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Review of automated insulin delivery systems for individuals with type 1 diabetes: tailored solutions for subpopulations

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Abstract

Automated insulin delivery (AID) systems have proven safe and effective in improving glycemic outcomes in individuals with type 1 diabetes. Clinical evaluation of this technology has progressed to large randomized, controlled outpatient studies and recent commercial approval of AID systems for children and adults. However, several challenges remain in improving these systems for different subpopulations (e.g. young children, athletes, pregnant women, seniors, and those with hypoglycemia unawareness). In this review, we highlight the requirements and challenges in AID design for selected subpopulations and discuss current advances from recent clinical studies.

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Introduction

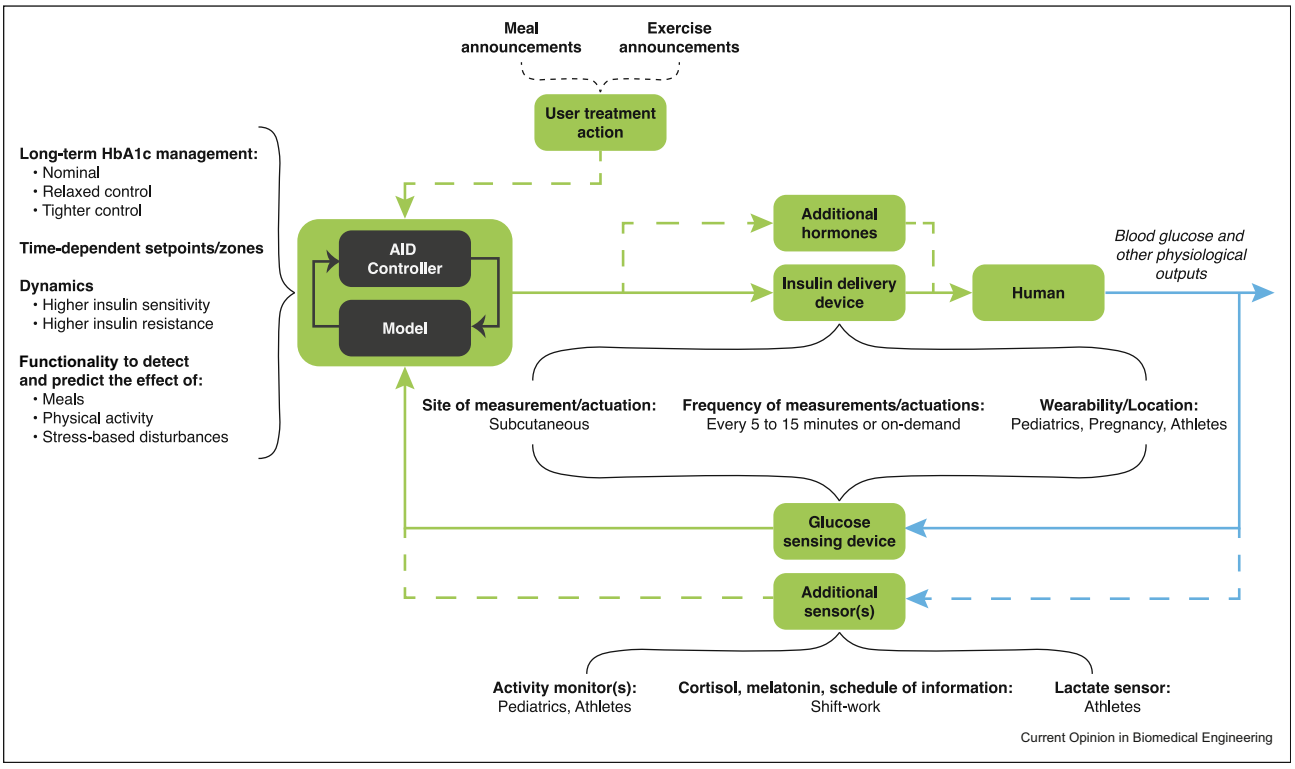
Individuals with type 1 diabetes (T1D) require lifelong replacement of insulin for maintaining glucose levels in a safe euglycemic range. Automated insulin delivery (AID) systems close the loop between a glucose sensing device and an insulin delivery device to compute and deliver insulin (typically every 5 min) to achieve a desired glucose level while reducing the risk of extreme glucose variations below (hypoglycemia) or above desired range (hyperglycemia) in individuals with T1D. There is increasing evidence that AID systems, even with limitations, such as requiring user-initiated meal and correction insulin boluses, improve outcomes over conventional open-loop therapy for adults and children [1,2].

