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RESEARCH ARTICLE

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# High TG to HDL ratio plays a significant role on atherosclerosis extension in prediabetes and newly diagnosed type 2 diabetes subjects

Roberto Scicali[1] | Philippe Giral[2,3] | Laura D'Erasmo[2,4] | Philippe Cluzel[5,6] | Alban Redheuil[5,6] | Antonino Di Pino[1] | Agata Maria Rabuazzo[1] | Salvatore Piro[1] | Marcello Arca[4] | Sophie Béliard[7] | Francesco Purrello[1] | Eric Bruckert[2,3] | Antonio Gallo[2,5]

[1]Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy

[2]Cardiovascular Prevention Unit, Department of Endocrinology and Metabolism, Paris Hospital Public Assistance, Pitié-Salpêtrière Hospital Group – Sorbonne University, Paris, France

[3]Dyslipoproteinemia and Atherosclerosis Research Unit, National Institute for Health and Medical Research (INSERM) and Pierre et Marie Curie University (UPMC – Paris VI), Paris, France

[4]Department of Translational and Precision Medicine, Sapienza Università di Roma, Rome, Italy

[5]Laboratoire d'imagerie Biomédicale, INSERM 1146, - CNRS 7371, Sorbonne University, Paris, France

[6]Département d'imagerie cardiovasculaire et de radiologie interventionnelle, Pôle Imagerie-Groupe Hospitalier Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Paris, France

[7]Aix Marseille Univ, INSERM, INRAE, C2VN, Marseille, France

**Correspondence**
Francesco Purrello, Department of Clinical and Experimental Medicine, University of Catania, Internal Medicine, Garibaldi Hospital, Via Palermo 636, 95122 Catania, Italy.
Email: fpurrell@unict.it

## Abstract

**Aims:** We investigated the role of TG to HDL ratio (TG/HDL) on atherosclerosis extension, defined as presence of coronary artery calcium (CAC), carotid and femoral plaque, in prediabetes or newly diagnosed type 2 diabetes (T2D).

**Methods:** We performed a retrospective, cross-sectional, single centre study involving 440 prediabetes or newly diagnosed controlled T2D subjects. Participants underwent CAC analysis by computed tomography and carotid and femoral plaque evaluation by ultrasonography and were stratified in high TG/HDL (H-TG/HDL) or low TG/HDL (L-TG/HDL) group according to TG/HDL median value. We estimated atherosclerosis extension according to the number of involved vascular districts.

**Results:** CAC was higher in the H-TG/HDL group than L-TG/HDL group (29.15 [0.0-95.68] vs 0.0 [0.0-53.97] AU, $P < .01$) and CAC > 0 was more prevalent in the H-TG/HDL group than L-TG/HDL group (64.5% vs 45%, $P < .001$). Femoral atherosclerosis was higher in the H-TG/HDL group than L-TG/HDL group (57.3% vs 43.6%, $P < .01$). H-TG/HDL group exhibited a lower prevalence of subjects with 0-TWP compared to L-TG/HDL group (21.8% vs 38.6%, $P < .01$) and higher percentages of subjects with 2-TWP or 3-TWP than L-TG/HDL group (for 2-TWP 29.5% vs 21.5%, $P < .05$; for 3-TWP 32.7% vs 20.9%, $P < .01$). Multiple logistic regression analysis showed that a H-TG/HDL was inversely associated to 0-TWP ($P < .05$) and positively associated with 2-TWP ($P < .05$) and 3-TWP ($P < .01$).

**Conclusions:** Our data suggest that TG/HDL is a marker of increased atherosclerotic extension in prediabetes and newly diagnosed T2D and may be useful to identify subjects with a higher cardiovascular risk profile.

KEYWORDS

atherosclerosis extension, cardiovascular risk, coronary artery calcium, prediabetes, TG to HDL ratio, type 2 diabetes

  

## 1 | INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of mortality in the world and it is caused by environmental, genetic and metabolic factors.[1] An impaired glucose homeostasis is involved in the pathogenesis and progression of atherosclerosis.[2] Several studies have demonstrated that ASCVD caused 50% of death in patients with type 2 diabetes (T2D)[3-5]; moreover, despite the global prevalence of ASCVD has been reduced in the last 15 years, T2D patients are still at increased cardiovascular mortality as compared to non-diabetic subjects.[6]

T2D is the last step of a damaged glucose homeostasis, that is often preceded by prediabetes and starts several years before T2D diagnosis.[78] In line with this concept, previous findings showed that also the onset of the atherosclerotic process preceds the diagnosis of diabetes and that prediabetes is associated with an increased atherosclerotic burden compared to normoglycemia.[910]. Some recent evidences have shown that prediabetes and newly diagnosed T2D represent a heterogenous population in which not all subjects exhibit the same cardiovascular risk.[1112] In this context, emerging metabolic biomarkers may be helpful to better discriminate the cardiovascular risk in these subjects. Various mechanisms are implicated in ASCVD in prediabetes and T2D; in particular, the insulin resistance promotes an increased inflammatory vascular damage and lipoprotein abnormalities that sustain the atherosclerotic process.[1314]

Previous findings showed that plasma triglycerides (TG) and high-density-lipoprotein (HDL) cholesterol were correlated to insulin action and that an increased TG to HDL ratio (TG/HDL) was associated with insulin resistance in non-diabetic subjects.[15,16] Moreover, several prospective cohort studies showed that an increased TG/HDL was an independent predictor of ASCVD and all-cause mortality.[17,18] However, no data exist on the possible role of TG/HDL on atherosclerosis burden in prediabetes and newly diagnosed T2D.

