Characterization of glucose variability and hypoglycaemia in patients with post-pancreatitis diabetes mellitus

Aalborg University Hospital

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Protocol signature page

Principal investigator's statement:
I have read and understand the foregoing protocol entitled "Characterization of glucose variability and hypoglycaemia in patients with post-pancreatitis diabetes" protocol version 4.0 and agree to conduct the study in compliance with the Research Ethics Committees in Denmark and the Danish Data Protection Agency (hereinafter referred to as "the competent authorities"), and within the principles of the Declaration of Helsinki (amended by the 52nd General Assembly, Edinburgh, Scotland, October 2000, clarified by the General Assembly in Washington 2002, Tokyo 2004, Seoul 2008, and Fortaleza 2013 as outlined herein).

Søren Schou Olesen	Professor, Chief Consultant
Principal investigator	Principal investigator
23-05-2022	
Date	Principal investigator´s signature

1. Glossary

ADA	American Diabetes Association
CGM	Continuous glucose monitoring
CP	Chronic pancreatitis
CRF	Case report form
CV	Coefficient of variation
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life questionnaire
EPI	Exocrine pancreatic insufficiency
HbA1c	Haemoglobin A1c
PP	Pancreatic polypeptide
PPDM	Post-pancreatitis diabetes mellitus
PRO	Patient reported outcome
SARC-F	Strength, assistance with walking, rising from a chair, climbing stairs, and falls
SD	Standard deviation
SMBG	Self-monitoring of blood glucose
SOP	Standard operating procedure
TAR	Time above range
TBW	Time below range
TIR	Time in range
VIM	Variability independent of the mean

2. General information

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3. Funding

The study was conceived and initiated by professor Søren Schou Olesen, Department of Gastroenterology & Hepatology, Aalborg University Hospital. It is economically supported from Steno Diabetes Centre North Denmark who will provide equipment and personal for continues glucose monitoring (CGM). Various funds will be applied for, to cover any additional financial expenses. Potential grants from other funds are deposited in a project account at Aalborg University Hospital, which principal investigator Søren Schou Olesen is responsible for. The involved researchers conduct the trial of general scientific interest without personal financial gain. All data will be publicly available after publication based on reasonable request.

4. Roles and responsibilities

The present studies will be conducted in compliance with this protocol, the guidelines of the World Medical Association Declaration of Helsinki in its revised edition (Fortaleza, Brazil, October 2013) and designated Standard Operating Procedures. The project will be conducted in collaboration between researchers from Centre for Pancreatic Diseases at Aalborg University Hospital and Steno Diabetes Centre North Denmark. The researchers have clinical and health technology backgrounds and a long track record on research into diabetes, pancreatic diseases, and epidemiology as well as major experience with leadership of clinical and epidemiological studies. The principal investigator Søren Schou Olesen is clinical professor in pancreatology at Aalborg University and chief physician at Aalborg University Hospital where he is the leader of Centre for Pancreatic Diseases. He has a long track record of clinical and epidemiological projects within acute and chronic pancreatitis and has a special interest in metabolic complications of pancreatic diseases. The co-investigator Morten Hasselstrøm Jensen is a senior researcher at Steno Diabetes Centre North Denmark and associate professor at Aalborg university. He has a proven track record of epidemiologic and health technology studies within type 2 diabetes and a special interest in CGM and management of hypoglycaemia. Staff at Steno Diabetes Centre North Denmark and Mech-Sense, Department of Gastroenterology and Hepatology will be employed to oversee the studies. For sub study 3, associate professors Srdan Novovic, Camilla Nøjgaard and Maiken Thyregod Jørgensen from Hvidovre University Hospital and Odense University Hospital will participate. They all have extensive experience with clinical management and research in pancreatic diseases. Professors Filip Knag Knop and Jens Juel Holst will provide assistance with analysis and interpretation of results from the arginine test and analysis of intestinal/pancreatic hormones. Professors Peter Vestergaard and Asbjørn Mohr Drewes are international leading experts in endocrinology and gastroenterology with extensive experience in research management and will serve as consultants on the project.

5. Time schedule

The project is expected to be initiated (first subject included) in April 2022 and concluded (last subject, last visit) by March 2023. An overview is given in the diagram below.

	2021		2022				2023				2024	
	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2
Writing of protocol												
Regulatory affairs												
Conduct of studies												
Data analysis												
Writing and submitting articles												

6. Purpose and scientific background

6.1 Introduction and purpose

Post-pancreatitis diabetes mellitus (PPDM) is a frequent complication of chronic pancreatitis and occurs in up to 80% of patients during their disease course[1,2]. PPDM prognosis and management has not been widely studied as patients with PPDM are typically excluded from observational studies and randomized controlled trials of glucose lowering therapies. Therefore, prognosis and management strategies have mostly been extrapolated from other diabetes subtypes. Furthermore, patients with PPDM are frequently misdiagnosed and treated as type 2 diabetes[3,4]. This is problematic as PPDM has a distinct pathophysiology and clinical presentation. Hence, patients with PPDM often have "brittle diabetes" characterized by fluctuating blood glucose levels, frequent hypoglycaemic episodes, and poor glycaemic control[1,5]. However, there is a lack of systematic investigations of glucose homeostasis in relation to PPDM.

The use of continuous glucose monitoring (CGM) improves glycaemic control and risk of hypoglycaemia compared to self-monitoring of blood glucose (SMBG) in people with type 1 and insulin-treated type II diabetes[6–9]. However, the effect of CGM on hypoglycaemic risk has never been investigated in PPDM patients.

