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ORIGINAL ARTICLE

Relationship Between Cholesterol Levels and Mortality in Patients Undergoing Hemodialysis

Hemodiyalize Giren Hastalarda Kolesterol Düzeyleri ile Mortalite Arasındaki ilişki

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Abstract

Introduction: Cardiovascular events and mortality rates are high in chronic renal failure patients who are undergoing hemodialysis treatment. Hence, patients with a higher mortality risk must be distinguished. Dyslipidemia is more frequently reported in hemodialysis patients. Inconsistent results are obtained between the cholesterol levels and mortality of patients undergoing hemodialysis. This study aims to inspect the association between the mortality rate and the mean total cholesterol, triglyceride, and high- and low-density lipoprotein cholesterol levels.

Methods: This study involved 506 patients undergoing hemodialysis retrospectively between January 2015 and December 2019. All patients following a hemodialysis program were monitored. The lipid level data for 6-month periods were recorded until death or study end date. Patients below 18 and those who were on hemodialysis for less than 60 days were excluded.

Results: Of the 506 participants, 288 (56.9%) survived. The mean followup period was 31.7 months. High- and low-density lipoproteins, triglyceride, total cholesterol levels, and lipid-lowering drug usage were significantly higher, but the duration on hemodialysis was significantly lower in surviving patients. The regression analysis showed that age, systolic blood pressure, and treatment with erythropoietin were related with mortality.

Discussion and Conclusion: In patients undergoing hemodialysis, decreases in the mean total cholesterol, triglyceride, and high- and low-density lipoprotein cholesterol levels increased the mortality risk, while antihyperlipidemic drugs decreased the mortality risk. Lowering the lipid levels below safe levels may increase the mortality risk; because of this, the target lipid levels for hemodialysis patients must be sparely determined.

Keywords: Cholesterol; Dyslipidemias; Hemodialysis; Mortality

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Cardiovascular events and mortality rates are high in patients with chronic renal failure (CRF), even if they are undergoing hemodialysis treatment.[1] CRF and mortality related to CRF are increasing globally. In 2040, it is expected to become as the fifth most frequent reason of mortality.[2] Fifty percent of patients undergoing hemodialysis are reported to have a 5-year survival rate.[3] Cardiovascular pathologies are the most frequent reason of mortality in hemodialysis patients.[4] Distinguishing which patients under hemodialysis treatment for CRF are in a higher mortality risk is important in properly managing patients and improving prognosis. A study from India showed that the frequency of dyslipidemia increases in hemodialysis patients.[5] Dyslipidemia was found to be an important comorbidity in 43% of hemodialysis patients.[6] It is a well-known risk factor for coronary artery disease.[7] Meanwhile, a US study involving 50,673 patients found that in patients undergoing hemodialysis, hypertriglyceridemia lowers mortality.[8] Interestingly, increases in high-density lipoprotein cholesterol (HDL-C) levels over recommended values were reported to be associated to increased mortality.[9] However, underlying mechanisms were not clearly elucidated. Some studies reported contradictory results. One study reported that hypertriglyceridemia and low HDL-C values were associated with increased mortality resulting from cardiovascular reasons.[10] In the literature, results between cholesterol levels and mortality in patients undergoing hemodialysis are inconsistent.[8–10]

This study aims to elucidate the association between cholesterol levels and mortality in hemodialysis patients with CRF. The associations between mortality and triglyceride, HDL-C, low-density lipoprotein cholesterol (LDL-C), and total cholesterol levels in patients ongoing hemodialysis are inspected.

Materials and Methods

This study was conducted retrospectively on patients with ongoing hemodialysis in a university hospital between January 2015 and December 2019. Patients undergoing hemodialysis thrice a week because of CRF were evaluated. The data required for the study could not be obtained in all patients; therefore, 506 of 710 patients were enrolled in this work. Patients below 18 years old who had malignancy and patients who were undergoing hemodialysis for less than 60 days were excluded. This study was approved by Lokman Hekim University Non-Interventional Clinical Research Ethics Committee (app. No: 2020077, 19.10.2020). No form of artificial intelligence help was used to prepare the study for publication.

