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RESEARCH LETTER

Triglyceride/HDL cholesterol ratio and premature all-cause mortality in renal transplant recipients

Josephine L. C. Anderson [1], Stephan J. L. Bakker[1] and Uwe J. F. Tietge[2,3,4]

[1]Department of Internal Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, [2]Department of Pediatrics, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, [3]Department of Laboratory Medicine, Division of Clinical Chemistry, Karolinska Institutet, Stockholm, Sweden and [4]Clinical Chemistry, Karolinska University Laboratory, Karolinska University Hospital, Stockholm, Sweden

Correspondence to: Uwe J.F. Tietge; E-mail: uwe.tietge@ki.se

The numbers of renal transplant recipients (RTR) are constantly increasing, already surpassing in several countries those of patients receiving haemodialysis treatment [1]. However, RTR still suffers an exceptionally high, but poorly understood, mortality burden [2]. This is partly attributable to a declining allograft function, and partly to dyslipidaemia, including decreased high-density lipoprotein cholesterol (HDL-C) and increased triglycerides (TGs) [3]. Frequently, HDL-C is low when TGs are high, a relationship particularly well reflected in the TG/HDL-C ratio [4]. As the only existing guideline that addresses lipid treatment in RTR, Kidney Disease: Improving Global Outcome (KDIGO), solely advises lifestyle changes to combat raised TG levels [5]. In the general population, the TG/HDL-C ratio constitutes a useful predictor of mortality, whereas interestingly in haemodialysis patients a protective effect is seen [6, 7]. Comparable data from RTR cohorts are not available. Therefore, we aimed to determine whether the TG/HDL-C ratio associates prospectively with mortality risk in RTR.

The detailed design of this longitudinal cohort study has been published [8]. The study was approved by the local ethics committee (METc 2001/039). Briefly, all RTR visiting the University Medical Centre Groningen outpatient clinic between August 2001 and July 2003 with a functioning allograft for at least 1 year were eligible. Exclusion criteria were congestive heart failure, malignant disease, endocrine abnormalities other than diabetes and evidence of acute inflammation at time of inclusion [high-sensitivity C-reactive protein (hs-CRP) values >20 mg/L]. None of the RTR received lipid modulating therapy other than statins. Of 847 invited patients, 606 gave informed written consent; a full dataset was available for the current analysis in 495 RTR (median follow-up 7 years, comparable in their baseline characteristics to the entire group of eligible patients). The main outcome measure was the TG/HDL-C ratio determined in the fasting state, the primary endpoint was all-cause mortality. Statistical analyses were performed using SPSS version 24.0. A $P < 0.05$ was considered statistically significant.

The 495 included RTRs (Table 1) were followed for a median of 7 years. During follow-up 102 patients died. Patients were divided into gender-stratified tertiles based on the TG/HDL-C ratio (Table 1). Patients with higher TG/HDL-C ratios had higher body mass index, more dyslipidaemia, used more statins and anti-hypertensive drugs, were more insulin resistant/diabetic, and had a higher inflammatory load and worse graft function. Since immunosuppressive medications can have a considerable impact on dyslipidaemia [9], we assessed the correlation between different immunosuppressants and the TG/HDL-C ratio. The use of cyclosporine was positively correlated with the TG/HDL-C ratio ($r = 0.11$, $P = 0.021$), whereas use of tacrolimus showed a negative correlation with the TG/HDL-C ratio ($r = -0.11$, $P = 0.024$). No correlation was seen with daily prednisolone doses ($r = 0.08$, $P = 0.088$) or use of proliferation inhibitors ($r = -0.02$, $P = 0.60$). Cox proportional hazard analyses demonstrated a strong significant association between the TG/HDL-C ratio and all-cause mortality in an age- and gender-adjusted model [hazard ratio (HR) = 1.49, 95% confidence interval (CI) 1.14–1.95; $P = 0.004$]. Therefore, patients in the third tertile, with a TG/HDL-C ratio between 2.7 and 4.4 mmol/L, have a 49% higher risk of mortality than those in the first tertile. This association remained significant when further adjusted for homoeostasis model assessment-estimated insulin resistance, insulin concentration and HbA1c (HR = 1.48, 95% CI 1.11–1.97; $P = 0.008$), use of statins (HR = 1.48, 95% CI 1.12–1.95; $P = 0.006$), calcineurin inhibitors (HR = 1.49, 95% CI 1.14–1.96; $P = 0.004$), total cholesterol (HR = 1.49, 95% CI 1.14–1.95; $P = 0.004$), estimated glomerular filtration rate (eGFR) and proteinuria (HR = 1.32, 95% CI 1.03–1.69; $P = 0.03$), hs-CRP (HR = 1.48, 95% CI 1.13–1.94; $P = 0.005$) and non-HDL-C (HR = 1.49, 95% CI 1.12–1.97; $P = 0.005$). Receiver operating characteristic analysis identified 1.8 as best discriminating cut-off value for the TG/HDL-C ratio, which corresponds to the second tertile in this study.