The overall purpose of this project is to study glucose variability and hypoglycaemia in patients with PPDM. The project is organized into three sub studies aiming to: 1) Investigate short-term glucose variability assessed by continuous glucose monitoring (CGM) and the effect of CGM on hypoglycaemia compared to SMBG, 2) investigate long-term glucose variability based on visit-to-visit haemoglobin A1c (HbA1c), and 3) investigate the prevalence of, risk factors for and awareness

of hypoglycaemia using standardized patient-reported outcomes. Patients with type 2 diabetes are included as the most clinically relevant comparison group[5]. The project will provide novel information on glucose variability and prevalence of hypoglycaemia among patients with PPDM using the most updated classifications and technologies. This information can be used to inform prognosis and identify relevant targets for optimization of management.

6.2 Scientific background and literature review

6.2.1 Pathophysiology of post-pancreatitis diabetes mellitus

Chronic pancreatitis is characterized by a fibro-inflammatory process that leads to islet cell injury with ensuing beta-cell loss and decreased insulin secretion[1,10]. This has for long been considered the primary mechanism of PPDM. However, injury to pancreatic islets also results in impaired secretion of pancreatic polypeptide resulting in hepatic insulin resistance and increased hepatic glucose production[11]. Likewise, impaired secretion of glucagon and somatostatin compromise glucose counter regulation during hypoglycaemia which may be an important mechanism for the frequent hypoglycaemic episodes observed in these patients[12]. The majority of patients with PPDM also have pancreatic exocrine insufficiency and malassimilation of intestinal nutrients, which has been associated with a blunted incretin response during oral feeding that are only partly reversed by pancreatic enzyme replacement therapy[1,13,14]. In addition, abdominal pain and other complications related to chronic pancreatitis may compromise nutritional intake and lead to malnutrition and depleted glycogen stores which again compromise gluconeogenesis during fasting[15]. Finally, type 2 diabetes related risk factors may also be implicated in the pathogenesis of PPDM[2]. The combined effects of these mechanisms are believed to result in greatly fluctuating blood glucose levels and excess risk of hypoglycaemia i.e., a "brittle diabetic state" - **figure 1**[2,16].

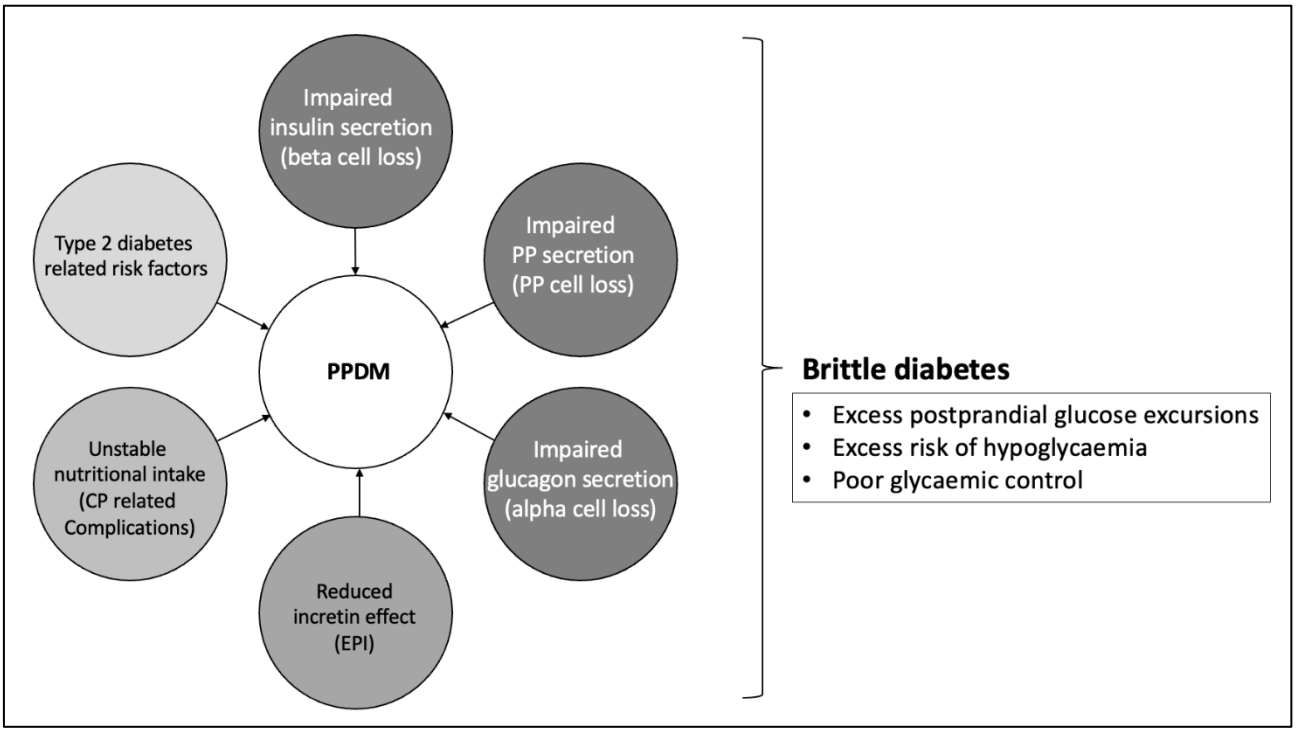

Figure 1. Pathophysiological mechanisms associated with the "brittleness" in PPDM. PP, pancreatic polypeptide; EPI, exocrine pancreatic insufficiency; CP, chronic pancreatitis; PPDM, post-pancreatitis diabetes mellitus

Notwithstanding the improved understanding of PPDM pathophysiology, most past observations of glucose homeostasis in PPDM patients come from small studies in poorly defined patient groups and have mostly been based on outdated definitions and technologies[1]. Also, the problem of "brittle diabetes" in relation to PPDM has not been investigated in the era of modern glucose lowering medications such as long-acting and ultra-long-acting insulin analogues that may reduce risk of hypoglycaemia.

