Novel biomarker delineating pathophysiology in human type 1 diabetes

Summary

Thomas Pieber, CBmed Center for Biomarker Research in Medicine, Division of Endocrinology and Diabetology, Department of Internal Medicine, Medical University of Graz

Supervisor: Prof. Dr. Thomas Pieber
Availability: This position has been occupied.
Offered by: Medical University of Graz
Application deadline: Applications are accepted between February 01, 2017 00:00 and March 19, 2017 23:59 (CEST)

Description

Background:
Multiple causes are thought to be involved in the development and pathophysiology of type 1 diabetes (T1D). Prenatal genetic factors such as distinct human leukocyte antigen (HLA) variants, are suspected to play a role in the pathophysiology of T1D. Apart from genetic susceptibility, environmental factors such as increased hygiene, altered diet, increased obesity and less breastfeeding seem to play a role in this autoimmune process. But also altered lifestyle, causing less endogenous vitamin D production by decreased exposure to sunlight are suspected to have an impact on T1D development. Another hypothesis suggests enteroviral infections to trigger the onset of T1D. A combination of all these factors probably leads to the onset of auto-reactivity, including production of auto-antibodies by B-cells, activation of self-reactive T-cell clones and decreased immune regulation. The subsequent destruction of insulin-producing pancreatic β-cells finally leads to insulin deficiency and the clinical onset of T1D.

In recent years, alterations in the microflora, immune system and epithelial barrier function of the gastrointestinal tract are put forward as key components in T1D progression. The impact of the intestinal microflora on immune homeostasis in the gut but also at systemic sites has gained tremendous interest in the last few years. Vitamin D deficiency in early life accelerates T1D in diabetes-prone mice, while high-dose vitamin D inhibits disease development in mice and improves suppressor function of regulatory T cells in patients with T1D.

The intestinal microbiota has been shown to interact with and modulate host metabolism, nervous system and cells of the immune system. Immune cells of the duodenum act as a first defense line for foodborne pathogens, together with immune cells of the stomach. Hence, studying this interface between host and the intestinal microbiota is subject of intense research.

Hypothese and Objectives:
Studying whether vitamin D combined with the GLP1 analogue liraglutide can alter the course of T1D by modifying the gut microflora/metabolites, modulating the intestinal and peripheral immune system, and/or changing the epithelial barrier function is of great importance in our understanding of disease progression but also of mechanisms by which vitamin D and liraglutide can affect disease progression. Longitudinal analyses and mechanistic studies can identify the basis for gut microbiome and immune system modulation of T1D and identify biomarkers and promising therapeutics to prevent disease, delay or even reverse diabetes onset. In this regards, we hypothesize that administration of regular high doses of vitamin D combined with a short-course of liraglutide might be a promising approach to restore immune homeostasis in T1D. This project aims to discover disease related biomarkers in subjects exposed to combination therapy of vitamin D together with insulinotropic agents such as glucagon-like peptide 1 (GLP-1) agonists in the early course of the disease. Keyplayer in the immune system will be characterised by immuno-phenotyping and functional assays will be used for the discovery of new biomarkers. We hypothesize that vitamin D could serve as one possible agent in the design of immunomodulatory combination therapies for T1D. GLP-1-targeted therapies, known to stimulate insulin secretion, may also affect inflammatory and immune pathways involved in T1D.

Milestone first year:
Identification of biomarkers for gut barrier function and immune Response (e.g. Treg function). Validation of identified biomarkers.
Milestone second year:
Intervention in newly diagnosed type 1 diabetic patients in a RCT or case control study

Milestone third year:
Data Analysis, publication, finalization of thesis

Timeline:
Month 1-3: Literature Analysis
Month 4-6: Clinical learning: pathophysiology of type 1 diabetes, state of the art therapy (intensified Insulin therapy, Patient education).
M 7-12: Screening, selection and Validation of gut barrier function test; Validation of Treg function test.
M 13-30: Development of clinical protocol and CRF, statistical Analysis plan, recruitment, and clinical study Performance.
M 31-36: Data Analysis, publication

Methodology:
Clinical Trial Performance according GCP Gut barrier function test Flow cytometry and cell culture Statistical Analysis of clinical trials

References


To get more information or to apply online, visit https://mug.glowbase.com/positions/64 or scan the code on the left with your smartphone.