ΠΑΝΕΠΙΣΤΗΜΙΟ ΠΕΙΡΑΙΩΣ

ΤΜΗΜΑ ΟΙΚΟΝΟΜΙΚΗΣ ΕΠΙΣΤΗΜΗΣ

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ
«ΟΙΚΟΝΟΜΙΚΑ και ΔΙΟΙΚΗΣΗ της ΥΓΕΙΑΣ»

ΑΠΟΤΕΛΕΣΜΑΤΙΚΟΤΗΤΑ ΤΩΝ ΣΥΣΤΗΜΑΤΩΝ ΚΛΕΙΣΤΟΥ ΒΡΟΧΟΥ ΧΟΡΗΓΗΣΗΣ ΙΝΣΟΥΛΙΝΗΣ ΣΤΗ ΓΛΥΚΑΙΜΙΚΗ ΡΥΘΜΙΣΗ ΑΣΘΕΝΩΝ ΜΕ ΣΑΚΧΑΡΩΔΗ ΔΙΑΒΗΤΗ ΤΥΠΟΥ 1: ΣΥΣΤΗΜΑΤΙΚΗ ΑΝΑΣΚΟΠΗΣΗ ΤΥΧΑΙΟΠΟΙΗΜΕΝΩΝ ΚΛΙΝΙΚΩΝ ΔΟΚΙΜΩΝ

Αικατερίνη Τζιωρτζιοπούλου

Διπλωματική Εργασία υποβληθείσα στο Τμήμα Οικονομικής Επιστήμης
του Πανεπιστημίου Πειραιώς για την απόκτηση
Μεταπτυχιακού Διπλώματος Ειδίκευσης στα Οικονομικά και Διοίκηση της Υγείας.

Πειραιάς, 2026

ΠΑΝΕΠΙΣΤΗΜΙΟ ΠΕΙΡΑΙΩΣ

ΤΜΗΜΑ ΟΙΚΟΝΟΜΙΚΗΣ ΕΠΙΣΤΗΜΗΣ

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Πανεπιστήμιο Πειραιώς

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ΠΑΝΕΠΙΣΤΗΜΙΟ ΠΕΙΡΑΙΩΣ

ΤΜΗΜΑ ΟΙΚΟΝΟΜΙΚΗΣ ΕΠΙΣΤΗΜΗΣ

M.Sc. in Health Economics and Management

Effectiveness of Closed-Loop Insulin Delivery Systems in Glycemic Control of Patients with Type 1 Diabetes: A Systematic Review of Randomized Clinical Trials

Aikaterini Tziortziopoulou

Master Thesis submitted to the Department of Economics
of the University of Piraeus in partial fulfillment of the requirements
for the degree of M.Sc. in Health Economics and Management
Piraeus, Greece, 2026

ΒΕΒΑΙΩΣΗ ΕΚΠΟΝΗΣΗΣ ΔΙΠΛΩΜΑΤΙΚΗΣ ΕΡΓΑΣΙΑΣ

«Δηλώνω υπεύθυνα ότι το έργο που εκπονήθηκε και παρουσιάζεται στην υποβαλλόμενη διπλωματική εργασία έχει γραφτεί από εμένα αποκλειστικά στο σύνολό της. Δεν έχει υποβληθεί, ούτε έχει εγκριθεί στο πλαίσιο κάποιου άλλου μεταπτυχιακού προγράμματος ή προπτυχιακού τίτλου σπουδών, ούτε είναι εργασία ή τμήμα εργασίας ακαδημαϊκού ή επαγγελματικού χαρακτήρα.

Δηλώνω επίσης, ότι αναφέρονται καταλλήλως στο σύνολό τους οι πηγές στις οποίες ανέτρεξα για την εκπόνηση της συγκεκριμένης εργασίας. Παράβαση της ανωτέρω ακαδημαϊκής μου ευθύνης αποτελεί ουσιώδη λόγο για την ανάκληση του πτυχίου μου».

Ονοματεπώνυμο Αικατερίνη Τζιωρτζιοπούλου

Υπογραφή Μεταπτυχιακού Φοιτητή

Ευχαριστίες

Με την ολοκλήρωση της παρούσας διπλωματικής εργασίας, θα ήθελα να εκφράσω τις θερμές μου ευχαριστίες σε όλους όσοι συνέβαλαν, με τον τρόπο τους, στην πραγματοποίησή της.

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Περιεχόμενα

Αποτελεσματικότητα των συστημάτων κλειστού βρόχου χορήγησης ινσουλίνης στη γλυκαιμική ρύθμιση ασθενών με Σακχαρώδη Διαβήτη Τύπου 1: συστηματική ανασκόπηση τυχαιοποιημένων κλινικών δοκιμών

Σημαντικοί Όροι: Σακχαρώδης Διαβήτης Τύπου 1, γλυκόζη, ινσουλίνη, υπογλυκαιμία, τεχνολογία, αυτοματοποίηση, μεταβλητότητα.

Περίληψη

Ο Σακχαρώδης Διαβήτης Τύπου 1 (ΣΔ1) αποτελεί μια χρόνια αυτοάνοση νόσο που χαρακτηρίζεται από απόλυτη ανεπάρκεια ινσουλίνης και απαιτεί δια βίου εξωγενή χορήγησή της. Η επίτευξη βέλτιστου γλυκαιμικού ελέγχου είναι καθοριστικής σημασίας για την πρόληψη οξέων και χρόνιων επιπλοκών, ωστόσο η διαχείριση της νόσου παραμένει σύνθετη και απαιτητική. Τα τελευταία χρόνια, η αξιολόγηση της ρύθμισης έχει μετατοπιστεί από τη μονοδιάστατη προσέγγιση της γλυκοζυλιωμένης αιμοσφαιρίνης (HbA1c) σε μια πολυπαραμετρική αποτίμηση που περιλαμβάνει δείκτες συνεχούς καταγραφής γλυκόζης, όπως ο χρόνος εντός στόχου (Time in Range), ο χρόνος κάτω από το εύρος στόχου και η γλυκαιμική μεταβλητότητα.

Σκοπός της παρούσας συστηματικής ανασκόπησης ήταν η αξιολόγηση της αποτελεσματικότητας της συνεχούς παρακολούθησης γλυκόζης (CGM) και των συστημάτων αυτοματοποιημένης χορήγησης ινσουλίνης (hybrid/closed-loop) σε άτομα με ΣΔ1, σε σύγκριση με τη συμβατική θεραπεία (πολλαπλές ημερήσιες ενέσεις και αυτοπαρακολούθηση γλυκόζης) ή με λιγότερο αυτοματοποιημένα τεχνολογικά σχήματα. Η ανασκόπηση βασίστηκε σε τυχαιοποιημένες ελεγχόμενες κλινικές δοκιμές και ακολούθησε συστηματική και αναπαραγώγιμη διαδικασία επιλογής και αξιολόγησης των μελετών. Συνολικά, συμπεριλήφθηκαν 65 κλινικές δοκιμές στην ποιοτική ανάλυση.

Τα ευρήματα της ανασκόπησης κατέδειξαν ότι τα συστήματα κλειστού βρόχου επιτυγχάνουν σταθερή και κλινικά ουσιαστική αύξηση του χρόνου εντός στόχου (Time in Range), συνοδευόμενη από μείωση του χρόνου σε υπεργλυκαιμικά επίπεδα, χωρίς αντίστοιχη αύξηση του κινδύνου υπογλυκαιμίας. Σε πολλές μελέτες καταγράφηκε παράλληλη βελτίωση της HbA1c και της γλυκαιμικής μεταβλητότητας, καθώς και μείωση του θεραπευτικού

φορτίου. Η συνεχής καταγραφή γλυκόζης, τόσο ως αυτόνομη τεχνολογία, όσο και ως μέρος συστημάτων αυτοματοποιημένης ινσουλινοθεραπείας, συμβάλλει στη βελτίωση της ασφάλειας και της σταθερότητας της γλυκαιμικής ρύθμισης, ιδίως σε άτομα με αυξημένο κίνδυνο υπογλυκαιμικών επεισοδίων.

Συμπερασματικά, οι τεχνολογικές παρεμβάσεις στη διαχείριση του ΣΔ1 υπερέχουν της συμβατικής θεραπείας ως προς την ποιότητα και τη σταθερότητα του γλυκαιμικού ελέγχου. Η ενσωμάτωσή τους στην κλινική πράξη δύναται να βελτιώσει ουσιαστικά τα γλυκαιμικά αποτελέσματα και την ασφάλεια των ασθενών, υπό την προϋπόθεση κατάλληλης εκπαίδευσης και εξατομικευμένης εφαρμογής.

Effectiveness of Closed-Loop Insulin Delivery Systems in Glycemic Control of Patients with Type 1 Diabetes: A Systematic Review of Randomized Clinical Trials

Keywords: Type 1 Diabetes, glucose, insulin, hypoglycemia, technology, automation, variability

Abstract

Type 1 Diabetes Mellitus (T1D) is a chronic autoimmune disease characterized by absolute insulin deficiency and requiring lifelong exogenous insulin administration. Achieving optimal glycemic control is crucial for the prevention of both acute and chronic complications; however, disease management remains complex and demanding. In recent years, the assessment of glycemic regulation has shifted from the unidimensional approach of glycated hemoglobin (HbA1c) to a multiparametric evaluation that includes continuous glucose monitoring (CGM) metrics, such as Time in Range (TIR), Time Below Range (TBR), and glycemic variability.

The aim of the present systematic review was to evaluate the effectiveness of continuous glucose monitoring (CGM) and automated insulin delivery systems (hybrid/closed-loop) in individuals with T1D, compared with conventional therapy (multiple daily injections and self-monitoring of blood glucose) or less automated technological regimens. The review was based on randomized controlled clinical trials and followed a systematic and reproducible process for study selection and evaluation. A total of 65 clinical trials were included in the qualitative analysis.

The findings demonstrated that closed-loop systems provide a consistent and clinically significant increase in Time in Range, accompanied by a reduction in hyperglycemia, without increasing the risk of hypoglycemia. Many studies also reported improvements in HbA1c and glycemic variability, as well as a reduction in treatment burden. Continuous glucose monitoring, both as a standalone technology and as a component of automated insulin delivery systems, contributes to safer and more stable glycemic control, particularly in populations at high risk for hypoglycemia.

In conclusion, technological interventions in the management of T1D appear to be superior to conventional therapy in terms of the quality and stability of glycemic control.

Their integration into clinical practice has the potential to substantially improve glycemic outcomes and patient safety, provided that appropriate education and individualized implementation are ensured.