The age, gender, body weight, fasting HDL-C, LDL-C, triglyceride and total cholesterol levels, erythropoietin, and lipid-lowering drug usage information and data on concomitant diseases, duration on hemodialysis, urea reduction ratio, Kt/V value, and blood pressure measurements of all patients were recorded. Patients with HDL-C levels above 0.91 mmol/L, LDL-C levels above 3.37 mmol/L, total cholesterol levels above 5.18 mmol/L, and triglyceride levels above 3.87 mmol/L were accepted to have high levels.

The data of patients, who were followed for 6-month periods until death or until the study end date, were extracted from the hospital computer database. The lipid values examined in 6-month intervals during followup periods were recorded and the mean cholesterol levels calculated to minimize the effect of the measurement-based differences. The demographic characteristics, existence of concomitant diseases, cholesterol levels, and effects of erythropoietin and lipid-lowering drug usage were compared between surviving patients and patients who died during the followup period.

The blood samples of the participants were obtained just before routine hemodialysis sessions while patients were fasting for at least 8 h. All patients were followed up in 6-month periods with routine blood tests. The LDL-C, HDL-C, triglyceride, and total cholesterol levels were analyzed using a Roche Hitachi Cobas 501 (Switzerland) device.

Statistical Analysis

Data were analyzed by SPSS for Windows 25.0 statistical software package (Armonk, NY, USA). Data distributions or normality tests were evaluated by the Shapiro–Wilk test. Data were presented as mean±standard deviation for normal distributed variables, and as median (minimum–maximum) for nonnormal distributed variables. The comparisons between groups were evaluated by independent-samples t-test. Qualitative data were compared with Chi-squared test. p-Values below 0.05 were considered significant. A linear regression analysis was performed to inspect the relationships between mortality and the study parameters. Variables with p-values below 0.2 were used for the binary logistic regression analysis. The relative risk ratio and 95% confidence interval were determined for all parameters. The Kaplan–Meier estimates were calculated for groups according to the mean cholesterol levels, below or above, for HDL-C 0.91 mmol/L, for LDL-C 3.37 mmol/L, for total cholesterol 5.18 mmol/L, and for triglyceride levels 3.87 mmol/L.

Table 1. Demographic characteristics, concomitant diseases, and basal cholesterol levels of patients

Parameter	Deceased (n=218)	Survived (n=288)	p
Age (years)	71.8±10.90	61.2±12.90	<**0.001***
Body weight (kg)	71.8±1.30	73.6±1.10	0.298*
Male/female (n)	108/110	153/135	0.472*
Duration of dialysis (months)	49.51±22.31	43.06±19.41	**0.001***
Urea reduction ratio	71.46±8.58	71.88±7.88	0.588*
Kt/V ratio	1.54±0.32	1.58±0.33	0.162*
Systolic blood pressure (mmHg)	120.31±17.29	124.61±22.95	**0.021***
Diastolic blood pressure (mmHg)	76±40.41	76.5±12.06	**0.048***
High-density lipoprotein (mmol/L)	0.96±0.02	1.02±0.02	0.053*
Low-density lipoprotein (mmol/L)	2.48±0.02	2.47±0.02	0.902*
Triglycerides (mmol/L)	4.47±0.19	4.62±0.16	0.535*
Total cholesterol (mmol/L)	4.29±0.08	4.37±0.07	0.412*
Lipid-lowering drug usage, n (%)	15 (6.8)	39 (13.5)	**0.019**†
Erythropoietin usage, n (%)	114 (52.3)	163 (56.6)	0.367†
Diabetes mellitus, n (%)	53 (24.3)	53 (18.4)	0.122†
Hypertension, n (%)	80 (36.7)	120 (41.6)	0.149†
Coronary artery disease, n (%)	75 (34.4)	75 (26)	**0.026**†
Cerebrovascular disease, n (%)	7 (3.2)	15 (5.2)	0.193†
Chronic obstructive pulmonary disease, n (%)	28 (13.1)	39 (13.5)	0.495†

*: Independent-samples t-test; †: Chi-squared test.

