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Gender-specific association of coronary artery calcium and lipoprotein parameters: The Heinz Nixdorf Recall Study

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ABSTRACT

Background: Coronary atherosclerosis can be detected by computed tomography. The amount of coronary artery calcification (CAC) is related to cardiovascular risk factors, the strength of the gender specific relation between lipoprotein parameters and CAC has not extensively been studied. Especially, the role of routinely determined lipoproteins in contrast to less common and computed lipid parameters (e.g. ratios) remains to be clarified.

Methods and results: The study cohort ($n = 3956$, 52% women, age 45–75 years) was randomly selected from three cities of a German metropolitan area. Lipoproteins—low-and high density lipoprotein (LDL-C/HDL-C), total cholesterol, apolipoprotein A-1 and B (apoA-1/apoB) as well as lipoprotein (a) (Lp(a)) were measured, while non-HDL-C was calculated. All participants received an electron-beam computed tomography (EBCT) for quantification of CAC. Adjusted for age and cardiovascular risk factors, CAC increased by a factor of 1.97 (1.51–2.57, 95% CI) and 1.94 (1.53–2.45, 95% CI) comparing the fourth to the first quartile of LDL-C for men and women, respectively. This association with LDL-C was also found after dichotomization of CAC at thresholds >0, ≥100 and ≥400. The best association of CAC was, however, found to be apoB and the second best was non HDL-C, in both men and women. For apoB, the model including all risk factors reached an explained variance for CAC of 20.2% in men and of 21.6% in women. When using LDL-C as a given parameter according to the current practice and advice, HDL-C in men and apoB in women provided an additional but small benefit.

Conclusion: ApoB showed the best association with CAC compared to all other tested lipoproteins. Neither the ratio LDL-C/HDL-C nor apoB/apoA-1, or Lp(a) revealed a closer association with CAC. While lipoproteins are related to CAC more closely in women than in men, their association with CAC is, however, not particularly strong. Our results may influence primary and secondary prevention advices in order to improve detection of subclinical atherosclerosis, for which lipoprotein parameters can only play a minor role.

1. Introduction

Subclinical signs of atherosclerosis can be detected by computed tomography (CT) based imaging of coronary artery calcification

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(CAC). The amount of CAC can be quantified using the Agatston score [1]. Three prospective cohort studies showed a strong association between the amount of CAC and the relative risk [2–4]. Thus, CAC scoring can be used as a surrogate marker of coronary atherosclerosis and to evaluate the association to traditional and to new risk factors.

The association of CAC to lipoproteins was recently analysed for high density lipoprotein cholesterol (HDL-C) [5], non-HDL-C [6,7], and low density lipoprotein cholesterol (LDL-C), lipoprotein (a) [8], metabolic syndrome [9] as well as LDL-C particles [10].

Apolipoprotein B (apoB) represents most of the protein content in LDL and apoA-1 is the main apolipoprotein in HDL-C [11]. Both have not been studied in prospective cohort studies despite the fact that both seem to be reliable markers of atherogenic risk [12–14]. The apoB/apoA-1 ratio may even be a better risk predictor than LDL-C/HDL-C for risk assessment [13]. Therefore, an international expert panel recommended apoB/apoA-1 to calculate the lipoprotein related risk of vascular diseases and adopt target levels of apoB as an alternative to LDL-C and non-HDL-C [15].

Lipoprotein (a) (Lp(a)) is a low density LDL-like particle bound to apolipoprotein–B100 [16] baring pro-thrombotic and pro-atherogenic properties [17]. Concerning the relevance of Lp(a) as an atherogenic risk factor, still considerable controversy exist despite the fact, that results of recent studies demonstrated that the increase of Lp(a) concentration lead to an increased risk. In observational studies the increase was, however, small [18].

Therefore, it was the aim of our study to evaluate, which of the different tested and used lipoproteins could show the best association with CAC as a marker of extent of coronary atherosclerosis with special attention to gender differences. These analyses may have an implication for treatment targets in primary and secondary prevention.

2. Methods

2.1. Participants

Details of the rationale of the Heinz Nixdorf Recall (Risk factors evaluation of coronary calcium and lifestyle cohort) study design, sampling methods, response rate, and data collection have been published in detail previously [19,20]. Participants, aged 45–75 years, were randomly selected from mandatory lists of residents in three adjacent cities (Essen, Bochum, Mülheim/Ruhr) of the densely populated Ruhr metropolitan area in Germany. Exclusion criteria were conditions that preclude follow-up, severe psychiatric disorders or illegal substance abuse, and pregnancy. The study had been approved by the institutional local ethics committee. An internal and external quality management system was established according to industrial standard norms DIN ISO 9001:2000/2008. All participants gave written informed consent. All findings, except the CAC values, were reported to the participants.