6.2.2 Continuous glucose monitoring

SMBG using a glucometer and a capillary blood sample drawn via finger-pricking is used by most people with diabetes. However, this technique has some disadvantages as it is user-dependent and does not capture nocturnal and asymptomatic hypoglycaemia. Also, SMBG cannot be used to predict impending hypoglycaemia as it is based on single-instant blood glucose readings. These limitations can be overcome by using CGM[6]. A CGM system is based on a subcutaneous sensor that automatically measures an individual's interstitial glucose levels continuously. Based on trends in glucose levels, CGM can predict impending hypoglycaemia and detect fluctuations in blood glucose levels[17,18]. In people with type 1 diabetes and those with type 2 diabetes on multiple daily insulin injections, CGM improves glycaemic control and reduces time in hypoglycaemia compared to SMBG[6–9]. It is likely that this effect is also present in patients with pancreatogenic diabetes, but this has never been investigated.

6.2.3 Characterization of glucose variability and association with hypoglycaemia risk

Variability of glucose homeostasis has been increasingly recognized as an important determinant of diabetes-related complications and adverse clinical outcomes beyond HbA1c levels[19]. It encompasses two categories of dysglycaemia: i) short-term daily glucose fluctuations that can be assessed by CGM and ii) long-term weekly, monthly or quarterly changes in glucose variability that have typically been assessed by changes in visit-to-visit HbA1c levels. Although the evidence for the relationship between glucose variability and adverse clinical outcomes is not fully clarified at this point, evidence supports a strong association between hypoglycaemic events and both short and long-term glucose variability[19]. To the best of our knowledge short and long-term glucose variability and prevalence of hypoglycaemia has not previously been investigated in the context of PPDM using modern technologies and definitions.

6.3 Hypotheses

- **Sub study 1**: Short-term glucose variability and time in hypoglycaemia, as determined by CGM, is increased in patients with PPDM compared to a matched group of individuals with type 2 diabetes; the use of CGM will lead to decreased time in hypoglycaemia compared to SMBG in PPDM patients.
- **Sub study 2**: Long-term glucose variability, as determined by visit-to-visit HbA1c, is increased in patients with PPDM compared to a matched group of individuals with type 2 diabetes.
- **Sub study 3**: Patients with PPDM report high frequencies of self-reported hypoglycaemic events and targetable risk factors for hypoglycaemia can be identified.

7. Methods I: design, setting, participants, and outcomes

7.1 Study designs

- **Sub study 1** is a prospective open-label crossover randomized controlled study of the effect of CGM on hypoglycaemia compared to SMBG in PPDM patients
- **Sub study 2** is a retrospective cohort study of long-term glucose variability, as determined by visit-to-visit HbA1c levels, in PPDM patients compared to matched individuals with type 2 diabetes
- **Sub study 3** is a multicentre cross-sectional study based on patient-reported outcomes (PROs)

7.2 Study settings

Sub studies 1 and 2 will be conducted at Centre for Pancreatic Diseases at Aalborg University Hospital and Steno Diabetes Centre North Denmark. These centres have comprehensive experience in diagnosing, treating, and conducting research on patients with pancreatitis and diabetes. Patients with PPDM will primarily be identified and included via the outpatient clinic at Centre for Pancreatic Diseases but may also be identified after admission with chronic pancreatitis as described in section 7.9 or in the diabetes outpatient clinic. For sub study 2 data are retrieved from Diabetesdatabasen in the North Denmark Region. Sub study 3 is a multicentre study that in addition to the above-mentioned sites also includes pancreas outpatient clinics at Hvidovre University Hospital and Odense University Hospital.

7.3 Eligibility criteria

7.3.1 Inclusion criteria PPDM patients

- Signed informed consent before any study specific procedures*
- Able to read and understand Danish
- Male or female age ≥ 18 ≤ 80 years
- A definitive diagnosis of chronic pancreatitis based on the M-ANNHEIM criteria[20]
- A diagnosis of insulin treated PPDM based on the World Health Organization criteria for diabetes (HbA1c ≥6.5 % (48 mmol/mol) and/or fasting plasma glucose ≥126 mg/dl (7.0 mmol/l) >3 months after diagnosis of pancreatitis

*a signed informed consent is waived for patients in sub study 2 which is a register-based study based on data from Diabetesdatabasen in the North Denmark Region.

