The association between Anticitrullinated peptide antibodies and adverse cardiovascular profile in patients with established rheumatoid arthritis

Thesis

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List of Abbreviations

ACC	:	American college of cardiology
ACE I	:	Angiotensin converting enzyme inhibitor
ACPAs	:	Anti-citrullinated peptide antibodies
AHA	:	American heart association
Ala	:	Alanine
APCS	:	Antigen presenting cells
APF	:	Antiperinuclear factor
APLs	:	Antiphospholipid antibodies
ARBs	:	Angiotensin 2 receptor blockers
Arg	:	Arginine
ATs	:	Subclinical atherosclerosis
BMI	:	Body mass index
CAD	:	Coronary artery disease
CCP	:	Cyclic citrullinated peptide
CD	:	Cluster differentiation
CDR3	:	Third complementarity determining region
CHF	:	Congestive heart failure
CMR	:	Cardiac magnetic resonance
CRP	:	C reactive protein
CT	:	Computed tomography
CTLA4	:	Cytotoxic T lymphocyte associated protein 4
CV	:	Cardiovascular
CVD	:	Cardiovascular disease
CVP	:	Cardiovascular disease prevention
3D TTE	:	3 dimension transthoracic echocardiography
DAS	:	Disease activity score
DD	:	Diastolic dysfunction
DM	:	Diabetes mellitus
DMARDs	:	Disease modifying antirheumatic drugs
E/A ratio	:	Early/atrial filling velocity ratio
EAS	:	European atherosclerosis society
EBN	:	Epstien bar virus nuclear protein

List of Abbreviations (Cont.)

EF	:	Ejection fraction
ELISA	:	Enzyme linked immunosorbent assay
EPCs	:	Endothelial progenitor cells
ESC	:	European society of cardiology
ESR	:	Erythrocyte sedimentation rate
EULAR	:	European league against rheumatism
FC γ receptor:		Fragment crystallizable gamma receptor
FRS	:	Framingham risk score
Gln	:	Glutamine
HBA1C	:	Glycated haemoglobin
HCQ	:	Hydroxichloroquine
HDL	:	High density lipoprotein
HLA	:	Human leucocytic antigen
HLA-DR	:	Human leucocytic antigen-antigen D related
HMGB1	:	High mobility group protein 1
HTN	:	Hypertension
IFN-α	:	Interferon α
IG G	:	Immunoglobulin G
IG M	:	Immunoglobulin M
IHD	:	Ischaemic heart disease
IL-6	:	Interleukin 6
IMT	:	Intima media thickness
LDL	:	Low density lipoprotein
LMT	:	Lipid modifying therapy
LV	:	Left ventricle
MCTD	:	Mixed connective tissue disease
MCV	:	Mutated citrullinated vimentin
MHC	:	Major histocomptability complex
MI	:	Myocardial infarction
MRI	:	Magnetic resonance imaging
MTX	:	Methotrexate
MVA	:	Mitral valve area

List of Abbreviations (Cont.)

NETs	:	Neutrophil extracellular traps
NFκB	:	Nuclear factor kappa-light-chain enhancer of activated B cells
NSAIDs	:	Non steroidal anti-inflammatory drugs
OSA	:	Obstructive sleep apnea
OXLDL	:	Oxidized low density lipoprotein
PA	:	Pulmonary artery pressure
PAD	:	Peptidyl arginine deiminase
PDG	:	Pyruvate dehydrogenase complex
PET scan	:	Positron emission tomography scan
PTPN22	:	Protein tyrosine phosphatase 22
PTX3	:	Pentraxin 3
RA	:	Rheumatoid arthritis
RMVS	:	Rheumatic mitral valve stenosis
SE	:	Shared epitope
SPECTscan	:	Single photon emission computerized tomography
SSZ	:	Sulfasalazine
T reg	:	T regulatory cell
TC	:	Total cholesterol
T-cell	:	Thymocytes cells
TCR	:	T cell receptor
Th 17	:	T helper 17 cells
TLR4	:	Toll like receptor 4
TNF	:	Tumor necrotic factor
TOE	:	Transoesophageal echocardiography
TTE	:	Transthoracic echocardiography
US	:	Ultrasound

