
As shown in Table 1, there were no significant differences among the three groups with regards to gender ($\chi^2 = 0.00, p = 1.000$), age ($F = 2.861, p = 0.058$), and history of hypertension ($\chi^2 = 1.527, p = 0.466$). Consistent with previous studies, TC ($F = 10.459, p < 0.0001$), TG ($F = 46.856, p < 0.0001$), and LDL-C ($F = 6.910, p = 0.001$) serum levels were significantly different in all three groups (Table 3). TC, TG, and LDL-C serum levels were significantly lower in the PD group compared to the CHD group ($p < 0.0001; p < 0.0001; p = 0.001$, respectively) (Table 4). However, HDL-C serum levels were significantly different in all three groups ($F = 30.694, p < 0.0001$) (Table 3); no significant difference was observed between the PD and CHD groups ($p = 0.196$) (Table 4).

TC/HDL-C ratios were significantly different in all three groups ($F = 32.675, p < 0.0001$) (Table 3); the TC/HDL-C ratio was 3.26 ± 0.90 in the PD group, 3.22 ± 0.88 in the OD group, and 3.71 ± 1.00 in the CHD group (Table 2). The TC/HDL-C ratio was significantly lower in the PD group compared to the CHD group ($p < 0.0001$). However, no significant difference was found between the PD and OD groups ($p = 0.7$) (Table 4).

TG/HDL-C ratios were also significantly different in the three groups ($F = 45.554, p < 0.0001$) (Table 3); the TG/HDL-C ratio was 2.03 ± 1.11 in the PD group, 2.03 ± 1.42 in the OD group, and 2.97 ± 1.81 in the CHD group (Table 2). The TG/HDL-C ratio was significantly lower in the PD group compared to the CHD group ($p < 0.0001$). There was no significant difference between the PD and OD groups ($p = 0.842$) (Table 4). The TC/LDL-C ratio was not significantly different in the three groups ($F = 2.518, p = 0.081$) (Table 3); the TC/LDL-C ratio was 1.85 ± 0.37 in the PD group, 1.89 ± 0.38 in the OD group, and 1.83 ± 0.35 in the CHD group (Table 2).

Pearson’s tests were used to evaluate the association of lipid parameters in each group. As shown in Table 5, there were strong positive correlations between TC and LDL-C within each individual group (all $p < 0.0001$). In line with previous findings [29-31], TG and HDL-C levels were negatively associated in the OD and CHD groups ($p < 0.0001$), but no significant negative association was observed in the PD group ($p > 0.05$). We also found a significant negative correlation in the CHD group ($p < 0.0001$) and weak positive correlations for TG/HDL-C and LDL-C ratios ($p = 0.159$ and $p = 0.199$, respectively) in the PD and OD groups.

DISCUSSION
Previous studies examining lipid levels in PD patients have produced contradictory results. Recent findings indicated that lipid levels are inversely related to PD occurrence [1,2,4-6], thus pointing to the possibility that lower TC, LDL-C, and TG levels are risk factors for PD pathogenesis. Consistent with these observations, our study also found lower TC, TG, and LDL-C levels in PD patients compared to CHD and non-CHD patients. Furthermore, some literature has suggested that decreased risk of CHD in PD patients could be attributed to low lipid levels. However, single lipid measurements may underestimate cardiovascular risk burden. According to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines [32], Baigent [33] reported that statins reduced mortality associated with coronary artery disease by approximately 20%. However, some studies that aimed to minimize CHD risk by modifying TG or HDL-C levels did not achieve appreciable outcomes. For instance, Landray et al. [34] reported that niacin or combination laropiprant therapy significantly elevated HDL-C levels and decreased TG levels but did not substantially reduce the risk of major vascular events as expected.

Nevertheless, recent studies that aimed to accurately reveal the underlying mechanism of lipid metabolism and atherosclerosis have provided encouraging data. For example, nuclear magnetic resonance (NMR) spectroscopy can directly quantify the number and size distribution of LDL and HDL particles (LDL-P and HDL-P), which may yield a more accurate assessment of atherosclerotic risk [35,36]. Specifically, NMR showed that the increased atherosclerotic risk was attributed to small dense LDL-P (sd-LDL-P), which can penetrate the arterial wall more easily and are susceptible to oxidation compared to large LDL-P [37]. However, NMR has limited clinical application due to its high cost of measuring lipoprotein particles. Elshazly et al. [38] found that the TC/HDL-C ratio was discordant with LDL-C and non-HDL-C levels, which carry additional information reflecting LDL-P size and concentration that is not available in cholesterol-based measurements. In our study, we found that LDL-C serum levels and the TC/HDL-C ratio were significantly lower in the PD group, suggesting that reducing atherogenic lipoprotein particles, such as sd-LDL-P, may reduce the risk of CHD in PD patients.