In the last few years, an emerging role has been attributed to coronary artery calcium (CAC) as a subclinical coronary atherosclerosis biomarker in asymptomatic individuals without ASCVD.[19,20] Recent guidelines recommended CAC for further stratification in low-intermediate risk subjetcts.[21]

To better discriminate the cardiovascular risk of prediabetes and newly diagnosed T2D subjects, in this study we aimed at investigating the role of TG/HDL on the atherosclerosis extension, evaluated by the presence of CAC, carotid and femoral plaque, in asymptomatic subjects with prediabetes or newly diagnosed T2D .

## 2 | METHODS

### 2.1 | Study design and population

This was a cross-sectional study on a population of subjects with prediabetes or newly diagnosed T2D that were referred to the Cardiovascular Prevention Unit of the Endocrinology and Metabolism Department at Pitié-Salpêtrière Hospital in Paris, France between January 2014 and May 2016. A total of 711 medical files satisfied the following inclusion criteria: subjects with prediabetes or newly diagnosed controlled T2D, asymptomatic for any ASCVD and age between 40 and 70 years who performed coronary, carotid and femoral atherosclerosis evaluation.

Prediabetes was defined as a fasting plasma glucose (FPG) between 100 and 125 mg/dL and/or glycated haemoglobin (HbA1c) 5.7% to 6.4%; also, newly diagnosed controlled T2D was defined as FPG ≥126 mg/dL on two consecutive readings and/or 6.5% ≤ HbA1c without previous diagnosis and no use of anti-diabetic medications[22]; we selected only this category of new T2D subjects in order to avoid any effect of longer-exposure to hyperglycaemia on atherosclerotic burden.[23] Arterial hypertension was defined as brachial blood pressure (BP) ≥140 mm Hg (systolic) and/or 90 mm Hg (diastolic) on at least two different occasions, or if the patient was on antihypertensive therapy. Dyslipidemia was defined as cholesterol levels above the range provided by the National Cholesterol Education Program Adult Treatment Panel III Guidelines.[24]

All patients on lipid lowering therapy, with a previous history of ASCVD as well as clinical evidence of advanced renal disease were excluded from the study. Advanced renal disease was defined as glomerular filtration rate (GFR) <30 mL/min. Current smoking habits were divided into either current smoking (defined as any cigarette in the last month) or past smoking. ASCVD was defined as documented previous myocardial infarction, acute coronary syndrome, coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery) or other arterial revascularization procedures, stroke or transient ischemic attack, or peripheral artery disease.

A total population of 440 subject with prediabetes (N = 347) or newly diagnosed controlled type 2 diabetes (N = 93) satisfied the inclusion criteria and was included in the study (Figure 1). After revision of the medical records (including CAC, carotid and femoral plaque assessment) the study population was stratified according to the median TG/HDL cut-off of 2.45.

This study was permorfed in accordance with the Declaration of Helsinki and informed consent was obtained from all participants.

### 2.2 | Measurements

All participants underwent routine clinical interview, physical examination and review of their clinical history. After a 12-hours fast, all participants had standard haematological and clinical biochemistry parameters measured. Fasting plasma glucose (FPG) was measured with the glucose oxidase method.[25] Serum total cholesterol (TC), TG, HDL cholesterol and high-sensitivity C-reactive protein (hs-CRP) were assessed by available enzymatic methods.[26] TG/HDL was derived from the baseline values. LDL cholesterol was calculated using the Friedewald formula. HbA1c was measured with high-performance liquid chromatography using a National Glycohemoglobin Standardization Program and standardized to the Diabetes Control and Complications Trial assay reference.[27] Chromatography was performed using a certified automated analyser [HPLC; HLC-723G7 haemoglobin HPLC analyser; Tosoh Corp.; normal range 4.25% to 5.9% (23-41 mmol/mol)]. Brachial BP measurements were performed under standardized conditions, with the patient in a supine position for at least 5 minutes using an oscillometric device (OMRON 905). Body weight and height were measured, and body mass

