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## Digestive Complications in Diabetes – the DICODI population study

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### ABSTRACT

**Background:** Diabetes type 1 and type 2 may develop gastrointestinal complications e.g., gastroparesis and gastroenteropathy. Concomitant celiac disease and pancreatic exocrine insufficiency occur with high prevalence in diabetes and with symptomatic overlap. Consequently, it is a challenge to disentangle symptoms of these conditions and separate them from functional dyspepsia. We aim to develop a clinical decision-support tool to differentiate the underlying disease in a plethora of gastrointestinal symptoms.

**Methods:** An internet-based computerized survey will collect basic characteristics (diabetes type, age, gender, duration, HbA1c, treatment) and patient reported outcomes by validated questionnaires focusing on (1) gastroparesis using Gastroparesis Cardinal Symptom Index; (2) gastroenteropathy using Gastrointestinal Symptom Rating Scale; (3) celiac disease using Celiac Symptom Index and (4) pancreatic exocrine insufficiency with Pancreatic Exocrine Insufficiency Questionnaire. Logistic regression and multiple regression analyses will identify risk factors and gastrointestinal complications. Cluster analyses and machine learning will classify different symptoms and co-existing presentations, into a likely diagnosis. We seek biomarkers for autonomic neuropathy by characterizing development of retinopathy using the Visual Function Questionnaire-25 and peripheral neuropathy by the Michigan neuropathy questionnaire. Participants are re-examined yearly for disease progression over time.

**Results:** From focus group studies gastrointestinal symptoms are of major concern in diabetes. Potentially, estimates of symptom prevalence, risk factor identification and classifications of gastrointestinal complications can be unraveled for feedback to health care providers.

**Conclusion:** The web-based DICODI project will open up possibilities to detect gastrointestinal complications of diabetes in a societal setting, benefitting people living with diabetes, health care professionals, and society.

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## Introduction

Over the last two decades, advances in our understanding of gastrointestinal physiology and systematic classification of symptoms have revealed that people with diabetes often have a considerable burden of gastrointestinal symptoms, known as diabetic gastro-enteropathy, which encompasses the cumulative impact that diabetes exerts on the entire gastrointestinal tract [1]. The underlying pathophysiology is incompletely understood, but impaired autonomic regulation, compromised microvascular blood supply, combined with loss of the cells of Cajal and smooth muscle myopathy, are associated with gastroenterological sensory and motor abnormalities. The most outspoken upper gastrointestinal symptom associated with diabetes is intractable vomiting, ascribed to delayed gastric emptying or gastroparesis. Slow gastric emptying in diabetes was first described a century ago by Boas [2] in 1925 and Kassander in 1958 who coined the term ‘gastroparesis diabeticorum’ [3]. It is commonly

accepted that diabetes-induced gastrointestinal dysfunction may affect the whole alimentary tract, known as pan-enteric dysfunction, presented with a plethora of symptoms including reflux, early satiety, bloating, abdominal pain, constipation and fecal incontinence [4–6]. However, these symptoms cannot be ascribed as a consequence of diabetes without excluding other relevant causes, such as celiac disease or pancreatic exocrine insufficiency [4]. Hence, the work-up of diabetic patients with gastrointestinal symptoms should involve full medical background and physical examination, followed by the pertinent investigations; same as would be done for any person with similar symptoms.

This position paper of the study Digestive Complications in Diabetes with the acronym DICODI discourses the common under-recognition of gastrointestinal symptoms in diabetes by use of patient-related outcomes (PROs) in a systematic and prospective way. We search to delimitate our presentation to the diabetic context in order to differentiate

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symptoms with a specific bearing on diabetic complications from those of functional dyspepsia. Herein, we particularly focus on diabetic gastroparesis, celiac disease and pancreatic exocrine insufficiency which commonly co-exist and can complicate the management of metabolic control in diabetes.

