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Original Article

The triglyceride to HDL-cholesterol ratio and chronic graft failure in renal transplantation

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KEYWORDS:
Triglyceride/HDL-C ratio;
Transplantation;
Dyslipidemia;
Chronic graft failure;
HDL;
Triglycerides;
Kidney

Abstract: **BACKGROUND:** Transplant vasculopathy (TV) is a major contributing factor to chronic graft failure in renal transplant recipients (RTR). TV lesions resemble atherosclerosis in several ways, and it is plausible to believe that some risk factors influence both atherosclerotic plaque formation and formation of TV.

OBJECTIVE: The objective of this prospective longitudinal study was to determine if dyslipidemia reflected by the triglyceride (TG)/high-density lipoprotein cholesterol (HDL-C) ratio is prospectively associated with death censored chronic graft failure in RTR.

METHOD: 454 prospectively included RTR with a functioning graft for at least one year, were followed for a median of 7 years. RTR were matched based on propensity scores to avoid potential confounding and subsequently the association of the TG/HDL-C ratio with the endpoint chronic graft failure, defined as return to dialysis or re-transplantation, was investigated.

RESULTS: Linear regression analysis showed that concentration of insulin, male gender, BMI and number of antihypertensives predict the TG/HDL-C ratio. Cox regression showed that the TG/HDL-C ratio is associated with chronic graft failure (HR = 1.43, 95%CI = 1.12–1.84, p = 0.005) in competing risk analysis for mortality. Interaction testing indicated that the relationship of the TG/HDL-C ratio with graft failure is stronger in subjects with a higher insulin concentration.

CONCLUSION: Our results demonstrate that the TG/HDL-C ratio has the potential to act as a predictive clinical biomarker. Furthermore, there is a need for closer attention to lipid management in RTR in clinical practice with a focus on triglyceride metabolism.

Abbreviations: ADA, American diabetes association; ANOVA, one way analysis of variance; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL-C, high density lipoprotein cholesterol; HR, hazard ratio; hsCRP, high sensitivity C-reactive protein; kg, kilogram; LDL, low density lipoprotein; RTR, renal transplant recipient; TG, triglycerides; TV, transplant vasculopathy.

Trial registry: The TxL-IRI Biobank and Cohort Study is registered at ClinicalTrials.gov with identifier NCT03272854.

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Introduction

Renal transplantation is the gold standard treatment for end-stage renal disease (ESRD). In many countries the number of renal transplant recipients (RTR) is by now even surpassing that of haemodialysis patients.[1] Availability of donor kidneys is sparse, and patients often spend years on waiting lists, or depend on a sacrifice by a family member or friend in the form of a living donation. Therefore, protection of donor kidneys and improving long-term graft survival is a major clinical, as well as ethical, necessity. However, although short-term graft survival is steadily improving, chronic graft failure still represents an important clinical challenge, eventually resulting in return to haemodialysis or re-transplantation.[2]

In addition to the risk of graft failure, renal transplant recipients also face an increased risk of atherosclerotic and other cardiovascular disease (CVD). Kidney disease is associated with an increased risk of CVD throughout the spectrum of decreased kidney function, with early stages of CKD translating to a 4 fold increased risk of CVD events, whereas in end-stage renal disease this rises to a 30 fold increased risk.[3,4] Even after transplantation the risk remains 4–6 times higher compared to the general population.[5]

Transplant vasculopathy (TV) is acknowledged as a major contributing factor to chronic graft failure. Interestingly, TV lesions resemble atherosclerosis in several ways, and factors influencing the development of atherosclerosis also have been implicated in TV.[6] Through various factors relating to the transplantation RTR frequently display dyslipidemia. The prevalence of dyslipidemia in RTR is estimated to be around 80%,[7,8] with mean reported triglyceride level values ranging from 160 to 200 mg/dL (1.8–2.26 mmol/L).[9] It has been shown that raised triglyceride (TG) levels, but not hypercholesterolemia, are associated with chronic graft failure.[10,11] TG levels however fluctuate substantially based on feeding status, limiting its utility as a predictive biomarker.[12,13] Combining TG levels with high-density lipoprotein-cholesterol (HDL-C) levels leads to a far more consistent measure of dyslipidemia and could therefore overcome this problem. And indeed, recent studies established that the combination of TG and HDL-C in form of a ratio has a greater predictive value for CVD events.[14,15] Conceivably, a high TG/HDL-C ratio could also reflect accelerated TV lesion formation. However, the possible impact of the TG/HDL-C ratio on chronic graft failure in RTR has not been investigated to date. In the present work we therefore aim to determine the association of the TG/HDL-C ratio with incident chronic graft failure in a well-characterised prospective cohort of RTR.