7.3.2 Exclusion criteria PPDM patients

- Known or suspected abdominal cancer (incl. intestine, pancreas, and the hepato-biliary system)
- Severe pre-existing comorbidities (assessed by investigator upon inclusion)
- Attack of acute on chronic pancreatitis requiring admission within four weeks prior to inclusion
- Use of glucocorticoid medications within four weeks prior to inclusion
- Presence of autoimmune antibodies suggestive of type 1 diabetes
- Prior pancreatic surgery (including total pancreatectomy, pancreaticoduodenectomy, distal pancreatectomy, pancreaticojejunostomy, enucleation, or Frey procedure)
- Prior gastric surgery or vagotomy
- Autoimmune pancreatitis

7.3.3 Comparator groups for sub studies 1 and 3 (individuals with type 2 diabetes)

- Individuals with type 2 diabetes enrolled in the DiaMonT study are included as comparator group in sub studies 1 and 3. Individuals participating in the DiaMonT study undergo CGM for up to three months and provide information on experience with hypoglycaemia and awareness. These data will be used for comparison with the data collected in sub studies 1 and 3. The DiaMonT study is already approved by relevant regulatory bodies (N-20200068) and participants have provided written informed consent upon inclusion and agreed that the collected data can be used for research purposes.
- Individuals with type 2 diabetes are matched to PPDM patients based on HbA1c levels and other relevant parameters including regimens of glucose lowering therapy.
- The following data from the DiaMonT study will be used:
    - Basic demographic and clinical characteristics
    - Information on glucose lowering therapies and other medications
    - Routine biochemical parameters including Hb1Ac
    - CGM metrics
    - Information on hypoglycaemia and hypoglycaemia awareness

Patients from the DiaMonT study will not provide any biological material for this project. Data will be used in compliance with with the rules on protection of personal data from the the Danish Data Protection Agency.

7.3.4 Comparator group for sub study 2 (individuals with type 2 diabetes)

- Individuals with type 2 diabetes enrolled in Diabetesdatabasen are included as comparator group in sub study 2. Diabetesdatabasen is a health registry maintained by the Business Intelligence Unit in the North Denmark Region and collect anonymised data on individuals with diabetes in the North Denmark Region. In agreement with Danish legislation use of anonymised data from Health Registries do not require informed consent from involved individuals.
- Individuals with type 2 diabetes are matched to PPDM patients based on HbA1c levels and other relevant parameters including regimes of glucose lowering therapy

7.4 Discontinuation or withdrawal from the study

If a participant is withdrawn from the study, the investigator should always ensure that the end of study page in the case report form (CRF) is completed for withdrawn participants. A participant should be withdrawn from studies, if at any time:

- It is the wish of the participant for any reason
- The investigator judges it necessary due to medical reasons
- Severe non-compliance to the protocol is judged by the investigator

If a participant does not turn up for a scheduled visit, the study personnel will contact him/her by telephone to rearrange the scheduled visit. In any circumstance, every effort should be made to document the participant health status.

7.5 Concomitant medication and care

Along with participation in the studies included patients will continue their usual treatments and scheduled visits and examinations in the outpatient clinic according to usual standard of care and clinical guidelines.

7.6 Outcomes

7.6.1 Primary endpoints

- **Sub study 1**: Difference (monitoring with CGM vs. SMBG) in time spent with glucose value <3.0 mmol/L (level 2 hypoglycaemia) during the last two weeks of each study period
- **Sub study 2**: Long-term glucose variability (up to 48 months) expressed as difference in visit-to-visit HbA1C VIM (Variability Independent of the Mean) between PPDM patients and individuals with type 2 diabetes patients
- **Sub study 3**: Proportions of patients with severe hypoglycaemia during the preceding 12 months. Hypoglycaemic endpoints are defined according to the latest ADA recommendations[21]

7.6.2 Secondary endpoints

Sub study 1:

- Short term (20 days) difference in CGM metrics between PPDM patients and individuals with type 2 diabetes
- CGM time in range (glucose value >3.9 mmol/L and ≤10 mmol/L)
- CGM time below range (glucose value ≤3.9 mmol/L)
- CGM time above range (glucose value >10 mmol/L)
- CGM metrics of glucose variability (SD (Standard deviation) and CV (Coefficient of Variance) of mean glucose, mean amplitude of glycaemic excursions [MAGE] and continuous overall net glycaemic action [CONGA])

Sub study 2:

- Difference in HbA1C CV between PPDM and type 2 diabetes patients during up to 48 months follow-up
- Difference in HbA1C average real variability between PPDM and type 2 diabetes patients during up to 48 months follow-up
- Difference in HbA1C level trajectories between PPDM and type 2 diabetes patients during up to 48 months follow-up

Sub study 3:

- Risk factors for hypoglycaemia including demographics and routine clinical and biochemical parameters
- Awareness of hypoglycaemia based on the Clarke hypoglycaemia awareness survey
- Proportions of patients with ketoacidosis during the preceding 12 months

7.6.3 Explorative endpoints

In sub study 1 an arginine test is employed to study pancreatic endocrine secretory capacity (insulin and glucagon). In addition, various baseline characteristics of PPDM patients including pancreatic and intestinal hormone profiles are associated with CGM metrics to explore putative mediators of short-term glucose variability.

7.7 Participant timelines

7.7.1 Sub study 1

Patients with PPDM will primarily be included from the outpatient clinic at Centre for Pancreatic Diseases, Alborg University Hospital as outlined below (7.9). Following written informed consent,

participants are randomized to monitoring with CGM followed by SMBG for 50 days or *vice versa*. Each study period is initiated by 20 days masked CGM (baseline) and patients using SBMG will also wear a masked CGM during the last 20 days of the SMBG period to allow comparison of CGM based endpoints between the two study periods. A timeline of study activities is illustrated in figure 2.