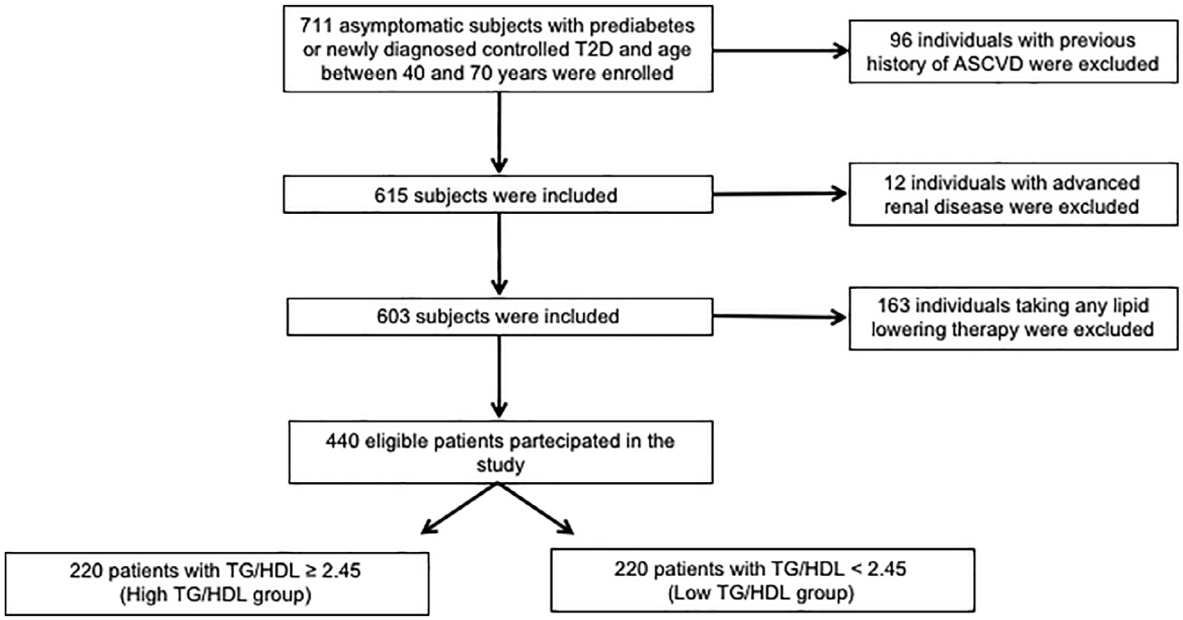


**FIGURE 1** Enrollment flowchart of the study population. T2D, type 2 diabetes; CAC, coronary artery calcium; ASCVD, atherosclerotic cardiovascular disease; GFR, glomerular filtration rate

index (BMI) was calculated as weight divided by the squared value of height (kg/m$^2$).

## 2.3 | CAC assessment

Each patient underwent a multi-detector computed tomography (CT) scan (Definition Flash, Siemens, Erlangen, Germany) for a total radiation exposure of 1 to 3 mSv. CAC was measured as previously described.[28] Briefly, coronary visualization was achieved without contrast by using the high resolution volume mode of the ultrafast computed tomographic scanner in conjunction with a 100 ms scan time, a 3 mm slice thickness, ECG triggering and breath holding. Twenty contiguous slices (60 mm) were acquired with the most cephalad at the lower margin of the bifurcation of the main pulmonary artery. To determine the presence and quantity of coronary calcium, each of the 20 levels was evaluated sequentially. The threshold for a calcific lesion was set at a computed tomographic density of 130 Hounsfield units having an area ≥1 mm$^2$. CAC was determined by the product of the calcified plaque area and maximal calcium lesion density (from 1 to 4 based on Hounsfield units).

All CT scans were quantified in an expert central reading center and supervised by a senior cardiovascular radiologist (A.R.) who was blinded to patients recent and past medical history.

CAC presence was defined as a CAC > 0.

## 2.4 | Carotid and femoral plaque assessment

Ultrasonography measurements of the carotid and femoral arteries were performed using an ACUSON Sequoia ultrasound machine with an 8 MHz transducer as previously described.[20]

Carotid measurements were performed over a 1 cm segment in the distal common carotid artery (1 cm proximal to dilation of the carotid bulb) and over 1 cm segment of the carotid artery bifurcation (1 cm proximal to the flow divider). Femoral measurements were performed on the common femoral artery (1 cm proximal to common femoral artery bifurcation). Three longitudinal sections of both right and left carotid and femoral arteries were acquired. Both carotid and femoral intima-media thickness (IMT) were measured on an area with no plaques on the common carotid and femoral arteries, respectively. Mean IMT was defined for each individual as the average of the right and the left common carotid/femoral IMT.

Both carotid and femoral plaques were defined as an IMT greater than 1.5 mm.[29] All the exams were performed by a single blinded operator.

