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## Lab Note

### Progression of carotid artery disease could stratify a risk of coronary artery disease patients with type 2 diabetes

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Diabetes is a common risk factor associated with coronary artery disease (CAD). Importantly, hereditary CAD cannot be discounted which accounts for about one quarter of the cases [1]. Carotid artery disease (CARD) shares the same risk factors as CAD [2]. C-reactive protein and fibrinogen also contribute to the progression of atherosclerotic plaques, CAD and to the clinical outcome of patients with CAD and type-2 diabetes (T2D) [3]. Early detection and intervention of CAD in T2D patients is therefore important in order to improve better treatment and survival of high risk patients, although recommendation is not high [4]. Despite many screening tests, there are a lack of studies that define factors for progression of coexistent CAD and T2D [5]. Herein, we assessed a potential value of carotid ultrasound in prognosis of patients with CAD and T2D.

In this cohort study, 264 patients with CAD and T2D were included. They were consequently selected from CAD registry from the University Clinic of Cardiology, Skopje, Republic of Northern Macedonia. T2D was defined by criteria of the International Diabetes Federation. CAD was defined as stable angina, or previous myocardial infarction, detected with coronary angiography. The study population had mean glycemia  $8.5 \pm 2.4$  mmol/l, calculated Gensini score  $82.3 \pm 18.4$  and creatinin value of  $102.5 \pm 12.8$  mmol/l. Basic characteristics of all patients are shown in **Table 1**. 94.1% of patients were on anti-aggregation therapy and 85.9% on statins. Oral anti-diabetics were prescribed in 35.9 % (of which 39.4 % were on monotherapy with metformin), and insulin therapy in 58.2 % of the patients. Of all patients, 222 (84.1%) were on beta blockers and 219 (82.9%) were on ACE (angiotensin converting enzyme) inhibitors or ARB (angiotensin receptor blocators). Study population was followed up for  $31.5 \pm 10.4$  months. Carotid ultrasound was used for detection of progression of CARD. And CAD in patients was confirmed with angiography. The study was conducted in accordance with the Helsinki declaration and was approved by the human ethics of the medical faculty Skopje. Carotid intima-media thickness (CIMT) was measured by B-mode ultrasound using a linear transducer (7.5-10 MHz) and was performed by experienced sonographers. CIMT is presented as a mean value of two measurements from both sides of the common carotid arteries. CIMT is defined as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line on the scans. Plaque was defined as a localized thickening lesion (1.5 mm). Carotid stenosis greater than 60% was considered significant in accordance to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria for carotid stenosis. In each longitudinal projection, the site with the greatest thickness (including plaques) was detected along the vessel from the common carotid artery to the internal carotid artery. Inter-observer variability was up to 5%.

Patients were followed up in the outpatient clinic after phone interview for total cardiovascular events (stroke, new angina, myocardial infarction). New angina was defined as new typical onset of symptoms in previously stable patients as proposed by the European Society of Cardiology (ESC) Guidelines 2013; stroke by the World Health Organization Monica' criteria, and myocardial infarction by ESC guidelines 2017.

Cohort follow-up showed that progression of CIMT was present in 86.8% of patients, progression of carotid stenosis in 17.8% and occurrence of plaques in 41.8% of these patients. In addition, the mean CIMT was 0.9176 mm and the maximal CIMT was 1.1212 mm, and the maximal value of CIMT changed by 0.07 mm annually. New cardiovascular events were registered in 145 patients with incidence of 0.55 events per patient. The independent indicators of future cardiovascular events are presented in **Table 2**. The indicators being a change from the mean of IMT for occurrence of new angina [odds ratio (OR) 1.25, 95%; confidence interval (CI) 0.94-1.67; Gensini score > 70 (OR 1.91, 95% CI 0.99-3.9)]. The progression of CIMT after being subjected to multivariate analysis did not show any significance regarding cardiovascular prognosis. This parameter has been shown to be a strong predictor for total cardiovascular events with OR 13.5 (95% CI 1.68-108.40).