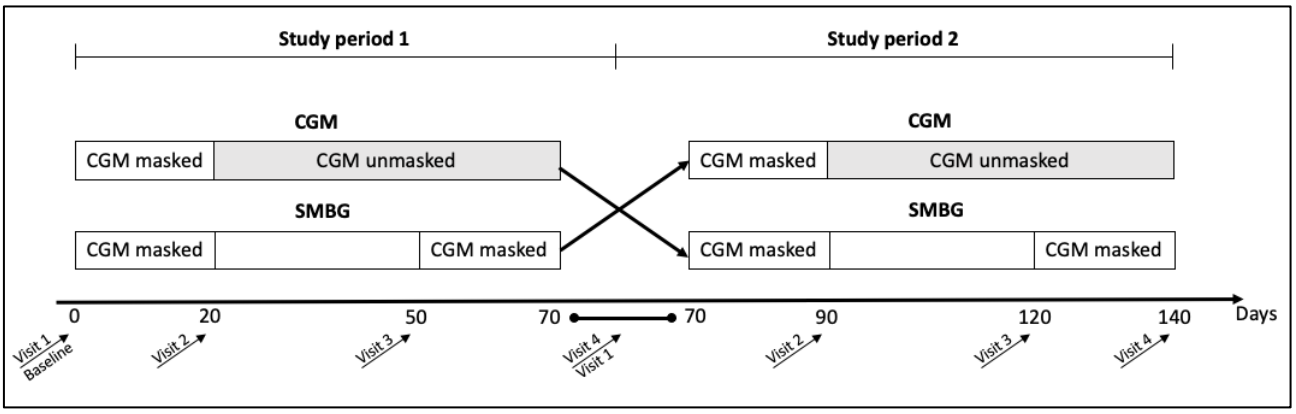

Figure 2. Timeline of sub study 1. CGM; Continuous glucose monitoring, SMBG; Self-monitoring of blood glucose.

Participants will undergo a total of 7 study visits, as illustrated in figure 2. The duration of the baseline visit (visit 1) is approximately 120 minutes, and the subsequent visits 15-30 minutes, making the total time required for participation in the study a maximum of 300 minutes. At the baseline visit, height and weight are registered, and body mass index is calculated. Pancreatic function (exocrine and endocrine) will be evaluated based on review of patients' medical records and supplemented by routine biochemical tests including autoantibodies and HbA1c. Also, blood is drawn for biobanking and assessment of basal intestinal and pancreatic hormone levels. An arginine stimulation test is done to assess endocrine pancreatic secretory capacity. Patients are instructed in use of an insulin and food diary and fill in questionaries. Finally, the CGM sensor is mounted and activated. Every 10 days the CGM glucose sensor is changed by the participant at home based on instructions from study staff (or alternatively they can choose to have the censor changed in the diabetes outpatient clinic). After 20±2 days (visit 2), participants meet to either unmask or remove the CGM. Then, on day 50±2 (visit 3), the participant with unmasked CGM returns to unload the CGM transmitter, while the participants randomized to SMBG come in and the CGM is again mounted and masked. The study periods end at day 70±2, where participants meet for a follow-up visit (visit 4), where the CGM transmitter is unloaded. The food and insulin diary is collected and reviewed together with the patient to ensure accurate registrations of insulin administration and food intake. Patients fill in questionaries and adverse events in relation to CGM monitoring or other study activities are registered. Since crossover will occur immediately at the end of the first study period, visit 4 in period 1 and visit 1 in period 2 are merged. Also, baseline data is only collected at the very first visit. In **Table 1** an overview of the various study activities in sub study 1 is reported.

Table 1: Participant timeline and study activities for sub study 1

	Study period 1				**Study period 2**		
	Baseline Visit 1 *Day 0*	Visit 2 *Day 20*	Visit 3 *Day 50*	Visit 4/1 *Day 70/0*	Visit 2 *Day 20*	Visit 3 *Day 50*	Visit 4 *Day 70*
Anthropometrics	X						
Biochemistry							
- Faecal elastase	X						
- HbA1c	X			X			
- Routine biochemistry	X						
- Blood for biobanking	X						
- Autoantibodies	X						
- C-peptide	X						
Arginine stimulation test	X						
Questionnaires	X			X			X
Registration of adverse events				X			X
Unloading CGM transmitter		X	X*	X	X	X*	X

*Unloading the CGM transmitter applies only when the participants are being monitored using unmasked CGM

7.7.2 Sub study 2

Sub study 2 is based on data from Diabetesdatabasen in the North Denmark Region and therefore no study-related visits or procedures pertain to patients included in sub study 2. The database is maintained and managed by the Business Intelligence unit in the North Danish Region.

7.7.3 Sub study 3

Patients with PPDM will primarily be included from the outpatient clinics of participating centres as outlined above. Following written informed consent, patients are asked to fulfil the relevant questionaries as described below. The required time to fulfil the questionaries is approximately 30 minutes, making total time required for participation in the study a maximum of 60 minutes. Patients can either choose to fill in the questionaries in the outpatient clinic or bring the questionnaires to their home and return them via postal service (stamped envelopes are provided for free) or alternatively use digital questionnaires linked to the individual subject's CRF in REDCap (see section 8.2.1).