ΚΕΦΑΛΑΙΟ 1
ΘΕΩΡΗΤΙΚΟ ΥΠΟΒΑΘΡΟ
ΣΑΚΧΑΡΩΔΗΣ ΔΙΑΒΗΤΗΣ ΤΥΠΟΥ 1 ΚΑΙ ΤΕΧΝΟΛΟΓΙΚΕΣ ΠΑΡΕΜΒΑΣΕΙΣ ΣΤΗ ΓΛΥΚΑΙΜΙΚΗ ΡΥΘΜΙΣΗ

Ο Σακχαρώδης Διαβήτης Τύπου 1 (ΣΔ1) αποτελεί χρόνια αυτοάνοση νόσο, η οποία χαρακτηρίζεται από προοδευτική καταστροφή των β-κυττάρων του παγκρέατος και επακόλουθη απόλυτη ανεπάρκεια ινσουλίνης, καθιστώντας αναγκαία τη δια βίου εξωγενή χορήγησή της (Donath, 2022; Roep et al., 2021). Παρότι παραδοσιακά θεωρούνταν κυρίως παιδιατρική νόσος, σύμφωνα με τα σύγχρονα επιστημονικά δεδομένα, η εμφάνιση της νόσου δεν περιορίζεται σε συγκεκριμένες ηλικιακές ομάδες, αλλά μπορεί να παρουσιαστεί σε οποιοδήποτε στάδιο της ζωής, με σημαντικό ποσοστό νέων διαγνώσεων να αφορά εφήβους, νεαρούς ενήλικες αλλά και μεγαλύτερες ηλικιακές ομάδες (Bell & Lain, 2025). Η διαχείριση του ΣΔ1 στοχεύει στη διατήρηση της γλυκόζης αίματος εντός ασφαλών ορίων, περιορίζοντας ταυτόχρονα τόσο τη χρόνια υπεργλυκαιμία όσο και τα επεισόδια υπογλυκαιμίας. Η σημασία του στόχου αυτού έγκειται στη στενή του συσχέτιση με την πρόληψη των οξέων μεταβολικών επιπλοκών (π.χ. σοβαρή υπογλυκαιμία, διαβητική κετοξέωση), καθώς και των μακροπρόθεσμων μακροαγγειακών και μικροαγγειακών επιπλοκών (Yoo & Kim, 2020).

Παραδοσιακά, η γλυκοζυλιωμένη αιμοσφαιρίνη (HbA1c) αποτελούσε τον βασικό δείκτη αξιολόγησης του γλυκαιμικού ελέγχου, καθώς αντανακλά τη μέση τιμή της γλυκόζης στο αίμα κατά τις τελευταίες εβδομάδες. Ωστόσο, η HbA1c δεν αποτυπώνει επαρκώς τη δυναμική φύση της ρύθμισης στον ΣΔ1, καθώς δεν παρέχει πληροφορίες για τη γλυκαιμική μεταβλητότητα ούτε για τη συχνότητα και διάρκεια των υπογλυκαιμικών επεισοδίων, παράγοντες που επηρεάζουν ουσιαστικά την ασφάλεια και τη βιωσιμότητα της θεραπείας (Lazar et al., 2023; Toschi et al., 2020). Στο πλαίσιο αυτό, η ευρεία χρήση της συνεχούς παρακολούθησης γλυκόζης (continuous glucose monitoring, CGM) ανέδειξε νέους, κλινικά σημαντικούς δείκτες, όπως ο χρόνος εντός στόχου (Time in Range, TIR), ο χρόνος κάτω από το εύρος στόχου (Time Below Range, TBR) και ο συντελεστής μεταβλητότητας (%CV), επιτρέποντας μια πιο ολοκληρωμένη και πολυπαραμετρική αξιολόγηση του γλυκαιμικού ελέγχου (Bell & Lain, 2025; Lazar et al., 2023). Παράλληλα, η τεχνολογική εξέλιξη στη χορήγηση ινσουλίνης οδήγησε στην ανάπτυξη συστημάτων αυτοματοποιημένης χορήγησης ινσουλίνης και υβριδικού

κλειστού βρόχου (closed-loop), τα οποία αξιοποιούν δεδομένα CGM για την αυτόματη προσαρμογή της βασικής ινσουλίνης και στοχεύουν τόσο στη βελτίωση της ρύθμισης όσο και στη μείωση του θεραπευτικού φορτίου (Freckmann, 2020; Heinemann et al., 2018a). Ωστόσο, δεδομένης της ετερογένειας των διαθέσιμων τεχνολογιών και των διαφορετικών συγκριτικών σχημάτων (συμβατική θεραπεία, αντλία χωρίς αυτοματοποίηση, SAP), καθίσταται αναγκαία η συστηματική αξιολόγηση των δεδομένων από τυχαιοποιημένες ελεγχόμενες δοκιμές, ώστε να αποσαφηνιστεί η κλινική επίδραση της CGM και των closed-loop συστημάτων τόσο στη HbA1c όσο και στους σύγχρονους δείκτες γλυκαιμικού ελέγχου.

1.1 Σκοπός

Σκοπός της παρούσας συστηματικής ανασκόπησης είναι να αξιολογηθεί, σε άτομα με Σακχαρώδη Διαβήτη Τύπου 1, η επίδραση της συνεχούς παρακολούθησης γλυκόζης (CGM) και των συστημάτων αυτοματοποιημένης χορήγησης ινσουλίνης (αντλία/closed-loop) στη μεταβολή της HbA1c και σε δείκτες γλυκαιμικού ελέγχου, σε σύγκριση με συμβατική θεραπεία (π.χ. SMBG, MDI) ή/και με λιγότερο αυτοματοποιημένα τεχνολογικά σχήματα (π.χ. αντλία χωρίς closed-loop, SAP), μέσω σύνθεσης δεδομένων από τυχαιοποιημένες ελεγχόμενες δοκιμές.

1.2 Σακχαρώδης Διαβήτης Τύπου 1 (ΣΔ1)

Ο Σακχαρώδης Διαβήτης Τύπου 1 (ΣΔ1) αποτελεί μια χρόνια, αυτοάνοση νόσο κατά την οποία το ανοσοποιητικό σύστημα στοχεύει και καταστρέφει προοδευτικά τα β-κύτταρα των νησιδίων του Langerhans στο πάγκρεας, οδηγώντας σε απόλυτη ή σχεδόν απόλυτη ανεπάρκεια ινσουλίνης και ανάγκη εξωγενούς χορήγησής της για την επιβίωση του ατόμου (Donath, 2022; Roep et al., 2021). Αν και ο ΣΔ1 έχει παραδοσιακά χαρακτηριστεί ως νόσος της παιδικής ηλικίας, τα σύγχρονα δεδομένα καταδεικνύουν ότι μπορεί να εκδηλωθεί σε οποιοδήποτε στάδιο της ζωής. Σημαντικό ποσοστό των νέων διαγνώσεων αφορά εφήβους, νεαρούς ενήλικες, αλλά και άτομα μεγαλύτερης ηλικίας (Bell & Lain, 2025).

Η ιστορική εξέλιξη της κατανόησης του ΣΔ1 είναι χαρακτηριστική για τον τρόπο με τον οποίο η ιατρική γνώση μετασχηματίζεται με βάση νέα ερευνητικά δεδομένα. Για αιώνες, ο διαβήτης αντιμετωπιζόταν ως μία ενιαία μεταβολική νόσος, η οποία στην προ ινσουλίνης εποχή οδηγούσε σε ταχεία απώλεια βάρους, αφυδάτωση και θάνατο. Η ανακάλυψη της ινσουλίνης το 1921 αποτέλεσε σημείο καμπής, καθώς μετέτρεψε μια θανατηφόρο νόσο σε χρόνιο, θεραπεύσιμο νόσημα, χωρίς όμως να εξηγεί την αιτιολογία της (Cavalli et al., 2025). Η δεκαετία του 1970 σηματοδότησε μια καθοριστική καμπή στην επιστημονική προσέγγιση της νόσου, όταν η συσχέτιση με HLA γονίδια, η παρατήρηση νησιδιακής φλεγμονής (insulitis) και η ανακάλυψη αυτοαντισωμάτων οδήγησαν στην επικράτηση του αυτοάνοσου μοντέλου παθογένειας (Cavalli et al., 2025).

Το κυρίαρχο παθοφυσιολογικό μοντέλο περιγράφει τον ΣΔ1 ως αποτέλεσμα δυσλειτουργίας της ανοσολογικής ανοχής. Σε γενετικά επιρρεπή άτομα, περιβαλλοντικοί ή ενδογενείς παράγοντες δρουν ως εκλυτικοί μηχανισμοί, οδηγώντας

σε ενεργοποίηση αυτοαντιδραστικών Τ-λεμφοκυττάρων και σε ανοσολογική επίθεση κατά των β-κυττάρων (Donath, 2022; Roep et al., 2021). Η διαδικασία αυτή εξελίσσεται συνήθως για μήνες ή και χρόνια πριν την κλινική διάγνωση, με σταδιακή μείωση της β-κυτταρικής μάζας και λειτουργίας (Donath, 2022; Roep et al., 2021). Κλασικά, ο ΣΔ1 θεωρήθηκε «Τ-κυτταρο-μεσολαβούμενη» αυτοάνοση νόσος. Ωστόσο, τα τελευταία χρόνια, η βιβλιογραφία υποστηρίζει ότι τα β-κύτταρα δεν αποτελούν απλώς παθητικά θύματα της ανοσολογικής επίθεσης. Αντίθετα, ενδέχεται να συμμετέχουν ενεργά στην παθογένεση μέσω μηχανισμών β-κυτταρικού stress, μεταβολικής δυσλειτουργίας, αυξημένης ανοσογονικότητας και αλλαγών στην παρουσίαση αντιγόνων (Roep et al., 2021). Η ανασκόπηση των Roep και συνεργατών υποστηρίζει ότι η β-κυτταρική ευαλωτότητα σε βιοσυνθετικό stress και φλεγμονώδεις καταστάσεις μπορεί να δημιουργεί ένα φαύλο κύκλο: το β-κύτταρο στρεσάρεται, εκφράζει/παρουσιάζει περισσότερα αντιγόνα και έτσι γίνεται πιο «ορατό» στο ανοσοποιητικό σύστημα, το οποίο με τη σειρά του εντείνει την επίθεση (Roep et al., 2021).

Σημαντικό στοιχείο υπέρ μιας πιο σύνθετης θεώρησης του ΣΔ1 είναι το γεγονός ότι σε ιστολογικές μελέτες παγκρέατος παρατηρείται συχνά περιορισμένη νησιδιακή διήθηση (insulitis) και ότι σε αρκετούς ασθενείς διατηρείται υπολειμματική β-κυτταρική μάζα για μεγάλο χρονικό διάστημα μετά τη διάγνωση (Donath, 2022; Roep et al., 2021). Αυτά τα δεδομένα αμφισβητούν ένα υπεραπλουστευμένο μοντέλο όπου η νόσος εξηγείται αποκλειστικά ως μαζική και άμεση ανοσολογική καταστροφή (Donath, 2022; Roep et al., 2021).

