**Institutet för miljömedicin**

# Cardiovascular Comorbidity in Rheumatoid Arthritis

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Äpplet, Akutkliniken Solna F4:04

**Fredagen den 19:e november, 2010, kl 09.00**

av
**Marie Holmqvist**

*Huvudhandledare:*
Docent Johan Askling
Karolinska Institutet
Institutionen för medicin
Enheten för klinisk epidemiologi

*Bihandledare:*
Professor Lars Alfredsson
Karolinska Institutet
Institutet för miljömedicin
Enheten för kardiovaskulär epidemiologi

*Fakultetsopponent:*
Professor Alan Silman
University of Manchester
School of translational medicine

*Betygsnämnd:*
Docent Olof Akre
Karolinska Institutet
Institutionen för medicin
Enheten för klinisk epidemiologi

Docent Ulla Lindqvist
Uppsala Universitet
Institutionen för medicinska vetenskaper
Sektionen för reumatologi

Docent Per Tornvall
Karolinska Institutet
Institutionen för medicin
Enheten för kardiologi

**Stockholm 2010**

# ABSTRACT

This thesis is based on four different studies, all focusing on co-morbidities in rheumatoid arthritis. Diabetes mellitus is assessed as a risk factor for rheumatoid arthritis, the temporal relationship between ischemic heart disease and rheumatoid arthritis, and the extent of coronary stenosis in rheumatoid arthritis, is studied. The rationale for this is that patients with rheumatoid arthritis suffer an increased risk of ischemic heart disease that cannot be explained by traditional risk factors for cardiovascular disease but is hypothesized to be related to rheumatoid arthritis specific factors, that patients with rheumatoid arthritis have been reported to have a more severe atherosclerosis and that autoimmunity seem to aggregate.

First, we studied diabetes mellitus and its relationship to rheumatoid arthritis using a population-based case-control study of rheumatoid arthritis. 1,419 patients with newly diagnosed rheumatoid arthritis and 1,674 age-, sex-, and residential area- matched controls were compared with respect to having diabetes mellitus prior to study inclusion. After validating self-reported information, 20 cases and 5 controls were classified as having type 1 diabetes mellitus and 42 cases and 46 controls as having type 2 diabetes mellitus. This study demonstrated that having type 1 diabetes mellitus conferred a seven-fold increased risk of developing a specific subset of rheumatoid arthritis defined by the presence of anti-citrullinated protein antibodies. This association depended to some extent on a genetic variant known to be involved in the pathogenesis of both type 1 diabetes and rheumatoid arthritis.

We then studied the temporal relationship between ischemic heart disease and rheumatoid arthritis in two population-based cohorts of patients with rheumatoid arthritis and age-, sex-, and residential area-matched controls from the general population. The occurrence of ischemic heart disease before first symptom of rheumatoid arthritis (controls were given the same date as their matched case) in two population-based cohorts of rheumatoid arthritis ($n_{cohort\ 1}$= 8,454, $n_{cohort2}$=2,025) was compared to the occurrence of ischemic heart disease among controls ($n_{cohort\ 1}$=42,267, $n_{cohort2}$=2,760) and revealed that having a history of ischemic heart disease before onset of first symptom of rheumatoid arthritis was as common among cases as controls; approximately 6% of cases and 6% of controls in cohort 1 had experienced an ischemic heart disease before first symptom of rheumatoid arthritis. After excluding those who had had any ischemic heart disease at diagnosis of rheumatoid arthritis, we followed cohort 1 over time and found that there indeed was an increased risk of ischemic heart disease in patients with rheumatoid arthritis (n=7,469) compared with the general population (n=37,024) and that this increased risk was apparent and manifest already within a few years following rheumatoid arthritis diagnosis. Among individuals included in cohort 1 who underwent angiography with indication acute coronary syndrome ($n_{rheumatoid\ arthritis}$=168, $n_{comparators}$=534) we found that although the development of ischemic heart disease was much more rapid in patients with rheumatoid arthritis, the extent of coronary stenosis was not related to rheumatoid arthritis.

In summary, these results indicate that type 1 diabetes mellitus increases the risk of developing a specific type of rheumatoid arthritis defined by a specific auto-antibody, that the risk of ischemic heart disease in rheumatoid arthritis goes from not being elevated to 60% increased compared to the general population within a few years following diagnosis of rheumatoid arthritis, and that the extent of coronary stenosis in rheumatoid arthritis with acute coronary syndromes is very similar to that in controls with the same clinical symptoms of acute coronary syndrome. The rapid increase in risk of ischemic heart disease could be related to factors associated with rheumatoid arthritis.