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Investigations of hypoglycemic events and the role of GABA in type 1 diabetes

HENRIK HILL

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Abstract

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Introduction: Hypoglycemia in type 1 diabetes (T1D) ranges from mild to life-threatening events, yet most studies of hypoglycemia frequency rely on self-reported or aggregated data. Residual endogenous insulin production is associated to fewer severe hypoglycemic events, highlighting the potential benefit of preserving or restoring insulin production. For this purpose, gamma-aminobutyric acid (GABA) has emerged from experimental studies as a potential therapeutic drug candidate.

Aim: This thesis aimed to investigate the real-world frequency of hypoglycemia in children and adolescents with T1D, and to evaluate GABA's therapeutic potential in a clinical trial.

Methods: Five studies were included. Endogenous GABA, C-peptide, counter-regulatory hormones and cytokine levels were analyzed in plasma. A controlled-release oral formulation of GABA (Remygen®) was assessed in a randomized controlled *Phase I/II* clinical trial in individuals with long-standing T1D (n=35) for safety, effect on endogenous insulin production and hypoglycemic counter-regulation.

The real-world frequency of hypoglycemia and its relationship to overall metabolic control and age was evaluated using retrospective continuous glucose monitoring (CGM)-data and clinical records. More than 50,000 hypoglycemic events were analyzed. Additionally, a single-metric scoring model for CGM-data evaluation was developed based on n=82,114 days of CGM-data by assessing three dimensions of glucose control. The models validity was evaluated against clinical treatment targets and interpretations of a clinical expert board (CEB).

Results: GABA levels did not differ between individuals with T1D and healthy controls, but correlated with anti-GAD and cytokines. GABA treatment showed no improvements in endogenous insulin production or hypoglycemic counter-regulation, but side-effects were commonly observed. In the retrospective studies on CGM-data, mild hypoglycemic events (<3.9 mmol/L) were common. On average occurring on a near daily basis, regardless of age or metabolic control. However, no increased risk of severe- or serious (<3.0 mmol/L) hypoglycemia was observed in children achieving HbA1c ≤48 mmol/mol. The developed CGM scoring model correlated well with CGM-metrics and CEB interpretations.

Conclusions: Despite technological advancements, hypoglycemia remains a persistent challenge in T1D. GABA failed to regain beta-cell function, underscoring the need for alternative therapies in this aspect. Meanwhile, models for enhanced CGM analyses may aid in optimizing glucose management.

Keywords: Type 1 diabetes, T1D, hypoglycemia, hypoglycemic events, CGM, GABA, clinical trial, beta-cell, Regenerative therapy

Henrik Hill, Department of Women's and Children's Health, Akademiska sjukhuset, Uppsala University, SE-751 85 Uppsala, Sweden.

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To Esther, Sigrid and Anna

List of Papers

This thesis is based on the following papers/manuscripts, which are referred to in the text by their Roman numerals.

I. **Hill, H**., Elksnis, A., Lundkvist, P., Ubhayasekera, K., Bergquist, J., Birnir, B., Carlsson, PO. and Espes, D. (2021) Endogenous levels of gamma amino-butyric acid are correlated to glutamic-acid decarboxylase antibody levels in type 1 diabetes. *Biomedicines,* 2021 Dec 31;10(1):91 .

II. **Hill, H**., Lundkvist, P., Tsatsaris, G., Birnir, B., Espes, D., and Carlsson, PO. (2025) Long-term gamma-aminobutyric acid (GABA) treatment fails to regain beta-cell function in longstanding type 1 diabetes in a randomized trial. *Scientific Reports,* 2025 April 4;15:11530

III. **Hill, H.**, Klaar, P. and Espes, D. (2023) Real-life data of hypoglycemic events in children and adolescents with type 1 diabetes. *BMJ Open Diabetes Research and Care,* 2023;11:e003485.

IV. Dawnbringer, J., **Hill, H.,** Lundgren, M., Catrina, S.B., Caballero-Corbalan, J., Cederblad, L., Carlsson, PO. and Espes D. (2024) Development of a three-dimensional scoring model for the assessment of continuous glucose monitoring data in type 1 diabetes. *BMJ Open Diabetes Research and Care,* 2024;12:e004350.

V. **Hill, H.**, Klaar, P. and Espes, D. (2025) Real-life data of hypoglycemic events in preschool- and school-aged children with type 1 diabetes. *Manuscript.*

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Additional Papers Not Included in Thesis

I. Espes, D., Liljebäck. H., **Hill, H.**, Elksnis, A., Caballero-Corbalan, J., Carlsson, PO. (2021) GABA induces a hormonal counter-regulatory response in subjects with long-standing type 1 diabetes. *BMJ Open Diabetes Research and Care*, 2021;9:e002442.

II. Cederblad, L., Eklund, G., Vedal, A., **Hill, H.**, Caballero-Corbalan, J., Hellman, J., Abrahamsson, N., Wahlström-Johnsson, I., Carlsson, PO., Espes, D. (2023) Classification of Hypoglycemic Events in Type 1 Diabetes Using Machine Learning Algorithms. *Diabetes Therapy*, 2023;14, 953-965.

Contents

Abbreviations

ADA	American Diabetes Association
AGP	Ambulatory Glucose Profile
AID	Automated Insulin Delivery
CGM	Continuous Glucose Monitoring
CNS	Central Nervous System
CSII	Continuous Subcutaneous Insulin Infusion
CV	Coefficient of Variation
DCCT	Diabetes Control and Complications Trial
DKA	Diabetes Keto Acidosis
DSMB	Data Safety Monitoring Board
EDIC	Epidemiology of Diabetes Interventions and Complications
ELISA	Enzyme-Linked Immunosorbent Assay
FOH	Fear of Hypoglycemia
GABA	Gamma-Amino Butyric Acid
GMI	Glucose Management Indicator
GVP	Glycemic Variability Percentage
HBGI	High Blood Glucose Index
HCL	Hybrid Closed Loop
IAbs	Islet Autoantibodies
ISPAD	International Society for Pediatric and Adolescent Diabetes
LBGI	Low Blood Glucose Index
LGS	Low Glucose Suspend
MARD	Mean Absolute Relative Difference
MDI	Multiple Daily Injections
MMTT	Mixed meal tolerance test
NDR	Swedish National Diabetes Registry
PLGS	Predictive Low Glucose Suspend
SMBG	Self-Monitoring of Blood Glucose
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
TAR	Time above range
TBR	Time below range
TEDDY	The Environmental Determinants of Diabetes in the Young

TIR	Time in range
TITR	Time in tight range
SMBG	Self-Monitoring of Blood Glucose
SD	Standard Deviation
QoL	Quality of Life

Introduction

Hypoglycemic events pose a significant challenge for individuals with type 1 diabetes (T1D). Symptoms of hypoglycemia range from mild events with palpitations and sweatiness to severe with neurological deficits and even death. The technological advancements in the treatment of T1D over the past years have led to a decrease of time spent in hypoglycemia. Despite this, hypoglycemia is still the most common side effect to insulin treatment and still constitutes a challenge for achieving optimal glucose control.

Remaining levels of endogenous insulin above 0.04 nmol/L have demonstrated a reduction in the frequency of severe hypoglycemic events in T1D (1). Consequently, it would be of great interest to regain endogenous insulin production in T1D, if not to retain normoglycemia, then to achieve sufficient levels to reduce hypoglycemic events.

Diabetes Mellitus

The term "diabetes" has its origins in ancient Greek, where it means "siphon" – to pass through. The Greek physicians observed excessive urination in individuals with diabetes and compared it to a siphon. This connection highlights the early recognition of the condition's hallmark signs, polyuria and polydipsia.

The word "mellitus" is from the Latin word for honey. This addition signifies the sweet taste of the urine in individuals with diabetes, indicating the presence of elevated sugar levels. This sweet taste was noted by ancient physicians, including the Greeks and Romans, as they attempted to diagnose and understand the condition.

Today, there are several known subgroups of diabetes mellitus, all presenting with elevated levels of blood glucose. Each subtype is characterized by distinct underlying causes, pathophysiology, and clinical features. Type 1 and type 2 diabetes are the most prevalent and well-understood subtypes, but many other forms of diabetes, such as gestational diabetes, maturity-onset diabetes of the young (MODY), late autoimmune diabetes in adults (LADA), monogenic diabetes and secondary diabetes, exist. Understanding the various subtypes of diabetes is essential for accurate diagnosis and treatment (2).

According to the 10th edition of the Diabetes Map, it was estimated that diabetes affected approximately 537 million people worldwide, with projections suggesting an increase to 643 million by the year 2030 (2). This implies that elevated blood glucose levels are present in about 10.5% of the world population. T1D accounts for 5-10% of all diabetes cases globally, but in children and adolescents it is the dominating diabetes diagnosis accounting for >90% of cases (2-4).

Type 1 diabetes

Pathogenesis

Even though the glucose homeostasis is a complex collaboration involving several organs and cell types, merely one hormone lowers the blood glucose; insulin.

The pancreas is a dual-purpose organ, with exocrine and endocrine functions. The exocrine tissue, comprising around 98% of the pancreatic mass, facilitates digestion by secreting enzymes as amylase and lipase into the pancreatic duct, ultimately reaching the duodenum, where they are involved in breaking down carbohydrates and fat. The endocrine tissue, accounting for the remaining 2%, is located within the islets of Langerhans, dispersed throughout the exocrine tissue. Here, various endocrine cell types, including beta-cells responsible for insulin secretion, alpha-cells releasing glucagon, delta-cells producing somatostatin, and PP-cells releasing pancreatic polypeptide (PP), intricately regulate glucose homeostasis.

Insulin is released in response to increased levels of blood glucose and exerts various functions such as; facilitating cellular glucose uptake, promoting conversion of glucose to glycogen and inhibiting gluconeogenesis, stimulating lipid storage and inhibiting lipolysis, enhancing cellular uptake of amino acids and protein synthesis as well as promoting cellular growth.

In T1D the glucose homeostasis is disrupted due to an immune-mediated destruction of the insulin producing beta-cells, leading to insulin deficiency and ultimately persistent hyperglycemia in affected individuals (5). Both in clinical practice and research, residual beta-cell mass is however indirectly assessed using Connecting-peptide (C-peptide) rather than insulin. This is because beta-cells produce proinsulin, which is later cleaved into equal amounts of insulin and C-peptide. C-peptide has a longer half-life and is cleared from circulation at a more consistent rate than insulin, making it a more reliable marker (6).

The histopathology in T1D is defined by a decreased beta-cell mass with infiltration of mononuclear cells into the islets of Langerhans, described by Opie in 1901 (7). This pathology was later termed “insulitis” and became the

hallmark of T1D. In terms of potential pathogenic mechanisms, post-mortem analysis of individuals newly diagnosed with T1D revealed that the insulitis lesions primarily harbored CD8+ T cells, succeeded by macrophages (CD68+), CD4+ T cells, B lymphocytes (CD20+), and plasma cells (8). In the 1970s, a genetic connection between the immune system and T1D was identified, as certain HLA antigens were found to be associated with insulin-dependent diabetes but not with insulin-independent diabetes (9).

The general view is that T1D is an autoimmune disease, where autoantibodies targeting beta-cell autoantigens are believed to initiate the immune attack. These autoantibodies are found in more than 90% of individuals with newly diagnosed T1D (10).

Etiology

The etiology of T1D is multifactorial, involving a complex interplay of genetic susceptibility and environmental triggers that are not fully understood.

Genetics

In terms of genetics, T1D is a polygenic disorder involving various loci that influence disease susceptibility. A key locus maps to the Human Leukocyte Antigen (HLA) class II genes on chromosome 6p21, thought to explain approximately 40-50% of the familial aggregation of T1D (11). The highest-risk haplotypes are currently known to be DR3/DR4 or DQ2/DQ8. Additionally, genome wide associations have identified over 60 non-HLA risk loci for T1D, contributing to the intricate genetic pattern (12). The significant genetic component is evident in the lifetime risk of inheritance, ranging from 6-9% if the father is affected, 1.3-4% if the mother is affected and 6-7% if siblings (70% in homozygotic twins) have T1D. Overall, 10-15% of children and youth diagnosed with T1D have a first-degree relative with the disease. Despite progress, challenges persist in translating genetic insights into clinical applications for diagnosis and risk assessment.

Environmental factors

Environmental factors are believed to play a role in both the triggering and the progression of islet autoimmunity. The lack of full concordance between homozygotic twins, the rising T1D incidence, and the differing risk based on parental influence underscore that role.

Various factors have been investigated, such as the role of breast-feeding (13), childhood obesity (14), gluten intake (15) and gut-microbiota (16). Although, the results have been debated and it has not to date been possible to prove causality for a unique environmental factor.

Several viruses, particularly enteroviruses, have been of interest due to the observed seasonal pattern in T1D incidence and their presence in blood, gut and pancreatic tissues of T1D patients (17-21). Furthermore, a prospective

study identified enterovirus B as the only virus in the human virome with a significant association with islet autoimmunity, albeit not to overt T1D (22). However, the overall conclusion from The Environmental Determinants of Diabetes in the Young (TEDDY), a large prospective cohort study investigating a number of environmental triggers, suggest that there are multiple pathways leading to the destruction of beta-cells (23).

Autoantibodies

Within the context of T1D etiology, accumulated evidence from longitudinal cohort studies and extensive screening efforts has led to the identification of four well-characterized Islet autoantibodies (IAbs). The four IAbs target insulin (IAA), insulinoma-associated antigen-2 (IA-2A), zinc transporter 8 (ZnT8A) and glutamic acid decarboxylase (GADA). Interestingly, GADA facilitates the production of gamma-amino butyric acid (GABA) from glutamate.

The IABs serve as key biomarkers for predicting the onset of T1D and also function as a diagnostic tool (24). Approximately 70% of individuals displaying ≥2 IAbs progress to clinical T1D within 10 years (25).

Genetic risk factors for T1D are found to be closely related to the development of IAbs (26). High-risk HLA haplotypes associate with both the type and the age of first IAb seroconversion. Individuals with HLA-DR4-DQ8 are most likely to primarily develop IAA, with peak seroconversion in the first years of life and a subsequent decline over the following years. In contrast, those with the HLA-DR3-DQ2 haplotype are more likely to initiate seroconversion with GADA, with the highest frequency of seroconversion observed until the second year of life and a relatively consistent pattern thereafter (27, 28).

However, the impact of HLA haplotype on T1D progression is relatively limited in individuals with two or more IAbs (29).

Epidemiology

In 2021, there were an estimated 8.4 million individuals with T1D worldwide. Of these, over 1.2 million were children and adolescents. In 2021, IDF estimated that 149,500 new cases among individuals less than 20 years of age were diagnosed (30). Furthermore, numbers of new and prevalent T1D cases are increasing each year due to rising incidence in many countries, and reductions in mortality (31, 32). By 2040, the global prevalence is expected to double according to a modelling study (33).

The incidence of T1D show great differences globally, with the highest incidence in Finland followed by Sweden. Data from many countries are of questionable accuracy due to lower case ascertainment rates in low-income countries. However, even when comparing Finland and Japan, two well-resourced countries, the incidence rate in individuals 0-14 years of age is 24-fold higher in Finland (52.2 vs 2.2 per 100,000 persons per year) (34). Despite

these large variations, the factors contributing to geographical variations in the incidence are not yet understood (35).

