Project Assignment

Background

Type 1 diabetes mellitus (T1D) is a multifactorial disease characterized by an absolute lack of insulin due to the destruction of beta cells by islet autoimmunity. It is generally accepted that various environmental factors influence the genetic background in determining T1D susceptibility, but the exact mechanism leading to beta-cell destruction remains elusive. The chief candidates for triggering and/or accelerating islet autoimmunity include viral infection and nutritional factors including gluten (collective name for glutenin and gliadin, proteins of wheat, barley and rye).

In animal models, a gluten-containing diet had a proinflammatory effect on the immune system, leading to proportional changes in regulatory T-cell subsets with increased numbers of Th17 cells in pancreatic lymph nodes and inflammatory cytokine patterns in comparison with a gluten-free diet (GFD). The exclusion of gluten from the diet of NOD mice led to a significant reduction in diabetes incidence, especially after elimination of gluten exposure in utero.

In humans, only a few works have been published studying the role of gluten on T1D risk and in the preclinical disease course. The results from epidemiological studies are ambiguous: the TEDDY study suggested a higher risk of T1D-associated autoimmunity with delayed introduction of gluten, whereas the German BABYDIET study found no association between the timing of gluten introduction and T1D in first-degree relatives carrying high-risk HLA genotypes. Another sizable birth cohort study suggested a window of exposure to cereals outside of which the risk for autoimmunity is increased. Anecdotal evidence also proposed a positive effect of a GFD on beta-cell preservation.

To date, only a few human intervention studies with a GFD have been published. Secondary T1D prevention was tested in a German study: no appreciable reduction was found in the autoantibody levels, nor was the diabetes onset delayed after 12 months of the GFD in 7 multiple-antibody-positive children compared to 30 matched children on a standard diet. Interestingly, none of the study subjects developed T1D while on the GFD; only after re-exposure to gluten did the subjects develop T1D. Another moderately sized secondary prevention study of 17 young multiple-antibody-positive first-degree relatives showed no decrease in autoantibodies after six months of a GFD, but rather interestingly, the insulin response to intravenous glucose significantly improved while on the GFD and dropped after its cessation.

Tertiary prevention, i.e., an intervention with a GFD to preserve beta-cell function in subjects with recent-onset T1D, was reported on 15 newly diagnosed T1D children from Denmark. The study showed a prolongation of the partial remission period as well as better metabolic control in the subjects on a GFD compared to historical controls. Together, although scarce, this evidence indicates that there may be an effect of a GFD on beta-cell autoimmunity, calling for a more robust prospective trial with closely selected controls and having the compliance controlled.

Study Design

Forty-six children from two tertiary-care pediatric diabetes centers were prospectively recruited into this nonrandomized intervention trial. Participation was offered to all patients newly diagnosed with T1D who came to these centers from Jan. 2016 to Jan. 2017 (135 from Motol University Hospital, 39 from Královské Vinohrady University Hospital in Prague, Czech Republic) and who fulfilled eligibility criteria (127 in both centers). Eligibility criteria were (i) T1D diagnosed according to the ADA, (ii) age between 4 and 18 years at the onset, (iii) the positivity of a least one T1D-associated antibody (IAA, anti-IA2, anti-GAD65), (iv) the presence of one or both T1D risk haplotypes (HLA-DQB1*03:02-DQA1*03, DQB1*02-DQA1*05), (v) no coeliac disease and a negativity for anti-tissue transglutaminase antibodies, (vi) body mass index below +2SD of the age and height standard and (vii) no concomitant disease potentially influencing immune response or gluten sensitivity.

The assignment between the intervention and control group was decided by the parents. The intervention group (26 subjects) started with a strict GFD immediately after the first mixed-meal tolerance test (MMTT), while 20 control subjects remained on a standard gluten-containing diet throughout the study period. A few subjects were withdrawn from the study by their parents and several GFD subjects who completed the study were subsequently disclosed as noncompliant with the GFD.

Mixed-meal tolerance tests (MMTTs) were performed at 1, 6 and 12 months after the T1D onset. All subjects received 4 ml per kg body weight of liquid meal Ensure Plus (Abbott Laboratories, Zwolle, The Netherlands), and their C-peptide and glycemia levels were measured at baseline and every 30 minutes up to 150 minutes. All MMTTs were performed after overnight fasting, and children received only their evening dose of long-acting insulin analog.

The study visits were scheduled at 1, 3, 6, 9, and 12 months after the T1D onset. During these visits, subjects' HbA1c, total daily insulin dose, body weight and height were collected and the insulin dose adjusted hemoglobin A1c (IDAA1c) was calculated. The value of IDAA1c at or below 9 is considered a marker of partial clinical remission.

Primary outcome Decline in residual beta-cell capacity to produce insulin assessed by a mixed-meal tolerance test (MMTT) at 12 months after diagnosis. This was measured by C-peptide area under the curve (AUC).

Secondary outcomes

- metabolic control (measured by glycated hemoglobin, HbA1c)
- insulin dose
- partial clinical remission marker IDAA1c
- fasting C-peptide assessed by MMTT
- peak C-peptide assessed by MMTT

Project Objectives

The primary aim of this study is to investigate the effect of GFD on the progression of beta-cell loss in nonceliac children during the first year after T1D onset.

1. Find out whether the decline in residual beta cell capacity was faster for the patients on standard diet compared to the patients on GFD.
2. Find out whether the study arms (standard diet vs. GFD) differed in the course of progression of the secondary outcomes.

Make conclusions and recommendations about the impact of gluten-free diet early after the diagnosis of Type 1 diabetes mellitus.

Dataset

The dataset can be downloaded from the course webpage in the SIS. The file contains a single dataframe called `glu`, with 46 observations. Attached in the SIS is a variable coding sheet explaining the meaning of all variables.

Requirements

Put together a project report that follows the required structure. In the report, describe the methods applied to the problem, summarize the results, meet the project objectives, make correct and justified conclusions, and discuss the appropriate interpretation of the results.