Η εμφάνιση αυτοαντισωμάτων έναντι αντιγόνων των νησιδίων αποτελεί ένα από τα πιο σταθερά ευρήματα στην προκλινική φάση του ΣΔ1. Τα πιο συχνά αυτοαντισώματα περιλαμβάνουν αντισώματα έναντι της ινσουλίνης, της GAD (glutamate decarboxylase), της IA-2 (insulinoma antigen 2) και του ZnT8 (zinc transporter 8) (Popoviciu et al., 2023; Roep et al., 2021). Η παρουσία πολλαπλών αυτοαντισωμάτων θεωρείται ισχυρός προγνωστικός δείκτης εξέλιξης προς κλινικό ΣΔ1 (Bell & Lain, 2025; Roep et al., 2021).

Με βάση σύγχρονες επιστημονικές προσεγγίσεις, ο ΣΔ1 δεν αντιμετωπίζεται πλέον ως ένα γεγονός που ξεκινά με τη διάγνωση, αλλά ως μια εξελισσόμενη διαδικασία με διακριτά στάδια. Όπως περιγράφεται και στην επιδημιολογική ανασκόπηση των Bell και Lain, ο ΣΔ1 αναπτύσσεται μέσα από δύο «σιωπηλά» προ-συμπτωματικά στάδια:

- Στάδιο 1: παρουσία ≥2 επίμονων αυτοαντισωμάτων με φυσιολογική γλυκαιμία

- Στάδιο 2: παρουσία ≥2 αυτοαντισωμάτων με δυσγλυκαιμία

και στη συνέχεια εξελίσσεται στο Στάδιο 3, όπου εμφανίζεται υπεργλυκαιμία και κλινικά συμπτώματα, με ανάγκη ινσουλινοθεραπείας (Bell & Lain, 2025).

Αυτή η σταδιοποίηση είναι ιδιαίτερα σημαντική όχι μόνο για την κατανόηση της παθογένειας, αλλά και για τη μελλοντική πρόληψη ή καθυστέρηση της κλινικής νόσου μέσω ανοσοτροποποιητικών παρεμβάσεων. Παράλληλα, αποτυπώνει ότι ο ΣΔ1 είναι μια χρόνια ανοσολογική διεργασία, η οποία συχνά ξεκινά πολύ νωρίτερα από την κλινική διάγνωση (Bell & Lain, 2025).

Η γενετική προδιάθεση αποτελεί κεντρικό στοιχείο του κινδύνου εμφάνισης ΣΔ1. Τα HLA γονίδια, ιδιαίτερα τα HLA class II loci, αντιπροσωπεύουν μεγάλο μέρος της κληρονομικότητας της νόσου. Σύμφωνα με την ανασκόπηση των Roep και συνεργατών, τα HLA γονίδια μπορούν να εξηγούν έως και το 50% του γενετικού κινδύνου για ΣΔ1, γεγονός που υποδεικνύει τη σημασία της παρουσίασης αυτοαντιγονικών πεπτιδίων στην παθογένεση (Roep et al., 2021). Παράλληλα, έχουν συσχετιστεί και μη-HLA πολυμορφισμοί (π.χ. INS-VNTR, PTPN22, CTLA4, IL2RA) με μηχανισμούς μειωμένης ανοσολογικής ανοχής και αυξημένης ενεργοποίησης Τ-κυττάρων (Roep et al., 2021). Ωστόσο, ο ΣΔ1 δεν μπορεί να εξηγηθεί μόνο από τη γενετική. Η μεγάλη αύξηση της εμφάνισης της νόσου σε πολλές χώρες μέσα σε σχετικά σύντομο χρονικό διάστημα υποδηλώνει ότι περιβαλλοντικοί παράγοντες διαδραματίζουν επίσης κρίσιμο ρόλο (Bell & Lain, 2025). Μεταξύ των πιθανών περιβαλλοντικών παραγόντων που έχουν συσχετιστεί με την εμφάνιση της νόσου συγκαταλέγονται οι ιογενείς λοιμώξεις, συγκεκριμένοι διατροφικοί παράγοντες και η ανεπάρκεια βιταμίνης D, αλλαγές στο μικροβίωμα και άλλοι μηχανισμοί που επηρεάζουν την ανοσολογική ρύθμιση (Popoviciu et al., 2023). Παρότι πολλοί από αυτούς έχουν συσχετιστεί με αυξημένο κίνδυνο, δεν υπάρχει ακόμη απόλυτα τεκμηριωμένος, ενιαίος αιτιολογικός παράγοντας (Popoviciu et al., 2023).

Η επιδημιολογία του ΣΔ1 μεταβάλλεται σημαντικά τις τελευταίες δεκαετίες. Σύμφωνα με τη σύγχρονη ανασκόπηση των Bell και Lain, η παγκόσμια επικράτηση του ΣΔ1 εκτιμάται ότι ανέρχεται σε περίπου 9,2 εκατομμύρια άτομα το 2024, εκ των οποίων 1,8 εκατομμύρια είναι παιδιά και έφηβοι κάτω των 20 ετών (Bell & Lain, 2025). Παράλληλα, το 2024 αναφέρονται πάνω από 500.000 νέες διαγνώσεις ετησίως παγκοσμίως, γεγονός που επιβεβαιώνει την αυξητική τάση (Bell & Lain, 2025). Η επίπτωση παρουσιάζει μεγάλες γεωγραφικές διακυμάνσεις, με υψηλότερα ποσοστά σε χώρες υψηλού εισοδήματος (π.χ. Φινλανδία, Αυστραλία), ενώ σε πολλές περιοχές

χαμηλού και μεσαίου εισοδήματος η καταγραφή πιθανώς υποεκτιμά το πραγματικό φορτίο λόγω περιορισμένης επιδημιολογικής επιτήρησης (Bell & Lain, 2025). Επιπλέον, οι Bell και Lain αναφέρουν ότι η νόσος εμφανίζει χαρακτηριστικές ηλικιακές κορυφώσεις στην παιδική ηλικία, με δύο peaks: 4–7 ετών και 10–14 ετών, ενώ οι μικρότερες ηλικίες φαίνεται να έχουν ταχύτερη εξέλιξη από τα πρώιμα στάδια προς την κλινική νόσο (Bell & Lain, 2025). Η σύγχρονη αυτή επιδημιολογική εικόνα είναι σημαντική, καθώς συνδέεται άμεσα με την ανάγκη ανάπτυξης στρατηγικών έγκαιρης ανίχνευσης, πρόληψης και αποτελεσματικής διαχείρισης (Bell & Lain, 2025).

Ιστορικά, η παθοφυσιολογία της κλινικής εικόνας του ΣΔ1 ερμηνευόταν σχεδόν αποκλειστικά ως αποτέλεσμα της αυτοάνοσης καταστροφής των παγκρεατικών β-κυττάρων. Ωστόσο, νεότερα δεδομένα δείχνουν ότι η β-κυτταρική δυσλειτουργία μπορεί να προηγείται ή να συνυπάρχει με την απώλεια β-κυτταρικής μάζας. Σε πρόσφατη μελέτη του 2025 (Cell Reports), η οποία βασίστηκε σε ζωντανές τομές ανθρώπινου παγκρέατος από δότες με πρόσφατα διαγνωσμένο ΣΔ1, παρατηρήθηκε ότι τα νησίδια που περιείχαν β-κύτταρα εμφάνιζαν σημαντική μείωση της απόκρισης στη γλυκόζη, παρά το γεγονός ότι τα κύτταρα διατηρούσαν βιωσιμότητα και ανταποκρίνονταν σε άλλες διεγέρσεις όπως το KCl (Huber et al., 2025). Ένα ιδιαίτερα ενδιαφέρον εύρημα ήταν ότι η δυσλειτουργία των β-κυττάρων δεν συσχετιζόταν άμεσα με την παρουσία τοπικής διήθησης από Τ-λεμφοκύτταρα σε επίπεδο νησιδίου, υποδηλώνοντας ότι η δυσλειτουργία είναι ευρύτερη και όχι αποκλειστικά αποτέλεσμα άμεσης κυτταρικής επίθεσης (Huber et al., 2025). Τα ευρήματα αυτά ενισχύουν την ιδέα ότι ο ΣΔ1 μπορεί να περιλαμβάνει όχι μόνο ανοσολογική καταστροφή, αλλά και σημαντικό μεταβολικό/κυτταρικό stress στα β-κύτταρα, με αλλαγές σε γονίδια και πρωτεΐνες που εμπλέκονται στη σύζευξη γλυκόζης-έκκρισης ινσουλίνης (Huber et al., 2025). Αυτό είναι ιδιαίτερα κρίσιμο για τη συνολική κατανόηση της νόσου, καθώς υποδεικνύει ότι θεραπευτικές στρατηγικές που στοχεύουν αποκλειστικά στην ανοσοτροποποίηση ενδέχεται να μην επαρκούν χωρίς παράλληλη υποστήριξη της β-κυτταρικής λειτουργίας (Huber et al., 2025; Roep et al., 2021).

Ο ΣΔ1 δεν αποτελεί μόνο μια ενδοκρινολογική νόσο που αφορά τη γλυκόζη. Αντίθετα, χαρακτηρίζεται από αυτοάνοση προδιάθεση. Σύμφωνα με την ανασκόπηση των Popoviciu και συνεργατών, οι ασθενείς με ΣΔ1 εμφανίζουν συχνά συνυπάρχουσες αυτοάνοσες νόσους, με πιο συχνές τις αυτοάνοσες παθήσεις του θυρεοειδούς (Hashimoto και Graves), ενώ αναφέρονται επίσης κοιλιοκάκη, Addison, αυτοάνοση γαστρίτιδα, λεύκη και ρευματολογικές παθήσεις (Popoviciu et al., 2023). Οι συγγραφείς

υπογραμμίζουν ότι η παρουσία συννοσηροτήτων μπορεί να επηρεάζει την πρόγνωση, την ποιότητα ζωής και τη συνολική διαχείριση του διαβήτη (Popoviciu et al., 2023).

