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Alpha-1 antitrypsin deficiency: From the lung to the heart?

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ABSTRACT

Background and aims: Alpha-1 antitrypsin (A1AT) is the most abundant serine protease inhibitor in human blood and exerts important anti-inflammatory and immune-modulatory effects. In combination with smoking or other long-term noxious exposures such as occupational dust and fumes, genetic A1AT deficiency can cause chronic obstructive pulmonary disease, a condition with elevated cardiovascular risk. The effects of A1AT deficiency on cardiovascular risk have hardly been studied today.

Methods: Using data from 2614 adults from the population-based SAPALDIA cohort, we tested associations of serum A1AT and *SERPINA1* mutations with carotid intima-media thickness (CIMT, measured by B-mode ultrasonography) or self-reported arterial hypertension or cardiovascular disease in multiple regression models using a Mendelian Randomization like analysis design. Mutations Pi-S and Pi-Z were coded as ordinal genotype score (MM, MS, MZ/SS, SZ and ZZ), according to their progressive biological impact.

Results: Serum A1AT concentration presented a u-shaped association with CIMT. At the lower end of the A1AT distribution, an analogous, linear association between *SERPINA1* score and higher CIMT was observed, resulting in an estimated 1.2% (95%-confidence interval -0.1-2.5) increase in CIMT per unit ($p = 0.060$). Genotype score was significantly associated with arterial hypertension with an odds ratio (OR) of 1.2 (1.0–1.5) per unit ($p = 0.028$). The association with cardiovascular disease was not significant (OR 1.3 (0.9–1.9)).

Conclusions: Our results support a possible causal relationship between genetic A1AT deficiency and increased cardiovascular risk, which needs to be better taken into account for the management of affected patients and first-degree relatives.

1. Introduction

Alpha-1 antitrypsin (A1AT) is an acute phase protein synthesized in the liver, and the most abundant serine protease inhibitor

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in human blood. Its longest known biological function consists of the enzymatic inactivation of elastase, which is expressed on cell surfaces or released by neutrophil leucocytes during inflammation [1]. This function impedes excessive degradation of elastin and collagen fibers in extracellular matrix, and prevents the consecutive activation of matrix metalloproteinases and inflammatory cascades [2] that result in inflammation associated tissue remodeling. In recent years, new functions have been discovered that suggest a broader biological role, including anti-inflammatory and immune-modulatory effects [3], and interactions with serum lipoproteins [4–6].

A1AT is coded by gene *SERPINA1* on chromosome 14. In Caucasian populations, the four alleles called Pi-M, Pi-S and Pi-Z are most frequently observed (Pi for "protease inhibitor" and letters given after the positions of the respective protein-bands in electrophoresis). Pi-M is the wildtype allele, while the S- and Z-alleles constitute functional single nucleotide polymorphisms (SNPs) with autosomal recessive inheritance patterns leading to reduced protein stability and impaired liver secretion, respectively [7,8]. The Pi-ZZ genotype is rare (<0.1% in our study population), but highly deleterious, and leads to a 80-90% drop in serum A1AT concentration below the critical threshold of 0.49 g/L defining severe A1AT-deficiency [7,9]. Genotypes SZ, MZ, and SS lead to intermediate deficiency with levels between 0.49 and 1.0 g/L[9]. A1AT concentration is also influenced by environmental and endogenous biological factors. Likewise, it's highly correlated with C-reactive protein (CRP) level through common upregulation during acute phase reactions. Further, serum A1AT has been positively associated with female sex, age, systolic blood pressure, and tobacco smoking in our cohort, while inverse associations have been observed with body mass index (BMI) and alcohol intake [10].

When combined with smoking or other long-term noxious exposures such as occupational dust and fumes, severe genetic A1AT deficiency highly increases the risk of developing chronic obstructive pulmonary disease (COPD), a relationship constituting the classical paradigm of gene-environment interaction. COPD is a systemic aging-related disease consistently associated with increased cardiovascular risk [11]. The health-related effects of intermediate A1AT deficiency are less clear, but there is evidence showing increased risk of airway obstruction for MZ and SZ genotypes, particularly with concomitant oxidative stress exposure [12–15].