Clinical investigations of AID systems have primarily focused on adults and children $\geq$6 years of age, in low-risk groups using well-defined clinical ranges, such as those below a maximum HbA1c threshold (a measure of average glucose) and minimum total daily insulin (TDI). These exclusion criteria are used to limit or reduce the risk of extreme glucose variations. However, other challenges such as the difficulty tailoring and prioritizing features of AID systems for precise needs of different subpopulations still limit the reach of AID. As the technology matures, there is an increasing need to extend the reach of AID systems to broader criteria. In this review, we discuss recent progress over the last five years, challenges, and opportunities in AID systems with a focus on select subpopulations based on age and those who require systems tailored to a specific metabolic condition.

AID technology: devices, algorithms, and their taxonomy

AID systems are feedback loops that comprise three primary components: the controller, the insulin delivery device such as an insulin pump, and the glucose sensing device such as a continuous glucose monitor (CGM), as illustrated in Figure 1. The AID systems have evolved from low glucose suspend systems, which only suspend insulin delivery to prevent low glucose, to closed-loop systems where insulin can be both decreased and increased with hybrid features, where users may also provide information such as meal and exercise announcements, to recent commercial approval of AID systems for children and adults [3]. The controller, implemented using algorithms such as model predictive control, fuzzy logic, optimal control, and proportional integral-derivative control [4] running on a dedicated

Figure 1



Taxonomy of the automated insulin delivery (AID) system. The model-based AID controller, supplemented with user treatment action, regulates blood glucose through the primary feedback loop (solid lines) composed of insulin–glucose components, with optional feedback loops (dashed lines) composed of additional hormones (e.g. glucagon, for which a second pump would be required) and sensors (e.g. activity monitors). Components that pertain to specific subpopulations are emphasized. For long-term HbA1c management, nominal (i.e. HbA1c less than 7%) pertains largely to adults, pediatric population, shift workers, and athletes; relaxed control (i.e. HbA1c greater than 7%) pertains to pediatric population and seniors at hypoglycemia risk; and tighter control (i.e. HbA1c much less than 7%) pertains to pregnancy subpopulation. Time-dependent set-points and/or zones pertain primarily to shift workers. Higher insulin sensitivity pertains to young children, athletes, and early pregnancy, whereas higher insulin resistance pertains to adolescents, the second half of pregnancy, and shift workers. The green lines indicate signals or actions conducted during closed-loop operation, whereas blue lines distinguish physiological states or properties from measured or digital signals.

device or a smartphone [5], incorporates design parameters to adjust how the controller will react to deviations in glucose from a desired concentration such as user-specific dynamic physiological information, such as insulin sensitivity, time-varying parameters, and functionalities to detect and predict the effect of meals, physical activity, stress, and other disturbances.

Subpopulation characterization

We define a subpopulation as a set of individuals who have distinct diabetes care requirements including glycemic disturbances and targets and who would benefit from tailoring of the AID design, including the pipeline from simulation tools to the regulatory approval. The differences due to subpopulation classification are separate from differences due to individual factors. Several subpopulations based on age (pediatric subpopulation, young adults, and seniors) and specific metabolic conditions (pregnant women, shift workers, and athletes) were selected to highlight advances and challenges in design and clinical evaluation of AID systems.

