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Triglycerides and carotid intima-media thickness in ischemic stroke patients

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ABSTRACT

Background: Common carotid artery intima-media thickness (CCA-IMT) is an established marker for atherosclerosis. The role of triglycerides in CCA-IMT remains controversial. We sought to determine if elevated fasting and post-challenge triglycerides are associated with CCA-IMT.
Methods: All acute ischemic stroke patients who participated in the Berlin "Cream & Sugar" study in the Charité Virchow and Charité Mitte Campuses between January 2009 and January 2014 and underwent carotid artery ultrasound studies were eligible for inclusion. A combined oral glucose and triglyceride tolerance test was performed 3–7 days after first ever ischemic stroke. Patients were classified according to triglyceride metabolism—namely, (1) patients reaching a maximum triglyceride levels 3 h post-challenge ("fast metabolizers," n = 37), (2) patients with increasing triglycerides 4 (medium metabolizers, n = 64), and (3) 5 h post-challenge ("slow metabolizers," n = 44; 13 missing).
Results: We included 158 patients (34% female; mean age 63 years, SD 14). Absolute non-fasting triglyceride levels were positively associated with CCA-IMT. A final multiple regression model revealed that older age, more severe strokes, and higher levels of fasting triglycerides were significantly and independently associated with higher mean CCA-IMT. Older age, higher waist-to-hip ratio, and higher levels of thyroid-stimulating hormone were independently associated with higher maximum CCA-IMT.
Conclusion: Fasting triglycerides but not post-challenge triglycerides associate with CCA-IMT. An oral fat challenge may not add information on atherosclerotic status in ischemic stroke patients.
Clinical Trial Registration Information: The Berlin "Cream & Sugar" study is registered with EudraCT (2009-010356-97) and clinicaltrials.gov (NCT 01378468).

1. Introduction

Common carotid artery intima-media thickness (CCA-IMT) is an established marker of atherosclerosis [1] and ischemic stroke risk [2,3]. Though impaired postprandial triglyceride clearance has long been thought to contribute to coronary atherosclerosis [4–6], surprisingly few studies have directly investigated the relationship between CCA-IMT and triglyceride metabolism [7–11].

Results from studies that have assessed the relationship between absolute triglycerides and CCA-IMT have been mixed. Some studies have found positive relationships to exist between CCA-IMT and postprandial [7–10] or fasting triglycerides [12–14]. Others have found no association to exist between CCA-IMT and fasting [15–17] or post-challenge triglycerides [11].

To date, most trials assessing triglyceride reduction strategies in patients with high cardiovascular risk profiles have used fasting levels when screening patients for inclusion [18–20]. However, evidence from large epidemiological studies shows that non-fasting triglycerides are likely more indicative of cardiovascular risk [21,22]. Therefore, it is possible that patient samples in trials with triglyceride lowering endpoints have not been optimally

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selected, which has led to the suggestion that implementing a standardized oral triglyceride tolerance test may be beneficial when screening patients for cardiovascular/stroke risk [23].

We sought to determine if fasting and post-challenge triglycerides associate with CCA-IMT in ischemic stroke patients.

2. Methods

2.1. Participants

The Berlin "Cream & Sugar" study (NCT 01378468) is an ongoing prospective cohort study with the purpose of determining if post-challenge triglycerides associate with recurrent stroke. Detailed methods have been presented elsewhere [24]. Briefly, we screened all suspected stroke patients within 3–7 days of symptom onset who were over 18 years of age and were admitted to one of three university campus hospitals in Berlin (Charité Mitte, Virchow, and Benjamin Franklin campuses). First ever acute ischemic stroke patients who were capable of participating in an oral triglyceride and glucose tolerance test were eligible for inclusion.

Ischemic stroke was defined as a focal neurological deficit lasting for at least 24 h with no signs of hemorrhage on cerebral imaging. All strokes were verified radiologically using diffusion-weighted images. First ever ischemic stroke was defined based on relevant medical history disregarding potential "silent" strokes on cerebral imaging that may have occurred prior to study enrollment. Stroke severity was assessed on hospital admission and on the day of testing (3–7 days after symptom onset) using the National Institute of Health Stroke Scale (NIHSS). Stroke was categorized according to a mechanism-based classification scheme (Trial of ORG 10172 in Acute Stroke Treatment, or TOAST) [25]. All patients provided informed consent and the study was approved by the local ethics committee.

2.2. Blood samples

Baseline data and venous blood samples were collected after participants had provided informed consent and fasted overnight for ≥10 h. Fasting blood samples were drawn at 8 AM, followed by a combined oral triglyceride and glucose tolerance test (oTTT/oGTT). The oTTT consisted of ingesting 250 mL of 32% fat cream within 30 min and took place immediately after the 8 AM fasting blood draw. At 11 AM, all patients provided venous blood samples and if no known diabetes was present, patients then immediately drank 75 g of Dextrose mixed in 250 mL of water (oral glucose tolerance test). Further venous blood samples were collected at 12 PM and 1 PM. Triglyceride and cholesterol concentrations were determined in freshly drawn venous blood samples enzymatically using a Cobas 6000 analyzer (Roche/Hitachi).

