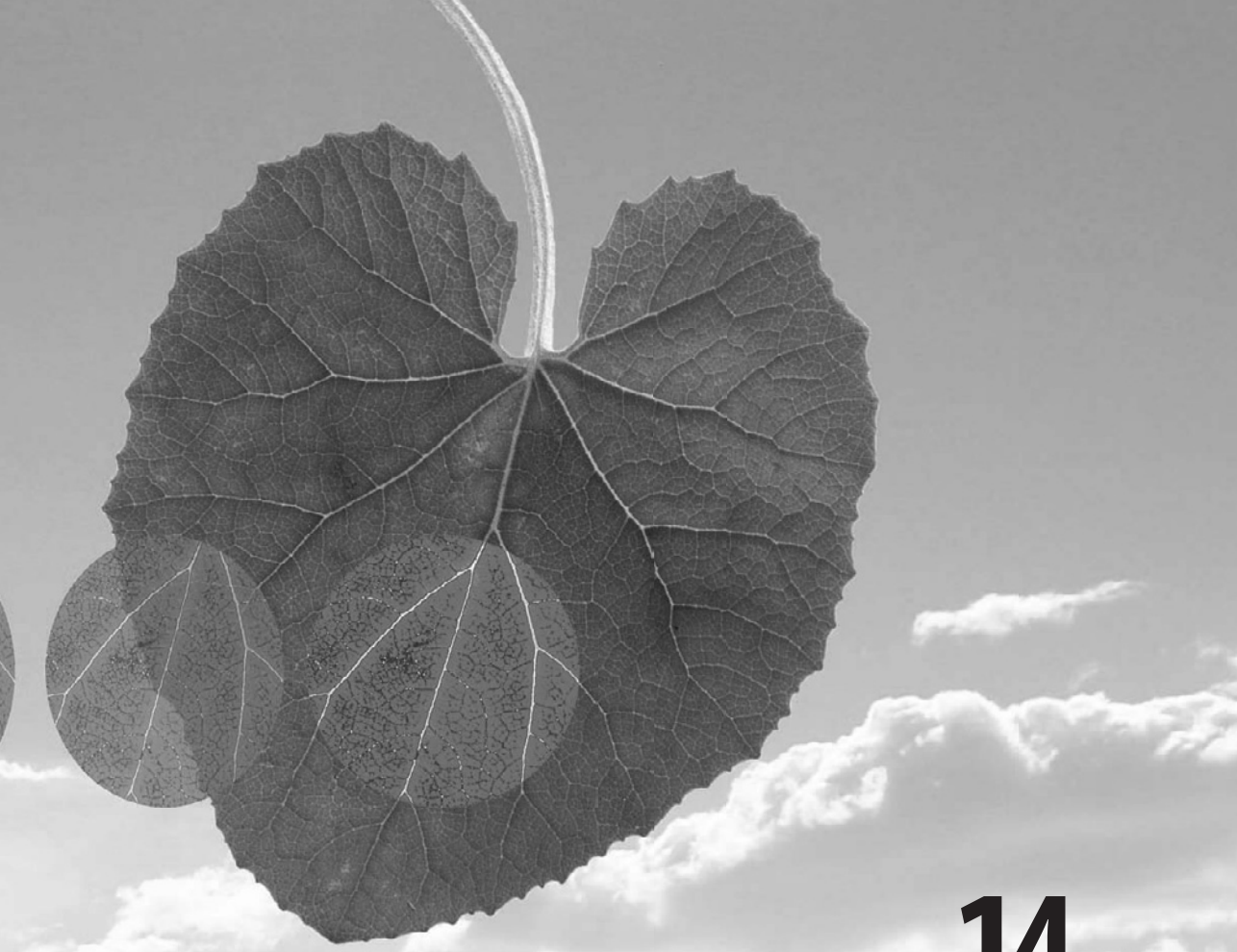

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Usefulness of Hypertriglyceridemic Waist Phenotype in Type 2 Diabetes Mellitus to Predict the Presence of Coronary Artery Disease as Assessed by Computed Tomography Coronary Angiography