1.3 Δείκτες γλυκαιμικού ελέγχου

Ο γλυκαιμικός έλεγχος αποτελεί θεμελιώδη πυλώνα στη διαχείριση του Σακχαρώδους Διαβήτη Τύπου 1 (ΣΔ1), καθώς συνδέεται άμεσα τόσο με την πρόληψη των χρόνιων μικροαγγειακών επιπλοκών, όσο και με την ελαχιστοποίηση του κινδύνου οξέων επεισοδίων, όπως η σοβαρή υπογλυκαιμία και η διαβητική κετοξέωση (Suh & Kim, 2015; Yoo & Kim, 2020). Παραδοσιακά, ο κύριος δείκτης εκτίμησης της ρύθμισης ήταν η γλυκοζυλιωμένη αιμοσφαιρίνη (HbA1c), η οποία θεωρήθηκε επί δεκαετίες το "gold standard" για την αξιολόγηση του μέσου επιπέδου γλυκόζης. Ωστόσο, η σύγχρονη βιβλιογραφία αναδεικνύει ότι η HbA1c, παρότι παραμένει απαραίτητη, δεν επαρκεί ως μοναδικός δείκτης, καθώς δεν αποτυπώνει κρίσιμες παραμέτρους όπως οι ενδοημερήσιες διακυμάνσεις, η συχνότητα και βαρύτητα των υπογλυκαιμιών και η γλυκαιμική μεταβλητότητα (Suh & Kim, 2015; Yoo & Kim, 2020).

Η HbA1c αντανακλά τη μη ενζυμική γλυκοζυλίωση της αιμοσφαιρίνης και χρησιμοποιείται ευρέως ως δείκτης του μέσου γλυκαιμικού φορτίου των τελευταίων 2–3 μηνών. Η κλινική της σημασία είναι ισχυρά τεκμηριωμένη, καθώς η μείωση της HbA1c έχει συνδεθεί με μειωμένο κίνδυνο μικροαγγειακών επιπλοκών (Yoo & Kim, 2020). Παρόλα αυτά, η HbA1c αποτελεί μέσο όρο και συνεπώς δεν μπορεί να διακρίνει αν η μέση τιμή προκύπτει από σχετικά σταθερά επίπεδα γλυκόζης ή από έντονες εναλλαγές μεταξύ υπεργλυκαιμίας και υπογλυκαιμίας. Όπως αναφέρεται, διαφορετικά γλυκαιμικά προφίλ μπορούν να έχουν παρόμοια HbA1c, αλλά να διαφέρουν ουσιαστικά ως προς τη μεταβλητότητα και τον κίνδυνο υπογλυκαιμίας (Yoo & Kim, 2020). Επιπλέον, η HbA1c επηρεάζεται από κλινικές καταστάσεις που μεταβάλλουν τη διάρκεια ζωής των ερυθρών αιμοσφαιρίων ή τη σύνθεση της αιμοσφαιρίνης, όπως αναιμία, αιμοσφαιρινοπάθειες, χρόνια νεφρική νόσος, κύηση και ηπατική δυσλειτουργία, οδηγώντας σε δυνητικά παραπλανητικές τιμές (Yoo & Kim, 2020). Αυτές οι περιορισμένες δυνατότητες της HbA1c καθιστούν αναγκαία τη συμπληρωματική χρήση δεικτών που περιγράφουν την πραγματική δυναμική της γλυκόζης (Yoo & Kim, 2020).

Η καθιέρωση της συνεχούς καταγραφής γλυκόζης (Continuous Glucose Monitoring, CGM) οδήγησε σε αναδιαμόρφωση του πλαισίου αξιολόγησης του γλυκαιμικού ελέγχου, μετατοπίζοντας το ενδιαφέρον πέραν της αποκλειστικής χρήσης της HbA1c. Η CGM επιτρέπει την καταγραφή τιμών γλυκόζης ανά 5–15 λεπτά, παρέχοντας 96–288 μετρήσεις ημερησίως, γεγονός που επιτρέπει την ανάλυση της γλυκαιμικής συμπεριφοράς σε πραγματικό χρόνο και τη δημιουργία ολοκληρωμένων γλυκαιμικών

προφίλ (Yoo & Kim, 2020). Η μετατόπιση αυτή συνοδεύτηκε από τη διαμόρφωση συγκεκριμένων “core metrics”, οι οποίες επιτρέπουν τόσο την κλινική λήψη αποφάσεων, όσο και τη συγκρισιμότητα μεταξύ μελετών. Σύμφωνα με τη σχετική βιβλιογραφία, η χρήση CGM δεν στοχεύει απλώς στη βελτίωση της HbA1c, αλλά στη συνολική βελτίωση της ποιότητας της γλυκαιμικής ρύθμισης, δηλαδή στην αύξηση του χρόνου εντός στόχου, στη μείωση των υπογλυκαιμιών και στη μείωση της γλυκαιμικής μεταβλητότητας (Toschi et al., 2020; Yoo & Kim, 2020).

1.3.1 Time in range: ο πιο κλινικά χρήσιμος δείκτης της CGM

Ο δείκτης Time in Range (TIR) ορίζεται ως το ποσοστό του χρόνου κατά τον οποίο οι τιμές γλυκόζης βρίσκονται εντός του προκαθορισμένου θεραπευτικού εύρους, συνήθως 70–180 mg/dL. Στη σύγχρονη βιβλιογραφία, ο TIR θεωρείται ένας από τους πιο σημαντικούς δείκτες γλυκαιμικού ελέγχου, καθώς αποτυπώνει όχι μόνο τη μέση γλυκόζη αλλά και τη σταθερότητα της ρύθμισης (Yoo & Kim, 2020). Η κλινική αξία του TIR ενισχύεται από δεδομένα που υποδεικνύουν ότι σχετίζεται με επιπλοκές του διαβήτη. Στη μελέτη των El Malahi και συνεργατών, η οποία περιλάμβανε 515 ενήλικες με ΣΔ1 σε θεραπεία με sensor-augmented pump, χαμηλότερος TIR συσχετίστηκε με αυξημένη πιθανότητα παρουσίας μικροαγγειακών επιπλοκών (σύνθετος δείκτης: νευροπάθεια, αμφιβληστροειδοπάθεια, νεφροπάθεια) (Yoo & Kim, 2020). Επιπλέον, ο TIR αναδείχθηκε ως ανεξάρτητος παράγοντας κινδύνου τόσο για τις μικροαγγειακές επιπλοκές όσο και για νοσηλείες λόγω υπογλυκαιμίας ή κετοξέωσης, ενώ δείκτες μεταβλητότητας (SD, CV) δεν εμφάνισαν ανεξάρτητη συσχέτιση με τις μικροαγγειακές επιπλοκές στο συγκεκριμένο μοντέλο (El Malahi et al., 2022). Τα δεδομένα αυτά υπογραμμίζουν ότι ο TIR δεν αποτελεί απλώς “ευκολότερη” απεικόνιση της HbA1c, αλλά δυνητικά έναν πιο άμεσα κλινικά σχετικό δείκτη (El Malahi et al., 2022).

1.3.2. Time Below Range (TBR) και υπογλυκαιμία

Η υπογλυκαιμία παραμένει από τις πιο σοβαρές και απειλητικές επιπλοκές της εντατικής ινσουλινοθεραπείας στον ΣΔ1, ιδιαίτερα σε ευάλωτους πληθυσμούς, όπως οι ηλικιωμένοι. Η CGM επιτρέπει την ποσοτικοποίηση της υπογλυκαιμίας με τρόπο που δεν είναι εφικτός μέσω της HbA1c ή ακόμη και της κλασικής αυτοπαρακολούθησης (SMBG), καθώς καταγράφει και ασυμπτωματικά επεισόδια (Yoo & Kim, 2020).

Η μελέτη των Toschi και συνεργατών σε ηλικιωμένους ≥65 ετών με ΣΔ1 ανέδειξε ότι η HbA1c δεν διαφοροποιούνταν σε ασθενείς με υψηλή και χαμηλή γλυκαιμική

μεταβλητότητα, ωστόσο οι ασθενείς με CV>36% εμφάνιζαν σημαντικά περισσότερο χρόνο σε υπογλυκαιμία τόσο <70 mg/dL όσο και ≤54 mg/dL. Το εύρημα αυτό είναι ιδιαίτερα σημαντικό, διότι δείχνει ότι ένας ασθενής μπορεί να έχει "αποδεκτή" HbA1c, αλλά παράλληλα υψηλό υπογλυκαιμικό φορτίο, άρα αυξημένο κίνδυνο ανεπιθύμητων συμβάντων (Toschi et al., 2020). Παράλληλα, στο ίδιο δείγμα παρατηρήθηκε ότι η απόλυτη διαφορά HbA1c–GMI ≥0.5% ήταν συχνή κι όταν η HbA1c ήταν υψηλότερη από το GMI, η διάρκεια υπογλυκαιμίας ήταν μεγαλύτερη. Αυτό υποδηλώνει ότι η ασυμφωνία μεταξύ εργαστηριακής HbA1c και CGM-εκτιμώμενης μέσης γλυκόζης μπορεί να έχει κλινική σημασία ως δείκτης κινδύνου (Toschi et al., 2020).

1.3.3. Glycemic Variability (GV): ο ρόλος της μεταβλητότητας ως ανεξάρτητου στόχου

Η γλυκαιμική μεταβλητότητα (glycemic variability, GV) περιλαμβάνει τις διακυμάνσεις της γλυκόζης τόσο εντός της ημέρας (intraday variability), όσο και μεταξύ διαφορετικών ημερών (interday variability). Η έννοια αυτή έχει αναδειχθεί ως σημαντικός συμπληρωματικός στόχος, καθώς οι απότομες μεταβολές μεταξύ υπεργλυκαιμίας και υπογλυκαιμίας θεωρούνται δυνητικά επιβαρυντικές για το καρδιαγγειακό σύστημα και τη μικροαγγειακή βλάβη (Suh & Kim, 2015). Οι Suh και Kim συνοψίζουν ότι, πέρα από τη χρόνια υπεργλυκαιμία, οι συχνές αιχμές και πτώσεις γλυκόζης μπορεί να ενισχύουν την οξειδωτική καταπόνηση και την ενδοθηλιακή δυσλειτουργία, μέσω μηχανισμών που συνδέονται με φλεγμονώδεις οδούς και αυξημένη παραγωγή αντιδραστικών ειδών οξυγόνου (Suh & Kim, 2015). Παράλληλα, η υπογλυκαιμία μπορεί να δρα ως προ-αρρυθμιογόνος παράγοντας, μέσω συμπαθητικο-επινεφριδικής ενεργοποίησης, αύξησης κατεχολαμινών και ενεργοποίησης αιμοπεταλίων. Συνεπώς, η μείωση της GV δεν αποτελεί μόνο "βελτίωση της ρύθμισης", αλλά ενδέχεται να αποτελεί και στρατηγική πρόληψης αγγειακής βλάβης (Suh & Kim, 2015). Ωστόσο, η μέτρηση της GV παραμένει σύνθετη, καθώς υπάρχουν πολλοί διαθέσιμοι δείκτες (π.χ. SD, MAGE, CV, CONGA), χωρίς απόλυτη ομοφωνία ως προς τον βέλτιστο. Οι Suh και Kim τονίζουν ότι πολλοί δείκτες GV επηρεάζονται από τη μέση γλυκόζη, επομένως είναι απαραίτητο να χρησιμοποιούνται δείκτες που διορθώνουν ή προσαρμόζονται στη μέση τιμή (Suh & Kim, 2015). Σε αυτό το πλαίσιο, ο συντελεστής μεταβλητότητας (coefficient of variation, CV) προτείνεται ως προτιμητέος δείκτης, διότι αποτελεί αναλογική μέτρηση (SD/mean ×100) και επιτρέπει καλύτερη συγκρισιμότητα μεταξύ ασθενών (Suh & Kim, 2015). Η πρόσφατη

ανασκόπηση των Lazar και συνεργατών επιβεβαιώνει τη συσχέτιση της γλυκαιμικής μεταβλητότητας (GV) με αυξημένο κίνδυνο μακροαγγειακών και μικροαγγειακών επιπλοκών, υποστηρίζοντας ότι η εν λόγω σχέση ενδέχεται να μεσολαβείται από μηχανισμούς που σχετίζονται με τη φλεγμονή και το οξειδωτικό στρες. Επιπλέον, η GV σχετίζεται με αυξημένο κίνδυνο θνησιμότητας και σοβαρών υπογλυκαιμιών, γεγονός που καθιστά τη συστηματική αξιολόγησή της κλινικά χρήσιμη, ειδικά σε ασθενείς με ΣΔ1 (Lazar et al., 2023).