Sweden

In total, >8000 children and youth (<18 years) live with T1D in Sweden. With an annual incidence of 44.1 per 100,000 persons per year (aged 0-14 years), the incidence in Sweden has levelled off in recent years, as in other high-income countries (34). According to latest available data on incidence from the Swedish National Diabetes Registry (NDR), 1023 children (<18 years) were diagnosed, of whom 56.7% were boys and 43.3% girls (36).

Type 1 diabetes in children and adolescents

T1D was previously referred to as juvenile diabetes, as it is the main type of diabetes in children. The peak of incidence varies in different countries, in Finland the peak is between 4-9 years of age, while 10-14 is more common in most non-European countries (31, 34).

Compared to adults, T1D initiating before the age of 18 is characterized by a shorter symptomatic duration before diagnosis and a lower residual beta-cell function (37). In addition, when comparing among children there is a substantial correlation concerning age and remaining beta-cell function, with a more rapid decline in the young patients (38, 39).

Diagnosis of type 1 diabetes

The diagnostic criteria for T1D have evolved to include both clinical and laboratory parameters. Traditionally characterized by symptoms such as polyuria, polydipsia and unexplained weight loss, contemporary diagnostic approaches also incorporate laboratory assessments, including elevated blood glucose levels and the presence of autoantibodies targeting beta cells, which enables a staging of the onset of disease.

Diagnostic criteria for diabetes mellitus are defined in guidelines by the International Society for Pediatric and Adolescent Diabetes (ISPAD) (40):

1. Classic symptoms of diabetes or hyperglycemic crisis with plasma glucose concentration ≥11.1 mmol/L. Or:
2. Fasting plasma glucose ≥7.0 mmol/L. Fasting is defined as no caloric intake for at least 8 h. Or:
3. Two-hour postload glucose ≥11.1 mmol/L during an oral glucose tolerance test (OGTT). The OGTT should be performed using a glucose load containing the equivalent of 75 g of anhydrous glucose dissolved in water or 1.75 g/kg of body weight to a maximum of 75 g. Or:
4. HbA1c ≥6.5% (≥48 mmol/mol). However, a value less than 48 mmol/mol does not exclude diabetes mellitus.

In the absence of unequivocal hyperglycemia, the diagnosis of diabetes requires two abnormal test results from the same sample or from two separate test samples.

After the initial step of diagnosing diabetes, the differentiation between T1D, T2D, MODY, and other forms of diabetes has important implications for both therapeutic decisions and educational approaches. Individuals with any form of diabetes may or may not require insulin treatment at various stages of their disease. Such use of insulin does not, of itself, classify the diabetes type. Diabetes-associated autoantibodies are an important diagnostic tool. The presence of GAD, IA2, IAA, and/or ZnT8 confirms the diagnosis of T1D in children. Measurements of autoimmune markers are useful in confirming T1D in those where presentation is not clear, in particular obese adolescents.

Stages of type 1 diabetes

Within recent years, staging of the progression to overt T1D has been established also in the clinical management, and are described in the American Diabetes Associations (ADAs) standards of care (24).

Stage 1: Presymptomatic. ≥2 T1D associated IAbs.
Stage 2: Presymptomatic. ≥2 T1D associated IAbs and dysglycemia.
Stage 3: Symptomatic. ≥2 T1D associated IAbs and onset of clinical symptoms and signs of diabetes.

Management of type 1 diabetes

Contemporary management of T1D is rooted in the discovery of insulin´s blood sugar-lowering effects by Frederick Banting and Charles Best, in 1921. Utilizing animal-based insulin, their breakthrough led to the successful treatment of the first patient with diabetes, thereby revolutionizing the management of a condition that was once considered incurable.

The ultimate metabolic goal in the treatment of T1D is to prevent both long term and acute complications by maintaining blood glucose levels within the physiological range. To accomplish this, lifelong meticulous administration of exogenous insulin is required.

Insulin treatment

To date, insulin is administered either through multiple daily injections (MDI) or via continuous subcutaneous insulin infusion (CSII), commonly known as insulin pump therapy (IPT). In the MDI regimen, individuals administer subcutaneous injections of both long-acting basal insulin and rapid-acting bolus insulin, whereas CSII continuously delivers only rapid-acting insulin to the subcutaneous tissue. Both strategies aim to mimic the physiological patterns of insulin secretion, thereby striving to maintain optimal blood glucose levels.

Glucose monitoring

Self-monitoring of blood glucose

In order to administer an appropriate dose of insulin it is necessary to closely monitor the blood glucose, which together with insulin administration are the medical cornerstones of T1D clinical management. Self-monitoring of blood glucose (SMBG), was widely introduced in the 1980s. SMBG requires regular puncturing of typically a finger with a lancet to obtain a small blood sample, applying a drop of blood onto a reagent strip inserted to a portable glucometer, enabling automated glucose reading (41). A positive correlation between frequency of SMBG and glycemic control in T1D was demonstrated, and it became standard of care (42-44). Unlike measurement of HbA1c alone, which could only detect poor glycemic control, self-monitoring could also show persons with T1D how to improve glycemic control (45). Although, over time, reports questioned whether the commonly applied daily frequency of SMBG was insufficient to adequately monitor type 1 diabetes patients properly (46, 47).

Continuous glucose monitoring

Continuous glucose monitoring (CGM), was clinically introduced in the early 2000s. CGM systems continuously or semi-continuously measure glucose levels in the interstitial fluid (ISF) using a sensor, typically inserted in the subcutaneous fat under the skin on the belly or arm and attached to the skin with a sticky patch. The sensor provides data at intervals ranging from 1 to 15 minutes, which is transferred from a transmitter in contact with the sensor, to a receiver. The receiver functions as a software program stored on various platforms, such as a smartphone, an insulin pump or a standalone device. Levels of glucose in the ISF have been shown to correlate well to blood glucose (48), but offers a lag time of around 4-10 minutes which soft-ware algorithms attempt to compensate for (49).

There are two distinct categories of CGM systems: real-time CGM (rtCGM) and intermittently scanned CGM (isCGM). RtCGM systems log glucose readings every 1-5 minutes, enabling users to visualize glucose levels, assess the direction of glucose change through trend arrows and provide alerts to the user for various situations such as hypo- or hyperglycemia. Some systems can also alert with the prediction of an urgent low glucose level. isCGM systems continuously measure glucose levels and log readings every 15 minutes. However, users need to scan the sensor with either a standalone device or a smartphone application to access and view the recorded glucose levels. Comparing the two systems, rtCGM has been shown to improve glycemic control and reduce hypoglycemia more efficiently compared to isCGM in T1D (50, 51).

Although correlating well, no CGM device reflects the blood-glucose perfectly in real-time. While debatable when used as a single metric, mean absolute relative difference (MARD) is the most widely used measure of CGM accuracy (52). It calculates the average absolute percentage difference between CGM readings and matched reference glucose values. A lower MARD means the CGM readings are closer to the actual blood glucose values, indicating better accuracy. A higher MARD suggests greater discrepancies, meaning the CGM may not be as reliable. For example, a MARD of 10% means that, on average, CGM values deviate by 10% from the reference measurements. Modern devices typically achieve a MARD between 7-10%, making them reliable for most diabetes management decisions (53).

Utilization of continuous glucose monitoring data

A tremendous amount of glucose data has become available with the introduction of CGM. Users can access CGM reports through their smartphone applications, while healthcare providers review these reports using various software platforms (Such as: Glooko, Abbott LibreView, Dexcom CLARITY and Medtronic CareLink) (54).

To facilitate the interpretation of this data, the ambulatory glucose profile (AGP) report has become an internationally agreed on and standardized format. Originally developed to plot the glucose data measured by SMBG (55), it has been modified and adopted into standard of care in the interpretation of CGM-data, graphically presented in a one page summary of glycemic control (56).

In the AGP report (*Figure 1*), glucose data over several days or weeks are displayed in the context of a typical 24-hour day, or "modal" day. Fourteen days of CGM data have shown to provide a good correlation of glucose metrics for a 3-month period, thereby mirroring the HbA1c and hence becoming the typical number of days for presentation (57, 58).

Core metrics to be included in the AGP report for clinical care were identified by a consensus group in 2017, with later updates (56, 59). These include mean glucose and a glucose management indicator (GMI), which represents average glycemia and can be compared to HbA1c (60). Furthermore, percent of readings in defined glucose ranges are presented and graphically depicted: time in range (TIR; 3.9-10 mmol/L), time below range level 1 (TBR 1; 3.0-3.8 mmol/L), time below range level 2 (TBR 2; <3.0 mmol/L), time above range level 1 (TAR 1; 10.1-13.9 mmol/L) and time above range level 2 (TAR 2; >13.9 mmol/L). Glycemic variability is presented as coefficient of variation (CV), and/or standard deviation (SD).

Over the recent years, there has been a shift towards adopting time in tight range (TITR; 3.9-7.8 mmol/L), as a pedagogical approach to determining "time spent in normoglycemia" (61, 62).

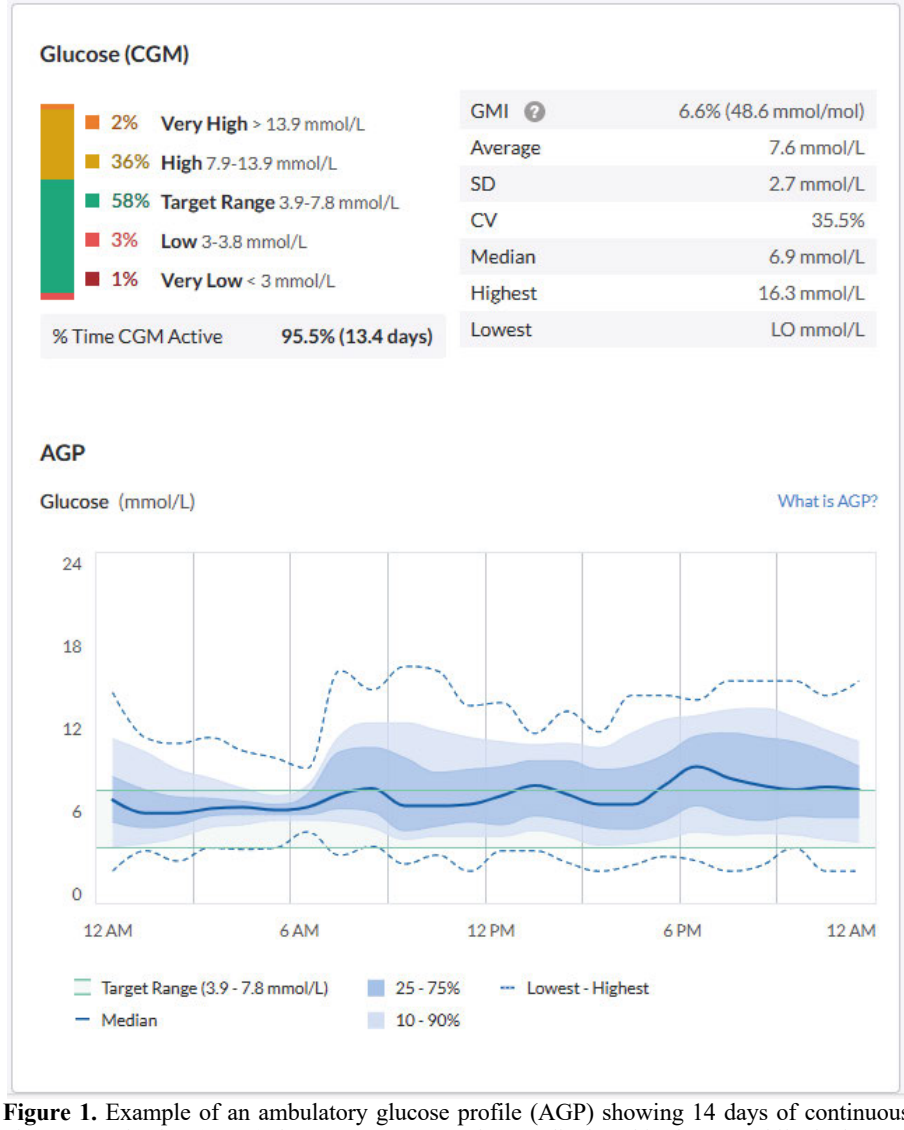

Figure 1. Example of an ambulatory glucose profile (AGP) showing 14 days of continuous glucose monitoring (CGM) data. Key CGM-metrics are displayed in the top, while the bottom section illustrates a typical daily glucose pattern (modal day).

Analyzing CGM data retrospectively with standardized data management tools like the AGP report, allows clinicians and individuals with diabetes to identify fulfilment of clinical target values and challenges in glycemic management in a more detailed manner than merely aiming for an HbA1c target.

Moreover, CGM data has become endorsed to be used either as a specified study endpoint or as supportive complementary glucose metrics in clinical trials, where HbA1c was previously the sole gold standard (63).

Looking ahead in CGM data assessment, a composite metric representing the complexity of glucose levels and fluctuations in a single score would be a great benefit since it could provide a more comprehensive and accessible overview of glucose control. Besides tracking data from individuals over time, a composite metric would enable a more effective monitoring of large number of patients at a diabetes clinic, i.e., population management. This would be of great assistance for caregivers in order to identify the patients in greatest need of care. While such models have been proposed, they are not yet implemented in clinical practice due limitations in capturing both overall glycemia, hypoglycemia and variability in one metric (64).

Combination of technologies

Despite the use of contemporary insulin analogs, replicating the normal physiology of blood glucose regulation remains a great challenge. To further reduce this gap, the latest technology advancements have incorporated the function of CGM systems into the utilization of CSII, for algorithm-driven automation of insulin delivery based on real-time sensor glucose values; automated insulin delivery (AID). The initial devices could only suspend insulin administration at low glucose values (low glucose suspend, LGS), while following models could suspend insulin delivery already at the prediction of an upcoming low glucose value (predictive low glucose suspend, PLGS). The latest devices entering the market are commonly referred to as "hybrid closed-loop" (HCL). These autonomously adjust insulin delivery based on real-time glucose readings.

While PLGS focuses on preventing low glucose by temporarily suspending insulin, HCL aims for dynamic glucose regulation through continuous adjustments. However, all clinically available systems of today still require a manual intervention for bolus doses during mealtime. Treatment with HCL has proven to improve the glycemic control compared to previous variants of CSII in both children and adults with T1D, including reduced occurrence of hypoglycemia (65-68).

In Sweden, according to the latest annual report from the national diabetes registry, 99.2% of all patients below the age of 18 were equipped with either an is- or rtCGM device and 82.2% used CSII (of whom 56.8% were HCL) compared to 17.9% on MDI (69).

Treatment goals

Swedish guidelines for pediatric T1D management recommend a target HbA1c ≤48 mmol/mol, with reservation for the occurrence of severe hypoglycemia or frequent mild hypoglycemic events (70). In addition to HbA1c, targets for CGM-metrics recorded over a 14 day period have been established in an international consensus, specifying how time in certain glucose ranges should be spent (59):

>70% 3.9-10 mmol/L, <25% >10 mmol/L, <5% >13.9 mmol/L, <4% <3.9 mmol/L and <1% <3.0 mmol/L. Glycemic variability (CV%) ≤36%.

Recommendations were adopted by ISPAD guidelines of 2022 with amendment in younger children concerning 50% of time or more spent in 3.9-7.8 mmol/L (62).

Complications

Long-term complications

These complications include microvascular types such as retinopathy, nephropathy, neuropathy and macrovascular disorders such as and coronary artery disease and stroke. This ultimately contributes to elevated mortality rates in T1D, particularly in cases of early-onset T1D (71). As demonstrated in the DCCT, the epidemiology of diabetes interventions and complications (EDIC) study and further supported in a more contemporary treatment setting, long-term complications in T1D are primarily correlated to chronic hyperglycemia (72-74). Effective management strategies, including glycemic control, blood pressure regulation, and lipid management, are crucial in mitigating these complications. Regular screening and early intervention are essential to prevent or delay the onset of long-term complications in pediatric and adolescent T1D patients (75).