## 2.5 | Statistical analysis

Normal distribution of data was confirmed by Kolmogorov-Smirnov test before further analysis.. Data are reported as mean ± SD for continuous parametric and median (Interquartile Range-IQR) for continuous non-parametric variables, and as frequency (percentage) for categorical variables. When necessary, continuous non-parametric variables were logarithmically transformed to reduce skewness. To compare qualitative variables, the $\chi 2$ test were used. For continuous variables, differences between groups were evaluated using Student *t* test. Atherosclerosis extension across the coronary, carotid and femoral territories was analysed stratifying the study population accoding to the number of involved vascular districts: no territory with plaque (0-TWP), 1 (TWP), two TWP (2-TWP) and 3 TWP (3-TWP). The association between high TG/HDL and atherosclerosis extension as

dichotomic variable (presence or not) was examined with logistic regression analysis, after adjustment for age, gender, smoke, FPG, HbA1c, BMI, systolic BP, hs-CRP. In order to evaluate the role of TG/HDL on the coronary (CAC presence or not) and peripheral (carotid/femoral plaque presence or not) atherosclerosis burden we separately performed two different logistic regression analysis for coronary and peripheral atherosclerosis district adjusted for age, gender, smoke, FPG, HbA1c, BMI, systolic BP, hs-CRP; the same logistic regression models were subsequently performed in the study population further stratified in two groups according to diabetes and prediabetes status. Prior to multivariate analyses, variance inflation due to covariates was verified by estimating a variance inflation factor <2; for this reason total cholesterol, Non-HDL cholesterol and TG were excluded.

All statistical analyses were performed using IBM SPSS Statistics for Windows version 23. For all tests, a $P < .05$ was considered significant.

## 3 | RESULTS

The general characteristics of the study population are presented in Table 1. Demographic characteristics were similar between the two groups and a similar prevalence of prediabetes/newly diagnosed controlled T2D was observed within the two groups.

As expected, TG/HDL value was higher in the H-TG/HDL group than L-TG/HDL group (4.74 [3.64-6.41] vs 1.39 [1.01-1.75], $P < .001$); moreover, H-TG/HDL group exhibited an increased level of TG and a lower amount of HDL cholesterol than L-TG/HDL group (177.0 [130.0-211.5] vs 129.5 [83.5-148.5] mg/dL, $P < .001$ and 50.42 ± 6.47 vs 56.04 ± 7.23 mg/dL, $P < .01$, respectively). Accordingly, while LDL cholesterol levels were similar between the two groups, H-TG/HDL subjects showed a higher non-HDL cholesterol compared with L-TG/HDL subjects (166.38 ± 11.45 vs 140.9 ± 10.95 mg/dL, $P < .001$). Moreover, FPG and HbA1c levels were higher in the H-TG/HDL group than L-TG/HDL group (101.01 ± 18.24 vs 93.12 ± 16.66 mg/dL, $P < .001$ and 6.4 ± 0.37 vs 6.2 ± 0.31%, $P < .05$, respectively). Finally, H-TG/HDL subjects showed higher levels of hs-CRP compared with L-TG/HDL subjects (1.7 [1.0-3.5] vs 1.2 [0.6-2.4] mg/dL, $P < .001$; Table 1).

The subclinical atherosclerosis markers are shown in Table 2. H-TG/HDL group exhibited a higher CAC compared with L-TG/HDL group (29.15 [0.0-95.68] vs 0.0 [0.0-53.97] AU, $P < .01$); moreover, the percentage of subjects with CAC > 0 was higher in the H-TG/HDL group than L-TG/HDL group (64.5% vs 45%, $P < .001$). Finally, there was no difference in mean carotid and femoral IMT measurements and carotid plaque prevalence while the H-TG/HDL group exhibited a higher femoral atherosclerotic burden than L-TG/HDL group (57.3% vs 43.6%, $P < .01$).

Figure 2 shows the extension of atherosclerosis 0-TWP, 1-TWP, 2-TWP and 3-TWP in the two groups; of note, while H-TG/HDL group exhibited a lower prevalence of subjects with 0-TWP compared to L-TG/HDL group (21.8% vs 38.6%, $P < .01$) the percentages of

**TABLE 1** General characteristics of the study population stratified according to TG/HDL

| | High TG/HDL group N = 220 | Low TG/HDL group N = 220 | *P* value |
|---|---|---|---|
| *Demographic characteristics* | | | |
| Age, years | 59.24 ± 6.09 | 57.44 ± 6.93 | .42 |
| Men, n (%) | 118 (53.6) | 112 (50.9) | .81 |
| TG/HDL, value | 4.74 (3.64-6.41) | 1.39 (1.01-1.75) | <.001 |
| Prediabetes, n (%) | 171 (77.7) | 176 (80.0) | .57 |
| Body mass index, kg/m$^2$ | 29.2 ± 2.69 | 28.63 ± 2.84 | .56 |
| Systolic blood pressure, mm Hg | 119.4 ± 13.69 | 117.13 ± 14.36 | .09 |
| Smoking, n (%) | 43 (19.5) | 40 (18.2) | .87 |
| *Biochemical characteristics* | | | |
| Fasting plasma glucose, mg/dL | 101.01 ± 18.24 | 93.12 ± 16.66 | <.001 |
| HbA1c, % | 6.4 ± 0.37 | 6.2 ± 0.31 | <.05 |
| Total cholesterol, mg/dL | 228.28 ± 14.84 | 225.94 ± 14.97 | .85 |
| HDL cholesterol, mg/dL | 50.42 ± 6.47 | 56.04 ± 7.23 | <.01 |
| Triglycerides, mg/dL | 177.0 (130.0-211.5) | 129.5 (83.5-148.5) | <.001 |
| LDL cholesterol, mg/dL | 133.71 ± 10.26 | 131.61 ± 9.81 | .28 |
| Non-HDL cholesterol, mg/dL | 166.38 ± 11.45 | 140.9 ± 10.95 | <.001 |
| Hs-CRP, mg/L | 1.7 (1.0-3.5) | 1.2 (0.6-2.4) | <.001 |
| *Treatment* | | | |
| Antihypertensive therapy, n (%) | 58 (26.4) | 51 (23.2) | .66 |

