Alpha-1-antitrypsin deficiency in a diverticular disease population

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Primary Objective: To determine the prevalence of A1AT-pathology by genotype analysis of patients with DD and comparing this to a population without DD.Secondary Objective:To determine whether the population with A1AT pathology develops more often...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Diverticular disorders
Study type	Observational invasive

Summary

ID

NL-OMON47360

Source
ToetsingOnline

Brief title
ALADDIN-study

Condition

- Diverticular disorders

Synonym
diverticulum, sac-like protrusion of the colonic wall

Research involving
Human

Sponsors and support

Primary sponsor: Noordwest Ziekenhuisgroep
Source(s) of monetary or material Support: Subsidie is aangevraagd en toegekend door Tergooi ziekenhuis en Noordwest academie

Intervention

Keyword: Alpha-1-antitrypsin pathology, Diverticular Disease, Diverticulitis, Diverticulosis

Outcome measures

Primary outcome

The main exposure factor is any kind of deviations in A1AT

Secondary outcome

Secondary exposure factors are:

- Concentration of alpha-1-antitrypsin

- Inflammation parameters

- Risk factors for developing diverticulosis such as

* Genetic factors

o Family history

* Environmental factors:

o Low-fiber diet

o Obesity

o Decreased physical activity

o Use of corticosteroids

o Use of NSAIDs

o Alcohol

o Caffeine intake

o Cigarette smoking

o Polycystic kidney disease

* Epidemiological factors

o Age

o Geography

o Life style

o Ethnicity

Other study parameters

Clinical course:

- Diverticulitis related hospital admission

- Days of hospital admission related to diverticullitis

- In need of surgery related to diverticulitis

Clinical course:

- Inflammation parameters (CRP, leucocytes) during diverticulitis episode

- Hinchey score during diverticulitis episode

- Complications during diverticulitis episode

Since A1AT is also an acute phase protein, this protein can interact with the inflammation process. The concentration of this protein is also affected by cancer, liver disease, pregnancy, estrogen therapy, blood transfusions and intravenous augmentation therapy. This is why genotype analysis needs to confirm the diagnosis.

Study description

Background summary

The incidence of diverticular disease (DD) is increasing worldwide and is becoming a significant burden on national healthcare systems.1 Diverticulosis is the most common pathological finding in routine colonoscopy. It comprises both diverticulitis and diverticular hemorrhage. Obesity, smoking, and various inheritable disorders raise an individual*s risk of diverticulosis5. The underlying pathophysiological mechanism that causes the formation of colonic diverticula is not clear. The dominant theory is based on fibre deficiency, which was set in 19712. This theory states that fibre deficiency results in decreased intestinal contents and smaller size of the lumen. Since the colonic muscles are contracting continuously in order to transmit and expel the stool, an increased intraluminal pressure is formed. This increased pressure leads to the formation of diverticula at the weakest anatomical locations in the wall. These predestined weak spots in the colonic wall are formed due to the entering of terminal branches of the colonic arteries and are called vasa recta.

However, within the last decade, a new hypothesis has emerged, which may be helpful in understanding the etiology of diverticulosis. This hypothesis is based on the fact that diverticulosis is an age-related disorder, since ageing eventually leads to the altering of colonic epithelia, colonic mucosal flora and microbial environment3. Ageing induces a declining colonic wall mechanical strength, which can be partly attributed to changes in collagen structure. Wess et al preformed a study to investigate how the collagen structure changes in colonic diverticulosis.4 The results indicated that colonic collagen from subjects affected by colonic diverticulosis had a higher number of cross-links than subjects with unaffected colonic tissue. This illustrates that the structural changes to tissue collagen affected by colonic diverticulosis have a greater impact than the changes that occur as part of the natural ageing process. Consequently, colonic diverticulosis could be the result of an exaggerated and premature ageing process and intrinsic changes in collagen structure.

Alpha-1-antitrypsin (A1AT) is a protease inhibitor of the proteolytic enzyme elastase and also of the proteases trypsin, chymotrypsin, and thrombin. It is part of a larger family of structurally unique serine protease inhibitors, referred to as serpins, which have also been implicated in the pathogenesis of neurodegenerative diseases, angioedema, and coagulation abnormalities, collectively called *serpinopathies*.6,7 It is assumed that there are at least 116 million carriers (PiMS and PiMZ) and 3.4 million deficiency allele combinations (PiSS, PiSZ, and PiZZ) worldwide. Furthermore, A1AT-deficiency is one of the most common hereditary disorders in the world and is not only a disease among Europeans, yet, is one that affects individuals

