Improved laboratory diagnostics for celiac disease.

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Develop cellular blood tests applicable in routine specialized diagnostic settings for CD in patients on a GFD and patients with idiopathic villous atrophy and atypical presentation of CD. **

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal inflammatory conditions
Study type	Observational invasive

Summary

ID

NL-OMON54772

Source
ToetsingOnline

Brief title
Celiac Disease Diagnostics

Condition

- Gastrointestinal inflammatory conditions

Synonym
celiac disease, gluten intolerance

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Maag Darm en Leverstichting en de Nederlandse Coeliakie Vereniging

Intervention

Keyword: Celiac Disease, Diagnostics, Peripheral Blood

Outcome measures

Primary outcome

1) Detection method for gliadin specific T-cells in peripheral blood

2) Determine celiac disease associated duodenal γδT-cell phenotype

3) Detection of γδT-cells with *CD-related phenotype* in peripheral blood

4) Sensitivity and specificity of cellular blood test (gliadin specific T-cells

and γδT-cells with *CD-related phenotype) for diagnosis of CD in patients on a

gluten containing or GFD in a routine specialized diagnostic setting.

5) Sensitivity and specificity of cellular blood test (gliadin specific T-cells

and γδT-cells with *CD-related phenotype) for diagnosis of CD in CD patients

that take a personalised glutenchallenge in a routine specialized diagnostic

setting.

Secondary outcome

Not Applicable

Study description

Background summary

Gluten intake is associated with irritable bowel disease and a gluten free diet (GFD) is increasingly used without prior diagnosis as it is thought to reduce abdominal complaints. While a GFD is essential for celiac disease (CD) treatment, it may be detrimental in the general population as it changes intake of fiber and vitamins. CD patients need additional diagnostics for other auto-immune diseases and specific follow-up. Identification of CD patients and exclude CD diagnosis in individuals on a self-initiated GFD is therefore important. Standard diagnostic tests fail as they become negative in

individuals on a GFD. Gluten challenge (GC) may induce reappearance of (auto)antibodies and duodenal abnormalities but in a substantial proportion of CD patients a GC is insufficiënt. Furthermore, in patients with atypical presentation of CD and/or patients with antibody deficiencies (Common Variable Immune Deficiency) standard diagnostic tests may be inconclusive. For this group of patients there is a medical need for additional tests that will help the clinician to either confirm or exclude the diagnosis CD.
Gliadin specific T-cells are detectable in blood of CD patients, even after prolonged GFD, but undetectable in gluten consuming controls. Furthermore, the γδ T-cell proportion among duodenal intraepithelial lymphocytes (IEL) is high in CD and remains high after recovery on a GFD.

Study objective

Develop cellular blood tests applicable in routine specialized diagnostic settings for CD in patients on a GFD and patients with idiopathic villous atrophy and atypical presentation of CD. **

Study design

IEL and LPL will be isolated from duodenal biopsies. Dextramer/Tetramer technology will be used to identify gliadin specific T-cells in peripheral blood, using the additional differentiation, activation and homing markers (CD45RA, CD62L, CD38, integrin β7). We will use the methodology used to detect rare malignant cells in minimal residual disease in whole peripheral blood of patients in remission of hematological malignancies. This will be applicable in a diagnostic routine setting as it does not require enrichment of cells prior to analysis but involves analysis of small populations in large numbers of cells after bulk-lysis of erythrocytes.

Extensive phenotyping of γδT-cells in IEL, LPL and peripheral blood will be done by multi (up to 24) parameter analysis using AURORA technology
The AURORA advanced flow-cytometry technology (3-laser system) enables a sensitive 24 color assay due to its special technology analyzing the full spectra of the fluorochromes. This approach overcomes limitations of spectral overlap in standard flow cytometry.

The methodology to detect gliadin specific T-cells and γδT-cell phenotyping panels using the markers listed above, will first be established. For this we will use both peripheral blood and duodenal biopsies from active CD patients, CD patients on a gluten free diet and non-celiac disease controls.

The phenotype of the cells of active CD patients and patients responding to a GFD will be compared to γδT-cells in IEL and LPL of patients with abdominal complaints without evidence of CD. Subsequently we will investigate whether these cells are detectable in peripheral blood and in potential CD patients on

a self-initiated GFD. We will initially focus on cell surface markers. The multidimensional data will be analyzed with specialized software such as FCS express and tSNE analysis to establish the most discriminating clinical relevant phenotype in order to limit the marker panel to a routinely applicable flow-cytometry based diagnostic test. If this panel does not lead to a *CD related phenotype*, we will explore additional markers which will also include intracellular functional markers such as IL-21, IL-17A, IFNγ, Granzyme B and CTLA4.

We will subsequently use the established optimized panels to determine presence of gliadin specific T-cells and γδT-cells with specific phenotypes in IEL (γδT-cells only), LPL and peripheral blood of active CD patients, patients on a GFD and controls to gather statistical support for the detection of gliadin specific T-cells and/or γδT-cells with a *CD-related phenotype* in peripheral blood of CD patients and CD patients on a gluten free diet.

Study burden and risks

There are no direct benefits for the patients in this study. The risk of participation is considered to be very low. In adults, there is a limited risk to taking extra biopsies during a planned endoscopy. Taking biopsies during endoscopy can cause intra-intestinal or intramural haemorrhage, or even perforation. The risk is estimated to be < 1 : 10000. A maximum total of 6 extra biopsies will be taken during endoscopy.

Celiac disease patients taking a gluten challenge can experience celiac diesease related complaints. There are no risks related to a short term (max 4 weeks) gluten use in CD patients. Blood will be drawn solely for the purpose of this study in the group of healthy volunteers and the group of celiac disease patients that take a glutenchallenge, risks of venapuncture are negligable. Healthy controls need to vistit the hospitla once, the CD patients will need to visist the hospital at least two times and maximal 5 times.

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 old
- Indication for a duodenal biopsy for the diagnosis or monitoring of:
active celiac disease, celiac disease on gluten free diet, suspicion
celiac disease, dyspeptia, potential celiac disease OR previously diagnosed
with celiac disease, dyspepsia or NCGS without an indication for duodenum biopsy
- Given informed consent
- HLA-DQ2.5 positive (in exceptional cases where endoscopic examination is
already performed before HLA typing and the patient turns out to be HLA-DQ2.5
negative, the γδT-cell data can be used for analysis.

Exclusion criteria

- No informed consent
- Insufficient knowledge of Dutch language and/or inability to understand the
information provided.
- Systemic immune suppressive treatment for the past 3 months,
- pregnancy (not applicable to groups 2b and 4b)
- HIV, Hepatitis B or C positive status
- Severe disorders within the last 6 months, e.g. cancer

Study design

Design

Study type:	Observational invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-01-2020
Enrollment:	90
Type:	Actual

Ethics review

Approved WMO Date:	25-04-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-01-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-09-2022
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	NL68731.029.19