Acute complications

Diabetes ketoacidosis (DKA) is an acute complication due to relative or absolute insulin deficiency. Diagnosis is based on hyperglycemia, ketosis and metabolic acidosis, with treatment predominantly managed in an intensive care unit (76). The incidence of DKA in Sweden in the latest annual report of the national diabetes registry was 1.5%, with 144 incidents among 121 patients (69).

Hypoglycemia is the most common acute complication of T1D, and is described below.

Hypoglycemic events in type 1 diabetes

Hypoglycemia in T1D poses a significant challenge due to several factors. In the acute setting, severe hypoglycemia can lead to dangerous situations, ultimately resulting in death (77). Still, the more frequent milder events cause disturbing symptoms for the patient and is known to increase inappropriate glycemic excursions (78).

In the long term, severe hypoglycemic events in children under the age of 6 have been linked to cognitive impairments (79), and structural brain abnor-

malities (80). Furthermore, hypoglycemia itself but also the fear of hypoglycemia has a negative impact on quality of life for both the affected patients and their families (81).

Risk factors for hypoglycemia include young age, long T1D duration, physical activity and alcohol consumption (82). Additionally, the physiological hormonal counter-regulatory response to hypoglycemia, including an increase in plasma glucagon and epinephrine, is often blunted in T1D making these patients even more susceptible to such events (83, 84).

Symptoms of hypoglycemia

Symptoms range from autonomic activation such as palpitations, sweatiness and shakiness to neuroglycopenic symptoms such as blurred vision, concentration difficulties, loss of consciousness and seizures. Symptoms and glycemic thresholds for symptom activation are individual and can change over time, as well as differ depending on chronic hypo- and hyperglycemia (85, 86). In healthy individuals, autonomic activation occurred at a higher glycemic threshold in children compared to adults (3.9 vs 3.2 mmol/L, respectively) (85).

Classifications of hypoglycemia

According to ISPAD Clinical Practice Consensus Guidelines, hypoglycemic events can be divided into three groups: *i)* Clinical hypoglycemia alert (< 3.9 mmol/L), *ii)* Clinically important or serious hypoglycemia (< 3.0 mmol/L) and *iii)* Severe hypoglycemia, i.e., events associated with severe cognitive impairment including coma and convulsions requiring external assistance by another person.

This interpretation becomes particularly challenging in very young children, who per definition needs external assistance by another person to treat a hypoglycemic event, and may not be able to recognize or communicate their symptoms.

As identified by ISPAD, assigning a numerical value as definition is difficult due to the individual variations in symptoms and glucose thresholds. Hypoglycemic events therefore include all episodes of plasma glucose low enough to cause symptoms and/or signs thereof (82).

Incidence of hypoglycemia

Over recent decades, the incidence of severe hypoglycemia has declined. According to NDR, 1.9% of individuals <18 years experienced a severe hypoglycemic event during 2023 (the most recent data available), with 210 events reported in 154 individuals (69). Contrary to earlier findings, reducing HbA1c levels is no longer a robust predictor for severe hypoglycemia in pediatric patients with T1D in modern treatment settings (87-89).

Earlier studies primarily focused on the occurrence of severe hypoglycemic events. In contrast, contemporary reports predominantly emphasize analysis of CGM data, where TBR is reported, thereby not capturing the frequency or symptoms of hypoglycemic events. This presents a challenge in assessing the occurrence of non-severe hypoglycemic events. Observational studies have reported frequencies of about two symptomatic events per week (90, 91).
Modern therapies with CSII, standalone CGM-devices and furthermore AIP therapy with PLGS and HCL-systems have improved glycemic outcomes including reduced frequency of severe hypoglycemia and time spent in hypoglycemia (66, 68, 92-94).

Treatment of hypoglycemia

Non-severe hypoglycemia is treated with the intake of fast acting carbohydrate in an amount adjusted to the individual´s weight, insulin treatment modality and amount of insulin on-board. Severe hypoglycemia, if the person is unable to swallow, is treated with glucagon which can be administered through various routes (82).

Future treatment approaches in T1D – beyond insulin

Despite the previously described progress in T1D management, the condition itself and its acute and long-term complications remain a substantial burden for both individuals and the society. Studies have demonstrated that residual insulin production lowers the risk of DKA and hypoglycemia, and furthermore is associated with a reduced risk of long-term complications (95-98).

A treatment that could either preserve or restore the endogenous beta-cell mass in T1D, at least to some extent, is therefore highly sought after. Currently, three categories to achieve this are described:

***i)* Replacement**

This involves the transplantation of either the whole pancreas or isolated islets of Langerhans from deceased organ-donors. Both these approaches are currently available treatment options for selected patients, especially those with repeated life-threatening hypoglycemic events. However, since they require lifelong immunosuppression to prevent rejection and the recurrence of autoimmunity, they are generally considered as a therapy rather than a cure and for the majority of patients not a favorable treatment option. Additionally, the donor availability is a limitation for considering as a large-scale therapy. As a result, it is typically reserved for patients with poor diabetes control despite intensive insulin therapy or those with brittle diabetes. Ongoing research is focused on developing strategies using stem cell-derived beta-cells to improve access to beta-cells and utilize hypo-immunized beta-cells, reducing the need for immunosuppression, which could in fact turn this approach into a potential cure for T1D (99).

ii) Retention

Retention aims to preserve the existing beta-cells at T1D diagnosis (or in the pre-symptomatic phase) by protecting the beta-cells from immune destruction and metabolic stress. This approach can maintain the insulin production from the point of initiation and stop or at least delay the disease progression. However, it does not restore lost beta-cells and unless truly efficient it only offers a temporary benefit, with potential side effects and limited long-term effectiveness.

Examples of such therapies include teplizumab**,** a CD3-directed monoclonal antibody, preserving beta-cell function by preventing immune attack. It shows promise in maintaining beta-cell function in individuals at risk or in the early stages of the disease (100). Additionally, a clinical trial involving allogenic mesenchymal stromal cells in recent-onset T1D demonstrated potential to preserve beta-cell function as well (101).

iii) Regeneration

Regeneration refers to stimulating the replication (proliferation) or restoration (neogenesis) of beta-cells. However, adult beta-cell replication is limited, and in T1D there is a risk that the immune mediated attack would lead to a destruction of also the newly formed beta-cells. Therefore, a combined approach involving both proliferation and immunomodulation would be preferable. In this context, GABA has emerged as an intriguing potential drug candidate for T1D since it has in experimental studies been found to act as both an immune modulator and to induce beta-cell proliferation.

GABA and its potential role in type 1 diabetes

GABA is synthesized from glutamate by glutamic acid decarboxylase (GAD), a major T1D autoantigen. It is well characterized within the central nervous system (CNS), where it acts as a key inhibitory neurotransmitter. The inhibitory role is primarily facilitated by two classes of GABA receptors, $GABA_A$ and $GABA_B$. $GABA_A$ receptors are ionotropic and mediate swift inhibitory signals (102). On the other hand, $GABA_B$ receptors function as metabotropic G protein-coupled receptors, delivering gradual inhibitory signals through G proteins and second messengers (103).

Outside the CNS, the highest concentrations of GABA are observed in the beta-cells and in immune cells (104, 105). Its presence in these tissues and its production via GAD, warranted an evaluation of GABA also in the context of T1D.

GABA in experimental and clinical studies of T1D

GABA has been attributed with three therapeutic effects related to T1D.

i) Increasing insulin production: Within beta-cells, stored in both large dense-core vesicles together with insulin, and in the cytosol separated from insulin, GABA has the capacity to be released in both a glucose dependent and independent manner (106, 107). The main effect of GABA in islets are found to be mediated through $GABA_A$ receptors, but in contrast to the CNS where it is predominantly inhibiting, the role of GABA in beta-cells is more uncertain.

In murine models and human islets, GABA has demonstrated the ability to stimulate insulin secretion (107, 108). However, a more recent study reported inhibitory effects (106), and other studies observed variability in the insulin-secreting effect based on glucose levels (109, 110). Furthermore, reports have indicated that GABA signaling plays a role in the process of transdifferentiation from glucagon-producing alfa-cells to insulin-producing beta cells (111, 112), however, the latter findings have been subject to debate, as other models have not identified such transdifferentiation (113, 114).

In human studies of healthy controls, GABA demonstrated a dose-dependent increase in plasma insulin following oral GABA ingestion (115). Additionally, a pharmacokinetic study on oral GABA treatment showed that plasma insulin levels rose both immediately after ingestion and during the postprandial state. This response was further enhanced after a 7-day treatment regimen (116).

Recently, the first human, prospective, double blind, placebo-controlled and randomized clinical trial of oral GABA with and without GAD65-alum (as a potential hypo-immunization strategy) in children with new-onset T1D was performed. Safety measures were met, but no preservation of C-peptide was seen (117).

ii) Reducing excessive glucagon levels: In addition to beta-cells, $GABA_A$ receptors have also been found in human alpha- and delta-cells. Glucagon release was decreased in human islets upon insulin stimulation of $GABA_A$ receptors (118). Moreover, in the previously mentioned trial on GABA with GAD65-alum in new-onset T1D, both fasting and meal-stimulated glucagon was decreased (117). A finding of interest, since excessive post-prandial secretion of glucagon is seen as a possible contributor to the development of diabetic hyperglycemia (119). Notably, in our phase 1 clinical trial the impaired glucagon response to hypoglycemia in T1D was improved with short term GABA (120).

iii) Reducing T-cell mediated immune destruction of beta-cells: From an autoimmune standpoint, research has demonstrated that CD8+ T cells, especially during the development of autoimmune diabetes in BB (Bio Breeding) rats, express $GABA_A$ receptor subunits. Furthermore, GABA has been shown to

markedly reduce T-cell proliferation and inhibit T-cell-mediated autoimmunity in T1D mouse models (121-124).

Additionally, preclinical studies show that combining GABA with low dose of positive allosteric modulators (PAMs) of the $GABA_A$ receptors, such as alprazolam (a benzodiazepine), enhances beta-cell regeneration, reducing the required GABA dose tenfold through synergistic receptor binding (125, 126).

Overall, these findings suggest that GABA in combination with a $GABA_A$ PAM could be explored as a novel class of diabetes therapy, targeting the underlying disease mechanisms.

Aims

The overarching aim of this work was to further explore GABAs potential role in T1D, enhance our understanding of hypoglycemic events and develop a clinically applicable tool for optimizing CGM analysis.

The specific aims of the included studies were:

Study I

To compare endogenous plasma levels of GABA in healthy controls to subjects with long-standing and new-onset T1D, and relate findings to disease state and metabolic features.

Study II

To evaluate the safety (primary objective) and the potential for beta-cell regeneration (secondary objective) of oral GABA treatment, both alone and in combination with alprazolam, in individuals with long-standing T1D.

Study III

To observe the frequency of hypoglycemic events and the relationship with over-all metabolic control in a real-world setting, based on retrospective CGM data in children and adolescents with T1D.

Study IV

To develop a clinically relevant CGM based scoring model, to identify the most critical CGM episodes and/or high-risk patients in a large cohort.

Study V

To explore hypoglycemic events in preschool- and school-aged children, using extended real-world CGM data.

Materials and Methods

Subjects and study design

Study I

In this cross-sectional single-center study conducted at Uppsala University Hospital, a total of 118 subjects were included of whom n=45 were healthy controls, n=60 had long-standing (>5 years duration) T1D and n=13 had new-onset (<6 months duration) T1D. Visits were performed in the morning following an overnight fast, at which peripheral blood was drawn for later analysis.

Study II

Study II was a phase I/II, 3-Arm, open label, single center study performed at Uppsala University Hospital, Sweden. Persons with T1D between the ages ≥18 and ≤50, who received their diagnosis ≥5 years before screening and before 25 years of age were qualified for screening. Persons with C-peptide levels ≥0.12nmol/L, females of child-bearing potential and males without adequate contraception were excluded. In total, 35 individuals with longstanding T1D were screened and included.

Included study participants were randomized in a 1:1:1 ratio to receive 200 mg of GABA (Arm 1) for 6 months, 600 mg of GABA for 6 months (Arm 2), or Alprazolam 0.5 mg combined with 600 mg of GABA for 3 months followed by treatment with 600 mg of GABA alone for another 3 months (Arm 3). The start of the arms with high dose GABA (Arms 2 and 3) was delayed until a Data Safety Monitoring Board (DSMB) evaluated and approved safety data of the first four included participants in arm 1. Randomization was stratified by C-peptide level. See *figure 2* for visual overview of study design and clinical visits.

Figure 2. Study design and scheduled clinical visits in the three treatment groups.

***** Data Safety Monitoring Board (DSMB) evaluated the safety data of the first 4 subjects included in treatment arm 1, after which arms 2 and 3 were allowed to start.
£ Treatment was initiated on day 44 with 0.5 mg of alprazolam. It was ramped up on day 45 with low-dose GABA (200 mg) and 0.5 mg of alprazolam, and further on day 46 with high-dose GABA (600 mg) and 0.5 mg of alprazolam. As an extra precaution, subjects remained under observation at the hospital for 3 h after tablet intake on days 44-46.
DSMB evaluated the safety of the first 4 subjects in arms 2 and 3 to ensure no safety concerns had arisen upon treatment with the higher dose of GABA (and alprazolam in arm 3).
$ Treatment with alprazolam stopped after 3 months, whereafter subjects continued with GABA alone for the remaining 3 months.

Safety

Throughout the study period, all participants maintained their regular intensive insulin therapy under the supervision of their personal physicians. As part of the study protocol, they underwent comprehensive safety evaluations at multiple time points, including assessments of adverse events (AEs), general physical examinations, neurological evaluations, and laboratory safety tests. The study was overseen by Uppsala Clinical Research Center, with data monitoring conducted by an independent Data Safety Monitoring Board (DSMB).

Efficacy

The three treatment groups were compared in terms of regained endogenous insulin secretion as measured by C-peptide under fasting and stimulated conditions, counter-regulatory hormonal response in reaction to hypoglycemic clamp, overall diabetes status, serum levels of GABA and quality of life (QoL) utilizing the DTSQ (Diabetes Treatment Satisfaction Questionnaire) and RAND-36 (Research And Development – 36 Item health survey) questionnaires).

Study III

214 subjects with T1D followed at the Department of Pediatric Endocrinology and Diabetology at Uppsala University Hospital, Sweden, were included in this single-center retrospective cohort study. The inclusion/exclusion criteria were *i)* established diagnosis of T1D, *ii)* data availability and *iii)* age ≤19. Subjects were divided into three groups based on estimated HbA1c (eHbA1c) levels; group **1.** ≤48 mmol/mol (n=58); group **2.** 49-64 mmol/mol (n=113) and group **3.** ≥65 mmol/mol (n=43). Data was retrieved from a time-frame of 2018-2021.