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ABSTRACT

The present study tested whether in patients with type 2 diabetes mellitus (DM), the combination of increased waist circumference and elevated plasma triglyceride (TG) levels can predict the presence of coronary artery disease (CAD) as assessed by multidetector computed tomography coronary angiography (CTA). In 202 patients with type 2 DM who were clinically referred for CTA, waist circumference and TG levels were measured. Patients were divided into 4 groups according to waist circumference measurements and TG levels. High waist circumference and TG levels (TG+Waist+, n=61, 31%) indicated the presence of the hypertriglyceridemic waist phenotype. Patients with low levels of both waist circumference and TG (TG-Waist-, n=49, 24%) were considered as the reference group. Physical examination and blood measurements were performed. CTA was used to determine the presence and severity of CAD. Additionally, plaque type was evaluated. Plasma cholesterol levels were significantly increased in the TG+Waist+ group while high density lipoprotein (HDL) cholesterol was significantly lower than in the reference group. There was a significant increase in the presence of any CAD (OR 3.3, confidence interval (CI) 1.31-8.13, $p<0.05$) as well as obstructive (≥50%) CAD (OR 2.9, CI 1.16-7.28, $p<0.05$) in the TG+Waist+ group. In addition, a significantly greater number of non-calcified and mixed plaques was observed. In conclusion, in patients with type 2 DM, the presence of the hypertriglyceridemic waist phenotype translated into a deteriorated blood lipid profile and more extensive CAD on CTA. Accordingly, the hypertriglyceridemic waist phenotype may serve as a practical clinical biomarker to improve risk stratification in patients with type 2 DM.

INTRODUCTION

The aim of the present study was to test whether the hypertriglyceridemic waist phenotype in patients with type 2 diabetes mellitus (DM) can predict the presence of CAD as assessed by multidetector computed tomography coronary angiography (CTA). A second aim was to assess differences in atherosclerotic plaque characteristics in diabetic patients with and without the presence of hypertriglyceridemic waist phenotype, using CTA.

METHODS

All patients were asymptomatic and were referred from a routine outpatient diabetes clinic for the purpose of cardiovascular risk stratification. Patients were diagnosed as having type 2 DM according to the American Diabetes Association criteria.[1] As a result, a total of 202 diabetic patients (120 men and 82 women, with a mean age of 54 ± 11 years) were enrolled in the study population. Exclusion criteria for CTA investigation were: 1) (supra)ventricular arrhythmias, 2) renal insufficiency (glomerular filtration rate < 30 ml/min), 3) known allergy to iodine contrast material, 4) severe claustrophobia, and 5) pregnancy. At physical examination, waist circumference and blood pressure measurements were performed. In addition blood samples were obtained in the morning after a 12-hour fast. TG, LDL cholesterol, HDL cholesterol, apolipoprotein-B and C-reactive protein (CRP) levels were measured.

Patients were divided into 4 groups using threshold values for waist circumference measurements (≤ or > 88 cm for women and ≤ or > 102 cm for men) and TG levels (< or ≥ 1.7 mmol/L for both men and women) as previously described by the National Cholesterol Education Program (NCEP) Adult Treatment panel III (ATP III).[2] Figure 1 illustrates the patient distribution over the 4 groups. Type 2 diabetic patients with a high waist circumference and increased TG levels, signifying the presence of the hypertriglyceridemic waist phenotype, were defined as TG+ Waist+. Diabetic patients with a low waist circumference and low TG levels were considered the reference group, defined as TG- Waist-, to which a CAD odds ratio of 1.0 was designated for comparison purposes.

