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Physical Activity and Exercise, Novel Therapies and Technologies in Adolescents with Type 1 Diabetes

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Abstract

Regular physical activity provides well-established benefits for individuals with type 1 diabetes (T1D), including improved insulin sensitivity, cardiovascular health, and psychological well-being. However, exercise is also associated with rapid glycaemic fluctuations and an increased risk of dysglycaemia. This risk is particularly pronounced in adolescents, as pubertal physiology and irregular activity patterns complicate glycaemic management. Accordingly, this cumulative dissertation aims to advance the understanding of exercise in adolescents with T1D, with a focus on safety, efficacy, and the role of diabetes technologies in supporting glycaemic control.

The first study, a randomized controlled trial (ChilDFiT1), evaluated a 4-week structured track and field training intervention combined with intensive glycaemic management in adolescents with T1D. Compared with intensive glycaemic management alone, the intervention resulted in significant improvements in key glycaemic outcomes, demonstrating the safety and feasibility of structured exercise in this population.

The second study assessed the performance of real-time continuous glucose monitoring (rtCGM) before, during, and after exercise sessions. While overall accuracy was acceptable, sensor reliability declined during rapid glucose changes, particularly during hypoglycaemia, underscoring the need for cautious, context-aware interpretation of CGM data around physical activity.

The third study synthesized current evidence on automated insulin delivery (AID) systems in the context of exercise. While AID systems effectively improve glycaemic outcomes when physical activity is announced, unannounced exercise remains a significant limitation, highlighting the need for further technological adaptation.

Taken together, these studies provide an integrative perspective on the interplay between exercise physiology, glucose monitoring, and diabetes technology in adolescent T1D. By combining clinical evidence, methodological evaluation, and technological analysis, this dissertation establishes a comprehensive framework to support safe exercise participation among this vulnerable population. The findings demonstrate that structured exercise can safely and effectively improve glycaemic outcomes in adolescents, with direct implications for clinical exercise counselling to support informed, confident, and individualized care. Overall, the work provides a coherent foundation for future research and for integrating exercise therapy and diabetes technology into paediatric T1D management.

Zusammenfassung

Regelmäßige körperliche Aktivität bietet bei Menschen mit Typ-1-Diabetes (T1D) nachweislich vielfältige gesundheitliche Vorteile, darunter eine verbesserte Insulinsensitivität, eine gesteigerte kardiovaskuläre Fitness und positive Effekte auf das psychische Wohlbefinden. Gleichzeitig ist körperliche Aktivität mit raschen glykämischen Schwankungen verbunden, die das Risiko für Dysglykämien erhöhen. Diese Herausforderungen sind bei Jugendlichen besonders ausgeprägt, da pubertätsbedingte physiologische Veränderungen und unregelmäßige Aktivitätsmuster das Glukosemanagement zusätzlich erschweren. Vor diesem Hintergrund zielt die vorliegende kumulative Dissertation darauf ab, das Verständnis körperlicher Aktivität bei Jugendlichen mit T1D zu vertiefen, mit besonderem Fokus auf Sicherheit, Wirksamkeit sowie die Rolle moderner Diabetestechnologien bei der Unterstützung der glykämischen Kontrolle.

Die erste Arbeit, eine randomisiert kontrollierte Studie (ChilDFiT1), untersuchte eine vierwöchige strukturierte Leichtathletik-Intervention in Kombination mit intensiviertem Glukosemanagement bei Jugendlichen mit T1D. Im Vergleich zur alleinigen intensivierten Insulintherapie führte die Intervention zu signifikanten Verbesserungen zentraler glykämischer Zielparameter und belegte die Sicherheit und Umsetzbarkeit strukturierten Trainings in dieser Altersgruppe. Die zweite Studie analysierte die Messgüte eines kontinuierlichen Echtzeit-Glukosemesssystems (rtCGM) vor, während und nach körperlicher Aktivität. Während die Gesamtgenauigkeit akzeptabel war, nahm die Verlässlichkeit bei raschen Glukoseänderungen (insbesondere im hypoglykämischen Bereich) ab, was eine vorsichtige und kontextsensitivere Interpretation von CGM Daten erfordert. Die dritte Arbeit fasste als narratives Review die Evidenz zu automatisierten Insulinabgabesystemen (AID) im Kontext körperlicher Aktivität zusammen. Während AID Systeme die glykämische Kontrolle bei geplanter Aktivität wirksam verbessern können, bleibt spontane Aktivität eine zentrale Limitation und erfordert weitere technologische Anpassungen.

Insgesamt liefern die drei Arbeiten eine integrative Perspektive auf das Zusammenspiel von körperlicher Aktivität, Glukosemonitoring und Diabetestechnologie bei Jugendlichen mit T1D. Die Ergebnisse zeigen, dass strukturiertes und betreutes Training die glykämische Kontrolle sicher und wirksam verbessern kann und direkte Implikationen für die klinische Bewegungsberatung bietet. Zugleich wird deutlich, dass eine sorgfältige klinische Umsetzung sowie fortlaufende technologische Weiterentwicklungen notwendig sind, um eine sichere und nachhaltige körperliche Aktivität im Alltag von Jugendlichen mit T1D zu ermöglichen.

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List of Abbreviations

AID	Automated Insulin Delivery
BCM	Body Cell Mass
BG	Blood Glucose
BMI	Body Mass Index
CGM	Continuous Glucose Monitoring
CI	Confidence Interval
CL	Closed-Loop
CV	Coefficient of Variation
EX	Exercise Group (ChilDFiT1 intervention group: exercise + intensive glycaemic management)
FFM	Fat Free Mass
GMI	Glucose Management Indicator
HbA_{1c}	Glycated Haemoglobin A_{1c}
HCL	Hybrid Closed-Loop
IDF	International Diabetes Federation
IPAQ	International Physical Activity Questionnaire
IQR	Interquartile Range
isCGM	Intermittently Scanned Continuous Glucose Monitoring
IT	Intensive Therapy Group (ChilDFiT1 control group: intensive glycaemic management only)
MARD	Mean Absolute Relative Difference
MedARD	Median Absolute Relative Difference
MET	Metabolic Equivalent of Task
MPC	Model Predictive Control
rtCGM	Real-Time Continuous Glucose Monitoring
SD	Standard Deviation
SD_{Gluc}	Standard Deviation of Glucose
TAR	Time Above Range
TAR1	Time Above Range 1 (181-250 mg/dL; 10.0-13.9 mmol/L)
TAR2	Time Above Range 2 (>250 mg/dL; >13.9 mmol/L)
TBR	Time Below Range
TBR1	Time Below Range 1 (54-69 mg/dL; 3.0-3.9 mmol/L)
TBR2	Time Below Range 2 (<54 mg/dL; <3.0 mmol/L)
TIR	Time in Range (70-180 mg/dL; 3.9-10.0 mmol/L)
T1D	Type 1 Diabetes

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1 Introduction

1.1 Background and Relevance

Type 1 diabetes mellitus (T1D) is a chronic autoimmune disease characterized by the destruction of pancreatic β-cells, resulting in absolute insulin deficiency. This requires lifelong insulin therapy and continuous blood glucose (BG) management to prevent acute complications, such as severe hypoglycaemia and ketoacidosis, as well as long-term micro- and macrovascular complications.[1] Advances in early diagnosis, diabetes technology, and structured education have substantially improved life expectancy and quality of life in individuals with T1D.[2,3] Nevertheless, achieving stable glycaemic control remains a significant challenge, influenced by a complex interplay of physiological, psychosocial, and lifestyle factors. These difficulties are particularly pronounced during adolescence, as puberty-related physiological changes, increasing self-management autonomy, and psychosocial demands further complicate daily T1D management.[4–6]

Regular physical activity is a key component of health promotion in T1D, improving insulin sensitivity, cardiovascular fitness, and psychological well-being, while helping to prevent T1D-related complications.[7,8] At the same time, maintaining glucose stability around exercise and other forms of moderate-to-vigorous physical activity remains one of the most complex challenges in T1D. This challenge arises from the increased risk of hypoglycaemia and pronounced glycaemic variability around these activities.[9,10] These risks often act as barriers to participation, particularly among adolescents, who tend to engage in spontaneous and irregular physical activity patterns rather than planned or structured exercise.[11,12] This highlights the need for effective strategies to support BG management before, during, and after exercise, particularly in the context of unplanned or spontaneous physical activity. Therefore, the physiological mechanisms underlying these benefits and challenges, as well as evidence-based management strategies, are addressed in detail in the following theoretical framework (Chapter 2.3).

In recent years, technological innovations such as continuous glucose monitoring (CGM) and automated insulin delivery (AID) systems have transformed T1D care.[13,14] By providing continuous glucose data and algorithm-driven insulin adjustments, these tools offer promising opportunities to enhance the safety and effectiveness of exercise and other forms of physical activity in T1D. However, their robustness in dynamic, real-world exercise contexts, characterized by rapid glucose fluctuations, variable insulin sensitivity, and irregular activity behaviours,

remains insufficiently established.[15,16] Consequently, essential gaps persist in mitigating exercise-related glycaemic disturbances, underlining the need for optimized approaches to integrate technology with exercise management in T1D. Taken together, these considerations highlight that although physical activity is strongly recommended, its safe and effective integration into adolescent T1D management remains insufficiently understood.

1.2 Research Gap and Rationale

Although the benefits of exercise in T1D are well established, there is limited robust evidence on the effects of structured exercise interventions in adolescents. Furthermore, although CGM devices are widely used in clinical practice, their accuracy around exercise remains insufficiently studied. This limitation is particularly relevant for real-world youth cohorts, where reliability is most critical. Finally, current AID systems, while effective in everyday settings, still rely heavily on user input. As a result, they show limited adaptability to unannounced or spontaneous exercise, as well as to intensified or irregular physical activity, which is especially relevant for adolescents.

While previous research has provided valuable insights into exercise physiology, CGM use, and diabetes technology in T1D, these aspects have largely been examined separately. Moreover, many studies focus on adult populations, observational designs, or controlled laboratory settings. Consequently, evidence that integrates structured exercise interventions, CGM performance, and AID under real-world conditions in adolescents remains scarce.

To close these gaps, there is a pressing need to integrate perspectives from exercise physiology, studies on CGM performance, and AID system optimization into one comprehensive framework. Addressing these issues is crucial to ensure that adolescents with T1D can experience the health benefits of exercise and physical activity without being exposed to disproportionate risks.

1.3 Aim and Contribution of the Dissertation

Therefore, this cumulative dissertation investigates the interplay between structured exercise and broader physical activity, CGM performance, and advanced diabetes technologies in T1D. Its overall aim is to improve understanding of how exercise can be safely and effectively integrated into daily T1D management, and how emerging technologies may support this process.

Accordingly, the central research question of this cumulative dissertation is:

How can physical activity and exercise be safely and effectively integrated into the daily management of adolescents with T1D, and to what extent can CGM and advanced diabetes technologies support glycaemic control under the dynamic conditions of exercise?

Addressing this overarching research question requires an approach that integrates clinical, methodological, and technological perspectives across different levels of evidence. Against this background, the novelty of this dissertation lies in its explicitly integrative design.

- By evaluating a structured track and field training program compared with intensification of insulin therapy alone, the ChilDFiT1 study provides one of the few randomized controlled trials on exercise efficacy and safety in adolescents with T1D. It thereby extends predominantly observational evidence with controlled interventional data in an underrepresented population.
- By analysing real-time CGM accuracy before, during, and after exercise, this work adds critical methodological evidence on sensor reliability under dynamic physiological conditions. It extends beyond resting or laboratory-based assessments by focusing on real-world exercise settings in adolescents.
- By systematically reviewing the performance of AID systems in the context of announced and unannounced exercise, it highlights current limitations. It outlines technological strategies for more adaptive, context-aware systems, addressing a clinically relevant scenario that has been insufficiently examined in controlled clinical trials.

By synthesizing the findings of these three complementary studies, this dissertation provides a comprehensive evaluation of the role of exercise in T1D. On the one hand, it demonstrates the potential of exercise as a key factor in improving glycaemic control and overall health in adolescents with T1D. On the other hand, it highlights novel strategies and technological innovations to optimize glycaemic management around exercise. In contrast to prior work focusing on single components, this dissertation emphasizes the interaction among exercise physiology, glucose monitoring, and diabetes technology. Moreover, it generates integrative insights relevant to clinical practice and future innovation in T1D care.

Following this introduction, Chapter 2 provides the theoretical framework, outlining the epidemiology and pathophysiology of T1D. It further addresses physiological and psychosocial aspects of exercise and physical activity in adolescents and the role of diabetes technologies in physical activity contexts. Chapter 3 specifies the dissertation's objectives and illustrates how the three studies interrelate. Chapters 4-6 present the peer-reviewed research articles included in this dissertation. These comprise (1) a randomized controlled trial on track and field training

in adolescents with T1D (ChilDFiT1), (2) an evaluation of CGM performance around exercise sessions, and (3) a narrative review on the progression of AID systems from announced to unannounced exercise. Chapter 7 synthesizes the findings across studies, discusses their clinical and practical implications, and outlines future research directions.

2 Theoretical Framework

2.1 Epidemiology of Type 1 Diabetes (T1D)

Globally, the incidence and prevalence of T1D continue to rise across all age groups. While T1D is most often diagnosed in childhood and adolescence, it can onset at any age. According to the International Diabetes Federation (IDF), approximately 9.50 million people worldwide were living with T1D in 2025, including about 1.85 million individuals under 20 years of age.[17] In children under 15 years old, global incidence has increased by 3-4% annually over the past 20-30 years, although trends differ by country.[17–19] Scandinavian countries such as Finland and Sweden continue to report some of the highest incidence rates in children, exceeding 50 per 100,000 person-years. Conversely, many countries in Asia and parts of South America report much lower rates, often below 5 per 100,000 person-years.[17–20] In addition, adult-onset T1D is increasingly recognized: recent IDF data indicate that over 60% of new T1D cases globally are diagnosed in individuals aged 20 or older.[17,21]

In Germany, data from the "Diabetes-Patienten-Verlaufsdokumentation" (DPV) registry and Robert Koch Institute (RKI) confirm a continued increase in incidence among children and adolescents. The annual incidence of T1D in individuals under 15 years has risen from 17.4 per 100,000 in 2002 to approximately 28 per 100,000 in 2023.[22] The latest data estimate that about 34,000 children and adolescents (<20 years) were living with T1D in Germany as of 2023.[23] Among adults in Germany, around 340,000 individuals were living with T1D in 2023[24], with an increased incidence from 9.5 to 11.6 per 100,000 persons between 2015 and 2021 (+22%).[25] Projections based on national health insurance data indicate a further rise in total T1D cases of 18-32% by 2040 compared to 2010. This increase reflects persistently rising incidence rates in the adult population in Germany.[26]

In Austria, similar upward trends are observed. The incidence of T1D in children <15 years has reached a peak of 28.7 per 100,000 person-years in 2021 (up from a plateau of ~22/100,000 during 2011-2020).[27,28] As of 2021, approximately 3,500 children and adolescents and an estimated 30,000 adults are living with T1D in Austria.[28,29]

In line with international data, gender differences in Germany and Austria are modest but consistent: boys tend to have slightly higher incidence rates than girls, especially in countries with high overall incidence.[18,19]

Overall, the burden of T1D is growing worldwide across all age groups, particularly among children, adolescents, and young adults. Therefore, investigating the role of physical activity,

novel therapies, and emerging technologies is of rising importance to improve T1D management and long-term health outcomes in this expanding population.

2.2 Pathophysiology of T1D

T1D is a chronic autoimmune disease characterized by T cell-mediated destruction of insulin-producing β-cells in the pancreatic islets of Langerhans.[1] This process leads to progressive and ultimately complete insulin deficiency, necessitating lifelong exogenous insulin therapy.[30] Genetic predisposition, particularly HLA-DR/DQ haplotypes, is considered a key contributor to T1D, but additional factors, including potential environmental triggers, likely influence disease onset.[31–34]

A hallmark of the autoimmune process is the presence of islet autoantibodies. These are commonly directed against insulin, including GAD65, IA-2, and ZnT8, and may appear months to years before the clinical diagnosis of T1D.[35] This defines a pre-symptomatic stage that progresses silently until residual β-cell capacity is insufficient to maintain euglycaemia.[36] At this point, typical symptoms such as polyuria, polydipsia, weight loss, and fatigue manifest.[37]

After T1D diagnosis and initiation of insulin therapy, many individuals, especially children and adolescents, enter a transient remission phase known as the “honeymoon phase.” This phase is characterized by partial recovery of β-cell function, increased insulin sensitivity, and reduced insulin requirements.[38] However, the autoimmune process continues, and residual insulin production typically declines over time.[39]

2.2.1 Autoimmune Mechanisms and Metabolic Consequences

Due to absolute insulin deficiency and the resulting dysregulation of glucose metabolism, individuals with T1D are susceptible to both acute and chronic metabolic complications.

Acute dysregulation can lead to diabetic ketoacidosis (DKA) and hypoglycaemia, both of which carry significant immediate risks. DKA, especially common at diagnosis and during adolescence, is defined by hyperglycaemia (BG >250 mg/dL or >13.9 mmol/L), metabolic acidosis (arterial pH <7.3 or bicarbonate <15 mmol/L), and the presence of ketones in blood or urine. It results from unrestrained lipolysis and ketogenesis in the absence of insulin and is amplified by counterregulatory hormones such as glucagon, cortisol, catecholamines, and growth hormone. This acute condition can cause severe dehydration, electrolyte imbalances, and cerebral oedema, and may result in coma or death if not promptly treated.[40,41]

Hypoglycaemia, on the other hand, a frequent consequence of insulin therapy, arises when insulin availability exceeds glucose supply. It is defined as BG <70 mg/dL (<3.9 mmol/L), with

clinically significant hypoglycaemia at <54 mg/dL (<3.0 mmol/L), and may lead to symptoms ranging from mild neuroglycopenia to seizures, coma, or death. [42,43]

Recurrent episodes of DKA and hypoglycaemia not only contribute to acute disease burden but are also associated with long-term complications. Persistent hyperglycaemia promotes microvascular complications such as retinopathy, nephropathy, and neuropathy, as well as macrovascular disease. Recurrent hypoglycaemia contributes to impaired hypoglycaemia awareness and cognitive dysfunction, underscoring the importance of achieving and maintaining tight glycaemic control from diagnosis onward.[44–46]

2.2.2 **Specific Challenges of T1D during Adolescence**

Adolescence introduces unique pathophysiological and psychosocial challenges in T1D.

Pubertal hormonal changes, particularly elevated growth hormone and sex steroids, induce a state of relative insulin resistance, increasing insulin requirements and complicating glycaemic management.[47–49] In addition, counterregulatory responses to hypoglycaemia, particularly glucagon and epinephrine secretion, may be blunted in adolescents with long-standing T1D or a history of recurrent hypoglycaemia. These impaired physiological defence mechanisms heighten the risk of severe hypoglycaemia and further complicate self-management.[50]

Beyond physiological factors, adolescence is shaped by psychosocial influences such as emotional volatility, increasing autonomy, and exposure to peer pressure or body image concerns. These factors contribute to variable treatment adherence and metabolic instability. Moreover, mental health issues such as diabetes distress and disordered eating, including intentional insulin omission ("diabulimia"), are particularly prevalent in this age group and can adversely affect glycaemic outcomes.[51–53] The transition from paediatric to adult care represents an additional vulnerable period, often associated with a decline in glycaemic control and gaps in structured follow-up.[54]

Thus, the combination of hormonal, metabolic, developmental, and psychosocial factors renders T1D management particularly challenging during adolescence. These vulnerabilities are particularly relevant in the context of exercise and physical activity, where dynamic physiological demands intersect with developmental challenges. Addressing these multifaceted issues is essential to optimizing long-term outcomes and supporting adolescents in developing independent, sustainable self-management skills. Accordingly, two of the three articles included in this dissertation focus specifically on this age group, aiming to address their unique needs and vulnerabilities.

2.3 Physical Activity and Exercise in People with Type 1 Diabetes

Physical activity and exercise are cornerstones of health promotion and essential factors in optimizing glycaemic outcomes in people with T1D.[55,56] Regular structured exercise improves insulin sensitivity, cardiovascular fitness, body composition, and psychological well-being.[57–59] At the same time, individuals with T1D face distinct physiological and behavioural challenges that require careful management before, during, and after physical activity.[7,60] Against this background, the following chapter outlines the mechanisms underlying glycaemic responses to exercise, reviews clinical guidelines, and discusses specific considerations for adolescents with T1D.

2.3.1 Physiological Responses and glycaemic Challenges around Exercise in T1D

Exercise induces complex metabolic and hormonal adjustments to match substrate availability with muscular energy demands.

In individuals without T1D, exercise reduces endogenous insulin secretion and triggers a compensatory rise in counterregulatory hormones, including glucagon, catecholamines, cortisol, and growth hormone. Together, these adaptations stimulate hepatic glucose output, enhance lipolysis, and prevent excessive peripheral glucose uptake, thereby maintaining euglycaemia around exercise.[7,9,61]

In contrast, individuals with T1D depend on exogenous insulin, which cannot be downregulated acutely. Elevated circulating insulin levels, e.g., after a recent bolus or during basal infusion, suppress hepatic glucose production, enhance peripheral glucose uptake, and inhibit lipolysis. Beyond these systemic effects, glucose uptake is also regulated locally within skeletal muscle. Muscle contractions stimulate insulin-independent glucose uptake via translocation of glucose transporter type 4 (GLUT-4) to the cell membrane. This process is regulated by several signalling pathways, including AMP-activated protein kinase (AMPK), p38 mitogen-activated protein kinase (p38 MAPK), calcium/calmodulin-dependent protein kinases (CaMKs), TBC1D1/4, and endothelial nitric oxide synthase (eNOS). Together, these pathways act synergistically with insulin to amplify glucose clearance during and after exercise.[62,63] Taken together, these systemic and molecular mechanisms substantially increase the risk of exercise-induced hypoglycaemia in individuals with T1D, both during activity and in the subsequent hours.[64,65]

Individual glycaemic responses to exercise vary and are influenced by factors such as insulin on board, time of day, fitness level, nutritional status, and pre-exercise glucose trends.[9] In addition, the type, intensity, and duration of exercise play a central role in shaping glucose dynamics:

- **Continuous moderate aerobic exercise** (e.g., cycling, jogging) increases muscular glucose uptake and progressively lowers BG levels. Prolonged aerobic exercise depletes glycogen and shifts metabolism toward lipid oxidation. Residual circulating insulin elevates hypoglycaemia risk during and after exercise, particularly overnight, when suppressed lipolysis and ketogenesis further limit metabolic flexibility.[9,60,65,66]
- **High-intensity or anaerobic exercise** (e.g., sprinting, resistance training) triggers a robust catecholamine response, stimulating hepatic glucose output and often causing transient hyperglycaemia. While this reduces the immediate hypoglycaemia risk, enhanced post-exercise insulin sensitivity increases susceptibility to delayed hypoglycaemia - especially in the presence of residual circulating insulin.[65–67]
- **Mixed or intermittent exercise** (e.g., team sports, high-intensity interval training (HIIT)) combines aerobic and anaerobic phases, producing variable glucose excursions. Acute sympathetic activation and elevated hepatic glucose production may transiently raise BG, while late-onset hypoglycaemia remains possible due to increased insulin sensitivity.[9,68–70] Recent evidence indicates that, under controlled conditions, HIIT does not inherently increase glycaemic variability compared to continuous aerobic exercise and may even carry a lower risk of immediate hypoglycaemia.[69–71]

In individuals with long-standing T1D or a history of recurrent hypoglycaemia, counterregulatory responses to falling BG are often blunted, a phenomenon known as hypoglycaemia-associated autonomic failure (HAAF). Impaired glucagon and epinephrine secretion reduces the ability to recover from hypoglycaemia, thereby increasing the risk of severe episodes, particularly around exercise.[72,73] This vulnerability is further amplified by a sustained increase in insulin sensitivity after moderate-to-vigorous exercise. This increase can persist for up to 24 hours and necessitates careful adjustments in insulin dosing and/or carbohydrate intake.[74] Exercise performed late in the day poses a particularly high risk for nocturnal hypoglycaemia, as enhanced insulin action coincides with impaired counterregulation and reduced overnight vigilance.[9,66] Taken together, these considerations underscore the importance of proactive, individualized management for safe and effective exercise participation in T1D, thereby reinforcing the value of evidence-based guidelines.[75,76]

2.3.2 Clinical Guidelines for Physical Activity in T1D

Glycaemic control in both clinical care and research is increasingly evaluated using continuous glucose monitoring (CGM) metrics. These include time in range (TIR 70-180 mg/dL or 3.9-10.0 mmol/L), time above range (TAR; TAR1 >180 mg/dL or >10.0 mmol/L; TAR2 >250

mg/dL or >13.9 mmol/L), and time below range (TBR; TBR1 <70 mg/dL or <3.9 mmol/L; TBR2 <54 mg/dL or <3.0 mmol/L). Consensus targets for most individuals with T1D are >70% TIR, <4% TBR, and <1% TBR2 (assessed over a typical 24-hour profile in daily life).[13]

Consensus guidelines from the American Diabetes Association (ADA), the International Society for Pediatric and Adolescent Diabetes (ISPAD), and the European Association for the Study of Diabetes (EASD) emphasize that physical activity is both safe and beneficial in T1D when embedded in individualized glycaemic management strategies.[7,9,77] Current recommendations highlight regular exercise and structured training as a means to improve insulin sensitivity, cardiovascular fitness, metabolic health, and psychosocial well-being, while reducing risks of acute dysglycaemia. They advise at least 60 minutes/day of moderate-to-vigorous activity for children and adolescents, including bone- or muscle-strengthening exercise on ≥3 days/week. For adults, ≥150 minutes per week of aerobic activity is recommended, complemented by resistance training on two or more days per week.[7,9,77]

To translate these recommendations into safe and effective practice, guidelines emphasize individualized strategies tailored to previous exercise response:

1. **Pre-exercise glucose assessment and carbohydrate intake**:

BG and CGM trends should be reviewed 15-30 min before exercise, with management decisions also considering insulin on board (IOB) and exercise parameters.