Study IV

In this retrospective, single-center study, a total of 82,114 days of retrospective CGM data from 2017 to 2020 available in electronic medical records were collected from n=613 individuals with T1D, followed at the Department of Endocrinology and Diabetology and the Department of Pediatric Endocrinology and Diabetology at Uppsala University Hospital, Sweden. A scoring model was developed based on three metrics; glycemic variability percentage (GVP), low blood glucose index (LBGI) and high blood glucose index (HBGI). Values for each metric was normalized to a 0-100 score. A score of 100 represented the optimal value, while score 0 represented the most alarming 2% (>98th percentile) of the cohort for that dimension. Various ways of combining the mean score of each dimension were tested in order to identify

the most representative single score over an extended time period. Correlations between the scoring model and CGM-metrics were analyzed, and the model was compared with interpretations from a clinical expert board (CEB) who individually evaluated five validation tests of CGM data based on their clinical judgement.

Study V

A retrospective analysis was conducted on CGM data (mean duration 173 ± 2.6 days) and clinical data from 70 children with T1D, cared for at the Department of Pediatric Endocrinology and Diabetology, Uppsala University Hospital, Sweden. Data was gathered from 2023-2024. Participants were divided into two age groups: <7 years (n=26) and 7–12 years (n=44). Descriptive data, CGM-metrics and detailed characteristics of each recorded hypoglycemic event were compared between groups.

Laboratory measurements

Routine clinical analysis

All presented studies utilized the Clinical Chemistry Laboratory, Uppsala University Hospital, concerning routine clinical analysis of venous blood samples. Antibodies GAD and IA2 were measured with a standard clinical assay and, according to clinical routine, considered positive if >5 IU/mL and >7 kU/L, respectively. Plasma C-peptide was detectable if above 0.01 nmol/L. HbA1c was analyzed according to the International Federation of Clinical Chemistry (IFCC) and expressed as mmol/mol. In study II, due to logistic reasons, epinephrine and norepinephrine were analyzed at laboratories in Karolinska University Hospital (Sweden) and Skåne University Hospital (Sweden).

Cytokine-analysis (Study I)

In study I, circulating cytokines were analyzed with magnetic bead-based Luminex using two commercially available assays (cat. no. HTH17MAG-14K and cat. no. HCYP4MAG64K) from Merck Millipore (Burlington, MA, USA) according to the manufacturer's protocol. The analyses were performed at the Plasma Profiling Unit, SciLifeLab (Stockholm, Sweden). Of the analyzed cytokines, IL-22, IL-24, IL-34, and IL-35 were excluded from analysis since >50% of the samples were below the detection level. For the remaining parameters, undetectable samples were assigned a numeric value corresponding to half of the lowest level of detection (single-value imputation).

GABA-analysis (Study I and II)

In study I and II, plasma levels of GABA were analyzed at the Mass Spectrometry Based Metabolomics Facility at Uppsala University by a validated protocol based on ultra-performance liquid chromatography tandem mass spectrometry. Samples were prepared by spiking with 30 µL of 100 ng/mL corresponding d6GABA into 100 µL plasma followed by liquid-liquid extraction after protein precipitation with methanol prior to the analysis. The chromatographic separation of the targeted GABA was achieved by using an ultra-performance liquid chromatography (UPLC, Waters ACQUITY®, Milford, MA, USA) coupled with tandem mass spectrometry (XEVO® TQ-S, Milford, MA, USA). The mass spectrometric detection was performed using electrospray ionization in the positive ionization mode (ESI+) with nitrogen and argon serving as desolvation and collision gas, respectively. Data acquisition range was 100 – 500m/z. Quantification was based on a multiple reaction monitoring (MRM) method with a deuterated isotope internal standard (d6GABA). The linearity of GABA was evaluated over a range of concentrations (1 - 5000ng/mL) and correlation coefficients (r^2) were 0.998. The limit of quantification (LOQ, signal-to-noise ratio = 10) and co-efficient of variation (CV) of GABA assay was 0.5 ng/mL, less than 10%, respectively. Duplicate analyses of each sample were carried out and the average values were reported (CV <5 %).

Ultrasensitive C-peptide-analysis (Study II)

In study II, besides routine analysis of C-peptide, plasma was separated from samples of EDTA blood and frozen at -70 C until concentration of C-peptide was analyzed with an ultrasensitive C peptide Enzyme-Linked Immunosorbent Assay (ELISA) (Mercodia, Uppsala, Sweden). The detection limit was set to 1.17 pmol/L.

Hypoglycemic clamp (Study II)

Hypoglycemic clamps were conducted on four occasions, each in the morning following an overnight fast (≥10 hours). An individualized insulin infusion dose determined by body weight (2 mIU x kg-1 x min-1), was administered. A separate glucose infusion of 100 mg/ml was provided at various rates to initially attain and sustain normoglycemia (5.5 mmol/L) for 30 minutes, followed by inducing hypoglycemia (2.5 mmol/L) for 30 minutes. Blood samples related to counter-regulatory hormones were collected once a stable plateau of blood glucose concentration had been reached for each target level. The insulin infusion was then stopped, and the patient was observed until normoglycemia was restored. The daily dose of the study drug(s) was administered

after the completion of the hypoglycemic clamp, except on treatment day 173, when it was given 20 minutes before the procedure began.

Mixed meal tolerance test (Study II)

Following an overnight fast lasting a minimum of 10 hours, a Mixed Meal Tolerance Test (MMTT) was conducted on four occasions in Arm 1 and five occasions in Arms 2 and 3. Participants using Multiple Daily Injections (MDI) were instructed to administer their regular dose of long-acting insulin on the preceding evening. Participants using Continuous Subcutaneous Insulin Infusion (CSII) maintained their basal rate throughout the test. No bolus dose of fast-acting insulin was to be administered within a 6-hour window preceding the test. A venous catheter was inserted to collect blood samples for plasma glucose (p-glucose) and C-peptide assessments at baseline (time 0) and at 15, 30, 60, 90, and 120 minutes following the oral intake of Resource protein (Nestlé Health Science, Switzerland) consumed in 5 minutes or less. The intake volume was calculated according to body weight (6 ml/kg), with a maximum dose of 360 ml. The daily study drug(s) were administered after the completion of the MMTTs.

Data resources and data handling

Clinical data (Study III and V)

Descriptive clinical data was collected from electronic medical records and the Swedish Childhood Diabetes Register (Swediabkids), which since 2018 is connected to NDR. The data was primarily from patient visits during the period of collected CGM data, but if no visit was registered during that time period, data from the visit closest in time to that period was registered instead. The collected data included age, gender, weight, height, BMI, isoBMI, disease duration, occurrence of coeliac disease and hypothyroidism, insulin treatment modality (MDI or CSII), insulin doses (IU/kg/day) and self-reported events of severe hypoglycemia.

CGM data (Study III, IV and V)

The retrospective CGM data was down-sampled to 15-minute intervals to ensure harmonization of the data between different CGM models. Days with data availability <70% were excluded. CGM-derived metrics was computed for the full extent of available data for each patient.

In Studies III and V, in addition to standard CGM-metrics, all unique events of hypoglycemia were identified. An event was defined as each episode with

a glucose level <3.9 mmol/L lasting until the glucose level returned to ≥3.9 mmol/L. The event was classified as serious if the lowest value during the event was <3.0 mmol/L. For each event, duration, lowest glucose level and time of day was registered. Events occurring between 10 PM and 6 AM were defined as nightly hypoglycemic events. The CGM data was processed by in-house algorithms developed by One Two Analytics AB (Solna, Sweden).

Statistical analyses

Statistical analyses were conducted with GraphPad Prism (GraphPad Software, Boston, Massachusetts USA). For all comparisons, p-values <0.05 were considered statistically significant. Data are, unless stated otherwise, presented as means ± SEM, with 95% CI.

Study I

Non-numeric parameters were compared with Fisher´s exact test. For numerical data, Student´s t-test was used for parameters that passed the D'Agostino & Pearson normality test, while the Mann-Whitney test was applied to data that were not normally distributed. Since correlations were found to be non-normally distributed according to the D'Agostino & Pearson normality test, they were analyzed using the Spearman rank-order test.

Study II

Statistical analyses were performed by Uppsala Clinical Research Center. Numerical data were compared using either parametric methods (ANOVA) or nonparametric methods (Wilcoxon test). Categorical data, such as quality of life and safety outcomes, were analyzed using Fisher´s exact test or the exact Chi-Square test. For isCGM-data, a nonparametric one-way ANOVA with Dunn´s multiple comparisons test was applied. The AUC of ultrasensitive C-peptide values from the MMTT, as well as delta values of counter-regulatory hormones and GABA levels compared to baseline visit were analyzed with mixed-effects analyses with Dunnett´s multiple comparisons test used to account for missing values.

Study III

Comparisons between three groups were made with a one-way ANOVA (for normally distributed data) or the Kruskal-Wallis test (for non-normally distributed data) followed by Dunnett's multiple comparison post-hoc test to compare with group 1. Non-numeric parameters were compared using the Chi-square test for three groups and Fisher´s exact test for two groups. Comparisons between two groups (i.e., MDI vs. CSII) were performed using a Student's t-test for data that passed the D'Agostino & Pearson normality test or a

Mann-Whitney test for non-normally distributed data. Correlations did not follow a normal distribution and were therefore computed using the Spearman rank-order test.

Study IV

Correlations between scoring values and CGM-derived metrics were analyzed using Spearman's rank-order test.

Inter-rater agreement within the CEB was calculated as the average agreement per question. If all five experts agreed on a question, the agreement was considered 100%. Additionally, each expert's agreement with the majority vote was determined.

Fleiss' kappa was used to assess reliability for each test completed by the CEB. For tests 1, 4, and 5, accuracy was defined as the proportion of questions where the majority vote of the expert panel matched the scoring, divided by the total number of questions.

For tests 2 and 3, accuracy was calculated separately for each dimension (hypoglycemia, hyperglycemia, and variability) using the formula:
Accuracy = (TP + TN) / (TP + TN + FP + FN), where
TP = true positive, TN = true negative, FP = false positive, and FN = false negative.

Study V

Numerical data were first tested for normality using the D'Agostino & Pearson normality test. If the data were normally distributed, groups were compared with the Student's t-test; otherwise, the Mann-Whitney test was applied. Categorical data were analyzed using Fisher's exact test. All computed correlations were non-normally distributed and therefore analyzed with the Spearman rank-order test.

Ethical considerations

The presented studies were conducted in accordance with the principles of the Declaration of Helsinki of 1964 and its subsequent amendments, and were approved by the Regional Research Ethical Committee in Uppsala. (**Study I**, Dnr 2014/485; **Study II**, Dnr: 2018/200; **Study III**, **IV** and **V**, Dnr: 2019-03726). **Study II** was also approved by the Swedish medical products agency (EudraCT No. 2018-001115-73). In **Study I** and **II,** participants were provided oral and written study information and signed a written consent before inclusion in the study. Concerning **Study III**, **IV** and **V**, in accordance with the decision of the Regional Research Ethical Committee, the retrospective data was collected without informed consent.

Results

Study I

Healthy controls and persons with T1D were of similar distribution concerning gender and age. Healthy controls exhibited a lower BMI compared to persons with longstanding T1D, and none of the healthy controls were positive for GAD or IA-2 autoantibodies. C-peptide was detectable in 100% of new-onset T1D and in 22% of persons with longstanding T1D. For full descriptive characteristics, see *Table 1*.

Table 1. **Descriptive characteristics of the study population in Study 1.**
Healthy controls (HC), persons with long-standing type 1 diabetes (T1D) and new-onset T1D. Plasma C-peptide was analyzed according to clinical routine and was detectable if above 0.01 nmol/L. C-peptide concentrations were missing for n=2 HC. In accordance with clinical routine, levels of autoantibodies were considered positive if anti-GAD was >5 IU/mL and anti-IA2 >7 kU/L, Statistical comparisons based on one-way ANOVA using Dunnet's test based on comparisons with HC.

Parameter	**HC (n=45)**	**T1D (n=60)**	**New-onset T1D (n=13)**
Female (n, (%))	24 (53%)	28 (47%)	6 (46%)
Age (years)	29.8 ± 1.6	28.4 ±0.8	24.2 ± 0.7
Disease duration (years)	n/a	16.3 ± 0.8	0.17 ± 0.03
Age at onset (years)	n/a	12.1 ± 0.9	24.2 ± 0.7
BMI (kg/m2)	23.1 ± 0.4	24.7 ± 0.5*	22 ± 0.6
fP-Glucose (mmol/L)	5.3 ± 0.07	11.6 ± 0.6***	8.1 ± 1.0*
HbA1c (mmol/mol)	31.2 ± 0.4	61.9 ± 1.7***	69.2 ± 7.4***
Detectable C-peptide (n, %)	43 (100%)	13 (22%)	13 (100%)
C-peptide (nmol/L)	0.61 ± 0.03	0.08±0.03***	0.3 ± 0.03***
GABA (ng/mL)	14.1 ± 0.6	15.6 ± 0.5	13.3 ± 0.7
GAD positive (n, %)	0 (0%)	34 (57%)	10 (77%)
IA-2 positive (n, %)	0 (0%)	31 (52%)	10 (77%)

Our main finding was that circulating systemic levels of GABA were not altered in neither new-onset nor long-standing T1D compared to healthy controls (*Table 1 and fig. 3A*). GABA levels were also similar when comparing C-peptide positive long-standing T1D (n=13) and those without detectable C-peptide (15.4 ± 0.75 vs. 15.6 ± 0.6; p=0.85), and furthermore when comparing C-peptide negative T1D and healthy controls (15.6 ± 0.5 vs. 14.1 ± 0.6; p=0.06). This implies that the systemic circulating levels of GABA remain unaltered in T1D despite the decline in beta-cell functionality. However, a negative correlation was observed for levels of GABA and titers of GAD-autoantibodies among anti-GAD-positive persons (n=45, R=-0.3, p=0.009) (*Fig 3B*). The correlation increased (r=-0.40, p=0.018) when applying a stricter criterion for anti-GAD positivity (>50 IU/mL).

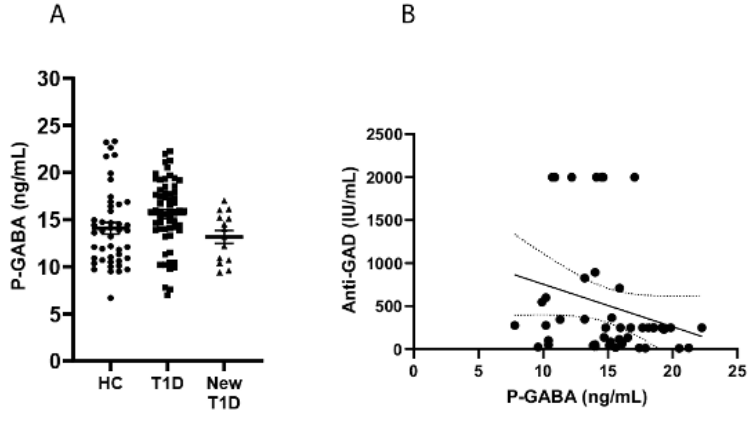

Figure 3 A and B. Circulating Endogenous GABA Levels in Healthy Controls and Type 1 Diabetes

(A) Systemic endogenous GABA levels were measured using mass spectrometry in healthy controls (HC, n=45), individuals with long-standing type 1 diabetes (T1D, n=60), and individuals with newly diagnosed T1D (New T1D, n=13). No significant difference in circulating GABA levels was observed between T1D and healthy controls. Data are presented as mean ± SEM, $p<0.05$ would be considered statistically significant.

(B) Among the individuals with T1D, 45 tested positive for GAD autoantibodies, and within this group, GABA levels showed a negative correlation with GAD autoantibody levels (r=-0.3, p=0.03). The upper limit for the clinically used GAD autoantibody assay is 2000 IU/mL.