CTA studies, including calcium scores, were performed using 2 different systems: 64-row CTA (Aquilion 64, Toshiba Medical Systems, Otawara, Japan) and 320-row CTA (Aquilion ONE, Toshiba Medical Systems, Japan) with 64 and 320 simultaneous detector rows, respectively (each 0.5 mm wide). Unless contra-indicated, oral β-blocker medication (metoprolol 50 or 100 mg) was administered to patients with a heart rate ≥ 65

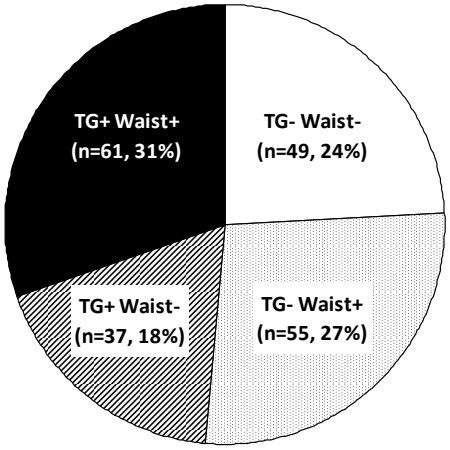

Figure 1. Distribution of patient with type 2 DM over 4 groups according to waist circumference and TG levels. The proportion patients with type 2 DM with the hypertriglyceridemic waist phenotype (TG+ Waist+) is depicted in black and the reference group (TG- Waist-) is depicted in white.

beats/min one hour prior to the investigation.[3] The total amount of non-ionic contrast media (Iomeron 400; Bracco, Milan, Italy) injected into the antecubital vein was 60-100 ml (depending on body weight and scanner type) at a flow rate of 5.0 ml/s or 6.0 ml/s, followed by a saline flush of 25-50 ml. In order to synchronize the arrival of the contrast media, bolus arrival was detected using a real-time bolus tracking technique.[4] All images were acquired during a single inspiratory breath-hold of maximally 12 seconds. For 64-row CTA, a helical-scanning technique was used[5 6] while for 320-row CTA, a volumetric scanning technique was used.[7] The average investigation time for the CT acquisition was approximately 20 minutes.

To examine the relation between hypertriglyceridemic waist and CAD in patients with type 2 DM, all CTA scans were evaluated for the presence of CAD. CTA reconstructions were transferred to a remote workstation with dedicated analysis software (for 64-row CTA reconstructions: Vitrea 2, Vital Images, Minnetonka, MN, USA; for 320-row CTA reconstructions: Vitrea FX 2.0, Vital Images, Minnetonka, MN, USA). Coronary arteries were evaluated using the reconstruction dataset with the least motion artifacts, typically acquired during a mid-diastolic phase. When multiple reconstructions from different cardiac phases were available, the reconstruction with the best image quality was evaluated. CTA scans were evaluated by 2 experienced observers. Discrepancies in the interpretation of CTA examinations were immediately resolved by consensus. Presence of CAD was assessed by scrolling through axial images, followed by visual assessment of curved multiplanar reconstructions in ≥2 orthogonal planes. Coronary segments, vessels and patients were classified as having 1) no CAD, 2) non-significant CAD (luminal nar-

rowing < 50% in diameter), 3) obstructive CAD (≥ 50%luminal narrowing), as previously described.[7] Plaque types were determined by scoring plaque in each diseased coronary segment as non-calcified, calcified or mixed.[8] Calcium score was assessed using dedicated software (Vitrea 2 or Vitrea FX 1.0, Vital Images for 64-row detector and 320-row detector CTA, respectively). An overall Agatston score was registered for each patient.

Statistical analysis was performed using SPSS software (version 16.0, Inc., Chicago, Illinois). Quantitative data were expressed as mean ± standard deviation (SD) and compared between groups using a 2-tailed unpaired Student's t test. Categorical variables were described as numbers and percentages and comparison was performed by chi-square test. Multivariate logistic regression analysis was performed (using backward elimination method) to determine the relationship of waist circumference and TG levels to the presence of CAD and obstructive CAD, correcting for clinical variables (age, gender, obesity, hypertension, smoking and family history of CAD). A p-value < 0.05 was considered statistically significant.