Materials and methods

Study population

In this study all RTR with a functioning graft for at least 1 year, who visited the University Medical Center Groningen (UMCG) between 2001 and 2003, were invited to join. Patients were excluded from the study if they had congestive heart failure or cancer, other than cured skin cancer, as well as endocrine abnormalities other than diabetes mellitus (DM). Patients were followed over a median of 7 years (interquartile range [IQR] 6.1–7.5 years), and there was no loss during follow-up. Of the 847 eligible patients, 624 patients gave written informed consent (Fig. 1). Of these patients, 170 were excluded due to a suspected infection, indicated by a high sensitivity C-reactive protein (hsCRP) value of above 10 mg/l at the time of blood sampling. The included 454 patients did not differ from the entire cohort with regards to baseline characteristics and are therefore a valid representation of the whole. None of the included patients received triglyceride lowering treatment. A more complete description of the study design and the obtained measurements has been published previously.[16] The study has been approved by the local Medical Ethics Committee (METc2001/039) and is in accordance with the Declaration of Helsinki. The TxL-IRI Biobank and Cohort Study is registered at ClinicalTrials.gov with identifier NCT03272854.

Measurements and definitions

Metabolic syndrome was defined based on the criteria of the National Cholesterol Education Program Expert Panel.[17] In 2008 the American Diabetes Association (ADA) suggested to use a lowered cut-off value for impaired fasting glucose at 5.6 mmol/L. This adaptation was used in our definition. Diabetes was defined as a fasting plasma glucose of 7.0 mmol/L or use of antidiabetic medication, in accordance with the ADA guidelines.[18] Body mass index (BMI) was calculated as weight in kilograms (kg) divided by height in meters squared.

Blood samples were drawn after a 8–12 h fasting period and routine laboratory measurements were conducted, as previously described.[16] Total cholesterol was determined using the cholesterol oxidase-phenol aminophenazone method (MEGA AU 510; Merck Diagnostica, Darmstadt, Germany). LDL-cholesterol was calculated using the Friedewald equation.[19] HDL-cholesterol was measured with the cholesterol oxidase-phenol aminophenazone method on a Technikon RA-1000 (Bayer Diagnostics, Mijdrecht, The Netherlands). Plasma triglycerides were determined with the glycerol-3-phosphate oxidase-phenol aminophenazone method (Roche Diagnostics). ApoB levels were determined by nephelometry using commercially available reagents from Dade Behring (BN II; Dade Behring, Marburg, Germany). Plasma hsCRP was assessed by ELISA.[16] The glucose-oxidase method was used to determine plasma glucose levels. Plasma insulin was measured using an AxSym autoanalyzer. HbA1c was assessed by high-performance liquid chromatography. Insulin resistance was calculated using the homeostasis model assessment-estimated insulin resistance (HOMA-IR) as follows: HOMA-IR = glucose (mmol/L) × insulin (μU/mL)/22.5.

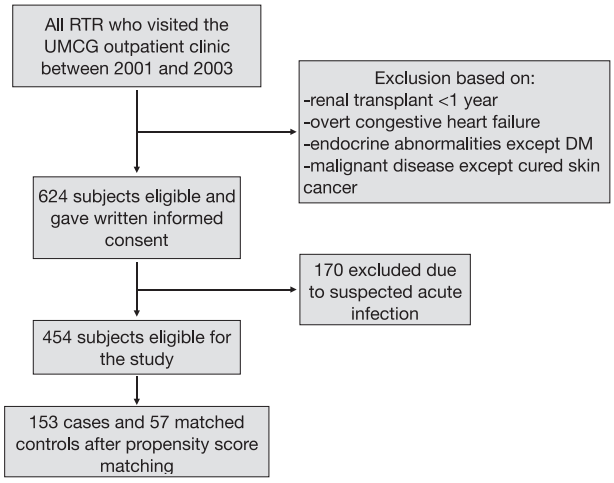

Fig. 1 Inclusion of renal transplant recipients. RTR, renal transplant recipients; UMCG, University Medical Center Groningen; DM, diabetes mellitus.