Our results establish the TG/HDL-C ratio in RTR as a relatively simple, cost-efficient, routinely available lipid biomarker with a substantial clinical impact. Thereby, this study identifies an unmet clinical need, since TG modulating therapy is thus far not represented as a treatment goal by current guidelines. Even

Table 1. Baseline characteristics according to gender-stratified tertiles of TG/HDL-C ratio

Characteristic	Gender-stratified tertiles of TG/HDL-C ratio			P-value
	First ($n = 166$)	Second ($n = 164$)	Third ($n = 165$)	
TG/HDL-C ratio	1.0 (0.7–1.1)	1.7 (1.5–2.1)	3.3 (2.7–4.4)	<0.001
Recipient demographics				
Age, years	51.9 (43.4–60.0)	54.2 (43.6–61.4)	51.3 (43.4–59.5)	0.88
Male gender, *n* (%)	90 (54)	90 (55)	89 (54)	1.00
Current smoking, *n* (%)	39 (24)	29 (18)	37 (22)	0.39
Metabolic syndrome, *n* (%)	83 (57)	94 (65)	84 (60)	0.34
Body composition				
BMI, kg/m^2	24.7 ± 3.8	25.8 ± 4.3	27.3 ± 4.2	<0.001
Lipids				
Total cholesterol, mmol/L	5.5 ± 0.9	5.5 ± 1.0	5.9 ± 1.3	0.008
LDL-C, mmol/L	3.6 ± 0.8	3.6 ± 0.9	3.5 ± 1.2	0.55
HDL-C, mmol/L	1.4 ± 0.31	1.1 ± 0.24	0.9 ± 0.21	<0.001
TGs, mmol/L	1.2 (0.9–1.5)	1.9 (1.6–2.2)	2.9 (2.5–3.5)	<0.001
Use of statins, *n* (%)	70 (42)	88 (54)	94 (57)	0.018
Cardiovascular disease history				
History of MI, *n* (%)	12 (7)	15 (9)	15 (9)	0.79
TIA/CVA, *n* (%)	6 (4)	10 (6)	9 (5)	0.58
Blood pressure				
Systolic blood pressure, mmHg	150.2 ± 22.7	153.1 ± 23.7	154.7 ± 22.4	0.20
Number of antihypertensive drugs, *n*	2 (1–2)	2 (1–3)	2 (2–3)	<0.001
Glucose homoeostasis				
Glucose, mmol/L	4.4 (4.0–4.8)	4.6 (4.0–5.0)	4.7 (4.2–5.5)	<0.001
Insulin, µmol/L	9.5 (6.4–13.0)	10.5 (7.8–14.5)	12.7 (9.6–18.9)	<0.001
HbA1c, %	6.2 (5.7–6.7)	6.4 (5.9–7.1)	6.5 (5.9–7.4)	0.002
HOMA-IR	1.9 (1.2–2.8)	2.1 (1.5–3.1)	2.7 (1.9–4.3)	<0.001
Post-Tx diabetes mellitus, *n* (%)	22 (13)	26 (16)	41 (25)	0.016
Use of anti-diabetic drugs, *n* (%)	17 (10)	23 (14)	28 (17)	0.20
Use of insulin, *n* (%)	9 (5)	11 (7)	12 (7)	0.78
Inflammation				
hs-CRP, mg/L	1.5 (0.7–3.4)	2.1 (0.7–4.9)	2.1 (1.1–5.2)	0.005
Donor demographics				
Age, years	34.0 (22.0–50.0)	39.5 (24.0–51.8)	40 (23.5–50.0)	0.23
Male gender, *n* (%)	91 (55)	97 (59)	68 (53)	0.49
Living kidney donor, *n* (%)	24 (15)	19 (12)	20 (12)	0.71
(Pre)transplant history				
Dialysis time, months	24.5 (12.0–46.0)	29.5 (13.0–50.0)	29.0 (14.0–49.0)	0.16
HLA mismatch	2.0 (0–3.0)	2.0 (1.0–2.8)	2.0 (1.0–3.0)	0.65
Primary renal disease				
Primary glomerular disease	41 (25)	47 (29)	46 (28)	0.69
Glomerulonephritis	14 (8)	11 (7)	7 (4)	0.30
Tubulo-interstitial disease	34 (21)	17 (10)	29 (18)	0.04
Polycystic renal disease	22 (13)	30 (18)	35 (21)	0.16
Dysplasia and hypoplasia	6 (4)	4 (2)	8 (5)	0.51
Renovascular disease	11 (7)	10 (6)	10 (6)	0.97
Diabetic nephropathy	11 (7)	3 (2)	3 (2)	0.02
Other or unknown cause	27 (16)	42 (26)	27 (16)	0.05
Immunosuppressive medication				
Daily prednisolone dose, mg/dL	10.0 (7.5–10.0)	10.0 (8.8–10.0)	10.0 (8.1–10.0)	0.17
Calcineurin inhibitors, *n* (%)	127 (77)	130 (79)	134 (81)	0.57
Proliferation inhibitors, *n* (%)	123 (74)	124 (76)	120 (73)	0.84
Renal allograft function				
eGFR, mL/min	51.9 ± 14.0	45.7 ± 15.6	44.3 ± 16.8	<0.001
Urinary protein excretion, g/24 h	0.1 (0.0–0.2)	0.1 (0.0–0.3)	0.1 (0.1–0.4)	0.011

