# The microbiome and the chance of recurrent venous thrombosis determined by the DASH-score (MIDAS-study)

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We want to explore whether disturbances in the oral and gut microbiome can be identified in patients with a high risk of recurrence (determined by a DASH score greater than 1) compared to the oral and gut microbiome of patients with a low risk of...

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

## Summary

### ID

NL-OMON47000

**Source**
ToetsingOnline

**Brief title**
MIDAS study

### Condition

- Other condition
- Embolism and thrombosis

**Synonym**
deep vein thrombosis

**Health condition**

parodontitis

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Universitair Medisch Centrum Groningen
**Source(s) of monetary or material Support:** Mandema stipendium

## Intervention

**Keyword:** microbiome, venous thrombosis

## Outcome measures

### Primary outcome

Any differences between cases (DASH score >1) and controls (DASH <=1) in absolute bacterial load of the oral and gut microbiome, and b) abundance of certain phyli of the oral and gut microbiome. We shall also carry out this analysis with patient who did suffer a venous thrombotic recurrence (cases) with patients who did not suffer a recurrent venous thrombotic event (controls).

### Secondary outcome

- Determine associations between pathologic changes in the microbiome with factor VIII:C, D-dimer, clot lysis time and the endogenous thrombin potential
- Determine associations between pathologic changes in the microbiome and complement activation
- Determine associations between pathologic changes in the microbiome with AGEs
- Determine associations between severity of periodontitis (expressed through PISA) and risk of recurrent venous thrombotic events.

# Study description

### Background summary

In around half of patients who suffer a venous thrombotic event (VTE), no clear cause can be found. The main clinical dilemma in these patients is to decide whether to continue anticoagulant treatment, which carries a significant risk of major bleeding, or to withdraw treatment, which puts patients at risk of a recurrent venous thrombotic event. Several models have been developed to more accurately predict the risk of recurrent VTE, but these have been shown to be too inaccurate for clinical decision-making. One of these models is the DASH-score. By contrast, there has been less attention in recent research for identifying novel, modifiable risk factors for a recurrent VTE beyond the classic risk factors (surgery, cancer, pregnancy/puerperium, estrogen/progestagens containing birth control methods). Identifying such risk factors and treating them would be an ideal strategy to solve the abovementioned clinical dilemma; by doing so, the individual risk of recurrence is lowered and thereby the necessity to expose patients to a risk of bleeding is removed. A possible risk factor for recurrent VTE might be inflammation associated with permeability of the gastrointestinal tract. Diseases in which permeability of this tract (i.e. periodontitis, inflammatory bowel disease) is elevated have already been shown to be associated with an elevated risk of thrombotic events, both arterial and venous. The inflammation associated with this elevated permeability is mainly caused by bacteria leaking into the bloodstream- these induce an inflammatory response with downstream changes in metabolic and coagulation status. This process has been termed endotoxemia. It has already been shown that administration of probiotics is effective for reversing endotoxemia. Disturbances of the human gut and oral microbiome have been associated with increased endotoxemia as well as with systemic low-grade inflammation. We intend to investigate whether such disturbances can be identified in patients who have a high risk of recurrent venous thrombosis, as determined by the DASH score.
Additionally, basic research has shown common pathways between the complement system and the coagulation cascade. Complement has already been implicated in several diseases that have a distinct thrombotic presentation, such as paroxysmal nocturnal hemoglobinuria, for which an inhibitor of complement (Eculizumab) has proven to be a promising therapeutic agent. To our knowledge, complement activity has not yet been explored by epidemiological methods as a risk factor for venous thrombosis.
Finally, skin autofluorescence (SAF) measurement of Advanced glycation end products (AGEs) has been validated as a non-invasive method of measuring skin AGEs. This measurement method has been shown to be predictive of of arterial cardiovascular disease. Epidemiologic research has shown that arterial disease and venous thromboembolism probably show common risk factors than previously thought.

**Study objective**

We want to explore whether disturbances in the oral and gut microbiome can be identified in patients with a high risk of recurrence (determined by a DASH score greater than 1) compared to the oral and gut microbiome of patients with

a low risk of recurrent venous thrombosis. Second, we will determine whether pathologic changes in the microbiome are associated with a procoagulant state, measured by factor VIII:C, D-dimer, clot lysis time and endogenous thrombin potential, or with activated complement pathway, or with increased load of AGEs. Finally, we will follow-up on patients for three years to assess the incidence of venous thrombosis. We will then compare microbiome composition between subjects who suffered a recurrent venous thrombotic event and those who havent.

### Study design

cross-sectional study and prospective cohort study

### Study burden and risks

Subjects will visit the UMCG outside of routine care once. Before this visit, subjects must collect a faeces sample and store this according to instructions. During the study visit subjects will undergo invasive procedures which may be painful (measurement of PISA). Formally, measurement of PISA is not a predefined outcome parameter in this study, but evaluation of periodontal status is necessary before selecting the appropriate site of sampling for our analysis of the oral microbiome: the oral microbiome sample will be collected from the deepest gingivocrevicular pockets in each quadrant.
Additionally, patients will undergo venous sampling once. We will draw approximately 28 ml of blood (2x 9ml citrate, 1x 10 ml EDTA) for measurements of coagulation parameters and complement levels

## 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

- 18 years of age or older
- First idiopathic or oral contraceptive use-associated deep vein thrombosis of the leg or idiopathic pulmonary embolism
- No further or other indication to continue anticoagulant therapy
- Understand spoken and written Norwegian or Dutch or English.
- Able to give written informed consent

## Exclusion criteria

- Liver failure
- Clinical active infection or auto-immune disease
- Pregnancy or puerperium

# Study design

## Design

**Study type:** Observational invasive

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

### Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 13-05-2016 |
| Enrollment: | 70 |
| Type: | Actual |

## Ethics review

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| Approved WMO Date: | 27-10-2015 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 23-08-2018 |
| 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 | NL51233.042.15 |