Aged-based subpopulations: children, adolescents, young adults, and seniors

For this review, we broadly group the pediatric subpopulation as young children, typically aged 2–6 years, school-aged children, typically aged 6–12 years (before the onset of puberty), and adolescents, aged 12–18 years (undergoing puberty), or as developmentally appropriate [6]. In the pediatric subpopulation, insulin dosages have to be continuously adjusted with age and pubertal stage to balance short-term risks, such as overnight hypoglycemia, as well as long-term risks of glycemic variability [7]. The young adult subpopulation consists of adults transitioning to full adulthood, typically aged 18–25 years.

The senior subpopulation consists of individuals, typically older than 65 years, who live with T1D. Aging and long-term duration of diabetes result in impaired

counter-regulatory responses, leading to a higher risk of hypoglycemia [8]. Seniors have often been excluded from clinical studies because of higher risks such as hypoglycemia unawareness, resulting in them not being aware of symptoms, and thus may not be intervening as others would with carbohydrate intake, as well as other cognitive and metabolic challenges [8].

Subpopulations with specific metabolic conditions: pregnant women, shift workers, and athletes

Pregnancy in T1D has unique dietary, insulin use, and target glycemic control requirements [9]. Because of the changes in insulin requirements throughout gestation, pregnant women with T1D are at a higher risk of hypoglycemia in early pregnancy and a higher risk of hyperglycemia for the remainder of their pregnancy [10]. The challenges of conducting clinical trials for AID systems in this subpopulation include lack of data on safety and effectiveness of continuous glucose monitor (CGM) use during pregnancy and the risks involving both the mother and fetus.

Shift workers engage in work outside of the usual daytime hours of 6 am to 6 pm. Common shift work schedules include evening, night, morning, rotating, and irregular shifts. Circadian misalignment causes a disruption of the glucose–insulin regulation system, resulting in impaired glucose tolerance and reduced insulin sensitivity [11,12]. Finally, we consider competitive athletes with T1D who train and professionally compete in sports [13]. Because athletes exercise and compete regularly, effective glucose management surrounding physical activity becomes essential for overall glucose control, as well as for harnessing enhanced athletic performance [14].

Differing goals and challenges for selected subpopulations

Table 1 provides a comparison of three main disturbances that affect glucose regulation:

1. Meal size and the macronutrient composition (e.g. carbohydrate, fat, and protein) cause an increase in glucose over the span of 4 h to 6 h, which is primarily rejected through insulin-dependent glucose uptake [15].
2. Physical activity increases insulin sensitivity over the following hours, but the immediate glycemic impact depends on the modality of activity (e.g. aerobic, anaerobic, or mixed) [16].
3. Psychological and physiological stress could lead to changes in stress hormones and insulin action [17].

Meals

Meal requirements, based on a balanced diet, can significantly vary based on age, pubertal stage, and activity levels [6,18]. The meal size and frequency can vary more in younger children, whereas meal sizes are relatively larger in adolescence. In seniors, a decline in food intake and loss of motivation to eat are common. Disease-related inflammation, illnesses, medication, impaired abilities, and dietary restrictions can contribute to loss of appetite [8].

For pregnant women with T1D, a moderately low carbohydrate diet with protein and fiber consumption is recommended [9]. Shift workers typically do not significantly modify their total energy intake; they change the timing and frequency of eating and the content of meals, and a greater proportion of snacks are consumed [19,20]. For athletes, nutrition is a crucial pillar of athletic performance, and effective nutrition strategies differ by exercise modality [21]. As a result, athletes have individualized training- and competition-specific dietary requirements.

Physical activity

Compared with adults, children and adolescents require greater regimentation in terms of exercise and daily scheduled activities, including moderate to vigorous intensity aerobic physical activity [22]. In addition, young children may be more active than adolescents. In seniors, muscle mass and strength decline with age. These decrements may be exacerbated by comorbidities and periods of hospitalization, leading to degradation in glucose regulation.