Regarding cytokines, in all T1D patients, GABA levels were positively correlated to IL-37 (r=0.30, p=0.026) and IL-36 beta (r=0.34, p=0.01). Additionally, T1D patients exhibited negative correlations between GABA levels and pro-inflammatory cytokines IL-12 (r=-0.29, p=0.033), IL-15 (r=-0.29, p=0.033) and IL-1 beta (r=-0.28, p=0.034). However, in HC, we observed no correlation between GABA levels and circulating cytokines.

Study II

In study II, forty-nine male subjects with T1D were screened, fourteen were screen failures and thirty-five were randomized into the three study arms (**Arm 1**, n=13; **Arm 2**, n=11; **Arm 3**, n=11). Two subjects in Arm 3 withdrew before starting treatment and were therefore not included in the full analysis set (see Flowchart in *figure 4*). The study arms were comparable in terms of age, BMI, and HbA1c. All participants met the inclusion criteria of fasting C-peptide <0.12 nmol/L. Stratification with C-peptide positive patients based on a clinical assay (cut-off 0.05 nmol/L) resulted in n=2 in Arm 1 and n=1 in Arms 2 and 3, respectively.

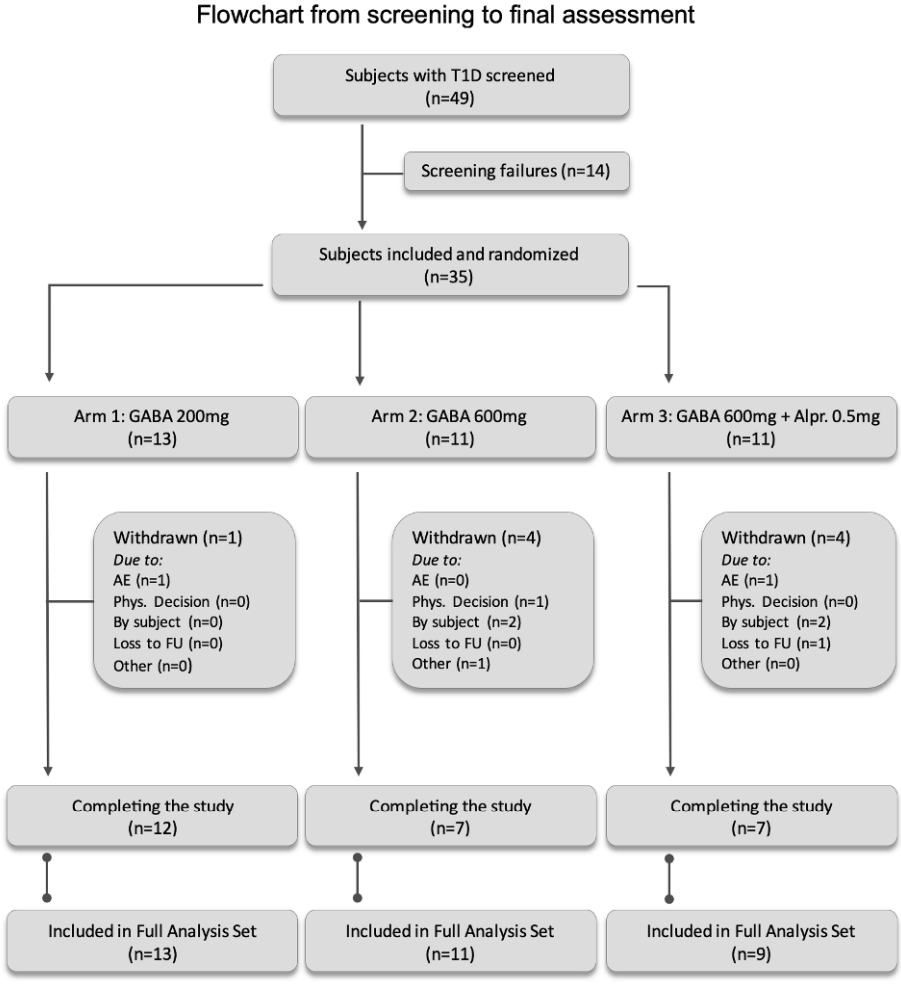

Figure 4. Subject Screening and Inclusion Flowchart
26 subjects completed the study, whereas the Full Analysis Set (n=33) included all randomized subjects who received at least one dose of GABA and had both a baseline measurement and at least one post-baseline assessment for any efficacy variable.

Safety evaluation

Safety data included all 33 randomized subjects who received at least one dose of GABA (Full analysis set). Adverse events (AEs) were reported in 30 participants, mostly mild. Three subjects discontinued treatment due to AEs or serious adverse events (SAEs), of whom two subjects were withdrawn from the study due to the events per se (elevated aspartate aminotransferase (AST)) whereas the third subject discontinued treatment because of stomach pain possibly related to treatment, but was later withdrawn due to mental health issues. The most common AEs were nausea, vomiting, dizziness, fatigue, and elevated AST levels.

In total, 9 subjects experienced transient increases of AST levels, with no dose-dependent differences as three subjects per treatment arm were affected at some point during the study treatment. Aside from AST elevations, no major safety concerns were identified in clinical assessments, including laboratory tests and physical examinations.

Two SAEs occurred, both in Arm 1: one case of severe liver transaminase elevation (as mentioned above) likely related to GABA, which resolved after treatment cessation, and one severe hypoglycemic event considered unrelated.

Efficacy evaluation

Of main interest in terms of efficacy, no changes in C-peptide levels were observed throughout the study, regardless of fasting values, peak levels, or AUC response to MMTT (*Figure 5*). This held true both between and within treatment arms when comparing follow-up visits to baseline including analyses using the ultrasensitive assay. Furthermore, participants with detectable C-peptide at baseline showed no measurable differences over time. Likewise, endogenous pro-insulin and insulin levels remained unchanged during MMTT assessments across all subjects.

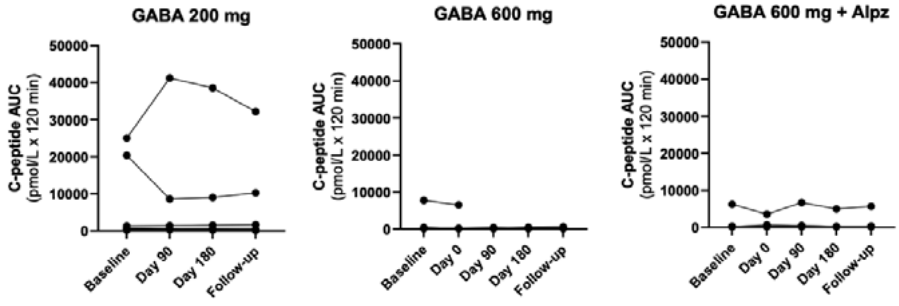

Figure 5. Stimulated C-Peptide in Treatment Groups
C-peptide levels (AUC mean 0–120 min) during the Mixed Meal Tolerance Test (MMTT) were compared at baseline (pre-treatment), after 3 and 6 months of treatment, and at the follow-up visit one month post-treatment. Each graph displays individual values connected by lines. A mixed-effects analysis with Dunnett's multiple comparison test was used, with p-values <0.05 considered statistically significant. No significant differences from baseline were observed in any treatment group.

Additionally, no differences in metabolic control were observed when comparing CGM-metrics (TBR, TIR and TAR) either between treatment arms or within treatment arms from the baseline visit. HbA1c also remained unchanged throughout the study (*Figure 6*). In the hypoglycemic clamps, there were no differences in the counter-regulatory hormonal response to induced hypoglycemia compared to baseline. Similarly, circulating GABA levels remained unchanged (*Figure 7*).

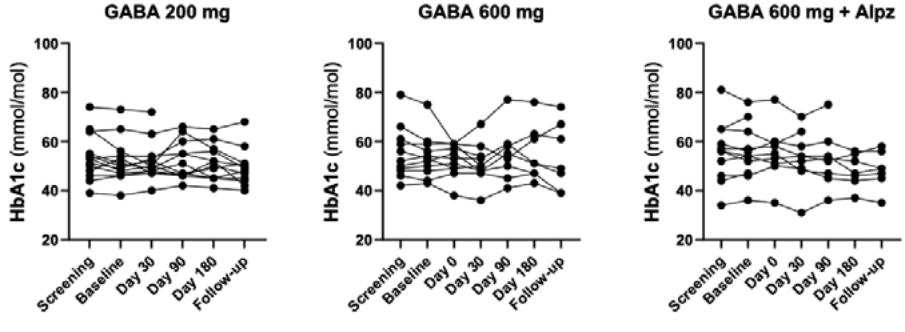

Figure 6. HbA1c Comparison Across Treatment Groups
No significant differences were observed between the screening visit and the 1-month follow-up after study drug termination. The data are shown as individual graphs. All groups maintained a mean HbA1c level below or near the treatment target of 52 mmol/mol (7%) for individuals with T1D.

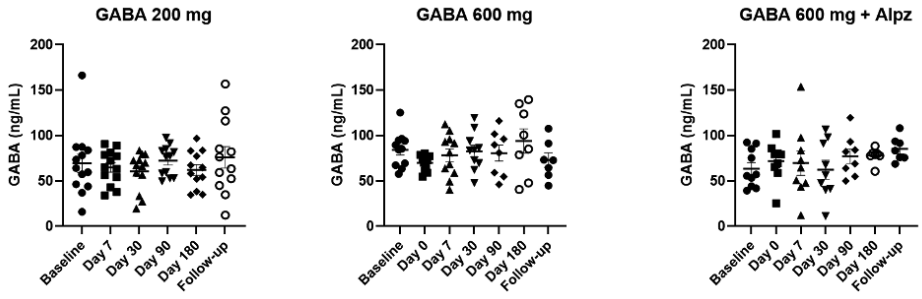

Figure 7. Plasma GABA Levels Across Treatment Groups
Samples were collected at trough levels, measuring the drug concentration just before the next dose. Mixed-effects analysis with Dunnett's multiple comparisons test was used and p-values <0.05 considered statistically significant. No differences were observed from the baseline visit onwards in any treatment arm, indicating that no accumulation of the study drug occurred over time.

Study III

The groups were similar in terms of gender, obesity, the occurrence of coeliac disease and hypothyroidism, treatment modality (MDI vs IPT) and days with CGM readings. Patients in group 1 were younger, had a shorter mean duration of T1D and lower daily insulin doses compared to group 3. Regarding glucose monitoring, group 1 was less frequently equipped with rtCGM than group 2, but more frequent than group 3 ($p < 0.01$, respectively). As for isCGM on the other hand, group 1 was more frequently equipped than group 2, but less frequent than group 3 ($p<0.01$, respectively). Detailed descriptive data is provided in *table 2.*

Table 2. Study participants were grouped based on their estimated HbA1c (eHbA1c) from continuous glucose monitoring data (CGM) from the full time period of available data. All other CGM derived metrics were also calculated for the full time period of available data. Statistical comparisons were performed with a one-way ANOVA (Kruskal-Wallis) using Dunnet's multiple comparison post-hoc test for comparison with group 1. Non-numeric parameters were compared using a Chi-square test. All applicable values are given as mean ± SEM. P-values <0.05 were considered statistically significant. * Indicates p<0.05, ** p<0.01, *** p<0.001 and **** p<0.0001 when compared with group 1

Parameter	Group 1 eHbA1c ≤48 mmol/mol	Group 2 eHbA1c 49-64 mmol/mol	Group 3 eHbA1c ≥65 mmol/mol
Total number, n	58	113	43
Female, n (%)	27 (45.0%)	55 (48.7%)	20 (48.8%)
Age (y)	12.6 ± 0.5	12.7 ± 0.4	15.0 ± 0.5**
Duration (y)	4.2 ± 0.5	5.4 ± 0.3	6.2 ± 0.5**
Insulin/kg/24h (IU)	0.66 ± 0.02	0.73 ± 0.02	0.84 ± 0.05****
BMI (kg/m2)	20.5 ± 0.4	20.8 ± 0.4	22.7 ± 0.8*
Overweight and Obese (isoBMI), n (%)	15 (25.9%)	37 (32.7%)	16 (37.2%)
Coeliac disease, n (%)	7 (12.1%)	11 (9.7%)	4 (9.3%)
Hypothyreosis, n (%)	3 (5.2%)	4 (3.5%)	5 (11.6%)
Insulin Pump Therapy n (%)	40 (69.0%)	79 (69.9%)	25 (58.1%)
Multiple daily injections, n (%)	18 (31.0%)	34 (30.1%)	18 (41.9%)
rtCGM, n (%)	30 (51.7%)	73 (64.6%)**	14 (32.6%)**
isCGM, n (%)	28 (48.3%)	40 (35.4%)**	29 (67.4%)**
Days with CGM readings	165.3 ± 5.9	171.6 ± 4.0	161.7 ± 6.3
eHbA1c (mmol/mol)	43.2 ± 0.5	55.5 ± 0.4****	73.0 ± 1.3****
Mean glucose (mmol/l)	7.2 ± 0.1	9.0 ± 0.1****	11.5 ± 0.2****
Time in range (%)	75.3 ± 1.4	59.8 ± 0.7****	39.2 ± 1.1****
Time in tight range (%)	56.0 ± 1.3	38.5 ± 0.6****	23.4 ± 0.8****
Time below range (%)	9.0 ± 0.8	5.7 ± 0.4***	5.2 ± 0.6**
Time above range (%)	15.7 ± 0.8	34.5 ± 0.6****	55.6 ± 1.2****
Coefficient of variation (CV%)	39.5 ± 1.0	42.4 ± 0.5*	45.3 ± 0.9****
Standard deviation (mmol/L)	2.9 ± 0.1	3.8 ± 0.1****	5.2 ± 0.1****

In Study III, our primary observation was the notable occurrence of hypoglycemic events among children and adolescents in a contemporary treatment setting, with an average frequency of 1.5 ± 0.1 events per 24 hours. Of these, 1.2 ± 0.1 events were categorized as clinical hypoglycemia alert (<3.9 mmol/L), while 0.3 ± 0.02 events were classified as serious (<3.0 mmol/mol). Group 1 exhibited a higher prevalence of both total and mild hypoglycemic events in comparison to Groups 2 and 3. However, the frequency of serious hypoglycemic events was similar in all groups, as illustrated in *figure 8*.