RESULTS

Baseline patient characteristics for the TG+ Waist+ and TG- Waist- groups are shown in Table 1. The TG+ Waist+ group had a significantly higher proportion of women, as well as an increased prevalence of hypertension and obesity as compared to the TG- Waist- group. Furthermore, clinical baseline measurements were performed, as shown in Table 2. Blood pressure measurements as well as all lipid and cholesterol blood measurements were significantly increased in the TG+ Waist+ group, except HDL cholesterol levels, which were significantly lower in the TG+ Waist+ group. In addition, C-reactive protein (CRP) levels of ≥ 3.0 mg/L, indicating an increased inflammatory profile, were present in a significantly larger proportion of TG+ Waist+ patients as compared to the reference group. However, hemoglobin A1c, a marker for glycemic control, was not significantly different between the two groups.

To investigate the relationship between the hypertriglyceridemic waist phenotype in patients with type 2 DM and CAD, CTA was performed. There was a significant increase in the presence of CAD in TG+ Waist+ patients as compared to TG- Waist- patients. In 79% of TG+ Waist+ patients CAD was present on CTA, as compared to 55% of TG- Waist- patients ($p<0.05$). In addition, the presence of obstructive CAD was examined on a patient basis. A significant increase in obstructive CAD in TG+ Waist+ patients as compared to TG- Waist- patients was observed. Obstructive CAD was observed in 43% of TG+ Waist+ patients as compared to 25% of TG- Waist- patients ($p<0.05$).

Table 1. Baseline patient characteristics

	TG- waist- (n=49)	TG+ Waist+ (n=61)
Gender (male/female)	37/12*	26/34*
Age (years)	54 ± 10	55 ± 10
Known Coronary Artery Disease	0	3 (4.9 %)
Previous Myocardial infarction	0	2 (3.3 %)
Previous Coronary Artery Bypass Grafting	0	1 (1.6 %)
Previous Percutaneous Coronary Intervention	0	1 (1.6 %)
Family History of Coronary Artery Disease	21 (43%)	25 (41%)
Hypertension	17 (34.7%)*	44 (72.1%)*
Obesity (body mass index ≥ 30 kg/m^2)	3 (6.1%)*	37 (60.7%)*
Smoking	10 (20%)	31 (21%)
Medication		
Beta-blockers	3 (7%)	4 (7%)
Diuretics	4 (9%)*	14 (25%)*
Statins	21 (49%)	25 (46%)
Calcium-antagonists	3 (7%)	10 (19%)

Data are mean ± SD or n (%). * p<0.05

Table 2. Clinical baseline measurements

	TG- waist- (n=49)	TG+ Waist+ (n=61)	p-value
Waist circumference (cm)	89 ± 7.4	113 ± 13.8	<0.001
Triglycerides			
mmol/L	1.1 ± 0.29	3.0 ± 1.53	<0.001
mg/dl	97 ± 26	266 ± 136	<0.001
Total cholesterol			
mmol/L	4.2 ± 0.87	5.1 ±1.04	<0.001
mg/dl	162 ± 34	197 ± 40	<0.001
Low-density lipoprotein cholesterol			
mmol/L	2.6 ± 0.90	3.1 ± 0.90	<0.05
mg/dl	101 ± 35	120 ± 35	<0.05
High-density lipoprotein cholesterol			
mmol/L	1.5 ± 0.42	1.2 ± 0.45	<0.05
mg/dl	58 ± 16	46 ± 17	<0.05
Apolipoprotein-B (g/L)	0.73 ± 0.29	0.94 ± 0.27	<0.001
Hemoglobin A1c (%)	7.4 ± 1.3	7.8 ± 1.8	ns
C-reactive protein level ≥ 3.0 mg/L	21 (35%)	40 (80%)	<0.001
Systolic blood pressure (mmHg)	131 ± 17	144 ± 17	<0.001
Diastolic blood pressure (mmHg)	78 ± 8	88 ± 10	<0.001

Data are mean ± SD or n (%)