### Prevalence and identification of risk factors

Despite large variations, community-based studies have provided us with data of the high prevalence of upper gastrointestinal symptoms in diabetes. For instance, is it largely overlooked that up to 14% of people with diabetes suffer from abdominal pain or discomfort [7]. Furthermore, cardinal symptoms of gastroparesis appears to be more common in people with type 1 diabetes than in those with type 2 diabetes, and delayed gastric emptying has been found in 27–58% of people with long-standing type 1 diabetes [8] and in up to 30% of people with type 2 diabetes [9]. However, studies also range from those reporting large increases in the prevalence of only upper gastrointestinal symptoms [10] to others reporting increased frequency of all different gastrointestinal symptoms [11–14] (Figure 1).

The disease duration has been reported as an independent risk factor of symptoms in diabetes [12], whilst others do not observe this association [7]. It has been assumed that gastrointestinal symptoms are secondary to autonomic neuropathy in the gut [15,16], but epidemiological studies do not support this assumption [17]. Another risk factor is hyperglycemia, which may precipitate dysfunction throughout the alimentary tract [18–21]. In line with this, plasma glucose excursions show association to gastrointestinal symptoms [7]. Taken together, a recent review indicates that gastrointestinal discomfort could be 70% higher in people with diabetes, describing that 25% experience gastrointestinal symptoms [22]. To further expand on this, population studies of people

living with diabetes are needed, but currently hampered by the lack of a reliable internet-based survey instrument designed to collect data. This can now be achieved by implementing validated questionnaires operated by internet-based computer technology in order to characterize and disentangle the diverse gastrointestinal symptom profiles.