Overall 4814 participants were enrolled in the study between 12/2000 and 08/2003. Of these 327 (6.8%) participants reported a history of coronary artery disease (CAD) at baseline and were excluded from the primary endpoint analysis, leading to a final cohort of 4487 study participants (52% women) and a baseline response of 56% [20].

2.2. Cardiovascular risk factor assessment

Cardiovascular risk factors assessment was conducted at the study centre in Essen by trained and certified medical personnel using various methods. Participants were interviewed about medical history, family history of coronary heart disease, history of hypertension and diabetes, smoking lifestyle and socio-economic status [4,20,21]. Ascertainment of current use of medication was performed documenting the medication taken in the last 7 days. Blood pressure was measured using an automated oscillometric blood pressure device (Omron, HEM-705CP-E) with participants in sitting position, using the mean of the second and third value of three measurements [22]. Hypertension was defined as systolic blood pressure $\geq$140/90 mmHg and/or use of blood pressure medication [23]. Body weight was measured to the nearest 0.1 kg, height to the nearest 0.5 cm with participants in light underwear without shoes. Body mass index (BMI) was calculated as weight (kg)/square of height (m^2), obesity defined as BMI $>$ 30 kg/m^2.

Standard enzymatic methods were used to measure total cholesterol (TC), LDL-C, HDL-C, triglycerides (TG) and glucose [4]. ApoA-1 and apoB were measured immunoturbidimetrically using an automatic clinical chemistry system (Advia Clinical, Chemistry Analyzer Siemens HealthCare Diagnostics, Eschborn, Germany). The ratios LDL-C/HDL-C and apoB/apoA-1 were calculated. Participants were asked to fast for at least 4 h, resulting in 60% of subjects with fasting status $>$8 h, 2% 6–8 h, 5% 4–6 h, 26% 2–4 h and 7% with $<$2 h of fasting, with no sex differences observed [24]. Participants were considered diabetics if they reported a diagnosis of diabetes, or when a fasting blood glucose level $\geq$126 mg/dl, a postprandial blood glucose level $\geq$200 mg/dl was found, or use of anti-diabetic medication was documented [24]. Glycosylated haemoglobin was determined by an affinity chromatography method (GB-system, Tosoh Bioscience, Tokyo, Japan). Creatinine was measured by the Jaffé method (Advia Clinical Chemistry Analyzer, Siemens HealthCare Diagnostics, Eschborn, Germany) and glomerular filtration rate (GFR in millilitres per minute per 1.73 m^2 of BSA) was estimated using the abbreviated Modification of Diet in Renal Disease equation [23]. High sensitive C-reactive protein (hs-CRP) was determined using an immune-nephelometric method (BN-II analyser and appropriate reagents, Siemens HealthCare Diagnostics, Eschborn, Germany). Homocysteine was measured using a fluorescence polarization immunoassay on the IMx analysed (Abbott Laboratories, Abbott Park, Il, USA). All analyses were done within 12 h at one central laboratory (MB, KM).

2.3. Electron-beam computed tomography (EBCT)

Non-enhanced EBCT scans were performed with a C-100 or C-150 scanner(GE Imatron, South San Francisco, USA) in two radiology institutions (DG,RS) scanned and analysed blinded and independently [4,7]. The scanners were operated in the single slice mode with an image acquisition time of 100 ms and a section thickness of 3 mm. The calcium score is the product of the area of each focus of detectable calcium and a factor rated one through four dictated by the maximum CT density within that focus. At least four pixels were required for each lesion. Total CAC score was computed by summing up calcium scores of all foci in the epicardial coronary system [1,4,23]. The calcium scores were not communicated with the participants.

2.4. Statistical analysis

Demographic and laboratory data are given as mean $\pm$ standard deviation (SD) and/or median (25th; 75th percentile), or count (%). Comparisons between men and women were evaluated using Student's *t*-test, Mann–Whitney *U*- or Chi-square-statistics, as appropriate. Due to a strongly skewed distribution, Lp(a) is characterized by 75th percentile, median and 90th percentile. Lipid-lowering medication is accounted for by shifting all subjects on such medication to the highest lipid parameter category (highest quartile/decile, lowest quartile in the case of HDL-C). Unless otherwise specified, *p*-values for trend with lipid parameter categories were computed from Spearman correlation test for continuous data,