- If BG is <6.0 mmol/L (108 mg/dL), 10-20 g of rapid-acting carbohydrates should be consumed before exercise, regardless of CGM trend.
- If BG is 6.0-8.3 mmol/L (108-150 mg/dL) with a downward CGM trend, carbohydrate intake is similarly recommended.
- If BG exceeds 13.9 mmol/L (250 mg/dL) and blood ketones >1.5 mmol/L, or if symptoms of insulin deficiency are present (e.g., nausea, vomiting, fatigue), corrective insulin should be administered, hydration encouraged, and exercise delayed until glycaemia and ketonemia have normalized.
- If BG is stable or rising and IOB is low, pre-exercise carbohydrate intake may not be necessary, especially for brief or low-intensity exercise.

2. **Insulin dose adjustment**:

For exercise within 90-120 min of a prandial insulin bolus, a 25-75% dose reduction is advised, depending on the duration and intensity of the activity. For fasted-state morning exercise, a temporary basal rate reduction of 20-50% or short-term pump suspension may be considered.[9,77]

3. AID system adjustments:

Temporary glucose targets (150-180 mg/dL; 8.3-10.0 mmol/L) should be activated 60-90 min before exercise to reduce insulin delivery and minimize hypoglycaemia risk. Device-specific features (e.g., exercise mode, suspension of auto-corrections) should be tailored to prior glycaemic responses and to the device's system design.[9,77,78]

As demonstrated in these guidelines, integration of CGM trend information has become a cornerstone of anticipatory exercise management.[9,77,78] Around exercise, continuous use of real-time CGM (rtCGM) enables detection of rapid glycaemic changes and timely intervention, with trend arrows and predictive alerts guiding carbohydrate intake and exercise adjustments.[9,77] Post-exercise monitoring is equally important, especially after late-day exercise, to mitigate delayed hypoglycaemia. Individualized strategies to reduce nocturnal risk include overnight CGM monitoring with customized alerts, bedtime snacks (e.g., 10-20 g carbohydrates), or temporary basal rate reduction.[7,9,77]

Furthermore, in line with the 2025 EASD/ISPAD consensus, safe exercise with AID systems requires adherence to device-specific, evidence-based protocols.[77] Key strategies include activating exercise mode 60-90 minutes before exercise and considering small manual correction boluses (~0.05 U) to avoid unintended auto-corrections. In addition, insulin delivery may be temporarily suspended during prolonged or contact-intensive exercise, and basal profiles and carbohydrate intake should be adjusted based on individual prior responses.[77,78] Despite improved safety and glycaemic stability, variability persists across systems, underscoring the need for proactive use, trial-based refinement, and personalized plans.[77,78]
In addition, consensus statements, such as those by Moser et al.[9], provide sport-specific recommendations on adapting management to exercise type, intensity, and duration. While these details are not covered extensively in this section, they are discussed later in this dissertation in the context of empirical findings. Overall, this highlights that safe and confident exercise participation in T1D depends not only on general frameworks. It also requires an individualized, patient-centred approach that considers insulin regimen, technology use, exercise type, prior responses, and psychosocial context.[7,9,13,77]

2.3.3 Specific Considerations for Exercise in Adolescents

Adolescents with T1D require exercise guidance that accounts for both physiological and psychosocial complexities of this life stage. Although physical activity offers well-established benefits for children and adolescents, exercise responses are less predictable than in adults. This is

due to pubertal insulin resistance, irregular daily routines with spontaneous physical activity, and the gradual shift from caregiver-led to self-managed care.[7,77,79] Post-exercise hypoglycaemia, particularly nocturnal episodes, is common and necessitates tailored, conservative insulin adjustments and proactive carbohydrate strategies.[9,66,79]

Psychosocial barriers significantly affect exercise participation during adolescence. Fear of hypoglycaemia, particularly in school or peer settings, remains a significant deterrent, alongside concerns about device visibility, performance-related anxiety, and negative prior experiences.[5,80,81] Many adolescents underuse safety strategies due to a desire for normalcy, reluctance to involve caregivers, or uncertainty about managing T1D independently around exercise.[5,82] Competing priorities, including academic demands, social activities, and screen time, further contribute to lower physical activity levels. Diabetes distress and disordered eating behaviours are also more prevalent in this age group, further undermining motivation and glycaemic control.[52,53]

Conversely, effective use of diabetes technology, particularly CGM and AID, can reduce fear of hypoglycaemia and build confidence when adolescents are trained to use these tools consistently and effectively.[77,79] Structured education emphasizing simple, actionable principles, combined with multilevel support from families, peers, schools, and coaches, fosters safer engagement in exercise.[9,79,80,82–85] Evidence-based behavioural strategies, such as motivational interviewing, peer-led education, and shared decision-making, improve self-efficacy and long-term adherence.[86,87] Encouraging adolescents to set personal goals, reflect on experiences, and select enjoyable activities further strengthens participation.[82,85]

In summary, safe and effective exercise participation in adolescents with T1D requires an integrated approach that combines physiological strategies, technological support, and psychosocial interventions. Consistent reinforcement of safe habits, thoughtful use of T1D technology, and confidence-building education are essential to promote sustainable engagement in physical activity during adolescence. These considerations directly underpin the rationale of this dissertation, in which two of the included studies specifically address exercise and technology use in adolescents with T1D.

2.4 Technology and Physical Activity in T1D

The management of T1D has been profoundly transformed by technological innovations that enable safer, more effective engagement in daily life, including physical activity. Among the most impactful advances are CGM and AID systems, most commonly in hybrid closed-loop

(HCL) configurations. These technologies have consistently been shown to improve glycaemic outcomes, including greater TIR and reduced hypoglycaemia risk, and to enhance quality of life in both children and adults.[13,88–91] Nevertheless, exercise remains a physiologically complex scenario that continues to challenge even advanced systems.

2.4.1 Continuous Glucose Monitoring and Physical Activity

CGM technologies, including real-time CGM (rtCGM) and intermittently scanned CGM (is-CGM), provide near-continuous glucose data, trend information, and predictive alerts. Their use has been associated with improved TIR, lower glycated haemoglobin (HbA_{1c}), and reduced TBR.[13,92,93]

However, CGM accuracy declines during periods of rapid glucose change, such as those induced by exercise and other forms of moderate-to-vigorous physical activity. Studies consistently show higher mean or median absolute relative differences (MARD/MedARD) during exercise, especially in hypoglycaemia-prone states.[94–96] While MARDs reported under resting conditions typically remain below 10%, in-exercise values sometimes exceed 20-30%.[94,97–99]

From a physiological perspective, these accuracy limitations reflect the dynamic nature of exercise-induced glucose regulation. Rapid muscle contraction-mediated glucose uptake, altered hepatic glucose production, and delayed counterregulatory responses lead to swift changes in BG that are only captured with temporal delay in the interstitial compartment. As CGM systems and their associated algorithms are optimized for more stable glycaemic conditions, these physiological dynamics directly challenge sensor performance during exercise. Consequently, reduced CGM accuracy in this context should not be interpreted as a purely technical shortcoming, but rather as a physiological constraint inherent to interstitial glucose sensing.

Taken together, these considerations underscore the need for cautious, context-aware interpretation of CGM data in the context of exercise and higher-intensity physical activity. Rather than relying solely on absolute sensor values, effective exercise management should emphasize glucose trends, rate-of-change information, and predictive alerts. Where appropriate, selective capillary confirmation can further support safe and informed decision-making.[9,13,93,94]

2.4.2 Automated Insulin Delivery Systems and Physical Activity

AID systems link CGM data to insulin pumps via control algorithms that continuously adjust basal insulin delivery and, in some designs, deliver correction boluses. Most commercially

available systems employ HCL designs, requiring user-initiated meal boluses and activity announcements. These configurations have been shown to improve TIR and reduce hypoglycaemia risk, particularly at night, thereby enhancing overall glycaemic control.[100–106]

Conceptually, AID systems aim to approximate physiological insulin regulation algorithmically. Around exercise, however, rapid shifts in insulin sensitivity, glucose uptake, and counterregulatory hormone activity fundamentally alter glucose kinetics. These physiological changes unfold on a timescale that often exceeds both the responsiveness of current control algorithms and the pharmacokinetics of subcutaneous insulin. In the absence of timely user input (such as announcing exercise or activating higher glucose targets), this temporal mismatch often leads to glycaemic excursions.[76,77]

These intrinsic limitations are particularly relevant in adolescents, whose physical activity patterns are often spontaneous and irregular and whose technology use may be inconsistent.[78,107]

Together, these considerations highlight that challenges of AID systems during exercise arise not solely from technological constraints, but from the interaction between dynamic physiological processes and algorithm-based insulin delivery.

2.4.3 **Current Gaps and Future Directions**

Although CGM and AID have substantially advanced T1D management, exercise continues to reveal essential limitations. For example, the reduced sensor accuracy during rapid glucose changes[94,95,108], pharmacokinetic delays of subcutaneous insulin[109–111]and the ongoing need for manual adjustments to accommodate unannounced exercise.[112,113] In addition, high inter-individual variability complicates the development of universal solutions.[9] Furthermore, much of the existing evidence derives from controlled laboratory or clinical settings, limiting transferability to everyday life, especially in youth, whose physical activity patterns are often unstructured. To strengthen real-world applicability, further research with higher ecological validity is needed.

At the same time, emerging research explores integrating physiological or behavioural signals with novel wearables to enable more autonomous system adaptation. While still experimental, such approaches may help systems respond more flexibly and with less user involvement.[114–119]

In summary, although CGM and AID technologies have substantially transformed the management of T1D, exercise remains a critical limitation, particularly in adolescents. Taken together, the theoretical framework highlights three interrelated challenges in adolescent T1D manage-

ment around exercise: (1) limited interventional evidence on the safety and efficacy of structured exercise programs in real-world settings. (2) insufficient methodological data on CGM performance under dynamic exercise conditions. And (3) technological limitations of current AID systems, especially during unannounced or spontaneous physical activity. These challenges underscore the need to better integrate physiological, methodological, and technological perspectives. Accordingly, the identified gaps directly informed the design and sequencing of the three complementary studies included in this dissertation. Together, these studies investigate a real-life exercise intervention, CGM performance around exercise, and AID system capabilities. The following chapter defines the specific study objectives and outlines how each study addresses these gaps in a coherent and interrelated manner.

3 Study Objectives

The overall aim of this cumulative dissertation was to improve understanding of exercise in adolescents with T1D, with a focus on safety, efficacy, and physiological implications. In addition, it explored how diabetes technologies may support glycaemic management around exercise in this population. Building on the theoretical framework, the dissertation addresses both the physiological benefits and challenges of exercise as well as the opportunities and limitations of emerging technologies.

To address the identified research gaps in a structured and logically sequenced manner, the dissertation follows a stepwise approach that integrates clinical, methodological, and technological perspectives. Specifically, the three studies are arranged to establish the safety and efficacy of structured exercise as the clinical foundation. They then evaluate the reliability of glucose monitoring under exercise-related physiological stress and synthesize current evidence on automated insulin delivery systems in scenarios where exercise remains insufficiently anticipated.

To address these aims, three complementary peer-reviewed studies were conducted:

(1) Exercise intervention (ChilDFiT1 study): A randomized controlled trial exploring the physiological and clinical implications of a 4-week track and field training program in combination with intensive glycaemic management, compared with intensive glycaemic management alone. The study aimed to provide a deeper understanding of how structured exercise interacts with glycaemic management in a real-world setting for adolescents with T1D.

(2) CGM accuracy study: An investigation of rtCGM performance before, during, and after exercise under dynamic physiological conditions, providing critical methodological evidence on sensor reliability in the context of exercise.

(3) Review on AID systems and unannounced exercise: A systematic evaluation of the performance, limitations, and future directions of AID systems around exercise, with particular emphasis on strategies to manage unannounced physical activity safely and autonomously.

Together, these studies constitute a coherent research framework: the intervention trial demonstrates the clinical and physiological impact of exercise in adolescents with T1D. The CGM analysis provides methodological insight into the reliability of monitoring technology under dynamic conditions. And the AID review integrates current evidence on algorithmic strategies to address the challenges of unannounced exercise. Collectively, they bridge physiological,

methodological, and technological perspectives, thereby advancing a comprehensive understanding and highlighting pathways for optimizing exercise participation in T1D.

The following chapters present each of the three studies in detail, outlining their objectives, methods, and main findings. Taken together, they directly address the research gaps identified in the introduction and theoretical framework. In doing so, they provide an integrated response to the clinical, methodological, and technological challenges of exercise in adolescents with T1D. Accordingly, the dissertation begins with the exercise intervention study, which establishes the clinical foundation for the subsequent methodological and technological analyses.

4 Impact of a 4-week intensive Track and Field Training Intervention on Glycaemia in Adolescents with Type 1 Diabetes: The ChilDFiT1 Study

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4.1 Abstract

Aim: To investigate the safety and efficacy of track and field training compared with intensification of insulin treatment only in adolescents with type 1 diabetes (T1D).

Materials and Methods: Eighteen adolescents (seven females) with T1D were included (age 15.1 ± 1.1 years, HbA_{1c} 7.3% ± 1.0% [56.3 ± 10.9 mmol/mol]). After a 4-week observational control phase, participants were randomized to either standalone intensive glycaemic management (IT; telemedicine or on-site visits, three times/week) or additionally performed track and field exercise (EX; three 60-minute sessions/week) for 4 weeks. Glycaemia was assessed via continuous glucose monitoring during observational control and intervention phases.

Results: Time in range (70-180 mg/dL; 3.9-10.0 mmol/L) significantly improved from the observational control phase to the exercise intervention phase in EX (69% ± 13% vs. 72% ± 11%, P = .049), but not in IT (59% ± 22% vs. 62% ± 16%, P = .399). Time below range 1 (54-69 mg/dL; < 3.9 mmol/L) improved in IT (3.1% ± 1.9% vs. 2.0% ± 0.8%, P = .017) and remained stable in EX (2.0% ± 1.7 vs. 1.9% ± 1.1%, P = .999). The EX group's HbA_{1c} ameliorated preintervention to postintervention (mean difference: ΔHbA_{1c} -0.19% ± 0.17%, P = .042), which was not seen within the IT group (ΔHbA_{1c} -0.16% ± 0.37%, P = .40). Glucose standard deviation was reduced significantly in EX (55 ± 11 vs. 51 ± 10 mg/dL [3.1 ± 0.6 vs. 2.8 ± 0.6 mmol/L], P = .011), but not in IT (70 ± 24 vs. 63 ± 18 mg/dL [3.9 ± 1.3 vs. 3.5 ± 1.0 mmol/L], P = .186).

Conclusion: Track and field training combined with intensive glycaemic management improved glycaemia in adolescents with T1D, which was not observed in the non-exercise group.

Keywords: adolescents, exercise, time in range, type 1 diabetes

4.2 Introduction

With an estimated 355 900 new cases globally in 2021,[120] type 1 diabetes (T1D) is one of the most common chronic diseases among children and adolescents.[121] T1D is classified as an autoimmune disease precipitating the destruction of insulin-producing beta cells,[30] including the necessity to learn to monitor glucose levels and adjust insulin doses to the individual life situation, such as food intake or physical activity.[122,123]

Regular physical activity and exercise are recommended in children and adolescents to improve metabolic, cardiovascular and mental health, promote adequate physical development and establish an active lifestyle at an early age.[7,60,124] This confronts young people with T1D and their caregivers with many concerns because glucose management is substantially challenging during physical activity and exercise.[5] Even minor errors in diabetes management, which are inevitable during exercise, can lead to serious complications. Among acute exercise-induced complications, severe hypoglycaemia and ketoacidotic derailments account for potentially life-threatening situations, contributing to a sustainable burden on physiological and psychological factors.[3] Therefore, physical activity and exercise require individualized and continuous T1D treatment adjustments.[5,60]

It was recently shown that the time in range (TIR) in young people with T1D is higher on physically active days compared with days of inactivity.[125] Additionally, this study associated a higher activity level with lower mean glucose levels ($P = .02$) and a better TIR ($P < .001$), without being accompanied by more hypoglycaemic events. On the other hand, children and adolescents in particular perceive the risk of hypoglycaemia as a greater barrier to exercise the more they have previously suffered from hypoglycaemia on nights after physical activity.[12] Conclusively, despite the scientifically proven benefits of exercise in T1D, the psychological fear of hypoglycaemia and losing glycaemic control seems to be the major barrier for children, adolescents and their parents to engaging in regular exercise.[5,12]

Studies need to show that with adequate support it is possible for children and adolescents with T1D to participate in a variety of sports, without the risk of hypoglycaemia. Therefore, the aim of this two-centre, prospective, randomized controlled trial was to explore the safety via the time below glucose range 1 (TBR1: 54-69 mg/dL; 3.0-3.9 mmol/L) and efficacy via the time in range (TIR: 70-180 mg/dL; 3.9-10.0 mmol/L) of a 4-week intervention of intensive glycaemic management with or without track and field training in adolescents with T1D.

4.3 Materials and Methods

The local ethics committees of the University of Bayreuth (O 1305/1.GB; 8 December 2021; Germany) and the Medical University of Graz (34-263 ex 21/22, 1070-2022; 9 August 2022; Austria) approved the study protocol and the trial was registered at the German Clinical Trials Register (DRKS00027954). The study was conducted in conformity with the Declaration of Helsinki and Good Clinical Practice. Before any trial-related activities, potential participants and their parents were informed about the study protocol and gave their written informed consent to participate in this trial.

4.3.1 Eligibility Criteria

The eligibility criteria included male or female individuals aged 10-17 years with a body mass index (BMI) within the 10th (P10)-90th (P90) percentile of the respective sex and age of children in Germany.[126] Participants with a diagnosis of T1D for at least 1 year (HbA_{1c} < 12% [< 108 mmol/mol] at screening) and with an insulin therapy established either with insulin pen therapy (multiple daily injections [MDI]) or continuous subcutaneous insulin infusion (CSII; pump therapy), were included (no hybrid closed-loop [HCL] systems). Participants reported no severe hypoglycaemia in the last 12 months and showed normal hypoglycaemia awareness (Gold score ≤ 2).[127] Abnormal ECG, heart rate or blood pressure at screening, any contraindicative medication, the presence or history of a clinically severe disease that could jeopardize the participant's safety or directly influence the study results, or clinically relevant hypoglycaemia or diabetic ketoacidosis requiring third-party help during the last 6 months, were reasons for not being included in the study.

4.3.2 Study Design

Following the screening visit and a 4-week observational control phase, participants were randomly assigned to one of two treatment groups[128]: the IT group, which underwent intensive glycaemic management, which was scheduled on at least 3 days per week and conducted via telemedicine or on-site consultations; or the EX group, which additionally performed track and field training on 3 days per week (Monday, Wednesday and Friday) over a 4-week period. For both groups, the ChilDFiT1 study consisted of a screening visit, a 4-week observational control phase, a follow-up visit, a 4-week intervention phase and an end-of-trial visit. The study design is presented in Figure 1.

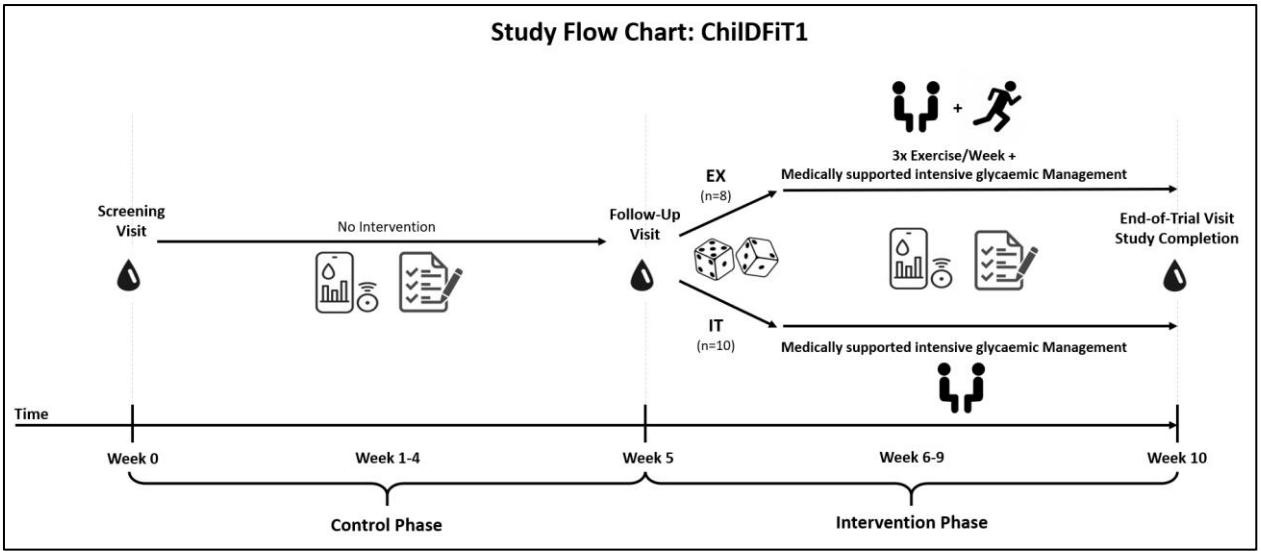


Figure 1: ChilDFiT1 study flow chart. = laboratory visit, = CGM use, = diaries, = randomization, = intensive glycaemic management, = exercise

4.3.3 Laboratory Visits

At the screening visit, participants and their parents were informed about all the study-related procedures. Anthropometric variables were assessed via bioelectrical impedance analysis (Inbody 720, Inbody Co., Seoul, Korea; BIACORPUS RX 4004M, MEDI CAL HealthCare GmbH, Karlsruhe, Germany) for body composition and via manual measurement for body height. For assessment of HbA_{1c} levels, a venous blood sample was obtained from the antecubital vein. After 5 minutes in a supine position, a 12-lead ECG (CardioPart 12, Amedtec, Aue-Bad Schlema, Germany) was recorded and a cardiac assessment (blood pressure, heart rate) was performed. All participants completed the International Physical Activity Questionnaire-Short Form (IPAQ) regarding their daily physical activity.[129] Participants were equipped with a Dexcom G6 continuous glucose monitoring (CGM) system (Dexcom Inc., San Diego, CA) to achieve standardized conditions for CGM and data analysis. Participants were instructed about the sensor placement, the features of functionality and the interpretation of sensor values. Sensor alarms were set individually (based on the European Association for the Study of Diabetes [EASD]/International Society for Pediatric and Adolescent Diabetes [ISPAD] exercise CGM position statement[9]). No significant therapy changes were performed during the screening visit.

4.3.4 Observational Control Phase

The 4-week observational control phase aimed to achieve noninterventional control data of glycaemia, insulin dosing and nutritional behaviour during real-life conditions. No specific recommendations for diabetes therapy were given, but participants kept a diary recording insulin

doses, ingested carbohydrates (CHO), physical activity and general health status. Glycaemia was assessed by the Dexcom G6 CGM system. All CGM metrics and glycaemic ranges were determined as recommended by the international consensus statement[13]: time below range 2 (TBR2: < 54 mg/dL; < 3.0 mmol/L), time below range 1 (TBR1: 54-69 mg/dL; 3.0-3.9 mmol/L), time in range (TIR: 70-180 mg/dL; 3.9-10.0 mmol/L), time above range 1 (TAR1: 181-250 mg/dL; 10.0-13.9 mmol/L) and time above range 2 (TAR2: > 250 mg/dL; > 13.9 mmol/L). Next to the respective glucose ranges, mean glucose, glucose standard deviation (SD_{Gluc}), coefficient of variation (CV) and the glucose management indicator (GMI), an estimated HbA_{1c} converting the mean glucose from CGM, were measured through CGM.

4.3.5 **Intervention Phase**

The 4-week intervention phase started the week after the follow-up visit, at which participants were informed about their group assignment (IT or EX). All participants wore a Dexcom G6 CGM and completed daily diaries. Both groups received intensive glycaemic management. For this, consultations with the study's diabetologist took place at least three times a week. The sessions were held online (telemedicine) or on-site and could be scheduled more frequently in case of acute demand. Apart from the counselling, the IT group continued their daily routine unchanged.

In addition to the intensive glycaemic management, the EX group performed track and field training three times per week on Monday, Wednesday and Friday afternoons (60 minutes of activity per session). Around exercise, sensor glucose was constantly recorded and, additionally, two capillary blood glucose (BG) samples were taken before and every 15 minutes during the training session from a hyperemized earlobe (Contour Next One, Ascensia Diabetes Care Deutschland GmbH, Leverkusen, Germany; BIOSENS S-Line Lab+, EKF-diagnostic GmbH, Barleben, Germany). It was anticipated that, in concordance with the EASD/ISPAD position statement for exercise management in T1D,[9] exercise start was allowed if sensor glucose was between 126 and 270 mg/dL (7.0-15.0 mmol/L). In case of lower values, an individual amount of CHO was supplemented, documented, and sensor as well as BG was rechecked.[9] If sensor glucose exceeded 126 mg/dL (7.0 mmol/L), the exercise session was initiated. In case of initial sensor glucose exceeding 270 mg/dL (15.0 mmol/L), ketones were determined via a capillary BG sample (FreeStyle Precision ß-ketone, Abbott Diabetes Care Inc., Abbott Laboratories, Chicago, IL) and insulin corrections were performed considering potential bolus insulin still on

board. If ketones exceeded 1.5 mmol/L, the exercise session was cancelled.[9] The exercise programme mirrored a children's track and field intervention and was based on the framework 'Kinderleichtathletik', developed by the DLV (German Athletics Association).[130] Participation in 75% or more of exercise visits was required not to be excluded from the study. Based on the international consensus statement on CGM and metrics for clinical trials,[13] a percentage of sensor data availability of less than 70% during both study phases was selected as exclusion criterion.

