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Plasma IL-5 concentration and subclinical carotid atherosclerosis

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ABSTRACT

Objective: Genetic variants robustly associated with coronary artery disease were reported in the vicinity of the interleukin (IL)-5 locus, and animal studies suggested a protective role for IL-5 in atherosclerosis. Therefore, we set this work to explore IL-5 as a plasma biomarker for early subclinical atherosclerosis, as determined by measures of baseline severity and change over time of carotid intima-media thickness (cIMT).

Methods: We used biobank and databases of IMPROVE, a large European prospective cohort study of high-risk individuals (n = 3534) free of clinically overt cardiovascular disease at enrollment, in whom composite and segment-specific measures of cIMT were recorded at baseline and after 15 and 30 months. IL-5 was measured with an immunoassay in plasma samples taken at baseline.

Results: IL-5 levels were lower in women than in men, lower in the South than in North of Europe, and showed positive correlations with most established risk factors. IL-5 showed significant inverse relationships with cIMT change over time in the common carotid segment in women, but no significant relationships to baseline cIMT in either men or women.

Conclusions: Our results suggest that IL-5 may be part of protective mechanisms operating in early atherosclerosis, at least in women. However, the relationships are weak and whereas IL-5 has been proposed as a potential molecular target to treat allergies, it is difficult to envisage such a scenario in coronary artery disease.

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Abbreviations: CVD, cardiovascular disease; CAD, coronary artery disease; IL, interleukin; cIMT, carotid intima-media thickness; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein; BMI, body-mass index; IMTmean, mean IMT of the whole carotid tree; IMTmax, maximum IMT of the whole carotid tree; IMTmean-max, average of maximum IMT values of the whole carotid tree; CC, common carotid artery; ICA, internal carotid artery; Bif, bifurcation (bulb); IMPROVE, Carotid **I**ntima **M**edia Thickness and IMT-**PRO**gression as Predictors of **V**ascular **E**vents in a High-Risk European Population.

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1. Introduction

Inflammation plays an important role in atherosclerosis and clinical cardiovascular disease (CVD) [1–3]. Epidemiological studies have shown that patients with chronic inflammatory diseases, such as rheumatoid arthritis, lupus erythematosus and psoriasis, run a significantly greater risk of contracting coronary artery disease (CAD) than the general population, a fact that is not fully explained by presence of traditional cardiovascular risk factors [3,4]. Instead, it appears that inflammation and an increased proportion of unstable plaques contribute substantially to the increased cardiovascular mortality in rheumatoid arthritis [4]. In addition, the absence of an increase in occurrence of clinical CAD *prior* to the onset of rheumatoid arthritis [5], and the reduced risk of CAD achieved by blocking tumor necrosis factor early in the course of rheumatoid arthritis [6], suggest that CAD develops *after* the onset of rheumatoid arthritis. Genetic studies have also supported the hypothesis that pro-inflammatory pathways play a causal role in CAD [7]. Interleukins (ILs) in particular can be considered as strong candidates because they are known to influence the cardiovascular system in either a harmful, pro-inflammatory way (IL-1, IL-2, IL-6, IL-7, IL-8, IL-15, IL-17, and IL-18) or in a protective, anti-inflammatory way (IL-4, IL-10, IL-11, IL-12, and IL-13) [8]. Accordingly, meta-analyses of genetic studies have provided strong evidence for IL-6 and the IL-6 receptor in CAD [9,10].

In 2011, genetic variants in the vicinity of the IL-5 locus were found to be robustly associated with CAD in a large case–control study including a total of 32,717 cases and 75,465 control subjects [11]. IL-5 was originally defined as a "T-cell-replacing factor" that drives activated B cells for terminal differentiation into antibody-secreting plasma cells in mice [12]. In humans, IL-5 is best characterized as a major maturation and differentiation factor for eosinophils [13]. Because of the importance of eosinophils for allergy and other associated disorders, IL-5 has been proposed as a potential molecular target for the treatment of these diseases, with a couple of IL-5 antagonist therapies currently under development [13,14]. Prior to the recent gene-centric study in CAD [11], the role of IL-5 in CVD had been barely touched upon, with one publication linking plasma IL-5 levels inversely to subclinical atherosclerosis [15] and two studies implicating raised IL-5 levels in unstable angina and myocardial infarction [16] and risk of recurrent CAD events [17].