For pregnant women, moderate intensity exercise is recommended, although there is a shortage of research on the effects of exercise during pregnancy with T1D [23]. The already reduced glucose target range may increase the risk of exercise-related hypoglycemia in this subpopulation. Shift work generally decreases opportunities for physical activity, but subjective and physiological responses can be altered, for example, if exercise occurs at unusual times of the day or if the shift worker is sleep-deprived [24]. In athletes, general guidelines about exercise-related glucose management need to be individually customized to avoid hypoglycemia. Glycemic response to exercise is affected by the timing, intensity, and duration of exercise, as well as the starting levels of glucose, ingested meals, and insulin [25].

Stress

The primary sources of stress in pediatric population arise from siblings and peer pressure, as well as from school performance [6,26,27]. In seniors, stresses come from aging, loneliness, failing health, and lack of mobility.

Pregnant women with T1D exhibit higher stress than pregnant women without diabetes [28]. Some of the pregnancy-specific stressors are concerns related to the

Table 1

Comparison of meals, physical activities, and stress disturbances on glucose, as well as design of the AID system using glucose targets, behavioral considerations, and AID controller features for subpopulations based on age and metabolic conditions.

Subpopulation	Disturbances			Design		
	Meals	Physical activities	Stress	Glucose targets	Behavioral considerations	Controller features
Adolescents (pubertal, age 12–18); young adults (age 18–25)	Typically large meals	Activities with peers, moderate to vigorous intensity	Peer pressure, school performance, changes in lifestyle	HbA1c < 7%	Less diligence in diabetes care, sedentary lifestyle	Prioritize extended hyperglycemia prevention; high absolute basal, insulin resistance and large TDI
School-age children (prepubertal, age 6–12)	Small and frequent meals	School activities, moderate to vigorous intensity	Related to friends/peers and siblings		Limited autonomy in diabetes care	Prioritize hypoglycemia and hyperglycemia prevention; low absolute basal, high insulin sensitivity, and small TDI, activity detection and announcement
Young children (age 2–6)	Irregular meals	Active in short bursts	Related to friends/peers and siblings		Completely dependent on others for diabetes care, challenges in communicating hypoglycemia symptoms	Prioritize glycemic variability and hypoglycemia prevention; very low absolute basal, larger portion of TDI for bolus, high insulin sensitivity with small TDI, activity detection and announcement
Pregnant women (pregnancy with pre-existing T1D)	Moderately low carbohydrate intake	Moderate intensity	Pregnancy-specific stressors	HbA1c <6% fasting: 95 mg/dL, 1-h postprandial: <140 mg/dL, 2-h postprandial: <120 mg/dL	Early pregnancy: decreased food intake; Mid-pregnancy to late pregnancy: increased food intake. Declined physical activity due to maternal fatigue and other discomfort	Adaptive to changing insulin requirements through pregnancy. Assertive postprandial control
Seniors (age $\geq$ 65 years)	Gradual decrease in appetite	Decline in muscle mass and strength	Depression due to grief, loneliness, failing health, lack of mobility	HbA1c <7–7.5%; healthy target: 90–150 mg/dL; severe chronic illness target: 100–180 mg/dL	Unidentified cognitive impairment and dementia leading to difficulties in self-monitoring and use of diabetes technology	Prioritize minimization of hypoglycemia and severe hyperglycemia; reduction of overall risk from hypoglycemia unawareness
Shift workers (people working outside typical 6 am to 6 pm schedule)	Change in timing and frequency, increased consumption of snacks	Decreased opportunities for physical activity, altered responses to exercise	Altered social life resulting in psychological stress and psychosomatic disorders	HbA1c <7%	Disruption of circadian rhythms and sleep deficits	Adapt timing and dosing to frequent changes in routine, incorporate circadian and impaired glucose dynamics
Athletes (people who train and compete in sports)	Training- and competition-specific dietary requirements	Highly active, schedules depend on training and competition goals	Increased risk of stress-induced hyperglycemia around competitions	HbA1c <7%; training: TIR >70%; competition: TIR >75%	Location and type of the wearable device preference based on sport type and convenience	Exercise-informed control with announcement or detection of exercise. Multihormone systems for better prevention against exercise-induced glycemic variations.