*Note:* Data are presented as mean ± SD, percentages or median (interquartile range).

Abbreviations: HbA1c, haemoglobin A1c; HDL, high-density lipoprotein; Hs-CRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein; T2D, type 2 diabetes; TG/HDL, triglyceride to high-density lipoprotein ratio.

**TABLE 2** Subclinical atherosclerosis markers of the study population

| | High TG/HDL group N = 220 | Low TG/HDL group N = 220 | *P* value |
|---|---|---|---|
| Subclinical atherosclerosis markers | | | |
| CAC, Agatston units | 29.15 (0.0-95.68) | 0.0 (0.0-53.97) | <.01 |
| CAC > 0, n (%) | 142 (64.5) | 99 (45.0) | <.001 |
| Mean c-IMT, mm | 0.76 (0.66-0.83) | 0.73 (0.64-0.80) | .19 |
| Carotid plaque, n (%) | 120 (54.5) | 105 (47.7) | .18 |
| Mean f-IMT, mm | 0.81 (0.70-0.89) | 0.77 (0.69-0.85) | .11 |
| Femoral plaque, n (%) | 126 (57.3) | 96 (43.6) | <.01 |

*Note:* Data are presented as percentages, or median (interquartile range).
Abbreviations: CAC, coronary artery calcium; c-IMT, carotid intima-media thickness; f-IMT, femoral intima-media thickness.

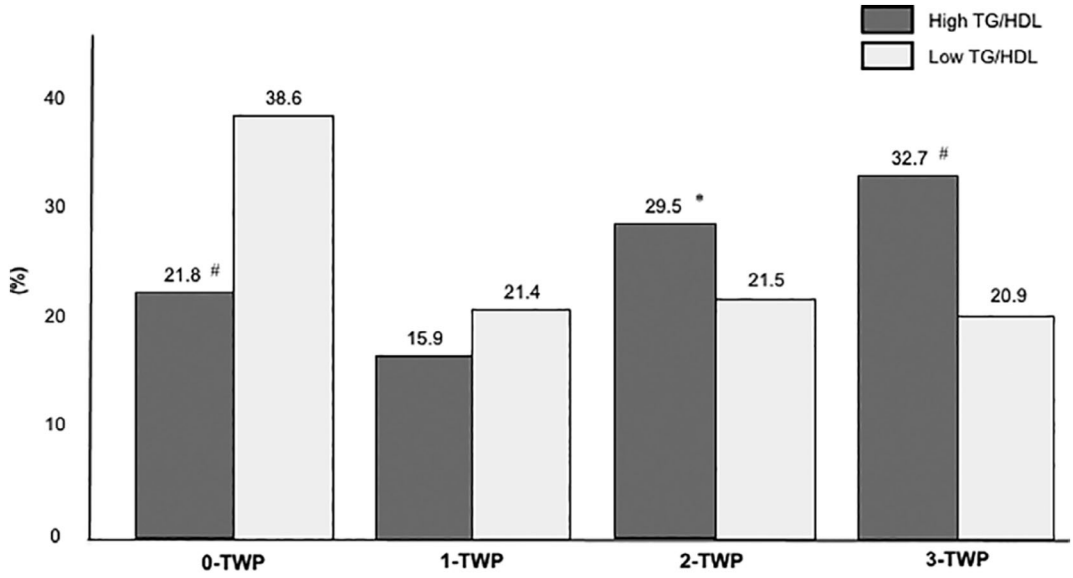


**FIGURE 2** Atherosclerosis extension in the study population according to the number of vascular territories involved. TG/HDL, triglyceride to high-density lipoprotein ratio; 0-TWP, no territory with plaque; 1-TWP, one territory with plaque; 2-TWP, two territories with plaque; 3-TWP, three territories with plaques. **P* value <.05 vs L-TG/HDL, #*P* value <.01 vs L-TG/HDL