4.3.6 **Statistical Analyses**

Data were summarized in a single trial master file and analysed via GraphPad Prism 8.0 (GraphPad Software, US). Data were tested for normal distribution via a Shapiro-Wilk test and are presented as mean ± standard deviation (SD). The % of time in glycaemic ranges is additionally presented as median with corresponding 95% confidence interval. For the primary outcome (TIR; TBR1 as co-primary outcome), as well as TBR2, TAR1, TAR2, mean glucose, SD_{Gluc}, CV and GMI, data were compared via a paired t-test for comparison of the two study phases. The control phases of each group (control: IT n = 10; EX n = 8) were compared with their corresponding intervention phase (IT n = 10; EX n = 8). TIR, TBR1, TBR2, TAR1 and TAR2 were additionally analysed as stratified day (06:00 AM-09:59 PM) and night (10:00 PM-05:59 AM) periods. For the secondary outcomes (HbA_{1c} and anthropometric data), data were compared via analysis of variance for repeated measurements (RM-ANOVA) with a Tukey post hoc test for screening, follow-up and end-of-trial visit. Differences between the groups at baseline were compared via an unpaired t-test. Statistical significance was accepted at P less than .05 (two-tailed). Sample size estimation was conducted via G-power (3.1.9.7, HHU-Düsseldorf, Germany) for TIR from a comparable study by Mohammed et al.,[131] which led to a power of 0.92 for n = 9 per group.

4.4 Results

Eighteen adolescents (seven females, n = 18 Caucasian) with T1D were included (age 15.1 ± 1.1 years, T1D duration 5.4 ± 4.1 years, HbA_{1c} 7.3% ± 1.0% [56.3 ± 10.9 mmol/mol], BMI 20.6 ± 2.4 kg/m^2). Ten were randomly allocated to the IT group (five females), while eight participants were allocated to the EX group (two females). One study participant from the EX group was withdrawn from the analysis because of an insufficient amount of conducted training visits. Baseline characteristics for both groups can be found in Table 1. There were no significant differences between the groups at baseline.

Six participants followed MDI therapy (EX: n = 4, IT: n = 2), while 12 participants were on CSII therapy (EX: n = 4, IT: n = 8). All participants were using CGM systems in their daily routine prior to the study. The IT group received a mean of 11.2 ± 2.1 consultations in total, whereas the EX group underwent 11.0 ± 1.8 consultation sessions (P = .835).

Table 1: Baseline mean and standard deviation as well as median with 95% CI of % time in specific glycaemic ranges according to the study group.

Baseline	IT	EX	*P* value
Age (y)	14.7 ± 1.2	15.5 ± 1.0	.138
BMI (kg/m^2)	20.3 ± 2.5	21.0 ± 2.3	.534
T1D duration (y)	5.0 ± 4.9	5.8 ± 3.8	.715
HbA1c (%) HbA1c (mmol/mol)	7.7 ± 1.2 60.6 ± 13.1	7.0 ± 0.6 53.0 ± 6.6	.149
GMI (%) GMI (mmol/mol)	7.50 ± 1.06 58.6 ± 11.6	6.99 ± 0.46 52.9 ± 5.0	.221
Mean glucose (mg/dL) Mean glucose (mmol/L)	175 ± 44 9.7 ± 2.4	154 ± 18 8.5 ± 1.0	.230
SD_{Gluc} (mg/dL) SD_{Gluc} (mmol/L)	70 ± 24 3.9 ± 1.3	55 ± 11 3.1 ± 0.6	.126
CV (%)	39.2 ± 7.7	34.7 ± 4.1	.152
TAR2 (%)	17.9 ± 19.3; 14.5 (1.0; 46.0)	6.8 ± 5.4; 6.0 (1.0; 18.0)	.135
TAR1 (%)	19.3 ± 5.6; 20.0 (15.0; 25.0)	21.6 ± 8.6; 23.5 (9.0; 31.0)	.499
TIR (%)	58.5 ± 21.8; 56.0 (32.0; 82.0)	68.9 ± 13.1; 66.5 (49.0; 88.0)	.255
TBR1 (%)	3.1 ± 1.9; 3.0 (1.0; 5.0)	2.0 ± 1.7; 1.5 (1.0; 6.0)	.212
TBR2 (%)	1.3 ± 0.7; 1.0 (1.0; 2.0)	1.0 ± 0.0; 1.0 (1.0; 1.0)	.230

Note: Baseline mean and standard deviation of HbA_{1c}, GMI, SDGluc and CV according to the study group. The level of significance was calculated by comparing both study groups at baseline (IT vs. EX).

Abbreviations: BMI, body mass index; CI, confidence interval; CV, coefficient of variation; EX, intensive glycaemic management and exercise; GMI, glucose management indicator; IT, intensive glycaemic management only; SDGluc, glucose standard deviation; TAR1, time above range 1 (181-250 mg/dL; 10.0-13.9 mmol/L); TAR2, time above range 2 (> 250 mg/dL; > 13.9 mmol/L); TBR1, time below range 1 (54-69 mg/dL; 3.0-3.9 mmol/L); TBR2, time below range 2 (< 54 mg/dL; < 3.0 mmol/L); TIR, time in range (70-180 mg/dL; 3.9-10.0 mmol/L); T1D, type 1 diabetes.

4.4.1 CGM-derived Glycaemia

In total, 270 187 CGM values were available (EX: 122 642 CGM values, IT: 147 545 CGM values), which corresponds to an average of 15 010 ± 896 (EX: 15 330 ± 689, IT: 14 755 ± 993) CGM values per person. Sensor usage was 95.0% ± 5.4% (EX: 97.1% ± 3.2%, IT: 93.4% ± 6.3%) of the time, with a data sufficiency of 94.3% ± 4.2% (EX: 95.3% ± 3.9%, IT: 93.5% ± 4.3%). There were no significant differences in sensor metrics when comparing the control with the intervention phases of the respective groups (P > .05). No major CGM sensor failures occurred and all participants obtained more than 70% of data availability over the whole study period.

For the EX group, TIR significantly improved throughout the exercise intervention phase when compared with the control phase (P = .049), which was not seen for the IT group (P = .399) (Table 2). Therefore, the recommended target of the consensus statement (> 70% TIR) was met only by the EX group during the intervention.[13] TBR1 showed a significant decrease in the IT group (P = .017) and remained stable in the EX group (P = .999). TBR2 did not vary in EX and IT (EX: P = 1.0; IT: P = .50). The consensus statement recommended target for TBR2 (< 1%) was not met by either group at any time point. The consensus target for total TBR (< 4%) was always met, except by IT in the control phase.[13] TAR1 did not change in EX during the intervention (P = .204), but showed a significant increase in the IT group (P = .037). TAR2 showed no change in EX and IT through the intervention (EX: P = .096; IT: P = .305). The consensus statement targets for TAR2 (< 5%) and total TAR (< 25%) were not met by any group in any phase.[13]

Nocturnal TBR1 increased significantly in the EX group (P = .0075), which was not seen in the IT group. Nocturnal TBR2, TIR, TAR1 and TAR2 did not change significantly in both groups.

Table 2: Mean and standard deviation as well as median with 95% CI of % time in specific glycaemic ranges according to the study group.

		IT		EX	
Glycaemic ranges		Control	Intervention	Control	Intervention
Overall	TAR2 (%)	17.9 ± 19.3; 14.5 (1.0; 46.0)	12.7 ± 13.5; 6.5 (4.0; 30.0)	6.8 ± 5.4; 6.0 (1.0; 18.0)	5.3 ± 4.5 5.0 (1.0; 15.0)
	TAR1 (%)	19.3 ± 5.6; 20.0 (15.0; 25.0)	22.3 ± 4.1; 22.0 (17.0; 28.0)*	21.6 ± 8.6; 23.5 (9.0; 31.0)	19.9 ± 6.5; 20.0 (11.0; 29.0)
	TIR (%)	58.5 ± 21.8; 56.0 (32.0; 82.0)	62.0 ± 15.7 68.0 (40.0; 74.0)	68.9 ± 13.1; 66.5 (49.0; 88.0)	72.1 ± 10.6; 71.0 (54.0; 87.0)*
	TBR1 (%)	3.1 ± 1.9; 3.0 (1.0; 5.0)	2.0 ± 0.8; 2.0 (1.0; 3.0)*	2.0 ± 1.7; 1.5 (1.0; 6.0)	1.9 ± 1.1; 1.5 (1.0; 4.0)
	TBR2 (%)	1.3 ± 0.7; 1.0 (1.0; 2.0)	1.1 ± 0.3; 1.0 (1.0; 1.0)	1.0 ± 0.0; 1.0 (1.0; 1.0)	1.0 ± 0.0; 1.0 (1.0; 1.0)
Night (10:00 PM-05:59 AM)	TAR2 (%)	15.8 ± 18.5; 10.8 (0.6; 36.4)	11.5 ± 11.8; 6.6 (4.4; 29.5)	4.5 ± 3.3; 4.7 (0.0; 9.1)	3.8 ± 2.6; 4.6 (0.0; 6.9)
	TAR1 (%)	19.1 ± 7.7; 21.4 (10.6; 26.3)	22.8 ± 4.4; 23.5 (17.4; 26.8)	19.1 ± 9.5; 23.7 (3.5; 27.6)	15.0 ± 7.8; 14.1 (2.5; 25.4)
	TIR (%)	61.1 ± 24.0; 59.9 (38.5; 87.8)	62.4 ± 15.3; 66.2 (39.5; 75.8)	74.5 ± 12.9; 67.6 (61.4; 94.9)	78.3 ± 10.6; 79.2 (64.6; 95.4)
	TBR1 (%)	2.9 ± 1.3; 2.7 (1.5; 4.6)	2.1 ± 1.2; 2.4 (0.5; 3.5)	1.6 ± 0.7; 1.6 (0.4; 2.8)	2.5 ± 1.1; 2.4 (0.9; 4.0)**
	TBR2 (%)	1.1 ± 1.1; 0.7 (0.3; 2.5)	1.1 ± 1.5; 0.7 (0.0; 2.9)	0.4 ± 0.4; 0.3 (0.0; 1.3)	0.5 ± 0.3; 0.6 (0.1; 0.9)

Note: The level of significance was calculated by comparing the control and intervention phase of the respective group (IT and EX).
Abbreviations: CI, confidence interval; EX, intensive glycaemic management and exercise; IT, intensive glycaemic management only; TAR1, time above range 1 (181-250 mg/dL; 10.0-13.9 mmol/L); TAR2, time above range 2 (> 250 mg/dL; > 13.9 mmol/L); TBR1, time below range 1 (54-69 mg/dL; 3.0-3.9 mmol/L); TBR2, time below range 2 (< 54 mg/dL; < 3.0 mmol/L); TIR, time in range (70-180 mg/dL; 3.9-10.0 mmol/L).
*P < .05. **P < .01.

4.4.2 **Glycaemic Variables**

In the EX group, HbA_{1c} ameliorated significantly from 7.0% ± 0.5% (53.0 ± 5.5 mmol/mol) preintervention to 6.8% ± 0.4% (50.8 ± 4.4 mmol/mol) postintervention (P = .042), which was not seen within IT (7.4% ± 1.2% vs. 7.3% ± 1.1% [57.3 ± 13.1 vs. 56.2 ± 12.0 mmol/mol], P = .400) (Figure 2A). The GMI showed no significant changes in EX (6.99% ± 0.46% vs. 6.91% ± 0.33% [52.9 ± 5.0 vs. 52.0 ± 3.6 mmol/mol], P = .222) or IT (7.50% ± 1.06% vs. 7.34% ± 0.72% [58.6 ± 11.6 vs. 56.7 ± 7.9 mmol/mol], P = 0.436) (Figure 2B). No significant changes in mean glucose were found for either EX (154 ± 18 vs. 151 ± 14 mg/dL [8.5 ± 1.0 vs. 8.4 ± 0.8 mmol/L], P = .154) or IT (175 ± 44 vs. 168 ± 31 mg/dL [9.7 ± 2.4 vs. 9.3 ± 1.7 mmol/L], P = .412). Glycaemic variability assessed by SD_{Gluc} improved significantly only for EX (EX: 55 ± 11 vs. 51 ± 10 mg/dL [3.1 ± 0.6 vs. 2.8 ± 0.6 mmol/L], P = 0.011; IT: 70 ± 24 vs. 63 ± 18 mg/dL [3.9 ± 1.3 vs. 3.5 ± 1.0 mmol/L], P = .186) (Figure 2C). The CV remained stable with a tendency to decrease for both groups (EX: 34.7% ± 4.1% vs. 33.6% ± 3.8%, P = .184; IT: 39.2% ± 7.7% vs. 37.0% ± 4.5%, P = .254) (Figure 2D). In addition, participants' diaries showed that daily bolus insulin did not change (EX: 30.4 ± 9.1 vs. 26.7 ± 9.8 IU, P = .083; IT: 23.6 ± 13.8 vs. 20.7 ± 13.6 IU, P = .070).

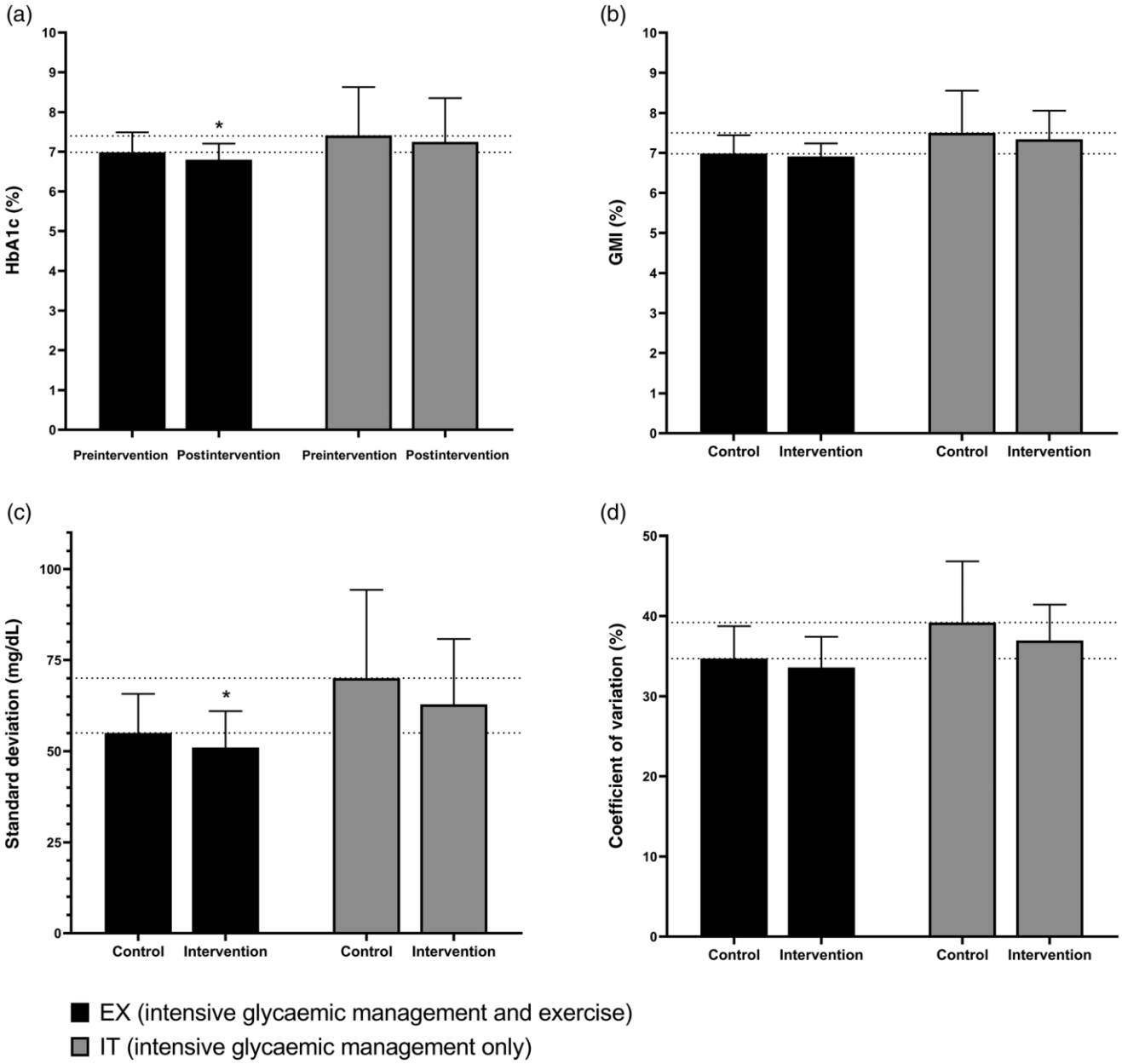


Figure 2: Continuous glucose monitoring-derived secondary outcome variables according to group (IT and EX), compared with the respective control and intervention phase. B, Glucose management indicator (GMI), C, Glucose standard deviation (SDGluc), and D, Coefficient of variation (CV) are presented as mean and standard deviation of control and intervention phases. A, HbA_{1c} is presented as mean and standard deviation at the preintervention and postintervention laboratory visits. Stars indicate the level of significance; *P < .05.

4.4.3 **In-exercise Glycaemia (EX Group)**

In total, 316 in-exercise, 83 pre-exercise and 47 post-exercise measurements were available. The calculated % time in respective glycaemic ranges during the active exercise period, the mean BG pre-, in- and post-exercise, as well as the mean CHO intake per exercise visit, are presented in Table 3. During the active training period, BG was significantly lower compared

with pre-exercise (P = .011). In-exercise, no values more than 250 mg/dL (TAR2; > 13.9 mmol/L) were detected.

Table 3: Mean ± SD as well as median with 95% CI of the respective glycaemic ranges during exercise, blood glucose pre-, in- and post-exercise, as well as CHO intake per exercise visit.

Variables around exercise		Mean ± SD	Median (95% CI)
In-exercise BG (%)	TAR2	0.0 ± 0.0	0.0 (0.0; 0.0)
	TAR1	7.0 ± 12.3	1.1 (0.0; 35.7)
	TIR	78.8 ± 15.8	82.5 (48.3; 97.1)
	TBR1	12.4 ± 11.5	8.3 (0.0; 34.5)
	TBR2	1.7 ± 2.6	0.0 (0.0; 6.9)
BG (mg/dL)	Pre-exercise	124.1 ± 19.2	129.1 (113.4; 139.7)
	In-exercise	106.7 ± 15.0*	107.5 (99.5; 113.5)
	Post-exercise	120.2 ± 20.0	115.5 (105.8; 138.1)
CHO intake (g)	Per exercise visit	21.1 ± 18.6	18.0 (12.0; 27.0)

Note: * indicates the level of significance to the respective preliminary phase.
Abbreviations: BG, blood glucose; CHO, carbohydrates; CI, confidence interval; SD, standard deviation; TAR1, time above range 1 (181-250 mg/dL; 10.0-13.9 mmol/L); TAR2, time above range 2 (> 250 mg/dL; > 13.9 mmol/L); TBR1, time below range 1 (54-69 mg/dL; 3.0-3.9 mmol/L); TBR2, time below range 2 (< 54 mg/dL; < 3.0 mmol/L); TIR, time in range (70-180 mg/dL; 3.9-10.0 mmol/L).
*P < .05.

4.4.4 **Anthropometry**

No significant changes in anthropometric variables occurred in the IT group. In the EX group, significant increases were recorded in fat-free mass (FFM; P = .044) and body cell mass (BCM; P = .005) from preintervention to postintervention (Table 4).

Table 4: Changes in anthropometric data according to the group (IT and EX), compared with the respective control and intervention phase.

Group	Time	Height (cm)	Body mass (kg)	BMI Z-Score[13]	Body fat (%)	Fat-free mass (kg)	Body cell mass (kg)
IT	Preintervention	167.0 ± 8.7	57.2 ± 8.2	0.13 ± 0.72	24.3 ± 9.9	41.9 ± 5.7	24.9 ± 3.4
	Postintervention	167.3 ± 8.9	57.2 ± 8.1	0.09 ± 0.75	24.5 ± 9.9	41.8 ± 5.7	24.4 ± 4.0
EX	Preintervention	172.3 ± 5.1	63.4 ± 8.8	0.29 ± 0.61	17.2 ± 7.0	52.2 ± 7.3	30.8 ± 7.1
	Postintervention	172.5 ± 5.2	63.4 ± 9.5	0.23 ± 0.68	16.4 ± 6.9	52.8 ± 7.5*	31.4 ± 7.2**

Note: * indicates the level of significance between preintervention and postintervention.
Abbreviations: BMI, body mass index; EX, intensive glycaemic management and exercise; IT, intensive glycaemic management only.
*P < .05. **P < .01.

4.4.5 **Daily Physical Activity**

The IPAQ showed that the daily not study-related physical activity of IT and EX (expressed as total metabolic equivalent of task [MET] minutes per week) did not change throughout the study (EX: 3134 ± 1808 vs. 3382 ± 1948 METs, P = .184; IT: 3308 ± 1968 vs. 3071 ± 1582 METs, P = .630) and was comparable for both groups ($P_{control\ phase}$ = .862, $P_{intervention\ phase}$ = .742).

4.5 Discussion

4.5.1 **Glycaemic Management**

The TIR improved significantly in the EX group, resulting in the EX group meeting the consensus statement goal (> 70% of time per day in TIR)[13] during the intervention phase. By contrast, the TIR of the IT group did not improve significantly, which illustrates the efficiency of track and field training combined with intensive glycaemic management over 4 weeks. In terms of glycaemic safety, a significant improvement was observed in the TBR1 of the IT group, while the EX group remained stable. IT thus achieved the consensus statement TBR target of less than 4% in the intervention phase. However, the EX group already had a very low TBR1 across the whole group during the control phase, which decreased the chance of further improvements. EX's TBR remained less than 4% in both study phases, fulfilling the consensus statement goals, and, therefore, the training intervention was able to maintain glycaemic safety. Furthermore, EX's improved glycaemic management is emphasized by the significant reduction of SDGluc, which showed that regular exercise kept mean glucose levels more stable and reduced glycaemic fluctuations. The exercise-induced benefits are additionally underlined by the significant reduction in HbA_{1c} levels, which was only observed in the EX group. Even although HbA_{1c} represents the last ~12 weeks and the absolute value may not exactly depict the intervention, the intervention was able to significantly improve HbA_{1c} levels in a short period of time. EX's significantly increased nocturnal hypoglycaemia (TBR1) in the intervention phase must be viewed mindfully. The risk of nocturnal hypoglycaemia after exercise is well known and a cause of fear for many children and adolescents with T1D, and should therefore be avoided. However, the international consensus statement on CGM and metrics for clinical trials recommends no more than 4% of time each day (i.e. approximately 1 hour) in TBR,[13] which was still achieved in the intervention phase of EX. Additionally, nocturnal TBR2, and therefore clinically relevant nocturnal hypoglycaemia, did not increase through the intervention.

Moreover, the results of both groups have to be evaluated considering that none of the participants used an HCL system. Children and adolescents in particular benefit from the use of HCL systems in the context of exercise, achieving higher TIR and lower TBR compared with people using non-supportive insulin pumps or MDI therapy.[132] Therefore, the positive effects of the exercise intervention must be considered even more clinically relevant.

The results of the ChilDFiT1 study partly differ from those reported by Mohammed et al.,[131] where a 12-week football programme with two 90-minute bouts per week was conducted with or without a nutritional programme. Here, only a significant improvement in HbA_{1c} was found for the exercise and nutrition group, but not for the groups with standalone exercise or nutrition. Therefore, the differences in effect might be attributable to the combination with glycaemic management in the ChilDFiT1 study, which was not implemented by Mohammed et al., except via post-exercise basal rate reductions. They showed, however, that 12 weeks of football coupled with nutritional adjustments can indeed improve glycaemia. Besides the combination of exercise and glycaemic management, the ChilDFiT1 exercise design may have contributed to a greater effect on glycaemia compared with Mohammed et al. Dividing 180 minutes of exercise per week into 3 x 60 minutes (ChilDFiT1) instead of 2 x 90 minutes,[131] and thus exercising more regularly with a shorter exercise duration, might be more conducive to improving HbA_{1c} and SD_{Gluc}, making exercise duration a marker that must be considered in exercise prescription.[133,134] Alternatively, the exercise type and thus the specific training stimuli could play a role. Football, as a primarily high-intensity sport,[135] could have a smaller effect on glycaemia than track and field, which combines a variety of stimuli as well as exercise types and intensities. Looking at the general body of research, the benefits of regular physical activity depend mainly on the type, intensity, duration and frequency of activity.[57–59,136,137] In children and adolescents with T1D performing aerobic and mixed aerobic-anaerobic exercise, respectively, medium-intensity exercise produced the most beneficial effects on both glycaemia and general health variables.[56,138–141] Aerobic exercise is recognized for its ability to improve insulin sensitivity, beneficially modify insulin resistance and decrease insulin requirements, as well as lower cardiovascular and overall mortality risk in T1D.[142] As a result, it is advisable to engage in frequent aerobic exercise to maintain a consistent improvement in physical health.[55,143]

Important to note, from a physiological point of view, the improvements in insulin sensitivity are mainly based on the prolonged accumulation of glucose transporter type 4.[60] Additionally, incorporating planned short bursts of high-intensity, sprint-like exercise alongside aerobic

workouts can reduce the likelihood of experiencing hypoglycaemia around exercise.[143,144] Physiologically, high exercise intensities act on the counter regulatory hormone response (catecholamines, cortisol) that enhance the rate of hepatic glycogenolysis.[69,144]

Additionally, as given in the World Health Organization recommendations for physical activity and exercise, it is recommended that exercise should be diversified, containing moderate- to vigorous-intensity aerobic activity as well as muscle-strengthening activities, which is in detail reflected by our exercise intervention.[124] Consequently, track and field possess the fundamental prerequisites necessary for achieving beneficial effects on glycaemia and general health variables. Furthermore, from our point of view, track and field's variety of components (running, sprinting, jumping, throwing) immensely improved the motivation and hence adherence to participate in our trial.

A meta-analysis by Shorey et al. showed that standalone physical activity and diet-based interventions had a limited, but positively trending effect, on HbA_{1c} in children and adolescents.[145] The generally favourable results underline the potential of exercise interventions to improve glycaemia and health-related quality of life. Consequently, a combination of exercise, medical consultations and individualized glycaemic plus nutritional training might be the gold standard.