2.3. Common carotid artery intima-media thickness

In this Berlin "Cream & Sugar" substudy, we searched our clinical database for CCA ultrasound images archived in the Virchow and Mitte Campuses. CCA ultrasounds were performed by our clinical neurology sonography lab using B-mode ultrasonography with the Acuson X300 (Siemens Healthcare, Germany; Virchow) and the Toshiba PowerVision 6000 (Toshiba, Japan; Mitte) 7.5 MHz high-resolution annular array scanner. All patients were evaluated in the supine position with the head turned 45° to the contralateral side of the artery being examined. One rater (KSL) evaluated CCA-IMT using the ImageJ software package (National Institute of Health, Baltimore, Md) [26]. Both the right and left CCA were evaluated. All measurements were performed in accordance with the "Mannheim carotid intima-media thickness consensus" (2004–2006) [27]. The region of interest (ROI) for CCA-IMT assessment was defined as at least a 10 mm plaque-free portion of the CCA far-wall at least 10 mm before the bifurcation. As illustrated in Fig. 1, to determine CCA-IMT, we measured the distance between the first hyperechogenic line (border between vessel lumen and intima, yellow line in Fig. 1) and the second hyperechogenic line (media–adventitia border, pink line in Fig. 1) of the CCA far wall. To assess associations between various patient characteristics and CCA-IMT, we used aggregated values per patient using two different aggregation methods: (1) maximum recorded CCA-IMT value (i.e. if the right CCA-IMT was larger than the left CCA-IMT, the right CCA-IMT value was used) and (2) mean CCA-IMT value of the right and left CCA. The number of heart cycles and time-point within the heart cycle was not taken into consideration.

2.4. Definitions and calculations

Diabetes was defined as current use of anti-diabetic medication or serum glycosylated hemoglobin (HbA1C) of >6.5%. Hypertension was defined as current antihypertensive medication use. Glomerular filtration rate was estimated using the Modification of Diet and Renal Diseases formula [28]. Adjusted triglyceride levels for 3, 4, and 5 h post-challenge (aTG3, aTG4, aTG5) were defined here as the triglyceride values at 3, 4, and 5 h post-challenge minus the fasting triglyceride value (TG0) respectively (e.g. aTG3 = TG3 − TG0). Peak triglyceride response refers to the maximum triglyceride level obtained minus TG0. Triglyceride area under the curve (AUC) and

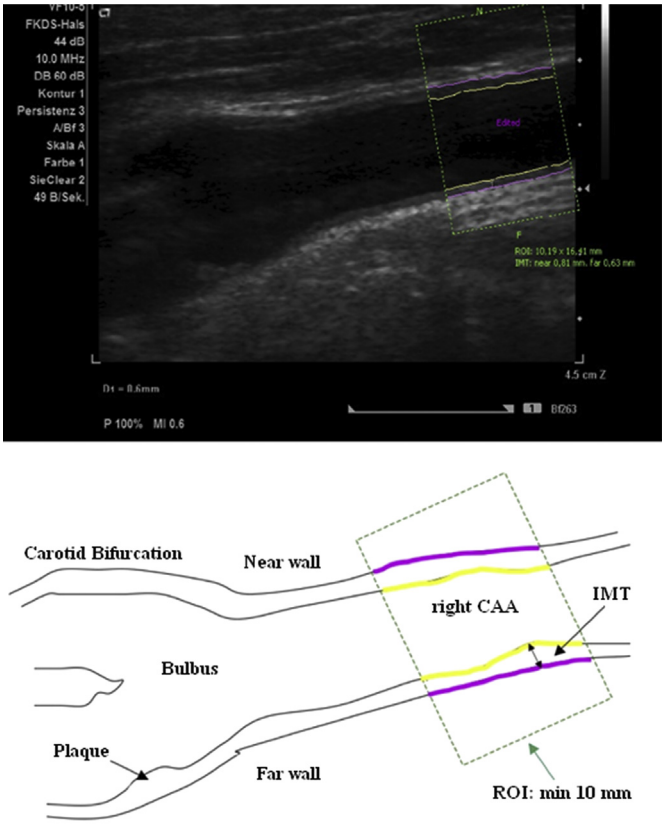

Fig. 1. Ultrasound and schematic representation of the common carotid artery. In the schematic representation, the yellow line represents the luminal intima and the pink line represents the adventitia. The space between the adventitia and intima on the far wall of the CCA is defined here as the intima-media thickness. CCA indicates common carotid artery; IMT, intima-media thickness; ROI, region of interest; min, minimum; mm, millimeters. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)