Table 2. Mean cholesterol levels of patients

Parameter	Deceased (n=218)	Survived (n=288)	p
Mean high-density lipoprotein (mmol/L)	0.82±0.34	0.99±0.31	<**0.001***
Mean low-density lipoprotein (mmol/L)	2.07±0.88	2.32±0.80	**0.001***
Mean triglycerides (mmol/L)	3.62±2.29	4.36±2.14	<**0.001***
Mean total cholesterol (mmol/L)	3.55±1.33	4.12±1.12	<**0.001***

*: Independent-samples t-test.

Results

The HDL-C, LDL-C, triglyceride and total cholesterol levels, and lipid-lowering drug usage ratio in the surviving patients were higher.

The mean age of the participants was 65.7±13.1 (64.1±0.8 in males and 67.4±0.8 in females). Two hundred and sixty-one (51.5%) were males, and 245 (48.5%) were females. The mean followup period was 31.7 months. During the follow-up period of the 506 patients, only 288 (56.9%) survived. The mean age of the deceased patients was 71.8±10.9, while that for the surviving patients was 61.2±12.9 years (p<0.001). The mean body weight of patients was 72.8±0.8 kg. The duration on hemodialysis in the surviving patients was lower. Table 1 shows the demographic characteristics, existence of concomitant diseases, and basal cholesterol levels of the patients. Coronary artery disease was less frequent in the surviving patients. The mean LDL-C, HDL-C, triglyceride, and total cholesterol levels were higher in surviving patients (Table 2).

Table 3. Binary regression analysis of parameters affecting mortality in hemodialysis patients

Parameter	OR (95% CI)	p
Age	0.926 (0.907–0.945)	<**0.001**
Gender	0.810 (0.514–1.276)	0.363
Weight	1.002 (0.989–1.015)	0.756
Systolic blood pressure	1.250 (1.119–1.396)	<**0.001**
Diabetes mellitus	0.706 (0.404–1.232)	0.220
Erythropoietin usage	0.320 (0.195–0.526)	<**0.001**
Duration of dialysis	1.013 (0.991–1.035)	0.245

OR: Odds ratio; CI: Confidence interval.

In the regression analysis, age, systolic blood pressure, and treatment with erythropoietin were found to be related with mortality, with p-values <0.001 for all (Table 3).

