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Research

Association of TG/HDL Ratio with Cardiovascular Mortality in Patients Who are on Hemodialysis

Hemodiyalize Giren Son Dönem Böbrek Yetersizliği Hastalarında TG/HDL Oranı ile Kardiyovasküler Ölüm Arasındaki İlişki

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ABSTRACT

Objective: There is a relation between triglyceride/high-density lipoprotein (TG/HDL) ratio, and cardiovascular and all-cause mortality. No study has been conducted on this relationship in cases with end-stage renal disease who are on hemodialysis in Turkey. Therefore, we aimed to see the relation between TG/HDL ratio and cardiovascular mortality in hemodialysis patients.

Methods: This study included 344 cases who were aged ≥18 years and on hemodialysis. These cases were divided into two groups as cardiovascular death (n=31) and survivors (n=313). Primary endpoint of this study was cardiovascular mortality.

Results: Among 344 patients, 74.1% were males, and the mean age was 43.7±12.6 years. Dialysis duration was 1.1 (3.1) years, and the total follow-up duration was 5.9 (2.9) years. TG/HDL ratio was similar in both groups (p>0.05). Age [human resource (HR): 1.02, 95% confidence interval (CI): (1,055-1.09), p=0.02], HbA1c [HR: 1,292, 95% CI: (1,080-1,546), p=0.05], and TG/HDL ratio [HR: 1,078, 95% CI: (1,009-1.51), p=0.026] were independent predictors of cardiovascular mortality. Kaplan-Meier curves revealed that cardiovascular mortality was higher in the group using fenofibrate [p (log-rank) =0.01].

Conclusion: TG/HDL ratio is an inexpensive, simply applicable tool that may predict cardiovascular mortality in hemodialysis patients. Therefore, it may significantly benefit in optimizing cardiovascular risk management and treatment goals in these patients.

Keywords: TG/HDL ratio, end-stage renal disease, hemodialysis, cardiovascular mortality

ÖZ

Amaç: Trigliserit/yüksek yoğunluklu lipoprotein (TG/HDL) oranı ile kardiyovasküler ve tüm nedenlere bağlı ölüm arasında bir ilişki olduğu bilinmektedir. Ülkemizde hemodiyalize giren son dönem böbrek yetersizliği hastalarında bu ilişkiyi inceleyen çalışma yapılmamıştır. Bu nedenle çalışmamızda hemodiyaliz hastalarında TG/HDL oranı ile kardiyovasküler ölüm arasında bulunan ilişkiyi incelemeyi amaçladık.

Gereç ve Yöntem: Çalışmaya 18 yaş ve üzerinde, hemodiyalize giren son dönem böbrek yetersizliği tanısı almış 344 hasta dahil edildi. Hastalar kardiyovasküler sebeplerle ölen (n=31) ve sağ kalan (n=313) hasta olarak ikiye bölündü. Çalışmanın birincil sonlanım noktası kardiyovasküler ölüm idi.

Bulgular: Çalışmaya alınan 343 hastanın %74,1'i erkek olup, yaş ortalaması 43,7±12,6 idi Ortalama diyaliz süresi 1,1 (3,1) yıl, toplam takip süresi ise 5,9 (2,9) yıldı. TG/HDL oranı her iki grupta da benzerdi (p>0,05). Yaş [human kaynak (HR): 1,02 %95 güven aralığı (CI): (1.055-1,09), p=0,02], HbA1c [HR: 1.292 %95 CI: (1.080-1.546), p=0,05] ve TG/HDL oranı [HR: 1.078 %95 CI: (1.009-1,51), p=0,026], kardiyovasküler ölümün bağımsız öngörücüleri olarak bulundu. Kaplan-Meier eğrileri, fenofibrat kullanan grupta kardiyovasküler mortalitenin anlamlı olarak daha yüksek olduğunu ortaya koydu [p (log-rank) =0,01].