An elevated TG/HDL-C ratio presents great residual vascular risk (RVR), even when LDL-C levels are in accordance with the guidelines of NCEP ATP III. Gaziano [39] reported that a high TG/HDL-C ratio increased the risk of myocardial infarction 16-fold compared to the
Table 1. Demographic data of patients.

<table>
<thead>
<tr>
<th></th>
<th>PD (n = 92)</th>
<th>OD (n = 450)</th>
<th>CHD (n = 450)</th>
<th>χ²/F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>49/43</td>
<td>240/210</td>
<td>240/210</td>
<td>0.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Age (year)</td>
<td>70.09 ± 7.08</td>
<td>68.48 ± 7.48</td>
<td>69.40 ± 7.02</td>
<td>2.861</td>
<td>0.058</td>
</tr>
<tr>
<td>Hypertension (Y/N)</td>
<td>51/41</td>
<td>259/191</td>
<td>274/176</td>
<td>1.527</td>
<td>0.466</td>
</tr>
</tbody>
</table>

PD - Parkinson’s disease group, OD - non-CHD group, CHD - CHD group, χ² - Chi-square test, F - one-way analysis of variance.

Table 2. Serum lipid levels and lipid ratios.

<table>
<thead>
<tr>
<th></th>
<th>PD (n = 92)</th>
<th>OD (n = 450)</th>
<th>CHD (n = 450)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC (mg)</td>
<td>160.37 ± 30.36</td>
<td>173.14 ± 29.91</td>
<td>176.88 ± 33.48</td>
</tr>
<tr>
<td>TG (mg)</td>
<td>95.35 ± 34.14</td>
<td>103.21 ± 51.56</td>
<td>135.43 ± 64.07</td>
</tr>
<tr>
<td>HDL-C (mg)</td>
<td>51.79 ± 13.33</td>
<td>56.95 ± 15.60</td>
<td>49.70 ± 12.36</td>
</tr>
<tr>
<td>LDL-C (mg)</td>
<td>90.21 ± 25.92</td>
<td>95.48 ± 26.25</td>
<td>100.27 ± 27.76</td>
</tr>
<tr>
<td>TC/HDL-C (mg)</td>
<td>3.26 ± 0.90</td>
<td>3.22 ± 0.88</td>
<td>3.71 ± 1.00</td>
</tr>
<tr>
<td>TG/HDL-C (mg)</td>
<td>2.03 ± 1.11</td>
<td>2.03 ± 1.42</td>
<td>2.97 ± 1.81</td>
</tr>
<tr>
<td>TC/LDL-C (mg)</td>
<td>1.85 ± 0.37</td>
<td>1.89 ± 0.38</td>
<td>1.83 ± 0.35</td>
</tr>
</tbody>
</table>

PD - Parkinson’s disease group, OD - non-CHD group, CHD - CHD group. TC - total cholesterol, TG – triglycerides, HDL-C - high density lipoprotein cholesterol, LDL-C - low density lipoprotein cholesterol, Log (TG) - log-transformed TG.

Table 3. Overall differences in lipid values and lipid ratios among three groups.

<table>
<thead>
<tr>
<th></th>
<th>TC (mg)</th>
<th>TG (mg)</th>
<th>HDL-C (mg)</th>
<th>LDL-C (mg)</th>
<th>TC/HDL-C</th>
<th>TG/HDL-C</th>
<th>TC/LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>10.459</td>
<td>46.856</td>
<td>30.694</td>
<td>6.910</td>
<td>32.675</td>
<td>45.554</td>
<td>2.518</td>
</tr>
<tr>
<td>P</td>
<td>0.000 *</td>
<td>0.000 *</td>
<td>0.000 *</td>
<td>0.001 *</td>
<td>0.000 *</td>
<td>0.000 *</td>
<td>0.081</td>
</tr>
</tbody>
</table>

PD - Parkinson’s disease group, OD - non-CHD group, CHD - CHD group. TC - total cholesterol, TG – triglycerides, HDL-C - high density lipoprotein cholesterol, LDL-C - low density lipoprotein cholesterol. The results were obtained using one-way analysis of variance; F - one-way analysis of variance. * - p < 0.01.

Table 4. Post-hoc comparisons of lipid values and lipid ratios.