In line with the ChilDFiT1 results, Riddell et al. showed that the TIR in adults with T1D is higher on exercise days than on sedentary days.[146,147] Likewise, Gal et al. were able to show this for children and adolescents: higher activity levels in 9-17 year-old participants with T1D were associated with better TIR ($P < .001$), without being linked to higher TBR.[125] Overall, the current research along with the ChilDFiT1 results show that adults as well as adolescents with properly

guided assistance and the appropriate level of knowledge can participate in exercise without fear. However, especially for children and adolescents who may not have much T1D-specific experience,[148] it is important to be educated in glycaemic management around exercise.[60] Moser et al. also suggested an approach that uses personalized treatment adjustments in the EASD/ISPAD position statement.[9]

Interestingly, as given in our study, FFM and BCM significantly increased only in the EX group, which is associated with positive effects such as improved cardiovascular health, better functional ability and an increased metabolic rate,[59,136,137] and shows further potential benefits of regular training in T1D.

4.5.2 **Glycaemia during Exercise**

When evaluating the acute exercise effects, the mean TIR during exercise was 78.8%, which was even higher than seen over the 4-week intervention period. Looking at other exercise studies in children and adolescents with T1D, Elleri et al.[149] recorded TIRs between 56% and 79% during 60 minutes of continuous moderate-intensity cycling for different therapies and times of the day. Dovc et al.[101] found TIRs of 80.9% when using a closed-loop system (CL) and 68.1% in the open-loop mode (OL) for 40 minutes of moderate-intensity cycling. Additionally, they found TIRs of 75.3% (CL) and 68.4% (OL) for a 40-minute mixed protocol consisting of moderate-intensity cycling combined with high-intensity sprinting.[101] However, these studies took place in a laboratory setting in which the children and adolescents were controlled for 22[101] or 36 hours,[149] while in the present study, exercise preparations and follow-up were independently managed by the participants. The comparatively high TIR of the ChilDFiT1 study can thus show that TIR around exercise can also be ensured in everyday life, and not only in a controlled setting.

To date, there are very few comparable sport-specific studies in a non-laboratory setting that have investigated TIR involving children and adolescents. Of these, skiing studies with children and adolescents showed that the structural conditions of a sport can be a hurdle that must be taken into consideration. TIRs of 63.2% (CL) and 62.8% (CSII) for 330 minutes,[150] and of 57.8% (CL) and 55.9% (CSII) for 240 minutes,[151] for moderate-intensity skiing, were recorded. The lower TIRs could be a result of the intense, prolonged physical activity, cold temperature, altitude and psychological strain.

Despite excellent in-exercise TIR and almost no hyperglycaemic events, the acute hypoglycaemia level increased in-exercise with an average TBR1 of 12.4%, which was mainly based on the CGM lag time and inaccuracy during hypoglycaemia. McClure et al. showed in their meta-analysis that the effect of high-intensity interval exercise on BG is inconsistent, complicating the avoidance of rapidly falling glucose levels and hypoglycaemia.[152] In the context of aerobic exercise, a decline in BG levels can be anticipated and counteractive measures can accordingly be taken.[143] Conversely, anaerobic exercise, influenced by a multitude of factors, can yield variable, and often even elevated, BG responses.[143,152] Logically, track and field's multifaceted nature, characterized by the occurrence of aerobic and anaerobic stimuli in variable sequences and magnitudes, might challenge glycaemia, even although we have now shown within our ChilDFiT1 study significant improvements in TIR. To address this, providing children and adolescents with T1D with weekly training plans might improve glycaemia by allowing proactive

adjustments to therapy before, during and after exercise, potentially reducing dysglycaemia. However, of utmost importance, clinically relevant hypoglycaemia (< 54 mg/dL; < 3.0 mmol/L) was very low and no exercise visit had to be discontinued because of hypoglycaemia.

4.5.1 **Study Limitations**

First, while a 3% change in TIR may not reach the commonly accepted 5% threshold for clinical significance, it is essential to acknowledge that this threshold is often based on specific, narrowly selected groups and its link to HbA_{1c} values.[153,154] It is crucial to view our study in context, as in the field of TIR research among children and adolescents in specific sports, limited data are available. Our study paves the way for future research, emphasizing the potential for investigating interventions that could yield more substantial improvements in TIR. Consequently, particularly for the understudied group of children and adolescents with T1D, even a 1% improvement in TIR can be considered clinically meaningful from our perspective. Additionally, an improvement of HbA_{1c} from 7.0% ± 0.5% to 6.8% ± 0.4% should be interpreted for this specific group of children and adolescents with T1D as clinically meaningful. Most importantly, our study proved the superiority of track and field sessions over controls for glycaemic control.

Second, a not significant trend towards improvement could be seen in the EX group's TAR1, TAR2, GMI, mean glucose, CV and daily bolus insulin. Therefore, a follow-up study should cover an extended period of intervention to determine long-term effects for glycaemia. However, our short-term track and field training showed that just one month of exercise can improve glycaemia and therefore clearly supports the importance of regular exercise, even for a short period of time (1 month). As children and adolescents often spend their summer holidays on sports camps (_over a period of 4 weeks), our findings further support the importance of the inclusion of children and adolescents with T1D, for whom this could offer not only joy, but also improvements in glycaemia.

Furthermore, although the study setting was designed to be close to reality, it could not be implemented 100% realistically. For example, a supervising diabetologist was always present during the exercise sessions or capillary blood measurements were taken every 15 minutes, which is not feasible in everyday life. Also, the small sample size must be viewed critically. Nevertheless, we conducted a sample size estimation and fulfilled the requirement for the number of study participants for our study, which was comparatively low. However, follow-up studies should aim for a higher number of participants (which would also lead to more homogeneous

groups in terms of TIR and HbA_{1c} at baseline). In addition, the EX group was already glycaemically well-adjusted during the control phase, resulting in limited possible improvements in glycaemic control. Future studies should therefore perform a stratified randomization based on the TIR and specific baseline characteristics (gender, BMI) to achieve more homogenous groups. Additionally, information on socioeconomic status and parental education would have enabled better contextualization of the results. Moreover, it is essential to delve into the psychological stress experienced by the different groups, along with assessing the practicality of sustaining the exercise routine independently, with reduced consultation frequency. In the context of this manuscript, we are unable to address this crucial psychological aspect because we did not assess this in detail.

4.6 Conclusion

In conclusion, track and field training in combination with intensive glycaemic management improved glycaemic efficacy in adolescents with T1D, which was not observed in the non-exercise group. At the same time, track and field training in combination with supported intensive glycaemic management resulted in stable and generally low TBR and contributed to an improvement in the anthropometric status. Therefore, we can consider track and field exercise in adolescents with T1D as feasible and safe under properly guided assistance and detailed training.

Linking Statement

The ChilDFiT1 trial demonstrated that structured track and field training can be implemented safely and improves overall glycaemic outcomes. However, these conclusions rely on the assumption that CGM data accurately reflect glucose dynamics around exercise. However, exercise is characterized by rapid glucose fluctuations that can challenge sensor performance. Therefore, the second study builds directly on the ChilDFiT1 intervention setting by systematically evaluating rtCGM accuracy before, during, and after exercise sessions.

5 Performance of real-time continuous Glucose Monitoring during Track and Field Training in Adolescents with Type 1 Diabetes

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5.1 Abstract

Introduction: Real-time continuous glucose monitoring (rtCGM) has become an integral component of modern diabetes management. However, sensor performance data of adolescents, especially during exercise, are scarce. Therefore, this investigation aimed to determine the performance of a rtCGM system before, during, and after exercise around a 4-week track and field training intervention in adolescents with type 1 diabetes (T1D).

Material and methods: Eight adolescents (2 females, 15.5 ±1.0 years, BMI: 21.0 ±2.3 kg/m2) with T1D and an HbA_{1c} of 7.0 ±0.6% (53.0 ±6.6 mmol/mol) participated in a 4-week track and field intervention consisting of three 60-minute exercise sessions per week. Sensor glucose levels (Dexcom G6; Dexcom Inc., San Diego, CA) were obtained at rest and after 15, 30, 45, and 60 minutes during, as well as 5 minutes after exercise and compared to a reference capillary blood glucose value (Biosen S-Line, EKF Diagnostics, GER). rtCGM performance was assessed using the median absolute relative difference (MedARD) and interquartile range [IQR] as well as the Bland-Altman method.

Results: 443 points of comparison were available for analysis. The overall MedARD (IQR) was 19.1% (12.2-27.3). MedARDs for time in range (70-180 mg/dl), below range (< 70 mg/dl), and above range (> 180 mg/dl) were 22.0% (17.8-29.2), 28.4% (18.8-36.3), and 15.9% (9.4-20.7), respectively. The in-exercise MedARD was 19.4% (12.3-27.8), and pre- and post-exercise MedARDs were 21.6% (14.5-28.3) and 14.9% (9.0-21.6), respectively.

Conclusions: In structured track and field training involving adolescents with T1D, the accuracy of the Dexcom G6 system is limited. This supports the importance of considering glucose trend arrows and, when in doubt, blood measurements during exercise.

Keywords: accuracy, continuous glucose monitoring (CGM), exercise, paediatrics, type 1 diabetes

5.2 Introduction

Children and adolescents with type 1 diabetes (T1D) have to independently ensure appropriate diabetes management, which requires careful interaction between insulin administration and carbohydrate intake.[7,148,155] This includes, among others, the interpretation of both continuous glucose monitoring (CGM)-derived glucose values and trend arrows so that the insulin dose can be adjusted to individual life situations, such as food intake or physical activity.[122,123] Of note, physical activity is exceedingly complex and can lead to increased risk of hypoglycaemia and loss of glycaemic control[156], often discouraging children and adolescents as well as their caregivers from engaging in regular exercise.[5,12,81] On the other hand, regular physical activity and exercise are recommended at an early age to improve metabolic, cardiovascular, and mental health and to promote adequate development.[7,60,124,125] This presents young people with T1D and their caregivers with a multitude of concerns because specific as well as individualised and regular adjustments of diabetes therapy are required.[5,60]

These days, one integral part of diabetes management is real-time continuous glucose monitoring (rtCGM).[92] Regular CGM use enables an increased quantity of readings per day[93] and is associated with improved glycaemia by means of improved HbA_{1c} levels, increased time in range (TIR, 70-180 mg/dl), reduced time below (< 70 mg/dl) and above range (> 180 mg/dl), and lower glycaemic variability.[88,89,92,157–159] However, data on CGM performance in children and adolescents, especially during exercise, is still scarce. It is therefore of great interest to collect further data quantifying rtCGM sensor performance for paediatric individuals during exercise. Reviewing current studies, the mean absolute relative difference (MARD) of CGMs compared to venous/capillary glucose under different physiological or experimental conditions is comparable for the widest range of new-generation systems and lies between 10% and 20% overall.[9,96,160–162] However, periods of high rates of change in glucose are a particular limitation for the performance of CGM systems because the diffusion of glucose from the bloodstream to the interstitial fluid, where the CGM sensor is detecting glucose, results in a physiological lag time of 3-12 minutes.[94,163,164] Consequently, as shown in multiple studies, the use of CGM systems around exercise decrease sensor performance to a certain extent.[94–96,162] Furthermore, sensor accuracy performs worse during hypoglycaemia than in hyperglycaemia. Therefore, the often-increased rates of hypoglycaemia during and after physical workouts pose another additional challenge.[96,165]

Based on the results of these previous CGM performance studies, Eichenlaub *et al.*[166] published guidelines for comparator data characteristics and testing procedures for the clinical performance evaluation of CGM systems. These guidelines propose characteristics of the comparator measurements collected during CGM performance studies that include the blood glucose (BG) concentrations and their rate-of-change (RoC).

Aim of the Study

This investigation aimed to determine the sensor accuracy of the Dexcom G6 rtCGM system (Dexcom Inc., San Diego, CA) around the acute glycaemic challenges of the exercise sessions of a 4-week intensive track and field training, combining a variety of stimuli as well as exercise types and variable intensities, in adolescents with T1D. Additionally, this study considers the validity of the results based on the guidelines for CGM performance assessment.

5.3 Material and Methods

This study is an analysis of a prespecified secondary outcome of the ChilDFiT1 study.[167] The trial was registered at the German Clinical Trials Register (DRKS00027954). The study was conducted in conformity with the declaration of Helsinki and Good Clinical Practice. Before any trial-related activities, potential participants and respective legal guardians were informed about the study protocol and gave their written informed consent to participate in this trial. This sub-study included 4 participants from the study conducted by the University of Bayreuth and 4 participants from the Medical University of Graz who were allocated to the exercise group according to the randomisation.

5.3.1 Eligibility Criteria

Eligibility criteria included male or female individuals aged 10-17 years (both inclusive) with a body mass index (BMI) within the 10th (P10) to 90th (P90) percentile of the respective sex and age of children in Germany (Bayreuth) and Austria (Graz). Participants with a diagnosis of T1D for at least one year (HbA_{1c} < 12% at screening) and with an insulin therapy established either with insulin pen therapy (multiple daily injections) or continuous subcutaneous insulin infusion (pump therapy) were included. All adolescents had avoided recurrent severe hypoglycaemia (defined as >1 severe hypoglycaemic event during the previous 12 months), and demonstrated normal hypoglycaemia awareness (Gold score ≤ 2).[127,168] Significant abnormal ECG, heart rate, or blood pressure at screening or any contraindicative medication were reasons for

non-qualifying to participate in the study. Further exclusion criteria were as follows: the presence or history of a clinically severe disease that could jeopardise the participant's safety or directly influence the study results, clinically relevant hypoglycaemia or diabetic ketoacidosis requiring third-party help during the last 6 months, and any other condition that would interfere with trial participation or evaluation of results as judged by the investigator.

5.3.2 **Study Design**

This is a sub-study of the ChilDFiT1 trial.[167] The ChilDFiT1 study included 10 adolescents with T1D, who received medically supported intensive glycaemic management only (3 times per week for 4 weeks), and 8 participants who additionally performed track and field training 3 times per week for 4 weeks.

At the screening visit, participants and their respective legal guardians were instructed on all study-related procedures. At the pre- and post-intervention laboratory visits, the medical and therapy history were queried. Anthropometric parameters of the participants were assessed via bioelectrical impedance analysis (Inbody 720, Inbody Co., Seoul, Korea; BIACORPUS RX 4004M, MEDI CAL HealthCare GmbH, Karlsruhe, Germany) for body composition and via manual measurement (mobile stadiometer) for body height. Additionally, a venous blood sample from the antecubital vein was obtained. At the screening, a 12-lead ECG (CardioPart 12, Amedtec, Aue-Bad Schlema, Germany) was recorded and a cardiac assessment (blood pressure, heart rate) was performed for safety reasons.

The 4-week track and field intervention phase began the week after the pre-intervention laboratory visit. All participants continuously wore a Dexcom G6 rtCGM and received online or on-site consultations with the study diabetologist 3 times per week. Track and field training was performed every Monday, Wednesday, and Friday afternoon (60 min activity per session) over 4 weeks). Sensor glucose and rates of change (trend arrows) were constantly monitored by rtCGM (Dexcom G6) and documented before, every 15 min during the training session, and 5 min post-exercise. At these depicted time points, simultaneously, BG sampling from the earlobe (BIOSENS S-Line Lab+, EKF-diagnostic GmbH, Barleben, Germany) was performed.

For the exercise sessions, it was anticipated that in concordance with current guidelines for exercise management in T1D[9], the start of exercise is possible if the sensor glucose is between 90 and 270 mg/dl. In the case of lower values, an individual amount of carbohydrates was given orally, documented, and glucose was rechecked. If the sensor glucose exceeded 90 mg/dl, the exercise session was initiated. In case of initial BG exceeding 270 mg/dl, blood ketones were

determined, and insulin correction was applied considering potential bolus insulin still onboard. If blood ketones exceeded 1.5 mmol/l, the exercise session was cancelled for this day [34]. The exercise program mirrored a children's track and field intervention and was based on the framework for the competition program “Kinderleichtathletik”, developed and implemented by the DLV (German Athletics Association).[130] Participation in ≥ 75% of the exercise visits were required not to be excluded from the main ChilDFiT1 study (at least 9 of 12 exercise visits had to be performed). In the week after the last exercise session, the postintervention laboratory visit was performed.

5.3.3 **Statistical Analysis**

Data were collected and summarised in a trial Masterfile in Microsoft Excel version 16.0 (Microsoft Corporation, Redmond, USA) and analysed via Prism software version 8.0 (GraphPad, La Jolla, CA, USA).

Data were tested for normal distribution via Shapiro-Wilk normality test. Descriptive statistics are given as mean ± standard deviation (SD). RtCGM sensor performance was evaluated by comparison of sensor glucose against capillary BG for the same time point by median absolute relative difference (MedARD) analysis (interquartile range) and Bland-Altman method (bias and 95% limits of agreement) for overall glucose values immediately before, during, and after exercise and stratified for glycaemic ranges (hypoglycaemia: < 70 mg/dl, euglycaemia: 70-180 mg/dl, hyperglycaemia: > 180 mg/dl). MedARD for BG ranges, time points, and RoC was tested for significant differences through a linear regression model with patient ID as a fixed offset effect, a Mann-Whitney U test, and a Clarke’s error grid. Statistical significance was accepted at $p < 0.05$ (2-tailed). Comparator data distribution was analysed as proposed by the guidelines for clinical performance evaluation of CGM systems by Eichenlaub et al.[166]

5.3.4 **Bioethical Standards**

The local Ethics Committees of the University of Bayreuth (O 1305/1.GB; December 08, 2021; Germany) and the Medical University of Graz (34-263 ex 21/22, 1070-2022; August 09, 2022; Austria) approved the study protocol.

5.4 Results

In the main ChilDFiT1 study, 10 participants were randomly allocated to the control group (no exercise), while 8 participants were allocated to the intervention group (exercise). A ninth intervention group participant had to be withdrawn from the analysis due to an insufficient amount of training visits. Therefore, all 8 adolescents (2 females) with T1D from the exercise group were included in this sub-study (age 15.5 ±1.0 years, T1D duration 5.8 ±3.8 years, HbA_{1c} 53.0 ±6.6 mmol/mol [7.0 ±0.6%], BMI 21.0 ±2.3 kg/m2, BMI Z-score 0.20 ±0.65, BMI percentile 57.0 ±23.3).[126] Four participants followed an MDI therapy, and 4 participants were on pump therapy. All participants wore the Dexcom G6 rtCGM on the upper arm.

5.4.1 Median absolute relative Difference

Overall, 443 glucose data pairs (CGM and BG) were available (pre-exercise: 82, during exercise: 315, post-exercise: 46). The overall median absolute relative difference (MedARD) for time in range (TIR, 70-180 mg/dl), time below range (TBR, < 70 mg/dl), and time above range (TAR, > 180 mg/dl) as well as pre-exercise (Pre-Ex), during exercise (In-Ex), and post-exercise (Post-Ex) are given in Table 5. The total In-Ex MedARD was 19.4% [12.3-27.8], further detailing an In-Ex MedARD for TIR of 19.1% [12.1-27.2], for a TBR of 28.7% [18.7-35.4] and TAR of 17.4% [11.9-20.5], respectively.

Table 5: Median absolute relative difference (MedARD) and interquartile range (IQR) between interstitial glucose (rtCGM) and reference BG around exercise. „Overall“ summarises Pre-Ex, In-Ex, and Post-Ex values.

Area	rtCGM System Accuracy, Median absolute relative difference** [IQR], in %	*n**
Overall	19.1 [12.2–27.3]	443
TIR		
Overall	22.0 [17.8–29.2]	359
In-Ex	19.1 [12.1–27.2]	252
TBR		
Overall	28.4 [18.8–36.3]	45
In-Ex	28.7 [18.7–35.4]	39
TAR		
Overall	15.9 [9.4–20.7]	39
In-Ex	17.4 [11.9–20.5]	24
Pre-Ex	21.6 [14.5–28.3]	82
In-Ex	19.4 [12.3–27.8]	315
Post-Ex	14.9 [9.0–21.6]	46

*n - number of points of comparison.

**Median absolute relative difference is expressed as a percentage. Median absolute relative difference indicates absolute values of difference and thus ignores the direction of the measurement error but indicates the size of the error expressed as percentage error.

The MedARD [IQR] per participant before, during, and after the exercise sessions can be found in Figure 3, and the overall MedARD, ranges, Q1, Q3, and IQR for the individual participants in Table 6. There were no significant differences between MedARDs for different BG ranges or between Pre-Ex, In-Ex, and Post-Ex.

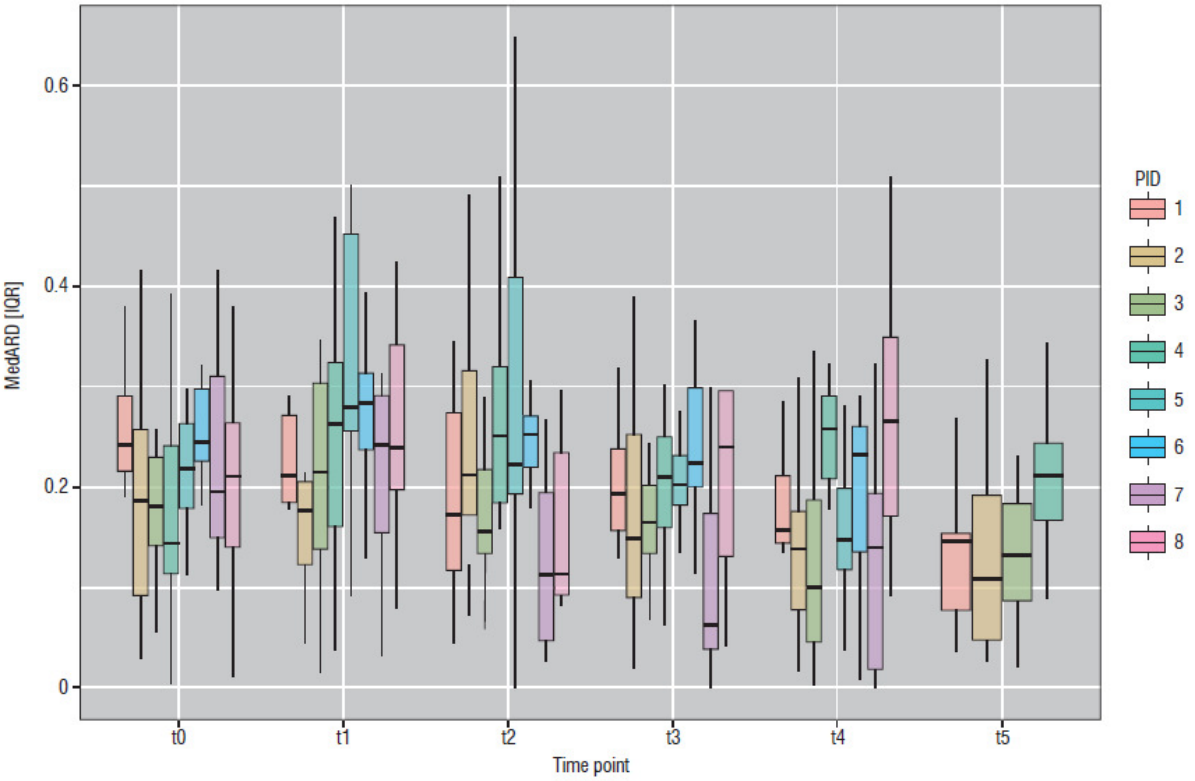


Figure 3: Median absolute relative difference [interquartile range] per participant before (t0), during (t1-t4), and after (t5) the exercise session.

Table 6: Median absolute relative difference (MedARD), range, Q1, Q3, and interquartile range (IQR) between interstitial glucose (rtCGM) and reference BG for the individual participants around exercise.

Participant	1	2	3	4	5	6	7	8
*n**	70	71	69	65	45	43	46	34
MedARD [%]**	19.1	16.6	15.8	22.2	21.5	24.5	16.8	21.4
Range [%]	0.2–45.4	1.6–49.1	0.3–41.3	0.3–56.1	0.0–64.9	0.8–62.1	0.0–47.8	1.1–59.2
Q_1, Q_3 [%]	14.4, 25.5	9.9, 23.4	10.2, 22.6	15.8, 29.2	13.5, 28.0	20.5, 29.7	5.4, 24.3	11.5, 31.4
IQR [%]	11.1	13.5	12.3	13.4	14.5	9.1	19.0	19.9

* *n* - number of points of comparison.
** Median absolute relative difference is expressed as a percentage. Median absolute relative difference indicates absolute values of difference and thus ignores the direction of the measurement error but indicates the size of the error expressed as percentage error.

The overall MedARD for different RoCs (> ±2 mg/dl/min [> ±0.11 mmol/l/min], ±1-2 mg/dl/min [±0.06-0.11 mmol/l/min] and < ±1 mg/dl/min [< ±0.06 mmol/l/min]) are given in Table 7. There were no significant differences between MedARDs for different RoCs.

Table 7: Median absolute relative difference (MedARD) and interquartile range (IQR) between interstitial glucose (rtCGM) and reference BG for different rates of change around exercise. „Overall" summarises Pre-, In-, and Post-Ex values.

Rate of change, [mg/dl/min]***	rtCGM System Accuracy, Median absolute relative difference** [IQR], in %	*n**
> +2		
Overall	33.2 [29.9–40.7]	7
In-Ex	33.9 [31.8–43.8]	6
+1–2		
Overall	19.3 [12.3–25.7]	49
In-Ex	21.2 [14.9–28.2]	30
< ±1		
Overall	18.5 [11.3–24.9]	318
In-Ex	18.4 [11.1–25.2]	225
–1–2		
Overall	24.5 [14.7–32.5]	49
In-Ex	23.7 [15.3–32.5]	39
> –2		
Overall	28.7 [19.7–33.8]	20
In-Ex	31.3 [22.9–36.7]	15

**n* - number of points of comparison.
***Median absolute relative difference is expressed as a percentage. Median absolute relative difference indicates absolute values of difference and thus ignores the direction of the measurement error but indicates the size of the error expressed as percentage error.
****The RoCs were derived from the trend arrows displayed by the rtCGM sensor at each measurement point, reflecting the RoC participants responded to.

5.4.2 Bland-Altman Analysis

The Bland-Altman method derived bias ±SD of bias and 95% levels of agreement for absolute values of glucose (rtCGM to BG) were found to be 28.0 ±25.4 (-21.8, 77.9) mg/dl for TIR, 25.0 ±19.2 (-12.5, 62.6) mg/dl for TBR, and 38.1 ±25.3 (-11.4, 87.7) mg/dl for TAR. The bias amounted to 32.4 ±24.2 (-15.0, 79.7) mg/dl for Pre-Ex, 28.7 ±25.7 (-21.7, 79.0) mg/dl for In-Ex, and 21.6 ±20.3 (-18.2, 61.4) mg/dl for Post-Ex. The respective Bland-Altman plots are presented in Figure 4A-F. The overall bias was found to be 28.6 ±25.0 (-20.4, 77.6) mg/dl (Fig. 4G). Overall, the results in every scenario show a positive bias, indicating an overestimation of BG values by the rtCGM on average.