1.3.4. Coefficient of Variation (CV): δείκτης σταθερότητας και υπογλυκαιμικού κινδύνου

Ο CV έχει καθιερωθεί ως ο πιο πρακτικός δείκτης GV στην κλινική πράξη, λόγω της εύκολης ερμηνείας του. Το όριο CV ≤36% προτείνεται ως ένδειξη σχετικά σταθερού γλυκαιμικού προφίλ, ενώ CV >36% χαρακτηρίζει “ασταθή” ρύθμιση με αυξημένο κίνδυνο υπογλυκαιμίας (Lazar et al., 2023; Toschi et al., 2020). Η σημασία του CV φαίνεται ιδιαίτερα σε πληθυσμούς, όπου ο στόχος δεν είναι μόνο η μείωση της HbA1c, αλλά κυρίως η ασφάλεια. Η ανάλυση των Toschi et al. δείχνει ξεκάθαρα ότι η HbA1c μπορεί να μην διαχωρίζει τους ασθενείς ως προς τον κίνδυνο υπογλυκαιμίας, ενώ ο CV το επιτυγχάνει, καθιστώντας τον σημαντικό δείκτη στην εξατομικευμένη θεραπεία (Toschi et al., 2020).

1.4 Τεχνολογίες διαχείρισης διαβήτη

Η διαχείριση του Σακχαρώδους Διαβήτη Τύπου 1 (ΣΔ1) έχει μετασχηματιστεί ριζικά τις τελευταίες δεκαετίες, κυρίως λόγω της εξέλιξης των τεχνολογιών παρακολούθησης γλυκόζης και χορήγησης ινσουλίνης. Η παραδοσιακή προσέγγιση βασιζόταν στη διαλείπουσα αυτομέτρηση σακχάρου αίματος (self-monitoring of blood glucose, SMBG) μέσω δακτυλικών νυγμών, σε συνδυασμό με πολλαπλές ημερήσιες ενέσεις ινσουλίνης ή χρήση αντλίας. Ωστόσο, η ανάγκη για πιο ακριβή, συνεχόμενη και προληπτική ρύθμιση της γλυκαιμίας οδήγησε στην ανάπτυξη και ευρεία υιοθέτηση τεχνολογιών, όπως η συνεχής καταγραφή γλυκόζης (continuous glucose monitoring, CGM) και τα συστήματα αυτοματοποιημένης χορήγησης ινσουλίνης (Freckmann, 2020).

Η χρήση αυτών των τεχνολογιών δεν έχει μόνο τεχνική ή εργονομική αξία, αλλά συνδέεται άμεσα με κλινικά σημαντικά αποτελέσματα: βελτίωση της HbA1c, αύξηση του χρόνου εντός στόχου (time in range, TIR), μείωση της υπογλυκαιμίας, μείωση της γλυκαιμικής μεταβλητότητας, καθώς και βελτίωση δεικτών ποιότητας ζωής. Ταυτόχρονα, η αποτελεσματικότητα των τεχνολογικών παρεμβάσεων εξαρτάται από την ακρίβεια των συστημάτων, τη συμμόρφωση των ασθενών, τη σωστή εκπαίδευση, αλλά και από την προσαρμογή τους σε διαφορετικές ηλικιακές ομάδες και κλινικά προφίλ (Freckmann, 2020).

1.4.1. Περιορισμοί της SMBG και ανάγκη για συνεχόμενη παρακολούθηση

Η SMBG αποτέλεσε για δεκαετίες το βασικό εργαλείο αυτοδιαχείρισης του ΣΔ1, επιτρέποντας στον ασθενή να εκτιμά το επίπεδο γλυκόζης σε συγκεκριμένες χρονικές στιγμές, ώστε να προσαρμόζει τη δόση ινσουλίνης ή τη λήψη υδατανθράκων. Ωστόσο, η μέθοδος αυτή έχει σημαντικούς περιορισμούς. Πρώτον, παρέχει μόνο «στιγμιότυπα» της γλυκαιμικής κατάστασης, χωρίς πληροφορίες για τη δυναμική μεταβολή της γλυκόζης, όπως την ταχύτητα αύξησης ή πτώσης. Δεύτερον, η συχνότητα μετρήσεων είναι συνήθως ανεπαρκής για την ανίχνευση ασυμπτωματικών ή νυχτερινών υπογλυκαιμιών, οι οποίες αποτελούν σημαντικό κίνδυνο για την ασφάλεια του ασθενούς. Επιπλέον, η SMBG είναι επεμβατική και συχνά επώδυνη, γεγονός που μπορεί να μειώνει τη συμμόρφωση, ιδιαίτερα σε εφήβους και νεαρούς ενήλικες (Freckmann, 2020). Οι περιορισμοί αυτοί αποκτούν ιδιαίτερη κλινική σημασία στον

ΣΔ1, όπου οι γλυκαιμικές διακυμάνσεις είναι συχνές και η υπογλυκαιμία μπορεί να εμφανιστεί αιφνίδια, ιδίως σε περιπτώσεις έντονης φυσικής δραστηριότητας, μη προγραμματισμένων γευμάτων ή σφαλμάτων στην ινσουλινοθεραπεία. Η ανάγκη για καλύτερη κατανόηση της γλυκαιμικής συμπεριφοράς οδήγησε στη δημιουργία συστημάτων συνεχούς παρακολούθησης, τα οποία επιτρέπουν πιο ολοκληρωμένη και «προληπτική» προσέγγιση (Freckmann, 2020).

1.4.2. Συνεχής καταγραφή γλυκόζης (CGM): βασικές αρχές λειτουργίας

Η CGM αποτελεί τεχνολογία η οποία μετρά τη γλυκόζη στο διάμεσο υγρό (interstitial fluid) μέσω υποδόριου αισθητήρα. Οι μετρήσεις πραγματοποιούνται σε τακτά χρονικά διαστήματα (συνήθως κάθε 5 λεπτά), παρέχοντας περίπου 288 τιμές ημερησίως, με δυνατότητα παρουσίασης τόσο της τρέχουσας τιμής όσο και των τάσεων (trend arrows) (Freckmann, 2020). Η μέτρηση της γλυκόζης στο διάμεσο υγρό συνοδεύεται από φυσιολογική χρονική καθυστέρηση σε σχέση με το τριχοειδικό αίμα. Ο Freckmann περιγράφει ότι η φυσιολογική καθυστέρηση λόγω διάχυσης της γλυκόζης από το ενδαγγειακό στο διάμεσο διαμέρισμα είναι περίπου 7–8 λεπτά, ενώ επιπλέον υπάρχει και τεχνολογική καθυστέρηση 4–6 λεπτών λόγω επεξεργασίας δεδομένων και αλγορίθμων (Freckmann, 2020). Αυτή η καθυστέρηση είναι ιδιαίτερα σημαντική κατά τη διάρκεια ταχείας μεταβολής της γλυκόζης, όπως μετά από γεύμα ή μετά από χορήγηση διορθωτικής δόσης ινσουλίνης.

Τα συστήματα CGM διακρίνονται σε δύο κύριες κατηγορίες:

1. **Real-time CGM (rtCGM)**: εμφανίζουν συνεχώς τις τιμές γλυκόζης, παρέχουν ειδοποιήσεις και alarms για επικείμενη υπογλυκαιμία ή υπεργλυκαιμία.

2. **Intermittently scanned CGM (iscCGM ή “flash”)**: καταγράφουν τις τιμές αλλά απαιτούν σάρωση (scan) για να εμφανιστούν στον χρήστη.

Η διάκριση αυτή έχει άμεση κλινική σημασία, καθώς τα rtCGM παρέχουν ενεργητική ειδοποίηση κινδύνου, ενώ τα iscCGM βασίζονται στη συμπεριφορά του χρήστη (Freckmann, 2020)**.** Η αποτελεσματικότητα των CGM συστημάτων εξαρτάται σε μεγάλο βαθμό από την ακρίβειά τους. Η ακρίβεια αποτελεί κρίσιμο παράγοντα, διότι

επηρεάζει την αξιοπιστία της λήψης θεραπευτικών αποφάσεων, ιδιαίτερα όταν οι τιμές CGM χρησιμοποιούνται άμεσα για δοσολογία ινσουλίνης (Freckmann, 2020)**.**

Ένα από τα πιο διαδεδομένα μέτρα ακρίβειας είναι το **Mean Absolute Relative Difference (MARD)**, το οποίο εκφράζει τη μέση απόλυτη σχετική απόκλιση μεταξύ των τιμών CGM και των τιμών αναφοράς (συνήθως SMBG). Ο Freckmann αναφέρει ότι τα πρώτα συστήματα CGM εμφάνιζαν MARD περίπου 20%, ενώ τα σύγχρονα συστήματα φτάνουν σε τιμές περίπου 9–14% (Freckmann, 2020).Επιπλέον, σημειώνει ότι MARD ≤10% συζητείται ως πιθανό όριο ακρίβειας για ασφαλή δοσολογία ινσουλίνης με βάση τις τιμές CGM (Freckmann, 2020). Παρά τη χρησιμότητά του, το MARD έχει περιορισμούς. Δεν παρέχει πληροφορία για την κατεύθυνση του σφάλματος (υπερεκτίμηση ή υποεκτίμηση), ενώ μπορεί να διαφέρει σημαντικά ανάλογα με τη γλυκαιμική περιοχή. Συχνά, η ακρίβεια μειώνεται στο εύρος της υπογλυκαιμίας, κάτι που έχει ιδιαίτερη σημασία για την ασφάλεια (Freckmann, 2020).