End points and outcome measures

The main predictor in this study was the TG/HDL-C ratio, which was computed by dividing the triglyceride concentration by the HDL-C concentration (both in mmol/L). The primary end point is graft failure, which is defined as return to dialysis therapy or re-transplantation.

Study design

In order to reduce potential confounding we used propensity score matching to compare the incidence of death censored graft failure between subjects of high and low TG/HDL-C ratio values. Since there is no validated cut-off for the TG/HDL-C ratio, RTRs were dichotomized into high versus low TG/HDL-C ratio by dividing the group at the median (1.27). A logistic regression was fitted for high versus low TG/HDL-C ratio, including variables that, based on literature, are related to the outcome. This included patient demographics (age and sex), lifestyle factors (BMI), renal disease history (primary renal disease, dialysis time), transplantation demographics (type of transplantation, number of human leukocyte antigen [HLA] mismatches, acute rejection), medication use (use of calcineurin inhibitors, use of proliferation inhibitors, prednisolone dose, number of anti-hypertensives), lipid factors (use of statins, total cholesterol), renal function (estimated glomerular filtration rate [eGFR], urinary protein excretion) and co-morbidities (diabetes, HbA1c, insulin concentration).[20] Propensity scores were obtained from the outcome of the logistic regression.

Subjects with high versus low TG/HDL-C ratios were matched by one to one nearest-neighbor matching with replacement based on propensity scores, meaning that a control subject could be used in multiple case-control pairs, allowing for more optimal matching.[21] Quality of matching was graphically evaluated (supplemental figure) and the reduction of bias assessed using a *t*-test for equality of means, the standardized percentage bias and the variance ratio (supplemental table 1).

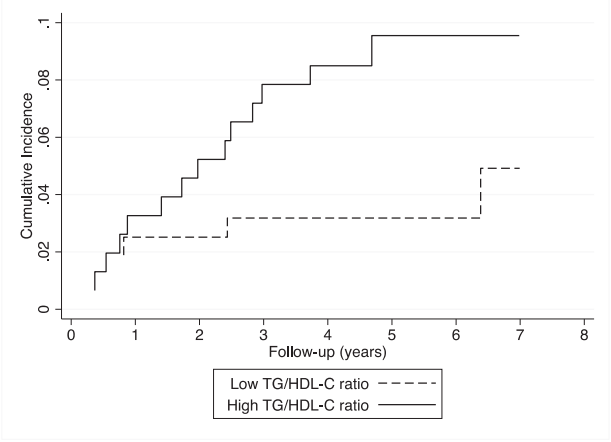

Fig. 2 A lower triglyceride/HDL-C ratio is associated with an increased graft survival. Cumulative incidence curves of the association of a high versus low TG/HDL-C ratio with chronic graft failure. Abbreviations: TG, triglycerides; HDL-C, high-density lipoprotein cholesterol.

Statistical analysis

Differences in baseline characteristics were tested between groups of high versus low TG/HDL-C ratio in the propensity matched cohort. Due to matching with replacement and categorizing the low TG/HDL-C group as control group, there were fewer subjects in the low TG/HDL-C ratio category in the propensity matched cohort. Categorical values are given as absolute numbers (percentages) and differences were tested by the chi-squared test. Normally distributed continuous variables are given as mean ± standard deviation and differences were tested by one-way analysis of variance (ANOVA). Skewed continuous variables are presented as median [25th to 75th percentile] and differences between groups were determined by Kruskal-Wallis test.

In order to identify variables independently associated with the TG/HDL-C ratio all characteristics with a $P < 0.10$ between high versus low TG/HDL-C ratio in the entire, unmatched cohort at baseline were entered into a step-wise multivariable linear regression model with backward elimination ($P < 0.05$). This included urinary protein excretion, eGFR, daily prednisone dose, hsCRP, use of antidiabetics, HbA1c, insulin concentration, glucose concentration, use of diuretics, use of beta blockers, use of ace inhibitors, number of antihypertensives, use of statins, total cholesterol, concentration of apolipoprotein B (apoB), BMI and sex.

Cumulative incidence curves with competing risk for mortality were computed in order to assess the association of the TG/HDL-C ratio with graft survival. The association of the TG/HDL-C ratio levels with graft failure was evaluated using Cox proportional hazards regression. Competing-risk regression for mortality using the Fine and Gray model was performed.[22] Cox proportional

hazards regression was performed in the propensity matched cohort, using weighted estimations based on the frequency with which a single observation was used as a match. Cumulative hazards were computed for the endpoint. Analyses were performed both crude, as well as with further adjustment for covariates for which balance was not achieved with matching, as indicated by significant differences between groups, namely presence of the metabolic syndrome.

