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Risk factors for the progression of carotid intima-media thickness over a 16-year follow-up period: The Malmö Diet and Cancer Study

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ABSTRACT

Objective: To evaluate the progression of carotid intima-media thickness (IMT) in the common carotid artery (CCA) and the bifurcation over a mean follow-up of 16 years in relation to cardiovascular risk factors.

Methods: The study population included 3426 middle-aged Swedish men and women participating in the 1991–1994 (baseline) and the 2007–2012 (re-examination) investigation of the cardiovascular cohort of the Malmö Diet and Cancer Study (MDCS).

Results: There were differences in risk factor patterns in arterial segments in that diabetes and male sex were associated with the progression of IMT in the bifurcation, but not in the CCA, and high-density lipoprotein cholesterol (HDL) was associated with the progression of IMT in the CCA, but not in the bifurcation. Favourable changes in systolic blood pressure (SBP), low-density lipoprotein cholesterol (LDL) and HDL during follow-up decreased the IMT progression rate in the CCA. There was a cumulative relationship between traditional cardiovascular risk factors (i.e., regular smoking, LDL/HDL-ratio $\geq$ 3, hypertension) and IMT progression rates. The odds ratio (OR) of high IMT CCA progression rate (>75th percentile) was 1.0 (reference), 1.4 (95% CI: 1.1, 1.7), 1.7 (95% CI: 1.3, 2.2) and 2.1 (95% CI: 1.4, 3.1), respectively, for individuals with none, one, two, and three risk factors.

Conclusion: There were differences in the associations between risk factors and progression rate in different arterial segments. Favourable changes in SBP and lipids during the follow-up period were associated with reduced IMT progression rates in the CCA.

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1. Introduction

The atherosclerotic disease process is known to begin in childhood [1]. It develops during the life-course with the onset of cardiovascular symptoms usually in late middle age. The long "silent" preclinical phase of the process, allows intervention before any major complications, such as harm to the heart or brain, have occurred.

Prevention of cardiovascular disease has focused primarily on strategies directed towards risk factors known to be related to clinical events. However, in order to understand which factors play a role in the earlier and later stages of atherosclerotic disease, it is important to differentiate risk factors associated with the progression of atherosclerosis from those associated with plaque rupture or thrombus formation. In recent years high-resolution B-mode ultrasonography has been shown in large populations to be a valid non-invasive method of monitoring atherosclerotic changes such as progression of intima-media thickness (IMT) and increased plaque burden in the carotid arteries. The value of carotid IMT as a surrogate end-point in intervention or observational studies as an alternative to cardiovascular disease (CVD) or death is strengthened by its associations with risk factors [2–4] and coronary or cerebrovascular events [5–15]. Recent studies, however, have shown only small improvements in the risk prediction of cardiovascular

Abbreviations: ARIC, atherosclerosis risk in communities; BCAPS, the beta-blocker cholesterol-lowering asymptomatic plaque study; BMI, body mass index; CCA, common carotid artery; CRP, C-reactive protein; CVD, cardiovascular disease; HDL, high-density lipoprotein cholesterol; IMT, intima-media thickness; LDL, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

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events over the Framingham Risk Score [16,17]. Furthermore, progression of carotid IMT has been shown to be associated with increased risk of cardiovascular events [18,19], although some studies failed to show an association [20].

Since atherosclerosis progresses across decades, single measurements of cardiovascular risk factors at the time of measurement of carotid atherosclerosis, do not capture the impact of past exposure to risk factors. During recent years longitudinal studies on the association between risk factors and progression of carotid IMT have evolved [21–30]. Most studies, however, do not separate such associations between various segments of the carotid arteries, but rather use composite measures of IMT even though cross–sectional associations with risk factors have been shown to differ across various segments of the carotid wall [31–34]. Few studies have investigated the importance of change in risk factor patterns at re-examination after a long follow-up period.

The objective of the present study was to investigate the long–term associations between baseline levels of traditional risk factors in the progression of IMT in the common carotid artery (CCA) and in the bifurcation. In the analyses, we also investigated the additive impact of various traditional cardiovascular risk factors on IMT progression rates and specifically studied the importance of changes in risk factor patterns on the carotid IMT progression rate.