Sonuç: TG/HDL oranı hemodiyaliz hastalarında kardiyovasküler mortaliteyi öngörebilen ucuz, kolay uygulanabilir bir yöntemdir. Bu nedenle, bu hastaların kardiyovasküler risk yönetiminde ve tedavi hedeflerini optimize etmede önemli bir fayda sağlayacaktır.

Anahtar Kelimeler: TG/HDL oranı, son dönem böbrek yetersizliği, hemodiyaliz, kardiyovasküler ölüm

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INTRODUCTION

Although hemodialysis-related complications gradually decrease in cases with end-stage renal disease (ESRD), mortality rates are still greater than that of the normal population. As expected, a significant proportion of this is cardiovascular mortality (1). As traditional risk factors are inadequate to define cardiovascular outcomes in patients with ESRD, practical, easily applicable, new risk markers are frequently sought in this area (2-4).

Lipid disorder is common in ESRD cases, and triglyceride (TG) level is high and high-density lipoprotein (HDL) level is low (5). Pathophysiologically, high TG levels and low HDL levels interact during lipid metabolism, and each alone is a risk factor for atherosclerosis. TG/HDL ratio is a practical, validated tool, which better demonstrates this complex interaction in ESRD patients with dyslipidemia (6). It is known that a high TG/HDL ratio is associated with metabolic syndrome, hypertension (HTN), diabetes, and cardiovascular events (7-10). Furthermore, it is proven that there is a significant relationship between TG/HDL ratio and cardiovascular and all-cause mortality (11,12).

Many studies have revealed the relationship between TG/HDL ratio and cardiovascular events in ESRD patients, but these results have been controversial (13-15). Moreover, no study has been conducted only in cases with ESRD who are on hemodialysis in our country. Therefore, we aimed to see the relation between TG/HDL ratio and cardiovascular mortality in the hemodialysis patients.

METHODS

This study included patients aged ≥18 years who were undergoing hemodialysis between 2015 and 2020. All the patients were divided into two groups: group 1, cardiovascular death (n=31) and group 2, survivors (n=313).

Patients who were <18 years of age, with peritoneal dialysis (n=23), or who died from non-cardiac causes (n=9) were removed from the study. Approval for the study was granted by the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Regional Ethics Committee (no: 2021-14-11, date: 12/07/2021). All the participants' rights were protected, and written informed consent was taken from the patients before the procedures.

Demographic data and laboratory findings of cases were collected from Nephrology Clinic Database. Etiology of ESRD, duration of hemodialysis, and cardiac mortality were recorded. Hemogram, routine biomarkers, and total cholesterol (TC), HDL-C, LDL-C, TG, and non-HDL-C values were recorded. Traditional cardiovascular risk factors, history of cardiovascular disease, and coronary revascularization were recorded along with the use of lipid-lowering drugs.

Fasting blood tests included TC, LDL-C, HDL-C, non-HDL-C, and TG. TG was determined using the enzymatic color method (Biotrol), and TC with the photometric method (Siemens, Dimension EXL 200, Germany). The TG/HDL ratio was calculated. Primary endpoint of this study was cardiovascular mortality.

Statistical Analysis

Data were analyzed statistically using SPSS (Version 20 software). We confirmed continuous variables to be normally distributed according to the Kolmogorov-Smirnov test. Demographic, clinical, and laboratory values of the two groups were compared by using a t-test or the Mann-Whitney U test for continuous variables according to the distribution pattern of the data. Chi-square test or Fischer's Exact test were used to compare the categorical data. Kaplan-Meier survival analysis was conducted for cardiovascular mortality, and log-rank test was used to compare the two curves. Cox proportional hazard regression analysis was applied with cardiovascular mortality assigned as a dependent variable. Covariates with p-value <0.15 or those which were clinically significant were entered into the multivariate model. For all analyses, a two-sided p-value <0.05 was considered as statistically significant.

RESULTS

An evaluation was made of 344 patients, comprising 74.1% males and 25.9% females. Mean age was 43.7±12.6 years. The group with mortality was older than the survivors' group (p>0.001). A history of HTN, diabetes mellitus (DM), or coronary artery disease (CAD) was greater in the non-survival group than in the survivors' group (p=0.034, p<0.001, p<0.001, respectively). Mean hemodialysis duration was similar in both groups (p=0.615) (Table 1).