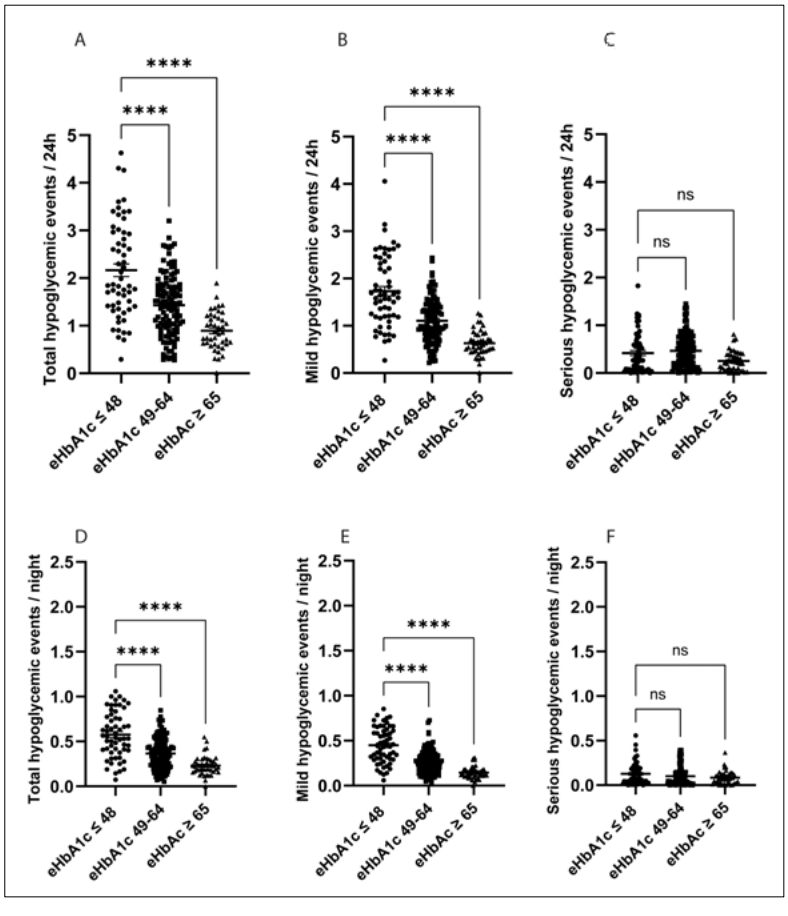

Figure 8. Frequency of hypoglycemic events in children and adolescents with type 1 diabetes. Patients with type 1 diabetes who reach the current treatment target of an HbA1c ≤ 48 mmol/mol estimated based on long-term readings of CGM-data (eHbA1c) have a higher frequency of both total- and mild (3.0 – 3.9 mmol/L) hypoglycemic events **(A, B)** but not serious (<3.0 mmol/L) hypoglycemic events **(C)**. The same pattern was observed when comparing only hypoglycemic events occurring at night (22 PM – 6 AM) **(D,E,F).**
Values are presented as individual values and mean ± SEM is indicated in the figure. **** indicates p<0.0001.

Consistent with the findings on the frequency of hypoglycemic events at the group level, we identified a negative correlation between eHbA1c and both total daily and mild hypoglycemic events ($r=-0.57$ and $r=-0.66$, respectively; $p<0.0001$), while the correlation with serious hypoglycemic events was borderline significant ($r=-0.13$, $p=0.05$).

When examining the correlation between hypoglycemic events and clinical parameters, age was negatively associated with both the total number of hypoglycemic events and mild hypoglycemic events ($r=-0.33$ and $r=-0.44$, respectively; $p<0.0001$), whereas no significant correlation was observed for serious events ($r=-0.05$, $p=0.45$). Disease duration showed a negative correlation with mild hypoglycemic events ($r=-0.15$, $p=0.029$) but a positive correlation with serious events ($r=0.23$, $p< 0.001$).

Regarding treatment modality, no differences were detected in CGM-metrics or hypoglycemic event frequency, between individuals on MDI (n=70) and those using IPT (n=144). However, participants treated with MDI experienced a longer average duration of hypoglycemia, including during nighttime (61.9 ± 3.0 vs. 53.2 ± 2.2 min, $p<0.01$; and 96.4 ± 6.4 vs. 82.0 ± 4.4 min, $p=0.021$, respectively). Notably, only 12 participants in this cohort used IPT with PLGM, and excluding these individuals did not alter the observed difference. The shorter duration of hypoglycemia in the IPT group remained significant (62.5 ± 3.0 vs. 54.5 ± 2.4 min, $p=0.043$), suggesting that PLGM did not account for this effect.

Study IV

Correlations between the score and commonly used AGP metrics were analyzed using n=5,182 14-day series from 613 individuals with T1D. All dimension scores showed significant correlations with the respective AGP metrics ($p<0.0001$). As expected, the hypoglycemia and hyperglycemia scores were strongly correlated with their corresponding AGP metrics (TBR, $r=-0.98$ and TAR, $r=-0.98$, respectively). The hyperglycemia score also showed strong correlations with the Glucose Management Indicator (GMI) ($r=-0.98$) and average glucose ($r=-0.98$). The variability score correlated with CV% ($r=-0.53$); however, the correlation was lower due to inherent differences between GVP and CV%.

The model was also evaluated in five tests comparing its interpretation of real-life CGM curves to the CEB's majority vote (*Table 3)*. It demonstrated strong accuracy in identifying hypoglycemia, hyperglycemia, and variability. Furthermore, it was highly effective in detecting the most concerning CGM curves for each dimension of glucose control, achieving an overall accuracy of 86.5%.

Table 3. Accuracy of the scoring algorithm when compared with the majority vote of the clinical expert board

Parameter	Scoring accuracy (%)
Test 1	
Hypoglycemia	87.5
Hyperglycemia	96.9
Variability	75.0
Overall	86.5
Test 2	
Hypoglycemia	88.5
Hyperglycemia	80.8
Variability	69.2
Test 3	
Hypoglycemia	74.1
Hyperglycemia	92.6
Variability	66.7
Test 4	
Overall	68.0
Test 5	
Overall	74.0

Applying a cut-off single score of ≥80 resulted in an accuracy of 93.4% when compared to fulfillment of all CGM-based treatment criteria. The specificity was 97.1%, indicating that very few CGM periods were falsely classified as meeting treatment targets when attributed a score of ≥80. However, the sensitivity was 61.4%, showing that the score is a stricter measure of glucose control than commonly used AGP metrics.

Based on these results, a score of ≥80 was assigned to represent a high likelihood of fulfilling all treatment targets, which is visually indicated by the green color in *Figure 9*.

Scores below 80 were divided into four segments of 20 points each: the lowest (0–19) was assigned dark red, the next segment (20–39) was also marked red, representing values still far from treatment targets. The segments of 40–59 and 60–79 were assigned orange and yellow colors, respectively. The distribution of these scores in relation to each relevant AGP metric is shown in *Figure 9*, where it is evident that most patients fall within the yellow and orange segments (scores between 40 and 79).

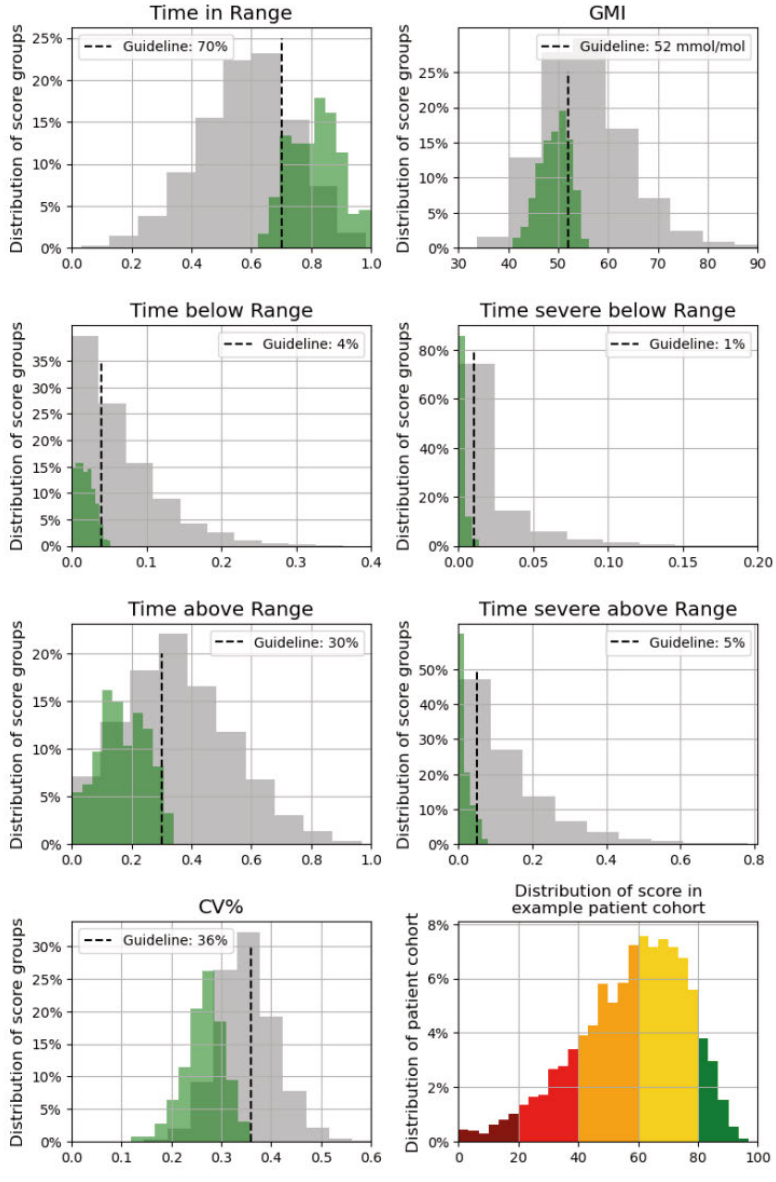

Figure 9. Identification of Cut-Off Values for the Scoring Model
The distribution of AGP (Ambulatory Glucose Profile) metrics and scores is shown. The green segment represents the highest scoring category, where the likelihood of meeting treatment targets is greatest. Dotted lines indicate current target values for each AGP metric. Patients with scores <80 are shown in gray to emphasize their relationship to the green segment. The lower right graph illustrates the overall score distribution across the cohort, divided into five color-coded segments (20-point intervals). Dark red and red indicate the lowest scoring groups, furthest from CGM treatment targets, while most patients fall within the orange and yellow ranges (scores between 40 and 79).

Study V

According to the study design, patients in Group 1 were younger than those in Group 2 (4.2 ± 0.3 vs. 9.9 ± 0.3years, $p<0.0001$). The duration of T1D was shorter in Group 1 (28.4 ± 4.0months) compared to Group 2 (54.0 ± 5.1 months, $p<0.01$), though the number of subjects with a duration of T1D less than 12 months was similar between the groups (Group 1: n=4 vs. Group 2: n=3, p=0.41). The number of days with CGM readings was comparable (175.0 ± 3.5 vs. 171.8 ± 3.5 days, $p = 0.93$) and both groups were similar in terms of gender distribution, HbA1c levels, insulin doses (IU/kg/day), as well as the presence of hypothyroidism and coeliac disease. The distribution of treatment modalities (MDI or IPT) was also similar between the groups. All subjects in Group 1 were using insulin pumps, with 19 out of 26 equipped with HCL systems, while 23 out of 38 patients in Group 2 with insulin pumps had HCL systems (p=0.42). Full descriptive data are provided in *Table 4*.

Table 4. Descriptive data of the two study groups.
Non-numeric parameters were analyzed using Fisher's exact test. Numerical data were assessed using Student's t-test for parameters that passed the D'Agostino & Pearson normality test, while the Mann-Whitney test was applied for non-normally distributed data. Results are presented as means ± SEM, with p-values <0.05 considered statistically significant.
MDI = multiple daily injections; AID = Automated Insulin Delivery; HCL = Hybrid Closed Loop.

Descriptive data	Group 1 <7 years	Group 2 7-12 years	p
n	26	44	
Age (years)	4.2 ± 0.3	9.9 ± 0.3****	<0.0001****
Gender, female n (%)	8 (30.8)	25 (43.2)	0.32
Duration (months)	28.4 ± 4.0	54.0 ± 5.1***	0.0003***
Duration <12 months, n (%)	4 (15.4)	3 (6.8)	0.41
isoBMI Overweight/Obese, n (%)	8 (36.4)	15 (34.1)	>0.99
IU/kg/24h	0.66 ± 0.04	0.77 ± 0.04	0.08
Hypothyroidism, n (%)	0 (0)	1 (2.2)	>0.99
Coeliac disease n (%)	2 (7.7)	5 (11.4)	>0.99
MDI, n (%)	0 (0)	6 (13.6)	0.08
Insulin pump, n (%)	26 (100)	38 (86.4)	0.08
Pump: with AID (HCL)	19 (73.1)	23 (60.5)	0.42
Pump: without AID (HCL)	7 (26.9)	15 (39.5)	
Reported severe hypoglycemia (n)	0 ± 0	0 ± 0	-
Episodes with DKA (n)	0 ± 0	0 ± 0	-
HbA1c (mmol/mol)	51.9 ± 1.3	51.5 ± 0.8	0.75

In Study V, our main finding was the similarity between the groups regarding all investigated CGM-metrics, including TBR (Group 1: 3.7 ± 0.004% vs Group 2: 3.5 ± 0.004%, p=0.54), and the occurrence of frequent but comparable daily hypoglycemic events (Group 1: 1.15 ± 0.1 vs Group 2: 0.97 ± 0.08, p=0.26, *Figure 10*). Additionally, the average duration of all hypoglycemic events was similar between the groups (25.6 ± 1.0 vs. 30.2 ± 1.7 minutes, p=0.07), as was the duration of nightly hypoglycemic events (31.7 ± 1.8 vs. 36.9 ± 2.7 minutes, p=0.46). The duration of serious hypoglycemic events was also comparable (37.0 ± 1.8 vs. 53.9 ± 7.5 minutes, p=0.07, *Table 5*).

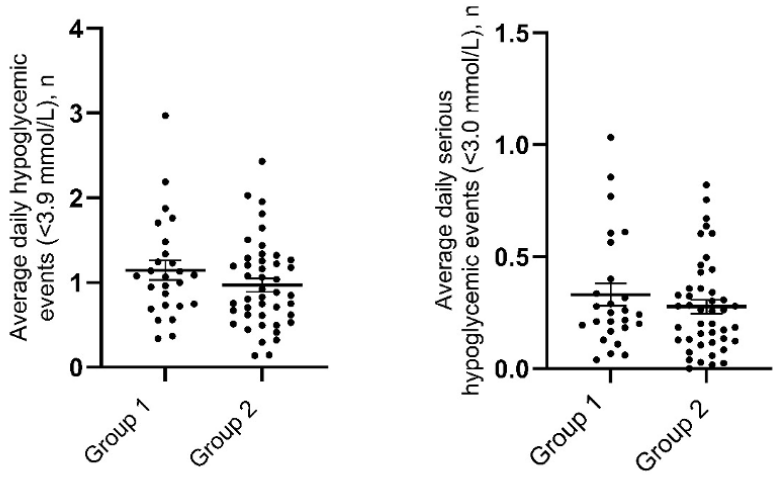

Figure 10. Comparison of daily average- and daily serious hypoglycemic events in preschool and school-aged children. Both preschool-aged children (<7 years, Group 1) and school-aged children (7-12 years, Group 2) exhibited comparable frequencies of daily average hypoglycemic events (<3.9 mmol/L) and serious hypoglycemic events (<3.0 mmol/L). Hypoglycemic events were prevalent across both groups, occurring consistently on a daily basis regardless of age. The data are presented as individual values, with the mean ± SEM shown in the figure. Statistically significant differences were defined by p-values <0.05.

Table 5. Comparisons of continuous glucose monitoring (CGM) metrics and hypoglycemic events were conducted using statistical tests based on data distribution. Student's t-test was applied to parameters that met the normality assumption according to the D'Agostino & Pearson test, while the Mann-Whitney test was used for non-normally distributed variables. Results are expressed as means ± SEM, with p-values < 0.05 considered statistically significant.
Nigthly average refers to episodes occurring between 22 PM and 6 AM.