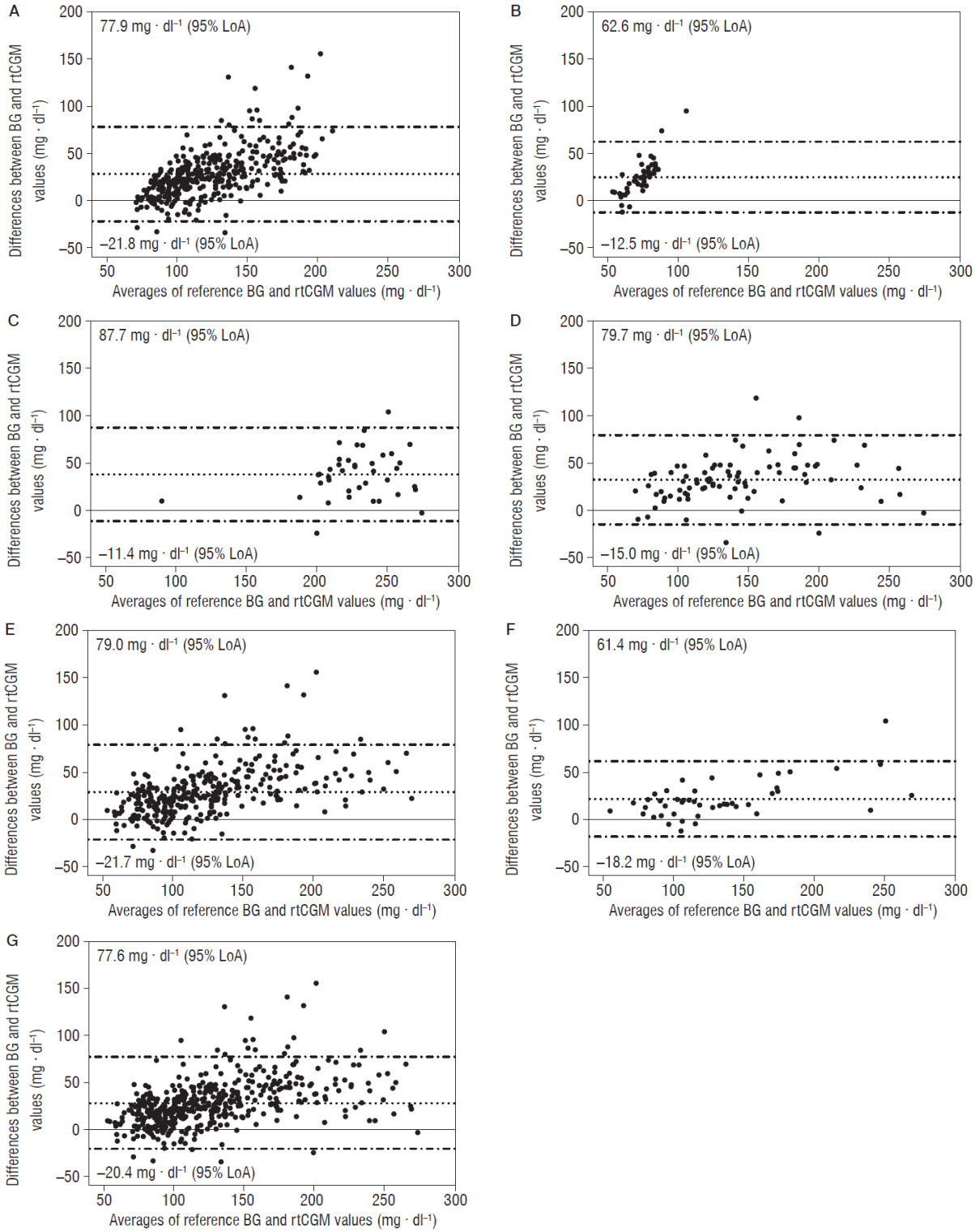


Figure 4: Bland-Altman plots comparing reference glucose and rtCGM values for time in (A), below (B), and above (C) the target range, as well as before (D), during (E), and after (F) exercise and (G) overall.

5.4.3 Comparator Data Distribution

Table 8 shows the definitions of the glucose regions and recommended percentages of RoC-BG data points in each region as proposed by the guidelines for clinical performance evaluation of CGM systems by Eichenlaub et al.[166] Additionally, Table 8 shows the percentage of the present study's CGM values that fell within these regions, and whether or not the guidelines were met.

Table 8: BG-RoC region recommendations for the comparator data distribution [30] and comparison to the percentages achieved by the ChilDFiT1 study.

Region	Definition	Recommended percentage [%]	Percentage achieved in-study* [%]	Recommendation met?
BG low	BG < 70 mg/dl (3.9 mmol/l) Any RoC	≥ 7.5%	2.9%	No
BG high	BG > 300 mg/dl (16.7 mmol/l) Any RoC	≥ 7.5%	0.4%	No
Alert low	BG ≥ 70 mg/dl (3.9 mmol/l) RoC < –1 mg/dl/min (–0.06 mmol/l/min) BG < 70 mg/dl (3.9 mmol/l) within 30 min at current RoC	≥ 7.5%	9.4%	Yes
Alert high	BG ≤ 300 mg/dl (16.7 mmol/l) RoC > +1.5 mg/dl/min (+0.08 mmol/l/min) BG > 250 mg/dl (13.9 mmol/l) within 30 min at current RoC	≥ 7.5%	3.8%	No
IQR [%]	All other RoC–BG pairs	≤ 70%	83.5%	No

* Of the RoC-BG data points measured by the Dexcom G6 rtCGM in study.

5.5 Discussion

This secondary analysis of the ChilDFiT1 study showed that the accuracy of glucose values measured using the Dexcom G6 rtCGM system was lower compared to capillary glucose testing during track and field exercise. With an overall MedARD [IQR] of 19.1% [12.2-27.3], and a clinically relevant in-exercise hypoglycaemia of 28.7% [18.7-35.4], the results clearly showed that trend arrows should be used as a supporting tool during exercise to maintain euglycaemia. When in doubt, additional capillary blood assessment should be performed to ensure glycaemic safety during exercise.

In addition, an overestimation of rtCGM values in comparison to BG reference values was demonstrated by Bland-Altman analysis, which might mask hypoglycaemia and therefore increase the risk of wrong therapeutic decisions during exercise.

In the following, MedARD (Median absolute relative difference) is compared with MARD (Mean absolute relative difference). MedARD is used in the present study due to non-normal

data distribution (Shapiro-Wilk test) and a relatively small sample size (443 glucose data pairs). In this dataset, MedARD offers greater robustness to outliers, better reflecting central tendency and improving interpretability. However, for normally distributed data with larger sample sizes, MARD is preferred for its higher sensitivity to changes.

For children aged 2 to 17 years, the manufacturer Dexcom Inc. reports an overall MARD of approximately 9.3% for the Dexcom G6, which is notably lower than the 19.1% MedARD observed in the present study. However, these values were generated in clinical studies conducted by the manufacturer and were not specifically assessed during exercise, which may account for the discrepancies in other independent studies. In turn, this argument raises the question of why Pre-Ex MedARD values of the present study are worse compared to everyday conditions reported in the literature. Before exercising, physiological stress and adrenaline can cause temporary fluctuations in BG levels. Additionally, pre-exercise strategies such as insulin adjustments and snacks, along with increased physical activity from arriving at the session, can also lead to rapid BG changes, further worsening the MedARD.

For the Dexcom G6 in children and adolescents, Welsh et al.[169] reported an even lower overall MARD throughout the day with 7.7%. This is probably because the clinical trial was also not conducted specifically targeting exercise. Although CGM performance was more accurate than in the ChilDFiT1 study, the following tendencies could be observed: First, performance in hypoglycaemia was reported to be the weakest with a MARD of 13.3%. Second, rapidly falling glucose levels (< -2 mg/[dl·min]) had a worse MARD (11.9%) than all other CGM rate changes, which varied between 7.3% and 7.8% MARD. Rapidly decreasing glucose values thus seem to be more difficult to detect correctly even in a clinical setting.

These tendencies are supported by the study of Nagl et al.[170], conducted in a quasi-real-life setting of a diabetes summer camp for children and adolescents, where overall MARDs of 10.3% for the Dexcom G6 were recorded, which were also significantly higher at 18.7% for hypoglycaemia. While the present study found that the In-Ex MedARD during hypoglycaemia was not significantly worse than in other BG ranges, the clinically relevant MedARD of 28% in this range nonetheless underlines these observations.

The trends observed in the independent studies as well as the clinically relevant result of the present study are directly linked to the reason for the low MedARD values of the rtCGM sensor during track and field. During exercise, people with T1D tend to spend more time in hypoglycaemia, and glycaemic management suffers from high fluctuation rates and rapidly falling BG levels. This is particularly true for children and adolescents, who often have problems with

efficient glycaemic management[5,81], especially in a challenging situation such as exercise. Therefore, exercise has been shown to significantly worsen the performance of the Dexcom G6 rtCGM, which can mainly be attributed to the fact that the diffusion of glucose from the blood-stream to the interstitium has a physiological lag time of 3-12 minutes.[94,163,164]

This is also supported by the study of Dyess et al.[97], where the MARD of the Dexcom G6 rtCGM in adolescents increased from 14% at the beginning of a cycling training to 33% at the end of the exercise session. Furthermore, MARD improved after exercise. This tendency also suggests that the primary challenge for the CGM sensors is the high rate-of-change in glucose during exercise, which is why the MARD or MedARD improves significantly as soon as exercise no longer affects BG.

Comparable tendencies were also found for the FreeStyle Libre 1 isCGM by a previous study of our research group.[95] Here, an overall MedARD of 22.0% [13.9-29.7] and 36.3% [24.2-45.2] during hypoglycaemia for 55 min of moderate-intensity cycling exercise in adults with T1D was observed. Similarly to the present study, an overestimation of CGM glucose values compared to the reference BG was detected (Bland-Altman analysis). Overall, CGM inaccuracy seems to be a challenge resulting predominantly from exercise physiology and only to a limited extent from technological aspects of the specific CGM sensors. As a result, in addition to improved CGM systems, novel approaches to overcome the lag time and reduce the risk of inadequate therapy decisions are necessary. Possible solutions could be an exercise-related algorithm[163,171], the integration of additional physiological parameters[117,172], or faster-acting insulins[16]. However, technological advancements as well as expanded research in multiple areas are necessary to overcome this hurdle completely.[173]

In addition, the study-specific BG-RoC data distribution was compared with the data distribution recommended by the guidelines to test the validity of the accuracy calculations.[166] The recommended 7.5% for glucose values "> 300 mg/dl", "< 70 mg/dl", and "Alert high" as well as the ≤ 70% for "neutral" glucose values could not be achieved in our study. However, it should be emphasised that the aim of this study was to evaluate the accuracy for a specific type of sport - track and field - in real-life conditions. Therefore, only a conclusion about the sensor accuracy in a very specific situation can be made.

In addition to not meeting the glucose area targets, limitations of the present study include the small number of participants. This can be partly compensated by the fact that all participants took part in 9-12 exercise visits, resulting in 443 measurement pairs being evaluated. Further-

more, the absence of Post-Ex values for n = 4 participants due to organizational reasons introduces a bias, resulting in the Post-Ex values appearing artificially better than those obtained Pre-Ex and In-Ex. However, no significant differences were observed between Pre-, In-, and Post-Ex measurements. When working with children and adolescents in real-world settings, organizational challenges may inevitably arise. These hurdles should be considered in future studies. Additionally, to simulate real-world conditions, we did not control insulin dosing, carbohydrate intake, or sensor calibration prior to exercise, which can influence the sensor accuracy.[95] Furthermore, the sampling of capillary BG during exercise visits could reduce the accuracy of the reference values. However, the collection never took place during active movement, so this limitation should be minimal. Additionally, it could be argued that the type of exercise may play a role in the performance of the sensor. This is refuted by the study of Guillot et al., who showed that the Dexcom G6 system showed no significant changes in MedARD across aerobic, resistance, and HIIT exercise.[174]

5.6 Conclusions

In the context of structured track and field training involving adolescents with T1D, the accuracy of the Dexcom G6 system appears reduced across pre-, during, and post-exercise periods. Especially the observation of a clinically relevant 28% MedARD during exercise-related hypoglycaemia and the overestimation of CGM BG values underscores the importance of considering glucose trend arrows and, when in doubt, conducting capillary blood checks to maintain euglycaemia during physical activity.

Linking Statement

The findings of reduced rtCGM accuracy during periods of rapid glucose change have implications beyond glucose monitoring alone. Because CGM data constitute the primary input for automated insulin delivery systems, sensor limitations during exercise may propagate into algorithm-driven insulin dosing errors. Consequently, the third study extends the methodological insights gained from the CGM analysis. It synthesizes current evidence on AID system performance during physical activity, with a focus on the challenges posed by unannounced exercise.

6 (Hybrid) Closed-Loop Systems: From Announced to Unannounced Exercise

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6.1 Abstract

Physical activity and exercise have many beneficial effects on general and type 1 diabetes (T1D) specific health and are recommended for individuals with T1D. Despite these health benefits, many people with T1D still avoid exercise since glycaemic management during physical activity poses substantial glycaemic and psychological challenges - which hold particularly true for unannounced exercise when using an AID system.

Automated insulin delivery (AID) systems have demonstrated their efficacy in improving overall glycaemia and in managing announced exercise in numerous studies. They are proven to increase time in range (70-180 mg/dL) and can especially counteract nocturnal hypoglycaemia, even when evening exercise was performed. AID systems consist of a pump administering insulin as well as a CGM sensor (plus transmitter), both communicating with a control algorithm integrated into a device (insulin pump, mobile phone/smart watch). Nevertheless, without manual pre-exercise adaptions, these systems still face a significant challenge around physical activity. Automatically adapting to the rapidly changing insulin requirements during unannounced exercise and physical activity is still the Achilles' heel of current AID systems. There is an urgent need for improving current AID systems to safely and automatically maintain glucose management without causing derailments - so that going forward, exercise announcements will not be necessary in the future.

Therefore, this narrative literature review aimed to discuss technological strategies to how current AID systems can be improved in the future and become more proficient in overcoming the hurdle of unannounced exercise. For this purpose, the current state-of-the-art therapy recommendations for AID and exercise as well as novel research approaches are presented along with potential future solutions - in order to rectify their deficiencies in the endeavour to achieve fully automated AID systems even around unannounced exercise.

Keywords: closed-loop, artificial pancreas, automated insulin delivery, type 1 diabetes, exercise

6.2 Introduction

Type 1 diabetes (T1D) is one of the most prevalent autoimmune diseases worldwide, with an incidence of 15 per 100,000 people,[175] leading to a destruction of the insulin-producing beta cells in the endocrine part of the pancreas.[30] This entails the need to administer insulin subcutaneously, learn to assess blood and/or interstitial glucose, and adjust the insulin dose based on individual circumstances, e.g. food intake and/or physical activity.[9,176] However, insulin action is influenced by multiple variables including insulin dose and type, timing of administration, meal composition, body composition, etc., that must be considered when therapy decisions are made.[111] Furthermore, exogenous insulin does not exactly mimic physiological insulin action, leading to challenges, including delayed onset of action and the inability to downregulate systemic insulin levels. Moreover, the inverse relationship between glucagon secretion and insulin is diminished over time, which increases the risk of hypoglycaemia.[1] Taking this together, glucose regulation is extremely complex for people with T1D.

Regular physical activity and exercise provoke many beneficial effects as shown in numerous studies, for example, reduction of all-cause mortality, improvement of lipid profiles, lowering resting heart rate (HR) as well as systolic blood pressure, and decreasing depression and anxiety symptoms in all population groups.[57,124,136] Furthermore, studies in people with T1D showed that the total daily insulin dose can be reduced by exercise[57,177], and those who are more physically active face a lower risk of being overweight or obese.[178] Even in the younger population with T1D, it is shown that time in range (TIR; 70-180 mg/dL)[13] is highest during days with more physical activity.[125]

Despite these health benefits, many people with T1D still avoid exercise since acute glucose management is substantially challenging[5], especially if performed spontaneously, and this requires individualized adjustments around physical activity.[9] Even minor errors in glucose management around exercise can lead to serious acute and long-term complications. Acute exercise-induced complications in people with T1D can range from mild symptoms disrupting ongoing activity to severe hypoglycaemia and ketoacidotic derailments, which can be potentially life-threatening[42], contributing to a sustainable burden on health and psychological status.[3] Bohn et al. (2015) even showed in their study that the highest risk of severe hypoglycaemia is among people who are most physically active.[178] As a result, fear of hypoglycaemia and losing glycaemic control seems to be the major barrier for many individuals with T1D to engaging in regular exercise.[5,12]

To overcome these challenges, more and more people with T1D are now using automatic insulin-delivery systems (AID), which are highly efficient in managing the delayed risk of post-exercise and nocturnal hypoglycaemia, specifically.[16,179] AID systems consist of a pump administering insulin as well as a continuous glucose monitoring (CGM) sensor (plus transmitter), both communicating with a control algorithm integrated into a device (insulin pump, mobile phone/smart watch) and were shown to improve the quality of therapy.[78,180] However, when observing the improvements in AID systems, one might ask the question, why physical activity and exercise are still the Achilles' heel of these devices, especially as evidence supports the benefits of a physically active lifestyle?

To ensure spontaneous physical activity and exercise in T1D, there is an urgent need to improve current AID systems so that they could safely and automatically maintain glucose management without derailments - even during unannounced exercise. Therefore, in this narrative literature review, we aimed to discuss technological strategies to how current AID systems can be improved and become more proficient in overcoming the hurdle of unannounced exercise.

6.3 Materials and Methods

For this narrative review, a non-systematic literature search was conducted in the PubMed database between June 2022 and May 2023, including publications appearing online up to May 2023. Accessibility in PubMed was defined as including a link to purchase the article or open access. The following keywords were used for the search: closed-loop, hybrid closed-loop, artificial pancreas, automated insulin delivery, type 1 diabetes, and exercise. Each title and abstract were screened and key articles meeting the eligibility criteria were included, which encompasses original articles in either English or German assessing AID systems and exercise. Following this initial article screening, references in key articles were also explored to provide more information on the different opportunities for improvement of the AID systems which, as they are future transfer opportunities, may not have been considered in the initial article screening due to the limitation to exercises. We then repeated the review of references one more time, to incorporate articles on more specialized technological studies and advancements. Furthermore, to obtain up-to-date information on the available AID systems, information was obtained from the official manufacturers' websites.

6.4 Type 1 Diabetes and Exercise

6.4.1 Physiological Background of T1D and Exercise

Exercise as planned, structured, and repetitive physical activity[181] leads to skeletal muscle contraction and therefore higher energy demand, which is primarily supplied by glucose.[182,183] In people with T1D, insulin cannot be suppressed after application, leading to an elevated risk of hypoglycaemia around exercise through increased glucose uptake and insulin sensitivity.[73,184,185] On the other hand, although glucagon response to hypoglycaemia is blunted a few years after disease onset, the responses of counterregulatory hormones to intense exercise are still available, potentially raising blood glucose.[73,179] Therefore, depending on the exercise, the individual glycaemic response can vary significantly, making the therapy management even more difficult[7,9] - especially if exercise is performed spontaneously.

The glycaemic response to exercise is primarily determined by circulating insulin levels, the location of insulin delivery, pre-exercise blood glucose levels, recent meal composition as well as exercise type, intensity, and duration.[74]

In general, exercise types can be categorized into aerobic, anaerobic and strength-based training, depending on its main energy supply. Aerobic exercise typically involves sustained, low- to moderate-intensity activity utilizing aerobic energy systems and large muscle groups (e.g. swimming, walking). Aerobic exercise mainly causes a decrease in glucose levels in individuals with T1D[143] due to the high muscular glucose uptake and low-stress hormone levels.[5] Longer duration of aerobic exercise, higher intensity, higher fitness status, more insulin on board, and lower pre-exercise glucose concentration result in a further reduction in blood glucose (BG) levels and in increased reliance on carbohydrate sources.[7,72,186]

Anaerobic training mainly covers high-intensity training (HIT), where local lactate production exceeds systemic lactate clearance, inducing the need for rest.[69] Therefore, HIT continuous exercise sessions get separated into intervals of rest and exercise, resulting in high-intensity interval training (HIIT). Also, during resistance training, energy is mainly provided via anaerobic pathways[67], even though total energy needs are mostly lower.[181] To summarize for HIT, HIIT, and resistance training, increased counterregulatory hormone levels lead to either stable or increasing glucose levels, depending on exercise duration respectively number of intervals, exercise intensity, insulin concentration, lactate concentration, fitness, nutrition and initial glucose levels.[7,9,65,73,75,143,184]

However, most exercise activities include a combination of energy systems and reactions to exercise depend on numerous additional variables like time of the day, prandial status, personal risk of hypoglycaemia or type of insulin used, etc.[57,136], meaning all glycaemic responses to exercise in people with T1D are highly individual, posing a complex challenge for AID systems.

6.4.2 **Recommendations for Exercise with Insulin Pump Therapy or AID**

Exercise without adjustments in insulin dose and/or carbohydrate intake might induce severe dysglycaemia.[12,178]

For those using AID systems, the EASD/ISPAD position statement can be used as a basis for understanding CGM and exercise[9,76], and Zaharieva et al. summarized additional strategies, exercise targets, and settings around planned and unplanned/spontaneous exercise, supporting users to individualize their therapy around exercise and to counteract potential exercise risks.[78] One potential risk, especially for low to medium intensity aerobic exercise, is exercise-induced hypoglycaemia during and up to 11 hours after exercise.[3,12,184] Potential strategies to counteract exercise-induced hypoglycaemia could be setting the individualized exercise target 1-2 hours in advance (or analogue: lowering basal insulin rates approximately 90 minutes to 2 hours before exercise by up to 80%.[9,64,73]) and/or reduce mealtime bolus insulin 1-3 hours before planned exercise.[7,66,78,107,180,187] Potential strategies for unannounced exercise are carbohydrate consumption before/during exercise, insulin pump suspension at exercise onset or leaving the usual AID setting with no changes for exercise.[78,107] To ensure the safety of the last strategy, AID systems must optimize their performance for unannounced physical activity. To counteract the risk of post-exercise hypoglycaemia, extending the exercise target for 1-2 hours into post-exercise recovery, setting an overnight post-exercise target or reducing post-exercise meal bolus can be helpful[7,66,78,107,180,187] (analogue: lower basal rates under post-exercise conditions by about 10-30%[69,184,185]). However, most AID systems manage overnight glycaemia already really well.[16,179]

Next to hypoglycaemia, another risk can be exercise-induced hyperglycaemia, especially when performing pre-prandial, high-intensity exercise or resistance exercise. Here, one potential approach is to maintain the regular AID's glucose target without modification, as increasing it could result in notable hyperglycaemia.[78] However, this relies on multiple variables and needs to be cautiously individualized based on the person's experience.[3,9]

Moreover, when implementing countermeasures such as personalized carbohydrate intake and insulin adjustments, factors like meal timing and quantity, insulin on board, and individual experiences must also be considered.[9,64,69,188]

Additionally, based on the fact, that especially different types, modes and intensities of exercise result in different glucose responses, additional "bonus exercise targets" may support people with T1D achieving their individualized glucose goals around exercise. Furthermore, based on the insulin on board (IOB), personalized and variable glucose targets may support the opportunity to engage into more spontaneous exercise. Taking this into account, for exercise where an increase in glucose levels is anticipated a lower glucose target with a more aggressive insulin dosing may stabilize glucose levels and vice versa, for exercise with expected decreasing glucose levels, the glucose target might be set at a higher level. For fully AID and exercise, this would mean, that for example based on a high amount of IOB, glucose target around exercise is set automatically higher and, in contrast, when massively increasing glucose levels are often detected around exercise for a specific person, the exercise glucose target might be in general lower.

Overall, these strategies can provide support for people with T1D around exercise, however, following all recommendations in detail might be intricate. Therefore, future AID systems should integrate the entire evidence and knowledge about T1D and exercise.

6.5 Current AID Systems and Exercise

AID systems are improving the clinical management of T1D and have shown significant technological advances in recent years.[90,189] However, improvements in different AID systems are associated with different algorithms, software, and hardware, making it more and more difficult to find "the right AID for the right person".

6.5.1 Definition and Technological Fundament

AID systems aim to mimic the endocrine physiology of the pancreas and are also called 'artificial pancreas' (AP). These systems consist of a pump administering insulin and in some cases glucagon (not approved yet), as well as a CGM sensor plus transmitter (integrated or separated), both communicating with a control algorithm integrated into a device (insulin pump, mobile phone/smart watch). The algorithm reacts in real-time to changes in sensor glucose (SG) levels and adjusts insulin delivery in a pump that delivers insulin subcutaneously in small boluses to keep SG levels within a flexible target range.[16] There are two main types of algorithms: model

predictive control (MPC) and proportional-integral-derivative (PID). MPC algorithms use a mathematical model, simulating the user's glucoregulatory system to predict glucose fluctuations and adjust insulin delivery to treat-to-target or treat-to-range while taking insulin sensitivity into account. PID algorithms adjust the AID using the difference between measured and targeted glucose levels (proportional element), the area under the curve of said difference (integral element), and the rate-of-change over time in glucose levels (derivative element).[190]

Based on the level of automation, the Juvenile Diabetes Research Foundation (JDRF) defined six categories of AID systems (Fig. 5).[191]

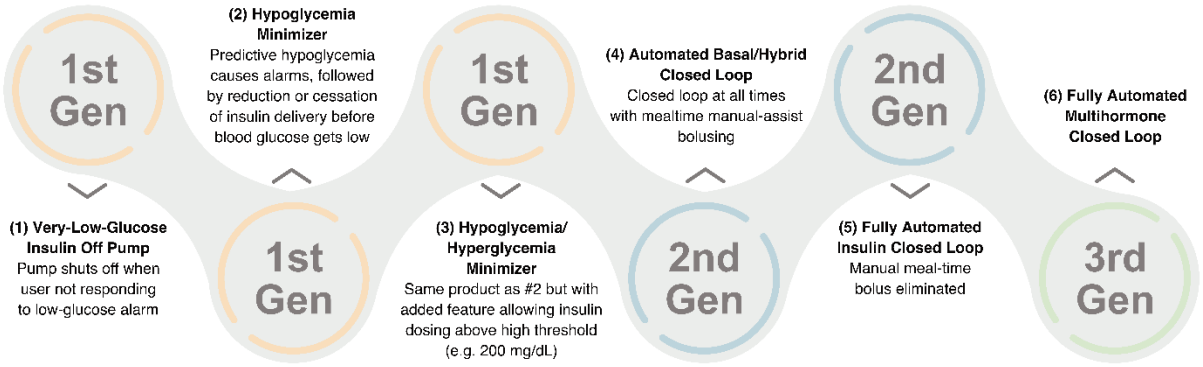


Figure 5: Categories of artificial pancreas systems, content based on artificial pancreas project plan by the JDRF[191,192], graphically modified (copyright JDRF).

