



## Increased Risk of Cardiovascular Diseases in Female Rosacea Patients: A Nested Case-control Study

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Rosacea is a chronic inflammatory disease with a prevalence varying between 1 and 20% and is the highest in fair-skinned Europeans (1). The appearance of rosacea differs between the sexes; there is a female predominance and the onset of the disease is earlier in females than in males (1). Of the 4 subtypes of rosacea (erythematoteleangiectatic, papulopustular, ocular and phymatotic) the erythematoteleangiectatic type is more common in females and the phymatous type in males (2).

There is a rising consensus that rosacea is not only limited to the skin but is a chronic systemic inflammatory disease. Several systemic diseases have recently been shown to be associated with rosacea (3). However, it is disputed whether rosacea is associated with cardiovascular (CV) diseases. The risk for comorbidities in rosacea has also been suggested to differ between sexes. Egeberg et al. found that rosacea is associated with type 1 diabetes, celiac disease, multiple sclerosis and rheumatoid arthritis particularly in females (4).

The aim of this study was to clarify the CV risk factors in rosacea patients by comprehensively studying the CV risk profile of middle-aged patients with rosacea.

### PATIENTS AND METHODS

This was a nested case-control study of the Northern Finland Birth Cohort 1966 (NFBC1966). NFBC1966 is a longitudinal research program, which initially included 12,058 children, in the two northernmost provinces in Finland, whose expected dates of birth were between 1<sup>st</sup> of January and 31<sup>st</sup> of December 1966. The whole cohort population has been regularly evaluated, since birth, by the means of health questionnaires and clinical examinations. At the age of 46 years the cohort subjects were invited to participate in a multidisciplinary health study, which included a full dermatological examination. A dermatologist or an experienced resident performed the examination. All skin diseases, including rosacea, were documented (5).

Evaluable data were available for 1,932 cohort members in the Oulu area; 292 of which had been diagnosed with rosacea. The majority of them presented with erythematoteleangiectatic rosacea ( $n=242$ , 82.9%), while 45 cases (15.4%) had papulopustular rosacea. Three cases (1.0%) had symptoms of phymatous rosacea and one case (0.3%) had ocular rosacea. Each case was matched to two control subjects by body mass index (BMI) and tobacco use. Controls were free from both rosacea and other skin diseases and presented only with benign melanocytic naevi. (Table S1<sup>1</sup>) Cardio-

vascular risk factors were comprehensively studied in all subjects and the carotid intima-media thickness (CIMT) was assessed by a cardiologist. All methods are described in detail in Appendix S1<sup>1</sup>.

The characteristics of the study population are presented as proportions, means and medians. The Mann-Whitney *U*-test and Person's Chi-square test were used to compare the distribution of cardiovascular risk factors in rosacea cases and controls. Statistical analyses were performed using the SAS software package (version 9.4, SAS Institute, Inc, Cary, NC) and a *p*-value <0.05 was considered statistically significant.

### Confounders

Socioeconomic status (SES) was based on the education level, which has been defined as the most specific indicator of the socioeconomic status. The cohort members were classified into 3 subgroups based on education. Data concerning education were obtained from the National Education Register and were supplemented by self-reported questionnaires, regarding personal educational history. Study participants were classified into 4 groups according to the body mass index (BMI) (Table S1<sup>1</sup>). The information on smoking, physical activity, alcohol consumption and skin type was self-reported (5).

### RESULTS

We found that the mean CIMT was significantly greater in the rosacea group than in controls, as were levels of insulin and serum free testosterone. The free androgen index was significantly higher in female rosacea patients. Other cardiovascular risk factors did not differ between the female groups (Table SII<sup>1</sup>). None of the studied risk factors were associated with rosacea in male patients (data not shown).

### DISCUSSION

We found that females with rosacea had increased CIMT when compared with the controls. CIMT has been considered as a surrogate marker of atherosclerosis and an early stage of hidden systemic inflammation (6). An increased CIMT is associated with several CV risk factors and with prevalent CV diseases, such as stroke (6). Our finding supports the previous finding of Belli et al. who first reported the relationship between rosacea and CIMT (7). However, the association has not been previously studied by sexes. Our female study cases with rosacea had increased testosterone and insulin levels. High testosterone levels correlate with the degree of atherosclerosis

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in females during midlife and later on (8). One study has previously found an association between insulin resistance and rosacea (9) and our finding of increased insulin levels are in agreement with that study.

Previously, several studies have suggested an association between rosacea and CV diseases (9–12) but there are opposing results as well (13, 14). Duman et al. evaluated 60 patients with rosacea and found increased CV risks, including dyslipidemia and highly sensitive C-reactive protein levels (10). A large Taiwanese cohort study of 30,000 rosacea patients presented an association between rosacea and independent coronary artery disease (12). A corresponding finding was made in a twin study ( $n=550$ ) where higher risk for cardiac comorbidity was evident in patients with rosacea (15). On the contrary, a Turkish case-control study ( $n=85$ ) did not find any association between rosacea and CV risk factors (14), and a Danish cohort study ( $n=4,948$ ) reported no increased risk of death due to CV events in rosacea patients (13). The controversial findings between the studies may be explained by different study methods, such as varying diagnosing of rosacea: The Taiwanese register study was based on the International Classification of the Diseases (ICD) (12), while the Danish register-based study comprised of the in-hospital treated patients or those treated in the secondary care setting (13). Also, the fact that information about the confounding factors, such as tobacco smoking, was based on the ICD codes may have led to some underestimation (13). The major strength of our study was the clinical skin evaluation, performed by dermatologists instead of self-reporting or register based data. CV risk factors were enrolled comprehensively; trained nurses performed measurements, the cardiologist measured CIMT and risk scores for CV diseases were used. National Registers (concerning medical history, previous chronic diseases, education status) were used to supplement self-reporting. Life style factors were surveyed widely. We were also able to survey variety of possible confounding factors, such as tobacco smoking and BMI, due to the unique birth cohort study design.

Our findings suggest that female patients with rosacea may have an increased risk of CV diseases, which should be taken account when evaluating rosacea patients in clinical practice. However, further case-control studies among females of different age groups are needed to verify our findings. Our finding of high testosterone

levels in rosacea patients raises an important question of whether anti-androgen treatments, such as spironolactone, should be used more often in the treatment of rosacea in middle-aged females, especially in cases that are unresponsive to a more conventional therapy.

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