Normally distributed continuous variables are presented as mean ± SD, and differences were tested with one-way analysis of variance followed by Bonferroni *post hoc* test. Continuous variables with a skewed distribution are presented as median (25–75th percentile), and differences were tested by Kruskal–Wallis test followed by Mann–Whitney U-test. Categorical data are summarized as *n* (%), and differences were tested by Chi-squared test.

LDL-C, low-density lipoprotein cholesterol; TIA, transient ischaemic attack; CVA, cerebrovascular event; Tx, transplantation; MI, myocardial infarct; HOMA-IR, homeostasis model assessment-estimated insulin resistance; HLA, human leucocyte antigens.

when adjusted for a number of strong potential confounders, such as kidney function, the TG/HDL-C ratio remained significantly associated with future mortality. Interestingly, if we would apply the National Cholesterol Education Program cut-off values for 'borderline high TG' and 'low HDL-C' [10], the resulting recommended TG/HDL-C ratio would be 5, a value that is higher than the highest tertile in our study, therefore posing at least two-thirds of the RTR population at increased risk.

Based on these data, we believe that special awareness of TG levels in RTR is required. Furthermore, we think that in RTR prospective intervention trials with the treatment goal to lower TGs are warranted. A multicentre approach would be helpful to establish TG and TG/HDL-C ratio normal values specifically for RTR. We would also like to stimulate lipid guidelines for RTR to take account of the mortality risk associated with disturbances in TG metabolism.

AUTHORS' CONTRIBUTIONS

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

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare. The results presented in this article have not been published previously in whole or part.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

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Urinary ezrin and moesin as novel markers for recovery from acute kidney injury

Win Kulvichit[1,2,3], Xiaoyan Wen[1], Nattachai Srisawat[1,2], Trairak Pisitkun[3], Ali Smith[1], Paul M. Palevsky[4] and John A. Kellum[1]

[1]Department of Critical Care Medicine, Center for Critical Care Nephrology, CRISMA Center, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA, [2]Excellence Center for Critical Care Nephrology, King Chulalongkorn Memorial Hospital, Bangkok, Thailand, [3]Faculty of Medicine, Center of Excellence in Systems Biology, Chulalongkorn University, Bangkok, Thailand and [4]Department of Medicine, Renal-Electrolyte Division, University of Pittsburgh, Pittsburgh, PA, USA

Correspondence to: John A. Kellum; E-mail: kellum@pitt.edu

Acute kidney injury (AKI) is a common disorder associated with high morbidity and mortality among critically ill patients. Approximately 5% of all patients admitted to intensive care units around the world develop severe AKI requiring dialysis [1]. Currently there is no effective treatment to facilitate renal recovery in patients with AKI. The ability to forecast renal recovery is extremely valuable since it will provide physicians with an insight to optimize utilization of renal replacement therapy (RRT) and appropriate follow-up timing for these patients.