7.8 Sample size considerations

- **Sub study 1:** The sample size calculation is based on the primary endpoint described for sub study 1 (time in level 2 hypoglycaemia). A sample size of 24 patients is determined to have at least 80% power to detect a reduction in the percentage of time spent with a glucose value <3.0 mmol/l (level 2 hypoglycaemia), assuming a relative treatment reduction of 50% from a percentage of time spent with glucose value <3.0 mmol/l of 3%, standard error of 2.5%, and type I error rate (2 sided) of 5%. To account for approximately 25% dropouts, the final sample size is set to 30 patients. As there are currently no adequate data on CGM in patients with pancreatogenic diabetes to inform sample size calculations, assumptions are based on findings in older adults with long-standing type 1 diabetes who have an increased risk of hypoglycaemia[7].
- **Sub study 2:** This is a retrospective cohort study based on data already collected in Diabetesdatabasen and the sample size will therefore be dictated by the number of individuals in the

database. Previous population-based studies from our group have shown that the proportion of patients with PPDM among patients clinically diagnosed type 1 or type 2 diabetes is approximately 1.5%[4,22]. In Diabetesdatabasen there are currently >5000 unique adult individuals registered, and thus we expect to identify at least 75 PPDM cases which should provide sufficient statistical power to the planned analyses according to a previous study from our group[22].

- **Sub study 3:** This is a cross-sectional survey. No previous studies have evaluated the prevalence of self-reported severe hypoglycaemia and related risk factors in patients with PPDM. However, according to recent population-based registry data from our group, patients with PPDM have a risk of hospitalization for hypoglycaemia comparable to that observed for individuals with type 1 diabetes (*unpublished data*). In type 1 diabetes, the yearly prevalence of self-reported severe hypoglycaemia range between 10–53%[23]. Thus, we consider a sample size of 200 patients will provide sufficient power to obtain prevalence estimates with reasonable precision and allow for multivariate modelling of putative risk factors associated with severe hypoglycaemia.

7.9 Recruitment

Eligible patients with PPDM from the outpatient clinic are contacted during scheduled clinical visits in the outpatient clinic. Information regarding medical history and previous treatment can be passed on from the treatment-responsible physician from medical records to study personnel. Potentially eligible patients from the outpatient clinic, may subsequently be contacted by study personnel, but only if permission has been granted by the treatment-responsible physician. This will be conducted in accordance with "Sundhedsloven § 46, stk 1", under the responsibility of the primary investigator. Patients can be included, four weeks after discharge from an acute on chronic pancreatitis attack if they are clinically stable at the time of inclusion. We expect to enrol about 1 to 2 patients per week for sub study 1 and 5-10 patients per week for sub study 3.

7.10 Information about the study

All patients will be informed both oral and written before they decide whether they want to participate in the study. Furthermore, they will be informed that they can withdraw from the study at any given time without giving a reason. The participants are also allowed to have an assessor with them to the interview. Competent delegated personnel (medical doctors affiliated with the study or trained site staff) will give the oral information according to the Research Ethics Committee's guidelines. The information interview will take place in quiet surroundings at one of our respective inclusion sites. During the interview, the participant will be informed thoroughly about the purpose of the study, the specific procedures the study entails, and potential benefits and risks. Any questions the participant have, will also be answered here. The written information ("Deltagerinformation") is given or sent (in the case they contact us first) to the participants so they have it at least one day before the oral information takes place. After the interview where the participant has received information (oral and written) about the study, they are encouraged to go home and consider whether they want to participate in the study or not, for a minimum period of 24 hours. They may also sign the informed consent immediately if they are ready. After the participant has signed the informed consent and is included in the study, they will be receiving an ID-number. For additional information on informed consent and confidentiality see section 9.3.

8. Methods II: Data collection, management, and analysis

8.1. Data collection methods

8.1.1 Continues glucose and activity monitoring

Participants in sub study 1 will be provided with a CGM and an activity tracker. The CGM device consists of three components: A sensor, a transmitter, and a receiver. The receiver can be a mobile phone app or a dedicated device. The sensor penetrates the skin and is localized in the subcutaneous tissue on the upper arm or the abdomen and measures the interstitial glucose levels continuously. The signal is processed by the receiver and an interstitial glucose value is shown every 5 minutes. The participants will be trained in using the provided technologies at study initiation and use the devices continuously at home to measure and log tissue glucose levels, activity, and sleep for the entire study duration. Participants are in periods blinded to the results from both CGM and are informed that they remain responsible for monitoring and managing their blood glucose levels according to their usual standard of care, despite the telemonitoring. For technical challenges, participants can contact Steno Diabetes Centre by phone via a technical support line. Use of the devices do not restrict the daily activities of the participants.

8.1.2 Food diary and monitoring of insulin administration

Participants in sub study 1 are instructed to register their daily food intake and insulin administration (both basal and bolus) in a "food and insulin diary" during the CGM monitoring period. A diary provided by Diabetesforeningen is used. Thorough instructions on how to use and fill in the diary is provided by study staff. An example of the "food and insulin diary" is provided in the appendix.

8.1.3 Questionnaires

All questionaries will be filled in by participants in sub studies 1 and 3.

8.1.3.1 Clarke hypoglycaemia awareness survey

The Clarke questionnaire for assessment of hypoglycemia awareness comprises eight questions characterizing the participant's exposure to episodes of moderate and severe hypoglycemia. It also examines the glycemic threshold for, and symptomatic responses to, hypoglycemia. A score of four or more implies impaired awareness of hypoglycemia.

8.1.3.2 The Comprehensive Pain Assessment Tool Short Form (COMPAT-SF)

The Comprehensive Pain Assessment Tool Short Form is a questionary that has been specifically developed and validated for pain assessment in patients with chronic pancreatitis. It comprises of 6 questions describing 5 pain dimensions: a) pain severity, b) pain pattern, c) factors provoking pain, d) widespread pain, and e) a qualitative pain-describing dimension. The questionary can be summarized in a total score in addition to the 5 pain dimension sub scores[24].

