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Levels of soluble tumor necrosis factor receptor 1 and 2, gender, and risk of myocardial infarction in Northern Sweden

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ABSTRACT

Background and aims: Soluble receptors for tumor necrosis factor alpha (sTNFR1 and sTNFR2) have been associated with cardiovascular diseases, and some evidence points towards a difference in associated risk between men and women. We aimed to study the association between sTNFR1 and sTNFR2 and incident myocardial infarctions (MI) and to explore the influence of established cardiovascular risk factors in men and women.

Methods: We conducted a nested case control study in three large Swedish cohorts, including 533 myocardial infarction cases, and 1003 age-, sex- and cohort-matched controls. Odds ratios (OR) with 95% confidence intervals (CI) were calculated.

Results: An association between circulating sTNFR1 and sTNFR2 and an increased risk for MI was found when comparing cases and controls. The odds ratios were significant after adjustment for established cardiovascular risk factors and C-reactive protein in women (OR 1.44, 95% CI 1.08–1.93 for TNFR1, and 1.61, 95% CI 1.11–2.34 for TNFR2), but was abolished in men. Women with a combination of elevated CRP and values in the upper quartile of TNFR1 or TNFR2 had a 5-fold higher risk of myocardial infarction *versus* those with normal CRP and values in the lower three quartiles of TNFR1 or TNFR2.

Conclusions: As the risk estimates for TNFR1 and TNFR2 were higher and remained significant after adjustments for established cardiovascular risk factors in women but not in men, a potential role for TNFR1 and TNFR2 in identifying women with a higher MI risk is possible. The future clinical role of TNFR1 and TNFR2 in combination with CRP to identify high risk patients for coronary heart disease has yet to be determined.

1. Introduction

The soluble receptors for tumor necrosis factor (TNF)-α (TNFR1 and TNFR2) are involved in several of the mechanisms underpinning plaque rupture [1], the primary event leading to most myocardial infarctions (MI), such as stress response cascades and inflammation [2,3].

TNFR1 and TNFR2 have been studied as risk markers for cardiovascular death in patients with type 2 diabetes [4], and both TNFR1 and TNFR2 have been shown to predict cardiovascular events and total mortality in patients with type 2 diabetes [5], as well as in chronic kidney disease [6]. Conflicting results have, however, been reported; TNFR1 and TNFR2 have been associated with coronary heart disease risk in women but not in men [7]. Yet, large studies of community based data on the effects of circulating levels of TNFR1 and TNFR2 on incident myocardial MI are sparse [8].

In the present study, we hypothesized that elevated levels of sTNFR1 and sTNFR2 are causally associated with an increased risk of suffering from MI. Herein, we primarily aimed to investigate the

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association of sTNFR1 and sTNFR2 with incident MI, with pre-specified separate analyses in men and women.

2. Materials and methods

2.1. Study population

We used a prospective nested case control study design. Participants were recruited from three large epidemiological projects: the Northern Sweden MONItoring of Trends and Determinants in CArdiovascular Diseases (MONICA) project [9], the Västerbotten Intervention Program (VIP) [10], and the Mammary Screening Program (MSP) [11].

The participants in the MONICA project health surveys in 1986, 1990, 1994 and 1999 came from randomly selected samples of 2000–2500, 25–74-year-old inhabitants of Västerbotten and Norrbotten counties. The mean participation rate in the surveys was 77.2%.

The VIP is a community intervention program for prevention of cardiovascular disease and diabetes in the Västerbotten County in Sweden. About 66,300 individuals took part in the VIP health surveys between 1985 and 2000. Men and women were invited to a health examination, with a similar study design as in the MONICA population surveys, at their primary health care center when they turned 30, 40, 50, and 60 years old (since 1996: 40, 50 and 60 years) [12]. The participation rate increased from 56% in 1995 to 65% at the end of the studied period. Differences in education level and urbanization between participants and non-participants in VIP were minimal.

Regular mammography screening (MSP) is offered to all women older than 50 years in the Västerbotten county, n = 28,400 between 1995 and 2000.

The participants in both MONICA and VIP were asked to complete a questionnaire about living conditions and cardiovascular risk factors, and anthropometry and blood pressures were measured. An OGTT and blood sampling for blood lipids and glucose were undertaken. A somewhat different protocol with anthropometry and blood pressure measurements was used in the MSP.

The participants in all epidemiological projects above were requested to donate fasting blood samples for long-term storage at the Northern Sweden Medical Research Bank for research. Accordingly, all analyzed blood samples were collected prior to the incident myocardial infarctions studied in the present work.

