# The influence of apical periodontitis on the concentration of inflammatory mediators in peripheral blood plasma and the metagenomic profiling of endodontic infections.

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First objectives To assess the influence of apical periodontitis on the peripheral blood-plasma concentration of inflammatory mediators and to investigate the metagenome of root canal infections. Other objectives: To search for clusters and patterns...

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Other condition |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON46094

**Source**
ToetsingOnline

**Brief title**
AP, health & metagenome

### Condition

- Other condition
- Ancillary infectious topics

**Synonym**
root tip disease, root tip inflammation

**Health condition**

tandheelkundige infecties

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Academisch Centrum Tandheelkunde Amsterdam
**Source(s) of monetary or material Support:** Ministerie van OC&W,Subsidieaanvragen zijn ingediend bij de Nederlandse Vereniging voor Endodontologie en de Eklund Foundation

## Intervention

**Keyword:** apical periodontitis, blood plasma, inflammation, metagenome infection

## Outcome measures

### Primary outcome

EDTA-plasma values of CRP, IL-8/CXCL-8, MIP-1, MIP-2/CXCL-2, GM-CSF, GCSF, IL-1 alpha, IL-1 beta, IL-1RA, TNF alpha, IL-4, IL-6, IL-12, IL-10, IL-17A, IL-17E, VEGF, RANKL, OPG, interferon gamma, interferon gamma inducing factor and leukotoxin expressed in pg - mcg/L.

Functional metagenome profiles obtained in terms of gene family abundance.

### Secondary outcome

Determination of clusters and patterns in EDTA-plasmavalues before and after the treatment of apical periodontitis.

The composition of the microbial infection and functional metagenomic profiles of the extracted AP-teeth can be correlated to the concentration of inflammatory mediators, previous signs and symptoms of the AP, the size of the radiographic AP lesion and age of the subject.

# Study description

**Background summary**

Good oral health is essential to general health and quality of life. Oral diseases are major public health problems. The impact of oral disease on individuals and communities, as a result of pain and suffering, loss of function and reduced quality of life, is considerable and obvious. Oral disease can also prevail in an a-symptomatic manner. Chronic gingivitis, periodontitis or root-tip inflammation can occur unnoticed for lengths of years. Although they are non-symptomatic, these *silent* chronic inflammatory responses may also have an impact on general health. On the other hand, good or poor general health is likely to contribute to the oral-health status.
The literature suggests various associations between oral and systemic disease. Systemic diseases such as diabetes or cardiovascular disease have been associated with marginal periodontitis and dental caries is correlated with higher blood-serum levels of *1-acid glycoprotein, a pro-inflammatory acute-phase protein. Yet, no causal relationships have been established and so, we do not know if and how one influences the other.
We are keen to investigate whether a local oral inflammatory condition contributes to systemic health. If there is a causal relationship between oral disease and systemic health then, prevention of oral disease becomes even more important than it is today. On the other hand, lifestyle changes towards improved general health may then benefit oral health.
For all inflammatory responses it can be said that the body system engages in a stress response that aims to restore homeostasis. Two types of inflammation can be distinguished. The first is induced by irritants (including pathogens, toxins, damaged tissue and allergens). The other type is induced by extreme deviations of regulated body systems and is modulated by factors such as diet, bodyweight, age, exercise, smoking, fatigue, emotional state etc. This type of inflammation is called chronic low-grade inflammation. Even in healthy individuals some degree of low-grade inflammation can be measured in systemic blood. For good health, it is believed that low-grade inflammation, should be as minimal as possible.
The inflammatory response is dynamic and responsive to challenges and thus, to be able to establish an impact of oral disease on low-grade inflammation an intervention type study should be conducted. The study must be designed to measure possible differences before and after a challenge. However, few oral diseases are suitable challenges, because resolution of oral disease can be very dependent on patient compliance. Lifestyle choices are often major contributors to oral disease and for the patients it can be very difficult to commit to lifestyle changes. Apical periodontitis (AP) or root-tip inflammation on the other hand may provide a good model because after treatment, AP resolves quickly and its resolution hardly relies on patient compliance.
AP is triggered by infection of the root canal system by bacteria from the oral