8.1.3.3 Strength, assistance with walking, rising from a chair, climbing stairs, and falls (SARC-F) questionnaire

The SARC-F questionnaire is a screening tool that can be rapidly implemented by clinicians to identify probable sarcopenic patients. The questionnaire screens patients for self-reported signs suggestive of sarcopenia, which include deficiencies in strength, walking, rising from a chair, climbing stairs, and experiencing falls. Each of the self-reported parameters receives a minimum and maximum score of 0 and 2, respectively, with the greatest maximum SARC-F score being 10[25].

8.1.3.4 EORTC QLQ-C30 questionnaire

The EORTC QLQ-C30 questionnaire is used to document life quality, physical function, and a number of other health-related parameters[26] and will be filled in by participants in sub study 1 at baseline. The questionnaire has been validated for assessment of quality of life in patients with chronic pancreatitis and is composed of single-item measures and multi-item scales with scores ranging from 0 to 100 after linear transformation of the raw score[27]. A high score for a functional scale represents a high level of functioning, as does a high score for the global health status, while a high score for the symptom items represents a high level of symptomatology.

8.1.4 Biochemistry

Patients in sub studies 1 and 3 will have their pancreatic exocrine function evaluated by means of faecal-elastase test at baseline. At the same time, they will have routine clinical blood sample tests performed (including HbA1C, electrolytes, creatinine, albumin, haemoglobin, liver tests, pancreas specific amylase, c-peptide and autoantibodies) corresponding to approximately 20 ml blood. The blood samples are analysed immediately as part of routine clinical practice. Patients in sub study 1 will also have extra blood tests drawn to detect circulating levels of pancreatic hormones (insulin, glucagon, pancreatic polypeptide) and intestinal hormones (GLP-1 and GIP) as well as markers of hypoglycaemia and postprandial glucose excursions corresponding to approximately 30 ml blood. These blood samples will be separated by centrifugation and processed as plasma, serum, buffy coat, and full blood and subsequently transferred in aliquots to vials labelled with the protocol number (PPDM-CGM_2022), subject number, and date of sample collection. Samples will be frozen and stored at approximately -80°C or cooler in a freezer at Aalborg University Hospital until analysis. The samples will be batch analysed at a central laboratory to measure the analytes of interest. After the analyses, spare blood will be kept in the biobank for future research purposes and destroyed at the latest 15 years after termination of the study. Ethics according to "databeskyttelsesforordningen" and" databeskyttelsesloven" will be ensured in this regard. Based on the blood samples drawn at baseline (20 ml + 30 ml blood) a total of 50 ml blood will be drawn from each participant in sub study 1 and 20 ml from each participant in sub study 3.

8.1.5 Arginine stimulation test

An intravenous catheter is inserted into the cubital vein for blood sampling and arginine infusion with arterialization of the venous blood using the heated hand technique. At time -1 min 5 g argininehydrochlorid (100 mg/mL) is infused over 1 minute. Blood samples are drawn at time -15, 0, 2, 5, 10, 15 and 30 min for the analysis of blood glucose, plasma C-peptide and glucagon. These blood samples will be kept on ice and immediately separated by centrifugation and processed as plasma and subsequently transferred in aliquots to vials labelled with the protocol number (PPDM-CGM_2022), subject number, and date of sample collection. Samples will be frozen and stored at approximately -80°C or cooler in a freezer at Aalborg University Hospital until analysis. The samples will be batch analysed at a central laboratory to measure the analytes of interest. After the analyses, spare blood will be kept in the biobank for future research purposes and destroyed at the latest 15 years after termination of the study. Ethics according to "databeskyttelsesforordningen" and" databeskyttelsesloven" will be ensured in this regard. In total, 56 ml blood will be drawn from each participant during the arginine stimulation test.

8.1.6 Demographic and clinical parameters

For all sub studies, demographic and clinical information are obtained from medical records and patient interviews (sub studies 1 and 3) or Diabetesdatabasen (sub study 2). The following clinical information is registered:

Demographic information:

- Age and sex
- Height and weight
- Body mass index

Information on chronic pancreatitis:

- Duration and aetiology
- Smoking and drinking history
- Complications including exocrine pancreatic insufficiency and pain
- Treatment (medical treatment including pancreatic enzyme replacement therapy, history of endoscopic treatment or surgery)

Information on diabetes:

- Duration of diabetes
- Information on past hypoglycaemic episodes according to the ADA definitions of hypoglycaemia[21]
- Presence of micro- and macrovascular complications
- Glucose lowering therapy including insulin regime and daily insulin units
- HbA1c and other relevant biochemical parameters in Diabetesdatabasen (sub study 2 only)

Information on comorbidity is registered using the Charlson Comorbidity index.

Information on demographic and clinical parameters including comorbidities are registered for two reasons: First, the information is obtained to ensure the suitability of the subjects in relation to inclusion in the study. Second, the information must be used for later analysis in an anonymized form.