The subpopulations are ordered by the quality of clinical validation starting with the adolescents and young adult subpopulation. Studies involving children, pregnant women, and senior subpopulations have only recently been initiated. In particular, AID systems for shift workers and athlete subpopulations require clinical validation.

baby's health, physical discomforts due to pregnancy, and childbirth [29]. Shift workers experience stress from sleep debt and reduced participation in regular social life, resulting in psychological stress and psychosomatic disorders [19]. For athletes, stress from competition may lead to an increased risk of hyperglycemia [30].

Glucose targets

The primary goal of AID systems is to regulate glucose by rejecting previously noted disturbances on glucose to maintain an average glucose approximated by an HbA1c $<7\%$ for adults and pediatric population [18], with a percent time in range (TIR) of 70−180 mg/dL $>70\%$, percent time below (TB) 70 mg/dL $<4\%$, and percent time above (TA) 180 mg/dL $<25\%$ [31]. In pediatric population, a more relaxed HbA1c $<7.5\%$ is recommended for those with hypoglycemia unawareness and other special conditions.

For seniors, depending on coexisting chronic illnesses and cognitive function, HbA1c $<8\%$ and TIR $>50\%$ are recommended. Furthermore, the recommended fasting glucose range for seniors is 90−150 mg/dL for those with few complications or 100−180 mg/dL for those with poor health [8].

Glucose targets for pregnancy are tighter at HbA1c $<6\%$ with TIR using 63−140 mg/dL, TB using 63 mg/dL, and TA using 140 mg/dL [31]. In addition, recommended glycemic targets for pregnancy are fasting plasma glucose levels below 95 mg/dL and either 1-h postprandial glucose below 140 mg/dL or 2-h postprandial glucose below 120 mg/dL [9].

For shift workers, the recommendations are generally similar to adults. For athletes, the recommendation is to have TIR $>70\%$ during training and TIR $>75\%$ during competitions [30].

Behavioral considerations and controller features

Although all subpopulations share the larger goal of safe and tight glucose regulation, differences in nominal magnitude and frequency of disturbances, as well as behavioral considerations, motivate the design of tailored AID systems. These systems must prioritize and find a balance between several controller features and posed glycemic risk for each subpopulation, as discussed in this section and in Table 1.

Children have limited ability to communicate hypoglycemia symptoms, count carbohydrates, and manage diabetes care independently. Challenges with adherence to diabetes care practices are seen in adolescents and young adults [32]. In addition, in young children, user-announced boluses may increase the risk of hypoglycemia if the meal is not completed or if emesis occurs. Compared with the adult subpopulation, insulin sensitivities are higher for children requiring smaller TDI and lower (i.e. increased insulin resistance) for adolescents and young adults requiring large TDI. Varying stages of puberty and the confounding effects of other hormones also factor into the changing insulin requirements. Children have relatively low absolute basal rate, whereas these are higher for adolescents and young adults. In children, the bolus insulin forms a larger portion of TDI [33].

Consequently, the controller has to cover a wide range of insulin requirements while having limited margin of error, especially in young children. For children, the controller should prioritize glycemic variability, hypoglycemia and hyperglycemia prevention; for adolescents, the controller should prioritize extended hyperglycemia prevention. In addition, the controller may require exercise announcements and detection with predictive modulation of insulin delivery to prevent hypoglycemia.