**TABLE 3** Logistic regression of atherosclerosis extension in the study population

| Dependent variable<br>Independent variable | 0-TWP<br>Multivariate ORs (95% CIs)<br>Model | 1-TWP<br>Multivariate ORs (95% CIs)<br>Model | 2-TWP<br>Multivariate ORs (95% CIs)<br>Model | 3-TWP<br>Multivariate ORs (95% CIs)<br>Model |
|---|---|---|---|---|
| TG/HDL, high = 1 | 0.274 (0.103-0.730)* | 1.340 (0.682-2.630) | 1.981 (1.062-2.939)* | 2.348 (1.263-4.019)# |
| Age, years | 0.237 (0.101-0.683)* | 1.070 (1.045-1.096)† | 1.074 (1.041-1.108)† | 1.164 (1.118-1.211)† |
| HbA1c, % | 0.557 (0.321-0.968)* | 1.295 (0.432-2.457) | 1.576 (1.029-2.416)* | 2.133 (1.180-3.857)* |

*Note:* Logistic regression model was used to estimate ORs and 95% CIs. Model was adjusted for TG/HDL, age, gender, HbA1c, systolic BP, fasting plasma glucose, smoking status (yes = 1), body mass index, hs-CRP.
Abbreviations: 0-TWP, no territory with plaque; 1-TWP, one territory with plaque; 2-TWP, two territories with plaque; 3-TWP, three territories with plaques; HbA1c, glycated haemoglobin; TG/HDL, triglyceride to high density lipoprotein ratio.
**P* value <.05, #*P* value <.01, †*P* value <.001.

subjects with 2-TWP or 3-TWP were higher in the H-TG/HDL group than L-TG/HDL group (for 2-TWP 29.5% vs 21.5%, *P* < .05; for 3-TWP 32.7% vs 20.9%, *P* < .01). The percentage of subjects with 1-TWP was similar between the two groups.

Multiple logistic regression analysis showed that a H-TG/HDL was inversely associated to 0-TWP (*P* < .05) and positively associated with 2-TWP (*P* < .05) and 3-TWP (*P* < .01); these associations were independent after adjustment for age, gender, HbA1c, FPG, smoking

status, SBP, BMI, hs-CRP (Table 3). No association of H-TG/HDL and 1-TWP was found in the study population.

In order to evaluate the role of TG/HDL on the coronary (CAC presence or not) and peripheral (carotid/femoral plaque presence or not) atherosclerosis burden we separately performed two different logistic regression analysis for coronary and peripheral atherosclerosis districts adjusted for age, gender, smoke, FPG, HbA1c, BMI, systolic BP, hs-CRP (Table 4). H-TG/HDL was significantly associated with coronary ($P < .001$) and peripheral ($P < .01$) atherosclerosis burden and these associations were independent after adjustment for age, gender, HbA1c, FPG, smoking status, SBP, BMI, hs-CRP.

Finally, we evaluated the impact of H-TG/HDL on coronary and peripheral atherosclerosis in the study population stratified in two groups according to diabetes and prediabetes status (Table 5). H-TG/HDL was significantly associated with coronary and peripheral atherosclerosis burden in both groups (for CAC presence $P < .001$ and for Carotid/Femoral plaque presence $P < .01$ in both groups) and these associations were independent after adjustment for age, gender, HbA1c, FPG, smoking status, SBP, BMI, hs-CRP.

**TABLE 4** Logistic regressions of coronary and peripheral atherosclerosis burden in the study population

| Dependent variable | CAC > 0 Multivariate ORs (95% CIs) Model | Carotid/femoral plaque presence Multivariate ORs (95% CIs) Model |
|---|---|---|
| Independent variable | | |
| TG/HDL, high = 1 | 2.830 (1.415-4.610)† | 2.319 (1.312-4.110)# |
| Age, years | 1.129 (1.091-1.168)† | 1.066 (1.036-1.097)† |
| HbA1c, % | 2.261 (1.053-4.258)* | 2.171 (1.119-4.100)* |

*Note:* Logistic regression model was used to estimate ORs and 95% CIs. Model was adjusted for TG/HDL, age, gender, HbA1c, systolic BP, fasting plasma glucose, smoking status (yes = 1), body mass index, hs-CRP.
Abbreviations: CAC, coronary artery calcium; HbA1c, glycated haemoglobin; TG/HDL, triglyceride to high density lipoprotein ratio.
*$P$ value <.05, #$P$ value <.01, †$P$ value <.001.

## 4 | DISCUSSION

In this study, we evaluated the predictive role of TG/HDL ratio on atherosclerotis extension in prediabetes and newly diagnosed T2D. Subjects with a H-TG/HDL had increased CAC and femoral atherosclerosis; moreover, a H-TG/HDL was found to be an independent marker of multidistrict atherosclerosis distribution. To the best of our knowledge, this is the first study that evaluates the contribution of TG/HDL ratio on sublinical atherosclerosis in prediabetes and newly diagnosed T2D.