8.2 Data management

The study will be submitted to the Northern Region of Denmark ("Forskningsanmeldelse Region Nordjylland – Registrering af forskningsprojekter"). Standard operating procedures (SOPs) for data handling and record keeping exists within the research centres and these will be followed. The principal investigator must maintain complete and accurate records to ensure that study execution is fully documented, and the study data can be subsequently verified. REDCap, a secure browser-based software, will be used for filling an electronic case report form for each participant (sub studies 1 and 3). REDCap meets all regulatory safety requirements and is approved for data collection by the North Danish Region. Data recording will begin when a participant is included and will occur gradually to the end of the study. Any corrections will be made in such a way that information from the original version is still available. Putative changes are endorsed by initials and date. All forms are filled out during (or immediately after) the assessment of a participant and must be legible. Data will be stored at Aalborg University Hospital, Department of Gastroenterology and Hepatology, for a minimum of 5 years after the study has ended. Relevant information from the participants' medical records will be given to the investigator if needed to assess the in- and

exclusion criteria. After five years all data will be anonymized. The principal investigator allows direct access to all source data and documents at monitoring, auditing, and inspection from the competent authorities. A participant identification list is created for all persons included in the study. This list contains patient number, full name, and civil registration number. The list is populated and updated by a study nurse or other competent person and is stored at Department of Gastroenterology, Aalborg University Hospital.

8.2.1 Case report forms

All data from sub studies 1 and 3 are entered directly into electronic CRFs using REDCap, licensed by Aalborg University Hospital, and saved electronically. All forms are filled out during (or immediately after) the assessment of a subject and must be legible. Errors and corrections are logged as provided by the REDCap interface. It is possible to export validated data from REDCap to e.g., a statistical program (e.g., STATA) for further statistical analysis. When data have been entered, reviewed, and verified the data will be frozen to prevent editing. Digitalized data are backed up and stored on specific drives at each site under the responsibility of the principal investigators for a minimum of 5 years after the study has ended.

8.2.2 Source data identification and protection

Patient Identification List containing patient number, full name, civil registration number for all participants included in sub studies 1 and 3 are created, and ethics according to "databeskyttelsesforordningen" and "databeskyttelsesloven" is ensured. The list is populated and updated by a project nurse or other competent person. A list of all source documents will be devised at the initiation of the study. All source documentation will be stored on a secure drive under the responsibility of the principal investigator.

8.3 Plan for statistical analyses

8.3.1 Statistical methods

- **Sub study 1**: CGM metrics collected in periods with monitoring using CGM vs. SMBG are compared using multiple linear regression models. Further, regression models are fitted to investigate associations between baseline characteristics and measures of glucose variability.
- **Sub study 2**: HbA1c variability metrics are compared between PPDM and type 2 diabetes patients using multiple linear regression models. Hb1Ac level trajectories are visually characterized and latent class analysis is used to define distinct patient clusters.
- **Sub study 3**: Prevalence estimates of hypoglycaemia are reported as point prevalence estimates with 95% confidence intervals. Logistic and Poisson regression models are fitted to investigate associations between patient characteristics and hypoglycaemia risk.

8.3.2 Criteria for termination of the studies

The sub studies are terminated when observations corresponding to planned sample sizes have been collected.

8.3.3 Missing data

Handling of missing data will be defined in the final statistical analysis plan and finalized before unblinding of data.

8.3.4 Deviations from the original statistical plan

It will be reported if any deviations from the original statistical plan occur.

9. Ethics and dissemination

The studies will be conducted in compliance with the principles of the Declaration of Helsinki (amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013). The studies will only be initiated once they are approved by the competent authorities. Any significant modifications to the protocol, will be submitted as protocol amendments and subsequently approved by the competent authorities before implementation.

9.1 Risk and benefits

The risks and potential side effects associated with participation in the study are considered to be limited. Biochemical tests including blood samples and fecal-elastase1 as well as CGM bear little risk for the patients and furthermore are all part of the standard evaluation/management of the disease. Potential side effects include the inconvenience and slight discomfort associated with blood sampling. Furthermore, use of the CGM can rarely cause local skin irritation and increased risk of infection. The potential benefit, on the other hand, is significant, as the proposed studies are expected to provide insight into modifiable risk factors for hypoglycaemia and to identify targets for improved glycaemic control in PPDM. As many of parameters under investigation are available through routine clinical management, it will be straightforward to implement findings into clinical practice. It is envisioned that information from the proposed studies can be used to identify patients at excess risk of hypoglycaemia and thus to optimize clinical management including intensified outpatient monitoring strategies. Accordingly, most patients with PPDM are currently treated by general practitioners that may have limited knowledge of the special considerations for management of PPDM. Identification of PPDM patients with high risk of complications would facilitate a rational triage of patients to specialized outpatient clinics with special interest in PPDM management.

9.2 Patient insurance

Clinical responsibility befalls Aalborg University Hospital. All participants will be covered by the patient insurance of Aalborg University Hospital.

9.3 Consent and confidentiality

The informed consent will be obtained following oral and written information has been given by competent delegated study personnel as previously described in section 7.8. Once informed consent is signed, this allows investigators and other local competent authorities to assess patients' medical records with the purpose of retrieving information necessary for study conduction, monitoring and inspection. Detailed clinical characterization of the patient, complementary information in relation to the study will be made available from medical records so that sponsor and monitor can control the quality of the study regarding "informationsbekendtgørelsen". Information about participants is protected by "databeskyttelsesforordningen", "databeskyttelsesloven" and "sundhedsloven".

9.4 Declaration of interests

None.

9.5 Access to data

All results will be published as open access whenever possible using both scientific and public media. When the studies end, the anonymized data will be made available to other researchers upon reasonable request.

9.6 Dissemination policy

Results, positive as well as negative and inconclusive, will be released to the public, and may be published in peer-reviewed scientific journals. Results may also be used in submission to regulatory authorities. The first author will be appointed according to the Vancouver system. The investigator will inform the competent authorities after the termination of the studies. The Research Ethics Committee will be notified of results from this study. Published articles are sent to the competent authorities.

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