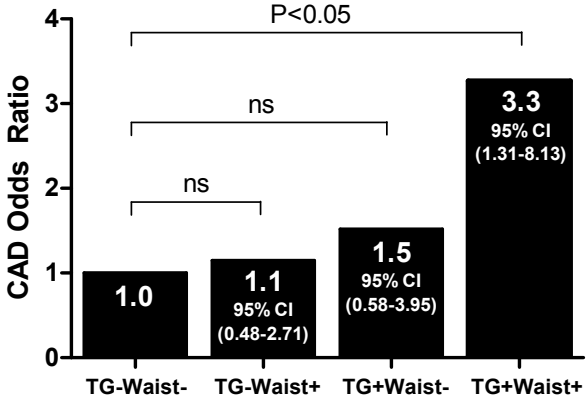

Figure 2. Odds ratio for finding CAD as determined by CTA in patients classified on the basis of waist circumference and fasting TG (corrected for age, gender, obesity, hypertension, smoking and family history of CAD)

Figures 2 and 3 show the results of multivariate logistic regression analysis performed to determine the independent relationship between waist circumference and TG versus the presence of CAD and obstructive CAD, respectively. The odds ratio of finding any CAD and obstructive CAD were significantly increased among diabetic patients with the hypertriglyceridemic waist phenotype as compared to diabetic patients without this phenotype. The CTA characteristics of both groups were compared on a coronary segment and vessel basis (Table 3). TG+ Waist+ patients had a significantly larger number of narrowed coronary segments and vessels as compared to TG- Waist- patients. In addition, the prevalence of 3-vessel coronary disease was significantly higher in the TG+ Waist+ group. Furthermore, TG+ Waist+ patients had a significantly larger number of

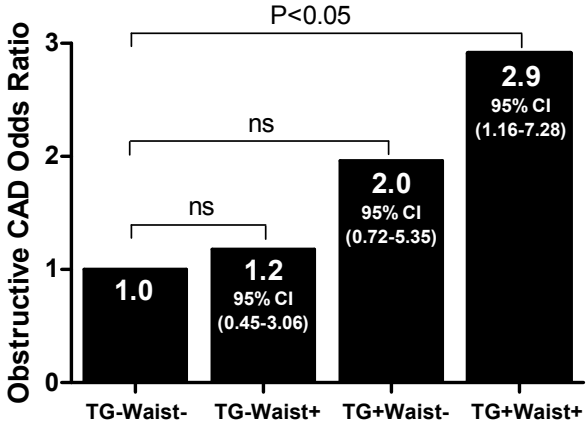

Figure 3. Odds ratio for finding obstructive CAD as determined by CTA in patients classified on the basis of waist circumference and fasting TG (corrected for age, gender, obesity, hypertension, smoking and family history of CAD)

Table 3. Computed tomography coronary angiography characteristics in patients with the hypertriglyceridemic waist phenotype (TG+ Waist+) and the reference group (TG- Waist-)

	TG- waist- (n=49)	TG+ Waist+ (n=61)	p-value
Calcium score (Agatston)	289 ± 826	424 ± 1238	ns
Average number of narrowed coronary vessels	1.27 ± 1.29	1.92 ± 1.22	<0.05
Average number of obstructed coronary vessels	0.37 ± 0.73	0.66 ± 0.93	<0.05
Average number of narrowed coronary segments	2.96 ± 3.87	4.82 ± 4.15	<0.05
Average number of obstructed coronary segments	0.71 ± 1.99	0.90 ± 1.62	ns
3-vessel coronary disease	13 (27%)	29 (48%)	<0.05
Obstructive 3-vessel coronary disease	1 (2%)	5 (8%)	ns
Average number of non-calcified plaque	0.82 ± 1.55	1.52 ± 1.90	<0.05
Average number of mixed plaque	1.00 ± 1.81	2.07 ± 2.90	<0.05
Average number of calcified plaque	1.14 ± 2.60	1.23 ± 2.41	ns

Data are mean ± SD or n (%).

obstructed coronary vessels. Although an increased percentage of obstructive 3-vessel coronary disease was found in the TG+ Waist+ group as compared to the TG- Waist- group, the difference was not significant. Additionally, TG+ Waist+ patients had a significantly higher non-calcified and mixed plaque burden as compared to the reference group. However, neither the number of calcified plaques nor the Agatston calcium score were significantly different between the two groups (Table 3).