Parameter	Group 1 <7 years	Group 2 7-12 years	p
CGM-Metrics			
Days with CGM readings	175.0 ± 3.5	171.8 ± 3.5	0.93
Mean glucose (mmol/l)	8.8 ± 0.3	8.7 ± 0.2	0.57
Time below range (%)	3.7 ± 0.004	3.5 ± 0.004	0.54
Time in range (%)	69.5 ± 2.1	70.8 ± 1.5	0.58
Time in tight range (%)	47.7 ± 2.1	48.1 ± 1.5	0.93
Time above range (%)	26.1 ± 0.02	26.2 ± 0.01	0.85
Time above tight range (%)	48. 1± 0.02	49.0 ± 0.01	0.43
Hypoglycemic events			
Average of total hypoglycemic events / 24h	1.15 ± 0.1	0.97 ± 0.08	0.26
Average of serious hypoglycemic events / 24h	0.33 ± 0.1	0.27 ± 0.03	0.50
Nightly average of hypoglycemic events	0.35 ± 0.04	0.3 ± 0.03	0.35
Average duration of hypoglycemic events (minutes)	25.6 ± 1.0	30.2 ± 1.7	0.07
Average nightly hypoglycemia duration (minutes)	31.7 ± 1.8	36.9 ± 2.7	0.46
Average duration of serious hypoglycemic events (minutes)	37.0 ± 1.8	53.9 ± 7.5	0.07
Hypoglycemic events > 60 minutes (%)	16.7 ± 4.0	19.2 ± 3.4	0.51
Serious hypoglycemic events >60 minutes (%)	12.3 ± 3.1	12.5 ± 2.2	0.65

Correlation analysis showed that both age and duration of T1D were positively correlated with the duration of total hypoglycemic events ($r=0.36$, $p<0.01$ and $r=0.35$, $p<0.01$, respectively) as well as the duration of serious hypoglycemic events ($r=0.35$, $p<0.01$ and $r=0.25$, $p<0.05$, respectively). These factors aside, no other parameters related to hypoglycemia were found to correlate with age. However, the duration of T1D was positively correlated with several additional hypoglycemia-related factors, including TBR ($r=0.28$, $p<0.05$) and frequency of serious hypoglycemic events (<3.0 mmol/L, $r=0.29$, $p<0.05$).

Discussion

GABA in T1D (Study I and II)

The potential role of GABA in T1D has been investigated from various perspectives including beta-cell mass and immunology, and our understanding of its mechanisms of action continues to evolve. While research findings have been complex and sometimes contradictory, GABA has remained an intriguing candidate for future therapeutic use in T1D. Through Study I and II, our contribution to the field aimed to deepen the understanding of GABA's physiological mechanisms in T1D, ultimately assessing its potential effects as a therapeutic agent in a clinical trial.

Endogenous production of GABA (Study I)

One key aspect of GABA's relevance to T1D lies in its production from glutamate by the enzyme GAD65, a well-known major autoantigen in T1D (127). This connection provided important context for our findings in Study I. Given that GAD autoantibodies are detected early in most T1D cases, a potential consequence is that pancreatic islets could be depleted of GABA due to inhibitory effects of GAD by autoantibodies. Our observation of a negative correlation between the presence of GAD autoantibodies and plasma GABA levels supports this hypothesis.

Interestingly, our findings however suggest that systemic circulating GABA levels remain unaffected by beta-cell loss in both new-onset and long-standing T1D. Moreover, a previous study reported higher GABA levels in individuals with T1D compared to healthy controls, challenging the hypothesis that GABA depletion contributes to beta-cell loss (128). However, the specific status of local pancreatic GABA levels remains unclear. While previous research has shown reduced GABA levels in donor islets from individuals with T1D, in vivo data on pancreatic GABA concentrations are still lacking (106).

Since GABA regulates beta- and alpha-cell function through autocrine and paracrine mechanisms in experimental studies, determining its local pancreatic levels in vivo would be of great interest (129, 130). Currently, no non-invasive method exists to directly assess this. In theory, magnetic resonance spectroscopy (MRS), a technique used to detect GABA in the central nervous

system (CNS), could be applied to the pancreas (131). However, technical limitations, such as motion artifacts from breathing and insufficient resolution, currently prevent its effective use in this context.

GABA and the immune system (Study I)

As type 1 diabetes (T1D) is an autoimmune disease in which the immune system attacks and destroys insulin-producing beta-cells, many therapeutic strategies focus on suppressing this immune response to slow or prevent further beta-cell loss (5). One such therapy is the anti-CD3 monoclonal antibody (teplizumab) (132). However, systemic immune suppression carries risks, including increased susceptibility to infections, making more targeted approaches desirable.

The immunomodulatory effects of GABA are not yet fully understood, but appear to be primarily suppressive. For instance, GABA has been found to inhibit pro-inflammatory cytokines released from Th1 and Th2 cells in peripheral blood mononuclear cells (PBMCs), and the effect was more pronounced in PBMCs from individuals with T1D (128). Since T1D progression is driven by Th1 cytokine responses and CD8+ effector T cells infiltration of the islets, targeting antigen-specific autoreactive T cells could be a promising strategy to preserve remaining beta-cell function and slow disease progression. GAD65 is a potential antigen target for such therapies, as GAD65-specific autoreactive T cells contribute to beta-cell destruction. A recent study investigated treatment with GABA alone and in combination with GAD65-alum over 12 months on children with new-onset T1D, and found inhibited Th1 cytokine responses (133).

In Study I, a negative correlation was found between GABA levels and several pro-inflammatory cytokines (IL-1β, IL-12 and IL-15). Additionally, all individuals with T1D exhibited a positive correlation between GABA levels and cytokines IL-36 beta and IL-37. This finding is however somewhat contradictory, as IL-36 beta promotes inflammation via NF-Kappa B activation, whereas IL-37 suppresses inflammation by inactivating NF-Kappa B. One possible explanation for these mixed results is that glucose levels, which fluctuate frequently in T1D, may influence GABA's effects. A recent study suggested that high glucose levels impair the GABA-mediated inhibition of CD4+ T cells whereas insulin enhance it (134).

Overall, the findings in Study I align with the notion that cytokine fluctuations in T1D are influenced by GABA, suggesting a predominantly suppressive effect. However, the exact mechanisms at play in vivo under disease conditions require further investigation.

GABA as a potential therapeutic agent (Study II)

Safety

In all pharmacologic interventions, a minimum threshold concentration must be reached for the treatment to be effective. However, in a clinical setting, this efficacy must be carefully balanced against possible side-effects.

Human studies indicate that GABA is well tolerated, even at high doses. A single dose of 10 grams caused only mild, transient fatigue and weakness, while daily intake of 18 grams for four days showed no impact on vital signs, with only occasional reports of mild fatigue and weakness (115, 135). Long-term exposure to GABA has also demonstrated a favorable safety profile. In a large multicenter, double-blind study adults received 3 grams of GABA daily for eight weeks (136). Mild elevations in liver enzymes (transaminitis) were observed in only 2% of participants, all of which resolved after discontinuation of the drug. Furthermore, in the recent trial of GABA and GAD65-alum in children with T1D, GABA was given in doses equivalent to 1.75-2.25g/day, about 1 g per dosing twice daily, for a duration of 12 months without any serious related adverse events (117).

To achieve efficacy on beta-cell response yet have a beneficial risk-benefit profile, results from Diamyd Medical AB´s proprietary studies in animals in combination with data from the published literature were converted to human equivalents. Since dose conversions from animals to humans is a task known to be difficult, findings from our previous Phase 1 dose-escalation study were also considered (120, 137). In that study, 600 mg of GABA resulted in a counter-regulatory hormonal response to hypoglycemia while still not resulting in any severe side effects. The higher dose of 1200 mg displayed no additional beneficial effects. Therefore, in study II, daily doses of 200 and 600 mg were considered reasonable.

For alprazolam, in vivo studies together with GABA suggest human-equivalent doses of 1.5–4.5 mg/day in a 70 kg human, with peak effect on beta-cell proliferation at 1.5 mg or potentially lower. Consequently, a daily dose of 0.5 mg was considered justified.

Albeit, safety concerns arose, mainly in terms of elevated liver transaminases. This is in line with a previous long-term treatment with GABA, although, apart from two individuals the increase was modest and spontaneously resolved (136). It is therefore possible that the temporarily increase was caused by other circumstances such as physical exercise or alcohol consumption. Albeit, it cannot be excluded that it was due to the study drug.

Although it was a slow-release compound, no signs of drug accumulation was seen over time, as nadir plasma GABA levels were unaltered from baseline.

Effect

GABA´s regenerative effect on beta-cell mass has been ascribed as a result from two different mechanisms; *i)* stimulating beta-cell neogenesis, *ii)* promoting beta-cell proliferation.

In study II, we examined the effects of GABA in individuals with long-standing T1D to specifically assess whether GABA could increase beta-cell mass through either neogenesis or proliferation. However, no evidence of such effects was observed. Both fasting and stimulated C-peptide levels remained unchanged, and there were no improvements in glycemic markers such as HbA1c or CGM-metrics.

Also, when analyzing a sub-cohort of C-peptide positive patients (analyzed with ultrasensitive C-peptide assay), C-peptide levels remained stable, suggesting that neither proliferation of existing beta-cell mass had occurred. The fact that only one individual, in the low-dose treatment arm of 200mg daily, exhibited an increased AUC from baseline rendered further subgroup analyses obsolete.

While the lack of efficacy may be valid, it remains uncertain whether a higher dose of either GABA itself or alprazolam could have influenced C-peptide levels or enhanced the counter-regulatory hormonal response to hypoglycemia. In mouse studies demonstrating GABA's effects on beta-cell mass, varying doses and administration routes were used, with some studies employing human-equivalent doses of up to 8.5 g/day. However, despite the absence of the desired outcome, the presence of side effects suggests that GABA concentrations were sufficient to impact participants' physiology, raising concerns about the feasibility of further dose escalation. Moreover, experimental studies have shown that using alprazolam as a PAM to GABA reduced the required GABA dose for robust beta-cell proliferation by tenfold. This suggests that the combined approach of GABA and alprazolam in treatment arm 3 could achieve effects comparable also to the higher doses used in rodent studies (138).

The future of GABA in T1D

The fact that GABA in experimental studies of T1D has shown both immunomodulatory and beta-cell responsive capacities is of high interest. However, rodent models of diseases are not the same as clinical studies in humans, contributing to the discrepancy between preclinical and clinical outcome (139).

With an absent effect on beta-cell regeneration in clinical trial despite the utilization of a PAM, and failure to preserve beta-cell function in new-onset T1D in the pediatric trial by Martin et al, current clinical data clearly argues against GABA as a potential beta-cell regenerative treatment in T1D. Effects can however not be completely ruled out, and a possible approach for future

studies could include combining GABA with other immunomodulatory or antidiabetic agents that act through different mechanisms, such as GLP-1 agonists or DPP-4 inhibitors (140-142).

Hypoglycemic events and CGM in T1D (Study III, IV and V)

General aspects of CGM in T1D

CGM has revolutionized our understanding of metabolic control in T1D, enhancing glucose management for both patients and caregivers. Used alone, and even more effectively in combination with IPT, CGM has been shown to improve metabolic outcome (68).

As the technology constantly advances, guidelines for glucose targets and CGM-metrics are regularly updated. However, hypoglycemia remains a challenge, and its reporting is still limited to time below range (TBR). Additionally, the interpretation of CGM-curves remains a manual process, introducing interrater variability.

Despite the significant benefits of CGM, there is still considerable potential for further improvements. Our contributions to the field through Studies III, IV, and V focus on analyzing hypoglycemic event frequency in relation to metabolic control and age, as well as developing a tool for comprehensive metabolic evaluation in clinical practice.

Hypoglycemic events and CGM

Previous studies have demonstrated a decline in the rate of severe hypoglycemia among children and adolescents in developed countries over the last decades (143, 144). This is in line with results from Studies III and V, where only one severe hypoglycemic event was registered in total. Furthermore, contemporary treatment approaches have dissociated a low HbA1c from acting as an elevating risk factor of severe hypoglycemia (87, 88, 144). Our findings in Study III support this, and moreover indicate that a low HbA1c neither is a predictor of serious hypoglycemic events.

According to ISPAD guidelines, serious hypoglycemic events are clinically significant since neurogenic symptoms and cognitive dysfunction can occur at these glucose levels (82). To avoid these events, individuals with T1D may intentionally maintain higher blood glucose, a pattern reflected in studies showing increased HbA1c following severe hypoglycemic events (145). In this context, our findings could hold clinical significance in suggesting that elevated HbA1c on group level does not prevent serious hypoglycemic events. Moreover, the mere awareness of the significant difference in the dataset of

54,390 identified hypoglycemic events, with only one self-reported as severe, may help alleviate Fear of Hypoglycemia (FOH) in both patients and their caregivers.

In Study III, the increased frequency of mild hypoglycemic events (<3.9 mmol/L) in the group that achieved the target HbA1c of ≤48 mmol/mol warrants discussion. A reasonable explanation is that these events result from more intensive insulin therapy combined with a high adherence to hypoglycemia treatment before glucose levels drop below 3.0 mmol/L. However, correlation analysis showed that mild hypoglycemic events were positively associated with time in range (TIR), while negative correlations were observed with time above range (TAR) and glucose variability, as measured by standard deviation (SD). Based on these findings, an increased frequency of mild hypoglycemia could be considered a marker of good metabolic control.

In clinical practice, patients are advised to be cautious and attentive when CGM values are between 3.5 and 3.8 mmol/L. However, if glucose levels remain stable and no additional risk factors for further decline are present, such as ongoing or planned physical activity or active insulin on board following a meal bolus, no specific treatment for hypoglycemia is required given that the patient is symptom-free.

Due to the retrospective design of Study III, data on symptoms and hypoglycemia treatment are unavailable, making such interpretations speculative. Although, regardless of whether symptoms or treatment occur, mild hypoglycemic events in the 3.5–3.8 mmol/L range remain a concern. Being "attentive" to these situations diverts focus from other daily activities, impacting both patients and/or caregivers. This concern is particularly relevant for caregivers of very young children, who cannot be expected to recognize or communicate hypoglycemic symptoms, why they must be even more cautious in such situations (82).

Notably, despite all subjects being equipped with some form of CGM system per study design, none of the three groups met the recommended time below range (TBR) of <4%. Since the study was conducted during the early market introduction of AID systems, only 12 individuals used PLGS technology. When comparing IPT vs MDI, those with IPT had shorter durations of hypoglycemia. This remained true even after excluding subjects with PLGS from the IPT group, suggesting that PLGS had little or no impact on this outcome. Furthermore, the frequency of hypoglycemic events did not differ between groups.

Our conclusion is that AID systems with PLGS did not significantly affect hypoglycemic outcomes in Study III. However, given the small number of subjects using PLGS, these results should be interpreted with caution.

A comparison with Study V provides further insight. Although there were differences in study design, both studies shared similar treatment settings and data was collected from the same hospital setting but with 2-6 years apart. Albeit, a clear difference was noted for the percentage of TBR, with both groups in Study V meeting the recommended criteria of a TBR <4%. Age alone is unlikely to explain this, as younger age is generally considered a risk factor for hypoglycemia. Additionally, in Study III, a negative correlation was observed between age and total/mild hypoglycemic events ($r = -0.33$ and $r = -0.44$, respectively, $p < 0.0001$). However, in the years between the studies, HCL systems became widely available, and Study V had a high representation of these systems. This aligns with previous findings showing that HCL systems reduce TBR compared to other treatment modalities (146).

Despite this, hypoglycemic events still occurred daily in both age groups in Study V (Group 1: 1.15 ± 0.1 vs Group 2: 0.97 ± 0.08, $p=0.26$). This indicates that even with modern treatment approaches including utilization of HCL systems, hypoglycemia remains a significant challenge in preschool- and school-aged children. Additionally, hypoglycemic events may be even more frequent than reported, as the down-sampling of data from 5- to 15-minute intervals in Study III and V could have led to an underestimation of event frequency, as previously observed (147).