Against this background, we examined the role of IL-5 as a plasma biomarker for early, subclinical carotid atherosclerosis, as determined by measures of baseline severity and change over time in carotid intima-media thickness (cIMT), in a large prospective cohort study of high-risk individuals who were free of clinically overt CVD at enrollment [18].

2. Materials and methods

2.1. Study population

The present study was performed using the biobank and databases of a multicentre, European, longitudinal cohort study (acronym: IMPROVE (Carotid **I**ntima **M**edia Thickness (cIMT) and IMT-**PRO**gression as Predictors of **V**ascular **E**vents in a High-Risk European Population) [18]). In brief, inclusion criteria were age from 55 to 79 years, presence of at least three cardiovascular risk factors and absence of symptoms of CVD, as well as of conditions that might limit longevity or cIMT visualization. Participants were recruited in seven centers in five European countries: Italy (centers in Perugia and Milan), France (Paris), the Netherlands (Groningen), Sweden (Stockholm) and Finland (two centers in Kuopio). These centers are located from South to North of Europe at latitudes 43, 45, 48, 53, 59 and 62, respectively. Between March 2004 and April 2005, 3711 participants were enrolled, of whom 3534 (1701 men and 1833 women) were included in the present report. Participants were excluded because of inaccuracy of data at recruitment, technical difficulty to acquire cIMT or incomplete follow-up, as detailed [19]. Ethics committee approvals for the study were obtained in each of the 7 recruiting centres and written informed consents were obtained from all participants.

Baseline characteristics of the entire IMPROVE cohort and methods for determination of established cardiovascular risk factors have been published [18].

2.2. Quantification of IL-5 in plasma

The concentration of IL-5 was measured in duplicate in EDTA-plasma samples by a sandwich immunoassay with electrochemiluminescense detection using the ultra-sensitive kit for human IL-5 assay from MesoScale Discovery, Gaithersburg, MD, USA (Catalog #: K1151AJC-4, Lot: K0022251). All samples were incubated overnight at 4 °C with the antibody on the wells of plates, on a shaker at 600 rpm. Otherwise the protocol followed the manufacturer's instructions. The mean intra-assay coefficient of variation (CV) for all samples was 8%, and the inter-assay CV for the control plasma was 13% (n = 94 plates).

2.3. Carotid ultrasonography

Details of the protocol and validation of the carotid ultrasound measurements have been published [18]. In the present report, the following cIMT variables were studied in relation to IL-5: the mean and maximum IMT of the whole carotid tree (IMTmean and IMTmax), and the average of maximum IMT values of the whole carotid tree (IMTmean-max); the mean and maximum IMT of the common carotid arteries (CC-IMTmean and CC-IMTmax), excluding the first centimetre closest to the bifurcation; the mean and maximum IMT of the internal carotid artery (ICA-IMTmean and ICA-IMTmax); and the mean and maximum IMT of the bifurcations (Bif-IMTmean and Bif-IMTmax). Participants underwent cIMT measurements at 3 time-points: baseline and after 15 and 30 months. Changes in cIMT over 30 months, expressed in mm/year, were calculated by linear regression of IMT versus time using data from the 3 time-points.

2.4. Variable definitions

Hypertension was defined as a diagnosis of hypertension and/or treatment with antihypertensive drugs. Diabetes was defined as a diagnosis of diabetes and/or treatment with insulin or other hypoglycemic drug, and/or fasting glucose $\geq$7 mmol/L at the baseline examination. Smoking habits, identified from a structured questionnaire performed at baseline, included variables reflecting current smoking status, duration/cessation of smoking and the average number of cigarettes being consumed. As a measure of cumulative smoking, a 'pack-years' variable was calculated by multiplying the average number of cigarettes smoked per day by the number of years of smoking divided by 20. The 'pack-years' was used as a 5-level categorical variable where first group included never-smoker status and four other included quartiles of 'pack-years'. Results were presented as percent of population in smoking groups 0/1/2/3/4: 0: non-smokers; 1 to 4 correspond respectively to 0–7.99; 8–17.99; 18–29.99; 30-250 pack-years.

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