Figure 4 shows a normal CTA scan of a patient with type 2 DM without hypertriglyceridemic waist. Figure 5 depicts the CTA of a patient with type 2 DM in the presence of the hypertriglyceridemic waist phenotype, revealing 3-vessel coronary disease with non-calcified and calcified plaque components.

DISCUSSION

In the present study it was shown that the hypertriglyceridemic waist phenotype was significantly associated with a deteriorated blood lipid profile (characterized by increased triglycerides, total cholesterol and LDL cholesterol levels and decreased HDL cholesterol levels), an increased inflammatory profile as well as with the presence of CAD on CTA in patient with type 2 DM. Therefore, the hypertriglyceridemic waist phenotype translated into an increased likelihood of CAD on CTA and may serve as a practical clinical biomarker to improve risk stratification in patients with type 2 DM.

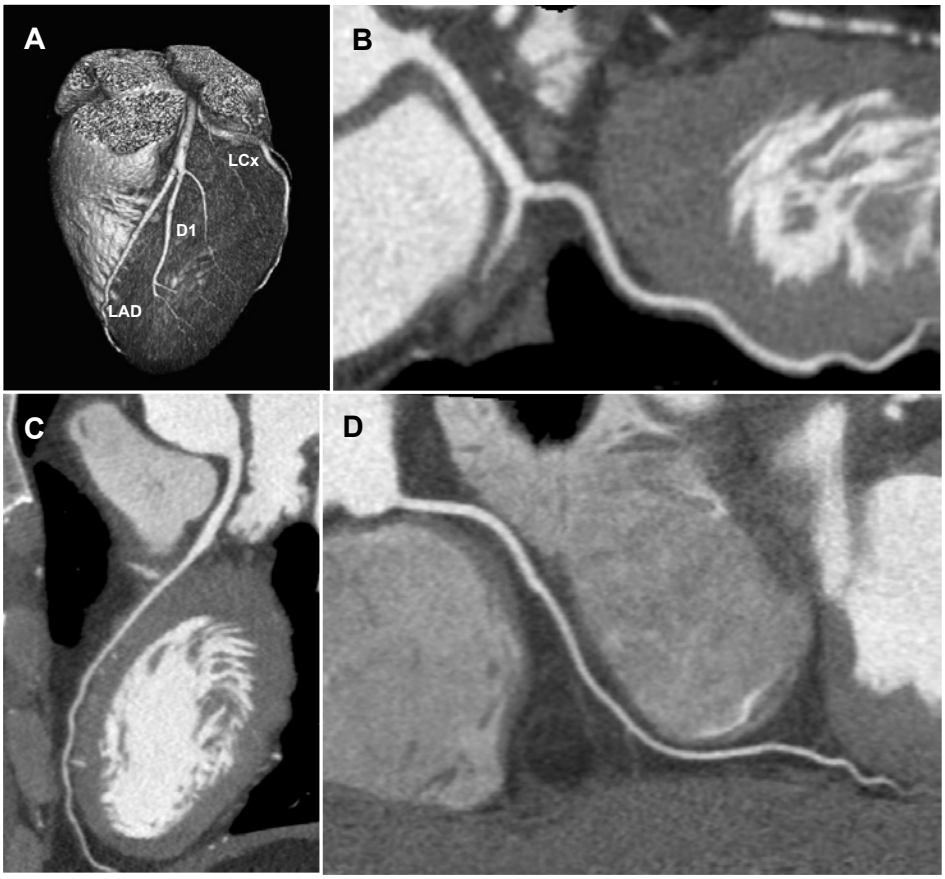

Figure 4. CTA of a 42 year-old man with type 2 DM without the hypertriglyceridemic waist phenotype showing normal coronary arteries. (A) Three dimensional volume rendered reconstruction of the heart giving an overview of the LAD, D1 and LCx. Multiplanar reconstruction of the LCx and OM (B) LAD (C) and RCA (D) showing normal coronary arteries.