<table>
<thead>
<tr>
<th></th>
<th>TC</th>
<th>TG</th>
<th>HDL-C</th>
<th>LDL-C</th>
<th>TC/HDL-C</th>
<th>TG/HDL-C</th>
<th>TC/LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD vs. OD</td>
<td>0.001 **</td>
<td>0.346</td>
<td>0.001 **</td>
<td>0.077</td>
<td>0.700</td>
<td>0.842</td>
<td>0.466</td>
</tr>
<tr>
<td>PD vs. CHD</td>
<td>0.000 **</td>
<td>0.000 **</td>
<td>0.196</td>
<td>0.001 **</td>
<td>0.000 **</td>
<td>0.000 **</td>
<td>0.563</td>
</tr>
<tr>
<td>OD vs. CHD</td>
<td>0.072</td>
<td>0.000 **</td>
<td>0.000 **</td>
<td>0.009 **</td>
<td>0.000 **</td>
<td>0.000 **</td>
<td>0.025 *</td>
</tr>
</tbody>
</table>

PD - Parkinson’s disease group, OD - non-CHD group, CHD - CHD group. TC - total cholesterol, TG – triglycerides, HDL-C - high density lipoprotein cholesterol, LDL-C - low density lipoprotein cholesterol. The results were obtained from Post-hoc comparisons (LSD test), * - p < 0.05, ** - p < 0.01.
Table 5. Pearson’s correlation analysis of lipids.

<table>
<thead>
<tr>
<th></th>
<th>PD</th>
<th>OD</th>
<th>CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC vs. LDL-C</td>
<td>0.895 **</td>
<td>0.835 **</td>
<td>0.878 **</td>
</tr>
<tr>
<td>TC/HDL vs. LDL-C</td>
<td>0.577 **</td>
<td>0.614 **</td>
<td>0.395 **</td>
</tr>
<tr>
<td>Log (TG) vs. HDL-C</td>
<td>-0.185</td>
<td>-0.289 **</td>
<td>-0.194 **</td>
</tr>
<tr>
<td>TG/HDL vs. LDL-C</td>
<td>0.148</td>
<td>0.061</td>
<td>-0.210 **</td>
</tr>
</tbody>
</table>

PD - Parkinson’s disease group, OD - non-CHD group, CHD - CHD group, TC - total cholesterol, TG - triglycerides, HDL-C - high density lipoprotein cholesterol, LDL-C - low density lipoprotein cholesterol, LOG (TG) - log-transformed TG. * - p < 0.05, ** - p < 0.01.

Potential underlying mechanisms that might explain this relationship have been put forth in several studies. 1) A previous cohort study showed a strong negative correlation between TG and HDL-C levels, with r-values ranging from -0.26 to -0.58 [29-31]. TG/HDL-C reflects the balance between atherogenic and protective lipoproteins and can be useful in predicting the risk of CHD independent of other risk factors, such as body mass index (BMI), waist circumference, and waist-to-hip ratio [40]. 2) High TG and low HDL-C levels are strongly associated with LDL phenotype B and insulin resistance [3], but also have inverse associations with HDL size [41]. Sd-LDL-P may be more prone to penetrating the arterial wall and are more susceptible to oxidation compared to large LDL-C particles, which stimulate monocytes and macrophages to secrete pro-inflammatory cytokines and chemokines.

In this study, we showed that the TG/HDL-C ratio was lower in the PD group compared to the CHD group. We also found a significant negative correlation between TG and HDL-C levels in the CHD group, and that the TG/HDL-C ratio negatively correlated with LDL-C in the CHD group, but not in the PD group. These observations may be attributed to the negative association of the TG/HDL-C ratio with LDL particle size and large LDL concentration [42]. Further, there was frequent discordance between LDL-C and LDL-P, especially at lower LDL-C and higher TG levels [23,38]. Therefore, the findings from the present study indicate that a lower TG/HDL ratio may be a critical factor for decreasing the prevalence of CHD in PD patients.

Our study has some limitations. First, the sample size was relatively small and could therefore present inclusion bias. Second, the TG levels were not significantly increased in our study population; when TG was greater than 400 mg/L, the LDL-C value was distorted, as determined by the Friedewald formula. Third, no parameters related to nutritional status were investigated in our study. However, Emanuele Cereda et al. [42] reported that PD patients have a more favorable cardiometabolic risk profile, independent of nutritional status, body composition, and fat distribution. Finally, although we found low TC/HDL and TG/HDL ratios in the PD group, the underlying mechanisms of the effects of these ratios on CHD risk remain to be elucidated.

CONCLUSION

In summary, our study demonstrates that PD patients have reduced TG, TC, and LDL levels, as well as reduced TG/HDL-C and TC/HDL-C ratios. Our data indicate that lipid ratios may play an important role in determining CHD risk in PD patients. Lastly, changes in TG/HDL-C and TC/HDL-C ratios are likely more powerful predictors of CHD risk than changes in any individual lipid level.

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Declaration of Interest:
The authors declare no conflicts of interest.

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