Fenofibrate usage was greater in the non-survival group than in the survivors' group (p=0.038)

Glucose and HbA1c levels were greater in the non-survival group (p<0.001, p=0.002, respectively). Other laboratory parameters and TG/HDL ratio were similar in two groups (p>0.05 for all). Baseline characteristics and laboratory parameters of the cases are shown in Table 1.

Dialysis duration was 1.1 (3.1) years, and the total follow-up duration was 5.9 (2.9) years. Survivors' group was followed-up significantly longer than the non-survival group (p<0.01) (Table 1).

Table 1. Baseline characteristics and laboratory findings of all the study participants

Variables	Total (n=343)	Non-mortal (n=312)	Mortal (n=31)	p
Gender (male), n %	254 (74.1)	229 (73.4)	25 (80.6)	0.380
Age (years)	43.7±12.6	42.9±12.6	52.0±10.4	**<0.001**
BMI (kg/m^2)	25.2±4.8	25.1±4.9	26.1±3.5	0.271
HTN, n (%)	128 (37.3)	111 (35.6)	17 (54.8)	**0.034**
DM, n (%)	81 (23.6)	64 (20.5)	17 (54.8)	**<0.001**
Smoking, n (%)	42 (12.2)	36 (11.5)	6 (19.4)	0.245
CAD history, n (%)	56 (16.3)	43 (13.8)	13 (41.9)	**<0.001**
Dialysis duration (years)	1.1 (3.1)	1.1 (3.4)	1.1 (2.8)	0.615
Follow-up (years)	5.9 (2.9)	6.1 (2.7)	2.6 (3.6)	**<0.001**
Medications, n (%)				
Fenofibrate	22 (6.4)	17 (5.4)	5 (16.1)	0.038
Statin	40 (11.7)	35 (11.2)	5 (16.1)	0.384
Laboratory findings				
BUN (mg/dL)	54 (26)	54.5 (26.8)	47 (26)	0.085
Creatinine, (mg/dL)	8.3±2.9	8.4±2.9	7.3±2.8	0.053
Sodium, (mg/dL)	137.6±3.3	137.6±3.4	138.2±2.5	0.348
Potassium, (mg/dL)	5.1±0.8	5.2±0.8	4.7±0.7	0.130
Calcium, (mg/dL)	9.1±0.9	9.1±0.9	8.9±0.8	0.288
Uric acid, (mg/dL)	5.6±1.6	5.7±1.6	5.3±1.6	0.281
Albumin, (mg/dL)	4.1±0.6	4.1±0.6	4.0±0.8	0.504
Glucose, (mg/dL)	91 (24)	91 (19)	108 (57)	**<0.001**
HbA1C	5.7±1.4	5.6±1.3	6.8±1.9	**0.002**
TC, (mg/dL)	188.9±45.4	187.9±42.3	199.5±68.9	0.173
LDL-C, (mg/dL)	116.9±36.2	116.8±35.6	118.3±42.6	0.827
HDL-C, (mg/dL)	50.9±16.7	51.1±16.9	48.6±15.1	0.425
Triglyceride, (mg/dL)	158 (111)	154.5 (111.8)	170 (92)	0.251
TG/HDL ratio	3.2 (3.3)	3.9 (2.7)	3.5 (4.4)	0.237
WBC (x10^3/uL)	7.5±2.3	7.5±2.3	7.9±2.7	0.219
Hb (g/dL)	11.5±1.9	11.4±1.9	11.5±1.6	0.788
Platelet (x10^3/uL)	219.3±71.3	218.8±71	223.9±75.5	0.706

BMI: Body mass index, HTN: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, TC: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TG: Triglyceride, WBC: White blood cell, Hb: Hemoglobin

During the follow-up, deaths due to cardiovascular causes were recorded in a total of 31 patients, of which 19 were due to myocardial infarction, 5 to sudden cardiac death, and 7 to stroke.