Given the broad biological activity of A1AT, its genetic deficiency could be an independent determinant of cardiovascular effects as observed in COPD. However, only a few studies have investigated this relationship to date, yielding conflicting results [16–18]. Using data from the Swiss population based SAPALDIA cohort, we therefore aimed to study the associations of A1AT serum level and its genetic determinants with CIMT by employing a Mendelian randomization design, to shed further light on the potential role of A1AT deficiency in atherosclerosis and cardiovascular disease.

2. Materials and methods

2.1. Study design and population

The SAPALDIA cohort provides detailed data on lifestyle, lung function, carotid intima-media thickness (CIMT) as marker of early atherosclerosis [19–21], and self-reported doctor's diagnoses of arterial hypertension and cardiovascular disease in participants aged 50 years or older. As depicted in Supplementary Fig. 1, we studied 2614 participants who underwent a CIMT scan at the third assessment (SAPALDIA3), and had A1AT concentration and *SERPINA1* genotypes measured 8.4 years earlier (SAPALDIA2). Cohort details were published before [22]. Ethical approval was obtained by the Swiss Academy of Medical Sciences and respective cantonal ethics committees. All participants gave written informed consent.

2.2. Carotid intima-media thickness

In the current study, we used CIMT measurements as marker of early atherosclerotic processes in our general population sample [19]. CIMT was measured at SAPALDIA3 in participants aged ≥50 years. In a previous study of our cohort, high cardiovascular risk profiles were associated with higher CIMT measures [20], and in international studies, CIMT has repeatedly been evidenced as predictor of future cardiovascular disease [21]. The details of CIMT measurements in SAPALDIA were published previously [23]. Briefly, CIMT was assessed following a standardized protocol using carotid Bmode ultrasound scans on Fukuda Denshi UF-870 equipment. Fieldworkers were trained and supervised by two collaborating vascular labs (the Department of Vascular Medicine at the Academic Medical Center/Imagelab, University of Amsterdam and Erichem, The Netherlands, and the Division of Sports and Exercise Medicine, Department of Sport, Exercise and Health, University of Basel, Switzerland). Bilateral measurements of the distance between the lumen-intima to the media-adventitia layer of the far artery wall were performed for the duration of three heart cycles on the left and right common carotid artery (CCA), 1 cm proximal of the carotid bifurcation in longitudinal ear to ear and horizontal angle. Imaging data was analyzed by the B-mode image analysis program Dynamic Artery Analysis (DYARA). As sonographers were not trained for plaque assessment and following the Mannheim Consensus [24], images of insufficient quality or containing plaque areas were excluded, resulting in the exclusion of N = 174 participants (~5% of the overall sample with available CIMT measurements). For each individual, average CIMT was calculated using the mean values of both CCA sides and scan angles. Duplicate scans were performed on different days within a period of 3 months in 165 randomly chosen participants to assess intra-fieldworker variability. Between-visit coefficient of variation was 3.98% (3.52–4.44) and the intra-class correlation coefficient was 0.89 (0.87–0.93) [20].

2.3. Spirometry and spirometric obstruction

In SAPALDIA3, spirometry was done with EasyOne handheld spirometers (EasyOne, ndd Medical Technologies, Zürich, Switzerland) following the protocol of the European Community Respiratory Health Survey [25]. Spirometry curves were subjected to ATS/ERS quality standards. SAPALDIA specific lung function equations were used for the calculation of lower limits of normal (representing the 5th percentile of the lung function distribution in healthy, non-smoking adults of our study population) [26]. Spirometric obstruction was defined as having a FEV_1/FVC ratio (a marker of airway obstruction) below the lower limit of normal.

2.4. Blood pressure, height, weight and BMI

Blood pressure was assessed with two measurements 3 min apart in SAPALDIA3 using automatic devices (705CP, Omron, Tokyo, Japan) and cuffs of appropriate size. Arithmetic means of diastolic and systolic values were used for analysis.

Participants wore no shoes or heavy clothes when measuring weight and height. BMI was categorized as <25, ≥25 and < 30, and ≥30 kg/m^2.

2.5. Questionnaire data

An interview administered questionnaire was used to gather