from all racial subgroups worldwide.8

A large part of the A1AT-deficiency population eventually develops severe pulmonary pathology. Sometimes a lung transplantation is necessary to improve long-term survival.9 In the field of lung transplant surgery, the correlation between A1AT-deficiency and gastro-intestinal complications has been highlighted. Gastrointestinal complications after lung transplantation have been reported with incidence rates ranging from 3% to 51%, but the underlying mechanisms are poorly understood.10,11,12 Elective abdominal operations are relatively safe in properly prepared lung transplant recipients. However, laparotomy for urgent surgical conditions, such as bowel resections and a subtotal pancreatectomy, are associated with increased morbidity and mortality rates. This is partly caused by the seriousness of acute abdominal conditions and the operation, but also by the status of the lung transplant as manifested by previous rejection episodes, perioperative steroid dosages and FEV1 values.13 Bredahl et al discovered that A1AT-deficiency is the only significant risk factor identified for gastrointestinal complications that required laparotomy within three months after lung transplantation.10 Recently Tanash investigated cause-specific mortality in individuals with severe A1AT deficiency in comparison with the general population in Sweden. They discovered PiZZ individuals had an increased mortality due to respiratory and hepatic disease, diverticulitis, and pulmonary embolism was markedly increased compared with the age- and sex-matched Swedish population. We think this finding supports our hypothesis that A1AT could have a direct relation with developing diverticula. 14

The ALADDIN-study aims to determine additional causes for developing diverticulosis with respect to the already poorly understood causes. An interesting hypothesis is that connective tissue diseases, in particular deviations in the A1AT protein contribute to the development of diverticulosis. Once there is a better understanding of the relation between A1AT and the prevalence of diverticulosis, it will be possible to investigate alternative treatment approaches for this global health issue. For example, a screening program for patients who are in need of lung transplantation could be evaluated since A1AT deficiency is common in this population. Moreover, preventive screening could be an option in these specific groups to identify early abdominal problems, focusing on diverticulosis and its complication diverticulitis, cholecystolithiasis and gastric/duodenal ulcers. Once it is clear that these patients have a higher risk on serious abdominal problems, a more aggressive approach could be used.

This study aims to investigate whether deviations in A1AT contributes to the development of diverticula. Better understanding of the association between A1AT and diverticula could possibly contribute to changes in the treatment of diverticulitis. After an extensive literature review, we have concluded that a link between A1AT and the presence of diverticula has never been explored before. However, there is a lot of circumstantial evidence that

there is a link between these pathologies.

Study objective

Primary Objective:
To determine the prevalence of A1AT-pathology by genotype analysis of patients with DD and comparing this to a population without DD.

Secondary Objective:
To determine whether the population with A1AT pathology develops more often an episode of diverticulitis, whether it leads to more hospital admissions and to more diverticulitis related surgeries compared to the population without A1AT pathology.

Study design

Patients with abdominal pain, who visit the ER from 2017 till 2019 or are admitted in hospital and develop abdominal pain and have to undergo an abdominal CT scan will be analysed. The flowchart in Figure 1 summarizes the process of inclusion and exclusion. The research group will consist of patients diagnosed with diverticula, whereas the control group will consist of patients who have no diverticula or only a few of them. A patient is eligible for the research group if an abdominal CT scan reveals several diverticula whereas a patient is eligible for the control group if an abdominal CT scan shows no diverticula or only a few of them. . 16,17,18,19,20,21

During the visit in which the patient undergoes an abdominal CT scan, each eligible patient will be asked if he or she wants to receive any information with regards to this study. The conversation will take place after the CT scan. If they do want to receive information, the patient information folder will be provided. After receiving the necessary information, the patient will reflect whether he or she wants to participate in this study. After this period, the individual will be asked whether he or she wants to participate. If they do want to be part of the study, informed consent will be obtained.

After the selection procedure, blood samples will be collected in order to determine the concentration of A1AT in serum. We will also perform genotype analysis to determine specific phenotypic variations. Genotype analysis uses allele-specific amplification that allows the variants to be identified, such as S or Z. Although the optimum formula for A1AT deficiency testing has not been formulated, serum level measurement combined with genotype analysis is often used in clinical setting.

Once all data is collected patients with diverticula will be compared to patients without diverticula(or only a few diverticula). Furthermore, evaluation on the development and severity of diverticulitis in both groups

will be performed by closely monitoring them during and after their hospital visit or hospital admission. We will also gain additional information from the questionnaires and patient records about previous hospital admissions as a result of diverticulitis.

The design of this study is a multi centre prospective case-controlled study.

Study burden and risks

The patients who will participate in our research will have to undergo a venepuncture procedure, which will result in 3 blood samples. During the same visit they will be asked to fill out a questionnaire to provide additional information.

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

Research group:
- Have acute abdominal pain existing more than two hours* and less than five days,
- Has a CT-abdomen that shows diverticular disease,
- Age above sixty,
- Be mentally competent, and
- Informed consent.;Control group:
- Have acute abdominal pain existing more than two hours* and less than five days,
- Has a CT-abdomen that shows no diverticular disease,
- Age above sixty,
- Be mentally competent, and
- Informed consent.

Exclusion criteria

- Does not meet the inclusion criteria
- Is mentally incompetent

Study design

Design

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

Recruitment status:	Recruiting
Start date (anticipated):	30-05-2017
Enrollment:	230
Type:	Actual

Ethics review

Approved WMO Date:	13-06-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-02-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Not approved Date:	18-01-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-12-2018
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

ID: 28920
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL55016.094.15
OMON	NL-OMON28920