Notably, this is the first study correlating hypertriglyceridemic waist phenotype in type 2 diabetic patients to coronary plaque type using CTA. The present results showed an increase in non-calcified and mixed plaque burden in type 2 diabetic patients with the hypertriglyceridemic waist phenotype. These plaque characteristics have been previously associated with unstable plaque types[9 10] as non-calcified and mixed plaque types possibly represent more active and vulnerable stages in coronary plaque development. These data suggest that the presence of the hypertriglyceridemic waist phenotype, translates into more extensive and potentially more active CAD.

Lemieux and colleagues first suggested that the simultaneous interpretation of waist circumference and fasting TG concentration may be a comprehensive and cost-effective

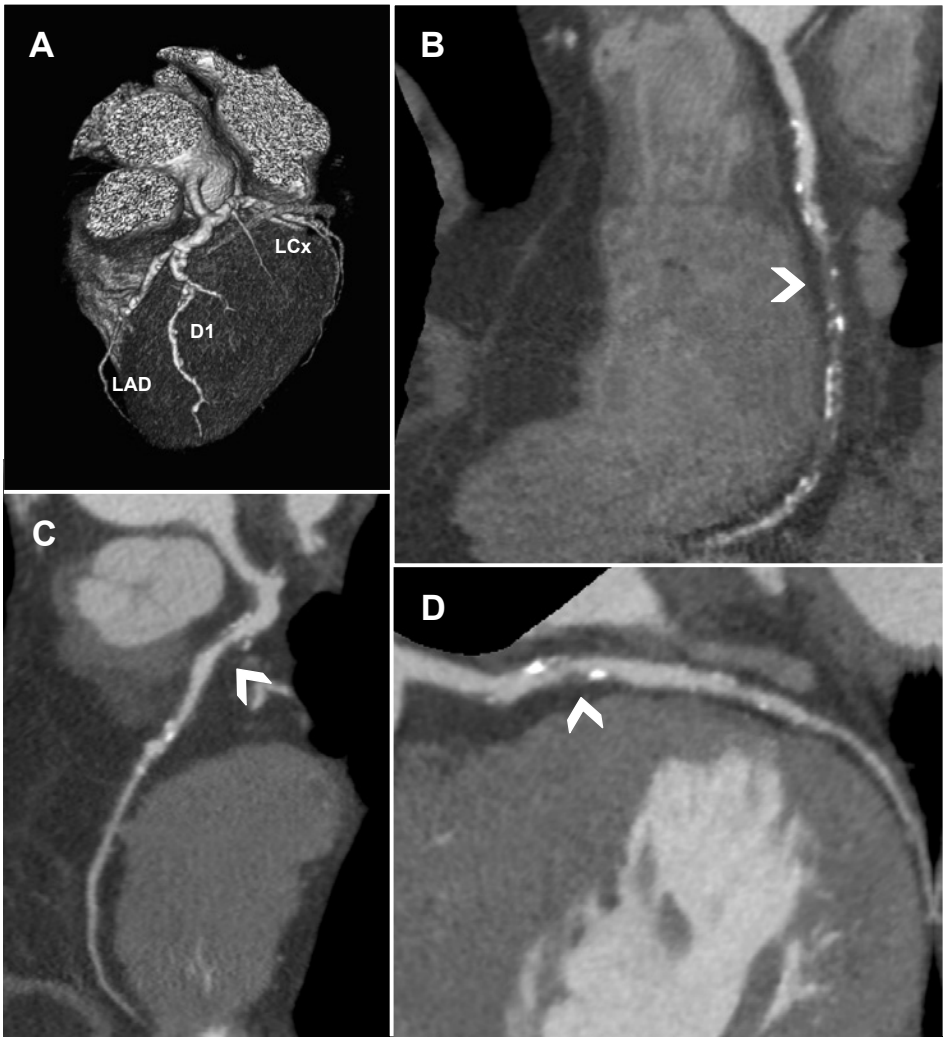

Figure 5. CTA of a 69 year-old man with type 2 DM and the hypertriglyceridemic waist phenotype revealing 3-vessel coronary disease. (A) Three dimensional volume rendered reconstruction of the heart giving an overview of the LAD, D1 and LCx. (B) Multiplanar reconstruction of the RCA revealing a total occlusion with calcified and non-calcified plaque (arrow). (C) Multiplanar reconstruction revealing a severe lesion in the proximal LAD (arrow). (D) Multiplanar reconstruction showing a severe lesion in the proximal LCx (arrow) with non-calcified and calcified plaque components.

screening method for the identification of individuals characterized by a cluster of atherogenic risk factors.[11] In the Quebec Cardiovascular Study, the presence of the hypertriglyceridemic waist genotype was associated with the presence of the 'atherogenic metabolic triad' defined as increased insulin, small dense LDL particles and apolipoprotein-B.[11] In this setting, abdominal obesity is considered a correlate of increased insulin and apolipoprotein-B concentration.[11] while increased fasting TG concentrations

are considered a crude measure for small, dense LDL concentration.[12 13] Importantly, angiographically detected CAD was significantly more likely in individuals with the hypertriglyceridemic waist phenotype as compared with those without this phenotype (OR 3.6, $p<0.03$).[11] These data indicate that, in the general population, testing for the presence of the hypertriglyceridemic waist phenotype may indeed effectively identify individuals with a constellation of atherogenic risk factors.