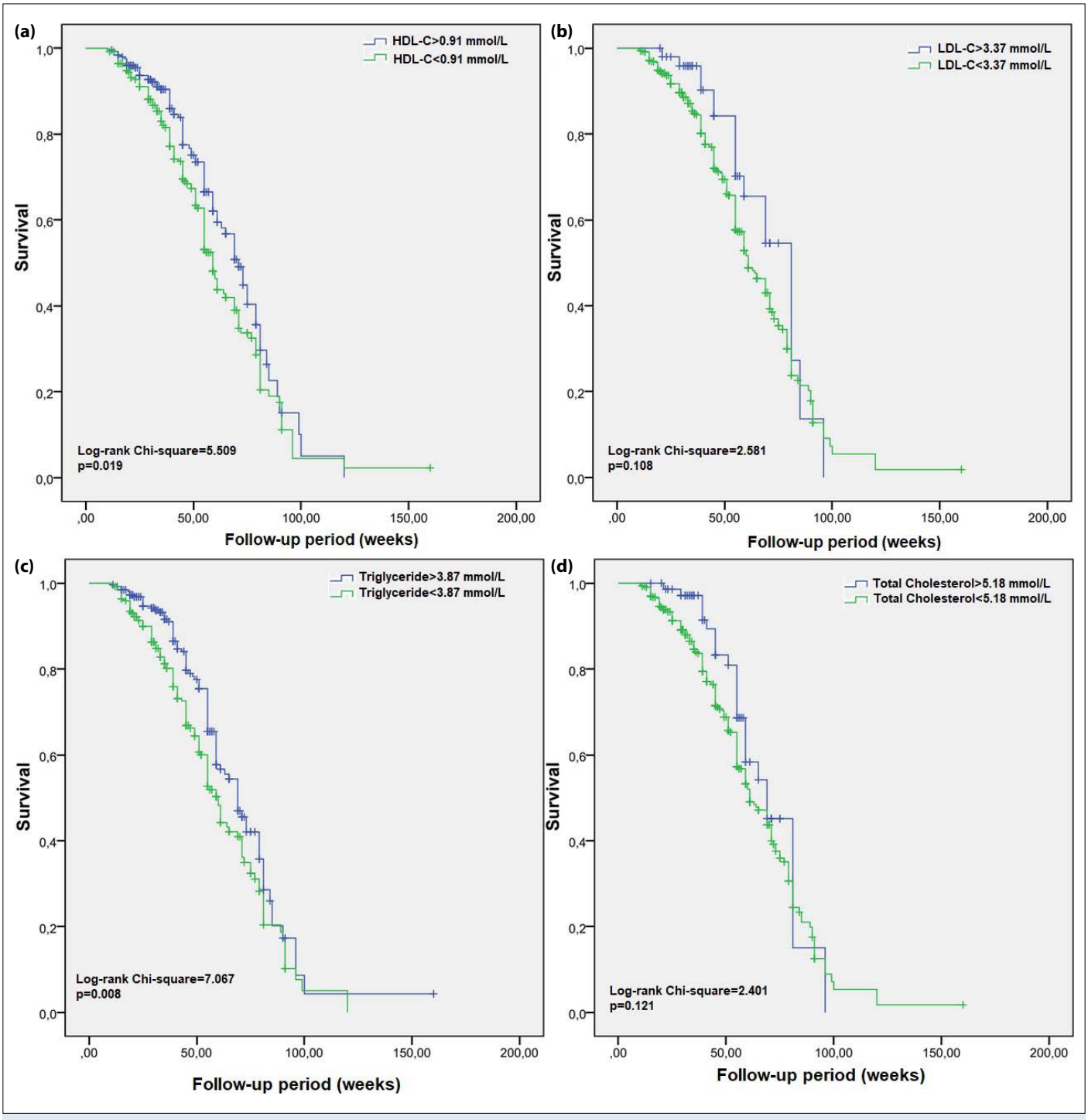

Figure 1. Kaplan–Meier estimates for time to all-cause mortality for mean HDL **(a)**, mean LDL **(b)**, mean TG **(c)**, and mean TC **(d)**.

The survival analysis was assessed by the Kaplan–Meier estimation method. Mortality was found to be lower in patients who had higher HDL-C and triglyceride levels (Fig. 1).

Discussion

According to the study results, lower plasma lipid levels and systolic blood pressures were associated with increased mortality, while lipid-lowering drugs and erythropoietin usage were associated with decreased mortality in hemodialysis patients.

Low HDL-C plasma levels were associated with increased mortality, as reported in a study.[11] Shoji et al.[12] investigated 45,390 hemodialysis patients, and their HDL-C levels were reported to be inversely associated with new-onset

myocardial infarction and cerebral ischemia. Concordantly, the present study revealed that low HDL-C levels are associated with increased mortality. HDL-C is known for its anti-inflammatory, antioxidant, and antithrombotic effects and for transporting cholesterol back to the liver; therefore, it has protective effects against cardiovascular diseases.[13]