All commercially available systems only deliver insulin and are therefore single-hormone AID systems.[192,193] Furthermore, for all obtainable systems, manual meal boluses are essential, which categorizes them as hybrid closed-loop systems (HCL systems).[90] Using the JDRF's model, today's technology represents the second generation or stage 4 of 6 48.[191]

6.5.2 AID systems and Exercise

Some general benefits of using AID systems are a higher TIR, less time below range (TBR; <70 mg/dL), reduced glycaemic variability, lower mean glucose (GMI or HbA_{1c}), and psychosocial benefits.[16,100,103,112,194–202] Furthermore, clinical trials showed that today's HCL systems can achieve improved TIR during exercise[179,203–205] - even if corrections in case of rapidly changing glucose levels still have to be performed.

In 2017, a randomized controlled trial (RCT) by Dovc. et al. showed that glucose control with a CL system during and after physical activity resulted in higher TIR (84.1% vs. 68.7%), lower bolus insulin requirement, and fewer hypoglycaemic events than with an open-loop (OL) sys-

tem.[101] A systematic review and meta-analysis by Eckstein et al. (2021) involving 152 participants demonstrated a superiority of 9.46% higher TIR during exercise for children and adolescents and 1.07% for adults on HCL therapy compared to standard of care (SOC).[149] In addition, as shown by Lee et al. (2020), today's AID systems are already excellent at minimizing the risk of nocturnal hypoglycaemia after exercise, even with impaired awareness of hypoglycaemia.[16,179] Overall, literature evidence illustrates the tendency that higher system autonomy improves glucose control around exercise and that, compared with current CSII therapy, CL systems improve TIR and decrease hypoglycaemic events in various exercise and post-exercise settings.[118,151,206,207] However, despite the excellent performance of AID systems around exercise, one Achilles' heel of these systems remains: hypoglycaemia around unannounced exercise.

An RCT by Viñals et al. (2021) used an HCL glucose-controller with carbohydrate recommendations for the user during and after unannounced (CLNA) and announced (CLA) exercise, comparing both outcomes with OL-therapy. The TIR was 91.9% for CLA, 87.8% for CLNA, and 81.1% for OL, whereby 3 (CLA), 4 (CLNA) and 8 (OL) hypoglycaemic events occurred.[208] Thus, while the AID system was able to handle the unannounced exercise well and performed significantly better than the OL, the results are still more efficient when the exercise is announced. Likewise, an RCT by Tagougui et al. (2020) compared announced exercise with (A-RB) and without (A-FB) bolus reduction with unannounced exercise (U-FB) in an HCL system. TBR up to 1-hour post-exercise was lowest in A-RB (2%), followed by A-FB (7%) and U-FB (13%). The TIR was highest in A-FB with 59.0% (U-FB 49.2%, A-RB 36.5%). Thus, the CL system seems to maintain TIR relatively well even during unannounced exercise.[107] However, the focus during exercise should be on preventing hypoglycaemia, where there is still a considerable need for improvement in AID systems during unannounced exercise. This issue was also evident in an AID study conducted by Elleri et al., in which 73 adolescents with T1D experienced substantial hypoglycaemia when engaging in unannounced exercise.[149] Furthermore, the study by Tagougui et al. highlighted another weakness of current AID systems that makes the announcement of exercise still necessary: the prandial status. A fully automated AID system would need to detect whether post-absorptive or post-prandial exercise is being pursued and perform postprandial pre-exercise bolus reduction to optimally prevent hypoglycaemia.[16,107] Furthermore, existing systems are not able to automatically detect the onset, type, intensity, or duration of exercise, or respond with appropriate countermeasures instantly. Additionally, current systems lack the ability to define intraindividual target values for various exercise types,

which can be additionally customized based on exercise phase (pre- or post-exercise) and prandial status. A singular or a small selection of exercise targets can never adequately address all these factors. As a result, unannounced exercise is still a major hurdle for current HCL systems and can lead to significant glycaemic fluctuations without manual adjustments. Finding new strategies to improve HCL performance around unannounced exercise is therefore an urgent need to be addressed.

6.5.3 **Commercially available HCL Systems**

There are numerous possible combinations of CGMs, insulin pumps, and algorithms (Fig. 6).[209] Particular attention should be paid to the control algorithm, as it serves as a link between the CGM and the insulin delivery system, thus regulating the AID.

Medtronic - MiniMed

Commercially available by Medtronic plc. (Northridge, CA, USA) are the MiniMed 670G, 770G, and 780G systems.[16] The most recent system, the MiniMed 780G HCL, measures SG levels every 5 minutes, allowing continuous auto-basal and auto-corrective bolus administration up to every 5 minutes.[210] A temporary target (Temp Target) of 150 mg/dL (8.3 mmol/L) can be set for exercise. If low SG is predicted within the next 4 hours (e.g. through exercise), the internal algorithm adjusts the auto-basal and auto-corrective boluses until it detects no further risk of hypoglycaemia.[210,211]

In an RCT by McCarthy et al. (2023), adults with T1D used the MiniMed 780G around 45 min of moderate intensity continuous exercise. The TBR during (23% TBR) and 1h post (56% TBR) unannounced exercise was significantly increased compared to announced exercise. Furthermore, a 25% bolus reduction 90 min pre-exercise reduced TBR during (1% vs. 8%) and post-exercise (2% vs. 29%) even more compared to a bolus reduction 45 min prior to exercise.[76] Additionally, an RCT by Dovc. et al. (2023) showed for a period of 4 weeks that with the MiniMed 780G high TIR (>70%) and low time above range (TAR >180 mg/dL; <25%) and TBR (<3%) can be achieved in children and adolescents during and after exercise, if exercise is announced at least 60 min in advance.[212] Overall, unannounced exercise is unfortunately a problem for the MiniMed 780G and careful planning of exercise is still necessary.

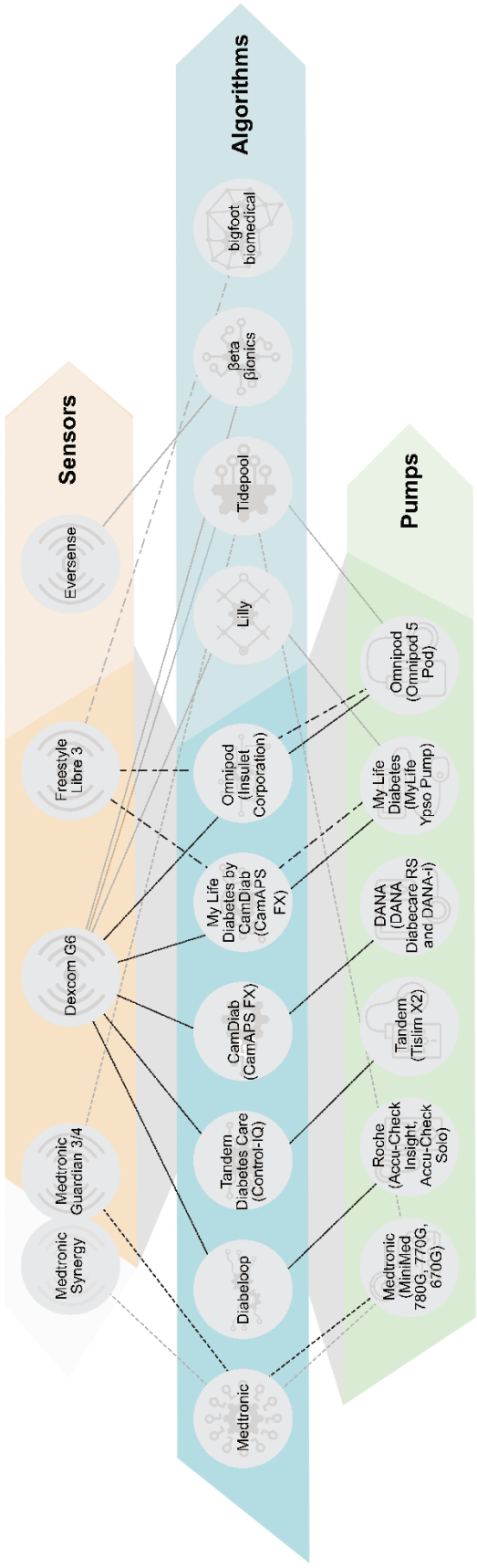


Figure 6: Currently available HCL Systems. Backed with bold color: Commercially available systems. Based on: Overview of commercial loop systems by nerdabetic[185].

CamDiab - CamAPS FX

CamAPS FX is an Android app by CamDiab Ltd. (Cambridge, UK). For the setup, the app requires the total daily dose (TDD) and the user's body mass (BM) to calculate the insulin sensitivity factor (ISF) and active insulin time. Based on ongoing calculations, extended boluses are administered every 10 to 12 minutes, thereby automatically adjusting to SG levels. The glucose target can be manually raised between 80 - 200 mg/dL (4.4 - 11.1 mmol/L) for exercise. It also offers a "Boost mode", when more insulin is needed, and an "Ease-off mode", when less insulin is required, which can both be useful during and post-exercise.[213–215] Unfortunately, however, no specific exercise studies on CamAPS are currently available.

Tandem Diabetes Care - Control-IQ22

The Control-IQ22 is an algorithm within the Tandem t:slim X2 insulin pump (Tandem Diabetes Care Inc., Sun Diego, CA, USA) and was the first "stand-alone" interoperable automatic glycaemic controller approved by the FDA in 2019.[151,216] For setting Control-IQ up, the user's BM and TDD are needed. It has three activity protocols: "standard", "sleep" and "exercise", whereby the algorithm keeps SG between 140 - 160 mg/dL (7.8 - 8.9 mmol/L) for exercise.[151,216] The algorithm tries to predict glucose levels 30 minutes ahead and adjusts insulin delivery accordingly.

For a 72h ski camp, Schoelwer et al. (2020) showed that the Control-IQ can manage TIR (>70%) as well as TBR (<3%) in 12-18 years old very well.[217] Furthermore, Ekhlaspour et al. (2019) demonstrated that the use of the Control-IQ improved TIR and safely reduced exposure to hyperglycaemia relative to CC in paediatric patients (6-18 years) with T1D during prolonged intensive winter sport activities.[151] However, in both studies, the exercise was announced and appropriate countermeasures such as CHO consumption were given manually.[151,217] Also in a 48-hour outpatient supervised hotel setting with daily 30-minute exercise requirements, the Control-IQ system was found safe and effective in improving glycaemic control for 2-5-year-old children with T1D.[102] Nevertheless, the study's brevity and limited exercise conditions necessitate further research, especially in unannounced and real-life exercise scenarios.

Diabeloop - DBLG1

The DBLG1, a handset by Diabeloop SA (Grenoble, France), hosts the algorithm, connecting CGM and insulin pump via Bluetooth.[218] Four values are needed to set the device up: BM, TDD, meal ratios, and safety basal rate profile. Customizable parameters like the glucose target,

adjustable between 100 - 180 mg/dL (5.6 - 10 mmol/L), hypo- and hyperglycaemia thresholds, and aggressiveness can be set to individual preferences for exercise.[218,219]

An RCT by Franc et al. (2021) demonstrated that over 12-weeks with DBLG1 under real-life conditions, the daily TBR was not significantly different between days with and without physical activity (2.0% vs. 2.2%), regardless of intensity or duration. However, physical activity was announced, whereby insulin adjustments as well as preventive CHO recommendations were made in advance by the algorithm.[220] DBLG1 can therefore ensure safety for announced exercise. In addition, it was shown that DBLG1 as a CL variant could achieve tighter glycaemic control than OL even on days with gastronomic dinners or sustained physical exercise.[221,222] However, specific studies with unannounced exercise still need to be performed.

Insulet Corporation - Omnipod

The Omnipod 5 (Insulet Corporation, Acton, MA, USA) is the only tubeless AID system using pods, which can be worn continuously for up to 72 hours.[223] The design removes the need for tubing to connect the insulin pump to the body, which may offer more freedom and flexibility for users. For example, when properly placed, the waterproof capabilities of the Omnipod 5 AID system could enhance glycaemic control even during aquatic activities like swimming.[224] Furthermore, the Omnipod 5 is specifically designed to control the pump and monitor glucose levels using a mobile app. The Omnipod 5 receives the CGM data every 5 minutes and aims to predict glucose levels for 60 minutes. The algorithm then adapts the AID by using the customizable glucose target of 110 - 150 mg/dL (6.1 - 8.3 mmol/L) and by incorporating trend data in their “SmartBolus Calculator”. For exercise, the total recommended bolus amount may be increased by up to 30% or decreased by up to 100% (zero boluses) and an exercise target of 150 mg/dL (8.3 mmol/L) can be set.[223,225] Forlenza et al. (2019) conducted a supervised 54-h study in adults in a hotel setting, where two moderate intensity exercise sessions of >30 min duration on consecutive days were held. The Omnipod performed well and safe over the whole study period (TBR <2%, TIR >80%).[206] 2020, Sherr et al. demonstrated that during 96-h supervised free-living conditions including daily physical activity and unrestricted meals, the Omnipod HCL system reduced TBR in adults and increased TIR in adolescents and children significantly compared to their CC.[226] However, in both trials exercise was announced and temporary raised glucose targets or reduced basal rates were set manually in advance.[206,226]

Beta Bionics - iLet Bionic Pancreas

The Insulin-only version of the iLet Bionic Pancreas is the first FDA approved (2023) AID system (Beta Bionics, Concord, Massachusetts, USA), which fully applies the insulin dose. Real-world studies over 13 weeks have shown that the iLet Bionic Pancreas can improve glycaemic management in terms of convenience and efficacy compared to current standard of care (SOC) in adults (significantly improved HbA_{1c} without increasing TBR)[227] and in 6-17 years old (improved HbA_{1c}, TIR, and hyperglycaemic metrics without increasing TBR)[228]. Exercise was also performed during these 13 weeks; however, no exercise-specific studies are currently available.

DIY Options

In addition to the already mentioned products (Tab. 9), there are also various DIY and open-source variants as well as devices currently in the clinical trial phase[16]. Tidepool Loop is a fully interoperable AID app, which is already FDA approved (2023), and represents a user-led community project created in collaboration with medical device partners and organized by the Tidepool Project, a non-profit organization[229]. It is compatible with various CGM and pump systems and highly customizable, including key factors for exercise e.g. pre-exercise glucose level or individualized exercise glucose targets[229,230]. Currently, no exercise-specific trials are available for Tidepool. However, a hypoglycaemia risk model based on Tidepool data from 6448 physical activity sessions of 50 individuals with T1D for in- and post-physical activity has already been developed after their FDA approval[231], which also illustrated the rapid technological progress that may be possible through these open DIY systems. Overall, DIY systems in general may enable highly flexible diabetes management, algorithm transparency and can provide impulses for technological progress, but have to be used and customized with appropriate expertise[219].

Table 9: General information on the current generation of commercially available HCL systems.

HCL system	Medtronic - MiniMed[232–234]	CamDiab - CamAPS FX[213–215]		Tandem Diabetes Care - Control-IQ22[151,216,235]	Diabeloop - DBLG1[219,236]	Insulet Corporation - Omnipod 5[223,225]
Company	**Medtronic plc.**	**CamDiab Ltd.**		**Tandem Diabetes Care Inc.**	**Diabeloop SA**	**Insulet Corporation**
Sensor	**Guardian 3/4 (09/2023: Synergy)**	**Dexcom G6**	**FreeStyle Libre 3**	**Dexcom G6**	**Dexcom G6**	**Dexcom G6, FreeStyle Libre 3**
Pump	**MiniMed 780G**	**Mylife YpsoPump**	**DANA Diabecare RS and DANA-i**	**Tandem T:slim X2**	**Accu-Chek Insight, Accu-Chek Solo**	**Omnipod 5 Pod**
Algorithm	**Advanced Hybrid Closed-Loop** (by Medtronic) PID + insulin Feedback and elements of MPC	**Smartadapt** (Mylife Diabetes by CamDiab) Treat-to-target adaptive MPC (advanced adaptive hybrid algorithm)	**Apidra DCL** (by CamDiab)	**Control-IQ** (Tandem Diabetes Care by Dexcom) Treat-to-range predictive MPC	**Integrated Personalised Diabetes Management (iPDM)** Treat-to-target MPC	**Horizon** (by Omnipod) "SmartAdjust" technology Treat-to-target MPC
Hardware	Pump (Smartphone as passive display)	Pump or Smartphone (Android only)	Pump or Smartphone	Pump (Smartphone only in the USA)	Pump or Smartphone	Smartphone (Samsung only)
Insulin	**Rapid-acting** (Humalog, NovoLog, NovoRapid	**Ultra-rapid and rapid-acting** (NovoRapid, Humalog, Apidra, Fiasp, Lyumjev; Insulin lispro Sanofi)		**Rapid-acting** (NovoRapid, Humalog)	**Rapid-acting** (NovoRapid, Humalog)	**Rapid-acting** (NovoRapid, Humalog, Admelog)
Commercially Available*	Globally	Globally (except USA)		Globally	Europe	Globally (Europe: only in UK)
Glucose Target	100, 110, 120 mg/dL (5.5, 6.1, 6.7 mmol/L)	80 - 200 mg/dL (4.4 - 11.1 mmol/L)		112.5 - 160 mg/dL (6.2 - 8.9 mmol/L)	100 - 180 mg/dL (5.6 - 10 mmol/L)	110 - 150 mg/dL (6.1 - 8.3 mmol/L)
Bonus Targets and Exercise Options	Exercise: 150 mg/dL (8.3 mmol/L)	Boost: when more insulin is needed Ease-off: when less insulin is needed		Sleep: 112.5 - 120 mg/dL (6.25 - 6.7 mmol/L) Exercise**: 140 - 160 mg/dL (7.8 - 8.9 mmol/L)	hypo- and hyperglycaemia thresholds	Exercise: 150 mg/dL (8.3 mmol/L)
Adjustable Settings (maybe supportive for exercise)	insulin to carbohydrate ratio (ICR), active insulin time, glucose target	ICR, glucose target		ICR, ISF, target range	TDD, glucose target, hypo-/hyperglycaemia thresholds, aggressiveness	ICR, glucose target, ISF, active insulin time
Non-adjustable Settings	Basal rates, ISF	Basal rates, active insulin time, ISF		Active insulin time (5 hours)	Basal rates, ICR, ISF	Basal rates

Data Sharing	MiniMed mobile App, Carelink	Diasend, Dexcom Share***	Tidepool, manual download for pump, Dexcom Share***	YourLoops, Dexcom Share***	PodderCentral + Glooko, Dexcom Share***
Additional Features	Overall learning: 48h warm-up period in manual mode required; safe meal bolus feature	Overall, prandial, and diurnal adaptive learning			Up to 8 segments of insulin targets may be programmed based on time of day

* refers only to the commercial availability; whether as well as which system version is approved by the respective country, has to be checked in each individual case
** availability depending on the latest software version accepted in the respective country
***only display of glucose values

6.6 From Announced to Unannounced Exercise

Several hurdles currently complicate unannounced exercise in AID systems. The following technological strategies (summarised in Fig. 7) could make the step from announced to unannounced exercise possible.

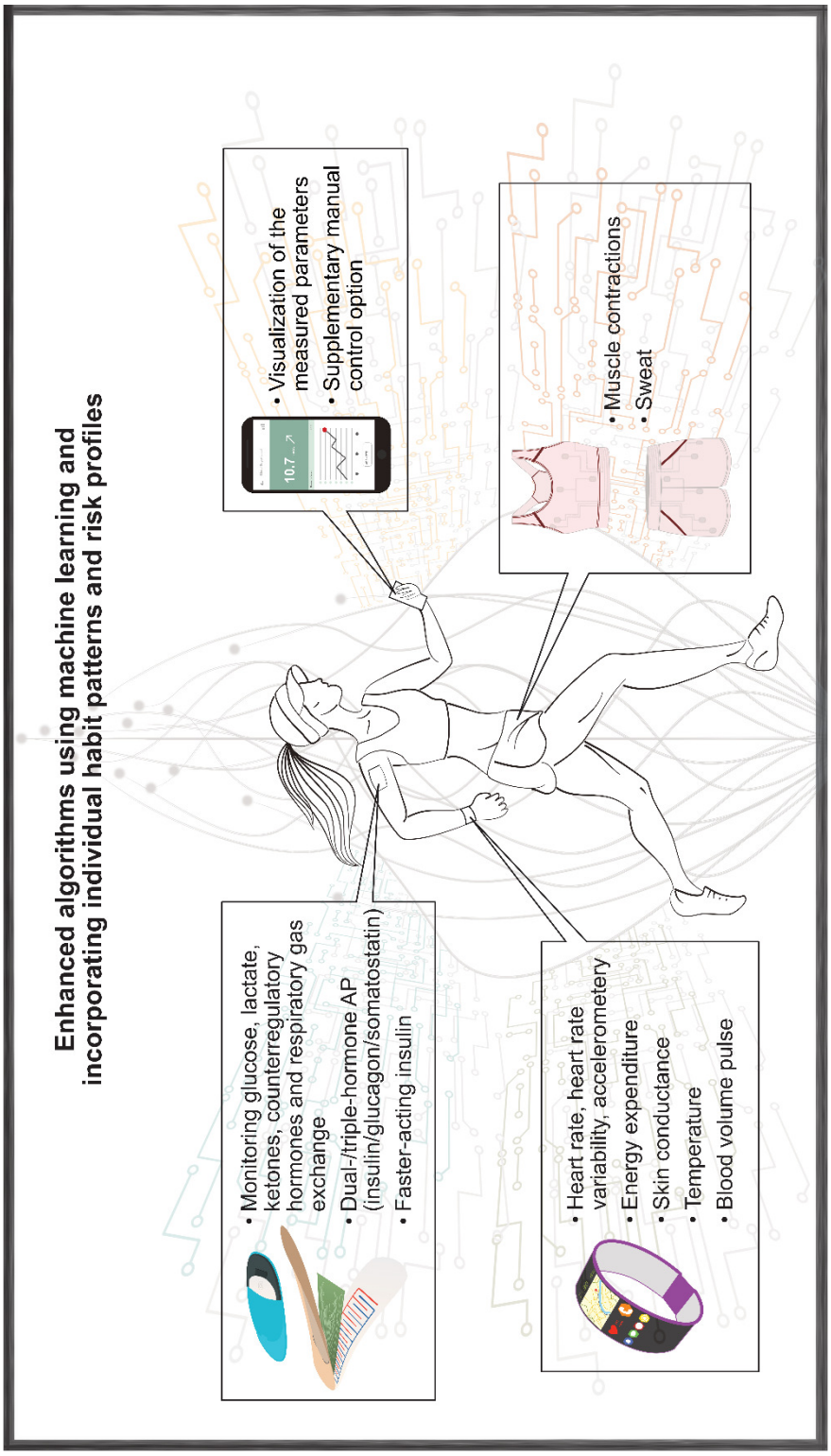


Figure 7: Summary of potential approaches to progress from announced to unannounced exercise, incorporated into one CL system.

6.6.1 **Faster-Acting Insulins**

One of the major hurdles for AID systems during exercise is the delayed onset of exogenous insulin, as insulin is administered into the subcutaneous fat tissue. In individuals without T1D, insulin is secreted directly into the portal circulation, where it has an on- and offset time of only up to a few minutes[16]. In people with T1D and subcutaneous administration, the on- and offset periods are depending on the type of insulin. The time to reach half-maximal concentration is 13 minutes for ultra-rapid lispro (Lyumjev; commercially supported only by CamAPS), 19 min for Fiasp, 26 min for Humalog, and 27 min for NovoRapid[110], with most pumps using rapid-acting insulin (Tab. 9). Furthermore, insulin levels remain elevated for a prolonged time after infusion. Even Lyumjev, the most rapidly subsiding insulin, does not return to baseline until about 4 hours after administration[110]. As a result, not setting exercise glycaemic targets in advance creates a significant risk for hypoglycaemia.[5] Overall, despite the still substantial delay in action, ultra-fast insulin seems promising[110], although it remains to be investigated whether postprandial physical activity timing could impact possible risks due to shorter onset-time. However, in adults, faster acting insulin has been shown to significantly reduce hypoglycaemia within the first 24 h after spontaneous exercise with a regular dose of faster acting IGlar U300 compared to standard IDeg U100[237]. Furthermore, Dovc et al. (2023) demonstrated that glycaemic outcomes in paediatric patients using hybrid AID during exercise or postprandial periods were similar for faster-acting and standard insulin aspart, with no instances of severe hypoglycaemia or ketoacidosis observed[212]. Still, algorithm adjustments are necessary to optimize postprandial exercise and CL scenarios, as the current algorithms are primarily tailored for standard insulins[238]. Overall, these favourable results observed with rapid-acting insulin formulations instil optimism regarding the absence of supplementary risks associated with postprandial exercise when using ultra-fast insulin. However, ultra-fast insulin still needs to be made accessible to more systems than CamAPS.

Consequently, insulins with more favourable pharmacokinetic characteristics could manage the potential risks of dysglycaemia around exercise more efficiently through a quicker reaction to rising glucose levels and through faster offset better avoidance of hypoglycaemia. Therefore, the need for counterregulatory measures like carbohydrate consumption or stopping exercise would be minimized.