Patient with type 2 have a significantly increased risk of CAD.[14 15] Accordingly, screening for CAD in asymptomatic patients with type 2 DM may reduce morbidity and mortality. Although screening for CAD in patients with type 2 DM in the presence of at least two additional traditional cardiovascular risk factors has previously been endorsed by the American Diabetes Association,[16] evidence for the effectiveness of routine screening of patients with type 2 DM is lacking.[17 18] Indeed, in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study routine screening of patients with type 2 DM had no effect on primary or secondary cardiac event rates.[19] These results suggest that the routine screening of all patients with type 2 DM is currently not justified. However, it is important to note that screening of selective sub-groups may have beneficial effect and outcome. In this setting, the hypertriglyceridemic waist phenotype may potentially serve as a practical biomarker for CAD to enhance risk stratification in this patient population.

Few studies are currently available concerning the value of the hypertriglyceridemic waist phenotype as a screening method to predict the risk of CAD in patients with type 2 DM. St-Pierre and colleagues previously showed that the hypertriglyceridemic waist phenotype indeed enabled the identification of individuals at increased risk of CAD in patients with type 2 DM or glucose intolerance.[20] Similarly, Blackburn et al showed that, in 250 women with type 2 DM, 68% of individuals with CAD had hypertriglyceridemic waist, whereas none of the individuals without CAD had this phenotype.[21] The present study provides further evidence for a significant contribution of the hypertriglyceridemic waist phenotype in the prediction of CAD in patients with type 2 DM. The present results suggest that the hypertriglyceridemic waist phenotype may potentially translate into a simple, low-cost biomarker for CAD, enabling the identification of patients who are at increased cardiovascular risk.

Several aspects of this study merit further consideration. First, the present findings were not confirmed on invasive coronary angiography, which is considered the gold standard for the evaluation of degree of coronary stenosis. In contrast to invasive coronary angiography, CTA not only allows the evaluation of degree of stenosis with good accuracy, but also allows the visualization of atherosclerosis. As a result, this technique is particularly valuable for the early identification of CAD. Furthermore, in the current

study, threshold values for waist circumference and serum TG were used as previously proposed by the NCEP ATPIII guidelines. Other threshold values have been reported[21 22] and threshold values may differ between populations.

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