2.2. Myocardial infarction cases

Since 1985, all incident cases (in-hospital and out-of-hospital) of acute MI among those 25–64 years of age, in the regions Västerbotten and Norrbotten, have been included in the Northern Sweden MONICA register by the use of a validated MONICA methodology and WHO criteria.

All possible MI events from screening of hospital discharge records, general practitioners' reports, and death certificates were identified with ICD 8 and 9 codes 410–413, corresponding to ICD 10 codes I20-I24. The codes 414 and 798–799 (ICD 8 and 9), and I25 and R96–99 (ICD 10) were also screened for in the death certificates. Information on medical history, symptoms, examinations, and presenting electrocardiogram (ECG) was also collected. About two subjects per year with MI included in the registry have, after information, not been willing to participate in further studies (0.2%).

MI diagnoses were based on typical chest pain, ECG findings and elevated cardiac enzymes. The criteria for MI were either a typical ECG progression or probable ECG progression and elevated cardiac enzymes, or elevation of cardiac enzymes to more than twice as high as the upper limit of normal, or typical symptoms of myocardial infarction and elevated cardiac enzymes as above. Troponins were introduced for diagnosis of MI in the late 1990s. An event was considered to be first ever for the patients if there was no previous clinically recognized MI in the patient record.

Two sex-, cohort- (MONICA, VIP or MSP), date (±4 months) of health survey-, and geographical area, and age-matched (±2 years) referents per case were randomly selected. We excluded all cases and referents with a previous history of MI or stroke (any time before survey), or cancer (less than 5 years before or 1 year after MI). To enable validation of data from the registries, a questionnaire about previous cardiovascular and cancer diseases was completed by all included surviving cases and controls.

The data handling was approved by the National Computer Data Inspection Board, Stockholm, Sweden, and the protocol was approved by the Research Ethics Committee of Umeå University, Umeå. Informed consent was obtained from all participants.

2.3. Clinical examinations and biochemical analysis

Subjects were classified as present smokers, ex-smokers, and non-smokers. In the VIP survey, blood pressure was measured after 5 min of rest in the recumbent position, until 1 September 2009 (measurements obtained with participants in the recumbent position were adjusted with a sex- and age-specific formula) [13]; it was thereafter measured in the sitting position with the devices described above. A systolic blood pressure $\geq$140 mmHg, and/or diastolic blood pressure $\geq$90 mmHg, and/or the use of antihypertensive medication was defined as hypertension. An oral glucose tolerance test, with measurements of fasting and post-load glucose levels, was performed routinely in the VIP, in 60% of MONICA participants, but not in the MSP. Diabetes mellitus (DM) was determined based on self-reported usage of anti-diabetic medication, fasting plasma glucose levels $\geq$7.0 mmol/L, and/or post-load plasma glucose levels $\geq$11.1 mmol/L (or $\geq$12.2 mmol/L based on capillary plasma measurements in the VIP). Impaired fasting glucose (IFG) was defined as a fasting glucose level $\geq$6.1 and < 7.0 mmol/L. Impaired glucose tolerance (IGT) was defined as a post-load glucose level $\geq$7.8 and < 11.1 mmol/L (or $\geq$8.9 and < 12.2 mmol/L in the VIP), combined with a non-diabetic fasting glucose level. The definition of glucose intolerance was IFG, IGT, or DM. Plasma samples were collected after a minimum of 4 h fasting (extended to 8 h 1992), and were stored at −80 °C until analysis. Commercial ELISAs were used to analyze CRP (IMMULITE, Siemens Healthcare, Solna, Sweden) and soluble TNFR1 (DY225, R&D Systems, Minneapolis, MN) and TNFR2 (DY726, R&D Systems). The assays had a 6% total coefficient of variation (CV). Apolipoprotein A-1 and apolipoprotein B were analyzed by immunoturbidimetry (Dako, Glostrup, Denmark). All measurements were made by laboratory staff, blinded for patent information. Plasma samples were obtained after fasting for a minimum of 4 h (extended to 8 h, 1992), and kept stored in a deep-freeze blood bank at −80 °C. All measurements were made by laboratory staff, unaware of participants' disease status.

2.4. Statistics

Spearman correlations were calculated to investigate the crude association between TNFR1 and TNFR2 and their correlation with CRP. TNFR1 and TNFR2 were log-transformed and standardized by their own standard deviation.

Within strata, cases and referents had the same follow-up times, in this nested, matched case-referent study. Therefore, we estimated odds ratios (OR) and 95% confidence intervals (CI) with