Another step in the right direction may have been taken recently through a novel U500 insulin aspart formulation (AT278 U500). In this trial by Svehlikova et al., compared to insulin aspart (IAsp U100), the glucose-lowering effect with AT278 U500 was 8.9-fold higher within the first 30 min

and reached 50% of maximum concentration 23 min faster, which might make this a soon accessible game changer in insulin therapy[239].

Further solutions to this effect delay could be nasal insulin[240], continuous intraperitoneal insulin infusion[241–243], or intravenously delivered insulin[244], enabling a more rapid response to hyperglycaemia. Nevertheless, due to technical barriers, invasiveness, and infection risks, this cannot be recommended for AID systems.

6.6.2 **Dual- and Triple-Hormone Systems**

Even though the response of glucagon, a direct antagonist of insulin, to exercise is impaired in people with T1D[179,205], available HCL systems cannot counteract low glucose levels except by lowering the insulin rate. Thus, a development towards dual- or triple-hormone AID systems is an option. Counterregulatory mechanisms would enable them to react quickly to falling glucose levels by actively raising BG.

Already in 2016, an RCT by Taleb et al. showed that dual-hormone (DH)AID (with glucagon) outperformed single-hormone (SH)AID (TBR 0% vs. 11%, TIR 100% vs. 71.4%) in regulating glucose levels during announced exercise in adults with T1D. In addition, it was found that increased amounts of glucagon were required during continuous exercise compared to interval exercise - which is extremely relevant for future algorithms. No adverse effects were reported in any of the interventions[245]. Wilson et al. (2020) demonstrated feasibility of a novel liquid stable glucagon formulation in a CL system. The DHAID effectively reduced hypoglycaemia during and after aerobic exercise compared to SHAID and a predictive low glucose suspend (PLGS) system, although there was a slight increase in hyperglycaemia[246].

In a randomized trial by Jacobs et al. (2016), the DHAID during announced exercise performed best, with the least TBR (0.3% DHAID announced, 0.8% SHAID announced; 3.1% DHAID unannounced)[247], but the heightened hypoglycaemia risk for unannounced exercise is seen.

A meta-analysis by Wu et al. (2022)[248] compared trials for the efficacy of DHAID, SHAID and SOC on post-exercise overnight glucose in people with T1D. The pooled data demonstrated, considering TIR, TBR, and TAR, both AID systems provided better night-time glucose control than SOC in both adults and adolescents. Furthermore, DHAID was able to provide better overnight glycaemic management than SHAID in adults (DHAID: 94.0% ± 11.9%, SHAID: 83.1% ± 20.5%, $p<0.05$).

Furthermore, Castle et al. (2018) showed that DHAID outperformed SHAID, PLGS, and continuation of current care not only in minimizing hypoglycaemic events during aerobic exercise, but also throughout four days of high physical activity[117]. Also, Blauw et al. (2021) demonstrated superiority in glycaemic control of a fully closed-loop DHAID in comparison to a SOC open-loop control (CSII) over the usage of two weeks. However, technical limitations are still existing: glucagon had to be replaced daily and glucagon tube occlusions, lump formation, as well as pain, were documented[193] and in the trial by Wilson et al. some participants experienced nausea related to glucagon[246]. Thus, there is still a clear need for improvement of glucagon DHAID to enable everyday use. A recent landmark development involves the bihormonal iLet Bionic Pancreas, which can be used with a single, prefilled dasiglucagon cartridge for 7 days, and showed no infusion site reactions or occlusions and minimal cases of nausea[249]. This suggests the practicality of using this liquid formulation clinically. Comparative trials demonstrated superior glycaemic control compared to CSII and even the in 2023 FDA-approved insulin-only iLet Bionic Pancreas[249,250]. These findings suggest potential future developments in clinical approval, though dedicated exercise studies are still pending.

An alternative approach entails subcutaneous pre-exercise mini-dose glucagon (MDG). In CSII pre-prandial exercise, Rickels et al. (2018) observed that MDG may be superior to insulin reduction alone in preventing exercise-induced hypoglycaemia and may also lead to reduced post-exercise hyperglycaemia compared to carbohydrate consumption[251]. Furthermore, Aronson et al. (2023) showed that ready-to-use MDG with or without 50% reduction in CSII basal delivery rate can decrease hypoglycaemia during and 30 min post-exercise in adults with T1D even in a in real-world setting[252]. This makes MDG a highly relevant strategy for T1D and exercise and has to be considered by future AID algorithms to optimize unannounced exercise.

One recent technological advance to pave the way for DHAID could be a transdermal polymeric microneedle patch for glucose-responsive insulin and glucagon delivery. The glucose-responsive DH-microneedle can dynamically tune the release ratio of the negatively charged insulin and the positively charged glucagon analogue from the patch upon the fluctuation of BG levels to maintain glycaemic homeostasis. In both T1D mouse and minipig models, the DH-microneedle patch demonstrated tight long-term regulation in BG levels and minimized the risk of hypoglycaemia[253].

Furthermore, the development of the "13C15N: glucagon-based novel isotope dilution mass spectrometry method" seems promising, which should allow the investigation of individual glucagon kinetics in vivo in humans, which, as an individual basis for algorithms, could increase the functionality in DH-systems[254].

Another possibility would be pramlintide, an analogue of amylin, a hormone that is secreted along with insulin but is insufficient in people with T1D. Haidar et al. (2020) compared a novel DHAID that delivered pramlintide in addition to insulin in a glucose-responsive, basal-bolus manner and in a fixed ratio to insulin to mimic coformulation[255]. Compared with the rapid insulin-alone AID system, the rapid insulin-and-pramlintide-system increased the TIR from 74 ± 18% to 84 ± 13% ($p<0.05$). Although 19 of the 28 participants took standardized 25 min walks during their 24-hour inpatient visits, this promising coformulation has yet to be tested in the exercise setting.

Somatostatin could be another promising opportunity to counteract the lack of glucagon response to hypoglycaemia. Somatostatin is a peptide hormone released by pancreatic delta-cells, mediated by five different subtypes of somatostatin receptors, SSTR1 - SSTR5[256]. In human and animal models, T1D leads to increased somatostatin on a systemic level and in the islet cells[257,258]. By antagonizing the SSTR2 with a selective antagonist (SSTR2a), mostly PRL-2903, glucagon and corticosterone responses to hypoglycaemia are improved[256,257]. The newly studied SSTR2a, ZT-01, seems even more promising, with better results when administered subcutaneously or intraperitoneally, as it exhibited more favourable pharmacodynamic properties on glucagon secretion[256]. Proof-of-concept studies in models and rats have been successfully performed. However, there have been no human trials yet and a better understanding of the mechanisms involved is still needed. Nevertheless, the results are promising and could lead to an SSTR2a "Triple-Hormone-AP" that counteracts the potential blunting effects of the glucagon response and endogenous glucose production to elevated insulin levels during exercise. However, the cost and complexity of a triple-hormone AID must be considered, as three tubes/pumps would be required.

Overall, introducing glucagon would be the first step, allowing for more aggressive insulin dosing, better and tighter glucose control, and minimizing the need for carbohydrate supplementation. Subsequently, with further technical maturity, the development of a triple-hormone AP that improves TIR (pramlintide) or the interaction between glucagon and insulin (somatostatin) would be conceivable.

6.6.3 **Glucose Sensor Performance**

CGM systems assess glucose levels in the interstitial fluid, differing physiologically from the actual BG concentration. Additionally, prolonged exercise can lead to lower interstitial glucose (IG) than venous or capillary BG levels, as possible dehydration reduces glucose supply in the interstitium[163]. Reviewing current studies, the mean absolute relative difference (MARD) compared to venous glucose of CGMs under different physiological or experimental conditions is comparable for new generation systems and ranges between 10% and 20%[9,15,96,160–162,259]. During exercise, a single-centre, open-label study by Aberer et al. (2017) showed MARDs of 8.7 ± 5.9% (Abbott; FreeStyle Libre), 15.7 ± 14.6% (Dexcom; G4) and 19.4 ± 13.5% (Medtronic; Guardian 3). All systems performed better in hyperglycaemia than in hypoglycaemia[96]. Around aerobic (anaerobic) exercise, Biagi et al. found MARDs of 9.5% (15.5%) pre-exercise, 16.5% (16.8%) during exercise and 9.3% (12.7%) post-exercise for the Medtronic Paradigm Enlite-2 sensor[260]. Li et al. (2019) confirmed this tendency: they found that the Dexcom rtCGM G4 Platinum performed significantly worse during high intensity interval training (HIIT) and early recovery (MARD 17.8%) than pre-exercise (10.4%), late recovery (10.6%) and post-exercise resting (11.6%)[261]. Likewise, this is evident in Taleb et al. (2016), where both sensors (Dexcom G4 Platinum and Medtronic Paradigm Veo Enlite) demonstrated significantly lower performance during exercise[262], and Zaharieva et al. (2019), where the MARD and associated overestimation of BG was highest during the first 30 minutes of exercise, at the time of the greatest decrease in BG[98]. The trend to overestimate capillary glucose was also found by Larose et al. (2019): here the overestimation was maintained at relatively stable mean values of +14 mg/dL over the exercise session[263]. Moser et al. (2016) further demonstrated with their study that intensity and type of exercise (continuous or HII-exercise) can also affect sensor accuracy[183]. Moreover, CGM sensors seem to measure not only inaccurately and overestimating during exercise, but also less accurately during hypoglycaemia than in euglycaemia or hyperglycaemia - which plays an important role especially for exercise-induced hypoglycaemia[95]. However, not only the glucose level as well as type and intensity of exercise have an impact on the sensor accuracy: also, the duration, the fitness status of the person, the prandial status in which exercise is performed and many other variables affect the sensor performance[15,259]. Overall, all these different conditions and potential sources of error must be considered by an AID algorithm.

This CGM inaccuracy has a primary physiological reason: A delay between IG and BG exists, which may result in the CGM over- or underestimating the change in glycaemia. Especially during exercise, where severe glucose fluctuations can occur within minutes, absolute glucose

values can be error-prone[162]. The physiological lag-time varies between 3 - 12 minutes due to the diffusion of glucose across the capillary endothelial barrier and the glucose-rate limiting membrane[164,264]. In addition, the average technical sensor delay-time is 1 to 2 minutes[264]. Therefore, the absolute lag-time between BG changes and CGM readings ranges from 4 to 14 minutes. A 2019 study by Zaharieva et al. confirmed this with a measured average delay time of 12 ± 11 minutes during prolonged aerobic exercise[94]. A further complication is the fluctuation of delay-time due to other factors like exercise intensity and circulating insulin[264]. For example, Li et al. (2019) even measured a rtCGM lag time of 35 min during HIIT[261].

Besides measurement inaccuracies, there are also mechanical problems of CGMs to be solved, as it is not perfectly possible to keep the CGM sensor in place or maintain connectivity in every sport (e.g. swimming).

Overall, the current CGM technology poses a challenge for AID systems during unannounced exercise, which highlights the need for further development. However, CGM MARDs have halved since the beginning of the millennium and thus further technical progress of CGMs can be looked forward to optimistically[264].

6.6.4 **Integrating Physiological Signals**

Another strategy to improve AID system's performance for unannounced exercise involves physiological signals. Current HCL systems use only IG to estimate insulin delivery. The purpose of additional „sensors" is to determine whether mental or physical stress is induced and thus to distinguish between rest and exercise. Additionally, exercise start, type, intensity, and duration are relevant for the algorithm to optimally adjust the dosage of insulin (and glucagon).

Cardiac Autonomic Function and Accelerometery

Additional parameters for exercise detection might be cardiological variables or/and accelerometery, which can nowadays be measured continuously integrated in smartwatches.

In an RCT with 25 participants, Castle et al. (2018) compared DHAID and SHAID with exercise detection, the use of a PLGS system, and the continuation of the participant's current care (CC). Each arm included three moderate-intensity aerobic exercises. The exercise detection algorithm used HR and accelerometery data in a regression equation. The TBR during exercise was lowest with 3.4% using the DHAID, compared with 8.3% SHAID, 7.6% PLGS, and 4.3% CC. DH achieved 84.3%, SH 83.3%, PLGS 78.3%, and CC 78.2% TIR for exercise. Overall, the DHAID and SHAID with exercise detection were able to demonstrate improved glycaemia

by adding HR and accelerometery to the system[117]. This is confirmed by Reddy et al. (2019): using a wearable sensor showed that pre-exercise HR and BG levels were predictive of exercise-induced hypoglycaemia with 80% accuracy[265].

These parameters could be complemented by heart rate variability (HRV) measurement, enabling an even more accurate distinction between mentally and physically induced stress. In a recent study by Rogers et al. (2022), Movesense Medical (Movesense Ltd, Vantaa, Finland), a chest strap that interoperates with a data logger smartphone app, was able to determine whether a person was at rest or exercise, to differentiate pre, during, and post-exercise as well as to detect different exercise intensities via HRV[266].

Another possibility would be adding QTc as a cardiac feature to the HRV measurement. QTc prolongation is a sign of stronger activation of sympathetic activity and inhibition of parasympathetic activity, as it occurs during hypoglycaemia, and would therefore be ideally suited to be implemented alongside HRV[116].

Consequently, a promising next step to manage unannounced exercise with AID systems would be the integration of cardiological variables and accelerometery via a single device, e.g. a smartwatch. Therefore, it seems advisable to run the AID algorithm in a smartphone app rather than in the pump itself.

Lactate Monitoring

As long as lactate production does not exceed clearance, lactate levels are stable and the athlete is below the anaerobic threshold, corresponding to moderate to (slightly) high intensities. With increasing intensity, high to very high, the athlete exceeds the threshold, and lactate level rises abruptly[267]. Consequently, continuous lactate measurement would allow the algorithm to distinguish between aerobic and anaerobic exercise, to detect the intensity of the exercise and to control glucose more tightly. Subcutaneous lactate monitors are being developed and tested but still have some limitations. In a clinical evaluation by Dror et al. (2022), the sensors had prominent technical and physiological problems associated with changes in blood flow, lag time, and diffusion rate[268].

Ketones and Counterregulatory Hormones

Exercise, especially at high intensities, is associated with an acute counterregulatory hormone release. Low levels of circulating insulin further increase the generation of ketone bodies. While unsuitable for specifying exercise, ketone measurement could increase safety around exercise.

After exercise, often a decrease in glucose levels occurs, which may be accompanied by an increase in ketone bodies[269]. Since all current systems only measure glucose, a reduction in insulin dose follows, which carries the risk of a further elevation of ketone levels[270]. Continuous measurement of ketones with a continuous ketone monitor (CKM) would therefore allow for a more precise therapy as well as exercise type and intensity adjustments, especially since during exercise higher glucose levels are generally recommended. Moreover, in severe instances of elevated ketone levels and potential elevation through exercise, the AID system may even advise against initiating exercise to increase safety. CKMs measuring beta-hydroxybutyrate in interstitial fluid have already been investigated in vitro and humans[271]. However, the still existing technical hurdles associated with their continuous measurement inhibit their use as complementary information for AID systems[179,204,205,269].

Respiratory Gas Exchange

Exercise in general leads to increased blood flow to the peripheral tissues and, primarily during aerobic exercise, O2 requirements are heightened to produce ATP for energy supply. CO2 on the other side, as a waste product of cellular respiration, accumulates and diffuses out of the cells into the bloodstream. CO2 builds up even during anaerobic exercise and its increase at the cellular level starts with a lesser delay than O2, already shortly after the muscle contraction. Consequently, during exercise, an increased amount of CO2 and, depending on the exercise type, O2, migrates through the interstitium[272] - where the CGM glucose sensor is located.

Consequently, if a sensor can also measure CO2 levels and its ratio to O2 in the interstitial fluid, this could enable the AID system to detect the start, type, and intensity of the exercise[272,273] and to adjust counterregulatory reactions accordingly.

However, the CO2 increase after exercise-start can vary depending on several factors, such as the intensity and duration of the exercise, the individual's fitness level, and breathing pattern. This complicates the estimations and should be complemented with additional physiological signals.

Further physiological Parameters

Next to HR and accelerometery, some wearables already offer additional physiological signals. Sevil et al. (2020) used a machine learning algorithm to classify physical states into sedentary, bicycling, resistance training, running, or daily activities and to obtain an estimate of energy expenditure (EE) in metabolic equivalents (METs). The wristband used integrated sensors for determining electrochemical skin conductance and temperature, acceleration, and blood volume

pulse. The combination of parameters reduced the mean square-error from 0.79 to 0.51 METs and the mean absolute percentage error from 22.0% to 12.1%, compared to the calculation through accelerometery alone[172]. Therefore, the merging of multiple sensor data into one algorithm could lead to better exercise categorization and allow more accurate dosing of insulin and possibly glucagon. Especially for post-exercise hypoglycaemia, the EE assessment could allow the algorithm to estimate glucose and insulin requirements for recovery more accurately. In addition, insulin dosing after exercise or during prolonged physical activity would benefit greatly, as changes in insulin sensitivity would be considerably easier to predict.

Furthermore, not yet tested in AID systems but already measurable through wearables, are oxygen saturation using near-infrared sensors[116], and via appropriate clothing, measuring muscle contractions, sweat production, or breathing patterns.

Reviewing all these possibilities, already the data analysis of a single sensor could provide advantages for an AID system to identify unannounced exercise and this could be further elevated by combining data from multiple sensors. However, considering the present state of technology, the incorporation of physiological data faces limitations due to the impracticality and inconvenience of integrating and wearing multiple sensors. Therefore, future advancements should strive to enable the measurement of as many of the mentioned parameters as possible using a single wearable sensor to maximize data collection while ensuring user comfort.

6.6.5 **Enhanced Algorithms**

A shortcoming of currently used algorithms is their reactive nature. Future algorithms should be able to predict insulin needs more accurately through, e.g., machine learning[171,274,275] or recognition of habit patterns[276]. If the algorithm could make a precise prediction of impending unannounced exercise, it could adjust therapy management in advance and thus initiate countermeasures before the exercise occurs, as well as compensate for slower on- and offset times of insulin. However, predictions are based on probabilistic calculations and probabilities are always at risk of error.

Another way to improve algorithm functionality could be a multi-controller combining algorithms, allowing them to work according to their respective strengths in the appropriate situation. Fushimi et al.[277] implemented this idea in an in-silico study in which the DH multi-controller activates one of the following three controllers when needed: a conservative insulin LQG (Linear Quadratic Gaussian) controller to regulate basal delivery, an aggressive insulin LQG

controller to counteract meals, or a glucagon LQG controller to avoid impending hypoglycaemia. The results show that the proposed DH strategy leads to a decrease in hypoglycaemia without increasing hyperglycaemia or insulin administration.

Another idea is to connect the AID system with calendar functions and GPS location. This could help the algorithm to recognize exercise events via machine learning, and thus prepare the exercise settings in advance[115].

Altogether, future algorithms should be capable of incorporating the mentioned physiological parameters to achieve tighter glucose control while being safe.

6.7 Conclusion

Unannounced exercise is particularly challenging for people with T1D and often leads to glycaemic derailments during and after exercise, especially during the nocturnal period. Therefore, the need for improving AID systems around exercise still exists.

The first implementable steps appear to be the integration of HR, HRV, and accelerometery for exercise detection, the development of a dual-hormone system with glucagon, faster insulins as well as the permanent improvement of sensors and algorithms. In the long term, the inclusion of further physiological signals as well as the potential introduction of dual-/triple-hormone-AIDs with glucagon/pramlintide/somatostatin, as well as predictive machine learning algorithms could also lead to better glycaemic control of AID systems.

However, no single aspect can suddenly achieve perfect therapy management and solve the problem of unannounced exercise on its own. This will require interaction and improvement of all the technologies mentioned above, which could compensate for each other's weaknesses and thus, as a combined system, create an AID that masters even unannounced exercise in a safe, automated, and enjoyable manner.

Linking Statement

The three studies combine clinical interventional evidence, methodological evaluation of glucose monitoring, and a synthesis of technological strategies for insulin automation. Together, they address complementary levels of exercise-related glycaemic management in adolescents with T1D. The following chapter integrates these findings, discusses their combined clinical implications, and outlines future directions for research and implementation.

7 Synopsis, Discussion, and Future Perspectives

7.1 Synopsis and Novel Findings

This chapter synthesizes the main findings of the three studies included in this cumulative dissertation. It discusses their overarching implications of integrating exercise and diabetes technology for adolescents with T1D. Each of the three studies addresses a distinct aspect of exercise-related glycaemic management in adolescents with T1D. Their combined interpretation, however, reveals insights that would not be apparent when considered separately. While Chapters 2 and 3 provided the theoretical and methodological foundations, the present chapter deliberately focuses on integrative interpretation rather than restating underlying physiological or technological principles in detail.

Prior research has predominantly examined exercise interventions, CGM performance, or diabetes technologies as isolated components, often in adult populations or controlled laboratory settings. In contrast, the present dissertation adopts an explicitly integrative and adolescent-focused perspective. By integrating clinical intervention data, methodological evaluation of CGM, and technological assessment of AID systems, it provides a comprehensive real-world framework that addresses three interrelated gaps in the field: the efficacy of structured exercise interventions, the reliability of CGM around exercise, and the adaptability of AID systems to (unannounced) exercise.

First, the randomized, controlled ChilDFiT1 trial provides rare and much-needed evidence in youth. It directly compares four weeks of structured track and field training plus intensive glycaemic management (EX) against intensive glycaemic management alone (IT) in adolescents (N = 18 overall; EX N = 8, IT N = 10). EX significantly improved TIR compared with its own control phase (P = 0.049) and was the only group to meet the >70% TIR consensus target during intervention, whereas IT showed no TIR gain (P = 0.399). HbA_{1c} decreased in EX from 7.0% ± 0.5 to 6.8% ± 0.4 (P = 0.042), alongside lower Standard Deviation of Glucose. Hypoglycaemia remained within consensus safety (total TBR <4%), though nocturnal TBR1 rose and warrants targeted mitigation strategies. **In sum, the trial demonstrates that exercise is not merely safe but provides measurable glycaemic and metabolic benefits beyond intensive glycaemic management alone.** These findings complement observational evidence showing that youth with higher levels of physical activity achieve better HbA_{1c}, greater insulin sensitivity, and more favourable cardiovascular profiles than inactive peers.[56,57,79] In doing so, they help fill a critical evidence gap highlighted by current guidelines.

Second, the CGM accuracy trial extends this work by generating paediatric-specific data on sensor performance around exercise, a setting where accuracy is most crucial yet least studied. The rtCGM sub-study in the ChilDFiT1 EX arm (8 adolescents; 443 paired points) assessed sensor performance around exercise sessions. Overall, MedARD was 19.1% (IQR 12.2-27.3%), and in-exercise MedARD reached 19.4% (12.3-27.8%), with hypoglycaemia showing the most significant error (28.4% [18.8-36.3%]). Bland-Altman analyses indicated a positive bias (CGM > BG) across states, suggesting that sensor bias could lead to systematic under-detection of hypoglycaemia. These findings support protocolized use of trend arrows and selective capillary confirmation around exercise. **Thus, while CGM enables real-time BG monitoring, its reduced accuracy during rapid glucose fluctuations emphasizes the importance of cautious, context-aware interpretation in exercise contexts.** These insights strengthen international recommendations that emphasize proactive use of CGM trend information for exercise management.[9]

Third, the narrative review situates unannounced exercise as a persistent limitation for current AID technology. While AID has proven effective in improving daily glycaemic control, the adaptability of current CL and HCL systems to unannounced exercise and spontaneous physical activity remains limited. This limitation is particularly relevant during adolescence and reflects both the reliance on user announcements and the pharmacokinetics of insulin. Building on the technological principles described in Chapter 2.4.2, the present synthesis highlights how these architectural constraints manifest specifically under real-world exercise conditions. Accordingly, exercise emerges as both a stress test for current AID systems and a frontier for innovation. It points toward future strategies that integrate faster insulins, (bi)hormonal approaches, wearable-derived physiological signals, and adaptive algorithmic designs. **Consequently, AID systems represent a decisive step forward, yet their current architecture still leaves exercise as a critical domain where further innovation is essential.**

Specifically, the intervention study demonstrates that structured exercise can improve glycaemic outcomes when embedded in intensive management strategies. However, the CGM accuracy analysis reveals that glucose monitoring is least reliable precisely during periods of rapid exercise-induced glucose change. The review of AID systems further shows that current technologies can only partially compensate for these limitations, particularly for unannounced exercise.

Taken together, these findings show that safe exercise participation in adolescents with T1D cannot be ensured by any single component alone. Instead, it requires the deliberate and coordinated interaction of structured exercise programs, informed interpretation of CGM data, and adaptive technological support.

Linking the present findings to underlying physiology reinforces both their coherence and biological plausibility. The glycaemic improvements observed in the ChilDFiT1 intervention are consistent with well-established exercise-induced mechanisms, including enhanced insulin sensitivity, contraction-mediated glucose uptake independent of insulin, and improved metabolic flexibility.[62,63] These adaptations help stabilize BG levels and explain why structured training, even over a relatively short period, can produce measurable metabolic benefits. In contrast, the limitations in CGM accuracy and AID performance observed around exercise mirror fundamental physiological constraints. These limitations reflect, for example, the temporal lag between interstitial and blood glucose, the variability of counterregulatory responses during adolescence, and the pharmacokinetic delay of subcutaneous insulin relative to rapid metabolic shifts.[164,168,241] Framing the results within these mechanisms clarifies that the interaction between exercise physiology and technological performance is biologically determined rather than coincidental. This strengthens the validity of the findings and reinforces the need to integrate physiological principles into future technological innovation.