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Introduction

Rheumatoid arthritis is a systemic autoimmune disease characterized by pain, functional disability, increased mortality, and high socioeconomic burden ***(Gonzalez et al., 2007).***

The most common presentation of RA is a symmetrical inflammatory polyarthritis, particularly of the hands and feet, although any synovial joint can be involved. Less widely appreciated is that RA is also a systemic illness, with extra-articular manifestations such as subcutaneous nodules, pulmonary disease, vasculitis, and neuropathy occurring quite commonly ***(Briggs et al., 2009).***

Rheumatoid arthritis is an independent risk factor for cardiovascular events such as ischemic heart disease or congestive cardiac failure ***(Warrington et al., 2005).*** which causes up to 40% of deaths in these patients ***(Sihvonen et al., 2004).***

Patients with RA have a 1.5- to 2.0-fold increased risk of developing coronary artery disease (CAD) compared with the general population (***Solomon, et al. 2006).***

At diagnosis, individuals with RA were more than 3 times as likely to have had a prior myocardial infarction (MI) than subjects without RA ***(Maradit-Kremers et al., 2005).***Patients with RA also have twice the risk of developing heart failure ***(Nicola et al., 2005).***

This risk is more pronounced in the patients with RA who are rheumatoid factor positive than among seronegative patients. Patients with RA are less likely to have typical signs and symptoms of heart failure, tend to be managed less

aggressively, and have poorer outcomes ***(Davis 3rd et al., 2008).***

Anticitrullinated peptide antibodies (ACPA) are highly specific serological markers for RA and are thought to be directly involved to disease pathogenesis ***(Vossenaar et al., 2004).***

ACPA have been suggested to be associated with more severe radiological outcome ***(Forslind et al., 2004).***

Subclinical vascular disease may be linked to the presence of ACPA ***(Szekanecz et al., 2007),*** and the presence of ACPA has been recently associated with stronger evidence of subclinical atherosclerosis in RA patient ***(Gerli et al., 2007).*** They are also independently associated with the development of ischemic heart disease ***(Lopez-Longo et al., 2007).***

Atherosclerotic vascular involvement and cardiac abnormalities including pericardial involvement in the form of pericardial thickening and effusion, myocardial involvement in the form of lower LV EF, LV diastolic dysfunction, and endocardial involvement in the form of valvular regurgitation were relatively higher among ACPA positive patients than in ACPA negative established RA patients ***(Banerjee et al., 2013).***

Aim of the Study

The aim of this study is to evaluate the association between anticitrullinated peptide antibodies and adverse cardiovascular profile in established rheumatoid arthritis patients as documented by carotid intima medial thickness and abnormal echocardiography.

Chapter One
Anti-citrullinated peptide antibodies

Introduction:

Rheumatoid arthritis (RA) is an autoimmune disease characterized by autoantibodies against citrullinated antigens. The importance of citrulline for the epitopes bound by these autoantibodies, referred to as ACPA (anti-citrullinated peptide/protein antibodies), was first described in 1998. In addition to citrullinated proteins, cyclic citrullinated peptides (CCP) can also be used as test substrates for detecting ACPA. The standard test for these antibodies is the second-generation CCP (CCP2) test, which is one of the best in terms of sensitivity and specificity. The generation of ACPA is an early event in the disease course, and is dependent on the presence of certain major histocomptability complex (MHC) class II alleles. ACPA in the inflamed synovium have been shown to associate with citrullinated antigens to form immune complexes, resulting in progression of the inflammatory process ***(Van Venroij et al., 2011).***

The involvement of ACPA in the chronicity of RA is probably the reason why ACPA-positive patients have a more erosive disease course than ACPA-negative patients. The presence of ACPA has been included in the 2010 RA classification criteria ***(Aletaha et al., 2010).*** Thus, it is important to further standardize ACPA testing, for example by including an internal serum standard, which may lead to a better distinction between low and high ACPA levels ***(Van Venroij et al., 2011).***

ACPA are present in nearly two thirds of RA patients and are more specific than the rheumatoid factor for RA ***(Alexio et al., 2007)***. In an early metaanalysis, the pooled