Carotid ultrasound is commonly used to measure CIMT and atherosclerotic plaques. However, the relationship to cardiovascular events is still controversial. In a systematic review, it was noted that for each change in CIMT of 0.1 mm, the risk of further coronary or cerebrovascular occurrence was 10-30% higher compared to controls. In addition, a change of CIMT in patients with CAD of 0.03 mm in 1 year has a high risk rate of 2.2 for future coronary events. The use of mean maximum CIMT rather than mean common CIMT is the preferred factor used to determine the efficacy of drug interventions in carotid artery atherosclerosis. Drugs such as statins or anti-hypertensives, aim at achieving stop of progression of CIMT and consequently it is expected that these would reflect on the rate of cardiovascular risk. Over 80% of our study population were taking anti-hypertensives or statins. A proven separate role of CIMT for prognosis of T2D population with CAD is only obtained within a certain period of time. However, studies completed until now, show only the progression of coronary atherosclerosis in relation to the occurrence of events in the general population and in those with T2D [6]. We noted an independent relationship between new angina and severity of CAD measured by Gensini score. Carotid artery disease and the change of CIMT, for a certain period of time, is preconditioned with the very same risk factors as those of CAD. It may explain the multipurpose prognostic role of CIMT with new coronary and cardiovascular events. On the other hand, the progression of carotid plaques have greater dynamics, when compared to the progression of CIMT. Recent studies have shown that the combination of calcification length and plaque surface irregularity has additional value beyond the traditional risk classification towards coronary events [2, 3, 7]. However, there is still debate whether CIMT and its progression could be a surrogate marker for future events in patients with T2D. The reason for this is that the diabetic population is defined as high risk or very high risk if artery disease is presented. CARD was presented as an increase in CIMT, and presence of carotid plaques was an independent predictor for 10 year coronary and stroke risk in T2D patients without known CAD [5]. As a result, the obtained risk factors can be suggested as surrogate markers when it comes to defining the process of progress of atherosclerosis with T2D and its connection with clinical outcome.

Atherosclerotic plaque detection by carotid artery scanning have been defined as risk modifiers for individual risk stratification according to the European guidelines for cardiovascular prevention. The question is still open regarding the patient cohort with CAD and/or T2D. Atherosclerosis is a common feature for coronary and cerebrovascular disease. Hence, in this high risk population there is a connection between CAD and CARD.

However, there are studies which contradict this relationship. Indeed, in 120 patients with stroke, there was no connection between CARD scanned by CT and outcome of future coronary events [8]. In the MESA study [9], carotid plaques scanned by ultrasound imaging were related to progression of CAD. Other studies (ARIC, CAPS) showed tight correlation between CIMT and cardiovascular events (OR 1.2 to 1.3 for stroke and myocardial infarction) [9]. Thus, carotid plaques may be a more sensitive marker than CIMT for predicting risk of CAD [10]. Corelation between progression of carotid artery stenosis and cerebrovascular disease, has been previously reported [5]. In a meta analysis study a link was reported between CIMT progression and cardiovascular events in the general population [11]. According to this study, progression of the CARD appears to be much more indicative for future cerebrovascular events in patients with T2D. Our study, shows that the occurrence of new carotid plaques is a strong indicator for the occurrence of all the cardiovascular events, included stroke, myocardial infarction and new angina. CIMT progression has been defined as a modest predictor for new angina. This study is limited in that it did not include many participants, which were non-randomly selected. Other limitations to the current study is the point for follow up: new angina, without diagnostic evidence for new ischemia, and information for new coronary revascularization. The advantages of our study is that it defines progression of CARD in predicting outcome due to a coronary and cardiovascular events in patients with very high risk i.e those with T2D and CAD.

The current study determined the factors which indicate the progression of atherosclerosis in a population cohort with T2D. Clinical implications of our study comes from defining progression of CARD to predict outcome due to coronary and cardiovascular events in a population cohort with T2D. In this predictive model for patients with T2D and CAD, carotid ultrasound has been shown to be of incremental value.

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