Furthermore, subgroup analysis using interaction tests were performed in which HR were determined across categories of baseline characteristics. For continuous variables the median value was used as cut-off. To assess the functional relationship of the TG/HDL-C ratio with graft failure we used a functional polynomial Cox regression model. The proportional hazards assumption was tested using log-log graphs, and was found not to be violated.

Since acute inflammation impacts lipid metabolism,[23] we performed a sensitivity analysis where we excluded all patients with a hsCRP above 5 mg/L. Furthermore, we also assessed the association of the TG/HDL-C ratio with graft failure with traditional survival analysis, not taking into account propensity score matching.

A P-value of <0.05 was considered statistically significant. All statistical analyses were performed using STATA® Statistical Software, Release 15.1 (StataCorp, College Station, TX).

Results

Baseline demographic characteristics

A total of 624 subjects from the "TransplantLines Insulin Resistance and Inflammation Biobank and Cohort Study" were assessed for eligibility (Fig. 1). After exclusion due to suspected acute infection, as determined by a hsCRP >10 mg/L, 454 subjects were eligible for inclusion in the cohort. The matching procedure matched 57 subjects with a low TG/HDL-C ratio to 153 subjects with a high TG/HDL-C ratio. Due to matching with replacement, this means that 153 case-control pairs were matched. Standardized percentage bias and the variance ratio are shown in supplemental table 1.

Baseline characteristics for subjects with low TG/HDL-C ratio versus high TG/HDL-C ratio are summarized in Table 1. Good balance was achieved with matching, leading to few differences between groups. In sensitivity analysis the analysis was repeated in subjects with a hsCRP of below 5 mg/L. Results were largely comparable to using the 10 mg/L cut-off, however, significantly more subjects used diuretics in the high TG/HDL-C group (32% versus 50%, p = 0.029, supplementary table 2).

Backward multiple linear regression analysis was used to assess which variables are determinants of the TG/HDL-C ratio in renal transplant recipients. Concentration of insulin, male sex, BMI and number of antihypertensives were positively associated with the TG/HDL-C ratio, whereas concentration of apoB was inversely associated (Table 2). Model R2 was 0.16.

Time to event analysis

The endpoint was reached in 21 of the included RTR in the propensity matched cohort, of which 5 were in the low TG/HDL-C ratio group and 16 in the high TG/HDL-C group. Graft failure occurred due to chronic allograft nephropathy in 11 subjects (52%), chronic allograft dysfunction in 8 subjects (38%) and return of primary disease in 2 subjects (10%). A cumulative incidence curve demonstrated that a lower TG/HDL-C ratio is associated with improved graft survival (Fig. 2). In a crude Cox regression analysis with competing risk for mortality the TG/HDL-C ratio levels were significantly associated with graft failure (HR = 1.43, 95% CI = 1.12–1.84, p = 0.005). In order to avoid residual confounding, we adjusted for variables that remained significantly different after matching, namely metabolic syndrome, which did not considerably impact the association (HR = 1.51, 95%CI = 1.17–1.94, p = 0.002, competing risk model). In sensitivity analysis we repeated the Cox regression for subjects with a hsCRP of below 5 mg/l. Results did not differ considerably from those reached with handling the 10 mg/l cut-off (crude HR = 1.58, 95%CI = 1.21–2.07, p = 0.001, competing risk model). Furthermore, optimal balance was not achieved with regards to use of diuretics, as indicated by a significant difference between groups (supplementary table 2). Therefore, additional adjustment was performed for use of diuretics, which did not considerably alter the association (HR = 1.46, 95% CI = 1.15–1.85, p = 0.002, competing risk model). Fractional polynomial regression showed that a TG/HDL-C ratio of under 2.2 (in mmol/L, or 5.0 in mg/dL) is inversely associated with graft failure, where after any rise in the TG/HDL-C ratio is associated with an increased risk of graft failure (Fig. 3).

In sensitivity analyses the association of the TG/HDL-C ratio with graft failure was assessed using Cox proportional hazard regression in the overall cohort not matched based on propensity scores. This confirmed that the TG/HDL-C ratio is associated with graft failure in a continuous scale in a crude model (HR per unit change = 1.10, 95%CI = 1.03–1.17, p = 0.003). This association was not significantly impacted by subsequent adjustment for potential confounders (supplementary table 3).