Ένα επιπλέον κρίσιμο στοιχείο, που επηρεάζει την ακρίβεια, είναι η διαδικασία βαθμονόμησης (calibration). Ο Freckmann αναφέρει ότι ορισμένα συστήματα απαιτούν βαθμονόμηση από τον χρήστη ανά 12 ώρες, γεγονός που τα καθιστά εξαρτώμενα από την ακρίβεια του SMBG κι επιρρεπή σε σφάλματα χειρισμού ή επιλογής ακατάλληλου χρόνου βαθμονόμησης (π.χ. κατά ταχεία μεταβολή γλυκόζης) (Freckmann, 2020). Αντίθετα, τα εργοστασιακά βαθμονομημένα (factory calibrated) συστήματα μειώνουν τα σφάλματα χρήστη, αλλά δεν επιτρέπουν διόρθωση bias, γεγονός που μπορεί να απαιτήσει αντικατάσταση αισθητήρα (Freckmann, 2020).

Ένα από τα σημαντικότερα πλεονεκτήματα της CGM είναι ότι δεν προσφέρει μόνο αριθμητικές τιμές, αλλά και λειτουργίες που στοχεύουν στην πρόληψη επικίνδυνων επεισοδίων. Τα rtCGM παρέχουν alarms και alerts για υπογλυκαιμία και υπεργλυκαιμία, ενώ οι trend arrows επιτρέπουν την εκτίμηση της ταχύτητας μεταβολής της γλυκόζης. Ο Freckmann υπογραμμίζει ότι τα alarms μπορούν να μειώσουν την πιθανότητα νυχτερινής υπογλυκαιμίας, αλλά μπορεί να προκαλέσουν «alarm fatigue» όταν είναι υπερβολικά συχνά, οδηγώντας σε μειωμένη συμμόρφωση (Freckmann, 2020). Επιπλέον, επισημαίνει ότι τα trend arrows δεν είναι τυποποιημένα μεταξύ εταιρειών, γεγονός που μπορεί να προκαλέσει σύγχυση και απαιτεί ειδική εκπαίδευση ανά σύστημα (Freckmann, 2020). Η κλινική σημασία αυτών των λειτουργιών είναι ιδιαίτερα υψηλή σε ασθενείς με ιστορικό σοβαρής υπογλυκαιμίας ή μειωμένης αντίληψης υπογλυκαιμίας, όπου οι ειδοποιήσεις λειτουργούν ως μηχανισμός «ασφαλείας».

1.4.3. Κλινική αποτελεσματικότητα της CGM σε εφήβους και νεαρούς ενήλικες: CITY Trial

Παρότι η CGM έχει αποδειχθεί αποτελεσματική σε ενήλικες, η αποτελεσματικότητά της σε εφήβους και νεαρούς ενήλικες αποτέλεσε αντικείμενο έντονης έρευνας, καθώς αυτή η ηλικιακή ομάδα παρουσιάζει συχνά χαμηλότερη συμμόρφωση και χειρότερο γλυκαιμικό έλεγχο. Η τυχαιοποιημένη κλινική δοκιμή CITY (CGM Intervention in Teens and Young Adults with T1D Study Group) δημοσιεύτηκε στο JAMA και περιέλαβε 153 άτομα ηλικίας 14–24 ετών με ΣΔ1 και HbA1c 7,5–10,9%. Οι συμμετέχοντες τυχαιοποιήθηκαν είτε σε χρήση CGM (Dexcom G5) είτε σε standard care με SMBG (Laffel et al., 2020). Το κύριο αποτέλεσμα ήταν η μεταβολή της HbA1c στις 26 εβδομάδες. Στην ομάδα CGM, η μέση HbA1c μειώθηκε από 8,9% σε 8,5%, ενώ στην ομάδα SMBG παρέμεινε 8,9%. Η προσαρμοσμένη μεταξύ-ομάδων διαφορά ήταν -0,37% (95% CI -0,66 έως -0,08, p=0,01), καταδεικνύοντας στατιστικά σημαντική βελτίωση (Laffel et al., 2020). Παρότι η μείωση της HbA1c μπορεί να χαρακτηριστεί «μέτρια», η σημασία της είναι ιδιαίτερα μεγάλη, καθώς αφορά πληθυσμό με ιστορικά χαμηλή ανταπόκριση σε τεχνολογικές παρεμβάσεις. Επιπλέον, η μελέτη ανέδειξε ότι σημαντικό μέρος των συμμετεχόντων δεν χρησιμοποίησε το CGM συστηματικά: στο τέλος του 6ου μήνα, 68% των συμμετεχόντων χρησιμοποιούσαν το CGM ≥5 ημέρες/εβδομάδα, ενώ 14% δεν το χρησιμοποιούσαν καθόλου (Laffel et al., 2020). Το εύρημα αυτό υπογραμμίζει ότι η αποτελεσματικότητα της CGM εξαρτάται ουσιαστικά από τη συχνότητα χρήσης. Επιπλέον, η μελέτη ανέδειξε βελτίωση σε αρκετούς δείκτες CGM, καθώς και σε ορισμένα patient-reported outcomes, χωρίς σημαντικές διαφορές σε σοβαρά ανεπιθύμητα συμβάντα μεταξύ των ομάδων (Laffel et al., 2020). Συνεπώς, η CITY Trial τεκμηριώνει ότι ακόμη και σε δύσκολη ηλικιακή ομάδα, η χρήση rtCGM μπορεί να προσφέρει κλινικά σημαντική βελτίωση στον γλυκαιμικό έλεγχο (Laffel et al., 2020).

1.4.4. CGM για αντιμετώπιση προβληματικής υπογλυκαιμίας: HypoDE Trial

Η υπογλυκαιμία αποτελεί έναν από τους σημαντικότερους περιοριστικούς παράγοντες της εντατικοποιημένης ινσουλινοθεραπείας. Σε ασθενείς με μειωμένη αντίληψη υπογλυκαιμίας (impaired hypoglycaemia awareness) ή ιστορικό σοβαρής υπογλυκαιμίας, ο κίνδυνος είναι ιδιαίτερα αυξημένος και μπορεί να επηρεάζει τη

θεραπευτική συμπεριφορά, οδηγώντας σε συνειδητή αποδοχή υψηλότερων επιπέδων γλυκόζης για λόγους ασφάλειας (Heinemann et al., 2018a)..

Η HypoDE Trial, πολυκεντρική τυχαιοποιημένη μελέτη που δημοσιεύτηκε στο Lancet, αξιολόγησε την αποτελεσματικότητα του rtCGM σε ενήλικες με ΣΔ1, οι οποίοι βρίσκονταν σε θεραπεία με πολλαπλές ημερήσιες ενέσεις (MDI) και είχαν είτε μειωμένη αντίληψη υπογλυκαιμίας, είτε ιστορικό σοβαρής υπογλυκαιμίας (Heinemann et al., 2018a). Τα αποτελέσματα έδειξαν ότι η χρήση rtCGM οδήγησε σε σημαντική μείωση τόσο των βιοχημικών, όσο και των κλινικών υπογλυκαιμιών. Παράλληλα, βελτιώθηκαν δείκτες κινδύνου υπογλυκαιμίας, όπως το ποσοστό υπογλυκαιμικών τιμών και ο Low Blood Glucose Index (LBGI). Επιπλέον, καταγράφηκε μείωση της γλυκαιμικής μεταβλητότητας, ενώ ιδιαίτερα σημαντικό ήταν ότι η μείωση υπογλυκαιμίας δεν επιτεύχθηκε εις βάρος της HbA1c, καθώς δεν παρατηρήθηκε επιδείνωση του συνολικού γλυκαιμικού ελέγχου (Heinemann et al., 2018a). Η μελέτη αναφέρει επίσης ότι η γλυκαιμική μεταβλητότητα μειώθηκε από 39,3% σε 34,1% στην ομάδα rtCGM, με το όριο <36% να θεωρείται σταθερότητα σύμφωνα με διεθνείς συστάσεις (Heinemann et al., 2018a). Αυτό είναι κλινικά κρίσιμο, καθώς η υψηλή μεταβλητότητα έχει συσχετιστεί με αυξημένο κίνδυνο υπογλυκαιμίας και δυσκολία επίτευξης σταθερού γλυκαιμικού ελέγχου (Heinemann et al., 2018a).

Σε επίπεδο ψυχοκοινωνικών δεικτών, η rtCGM οδήγησε σε βελτίωση της υπογλυκαιμίας-σχετιζόμενης δυσφορίας κι αύξηση της ικανοποίησης από το σύστημα παρακολούθησης, χωρίς ωστόσο να καταγράφονται σημαντικές αλλαγές στον συνολικό φόβο υπογλυκαιμίας (Heinemann et al., 2018a). Το εύρημα αυτό είναι ενδιαφέρον, καθώς υποδηλώνει ότι η μείωση επεισοδίων υπογλυκαιμίας δεν συνεπάγεται αυτόματα ψυχολογική αναδόμηση του φόβου, ο οποίος μπορεί να αποτελεί χρόνιο και πολυπαραγοντικό φαινόμενο. Η HypoDE Trial έχει ιδιαίτερη σημασία, διότι αφορά πληθυσμό υψηλού κινδύνου και τεκμηριώνει ότι το rtCGM μπορεί να λειτουργήσει ως βασικό εργαλείο πρόληψης σοβαρών επεισοδίων σε ασθενείς που δεν χρησιμοποιούν αντλία ινσουλίνης, αλλά MDI. Δεδομένου ότι παγκοσμίως η MDI παραμένει η συχνότερη μορφή θεραπείας στον ΣΔ1, το εύρημα έχει υψηλή κλινική εφαρμοσιμότητα (Heinemann et al., 2018a).

1.4.5. Κλινικές επιπτώσεις και συνολική αξιολόγηση των τεχνολογιών CGM

Τα παραπάνω δεδομένα επιτρέπουν την εξαγωγή ενός κεντρικού συμπεράσματος: η CGM αποτελεί τεχνολογία με σαφή κλινική ωφέλεια, η οποία επηρεάζει διαφορετικές διαστάσεις του γλυκαιμικού ελέγχου, πέρα από την HbA1c. Στην περίπτωση των εφήβων και νεαρών ενηλίκων, η χρήση rtCGM μπορεί να μειώσει την HbA1c, αλλά το μέγεθος της βελτίωσης εξαρτάται σημαντικά από τη συχνότητα χρήσης και τη συμμόρφωση, όπως αναδείχθηκε στη CITY Trial (Laffel et al., 2020). Αντίθετα, σε πληθυσμούς υψηλού κινδύνου για υπογλυκαιμία, η κύρια ωφέλεια μπορεί να είναι η μείωση των υπογλυκαιμικών επεισοδίων και η σταθεροποίηση της γλυκαιμικής μεταβλητότητας, όπως αποδείχθηκε στη HypoDE Trial (Heinemann et al., 2018a). Η τεχνολογία CGM έχει επίσης σημαντική αξία ως βάση για πιο σύνθετα συστήματα διαχείρισης, όπως τα συστήματα κλειστού βρόχου (closed-loop) ή υβριδικού κλειστού βρόχου (hybrid closed-loop).