For pregnancy, controllers need to adapt to the changes in insulin−glucose metabolism during gestation, increased risk of postprandial hyperglycemia during late gestation, and changing TDI requirements throughout pregnancy [34]. Design considerations for wearable glucose sensors and insulin injection devices must include pregnancy-related anatomic and physiologic changes (e.g. potential discomfort with these devices around the abdomen). Meal habits are likely affected by food cravings and aversion during pregnancy [35]. Similar to young children, pregnant women are at an additional risk of meal bolus-induced hypoglycemia as vomiting is a symptom during early pregnancy [36].

For seniors, higher rates of unidentified cognitive impairment and dementia lead to difficulties in adhering to complex diabetes self-care activities. Thus, the treatment regimens must focus on minimizing hypoglycemia and severe hyperglycemia, as well as reducing the overall risk of hypoglycemia unawareness by using a higher threshold for attenuation of insulin.

Current clinical studies are investigating use of AID systems in individuals prone to hypoglycemia, NCT04266379, because they are not aware of symptoms and may not be intervening as others would with carbohydrate intake.

For shift workers, glycemic control with rotating shift patterns, varied eating habits and times, alterations in physical activity, and fluctuations in hormone levels present challenges to optimal insulin dosing. The controller design should incorporate circadian dynamics and changes in routine to determine insulin requirements.

For athletes, the need for individualized and adaptive AID systems stems from training-related changes in energy metabolism, frequent physical activity engagement, increased risk for developing hypoglycemia unawareness, and compromised counter-regulation due to prolonged exercise [37]. Exercise-informed glucose control systems that can integrate the time, duration, and modality of exercise as well as training and competition schedules would improve glucose control in this subpopulation. Multihormone systems can also be used for improved hypoglycemia protection [38]. Design considerations must include convenience and degree of user interaction during active competition [39].

Recent advances in clinical trials

We analyzed original investigations of AID systems for T1D published in journals over the 5 years between 2017 and 2021. Studies reporting separate results for a mixed subpopulation or different AID configurations were included separately. Publications were excluded if the duration of investigation was less than one day, if they reported retrospective analysis, if they used multihormonal or low glucose suspend systems, or if they did not report all clinical outcomes described in the following. Data from the conventional therapy or control arm of the studies are not included.