The association of the TG/HDL-C with graft failure was different for subjects with a low versus high insulin concentration (p for interaction = 0.019, Fig. 4), showing that the relationship of the TG/HDL-C with graft failure is stronger in subjects with a higher insulin concentration. A number of other participant characteristics did not have a significant impact (Fig. 4).

Table 1 Baseline characteristics according to low and high levels of the triglyceride/HDL-cholesterol ratio in the propensity matched cohort.

Characteristics	Low TG/HDL-C ratio (n = 57)	High TG/HDL-C ratio (n = 153)	P value
Triglyceride/HDL-C ratio	1.3 [0.9, 1.5]	2.6 [2.1, 3.3]	<0.001
Recipient demographics			
Age, years	52.4 (12.4)	52.4 (11.3)	0.98
Male gender, *n* (%)	23 (40.4%)	73 (47.7%)	0.34
Current smoking, *n* (%)	9 (15.8%)	27 (17.6%)	0.75
Previous smoking, *n* (%)	27 (47.4%)	59 (38.6%)	0.25
Waist circumference, cm	97 (10.3)	99 (13.0)	0.26
Body composition			
BMI, kg/m^2	25.9 (3.5)	26.7 (4.3)	0.19
Lipids			
Total cholesterol, mmol/L	5.4 [4.9, 6.0]	5.6 [4.9, 6.2]	0.53
LDL-cholesterol, mmol/L	3.6 [3.1, 4.0]	3.5 [2.9, 4.1]	0.28
HDL-cholesterol, mmol/L	1.2 [1.1, 1.4]	0.9 [0.8, 1.1]	<0.001
Triglycerides, mmol/L	1.5 [1.1, 1.9]	2.4 [2.0, 3.0]	<0.001
Apolipoprotein B, g/L	1.0 (0.2)	1.2 (0.2)	0.06
Use of statins, *n* (%)	34 (59.6%)	87 (56.9%)	0.72
Cardiovascular disease history			
History of MI, *n* (%)	2 (3.5%)	14 (9.2%)	0.17
History of TIA/CVA, *n* (%)	5 (8.8%)	10 (6.6%)	0.58
Blood pressure			
Systolic blood pressure, mmHg	153.8 (23.0)	153.5 (23.0)	0.98
Diastolic blood pressure, mmHg	90.0 (9.5)	90.3 (10.1)	0.59
Use of ACE inhibitors, *n* (%)	2 (3.5%)	14 (9.2%)	0.17
Use of β-blockers, *n* (%)	5 (8.8%)	10 (6.6%)	0.58
Use of diuretics, *n* (%)	2 (3.5%)	14 (9.2%)	0.17
Number of antihypertensive drugs, *n*	5 (8.8%)	10 (6.6%)	0.58
Glucose homeostasis			
Glucose, mmol/L	4.7 [4.3, 5.2]	4.6 [4.2, 5.1]	0.38
Insulin, μmol/L	11.9 [8.9, 16.5]	11.7 [9.0, 15.3]	0.94
HbA1c, %	6.4 [5.9, 6.8]	6.3 [5.8, 7.0]	0.67
HOMA-IR	2.7 [1.8, 3.4]	2.4 [1.8, 3.6]	0.64
Use of anti-diabetic drugs, *n* (%)	7 (12.3%)	19 (12.4%)	0.98
Inflammation			
hsCRP, mg/L	1.5 [0.7, 3.4]	1.8 [0.9, 3.7]	0.23
Donor demographics			
Age, years	35.0 [24.0, 51.0)	40.0 [23.0, 52.0)	0.64
Male gender, *n* (%)	34 (59.6%)	88 (58.3%)	0.86
Living kidney donor, *n* (%)	7 (12.3%)	16 (10.5%)	0.71
(Pre)transplant history			
Dialysis time, months	35.0 [16.0, 48.0]	29.0 [13.0, 48.0]	0.41
HLA mismatch	1.0 [0.0, 2.0]	1.0 [0.0, 2.0]	0.91
Acute rejection, *n* (%)	33 (%)	90 (%)	0.90
Graft age, years	4.7 [2.7, 10.4]	5.7 [3.2, 10.7]	0.52
Primary renal disease			
Primary glomerular disease			
Glomerulonephritis	6 (10.5%)	9 (5.9%)	0.25
Tubulo-interstitial disease	11 (19.3%)	19 (12.4%)	0.21
Polycystic renal disease	10 (17.5%)	32 (20.9%)	0.59
Dysplasia and hypoplasia	0 (0.0%)	7 (4.6%)	0.10
Renovascular disease	3 (5.3%)	10 (6.5%)	0.73
Diabetic nephropathy	1 (1.8%)	1 (0.7%)	0.47
Other or unknown cause	9 (15.8%)	36 (23.5%)	0.22
Immunosuppressive medication			
Daily prednisolone dose, mg/dL	10 [9, 10]	10 [9, 10]	0.89
Calcineurin inhibitors, *n* (%)	43 (75.4%)	127 (83.0%)	0.21