1.4.6. Προκλήσεις και περιορισμοί της τεχνολογικής διαχείρισης

Παρά τα πλεονεκτήματα, οι τεχνολογίες CGM συνοδεύονται από πρακτικές και κλινικές προκλήσεις. Ένα βασικό ζήτημα είναι η μειωμένη ακρίβεια σε περιοχές υπογλυκαιμίας, η οποία μπορεί να απαιτεί επιβεβαίωση με SMBG σε κρίσιμες περιπτώσεις. Η χρονική υστέρηση που παρατηρείται μεταξύ των επιπέδων γλυκόζης στο διάμεσο υγρό και στο τριχοειδικό αίμα ενδέχεται να επηρεάσει την ακρίβεια της ερμηνείας των μετρήσεων, ιδίως κατά τη διάρκεια ταχέων μεταβολών της γλυκαιμίας (Freckmann, 2020). Επιπλέον, η συμπεριφορική διάσταση είναι καθοριστική. Η CITY Trial έδειξε ότι ένα σημαντικό ποσοστό νέων ασθενών δεν διατήρησε σταθερή χρήση CGM έως το τέλος της μελέτης (Laffel et al., 2020). Αυτό υποδεικνύει ότι η τεχνολογία από μόνη της δεν αρκεί χωρίς υποστήριξη, εκπαίδευση και ενσωμάτωση στην καθημερινότητα του ασθενούς (Laffel et al., 2020). Τέλος, ένα συχνό πρακτικό πρόβλημα είναι η κόπωση από ειδοποιήσεις (alarm fatigue), η οποία μπορεί να μειώσει τη συμμόρφωση ή να οδηγήσει σε απενεργοποίηση ειδοποιήσεων, περιορίζοντας την ασφάλεια του συστήματος (Freckmann, 2020).

Συμπερασματικά, οι τεχνολογίες διαχείρισης διαβήτη κι ειδικότερα η συνεχής καταγραφή γλυκόζης, έχουν μεταβάλει ουσιαστικά το θεραπευτικό τοπίο του ΣΔ1. Τα σύγχρονα CGM παρέχουν όχι μόνο βελτιωμένη ακρίβεια σε σχέση με παλαιότερα συστήματα, αλλά και δυνατότητες προληπτικής διαχείρισης μέσω ειδοποιήσεων και

trend arrows. Κλινικές δοκιμές υψηλής ποιότητας, όπως η CITY Trial και η HypoDE Trial, τεκμηριώνουν ότι η χρήση rtCGM μπορεί να οδηγήσει σε μείωση HbA1c σε νεαρά άτομα με ΣΔ1 και σε σημαντική μείωση υπογλυκαιμίας σε πληθυσμούς υψηλού κινδύνου χωρίς επιδείνωση του συνολικού γλυκαιμικού ελέγχου (Heinemann et al., 2018a; Laffel et al., 2020). Παράλληλα, η αξιοποίηση των τεχνολογιών αυτών απαιτεί σωστή εκπαίδευση, υποστήριξη συμμόρφωσης και κατανόηση των περιορισμών τους, ιδιαίτερα σε συνθήκες ταχείας μεταβολής γλυκόζης ή σε γλυκαιμικά εύρη όπου η ακρίβεια είναι χαμηλότερη. Συνολικά, η CGM αποτελεί πλέον θεμελιώδη τεχνολογία στον σύγχρονο ΣΔ1 και βάση για την περαιτέρω ανάπτυξη συστημάτων αυτοματοποιημένης χορήγησης ινσουλίνης (Heinemann et al., 2018a; Laffel et al., 2020).

1.5.Προκλήσεις στη ρύθμιση του ΣΔ1 και κλινική σημασία του βέλτιστου γλυκαιμικού ελέγχου

1.5.1. Η πολυπαραγοντική φύση της γλυκαιμικής ρύθμισης στον ΣΔ1

Η βασική δυσκολία στη ρύθμιση του ΣΔ1 έγκειται στο γεγονός ότι η εξωγενής ινσουλίνη δεν μπορεί να μιμηθεί πλήρως τη φυσιολογική ενδογενή έκκριση. Σε φυσιολογικές συνθήκες, το πάγκρεας ανταποκρίνεται δυναμικά στις μεταβολές της γλυκόζης, με άμεση προσαρμογή της βασικής και γευματικής έκκρισης ινσουλίνης. Στον ΣΔ1, η χορήγηση ινσουλίνης βασίζεται σε υπολογισμούς και εκτιμήσεις, οι οποίες επηρεάζονται από σημαντική ενδο- και δια-ατομική μεταβλητότητα (Bell & Lain, 2025). Η μεταβλητότητα αυτή δεν αφορά μόνο τη συμπεριφορά του ατόμου, αλλά και τη φαρμακοκινητική και φαρμακοδυναμική της ινσουλίνης. Η απορρόφηση μπορεί να διαφοροποιείται ανάλογα με το σημείο ένεσης, τη θερμοκρασία, την αιμάτωση, την άσκηση κι άλλους παράγοντες. Παράλληλα, το γλυκαιμικό προφίλ επηρεάζεται από στρεσογόνες καταστάσεις, λοιμώξεις, ορμονικές διακυμάνσεις, καθώς κι από διατροφικούς παράγοντες, όπως η σύσταση του γεύματος (π.χ. υψηλή περιεκτικότητα σε λιπαρά και πρωτεΐνη) που καθυστερεί ή παρατείνει την απορρόφηση της γλυκόζης (Bell & Lain, 2025).

Η υπογλυκαιμία αποτελεί την πιο σημαντική οξεία επιπλοκή της ινσουλινοθεραπείας και ταυτόχρονα έναν από τους κύριους λόγους που δυσχεραίνουν την εντατικοποίηση της θεραπείας. Είναι τεκμηριωμένο ότι η προσπάθεια επίτευξης χαμηλότερων τιμών HbA1c συχνά συνοδεύεται από αυξημένο κίνδυνο υπογλυκαιμικών επεισοδίων, ιδιαίτερα σε άτομα με υψηλή γλυκαιμική μεταβλητότητα (Bell & Lain, 2025). Ιδιαίτερα κρίσιμο είναι το φαινόμενο της «υπογλυκαιμικής ανεπίγνωσης», όπου το άτομο χάνει την ικανότητα να αντιλαμβάνεται τα προειδοποιητικά συμπτώματα. Η κατάσταση αυτή αυξάνει δραματικά τον κίνδυνο σοβαρής υπογλυκαιμίας, με πιθανές συνέπειες την απώλεια συνείδησης, επιληπτικές κρίσεις ή ανάγκη βοήθειας από τρίτους (Bell & Lain, 2025). Η υπογλυκαιμία δεν αποτελεί μόνο βιολογικό κίνδυνο, αλλά και ισχυρό ψυχολογικό εμπόδιο. Ο φόβος υπογλυκαιμίας μπορεί να οδηγήσει σε σκόπιμη διατήρηση υψηλότερων τιμών γλυκόζης, με αποτέλεσμα υποβέλτιστη ρύθμιση και αυξημένο κίνδυνο χρόνιων επιπλοκών (Bell & Lain, 2025).

Παραδοσιακά, η HbA1c αποτέλεσε τον βασικό δείκτη αξιολόγησης του γλυκαιμικού ελέγχου. Ωστόσο, η HbA1c εκφράζει έναν σταθμισμένο μέσο όρο της γλυκόζης των

τελευταίων ~3 μηνών και δεν αποτυπώνει επαρκώς τις ημερήσιες διακυμάνσεις, ούτε τη συχνότητα και διάρκεια υπογλυκαιμίας ή υπεργλυκαιμικών αιχμών. Η έλευση των συστημάτων συνεχούς καταγραφής γλυκόζης (CGM) ανέδειξε την ανάγκη για συμπληρωματικούς δείκτες, όπως ο χρόνος εντός στόχου (Time in Range, TIR) και δείκτες γλυκαιμικής μεταβλητότητας (glycemic variability, GV) (Lazar et al., 2023). Η γλυκαιμική μεταβλητότητα ορίζεται ως το εύρος και η συχνότητα των διακυμάνσεων της γλυκόζης σε συγκεκριμένο χρονικό διάστημα. Στη βιβλιογραφία υποστηρίζεται ότι οι απότομες αυξομειώσεις της γλυκόζης δεν αποτελούν απλώς «θόρυβο» στη ρύθμιση, αλλά πιθανώς συνδέονται με παθοφυσιολογικούς μηχανισμούς, που προάγουν την ενδοθηλιακή δυσλειτουργία, το οξειδωτικό stress και τη φλεγμονή, αυξάνοντας έτσι τον κίνδυνο μικρο- και μακροαγγειακών επιπλοκών (Lazar et al., 2023). Σημαντικό είναι ότι η υψηλή GV δυσχεραίνει την επίτευξη καλής HbA1c χωρίς υπογλυκαιμία, διότι το ίδιο μέσο επίπεδο γλυκόζης μπορεί να προκύπτει είτε από σταθερές τιμές, είτε από εναλλαγές ακραίας υπογλυκαιμίας και υπεργλυκαιμίας. Αυτό σημαίνει ότι η HbA1c, ως μοναδικός στόχος, μπορεί να οδηγήσει σε παραπλανητική εκτίμηση της ποιότητας της ρύθμισης (Lazar et al., 2023).

1.5.2. Δείκτες CGM και δυσκολίες στην κλινική εφαρμογή τους

Η αξιοποίηση των δεδομένων CGM προσφέρει μια πιο ολοκληρωμένη εικόνα της γλυκαιμικής συμπεριφοράς. Ο δείκτης TIR (70–180 mg/dL) έχει προταθεί ως πρακτικός και κλινικά χρήσιμος στόχος, καθώς σχετίζεται με την πιθανότητα εμφάνισης επιπλοκών και συσχετίζεται με την HbA1c. Ωστόσο, η εφαρμογή του δεν στερείται περιορισμών. Το TIR δεν αποτυπώνει πλήρως την GV, καθώς μπορεί να είναι χαμηλό τόσο σε περιπτώσεις έντονης μεταβλητότητας, όσο και σε περιπτώσεις σταθερής αλλά χρόνιας υπεργλυκαιμίας (Lazar et al., 2023).