In current CGM based hypoglycemia reporting, both groups in Study V met the TBR <4% recommendation, yet still experienced daily hypoglycemic events and serious events every third day. In clinical practice, this creates a challenge in interpretation—does the patient meet hypoglycemia criteria by staying within the TBR threshold, or fail by having frequent mild hypoglycemic events, which contradict national recommendations?

This highlights the complexity of hypoglycemia assessment, suggesting that incorporating event frequency alongside TBR could provide a more comprehensive understanding of its true impact on daily life with T1D. Moreover, it illustrates the challenge of relying on one-dimensional AGP-metrics, where patients may meet one criterion while failing another. This underscores the potential value of a composite scoring model to improve the interpretation of overall glucose control.

Scoring models for CGM in T1D (Study IV)

Developing a composite score for CGM data has been a challenge, as existing metrics either focus on overall glucose control or specific parameters such as hypo- or hyperglycemia. Many models correlate well with TIR or glucose management indicator (GMI) but fail to adequately capture hypoglycemia risk. Conversely, metrics designed to assess hypoglycemia often do not differentiate between varying levels of hyperglycemia risk (64, 148).

Our scoring algorithm was developed using an extensive dataset, including both adult and pediatric patients, with data extending well beyond 14 days per patient. It integrates LBGI and HBGI to assess hypoglycemia and hyperglycemia risk while also incorporating glucose variability percentage (GVP) to better capture glucose fluctuations. Unlike coefficient of variation (CV%), which only accounts for amplitude, GVP considers both amplitude and frequency of glucose excursions, allowing for a more precise assessment of glucose control challenges (149).

A key feature of our model is its ability to, in a single score, present the dimension of glycemia that most adequately represents the most alarming feature. This was made possible by normalizing data and weighing hypoglycemia risk appropriately against risks for hyperglycemia and variability. Since the single score reflects the most concerning dimension of glucose control, it per definition means that the scores of the other two dimensions are higher (i.e., less alarming).

Applying a single score cut-off ≥80 resulted in an accuracy of 93.4% when compared to the fulfillment of all CGM metrics. In other words, a patient with a single score of ≥80, will meet all guidelines for CGM-metrics with an accuracy of 93.4%. Furthermore, the specificity was 97.1%, indicating that very few CGM periods were incorrectly classified as meeting treatment targets when assigned a score of ≥80.

Our results showed strong correlations between hypoglycemia and hyperglycemia dimensions with corresponding AGP metrics, while the variability score was less correlated with CV%. This was however to be expected due to the fundamental differences in how these measures capture glucose fluctuations.

Additionally, the scoring model was validated through expert assessments, showing high accuracy in identifying alarming glucose patterns, particularly for hyperglycemia (97%) and to a lesser extent for variability (75%). This may reflect that clinicians are trained to consider variability primarily in terms of amplitude rather than integrating frequency, as when comparing CV% to GVP. Interestingly, when clinical experts assessed CGM curves without access to AGP metrics, inter-rater agreement decreased slightly (88% vs. 93%), suggesting that clinicians rely to a large extent on AGP metrics when making assessments.

Cohort management through CGM in T1D

Implementing this scoring algorithm in clinical practice could enable population management of large patient cohorts in near real-time based on CGM data. By adopting a CGM-centric workflow, clinics could prioritize follow-ups based on real-time glucose control rather than static scheduling intervals.

This approach could help identify the patients most in need of medical attention and facilitate targeted interventions for specific glycemic challenges. For example, structured checklists could be put into practice in order to ensure that all patients with frequent hypoglycemia are offered all relevant and possible clinical interventions. Ultimately, this model has the potential to improve personalized diabetes care by providing actionable insights based on individual glucose patterns. By integrating this approach, healthcare resources could be allocated more effectively, ensuring that patients receive the appropriate level of care based on their specific needs.

General conclusion

In conclusion, hypoglycemia is a frequent phenomenon in children and adolescents with T1D. Irrespective of age, this holds true in both patients who reach- and those who are far from the current treatment targets for HbA1c. Obviously this is a side effect of the insulin therapy, but it is most likely severely aggravated by the alpha-cell dysfunction and blunted hormonal counter-regulatory response observed in many patients with T1D (119). The use of IPT with HCL can partly resolve the problem by optimizing the dosing of insulin, and a more efficient utilization of CGM data on both an individual and population level may contribute to an improved care and reduction of hypoglycemic events. However, there is still a need for novel therapies that ideally would restore the beta-cell mass, i.e., provide a cure for T1D. Alternatively, as a second-best target, to at least restore the counter-regulatory hormonal response in order to minimize the risk of hypoglycemia, thereby greatly improving the chance of achieving optimal glucose control with insulin therapy. In the meantime, models for an effective interpretation of CGM data can contribute in the quest for improved metabolic outcomes

General discussion on strengths and limitations

The main limitation in **Study I** was the inability to distinguish the source of the circulating GABA levels, making assessments of local GABA levels in specific tissues, such as pancreatic islets, speculative. Strengths include novelty of findings and inclusion of both longstanding and new-onset T1D, allowing for a better comparison between individuals with depleted and preserved C-peptide.

In **Study II**, key strengths include the three-arm study design with different doses of study drug and the inclusion of a PAM. However, the absence of a placebo group and blinding made it challenging to evaluate especially the mild adverse events. However, for the analysis of C-peptide levels which served as

a surrogate marker for the functional beta-cell mass, each subject served as their own control, with results compared to baseline.

It cannot be excluded that a different pharmacokinetic profile, altered treatment duration or a higher dose of GABA might have induced a beta-cell regenerative effect. However, in the study of Martin *et al.* GABA was administered twice daily without further impact on C-peptide levels. Considering the safety profile in **Study II**, increasing Remygen® doses would be difficult to implement in clinical practice.

In Studies **III-V**, general strengths are the CGM data from extended time periods together with clinical descriptive data. Evaluating every single hypoglycemic event provides further insight to hypoglycemia in T1D compared to merely TBR.

Limitations are down-sampling of data to 15-minute intervals to harmonize different CGM-models. This could overestimate shorter hypoglycemic events, but on the other hand also underestimate hypoglycemic events, as previously described (147). In addition to the inherent accuracy of the different CGM devices, false hypoglycemic events could have been registered due to "compression low", especially concerning events registered during night-time.

The retrospective nature of the studies offers limitations as to lack of symptoms or confounding factors to hypoglycemia such as physical activity. Furthermore, surveys on QoL and Fear of Hypoglycemia would have been of interest in the assessment of impact on the daily life.

Also, the data was collected from a single center, a University Hospital in Sweden, why the presented data may not be completely generalizable.

Conclusions

Study I

- Endogenous systemic circulating levels of GABA are unaltered in persons with new-onset or long-standing T1D when compared to healthy controls.
- Endogenous systemic circulating levels of GABA are negatively correlated to levels of GAD-autoantibodies.
- Endogenous systemic circulating levels of GABA are negatively correlated to several pro-inflammatory cytokines.

Study II

- Side effects were frequently observed during GABA treatment, including elevated AST levels in nine subjects.
- No clinical evidence of a beta-cell regenerative effect of GABA was observed.

Study III

- Hypoglycemic events are common in children and adolescents with T1D, irrespective of their overall metabolic control.
- The treatment goals related to HbA1c can be met without an increased frequency of either serious or severe hypoglycemic events, although, achieving these targets may come with an elevated occurrence of mild hypoglycemic events.
- The hypoglycemic target set by ISPAD clinical practice consensus guidelines of 2022 (82) of a TBR <4% was not met in any of our examined groups.

Study IV

- The scoring model effectively captures the complexity of CGM data, identifying both the most concerning aspects of glycemia and individuals in most need of medical attention.
- As a health-care tool, it has the potential to support population management, helping to prioritize care for individuals in most need of clinical attention.

Study V

- Hypoglycemic events are frequently observed in preschool- and school-aged children, typically occurring on a daily basis despite meeting CGM-targets of <4%.
- Preschool-aged children did not experience a higher frequency of hypoglycemic events compared to school-aged children.

Future perspectives

In the current cohort of Study III and V, C-peptide data was unavailable. However, it would be of great interest to study how the frequency of hypoglycemic events, especially serious events, and the corresponding counter-regulatory response evolve in relation to the progressive loss of endogenous insulin production in T1D.

To investigate this in detail, I have initiated a clinical study including individuals with both new-onset and long-standing T1D, as well as healthy controls. These participants will undergo hypoglycemic clamps in order to investigate how the decline in endogenous insulin production affects the counter-regulatory hormonal response. A key objective is to determine whether specific C-peptide thresholds can be identified as critical points where physiological counter-regulatory alterations emerge.

To address the impact of hypoglycemia frequency on daily life, it would be highly valuable to perform a prospective study including both CGM-data, clinical-data, symptomatic reporting of hypoglycemia and questionnaires concerning QoL and Fear of Hypoglycemia.

Sammanfattning på svenska

Typ 1 diabetes är en av de vanligast förekommande kroniska sjukdomarna hos barn och unga i Sverige. Sjukdomen beror på att immunförsvaret felaktigt angriper kroppens egna insulinproducerande betaceller i bukspottkörteln, vilket leder till insulinbrist. Insulin är ett livsnödvändigt hormon och avgörande för att cellerna ska kunna tillgodogöra sig socker från blodet och använda det som energi. Utan insulin stiger blodsockret, vilket ger för typ 1 diabetes klassiska symtom som ökad törst, stora urinmängder, viktnedgång och trötthet.

Ännu finns ingen botande behandling, istället ges insulin som livslång behandling via dagliga injektioner eller insulinpump. Insulinbehovet är individuellt och varierar kraftigt beroende på faktorer som matintag, fysisk aktivitet och stress, vilket gör blodsockerkontroll avgörande. I Sverige har alla barn och unga tillgång till kontinuerliga glukosmätare (CGM) som ger realtidsdata och underlättar behandlingen.

Att hålla blodsockret inom rimliga gränser är trots tekniska framsteg en konstant balansakt, och lågt blodsocker (hypoglykemi) fortfarande den vanligaste akuta komplikationen. Symtomen på hypoglykemi varierar från lindriga besvär till allvarliga neurologiska komplikationer och i värsta fall död.

Studier visar att även små mängder kvarvarande kroppseget insulin kan minska risken för svåra hypoglykemier. Därför vore en återetablering av insulinproduktionen, även i liten skala, en viktig möjlighet för att förbättra blodsockerkontrollen och minska risken för allvarliga blodsockerfall.

Ett ämne som därav väckt intresse är GABA (gamma-aminosmörsyra), som bildas från aminosyran glutamat via enzymet glutaminsyradekarboxylas (GAD). En känd auto-antikropp vid typ 1 diabetes är riktad mot just GAD (anti-GAD). Prekliniska studier har visat att GABA kan stimulera tillväxt av betaceller, öka insulinfrisättning och dämpa immunförsvarets angrepp vid typ 1 diabetes. GABA har därför föreslagits som en möjlig framtida behandling.

Denna avhandling syftar till att öka kunskapen om hypoglykemier hos barn och unga med typ 1 diabetes, mildra dess förekomst genom att optimera användningen av data från kontinuerliga glukosmätare samt utvärdera GABAs potential som läkemedel vid typ 1 diabetes.

Studie I
I denna studie jämförde vi kroppsegna GABA-nivåer hos personer med typ 1 diabetes och friska kontroller. Totalt inkluderades 118 individer. GABA-nivåerna var likartade mellan grupperna, oavsett sjukdomsduration. Däremot fanns ett samband mellan GAD-antikroppar och GABA-nivåer hos de med diabetes, där högre nivåer av GAD-antikroppar var kopplade till lägre GABA-nivå, vilket är intressant med tanke på GADs roll i GABA-produktionen.

Hos personer med typ 1 diabetes observerades även ett samband mellan GABA och flera cytokiner, vilket antyder att GABA kan påverka immunsystemet vid sjukdomen. Detta sågs inte hos de friska kontrollerna.

Studie II
Här undersökte vi säkerhet och effekt på insulinproduktion av långtidsbehandling med Remygen® (GABA) hos vuxna med långvarig typ 1 diabetes. Trettiofem män med diabetes sedan minst fem år delades in i tre grupper som fick olika dagliga doser av läkemedlet (200 mg; 600 mg respektive 600 mg i kombination med 0,5 mg bensodiazepin) under sex månader. Säkerhetsaspekter, insulinproduktion och kroppens hormonella svar på hypoglykemi mättes vid flera tidpunkter. Resultaten visade inga tecken på att GABA återbildar insulinproducerande betaceller eller på annat sätt påverkar blodsockerregleringen. Däremot observerades biverkningar, såsom förhöjda levervärden, hos vissa deltagare.

Studie III
Denna studie undersökte förekomsten av hypoglykemier och deras koppling till metabol kontroll hos barn och unga med typ 1 diabetes, baserat på retrospektiva CGM-data från 214 personer. Deltagarna delades in i tre grupper utifrån sitt eHbA1c (långtidssocker). Resultaten visade att hypoglykemier var vanligt förekommande på daglig basis, oavsett metabol kontroll. Gruppen med lägre eHbA1c (≤48 mmol/mol), hade fler milda hypoglykemier än de andra grupperna, men det fanns ingen skillnad i förekomsten av allvarliga hypoglykemier. Därmed sågs inte ett eHbA1c som uppnår det nationella målet om ≤48 mmol/mol som en riskfaktor för att drabbas av allvarliga hypoglykemier (<3 mmol/L).

Studie IV
I denna studie skapades och utvärderades en modell för förenklad tolkning av CGM-data. Både patienter och vårdgivare har stor nytta av CGM-data i behandlingen av typ 1 diabetes, men tolkningen kan upplevas komplex och tidskrävande. Genom att använda retrospektiva CGM-data från 613 individer med typ 1 diabetes (totalt 82 114 dagars registrering), utvecklades en poängmodell som möjliggör tolkning av CGM-data utifrån ett enda värde på en 100-

gradig skala (100 = optimal glukoskontroll). Modellen visade god överensstämmelse med traditionella CGM-parametrar samt med en klinisk expertgrupps manuella tolkningar.

Förutom individuell användning skulle modellen kunna tillämpas inom vården för att systematiskt identifiera patienter med störst behov av vård utifrån metabol kontroll, och därigenom bidra till att fördela vårdens resurser på ett effektivt sätt.

Studie V

Denna studie byggde vidare på metodiken från studie III och undersökte förekomsten av hypoglykemier hos förskolebarn (<7 år) jämfört med något äldre barn i skolåldern (7-12 år). Retrospektiva CGM-data från totalt 70 barn med typ 1 diabetes analyserades. Hypoglykemier inträffade i genomsnitt en gång per dag i båda grupperna, trots att barnen tillbringade endast cirka 3,6 % av tiden under blodsockermålet (<4 mmol/L), i enlighet med gällande riktlinjer om <4% av tiden.

Trots att båda grupperna höll sig inom de nationella riktlinjerna för lågt blodsocker, framträder hypoglykemi som en daglig utmaning för barnen, oavsett ålder. Att komplettera rapporteringen med frekvensen av hypoglykemier kan ge en mer heltäckande bild av problemets omfattning.

Sammanfattningsvis är hypoglykemier fortsatt vanligt förekommande hos barn och unga med typ 1 diabetes, trots tekniska framsteg. Behovet av en behandling som återställer kroppsegen insulintillverkning är uppenbart. Samtidigt finns utvecklingsmöjligheter inom befintliga terapier, exempelvis med förbättrade modeller för analys av CGM-data.

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