(*continued on next page*)

Table 1 (*continued*)

Characteristics	Low TG/HDL-C ratio (n = 57)	High TG/HDL-C ratio (n = 153)	P value
Proliferation inhibitors, *n* (%)	44 (77.2%)	112 (73.2%)	0.56
Renal allograft function			
eGFR, mL/min	50.2 (16.3)	46.4 (16.8)	0.15
Proteinuria ≥0.5 g/24 h, *n* (%)	16 (28.1%)	37 (24.2%)	0.56

Normally distributed continuous variables are presented as mean (SD), and differences were tested with one-way analysis of variance (ANOVA). Continuous variables with a skewed distribution are presented as median [25th, 75th percentile], and differences were tested by Kruskal–Wallis. Categorical data are summarized as n (%), and differences were tested by chi-squared test. To calculate cholesterol in mg/dL, multiply by 38.7. To calculate triglyceride in mg/dL, multiply by 88.6.

Abbreviations: LDL, low-density lipoprotein; HDL, high-density lipoprotein; MI, myocardial infarct; TIA, transient ischemic attack; CVA, cerebrovascular event; HOMA-IR, homeostasis model assessment-estimated insulin resistance; hsCRP, high sensitivity C-reactive protein; HLA, human leukocyte antigens; eGFR, estimated glomerular filtration rate.

Discussion

The results of this study demonstrate that a higher TG/HDL-C ratio is associated with a significant increase in the incidence of chronic graft failure, independent of a large number of other risk factors. These data stress the importance of good lipid control in clinical practice, particularly of triglycerides.

RTR are a complex patient group, frequently presenting with an altered lipid profile. Several factors contribute to this dyslipidaemia. Immunosuppressive medication, in particular calcineurin inhibitors and mTOR inhibitors, as well as steroids cause both hypercholesterolemia and raised triglycerides.[24–26] Also, a large number of RTR have underlying diabetes, a frequent cause of ESRD leading to transplantation. Furthermore, RTR face a high incidence of new onset diabetes after transplantation. Insulin resistance and diabetes are well characterized pathophysiological states associated with high serum TG and low HDL-C.[27] Finally, RTR generally have a reduced kidney function, and consequently suffer from an uremic proinflammatory state, conceivably also contributing to raised TG levels.[28]

The disappointing lack of long-term improvement of graft survival stresses the clinical need to further assess possible mechanisms and predictors. TV, the formation of atherosclerosis-like lesions in the kidney graft,[29] is an important limitation in long-term graft survival. Indeed, within 5 years 50% of RTR will have significant TV lesions, and within 10 years 90% of patients are affected.[6] Numerous studies have shown a causal association between triglyceride levels and cardiovascular events.[30,31] Very low density and remnant lipoproteins rich in TG penetrate the arterial intima and can be bound and retained by the connective tissue matrix, thus contributing to the development and progression of atherosclerotic plaques.[32] Furthermore, postprandial TG have been linked to impaired vasodilation, upregulated pro-inflammatory cytokine production, increased inflammatory response and monocyte activation.[33–36]

Considering that the pathology of TV resembles that of atherosclerosis it is plausible to believe that TG also effect chronic graft failure. However, the clinical utility of TG measures is limited by the fact that plasma levels are highly dependent on feeding status. TG levels are inversely correlated to HDL-C and it has been suggested that HDL-C acts as a stable marker of average TG levels and can therefore be used to monitor long term TG changes.[37] Combining TG and HDL-C in a ratio therefore more accurately reflects dyslipidemia and allows for more stable, fasting independent measures. Based on our data and studies in the general population, it is plausible that the dyslipidemia reflected by the TG/HDL-C ratio contributes to the pathogenesis of TV. It is unknown whether TV is reversible, which is supposedly the case in atherosclerotic lesions.[29,38] It is therefore conceivable that good lipid management at least limits the progression, but might also be able to

Table 2 Predictors of triglyceride/HDL-C ratio.

