Periodontitis and ACPA positive Arthralgia*s; a link by protein citrullination

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Primary Objective: To investigate the presence of periodontitis in ACPA and or RF positive patients with arthralgia*s.Secondary Objective: to unravel the role of the cellular immune response in ACPA positive persons with arthralgia*s who are at risk...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational non invasive

Summary

ID

NL-OMON35274

Source
ToetsingOnline

Brief title
Periodontitis and ACPA positive Arthralgia*s

Condition

- Other condition
- Autoimmune disorders
- Bacterial infectious disorders

Synonym
RA risk group or pre-RA group

Health condition

parodontitis

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: ACPA, Arthralgia's, Periodontitis, RF

Outcome measures

Primary outcome

Clinical parameters:

Disease Activity Score 28 joint count (DAS28 and DAS44)

Periodontitis: Periodontal Inflamed Surface Area (PISA (Nesse et al. 2008) and

extent of alveolar bone loss measured on an panoramic radiograph.

Biomarkers: ACPA titer and anti-Pg titer

Secondary outcome

Leukocyte count, CRP and ESR.

Presence of citrullinated proteins, ACPA and expression of PAD-2 and -4 enzymes

in GCF, SF and tissue, cell types present in tissue.

Presence of P. gingivalis in subgingival plaque.

Presence of HLA-DRB1* shared epitope (SE) alleles.

Lymphocyte subsets with an emphasis on CD161 staining

Study description

Background summary

Patients with inflammatory arthralgia*s who have antibodies to citrullinated

proteins (ACPA) and/or rheumatoid factor (RF) have a 50-70% chance to develop of RA within 5 years. The prevalence of RA varies from 0.5-1.1%.
Genetic and environmental factors cause an immunological response with the production of ACPA and /or RF, and an inflammatory response characterized by an elevated CRP and ESR.
ACPA are directed to peptides post-translationally modified by the conversion of arginine to citrulline by the enzyme peptidyl arginine deiminase (PAD) and are specific serological markers for a subset of patients with rheumatoid arthritis (approximately 60%). The occurrence of these anti-citrullinated protein antibodies (ACPA) is seen several years before the onset of disease4. The association of HLA-DRB1 alleles is seen exclusively for the ACPA-positive subset of disease. These antibodies exist in around 2% of normal populations and are rare in other inflammatory conditions.
Independent of ethnicity, 10%-15% of an adult population will develop severe periodontitis. Microbial plaque accumulates in the subgingival area and causes an inflammatory response with destruction of the surrounding bone and soft tissue of the teeth. Bacteria are essential but not sufficient to cause the disease. By eliciting bacteraemia systemic inflammatory responses or cross-reactivity leading to auto-immune reactions periodontitis causes an inflammatory burden with damage far beyond the oral cavity. Several studies described a strong link between the presence of periodontitis and RA.
The incidence of the periodontal pathogen Porphyromonas gingivalis in severe adult periodontitis is 70%. P.gingivalis expresses peptidyl arginine deiminase (PAD), the enzyme responsible for citrullination of peptide antigens on arginine residues. Microbial PAD citrullinates arginine in fibrin found in periodontal tissue. The immune system in patients with periodontitis is exposed to citrullinated antigens that might become systemic immunogens. Autoantigens modified by citrullination through exposure to periodontal pathogens might induce the ACPA response in the context of untreated periodontitis. The levels of antibodies against P. gingivalis have been correlated with levels of ACPAs in patients with RA. Citrullinated *-enolase is an immuno-dominant epitope showing sequence similarity and cross-reactivity with enolase from P. gingivalis. This could indicate a role for infection with P. gingivalis in priming the autoimmune response towards ACPA production.
In order to understand molecular events that occur before the onset of RA, in particular related to adaptive immunity, we want to investigate ACPA and/or RF positive patients with arthralgia*s who are at risk for the development of RA.
The investigation will have two arms:
1. Investigation of periodontitis as a risk factor for the development of RA
2. Investigation of the role of cellular immune responses in the development of RA
Investigating risk factors for the development of RA on both a clinical (periodontitis) and immunological level may result in new opportunities for intervention and maybe even prevention of the development of RA.

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Study objective

Primary Objective: To investigate the presence of periodontitis in ACPA and or RF positive patients with arthralgia*s.
Secondary Objective: to unravel the role of the cellular immune response in ACPA positive persons with arthralgia*s who are at risk for the development of RA

Study design

Study design: observational cohort study.

Data to be collected at baseline:
Age, sex, ethnic group, body weight and height, smoking habits, profession or activities of daily living. A health assessment questionnaire (HAQ) (attachment 1) and a SF-36 (attachment 2).
Clinical examination: DAS44 and periodontal screening including a panoramic radiograph.
Sample taking: peripheral blood (5 tubes), gingivocrevicular fluid (GCF), subgingival plaque.
Synovial fluid (SF) will be drawn when applicable. When patients are eligible for periodontal or orthopaedic surgery tissue will be obtained

Study burden and risks

There are no risks associated with participation. The potential benefit to participants will be detection of periodontitis.

Contacts

Public
Universitair Medisch Centrum Groningen

Postbus 30.001
9700 RB Groningen
NL
Scientific
Universitair Medisch Centrum Groningen

Postbus 30.001
9700 RB Groningen
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients who are ACPA and or RF positive and who have arthralgia*s, aged > 18 years.

Exclusion criteria

Fullfilling ACR criteria for RA.
Exclusion criteria (according to the SENIEUR protocol 1984)
1. Infection other than periodontitis.
2. Inflammation other than periodontitis (RA, Crohn*s disease, collagen-vascular diseases).
3. Malignancy, past or present.
4. Other conditions which influence the immune system: diabetes, active thyroid disease, myocardial infarction, stroke or recanalisation of the femoral arteries for claudication <6 months prior to the study.
5. Pregnancy including a 6-months post-partum period as well as breastfeeding.
6. Malnutrition.
7. Alcoholism and drug abuse.
8. Pharmacological interference: prescribed medication for the treatment of a defined disease, use of corticosteroids >10mg/day, antibiotic use during 3 months prior to the study.
9. Periodontal treatment prior to the study.
10. Edentulism.

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-02-2012
Enrollment:	200
Type:	Actual

Ethics review

Approved WMO

Date:	06-02-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Not approved

Date:	12-12-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL38502.042.11