cavity. When the integrity of a tooth crown is damaged by dental caries or trauma, oral micro-organisms get access to the dental pulp. If the ingress of micro-organisms is not halted in time, the pulp becomes necrotic and the empty root canal system becomes populated with bacteria. Then, bone is resorbed to facilitate the recruitment of inflammatory cells and AP is established. For the resolution of AP, the infection should be eliminated and there are two ways to do so: with root-canal treatment or with tooth extraction. Root-canal treatment is not always effective because bacteria can harbor inside the root-canal system out of reach of disinfectants. Tooth extraction however results in quick resolution of AP.
AP is still poorly understood. Its diagnosis can be cumbersome and when it is detectable on a radiograph, the peri-apical lesions look smaller than they actually are. Histology studies have shown that inflammatory tissue can diffusely spread in between the trabeculae of the bone. Moreover, the cortical bone of the jaw acts as anatomical noise. Besides more understanding about the impact and course of apical periodontitis, additional more precise diagnostic tools are necessary. Many diseases result in a typical pattern of inflammatory mediators and it would be useful to start looking for new biomarkers of oral inflammation in general or AP in particular that can be used in the dental practice.
Resolution of inflammation is an active process and not simply a *turning off * of pro-inflammatory pathways because a whole cascade of anti-inflammatory mediators is initiated to clear the site of inflammatory cells. In case of AP for the repair of the bone defect in the jaw, also bone-stimulatory molecules are produced. For the study, by selecting inflammatory mediators that are likely to occur during the pro/anti-inflammatory or bone-repair stage the effect of the intervention can be followed in time. The intra-subject physiological variation in basal presence of inflammatory mediators will be controlled for by measuring repeatedly within the same subject. At present, blood-diagnostic tools are very sensitive and can detect low quantities of molecules of picograms or less.
Finally, root canal infections can vary greatly in composition of the microbiota and it would be interesting and useful to investigate whether the type of infection influences the severity of the apical inflammatory response.
In the planned study, the extracted teeth will be collected. From the extracted teeth, the microbial DNA is obtained and functional profiles will be determined.
In conclusion, this study has been designed to gain insights into the contribution of AP to low-grade inflammation, to investigate the microbial metagenome, and also to identify biomarkers specific for AP and to study relationships between the microbial metagenome and the plasma concentration of inflammatory mediators. This study is innovative in design, challenge and the choice of monitored inflammatory mediators. The results will aid in the design of evidence-based treatment guidelines of oral disease.

**Study objective**

First objectives To assess the influence of apical periodontitis on the

peripheral blood-plasma concentration of inflammatory mediators and to investigate the metagenome of root canal infections.
Other objectives: To search for clusters and patterns in the inflammatory mediator data before and after tooth extraction in order to identify specific markers of AP or biomarker signatures of AP. To correlate the metagenome data with the inflammatory mediator data to investigate whether type of infection influences the type and severity of the inflammatory condition and resolution thereof.

### Study design

In adults, subjects with AP that cannot be resolved with non-surgical or surgical root canal treatment, the AP-affected tooth will be extracted. The infected tooth will be investigated for the type of infection. At six timepoints, 3 pre- and 3 postoperatively (tooth extraction) peripheral blood plasma will be examined and the plasma concentration of 22 inflammatory mediators is measured. The concentrations are analysed within subjects. The root canal infections are analysed with moleculair biological methods.

### Intervention

not applicable

### Study burden and risks

The subject is requested to complete questionnaires regarding their medical and dental history. Subject undergoes an intra-oral examination possibly with an additional intra-oral radiographic examination depending on the presence of recent intra-oral radiographs. Subject is requested to donate the extracted tooth. The subject is requested to give peripheral blood by venepunction six times during 20 weeks. The subject is requested to visit the investigation site at three extra occasions. The burden is estimated to be doable and procedure related complications of venipuncture are expected to be minor (at the most a small bruise at the puncture site).

## Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

Intervention group
- The subject is 18 - 80 years old.
-After intra-oral examination, AP has been confirmed with an intra-oral radiograph and appears on the radiograph as a radiolucent area around one or more root tips of the affected tooth. AP is diagnosed when in the periapical region, the periodontal ligament is at least twice as wide as in the mid-root regions. A root canal treatment has a poor prognosis or the patient would rather have the affected tooth extracted. The AP tooth is non-symptomatic.
- No other teeth have AP. To confirm this, front teeth are clinically examined. Discoloured teeth or teeth with restorations that do not respond to cold testing or that are tender to percussion or palpation will also be examined with an intra-oral radiograph. In the (pre)molar region, recent bite-wing radiographs are used to screen for deep restorations or dental caries. When there are doubts about the vitality of restored or decayed (pre)molars an additional radiograph is taken.
- The subject has completed the medical history questionnaire.
- The subject wants to participate and donate six blood samples at six different time points and the subject wants to donate the extracted tooth. The subject has signed the IC letter.
- The subject will not undergo dental hygienist* treatments during the study.;Non-intervention group
- The subject is 18 - 80 years old.
- The subject has not had endodontic treatment in the past or previously root-canal treated teeth show no signs or symptoms of AP.
- The subject has completed the medical history questionnaire and is classified as healthy.

- The subject wants to participate and donate six blood samples at six different time points and the subject wants to donate the extracted tooth. The subject has signed the IC letter.
- The subject will not undergo dental hygienist* treatments during the study.

## Exclusion criteria

Intervention group
A potential subject who meets any of the following criteria will be excluded from participation in this study:
- smoking
- pregnancy or lactation
- diabetes mellitus type I,
- chronic inflammatory diseases like m. Crohn
- use of antibiotics 1 month prior with an indication other than AP of the aimed tooth.
- use of corticosteroids or NSAIDs
- chemotherapy or previous head/neck irradiation
- any surgery 6 months prior
- any existing extra-oral swelling
- malaise, colds or influenza one week before or at the start of the study
- prosthesis carriers with stomatitis
- absence of periapical radiolucency in the presence of tenderness to percussion.
- absence of periapical radiolucency in the absence of sensitivity
- previous surgery on tooth considered
- vertical root fracture of tooth considered
- localised periodontitis affecting tooth considered with absence of periodontal disease at other sites;Non-intervention group
A potential subject who meets any of the following criteria will be excluded from participation in this study:
- smoking
- pregnancy or lactation
- diabetes mellitus type I
- chronic inflammatory diseases like m. Crohn
- use of antibiotics 1 month prior
- use of corticosteroids or NSAIDs
- chemotherapy or previous head/neck irradiation
- any surgery 6 months prior
- any existing extra-oral swelling
- malaise, colds or influenza one week before or at the start of the study
- prosthesis carriers with stomatitis;Late exclusion takes place when in the Intervention group
- the healing has been complicated, think alveolitis
- the use of antibiotics for any infection
- change in periodontal scoring index
- change in health/surgery of any kind
- take-up smoking

- other changes in lifestyle
- malaise due to colds, influenza etc. one week before or at the blood-draw appointment ;Or in the non-intervention group
- the use of antibiotics for any infection
- change in health/surgery of any kind
- take-up smoking
- other changes in lifestyle
- malaise due to colds, influenza etc. one week before or at the blood-draw appointment

# Study design

## Design

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|---|---|
| Study type: | Observational invasive |
| Intervention model: | Other |
| Allocation: | Non-randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Basic science |

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 18-01-2017 |
| Enrollment: | 60 |
| Type: | Actual |

# Ethics review

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| Approved WMO Date: | 15-07-2016 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 06-11-2017 |
| Application type: | Amendment |

Review commission: METC Amsterdam UMC

# 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 | NL54832.029.16 |