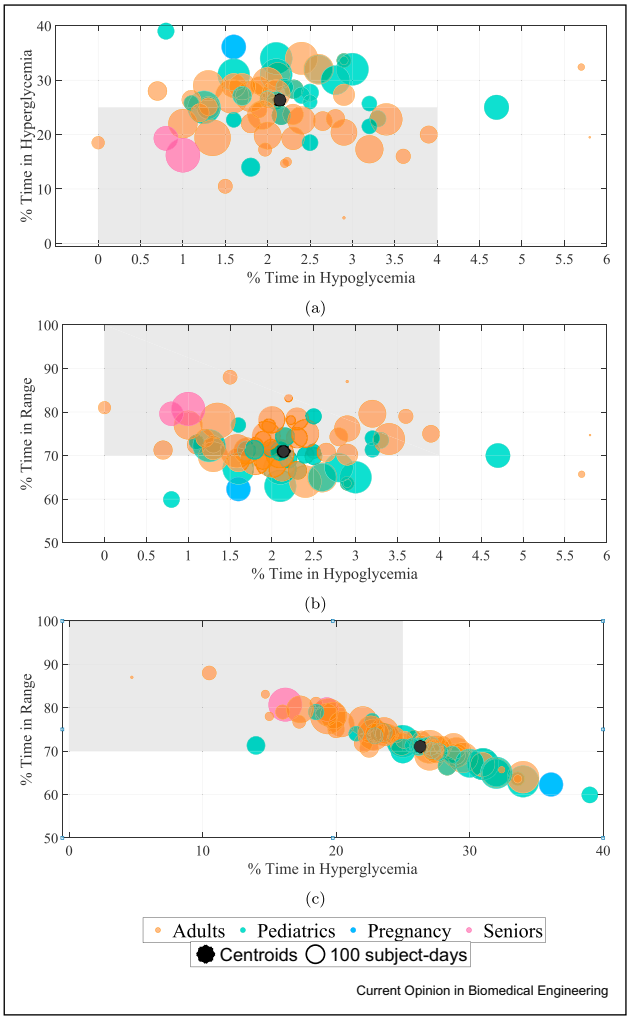
AID investigations in 2017–2021

Figure 2 compares the TIR, TB, and TA from eligible studies, and Figure 3 compares the number of studies over each of the five years. The eligible investigations (78) included adults (49), pediatric (29), pregnant women (1), and senior (2) subpopulations in various settings. Studies ranged from single-arm early feasibility studies [5] to large, randomized-crossover, multicenter, outpatient studies in adults, adolescents and children [40–43], pregnant women [44], and seniors [45,46] and to studies on subjects with hypoglycemia unawareness [47]. The number of participants in the AID arm ranged from 4 to 882, and the duration ranged from 1 to 182 days; the combination of the number of participants and the duration ranged from 7.5 to 56, 448 subject-days. The complete list of included studies is provided in Supplementary Table 1 [b]

Time in range

For all subjects, the TIR centroid was 71%. The TIR centroid in adults was 72.5%, in pediatric population was 67.5%, in pregnancy was 62.3%, and in seniors was 80.3%. A larger proportion of adult studies (36/49 or 73.5%) achieved the TIR target than that of pediatric studies (15/29 or 51.7%), highlighting the challenge of glucose control in children and adolescents.

Figure 2



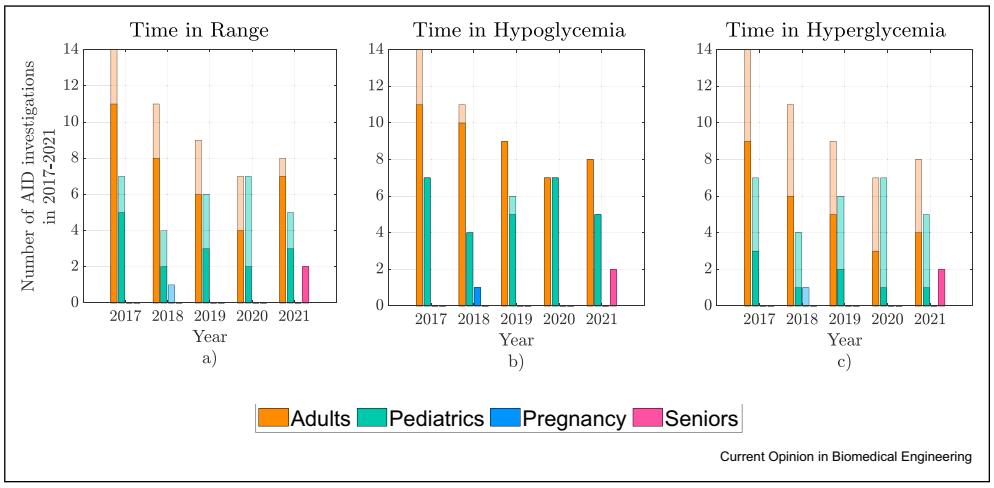
Comparison of percent time spent in range (TIR), percent time below (TB), and percent time above (TA) from investigations conducted in 2017–2021.Comparison of TA and TB is shown in **(a)**, TIR and TB in **(b)**, and TIR and TA in **(c)**. Each data point represents a measure of central tendency reported in the study; the size of the bubble is proportional to the number of participants in the AID arm times the length of the study. The centroid or the weighted average of percent time metrics is shown by an asterisk. The clinical targets of TIR >70%, TB <4%, and TA <25% for assessment of glucose control are shown by the shaded region, where TIR, TB, and TA are calculated using subpopulation-specific ranges and thresholds described in Section Glucose targets.