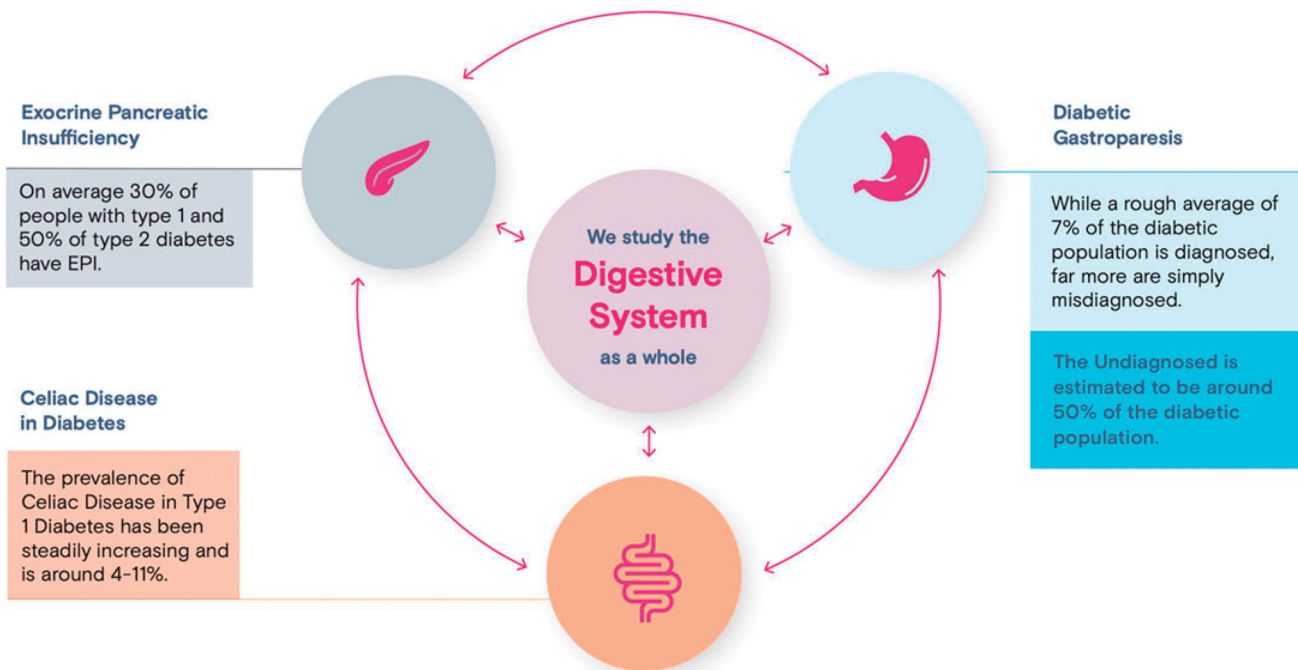
### Methods

People diagnosed with diabetes mellitus registered at the diabetes patient organizations in Denmark, Norway and Sweden will be informed and asked to participate in the study, starting late 2022. An internet-based computerized survey will collect basic characteristics (diabetes type, age, gender, duration, HbA1c, treatment) and PROs from diabetes populations in Denmark, Norway and Sweden by use of the validated questionnaires for gastroparesis; (1) gastroenteropathy; (2) celiac disease and; (3) pancreatic exocrine insufficiency. Using logistic regression and multiple regression analyses risk factors and gastrointestinal complications will be identified. Cluster analyses and machine learning will classify different symptoms and co-existing presentations, into the likely diagnosis. To achieve longitudinal data, participants will be yearly re-examined for progression of symptoms.

Inclusion criteria are diabetes mellitus type 1 or type 2 plus membership in patient organization for diabetes. Exclusion criteria are renal or hepatic insufficiency, planned abdominal surgery over the forthcoming year, not capable to use computer for login.

### Main symptoms of upper gastrointestinal dysfunction in diabetes

In the clinical setting we emphasize that people with diabetes presenting with different types of upper



**Figure 1.** Intermingled symptoms with upper gastrointestinal upset commonly seen in the plethora of late complications and concurrent diseases of diabetes mellitus.

gastrointestinal problems need a detailed anamnesis as well as diagnostic work-up in order to differentiate their symptoms and complications. However, this is seldomly done in full. In the clinic, symptoms referred to as dyspepsia, anemia or vomiting usually lead to an upper endoscopy with biopsies from the duodenum and stomach, or a fecal *Helicobacter* antigen test, but outside of that other diagnostic procedures are not routinely done. Hence, a diagnosis of functional dyspepsia or *Helicobacter*-induced dyspepsia, as well as celiac disease can be made after the above mentioned tests [23], but seldomly the medical work-up is seldomly carried forward beyond this point. As a supplement, we advocate the use of validated questionnaires in order to disentangle the most likely disorder underlying various upper gastrointestinal symptoms. For patients with constant nausea and repeat vomiting in addition to early satiety, loss of hunger and abdominal distension after a meal, the Gastroparesis Cardinal Symptom Index (GCSI) [24] could be used. In cases with diarrhea or constipation as dominant symptoms the Gastrointestinal Symptom Rating Scale (GSRS) would be more appropriate [25] along with added questions on dry mouth, swallowing, loss of appetite, nausea/vomiting, constipation and micturition. This in turn can then lead to further diagnostic steps called upon by the patient-related outcomes (PROs) of the questionnaires.

For differential diagnostic purposes we have to keep in mind that more than one in twenty patients with type 1 diabetes (e.g., 6%) have a biopsy-proven celiac disease [26]. Evidence regarding the role of celiac disease in type 2 diabetes is less clear. Some studies have linked the intake of a gluten-free diet to reduced obesity and type 2 diabetes, suggesting a role in reducing leptin and insulin-resistance with increasing beta-cell volume. Even if celiac disease may not be found in more than 2.8% of people with type 2 diabetes [27], current knowledge indicates that gluten may be an etiopathogenic factor for the development of type 2 diabetes [28]. The prevalence of celiac disease is high enough in both types of diabetes to motivate the use of a diagnostic questionnaire, the celiac symptom index (CSI), in order to disclose celiac as a concomitant disease, especially in patients with poor metabolic control.