Taken together, these studies align with and extend international consensus statements (EASD, ISPAD, ADA), which emphasize both the benefits of regular physical activity and the persistent challenges of preventing exercise-related glycaemic disturbances in T1D.[7,9,77,79]

Beyond the findings of the individual studies, this dissertation establishes a coherent translational framework that links intervention efficacy with technological performance and future innovation pathways. The work combines clinical trial evidence, sensor evaluation under real-world exercise conditions, and a forward-looking analysis of AID systems. **Together, these findings demonstrate that optimal glycaemic management in adolescents with T1D requires a synergistic integration of structured exercise programmes, advanced technologies, and tailored education, going beyond reliance on any single component.**

7.2 Implementation and Translation into Practice

A key question is how to translate the specific findings of this dissertation into routine care. Despite strong evidence for efficacy and safety, structured exercise remains underutilized in

paediatric T1D management. This gap is reflected in recent ISPAD, EASD, and ADA statements, which classify physical activity as a critical therapeutic adjunct, yet note its limited integration into everyday practice.[9,77,79]

The ChilDFiT1 trial demonstrated that structured and supervised track and field training can safely improve glycaemic outcomes when combined with intensive glycaemic management. Translating this into practice requires developing standardized, scalable exercise programmes for adolescents with T1D. However, current reimbursement models rarely cover exercise interventions, and outpatient clinics often lack the time and resources to provide them. Without recognition of exercise as a therapeutic intervention rather than a lifestyle choice, sustainable integration into routine care will remain limited.[7,278] Aligning healthcare policy and reimbursement models with this paradigm shift is therefore essential for closing this implementation gap.

At the professional level, implementation is further hindered by limited training in exercise physiology among diabetologists, diabetes educators, and nurses. This lack of expertise reduces confidence in prescribing and monitoring exercise in youth with T1D, despite growing evidence of its benefits.[5,12,279] To close this gap, exercise-related content should be incorporated into professional curricula, and interdisciplinary collaboration with exercise scientists and physiotherapists needs to be strengthened. The present findings underscore that structured exercise cannot be scaled into practice without clinicians who are both knowledgeable and confident in its delivery.

The CGM accuracy study showed that rtCGM performance decreases around exercise, particularly in hypoglycaemia, with a systematic bias toward overestimation. These results have direct implications for patient and clinician education: sensor data must be interpreted in context, with emphasis on trend information and selective capillary confirmation when values are rapidly changing or appear incongruent with symptoms. Importantly, recent exercise guidelines for youth with T1D already emphasize proactive use of CGM trend arrows and recommend confirmatory testing in situations of clinical uncertainty or elevated risk of hypoglycaemia.[9] The present findings therefore provide empirical support for these consensus-based recommendations and underscore their clinical relevance.

The AID review identified (unannounced) exercise as a persistent limitation of current systems, which rely on manual user announcements and are constrained by insulin pharmacokinetics. For translation, two priorities emerge. First, structured patient and clinician education on T1D technology - aligned with emerging consensus statements such as Moser et al. (2025)[77] - is needed to ensure that available AID features are used effectively in the context of exercise.

These guidelines provide device-specific recommendations, including adjustments to glucose targets, reduced meal boluses before exercise, and anticipatory strategies for unplanned activity, thereby offering a practical framework for current practice. Second, sustained interdisciplinary exchange among clinicians, exercise scientists, and technology developers is essential. It enables real-world experiences to be translated into algorithmic innovations that allow future systems to better accommodate the metabolic dynamics of spontaneous physical activity.[77]

Building on these results, digital health approaches offer promising opportunities. Tele-exercise programs, app-based coaching platforms, and wearable devices could provide scalable support beyond specialized clinics, particularly for adolescents balancing school, extracurricular activities, and social commitments. When integrated with CGM and AID, these tools could deliver real-time, personalized recommendations for insulin adjustment and carbohydrate intake based on both physiological and physical activity data.

Finally, the behavioural and psychosocial barriers to exercise participation - such as fear of hypoglycaemia, low self-efficacy, competing priorities, and the developmental challenges of adolescence - remain remarkably relevant.[5,12] Addressing these barriers requires more than knowledge transfer in exercise physiology and technology literacy; it also calls for educational approaches that integrate practical exercise strategies with empowerment. Such approaches should foster confidence in both planned and spontaneous physical activity and exercise, while providing iterative support, positive reinforcement, and opportunities for autonomous decision-making.

From a clinical implementation perspective, the present findings support several concrete actions. These include routine assessment of exercise habits and prior glycaemic responses during outpatient visits, proactive counselling on exercise-specific CGM interpretation, and early introduction of simple, individualized strategies for both planned and spontaneous physical activity and exercise. Embedding these elements into standard care pathways may substantially reduce barriers to participation and improve safety and confidence among physically active adolescents with T1D.

While these considerations primarily address individual-level factors related to patients, clinicians, and technology use, they also point toward broader system-level implications. The effective integration of exercise-based strategies into paediatric T1D care depends not only on individual adherence or device optimization, but on how healthcare services are organized and delivered. This includes the availability of multidisciplinary teams, clearly defined care pathways, and institutional structures that enable consistent exercise counselling and follow-up. Without

such system-level embedding, even well-established clinical strategies and technological solutions are unlikely to achieve sustainable reach or equity across care settings.

Furthermore, to achieve sustainable integration, future work should apply implementation science models such as the Consolidated Framework for Implementation Research (CFIR) and the RE-AIM framework (Reach, Effectiveness, Adoption, Implementation, and Maintenance) to evaluate the feasibility, acceptability, and scalability of exercise programmes in real-world settings.[280–282] Pragmatic, multi-centre trials in ecologically valid contexts, such as schools, sports clubs, and transition clinics, will be essential to narrow the evidence–practice gap. In addition, co-design methodologies involving adolescents, families, and clinicians will be crucial to ensure successful translation.

In sum, the studies presented in this dissertation directly inform the translational agenda:

- structured exercise interventions must be recognized and reimbursed as therapeutic options
- clinicians require enhanced training and interdisciplinary support to prescribe, individualize, and monitor exercise effectively
- CGM education should address both exercise-specific limitations and practical strategies for their management
- AID development must progress toward systems that can better adapt to the unique challenges of exercise.

Addressing these dimensions in tandem is key to establishing structured exercise as a cornerstone of paediatric T1D management.

7.3 Limitations and Future Perspectives

While the studies presented in this cumulative dissertation provide novel and integrative insights into exercise-related glycaemic management in adolescents with T1D, several limitations must be considered when interpreting the findings. These limitations affect different aspects of internal validity, generalizability, and translational relevance and should therefore be interpreted with appropriate weighting.

The most consequential limitation concerns the design of the ChilDFiT1 intervention study. Although the randomized controlled design strengthens internal validity, the relatively short intervention duration and small sample size limit conclusions regarding long-term sustainability and broader generalizability. Accordingly, the findings should primarily be interpreted as evidence of feasibility and short-term efficacy. This limitation is particularly relevant, given that

exercise-related adaptations in glycaemic control, cardiovascular fitness, and psychosocial outcomes typically evolve and may be more pronounced with extended intervention periods. To address this gap, future research should move beyond short-term proof-of-concept studies and employ randomized but pragmatically designed, adequately powered, multi-centre trials with extended follow-up periods. Such studies should deliberately include heterogeneous adolescent populations, encompassing different pubertal stages, therapy modalities, and transition phases from paediatric to adult care. This would allow more robust conclusions regarding sustainability and generalizability.

A second central limitation concerns CGM performance around exercise. As shown in the CGM accuracy study, sensor reliability declines during rapid glucose changes, particularly in the hypoglycaemic range, directly affecting safety-related interpretation around exercise. This limitation reflects a physiologically driven constraint inherent to interstitial glucose sensing rather than a methodological shortcoming. Importantly, the findings reinforce the need for context-aware CGM interpretation, emphasizing trend information and selective confirmatory testing when glucose dynamics are rapid or incongruent with symptoms. To strengthen evidence-based clinical and educational recommendations, future studies should systematically evaluate CGM performance across multiple sensor generations, exercise types, and ecologically valid real-world settings.

Regarding AID systems, the limitations identified in the narrative review primarily reflect current technological limitations. The limited adaptability of current CL and HCL systems to unannounced or spontaneous exercise is driven mainly by reliance on user input and the pharmacokinetic delay of subcutaneous insulin. While the conclusions remain clinically relevant, they represent a snapshot of a rapidly evolving field. Future research should increasingly examine exercise interventions in combination with emerging diabetes technologies. These include next-generation AID systems with faster-acting insulins, dual- or triple-hormone approaches, advanced CGM sensors, and adaptive algorithms that integrate physiological and contextual signals (e.g., heart rate, accelerometery, recent physical activity, or nutritional intake) to enable more proactive and automated insulin adjustment around exercise.

Additional limitations primarily affect the transferability of the findings rather than their core interpretation. The restriction to a single CGM system and to standardized track and field training limits generalization to other devices, sports, and highly unstructured real-world physical activity. Similarly, the controlled nature of the intervention does not fully capture the variability and unpredictability of adolescents' everyday physical activity. While these constraints were

necessary to ensure methodological rigor and participant safety, they underscore the importance of future studies that prioritize ecologically valid designs. Embedding exercise interventions and technology testing in everyday environments such as schools, sports clubs, and community programmes would allow simultaneous evaluation of glycaemic outcomes, feasibility, user acceptance, and implementation barriers.

Beyond methodological and technological considerations, behavioural and structural factors remain highly relevant. Psychosocial barriers such as fear of hypoglycaemia, low self-efficacy, and competing priorities continue to limit exercise participation during adolescence. Future exercise programmes should therefore place greater emphasis on adolescent-specific behavioural and educational components, combining tailored education with empowerment-based and longitudinal support. Interventions targeting autonomous decision-making, particularly during late adolescence and the transition to adult care, are essential to translate physiological and technological advances into sustained real-world physical activity. In addition, personalized approaches that account for sex, pubertal stage, fitness level, psychosocial context, and individual preferences may further enhance both safety and effectiveness.

Significantly, some limitations extend beyond the individual or technological levels and reflect broader constraints within the healthcare system. The availability of structured exercise programmes, trained professionals, and technology support differs substantially between regions and care settings, which may limit scalability and real-world transferability even when interventions prove efficacious. Addressing these barriers requires implementation-focused research that explicitly considers healthcare structures, interdisciplinary collaboration, and sustainable reimbursement models to enable long-term integration into routine care.

Finally, some limitations are inherent to the broader research and healthcare context. Evidence in adolescents remains limited, and the rapid pace of technological development constrains temporal generalizability. These factors highlight the need for continuous, interdisciplinary research and for implementation-focused studies supported by policy and reimbursement models that recognize structured exercise as a therapeutic intervention.

In summary, the limitations of this dissertation outline the boundaries within which the findings should be interpreted while simultaneously defining concrete and targeted priorities for future research and translation. By contextualizing and weighting these constraints, this work provides a robust foundation for advancing both clinical practice and research at the intersection of exercise, glucose monitoring, and diabetes technology in adolescents with T1D.

7.4 Practical Conclusions and Closing Remarks

This dissertation demonstrates that structured exercise, when embedded in individualized care, constitutes a safe and powerful therapeutic adjunct for adolescents with T1D. Beyond its physiological benefits, exercise provides a pathway to empowerment, resilience, and lifelong health. Yet, its full potential can only unfold when clinical routines, educational strategies, and technological innovations are aligned.

An important integrative implication of this dissertation is that the clinical benefits of exercise, the limitations of CGM, and the current constraints of AID must be considered jointly when translating evidence into practice. The findings show that exercise-related safety and efficacy do not arise from any single component in isolation. Instead, they result from the coordinated interaction of structured exercise programmes, informed interpretation of CGM data, and adaptive technological support under dynamic real-world conditions, with strengths at one level partially offsetting limitations at another.

Accordingly, exercise recommendations for adolescents with T1D should not be based solely on physiological effectiveness, but must explicitly account for monitoring reliability and technological responsiveness during and after exercise. This integrative perspective is essential to avoid both overreliance on technology and undue restriction of physical activity due to fear of glycaemic disturbances.

Against this background, three core conclusions emerge:

I. **Exercise as therapy**. Structured and supervised training should no longer be viewed as optional lifestyle advice. Instead, it should be considered an integral element of paediatric T1D care, supported by appropriate reimbursement, clinical infrastructure, and evidence-based implementation pathways. When embedded within intensive glycaemic management strategies, exercise can yield meaningful improvements in glycaemic outcomes while remaining safe and feasible for adolescents.

II. **Technology as an enabler**. Continuous glucose monitoring and automated insulin delivery systems are indispensable companions to exercise. Still, they require context-sensitive use, transparent education, and ongoing refinement to meet the demands of spontaneous and dynamic exercise.

III. **Integration through education and collaboration**. Building competence and confidence in young people requires early, continuous, and developmentally appropriate education, delivered through sustained collaboration between clinicians, exercise scientists, educators,

and families. Interdisciplinary cooperation with technology developers will be essential to translate empirical findings into sustainable, user-centred solutions that reflect the lived realities of adolescents with T1D.

From a clinical perspective, the findings yield clear, actionable recommendations for daily care. Adolescents should be actively encouraged to engage in regular physical activity, with clinicians explicitly addressing exercise-related glucose dynamics, CGM limitations, and practical strategies for both planned and unplanned exercise. Rather than discouraging physical activity and exercise due to technological uncertainty, clinical counselling should focus on empowering adolescents to use exercise, CGM, and AID systems in a complementary and informed manner.

Taken together, the findings underscore that safe, efficient, and confident participation in physical activity is achievable when human and technological dimensions are addressed in an integrated manner. Reducing barriers to exercise, therefore, depends not only on technological advancement but also on empowering adolescents with the knowledge and skills to navigate the inherent uncertainties of exercise-related glucose dynamics. Such an approach has the potential to reduce the daily burden of self-management while fostering autonomy and sustained engagement in health-promoting behaviours.

Against this background, the long-term impact of exercise-based and technology-supported strategies in adolescent T1D will depend not only on individual adherence and technological advances. It will also depend on their systematic integration into paediatric diabetes care structures. In this context, the present work provides a foundation for the next generation of research and practice at the intersection of paediatric diabetology, exercise physiology, and diabetes technology. By linking clinical evidence with innovation, it advances a paradigm shift toward establishing structured exercise as a core component of T1D management. It also promotes the design of technologies and care models that actively enable, rather than constrain, an active life. Ultimately, this dissertation contributes to empowering adolescents with T1D to live physically active, self-determined, and fulfilling lives with confidence in both their bodies and their technologies.

8 Own Contribution to the individual Publications

Article I. Impact of a 4-week intensive Track and Field Training Intervention on Glycaemia in Adolescents with Type 1 Diabetes: The ChilDFiT1 Study

Articles I and II were part of the ChilDFiT1 project. For this study, I designed the study protocol in consultation with Prof. Dr. Othmar Moser and PD Dr. Felix Aberer. In this context, I independently conducted the majority of the practical work in both laboratory and field settings. I was supported by PD Dr. Felix Aberer, who served as the study physician, overseeing the study from a medical perspective and providing substantial assistance in implementing the intervention. Subsequently, I performed the statistical analysis of the results and drafted the manuscript, which was revised in collaboration with the co-authors. Finally, I incorporated the recommendations of the external peer reviewers into the manuscript.

Article II. Performance of real-time continuous Glucose Monitoring during Track and Field Training in Adolescents with Type 1 Diabetes

This study is an analysis of a prespecified secondary outcome of the ChilDFiT1 study (Article I). Here, too, I conducted the statistical analysis of the results and drafted the initial version of the manuscript, which was subsequently revised in collaboration with the co-authors. I then incorporated the external reviewers' suggested revisions into the manuscript.

Article III. (Hybrid) Closed-Loop Systems: From Announced to Unannounced Exercise

I conceptualized the scope and structure of the review in consultation with Prof. Dr. Othmar Moser. I conducted an extensive literature search in collaboration with Mr. Alexander Auth, identified and analysed relevant studies, and synthesized the findings. In addition to summarizing existing research, I formulated ideas for future research directions and potential applications in consultation with Prof. Dr. Othmar Moser. Based on this analysis, I drafted the initial version of the manuscript, which was subsequently revised in collaboration with the co-authors. Finally, I incorporated the feedback from the external peer reviewers into the manuscript.

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Eidesstattliche Erklärung

Ich versichere hiermit an Eides Statt, dass ich die vorliegende Arbeit ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe; die aus fremden Quellen direkt oder indirekt übernommenen Gedanken sind als solche kenntlich gemacht.

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Die Arbeit wurde bisher weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde vorgelegt und ist auch noch nicht veröffentlicht.

Bei der Erstellung dieser Dissertation wurden KI-gestützte Werkzeuge unterstützend für sprachliche Überarbeitung und Textstrukturierung verwendet. Inhaltliche Konzeption, Datenauswertung, Interpretation und wissenschaftliche Schlussfolgerungen wurden ausschließlich von der Autorin vorgenommen.

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the guidelines of "Good Scientific Practice".

In the preparation of this dissertation, generative artificial intelligence tools were used to support language editing, sentence restructuring, and stylistic refinement. All scientific content, interpretations, analyses, and conclusions were developed by the author. The author takes full responsibility for the content of this work.

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APPENDIX I: List of Publications and Conference Contributions

I. Publications with Peer-Review as First Author

1. **Zimmer, R. T.**, Aberer, F., Schierbauer, J., Zimmermann, P., Birnbaumer, P., Fritsch, M., Fröhlich-Reiterer, E., Hofmann, P., Sourij, H., & Moser, O. (2024). Performance of real-time continuous glucose monitoring during track and field training in adolescents with type 1 diabetes. Dokładność ciągłego monitorowania stężenia glukozy w czasie rzeczywistym podczas treningu lekkoatletycznego u młodzieży z cukrzycą typu 1. Pediatric endocrinology, diabetes, and metabolism, 30(4), 211–220. https://doi.org/10.5114/pedm.2024.146685
2. **Zimmer, R. T.**, Birnbaumer, P., Sternad, C., Zunner, B. E. M., Schierbauer, J., Fritsch, M., Fröhlich-Reiterer, E., Hofmann, P., Sourij, H., Aberer, F., & Moser, O. (2024). Impact of a 4-week intensive track and field training intervention on glycaemia in adolescents with type 1 diabetes: The ChilDFiT1 study. Diabetes, obesity & metabolism, 26(2), 631–641. https://doi.org/10.1111/dom.15352
3. **Zimmer, R. T.**, Auth, A., Schierbauer, J., Haupt, S., Wachsmuth, N., Zimmermann, P., Voit, T., Battelino, T., Sourij, H., & Moser, O. (2023). (Hybrid) Closed-Loop Systems: From Announced to Unannounced Exercise. Diabetes technology & therapeutics, 10.1089/dia.2023.0293. Advance online publication. https://doi.org/10.1089/dia.2023.0293

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4. **Zimmer, R. T.**, Haupt, S., Heidenreich, H., & Schmidt, W. F. J. (2022). Acute Effects of Esports on the Cardiovascular System and Energy Expenditure in Amateur Esports Players. Frontiers in sports and active living, 4, 824006. https://doi.org/10.3389/fspor.2022.824006

II. Publications with Peer-Review as Co-Author

1. Schierbauer, J., **Zimmer, R.**, Wachsmuth, N. et al. Plasma Volume Shifts and Acid–Base Balance After a Single Bout of Resistance Training. J. of SCI. IN SPORT AND EXERCISE (2024). https://doi.org/10.1007/s42978-024-00314-8
2. Herz, D., Karl, S., Weiß, J., Zimmermann, P., Haupt, S., **Zimmer, R. T.**, Schierbauer, J., Wachsmuth, N. B., Erlmann, M. P., Niedrist, T., Khoramipour, K., Voit, T., Rilstone, S., Sourij, H., & Moser, O. (2024). Effects of Different Types of Intermittent Fasting Interventions on Metabolic Health in Healthy Individuals (EDIF): A Randomised Trial with a Controlled-Run in Phase. Nutrients, 16(8), 1114. https://doi.org/10.3390/nu16081114
3. Herz, D., Haupt, S., **Zimmer, R. T.**, Wachsmuth, N. B., Schierbauer, J., Zimmermann, P., Voit, T., Thurm, U., Khoramipour, K., Rilstone, S., & Moser, O. (2023). Efficacy of Fasting in Type 1 and Type 2 Diabetes Mellitus: A Narrative Review. Nutrients, 15(16), 3525. https://doi.org/10.3390/nu15163525
4. Schierbauer J, Günther S, Haupt S, **Zimmer R**, Herz D, Voit T, Zimmermann P, Wachsmuth NB, Aberer F and Moser O (2023). Acute Fluid Intake Impacts Assessment of Body Composition via Bioelectrical Impedance Analysis. A Randomized, Controlled Crossover Pilot Trial. *Metabolites*, 13, 473. https://doi.org/10.3390/metabo13040473.
5. Eckstein ML, Erlmann MP, Aberer F, Haupt S, Zimmermann P, Wachsmuth NB, Schierbauer J, **Zimmer RT**, Herz D, Obermayer-Pietsch B and Moser O (2022). Glucose and Fructose Supplementation and Their Acute Effects on Anaerobic Endurance and Resistance Exercise Performance in Healthy Individuals: A Double-Blind Randomized Placebo-Controlled Crossover Trial. *Nutrients*, 14,5128. https://doi.org/10.3390/nu14235128.
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11. Eckstein ML, Brockfeld A, Haupt S, Schierbauer J, **Zimmer RT**, Wachsmuth NB, Zunner BEM, Zimmermann P, Erlmann M, Obermayer-Pietsch B and Moser O (2022). Acute Changes in Heart Rate Variability to Glucose and Fructose Supplementation in Healthy Individuals: A Double-Blind Randomized Crossover Placebo-Controlled Trial. *Biology*, 11, 338. https://doi.org/10.3390/biology11020338.
12. Eckstein ML, Brockfeld A, Haupt S, Schierbauer J, **Zimmer RT**, Wachsmuth NB, Zunner BEM, Zimmermann P, Obermayer-Pietsch B and Moser O (2021). Acute Metabolic Responses to Glucose and Fructose Supplementation in Healthy Individuals: A Double-Blind Randomized Crossover Placebo-Controlled Trial. *Nutrients*, 13,4095. https://doi.org/10.3390/nu13114095.
13. Eckstein, M. L., Weilguni, B., Tauschmann, M., **Zimmer, R. T.**, Aziz, F., Sourij, H., & Moser, O. (2021). Time in Range for Closed-Loop Systems versus Standard of Care during Physical Exercise in People with Type 1 Diabetes: A Systematic Review and Meta-Analysis. Journal of clinical medicine, 10(11), 2445. https://doi.org/10.3390/jcm10112445
14. Haupt, S., Eckstein, M. L., Wolf, A., **Zimmer, R. T.**, Wachsmuth, N. B., & Moser, O. (2021). Eat, Train, Sleep-Retreat? Hormonal Interactions of Intermittent Fasting, Exercise and Circadian Rhythm. Biomolecules, 11(4), 516. https://doi.org/10.3390/biom11040516

III. Conference Contributions as First Author

1. **Zimmer R**, Aberer F, Schierbauer J, Birnbaumer P, Sternad C, Hamidi M, Zunner B, Fritsch M, Fröhlich-Reiterer E, Hofmann P, Sourij H, Moser O. Impact of a 4-week intensive track and field training on glycaemia in children and adolescents with type 1 diabetes: the ChilDFiT1 study. *59th Annual Meeting of the European Association for the Study of Diabetes 2023, Hamburg*.
2. **Zimmer R**, Aberer F, Schierbauer J, Birnbaumer P, Sternad C, Hamidi M, Zunner B, Fritsch M, Fröhlich-Reiterer E, Hofmann P, Sourij H, Moser O. Der Einfluss eines 4-wöchigen intensiven Leichtathletik Trainings auf das glykämische Management bei Kindern und Jugendlichen mit Typ-1-Diabetes - Die ChilDFiT1-Studie. *Diabetes Kongress 2023 - 57. Jahrestagung der Deutschen Diabetes Gesellschaft, Berlin*.
3. **Zimmer R**, Aziz F, Haupt S, Böckel S, Schierbauer J, Wachsmuth N, Herz D, Erlmann M, Eckstein ML, Sourij H, Moser O. Blood Glucose Response to Running versus Cycling in Individuals with Type 1 Diabetes: A Systematic Review and Meta-Analysis. *51. Jahrestagung der ÖDG 2022, Salzburg.* Book of Abstracts, Nr. 60, p. 264.

IV. Conference Contributions as Co-Author

1. Schierbauer J, **Zimmer R**, Herz D, Haupt S, Zimmermann P, Wachsmuth N, Birnbaumer P, Hofmann P, Fröhlich-Reiterer E, Fritsch M, Sternad C, Aberer F, Sourij H, Moser O. Performance of real-time continuous glucose monitoring during 4 weeks of track and field training in adolescents with type 1 diabetes. *59th Annual Meeting of the European Association for the Study of Diabetes 2023, Hamburg*.
2. Schierbauer J, **Zimmer R**, Herz D, Haupt S, Zimmermann P, Wachsmuth N, Birnbaumer P, Hofmann P, Fröhlich-Reiterer E, Fritsch M, Sternad C, Aberer F, Sourij H, Moser O. Messgenauigkeit des Dexcom G6 rtCGM-Systems während eines 4-wöchigen Leichtathletik-Trainings bei Jugendlichen mit Typ 1 Diabetes – eine sekundäre Analyse der ChilDFiT1 Studie. *Diabetes Kongress 2023 - 57. Jahrestagung der Deutschen Diabetes Gesellschaft, Berlin*.
3. Schierbauer J, Dobler F, Aziz F, Herz D, **Zimmer R**, Haupt S, Erlmann M, Wachsmuth N, Eckstein M, Sourij H, Moser O. Correlation between glycaemic control and maximum oxygen uptake in individuals with type 1 diabetes: a systematic review and comprehensive analysis. *51. Jahrestagung der ÖDG 2022, Salzburg.* Book of Abstracts, Nr. 46, p. 258.
4. Zimmermann P, Eckstein ML, Erlmann M, Wachsmuth N, Haupt S, **Zimmer R**, Schierbauer J, Herz D, Aberer F, Moser O. Glucose and fructose supplementation and their

impact on heart rhythm during anaerobic exercise in healthy individuals: secondary outcome analysis of a double-blind randomized crossover-controlled trial. *51. Jahrestagung der ÖDG 2022, Salzburg.* Book of Abstracts, Nr. 61, p. 265.

V. Awards and Scholarships

1. **DDG Poster Award**, awarded by the German Diabetes Association (Deutsche Diabetes Gesellschaft) at the Diabetes Congress 2023 in Berlin.
2. **Recipient of a doctoral scholarship** from the **German National Academic Foundation** (Studienstiftung des Deutschen Volkes) in 2022.