Time in hypoglycemia

For all subjects, the TB centroid was 2.1%. The TB centroid in adults was 2.1%, in pediatric population was 2.3%, in pregnancy was 1.6%, and in seniors was 0.9%. The plots reveal that AID systems reached the clinical target of TB consistently over the years and across the four subpopulations in 73 of 78 or 93.5% of study data points conducted in different settings. This result

[b] Readers can retrieve all published clinical studies of the AID systems by accessing the Artificial Pancreas Clinical Trial Database at https://www.thedoylegroup.org/apdatabase. This tool allows researchers to perform queries and comparisons of clinical trial details.

Figure 3



Year-by-year comparison of the number of AID investigations grouped by four subpopulations, with overlapping filled bars representing the number of investigations whose outcomes satisfied clinical targets of **(a)** TIR >70%, **(b)** TB <4%, and **(c)** TA <25%.

underscores the effectiveness of AID systems in reducing the primary risk associated with intensive insulin therapy [48].

Time in hyperglycemia

For all subjects, the TA centroid was 26.3%. The TA centroid in adults was 24.9%, in pediatric population was 29.6%, in pregnancy was 36.1%, and in seniors was 17.2%. As with TIR, a larger proportion of adult studies (27/49 or 55.1%) achieved the TA target than that of pediatric studies (8/29, or 27.5%). The proportion of studies satisfying the TA target was lower than that satisfying the TIR and TB targets, thus highlighting the challenges in postprandial glucose management even with meal announcements [49]. As shown in Figure 2, TIR and TA were negatively correlated ($\rho = -0.96, p < 0.001$), suggesting that reduction in TA could lead to direct improvements in TIR, whereas no correlations were observed between TIR and TB ($\rho = -0.1, p = 0.37$), nor between TA and TB ($\rho = -0.01, p = 0.90$).

Conclusions and future work

Recent advances in AID system development have led to improved clinical outcomes, including increased TIR and significant reduction in time in hypoglycemia. However, large barriers remain for reducing time in hyperglycemia. In this review, we emphasized age-based and specific metabolic condition—based subpopulations to discuss tailoring and prioritizing controller design to reject disturbances and achieve glucose regulation and highlighted areas for further research. Additional subpopulations and conditions not discussed in this review include individuals who are hospitalized, those with poor glycemic control, and during menstrual cycles, as well as aspects on use, access, and cost of AID systems. Future goals for AID algorithms, simulation tools, and device design, as well as its clinical validation, include the consideration of different requirements and use cases to bridge the care gap for all subpopulations with T1D.

Credit author statement

Eleonora M. Aiello: Conceptualization, Software, Validation, Visualization, Investigation, Data curation and Writing – original draft. **Sunil Deshpande:** Conceptualization, Validation, Investigation, Data curation and Writing – original draft. **Basak Ozaslan:** Conceptualization, Investigation, Data curation and Writing – original draft. **Kelilah L. Wolkowicz:** Visualization, Investigation, Data curation and Writing – original draft. **Jordan E. Pinsker:** Funding acquisition, Supervision, Writing- Reviewing and Editing. **Eyal Dassau:** Funding acquisition, Supervision, Writing- Reviewing and Editing. **Francis J. Doyle,** III: Funding acquisition, Supervision, Writing-Reviewing and Editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

E.D. reports receiving grants from JDRF, NIH, and Helmsley Charitable Trust, personal fees from Roche and Eli Lilly, patents on artificial pancreas technology, and product support from Dexcom, Insulet, Tandem, and Roche.

E.D. is currently an employee and shareholder of Eli Lilly and Company. The work presented in this

manuscript was performed as part of his academic appointment and is independent of his employment with Eli Lilly and Company.

J.E.P. is currently an employee of Tandem Diabetes Care, Inc. The work presented in the manuscript was performed as part of his academic appointment at Sansum Diabetes Research Institute and is independent of his employment with Tandem Diabetes Care.

F.J.D. reports equity, licensed IP and is a member of the Scientific Advisory Board of Mode AGC. All other authors report no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cobme.2021.100312.

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* of special interest
** of outstanding interest

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