	β	95% CI	Standardized β	*p*
Concentration of apoB	1.52	0.80, 2.23	0.27	<0.001
Patient gender	0.75	0.39, 1.12	0.18	<0.001
Number of anti-hypertensives	0.29	0.14, 0.45	0.17	<0.001
BMI	0.07	0.02, 0.11	0.13	0.007
Concentration of insulin	0.06	0.03, 0.08	0.21	<0.001

All variables with $p > 0.1$ between high versus low triglyceride/HDL-C ratio at baseline in the whole cohort before propensity score matching were entered into a stepwise linear regression with backward elimination.

Abbreviations: apoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; CI, confidence interval; BMI, body mass index.

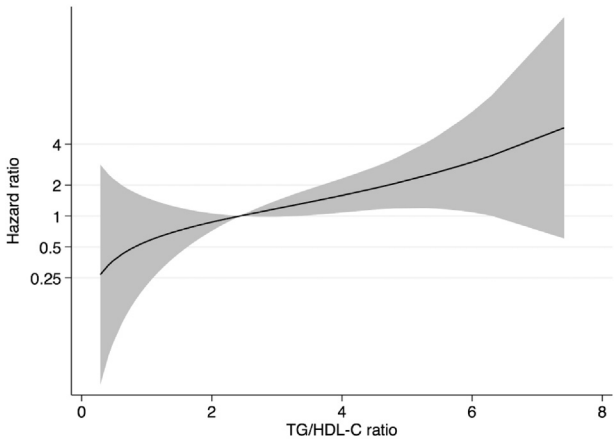

Fig. 3 A higher triglyceride/HDL-C ratio is associated with an increased incidence of graft failure. Hazard ratios (95% confidence interval) obtained by Cox regression of fractional polynomials.

reverse existing TV lesions, thereby decreasing the incidence of chronic graft failure.

Apart from de novo atherosclerosis in the kidney graft in the form of TV dyslipidemia reflected by the TG/HDL-C ratio might also impact chronic graft failure through immunomodulatory processes. TG rich lipoproteins, as well as their remnants, are associated with inflammation. A 1 mmol/l increase in non-fasting remnant cholesterol has been shown to translate into a 37% higher CRP level.[39] HDL-C on the other hand has well-documented anti-inflammatory capacities.[40,41] A higher TG and a lower HDL-C level, as reflected by an increased TG/HDL-C ratio, therefore potentially contributes to inflammation, an established risk factor for graft loss.[42–44]

We suggest that lipid levels are routinely monitored in RTR, including TG and HDL-C levels. In case of a high TG/HDL-C ratio, lifestyle changes are first warranted. The focus should be placed on elimination of sucrose- or fructose-sweetened beverages, avoidance of excessive and sometimes