In the last few years, thanks to better knowledge of metabolic diseases, an increasing attention has been taken into the cardiovascular risk heterogeneity of subjects with impaired glucose homeostasis, in particular prediabetes and newly diagnosed T2D.[30]

It has been known that apolipoprotein-B-containing lipoproteins have a causal role of ASCVD in general population[31] and several studies previously showed the central role of TG-rich ApoB-containing remnant lipoproteins (TRLs) over LDL on ASCVD in metabolic patients such as prediabetes and T2D.[32-34]

In particular, Bittencourt et al demonstrated that TRL were associated with higher CAC presence and severity in a large cohort of patients at moderate/high cardiovascular risk.[35]

Non-HDL has been proven as a better predictor of coronary artery disease than LDL in diabetic or prediabetic subjects.[36,37] In our study population, an atherogenic dyslipidemia profile was observed: the two groups did not differ for LDL cholesterol levels, but for an increased amount of non-HDL in the H-TG/HDL group. This reflects the higher amount of TRLs usually found in subjects with high TG levels such as diabetic or prediabetic subjects.[38,39] TG/HDL directly depends on TG levels; thus, taking into consideration the impact of TG/HDL on atherosclerosis burden, this is the first study showing an independent association between high TG levels and subclinical atherosclerosis detected by different methods in prediabetes or newly diagnosed T2D patients. Moreover, in our study despite a similar prevalence of T2D or prediabetes and cardiovascular risk factors, patients with a higher TG/HDL exhibited un unfavourable lipid and

**TABLE 5** Logistic regressions of coronary and peripheral atherosclerosis burden in the study population according to diabetes and prediabetes status

| | Diabetes | | Prediabetes | |
|---|---|---|---|---|
| Dependent variable | CAC > 0 Multivariate ORs (95% CIs) Model | Carotid/femoral plaque presence Multivariate ORs (95% CIs) Model | CAC > 0 Multivariate ORs (95% CIs) Model | Carotid/femoral plaque presence Multivariate ORs (95% CIs) Model |
| Independent variable | | | | |
| TG/HDL, high = 1 | 2.639 (1.367-3.948)† | 1.799 (1.229-2.633)# | 2.813 (1.630-3.980)† | 1.928 (1.303-2.854)# |
| Age, years | 1.121 (1.087-1.1)† | 1.097 (1.071-1.123)† | 1.116 (1.081-1.151)† | 1.058 (1.031-1.086)† |
| HbA1c, % | 1.842 (1.053-4.258)# | 1.695 (1.174-2.447)# | 2.310 (1.373-3.885)# | 1.648 (1.021-2.661)* |

*Note:* Logistic regression model was used to estimate ORs and 95% CIs. Model was adjusted for TG/HDL, age, gender, HbA1c, systolic BP, fasting plasma glucose, smoking status (yes = 1), body mass index, hs-CRP.
Abbreviations: CAC, coronary artery calcium; HbA1c, glycated haemoglobin; TG/HDL, triglyceride to high density lipoprotein ratio.
*$P$ value <.05, #$P$ value <.01, †$P$ value <.001.

glucose profile and also an inflammatory pattern. An increased TG/HDL could be therefore associated with impaired glucose homeostasis and insulin sensitivity better than classic lipid biomarkers. In this context, TG/HDL may be a useful clinical parameter by linking four separate conditions such as inflammation, dyslipidemia, hyperglycemia and atherosclerosis in the only appropriate definition of 'atherometabolic disease'. This concept is in line with previous findings focused on TG/HDL and these mentioned pathophysiological disorders[40,41]: Salazar et al found that high TG/HDL was able to identify subjects with insulin resistance and a greater cardiometabolic risk in a large cohort of individuals. Moreover, Jonas et al showed that subjects with an increased TG/HDL had a greater amount of inflammatory cytokine plasma levels such as IL-1β, IL-6 and MCP-1 than low TG/HDL subjects in a cohort of idiopathic pulmonary arterial hypertension subjects. In our study, however, hs-CRP was not an independent predictor of atherosclerosis.

Regarding coronary atherosclerosis, our results are in line with previous studies that documented similar findings in a different set of subjects.[30-32] Bampi et al showed that both CACs and TG/HDL were correlated to the extension of coronary atherosclerosis evaluated by coronary angiography in subjects with a clinical suspect of coronary disease. Our cohort consisted of asymptomatic subjects at the time of the observation, thus confirming a role of TG/HDL in discriminating asymptomatic hyperglycemic subjects with an increased risk of ASCVD. Moreover, both Lindt et al and Salazar et al affirmed a key role of TG/HDL in predicting cardiovascular events in two large cohorts of metabolic subjects. Further prospective studies are needed to evaluate the prediction of ASCVD by TG/HDL in a heterogeneous population such as prediabetes and type 2 diabetes.

