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RESEARCH LETTER
CVD Risk Factors

The triglyceride/HDL cholesterol ratio and TyG index predict coronary atherosclerosis and outcome in the general population

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The combination of increased plasma triglycerides (TGs) and low high-density lipoprotein cholesterol (HDL-C) is an emerging marker of 'atherogenic dyslipidaemia' and risk of cardiovascular events in the general population.[1] The TG-glucose (TyG) index is calculated as Ln(TG*FPG/2).[2] It predicted cardiac events in the general population,[3] and the progression of coronary atherosclerosis in patients with known coronary artery disease,[4] irrespective of other risk factors, or cholesterol levels. In a cohort from the general population, we investigated specifically the interplay between TG-related indices, findings from non-contrast computed tomography (CT) and patient outcome. From CT scans, epicardial fat volume (EFV) and coronary artery calcium (CAC) score were derived. Epicardial fat is a biologically active organ that surrounds the coronary arteries and promote the development of coronary atherosclerosis.[5] EFV then becomes a surrogate indicator of the lipid-rich coronary plaque burden, and then of high-risk atherosclerotic plaques, while the CAC score expresses more stable and calcific coronary atherosclerosis. EFV may have also a prognostic value for future adverse events also beyond CAC scoring.[6]

The present study was carried out among participants of the Montignoso Heart and Lung Project. Montignoso is a small city in Tuscany, Italy, with about 10 000 inhabitants. Between May 2010 and October 2011, all subjects aged between 45 and 75 years were invited to participate to a population screening. Among respondents ($n = 1672$, 52% of those invited), we enrolled subjects free from known cardiovascular or pulmonary disease, with no evidence of active neoplasia, a life expectancy longer than 1 year and able to express informed consent. The final study population included 1382 subjects. A team composed of a cardiologist and a pneumologist interviewed these patients using a standardized form focused on cardiovascular risk factors. Study participants also underwent a non-contrast CT chest scan. The study conformed to the Helsinki declaration and was approved by the Institutional Review board. All subjects gave written informed consent.

Study participants ($n = 1382$) were aged 61 years (interquartile interval 54–68), and 45% were men. They had a preserved renal function and normal left ventricular ejection fraction; 38% were hypertensive, 10% had diabetes, and 45% were current or previous smokers. As for the lipid profile, total cholesterol was 214 mg/dL (187–239), low-density lipoprotein cholesterol 130 mg/dL (108–152), HDL-C 61 mg/dL (50–73), and TG 88 mg/dL (63–128). The TG/HDL-C ratio was 1.5 (0.9–2.4), and the TyG index was 8.4 (8.0–8.8). Subjects were then stratified into quartiles of TG/HDL-C and TyG. Some of the most prominent changes from the first to the fourth quartiles of TG/HDL-C and TyG were increasing percentages of males, hypertensive, or diabetic patients.

CAC values were 0 (0–46), with 807 patients (58%) having CAC = 0, 341 (25%) having CAC <100, 134 (10%) having CAC 100–399, and 98 (7%) having CAC ≥400. Median EFV was 145 mL (105–197). Both CAC and EFV increased significantly across quartiles of TG/HDL-C and TyG. The TG/HDL-C and TyG displayed weak correlations with CAC and slightly stronger correlations with EFV. A model including univariate determinants of both CAC and EFV (avoiding multicollinearity) was created, and included age, sex, body mass index, hypertension, diabetes, smoking status, aspirin, and statins. TG/HDL-C and TyG were not independently related to CAC ($P = 0.859$ and $P = 0.768$, respectively), while they were both independently associated with EFV (coefficient = 0.111, $P < 0.001$, and coefficient = 0.160, $P < 0.001$, respectively).

During a follow-up of 10 years (9.5–10.5), 103 patients died, and 36 patients experienced the secondary endpoint of cardiovascular death or urgent revascularization over 10.1 years (9.6–10.6). By dose–response analysis, we found a non-linear association of TG/HDL-C with

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the risk of all-cause mortality (P for non-linearity = 0.003) and cardiovascular death or urgent revascularization (P for non-linearity = 0.013). In contrast, TyG displayed a linear association with the risk of both outcomes (P for non-linearity = 0.488 for all-cause mortality and P for non-linearity = 0.686 for cardiovascular death or urgent revascularization). Therefore, TG/HDLC was used in the ascending quartiles format while TyG as continuous variable in survival analyses. TG/HDL-C was associated with the incidence of all-cause death independently of traditional risk factors, CAC, and EFV. TG/HDL-C also predicted the cardiovascular endpoint regardless of traditional risk factors and CAC. Conversely, TyG predicted all-cause mortality and cardiovascular death or urgent revascularization after controlling for CAC, but not for traditional risk factors or EFV. TG/HDL-C improved reclassification for all-cause mortality and cardiovascular death or urgent revascularization on top of traditional risk factors, CAC, and EFV. Moreover, TG/HDL-C had incremental discrimination value for the two outcomes when added to CAC. TyG showed additive prognostic value beyond CAC for all-cause death (Δ area under the curve = 0.241, $P < 0.001$ and net reclassification index = 0.399, $P < 0.001$) and cardiovascular death or urgent revascularization (Net reclassification improvement (NRI) = 0.364, $P = 0.03$).

In subjects from the general population, two TG-related metrics, namely the TG/HDL-C ratio and TyG index, were weakly correlated with the burden of coronary artery calcifications, and displayed a slightly stronger correlation with the volume of the pro-atherogenic extracellular fat. The relationship with EFV was independent of traditional risk factors such as age, sex, body mass index, hypertension, diabetes, smoking status, aspirin, and statins. Furthermore, TG/HDL-C quartiles predicted all-cause mortality beyond the extent of coronary artery calcifications and EFV, and cardiovascular death or urgent revascularization beyond risk factors and CAC. Even TyG displayed an independent prognostic value from CAC for all-cause mortality and the composite cardiovascular endpoint. TG-related indices then emerged as effective tools for risk stratification in patients from the general population.

Some limitations must be acknowledged. The cohort was relatively small, and the number of events over a 10-year follow-up was limited. Changes over time in the lipid profile and CT findings could not be assessed. Neither coronary anatomy nor ischaemia were directly evaluated, which would have required at least contrast medium administration and a higher radiation exposure.

The implications of these findings are clear. TG-related indices can be easily calculated based on commonly available parameters, and yield strong prognostic significance in the general population, particularly the TG/HDL-C ratio. Furthermore, both TG/HDL and TyG express a metabolic condition not addressed by current treatments and which deserves consideration in future studies.

Conflict of interest: none declared.

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