Impairment of the pancreatic exocrine function is a frequent complication of diabetes mellitus. Abdominal symptoms such as nausea, bloating, diarrhea, steatorrhea, and weight loss can often be over-looked in diabetic patients. Using pancreatic elastase 1 activity, 51.1% of type 1 and 35.4% of type 2 diabetics were found to have reduced fecal elastase 1 activity, along with gastrointestinal symptoms [29]. In brief, also pancreatic exocrine function can often be affected in diabetes why we advocate the use of the pancreatic exocrine insufficiency questionnaire (PEIQ) for diagnostic purposes employing PROs.

With these differential diagnostic challenges in mind, we established a focus group in order to clarify the most common worries and burdens that people with diabetes experience, be it type 1 or type 2 diabetes (Table 1).

The results of the Focus Group data indicated that symptoms from the upper gastrointestinal tract was a major

**Table 1.** Questions raised by the Scandinavian focus group of people with diabetes type 1 or type 2.

- Upper gastrointestinal complications (bloating and satiety) related to diabetes?
- Effect of various foods on gastrointestinal symptoms, glucose and metabolic control?
- Relief of abdominal pain in diabetes?
- Relief of chronic diarrhea and incontinence?
- Prevention of chronic constipation?
- Association with celiac disease?
- Drug effects on the gastrointestinal tract?
- The medical risk of gastrointestinal disease in diabetes?

Sequence of questions ranked in order of concern.

concern among diabetics, while symptoms from the lower gastrointestinal tract were of less prominence, though not eligible. Against this background we chose to use a collection of validated diagnostic questionnaires in order to distinctly separate various diabetic complications and coherent diseases that can develop as late complications with the help of the patient's own reports. The questionnaires to be used are:

- Gastroparesis Cardinal Symptom Index (GCSI)
- Gastrointestinal Symptom Rating Scale (GSRS)
- Celiac Symptom Index (CSI)
- Pancreatic Exocrine Insufficiency Questionnaire (PEIQ)

These indices will primarily be used in a cross-sectional study to differentiate between different upper gastrointestinal symptoms in type 1 and type 2 diabetes. Additionally, the following questionnaires will be used to seek for a prognostic marker of early small fiber neuropathy:

- Visual Function Questionnaire-25 (VFQ-25)
- Michigan Neuropathy Questionnaire

We believe this will enable a longitudinal follow-up of gastrointestinal complications in diabetes with progressive systemic small and large fiber neuropathy along with diagnostic differentiation between gastroparesis, celiac disease and pancreatic exocrine insufficiency. We intend to use internet-based survey programming as the basis for computerized handling of PROs as measures of disease activity with future diagnostic end-points.

### **Importance of the study**

Recently, it has become increasingly clear that gastrointestinal symptoms are common in the diabetic population. We need large population studies to provide detailed estimates of the symptom prevalence and symptomatic overlap between the underlying causes. Hence, appearance of symptoms can be associated with motility abnormalities of the stomach, duodenum and jejunum as well as celiac disease or pancreatic exocrine insufficiency. Understanding the pathophysiology of gastrointestinal complications in diabetes is still in its early stages. While waiting for an ultimate diagnostic test, we have to rely on the medical history interview. These interviews can be optimally structured for PROs and

validated to obtain adequate results for diagnostic purposes and initiation of specific treatments tailored for each specific physiological abnormality. The complexity of gastric, intestinal and pancreatic functions and the multiple anatomical levels at which these organs can be affected in diabetes offers many therapeutic challenges.

As with all other late complications in diabetes, tight control of plasma glucose is the most useful and effectful intervention. Identification of independent risk factors, could lead to early recognition and improved preventive initiatives, and ultimately impact future clinical guidelines. Consequently, results of our population-based survey will benefit the future life for Scandinavians living with diabetes, health care professionals, and the surrounding society.

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