We also evaluated the carotid and femoral atherosclerotic burden. Subjects with H-TG/HDL only exhibited a significantly greater amount of femoral plaque presence; this result is in line with previous studies showing similar findings.[4243] In fact, Laclaustra et al showed that peripheral plaque presence was significantly more common in the femoral than in the carotid territory in a large cohort of subjects at intermediate cardiovascular risk. Moreover, Li et al found that T2D patients had a higher prevalence of femoral atherosclerosis than carotid atherosclerosis. Of note, several studies have previously shown that the pathophysiology of diabetes had a strong relationship with lower extremity and coronary atherosclerosis[4445]; in this context, in a cohort of prediabetics and diabetics a high TG/HDL may identify subjects with a worse glucose profile and so with a higher probability of femoral and coronary atherosclerosis. Finally, our results underline the need to perform the femoral ultrasound evaluation in all prediabetes and diabetes subjects to better evaluate the atherosclerosis burden in clinical practice.

When TG/HDL was evaluated separately on coronary and peripheral atherosclerosis burden, we found that H-TG/HDL was significantly associated with these distinct atherosclerosis districts. Of note, the relationship between H-TG/HDL and coronary as well as peripheral atherosclerosis was also confirmed in the study population stratified according to prediabetes and diabetes status; thus, our findings suggest that TG/HDL may be a useful biomarker of coronary and peripheral atherosclerotic injury in all subjects with abnormal glucose homeostasis.

The *ESC/EAS Guidelines for the management of Dyslipidemias* recently documented the need of subclinical polyvascular atherosclerosis evaluation for cardiovascular risk assessment.[21] Several prospective cohort studies showed that subjects with polyvascular atherosclerotic burden exhibited a higher risk of ASCVD and all-cause mortality.[4647] In particular, in the SAVOUR-TIMI trial Gutierrez et al demonstrated that T2D subjects with a polyvascular disease exhibited an increased risk of ASCVD than monovascular disease subjects.[48] In this context, to our knowledge this is the first study that explored the role of TG/HDL on the extension of atherosclerosis in coronary, carotid and femoral territories in asymptomatic prediabetes or newly diagnosed T2D subjects without history of ASCVD. Thus, TG/HDL may be useful for clinicians to ameliorate the diagnostic and therapeutic strategies in cardiovascular prevention.

Finally, in our study we found a significant association between the atherosclerosis extension and age and HbA1c in line with previous finding by McNeely et al who evaluated coronary atherosclerosis burden in large cohorts of subjects with impaired glucose homeostasis enrolled in the Multi-Ethnic Study of Atherosclerosis.[49]

There are several limitations to our study. First, because of its cross-sectional design, causal relationship and temporality cannot be established between changes in TG/HDL values and CAC, carotid and/or femoral plaque. It would have been of interest to detail the apolipoprotein profiling and the amount of small-dense LDL cholesterol, in order to confirm/exclude the contribution of ApoB-rich lipoproteins in the subclinical atherosclerosis in this population. This analysis is not available. Then, population size was relatively small; however, we were still able to show the independent association of TG/HDL and atherosclerosis extension. Moreover, we did not perform coronary CT angiography to detect non-calcified plaques: in our asymtomatic population this exam was not indicated.[50] Furthermore, the oral glucose tolerance test (OGTT) was not performed, thus it was not possible to better evaluate the impaired glucose tolerance status of enrolled subjects. However, OGTT is less convenient than FPG or HbA1c in clinical practice. Also, in this study, data regarding diet or physical activity have not been taken into considerations. Finally, we were not able to assay insulin plasma levels of study population; further studies are needed to evaluate a possible association between TG/HDL, insulin resistance and atherosclerosis extension.

In conclusion, prediabetes and newly diagnosed T2D subjects with H-TG/HDL exhibited an increased atherosclerosis extension compared to L-TG/HDL subjects. Our data suggest that a simple and reproducible biomarker such as TG/HDL may be useful to identify individuals with a higher cardiovascular risk profile within the large population of prediabetes and T2D subjects.

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## CONFLICT OF INTEREST

E.B. declares having received honoraria from AstraZeneca, AMGEN, Genfit, MSD, Sanofi and Regeneron, Unilever, Danone, Aegerion, Chiesi, Rottapharm-MEDA, Lilly, Ionis-pharmaceuticals, Ackea Therapeutics. A.G. declares having received honoraria from AMGEN, Novartis, Unilever, Sanofi and Regeneron, Ackea Therapeutics. R.S. declares having received honoraria from SANOFI. The other authors have no conflicts of interest to disclose.

## AUTHOR CONTRIBUTIONS

R.S., P.G. and A.G. made substantial contributions to the conception and design, they wrote and drafted the article; moreover, L.D.E., A.D.P. S.P., A.M.R., P.C. and A.G. critically revised the manuscript for important intellectual content; A.R. performed CACs analysis; R.S., P.G., E.B. and A.G. participated in the patient selection and recruitment, in the data collection and interpretation; R.S. performed the statistical analysis. M.A., F.P., E.B. and A.G. finally approved the manuscript to be submitted.

## ETHICAL APPROVAL

This study was permorfed in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

## INFORMED CONSENT

Informed consent was obtained from each participants included in the study.

## ORCID

*Francesco Purrello* https://orcid.org/0000-0002-7023-3649

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