2. Methods

2.1. Study population

The study population comprised men and women who participated in the 1991–1994 (baseline) and the 2007–2012 (re-examination) investigation of the cardiovascular cohort of the Malmö Diet and Cancer Study (MDCS) [35,36]. All participants in the baseline study (N = 6103) who were alive and had not emigrated from Sweden (N = 4924) were invited to the re-examination, including carotid ultrasound, from May 2007 to January 2012. A total of 3734 subjects attended the follow-up investigation (76% of the eligible population; Supplemental Fig. A). After the exclusion of 52 subjects with missing common carotid ultrasound data, 204 subjects with missing laboratory data, and 52 subjects with prevalent CVD, 1349 men and 2077 women were included in the present study. Subjects were considered to have CVD if they had been treated for myocardial infarction or stroke according to the national and regional myocardial infarction or stroke register [37,38]. All participants gave written informed consent. The Ethics Committee at Lund University approved the study (LU 51-90 and LU 532–2006).

2.2. Baseline examination

Risk factors were estimated on the basis of laboratory tests, physical examination, and a questionnaire administered at the baseline visit. The self-administered questionnaire gathered data about medical history, medical treatment, and smoking habits. Details of assessment procedures have been previously reported [39]. Regular smoking was assessed by questionnaire as the answer “Yes, I smoke regularly” to the question: ”Do you smoke?” Supine SBP was taken after 10 min of supine rest. Blood glucose, total cholesterol and high-density lipoprotein cholesterol (HDL) were measured according to standard procedures at the Department of Clinical Chemistry, University Hospital Malmö. Low-density lipoprotein cholesterol (LDL) was calculated using Friedewald's formula. Diabetes mellitus was identified through a self-reported physician's diagnosis of diabetes, use of anti-diabetic medications or a fasting blood glucose level ≥6.1 mmol/L. Fasting plasma samples were collected at the baseline examination, frozen and stored at −80 °C. High-sensitive C-reactive protein (Hs-CPR) was analysed from frozen samples using the Tina-quant® CRP latex high sensitivity assay (Roche Diagnostics, Basel, Switzerland) on an ADVIA® 1650 Chemistry System (Bayer Healthcare, NY, USA). Study samples were analysed as discrete samples and results were read in 6-s intervals for 1 min following incubation for 5 min. The mean value of these measurements was the result reported.

2.3. Follow-up examination

Similar to the baseline investigation, risk factors at follow-up examinations were estimated on the basis of laboratory tests, physical examination, and a questionnaire. Regular smoking was assessed by questionnaire as the answer “Yes, I smoke regularly” to the question: ”Do you smoke?” At the re-examination each subject was seen by a nurse for measurement of height, weight and blood pressure. Fasting blood was drawn for analysis of lipids and glucose and aliquots were stored at minus 80°. Blood pressure was measured after 10 min rest in supine position. Plasma glucose was measured using Hemocue (Hemocue, Ängelholm, Sweden). Total and HDL-cholesterol were measured using standard procedures at the Department of Clinical Chemistry, University Hospital Malmö, Sweden. LDL-cholesterol was calculated using Friedewald's formula.

2.4. Carotid artery measurement

Carotid atherosclerosis was assessed with B-mode ultrasound by specially trained and certified sonographers after completion of an extensive training program [36,40]. The bifurcation area of the right carotid artery was scanned for plaques, defined as focal thickening (>1.2 mm) of the arterial wall [41], within a pre-defined window encompassing 3 cm of the distal CCA, the bulb, and 1 cm each of the internal and external carotid arteries. IMT was determined off-line in the far wall of the right distal CCA as the mean thickness over a 10-mm segment proximal to the bifurcation according to the leading edge principle. The leading edges of the echoes representing the transitions between the lumen and the intima layer and between the media and adventitia layers, respectively, were outlined using a specially designed semi-automatic computer-assisted analysing system [42]. The distances between the two lines were measured at approximately 100 sites/cm by the computer, and the mean value of these measurements was calculated as IMT_{mean} in the CCA. Maximum IMT in the far wall of the bifurcation (i.e., the bulb) was also assessed. Such measurements were initiated in February 1992, therefore only those participating in MDCS between February 1992 and 1994 (n = 2837) could be included in analyses of IMT in the bifurcation. Of these, successful measurements of progression of IMT in the bifurcation were taken in 2287 individuals. IMT in the internal carotid artery was not specifically measured or analysed. Five sonographers performed the IMT measurements at baseline and five at re-examination. At regular intervals, intra- and interobserver variation analyses were performed with satisfactory results [39,43]. The mean follow-up period was 16.6 (±1.5) years.

2.5. Statistics

Baseline cardiovascular risk factors among attendees and non-attendees in re-examination were described by mean ± SD values or by percentages. Differences in risk factors between attendees and each of the three groups of non-attendees, were tested through t tests for continuous data and χ^2 test for categorical data. Progression of carotid atherosclerosis was analysed by estimating the annual change in mean IMT CCA and the maximum IMT in the

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