Cox regression analysis was performed to determine the predictors of cardiac mortality. Variables found to be significant in univariate analysis or with clinical relevance were included in the multivariate analysis. Age, HTN, DM, CAD history, fenofibrate usage, creatinine, HbA1c, TG, and TG/HDL ratio were found to be significant in univariate analysis. (p<0.001, p=0.026, p=0.001, p=0.015, p=0.035, p<0.001, p=0.02, p=0.006, respectively) (Table 2). Only age [human resource (HR): 1.02, 95% confidence interval (CI): (1,055-1.09), p=0.02], HbA1c [HR: 1,292, 95% CI: (1,080-1,546), p=0.05], and TG/HDL ratio [HR: 1,078, 95% CI: (1,009-1.51), p=0.026] were independent predictors of cardiovascular mortality (Table 2).

Table 2. Univariate and multivariate Cox regression analyses for cardiac mortality

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	HR (95% CI)	p
Sex (male)	1.316 (0.539-3.209)	0.546	-	-
Age (years)	1.061 (1.028-1.095)	**<0.001**	1.020 (1.055-1.090)	**0.002**
BMI	1.040 (0.969-1.116)	0.276	-	-
HTN	2.240 (1.103-4.550)	**0.026**	-	-
DM	3.400 (1.667-6.934)	**0.001**	-	-
Smoking	2.011 (0.825-4.905)	0.124	-	-
CAD history	3.726 (1.822-7.623)	**<0.001**	-	-
Dialysis duration	0.982 (0.888-1.086)	0.723	-	-
Fenofibrate	3.284 (1.256-8.588)	**0.015**	-	-
Statin	1.411 (0.541-3.678)	0.481	-	-
BUN (mg/dL)	1.005 (0.998-1.012)	0.168	-	-
Creatinine (mg/dL)	0.856 (0.741-0.989)	**0.035**	-	-
Sodium (mg/dL)	1.01 (0.956-1.156)	0.306	-	-
Potassium (mg/dL)	0.666 (0.423-1.048)	0.079	-	-
Calcium (mg/dL)	0.738 (0.499--1.092)	0.129	-	-
Uric acid (mg/dL)	0.834 (0.661-1.053)	0.128	-	-
Albumin (mg/dL)	0.637 (0.358-1.132)	0.124	-	-
Glucose (mg/dL)	1.004 (0.999-1.008)	0.101	-	-
HbA1C	1.395 (1.184-1.643)	**<0.001**	1.292 (1.080-1.546)	**0.005**
TC, (mg/dL)	1.005 (0.998-1.012)	0.168	-	-
LDL-C, (mg/dL)	1.001 (0.991-1.011)	0.832	-	-
HDL-C, (mg/dL)	0.988 (0.965-1.011)	0.295	-	-
Triglyceride, (mg/dL)	1.002 (1.000-1.003)	**0.020**	-	-
TG/HDL ratio	1.087 (1.024-1.155)	**0.006**	1.078 (1.009-1.151)	**0.026**
WBC ($x10^3$/uL)	1.000 (1.000-1.000)	0.171	-	-
Hb (g/dL)	1.024 (0.841-1.246)	0.814	-	-
Platelet ($x10^3$/uL)	1.000 (1.000-1.000)	0.646	-	-

BMI: Body mass index, HTN: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, TC: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TG: Triglyceride, WBC: White blood cell, Hb: Hemoglobin, OR: Odds ratio, CI: Confidence interval

Kaplan-Meier curves showed that cardiovascular mortality was greater in the group using fenofibrate [p (log-rank) =0.01] (Figure 1).

DISCUSSION

The findings of this study revealed that TG/HDL ratio is an independent predictor for cardiovascular mortality in hemodialysis cases. As expected, the non-survival group was older, and the rates of HTN, DM, and CAD were higher than in the surviving cases. A remarkable finding in the current study in terms of laboratory findings was that the TG and TG/HDL ratio in the cardiac death group was not different from that of the survivors' group. This was thought to be due to the significantly higher usage of fenofibrate in the non-survival group.