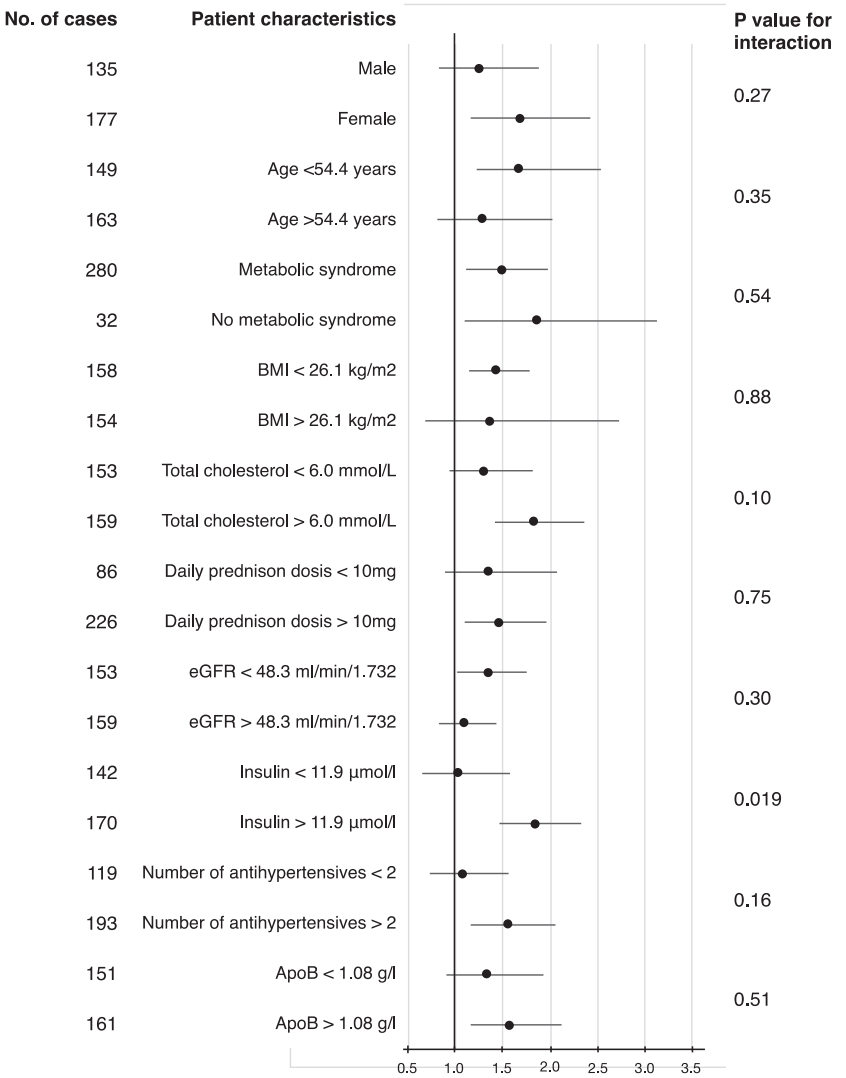

Fig. 4 Hazard ratios of TG/HDL-C ratio for incident graft failure, by several participant level characteristics. Data are hazard ratios (95% confidence interval) for incident graft failure obtained with Cox regression with competing risk for mortality. Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate based on the creatinine-cystatin C equation; ApoB, apolipoprotein B.

even moderate alcohol, limitation of refined carbohydrates,[45] weight loss[46,47] and aerobic exercise.[48] Whereas fibrates have been shown to be safe and effective in lowering risk of coronary events in the general population,[49] insufficient information is available about the safety in RTR. Studies with a low level of evidence indicated that initiation of fibrate treatment led to higher serum urea in RTR.[50,51] Omega 3 fatty acids however have a potent TG lowering effect and have been shown to be safe and effective in RTR.[52,53] Triglyceride lowering in the general population is an active field of study, reflected by numerous ongoing phase 3 trials of new emerging therapies.[45] Apolipoprotein C-III is an interesting potential target, with promising results in phase 2 clinical trials using antisense oligonucleotides showing an 80% reduction in TG levels.[54] However, similar to other antisense oligonucleotide therapies some adverse effects were documented in the treatment group, namely decreased platelet counts and injection-site reactions.[55] Pharmacological lowering of angiopoietin-like protein 3 is another emerging treatment modality, with TG reductions of 75% in a single-group, open-label study of homozygous familial hypercholesterolemia patients.[56] We would like to stress that statin therapy, although effective to lower LDL-C, has insufficient effects on either TG or HDL-C levels and is thus not a valid treatment option for hypertriglyceridemia.[57] More research is warranted to evaluate the optimal TG lowering treatment in RTR, as well as establishing a definite clinical cut-off value.

Some limitations warrant consideration. The study was conducted in a single center and all included RTR shared the same ethnicity. Despite the reasonable number of included RTR in this adequately powered study, the number of events was somewhat limited, leading to restricted possibilities with regards to statistical analysis. In particular, we cannot separate effects associated with TG/HDL-C ratio from those of closely related variables such as insulin resistance. Furthermore, single measures of lipids were taken, therefore we can not comment on the biological variability of lipid values over time.

In conclusion, our study shows that the TG/HDL-C ratio has potential to be utilized as a simple and valuable tool to predict chronic graft failure in RTR, a field in which limited improvement has been made in the last decade. The results of the present work demonstrate a need for closer attention to lipid management in clinical practice. Due to the low costs and broad availability of the measurements, using the TG/HDL-C ratio in daily clinical practice is realistic and potentially very valuable. Further research is required, with subsequent re-evaluation of existing guidelines in order to improve care for the vulnerable patient group of RTR.

Author contributions

J.L.C.A.: data acquisition and analysis, drafting the article, final approval for the version to be published; S.J.L.B.: data acquisition and analysis, critical article revision for important intellectual content, final approval for the version to be published; U.J.F.T.: conception and design of the study, interpretation of data, drafting the article, final approval of the version to be published.

Disclosures

The authors have no conflict of interest to declare.

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Supplementary data

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