Is the gut microbiome associated with residual beta cell function in longstanding type 1 diabetes?

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Primary Objective: Study associations between residual beta cell function and gut microbiome composition and circulating immune cell functionSecondary Objective: By recording residual beta cell function in these individuals, this study will act as a...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Observational invasive

Summary

ID

NL-OMON49369

Source
ToetsingOnline

Brief title
GUTDM1: Residual beta cell function and microbiome in type 1 diabetes

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
Juvenile diabetes, type 1 diabetes

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Beta cell function, Microbiome, Type 1 diabetes

Outcome measures

Primary outcome

2-hour post-meal urinary C-peptide / creatinine ratio as a validated marker of

beta cell reserve in type 1 diabetes mellitus.

Secondary outcome

Secondary study parameters/endpoints

• Frequency Hypoglycemia

• Awareness hypoglycemia

• Diabetic complications

• Circulating immune cell pannel

• Fecal microbial composition (ILlumina sequencing)

• Plasma metabolomics

• DNA buffycoat (epigenetics)

Other study parameters (covariates and confounders)

Derived from the questionnaire:

• Sex

• Age

• Duration of type 1 diabetes

• Smoking

• Medication use

• Diabetic complications

Recorded at the study visit

• Blood pressure

• Body weight

• Height

• Glucose time in range from continuous glucose monitoring device. In Netherlands these devices are reimbursed for all individuals with T1D. If a participant doesn*t have one a flash glucose monitoring device can be borrowed from the study group, provided by the investigator.

Biochemistry

• Serum creatinine and calculated eGFR

• Lipid profile (total cholesterol, HDL, LDL triglycerids)

• Albuminuria/creatinine ratio

• HbA1c

• CRP

Study description

Background summary

In the Netherlands, 100.000 people have type 1 diabetes mellitus (T1D), and this number increases by 4% each year. T1D is associated with considerable morbidity. In fact, childhood-onset T1D reduces life-expectancy by ±20 years, surpassing many childhood cancers. However, any therapeutics directly targeting underlying autoimmunity invariably have failed. Manipulation of the gut microbiome is thus a promising candidate to improve T1D outcomes.

Autoimmune β-cell destruction is the hallmark of T1D, and this process likely originates from an immune response to gut microbiota. Indeed, the composition of gut microbiota is altered in T1D, even before T1D is diagnosed. In fact,

antibodies against gut microbiota predict the onset of T1D. Activation of innate immunity by intestinal microbes may be critical for accelerating T1D, by expanding T-helper type 17 (Th17) cells in the small-intestine. Another mechanism linking the microbiome to immunological tone are microbial metabolites, and these compounds are altered in T1D. In addition to increased Th17 and decreased regulatory T-cells, the importance of T-cell exhaustion in T1D is increasingly recognized. Slow progression of T1D is linked to more exhausted cytotoxic T-cells in infiltrated islets. While most microbiome research focused on bacteria, gut virusses (virome) are implicated in development of T1D and T-cell exhaustion. The association between the gut microbiome/virome, T-cell exhaustion and immuno-tolerance in T1D constitutes an important knowledge gap and may serve as a therapeutic target in T1D, that will be adressed in this cohort study.

Study objective

Primary Objective: Study associations between residual beta cell function and gut microbiome composition and circulating immune cell function

Secondary Objective: By recording residual beta cell function in these individuals, this study will act as a data-base for follow-up study in which we will invite individuals with to employ fecal microbiota transplants from individuals with a preserved beta cell function into individuals with only minimal residual function in order to improve their beta cell function. In the current study we will only ask individuals if we may contact them for these envisioned future studies.

Study design

Participants are recruited from outpatient clinics in the greater Amsterdam region, and the study will be performed in the AMC location of the Amsterdam UMC. Participants are approached by call list or by their attending physician / diabetes nurse in the Amsterdam region and are asked to provide a urine sample (collected in boric acid preservative) that is given 2 hours after their main meal of the day. Urine C peptide is measured in all samples by an immunoassay in an external laboratory. Thresholds for c-peptide / creatinine ratios in the urine are defined as previously in: detectable (> 0.001 nmol / mmol), minimal (>= 0.03 nmol / mmol) and residual / conserved (>= 0.2 nmol / mmol) beta cell function, associated with a mild phenotype of reduced risk of diabetic complications and hypoglycemia.

We also collect:
1) blood pressure, weight and height
2) Blood samples for immunological and biochemical assays, gene expression and

HLA typing (and DNA from buffycoat)
2) Stool samples for microbiota sequencing
3) Questionnaires registering medication use, frequency and nature of hypoglycaemic episodes, presence of diabetic and cardiovascular complications
4) Food diary
5) With a continuous glucose monitor, we will record their glucose time in range, and hyper- and hypoglycemic episodes recorded by their device.

With these data, the associations between microbiome composition and residual beta cell function and T cell autoimmunity will be investigated.

Study burden and risks

Currently no causal therapy for T1D exists. This study aims to identify the gut microbiome as a completely new therapeutic target to improve the outcome of T1D by increasing the residual beta cell function by investigating associations between residual beta cell function and microbiome composition. Therefore, this study has no direct benefit for participants yet, but may play an important role in the development of promising treatment to finally find a causal therapy for T1D. The risk associated with this study is very low. Individuals are asked to be fasted for blood collection. This is associated with a small risk of hypoglycemia, similar to when individuals with T1D take blood fasted for usual care.

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

Type 1 diabetes, >18 years old, visit outpatient clinic Amsterdam region, ability to provide informed consent

Exclusion criteria

- Active infection at the time of inclusion (not to influence T-cell function)
- Antibiotic or proton-pump inhibitor use last 3 months (not to influence microbiome)
- Unwillingness to donate feces, urine and/or blood
- Inability to provide informed consent based on cognitive function, language barrier or other reasons
- Absence of large bowel (ie colostomy).

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting

Start date (anticipated):	23-11-2020
Enrollment:	500
Type:	Actual

Ethics review

Approved WMO Date:	03-07-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-09-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-04-2021
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	NL73189.018.20