One of the main risk factors for cardiovascular diseases in hemodialysis patients is dyslipidemia, which also contributes to decreased physical capacity and weight

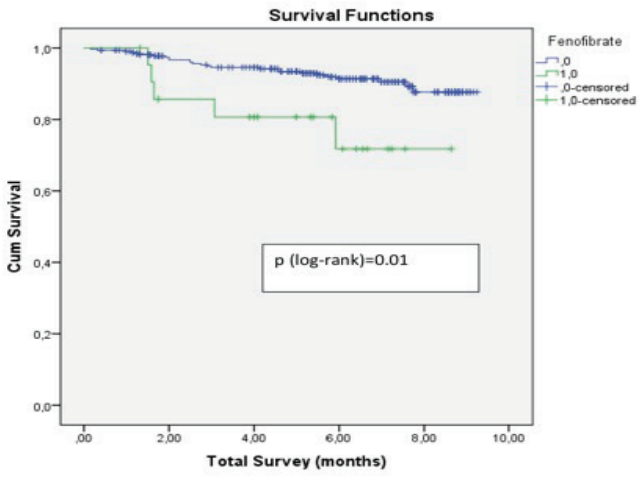

Figure 1. Kaplan-Meier curves revealed that cardiovascular mortality was significantly higher in the group using fenofibrate [p (log-rank) =0.01]

loss (16,17). Dyslipidemia is related to many factors such as diabetes, HTN, renal replacement treatment, and drugs used by the hemodialysis patients (18). It is thought that the TG/HDL ratio predicts cardiovascular outcomes better than the measurement of lipid levels alone, since an increase in TG and a decrease in HDL are prominent in these patients (19). Chen et al. (20) showed that high TG/HDL ratio increases the cardiac mortality in patients undergoing both hemodialysis (most of the patients) and peritoneal dialysis, and these results are consistent with those of the current study. Chang et al. (21) published a large-scale study that included only ESRD patients undergoing hemodialysis. Unlike the current study, a significant correlation was seen between a high TG/HDL ratio and low cardiac mortality (21). These conflicting results are attributed to the complex nature of lipid metabolism in dialysis, differences in patient numbers, ethnicity, inclusion criteria, etc. Nevertheless, the mechanism has not been elucidated. In addition to the huge patient population in the study by Chang et al. (21), the results may be considered more valuable due to its prospective design. The results were consistent with those of the current study. The new aspect of this study was the larger number of patients with the advanced renal failure who underwent dialysis. Another remarkable finding in this study was that the survival of the patients using fenofibrate was significantly lower than that in the non-users. This result seems to be the opposite of expectations. The reason for this unexpected result was thought to be that the target TG goals could not be reached in ESRD patients using fenofibrate (due to low dose or irregular use). Many studies have revealed that LDL-C is not a very strong predictor of mortality in hemodialysis patients. There is no significant reduction in cardiovascular mortality with statin (22-24). Therefore, in these cases, TG reduction with aggressive fenofibrate treatment is much more critical.

Study Limitations

This study was retrospective, single-center, and cross-sectional in design. The frequency of dialysis and the medications taken (except lipid drugs) might have affected the cardiac outcomes. The lack of these data could be considered as another limitation.

CONCLUSION

In conclusion, TG/HDL ratio is an inexpensive, easily applicable tool that may predict cardiac mortality in hemodialysis patients. It will provide significant benefits in optimizing cardiovascular risk management, and treatment goals in these patients. Nevertheless, there is a need for conducting multicenter, prospective, large-scale studies in the future for these results.

ETHICS

Ethics Committee Approval: Approval for the study was granted by the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Regional Ethics Committee (no: 2021-14-11, date: 12/07/2021).

Informed Consent: Written informed consent was taken from the patients before the procedures.

Authorship Contributions

Surgical and Medical Practices: G.Y., Concept: U.K., Design: G.Y., Data Collection or Processing: U.K., Analysis or Interpretation: G.Y., Literature Search: U.K., Writing: U.K., G.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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