In the general population, dyslipidemia is a well-known risk factor for cardiovascular disease. In hemodialysis patients, however, inconsistent results were reported in different studies, and the association between lipid levels and cardiovascular events was not clearly elucidated.[8-10,14] In a study from Korea, the elder population was inspected, and all-cause mortality was found to increase in people with low LDL-C levels.[15] In the current study, congruously, lower total cholesterol levels were associated with increased mortality. A possible explanation for this inverse association may be the synergetic effect of increased systemic inflammation and the existence of concomitant malnutrition resulting from numerous factors in CRF patients, which will result in lower total cholesterol levels and, eventually, increased mortality.[16] One study also reported that decreases in the total cholesterol levels during followups reflect cell function deterioration, which may be another explanation.[17]

Another study inspecting a huge number of patients, i.e., over 800,000 patients from Canada, showed that LDL-C was not a risk factor for cardiovascular diseases in hemodialysis patients.[18] In contrary, a study from Denmark showed that increased levels of total cholesterol and LDL-C decreased the mortality rate in CRF patients. Diseases with serious clinical courses may result in cholesterol level decreases, and this may be a reason for the increased mortality in patients with lower LDL-C levels.[19] The present study revealed that the LDL-C levels in surviving patients are significantly higher. Thus, in hemodialysis patients, the target LDL-C levels should be carefully determined, and the decision for antihyperlipidemic drug usage should be meticulously made.

In one study, over 50,000 hemodialysis patients were followed for 5 years. As a result, increased triglyceride levels were found to be related with decreased mortality.[8] The results of the current study are harmonious.

In a study reported from Japan, approximately one-fourth of the hemodialysis patients involved were using lipid-lowering drugs.[20] In another study from Canada, 17% of the hemodialysis patients were using antihyperlipidemic drugs.[18] The present study documented a lower antihyperlipidemic drug usage ratio (i.e., 10%) that was lower than those in the reported studies. A study from Sweden involving 2,776 hemodialysis patients showed that antihyperlipidemic drug usage was not associated with cardiovascular events.[21] Another study stated that lipid-lowering drug usage decreased the cardiovascular event risks by approximately 17% compared to the placebo group.[22] Reports on the effectiveness of lipid-lowering drugs in hemodialysis patients are inconsistent. According to the results of the present study, antihyperlipidemic drug usage is beneficial, but further lowering the lipids to a value lower than the recommended may result in increased mortality. Hence, the target lipid levels must be held higher in hemodialysis patients compared to the normal population. Cardiovascular events and their relationship with lipid levels are distinctively different in hemodialysis patients.[14]

An inverse relationship between the body mass index and mortality was reported in hemodialysis patients.[23] In the present study, surviving patients had a higher, but insignificant, body mass index. Malnutrition in hemodialysis patients resulted in accelerated atherosclerosis; therefore, maintaining a normal body mass index may have beneficial effects on mortality.[24]

In a study from Japan, all-cause mortality increased in patients who had lower blood pressure levels among hemodialysis patients.[25] Conformably, in the present study, an inverse relationship was observed between mortality and blood pressure levels, especially systolic blood pressure levels.

This study has some limitations. Although a significant difference was found between the study groups in terms of mean age, no patients were excluded to avoid selection bias. The etiologies mandating hemodialysis could not be evaluated for the participants. The data of conditions that might affect mortality, such as drugs consumed, smoking status, and history of trauma or surgery cannot be obtained in every patient enrolled in the study. In addition, all-cause mortality was inspected, but specific reasons for mortality could not be evaluated.

Conclusion

Decreases in the HDL-C, LDL-C, triglyceride, and total cholesterol levels increase the mortality risk in hemodialysis patients. Patients using antihyperlipidemic drugs have a lower mortality risk. However, further lowering the HDL-C, LDL-C, triglyceride, and total cholesterol levels below the recommended values may increase the mortality risk. Thus, the target lipid levels for hemodialysis patients must be determined sparely when compared to patients who have similar demographic characteristics and are unrelated with hemodialysis. Further studies with a larger number of participants are required to clarify issues affecting mortality.

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