Για τον λόγο αυτό, οι σύγχρονες προσεγγίσεις προτείνουν τη συνδυαστική αξιολόγηση TIR με δείκτες μεταβλητότητας, κυρίως τον συντελεστή μεταβλητότητας (%CV). Οι διεθνείς κατευθυντήριες οδηγίες υποστηρίζουν το %CV ως τον πιο χρήσιμο και εύκολα υπολογίσιμο δείκτη GV, με προτεινόμενο στόχο ≤36% ως ένδειξη «σταθερότερης» γλυκαιμικής ομοιόστασης (Bell & Lain, 2025). Ωστόσο, η κλινική εφαρμογή αυτών των δεικτών απαιτεί κατάλληλη εκπαίδευση τόσο των επαγγελματιών υγείας, όσο και των ασθενών, καθώς και χρόνο για ανάλυση των δεδομένων. Επιπλέον, η ακρίβεια των CGM παραμένει χαμηλότερη σε ακραίες τιμές γλυκόζης, γεγονός που

επιβάλλει προσεκτική ερμηνεία, ιδιαίτερα σε υπογλυκαιμικές ζώνες (Bell & Lain, 2025).

1.5.3. Ψυχολογικές και κοινωνικές προκλήσεις: διαβητική δυσφορία και αυτοδιαχείριση

Η διαχείριση του ΣΔ1 είναι συνεχής, απαιτεί καθημερινές αποφάσεις και συχνά συνδέεται με υψηλό ψυχολογικό φορτίο. Η έννοια της «διαβητικής δυσφορίας» (diabetes distress) περιγράφει τη συναισθηματική επιβάρυνση που σχετίζεται με τη διαχείριση της νόσου, την αβεβαιότητα, την αυτοπαρακολούθηση και την ανησυχία για επιπλοκές. Η δυσφορία αυτή μπορεί να μειώσει τη συμμόρφωση, να αυξήσει τη GV και να δυσχεράνει την επίτευξη σταθερής ρύθμισης (Bell & Lain, 2025). Παράλληλα, η τεχνολογία (π.χ. CGM) μπορεί να λειτουργήσει τόσο υποστηρικτικά, όσο και επιβαρυντικά. Για παράδειγμα, έχει περιγραφεί το φαινόμενο «alarm fatigue», όπου οι συχνές ειδοποιήσεις οδηγούν σε κόπωση και ενίοτε αποφυγή χρήσης της συσκευής. Επιπλέον, ορισμένοι ασθενείς αναφέρουν αυξημένο άγχος ή ακόμη και καταθλιπτική διάθεση λόγω της συνεχούς έκθεσης σε δεδομένα και υπενθυμίσεις της νόσου (Bell & Lain, 2025).

Παρά τις δυσκολίες, η επίτευξη βέλτιστου γλυκαιμικού ελέγχου παραμένει θεμελιώδης στόχος, καθώς συνδέεται άμεσα με τη μείωση του κινδύνου εμφάνισης επιπλοκών. Οι επιπλοκές του ΣΔ1 περιλαμβάνουν μικροαγγειακές βλάβες (αμφιβληστροειδοπάθεια, νεφροπάθεια, νευροπάθεια) και μακροαγγειακές εκδηλώσεις (στεφανιαία νόσος, εγκεφαλικά επεισόδια, περιφερική αρτηριοπάθεια). Η συσχέτιση του γλυκαιμικού ελέγχου με αυτές τις επιπλοκές αποτελεί έναν από τους ισχυρότερους άξονες τεκμηρίωσης στην ιστορία της διαβητολογίας (Lazar et al., 2023). Πέρα από τη μέση γλυκόζη, η GV έχει προταθεί ως ανεξάρτητος παράγοντας κινδύνου για αγγειακή βλάβη. Σε πειραματικά δεδομένα, έχει φανεί ότι οι διακυμάνσεις γλυκόζης μπορεί να προκαλούν μεγαλύτερη ενδοθηλιακή δυσλειτουργία και οξειδωτικό stress σε σύγκριση με τη σταθερή υπεργλυκαιμία (Lazar et al., 2023).

Αν και η βιβλιογραφία δεν έχει καταλήξει πλήρως στο κατά πόσο η GV είναι ανεξάρτητος αιτιολογικός παράγοντας ή δείκτης συνολικής δυσρρύθμισης, είναι σαφές ότι η σταθερότητα της γλυκόζης έχει ιδιαίτερη κλινική σημασία. Αυτό αντικατοπτρίζεται και στη σύγχρονη έμφαση σε δείκτες, όπως το TIR και το %CV, που στοχεύουν όχι μόνο στη μείωση του μέσου όρου, αλλά και στη βελτίωση της καθημερινής σταθερότητας (Bell & Lain, 2025; Lazar et al., 2023).

Συνολικά, οι προκλήσεις στη ρύθμιση του ΣΔ1 μπορούν να συνοψιστούν σε ένα κεντρικό δίλημμα: η επίτευξη αυστηρότερου γλυκαιμικού ελέγχου μειώνει τον κίνδυνο χρόνιων επιπλοκών, αλλά μπορεί να αυξήσει τον κίνδυνο υπογλυκαιμίας, ιδιαίτερα

όταν η GV είναι υψηλή. Η σύγχρονη προσέγγιση μετατοπίζεται σταδιακά από τη μονοδιάστατη στόχευση της HbA1c προς μια πολυπαραμετρική αξιολόγηση, όπου η HbA1c συνδυάζεται με δείκτες CGM όπως TIR, TBR (time below range) και %CV (Bell & Lain, 2025; Lazar et al., 2023). Η βελτίωση της ρύθμισης δεν αποτελεί πλέον μόνο θέμα εντατικοποίησης της ινσουλίνης, αλλά συνδέεται με την εξατομίκευση των στόχων, τη μείωση της μεταβλητότητας, την υποστήριξη της ψυχικής υγείας και την ενίσχυση της θεραπευτικής εκπαίδευσης. Με αυτόν τον τρόπο, ο «βέλτιστος γλυκαιμικός έλεγχος» ορίζεται όχι μόνο ως αριθμητική επίδοση, αλλά ως ισορροπία ανάμεσα σε αποτελεσματικότητα, ασφάλεια και βιωσιμότητα στην καθημερινή ζωή του ατόμου με ΣΔ1 (Bell & Lain, 2025; Lazar et al., 2023).

1.6. Συμβατική θεραπεία και σύγκριση με τεχνολογικές παρεμβάσεις (SMBG, MDI, αντλία, CGM, closed-loop)

Η θεραπευτική αντιμετώπιση του Σακχαρώδη Διαβήτη Τύπου 1 (ΣΔ1) έχει ως βασικό στόχο τη διατήρηση της γλυκόζης αίματος εντός ασφαλών ορίων, περιορίζοντας ταυτόχρονα τόσο τη χρόνια υπεργλυκαιμία, όσο και τα επεισόδια υπογλυκαιμίας (Freckmann, 2020). Η πρόοδος των τελευταίων δεκαετιών έχει οδηγήσει σε μία μετατόπιση από την παραδοσιακή προσέγγιση της εντατικοποιημένης ινσουλινοθεραπείας και της αυτοπαρακολούθησης μέσω δακτυλικών μετρήσεων (SMBG), προς ολοένα πιο αυτοματοποιημένες τεχνολογικές λύσεις, όπως η συνεχής καταγραφή γλυκόζης (CGM) και τα συστήματα υβριδικού κλειστού βρόχου (hybrid closed-loop, HCL). Η σύγκριση της συμβατικής θεραπείας με τις τεχνολογικές παρεμβάσεις είναι κλινικά κρίσιμη, καθώς σχετίζεται άμεσα με την επίτευξη βέλτιστων δεικτών γλυκαιμικού ελέγχου, με την πρόληψη επιπλοκών, αλλά και τη μείωση του θεραπευτικού φορτίου που φέρει ο ασθενής (Freckmann, 2020).

Η «συμβατική» ή κλασική προσέγγιση στη διαχείριση του ΣΔ1 βασίζεται σε δύο βασικούς πυλώνες: (α) την εντατικοποιημένη ινσουλινοθεραπεία, κυρίως με πολλαπλές ημερήσιες ενέσεις (multiple daily injections, MDI), και (β) την αυτοπαρακολούθηση της γλυκόζης μέσω μετρήσεων τριχοειδικού αίματος (self-monitoring of blood glucose, SMBG). Η MDI συνήθως περιλαμβάνει βασική ινσουλίνη μακράς δράσης και γευματικές δόσεις ταχείας δράσης, με προσαρμογές ανάλογα με την πρόσληψη υδατανθράκων, τη φυσική δραστηριότητα και τη μεταβλητότητα της ινσουλινοευαισθησίας (Freckmann, 2020). Παρότι η MDI θεωρείται αποτελεσματική, η πρακτική εφαρμογή της στην καθημερινότητα παραμένει απαιτητική. Ο ασθενής καλείται να πραγματοποιεί πολλαπλές μετρήσεις, να εκτιμά υδατάνθρακες, να υπολογίζει διορθωτικές δόσεις και να προβλέπει μεταβολές που προκαλούνται από άσκηση, στρες, λοιμώξεις ή ορμονικές διακυμάνσεις. Αυτή η πολυπλοκότητα συνδέεται με σημαντικό κίνδυνο τόσο υπογλυκαιμίας, όσο και υπεργλυκαιμίας, ενώ η ανάγκη για συνεχή λήψη αποφάσεων αυξάνει το γνωστικό και ψυχολογικό φορτίο του ασθενούς (Yoo & Kim, 2020). Επιπλέον, η SMBG έχει εγγενείς περιορισμούς, καθώς προσφέρει αποσπασματικές στιγμιαίες μετρήσεις και δεν παρέχει πληροφορίες για τάσεις, κατεύθυνση μεταβολής ή νυχτερινά επεισόδια υπογλυκαιμίας. Η απουσία συνεχούς πληροφορίας περιορίζει τη δυνατότητα έγκαιρης πρόληψης επικίνδυνων γλυκαιμικών

διακυμάνσεων, ειδικά σε ασθενείς με μειωμένη επίγνωση υπογλυκαιμίας (Yoo & Kim, 2020).

1.6.1. Θεραπεία με αντλία ινσουλίνης (CSII): εξέλιξη πέρα από την MDI

Η συνεχής υποδόρια έγχυση ινσουλίνης (continuous subcutaneous insulin infusion, CSII) μέσω αντλίας αποτελεί μια σημαντική εξέλιξη σε σχέση με την MDI, καθώς επιτρέπει προγραμματιζόμενη βασική έγχυση ινσουλίνης, πολλαπλά βασικά προφίλ, προσωρινές ρυθμίσεις και μεγαλύτερη ευελιξία στη γευματική κάλυψη. Σε θεωρητικό επίπεδο, η αντλία μπορεί να προσομοιώσει καλύτερα τη φυσιολογική βασική έκκριση ινσουλίνης σε σχέση με τις ενέσεις (Heinemann et al., 2018b).

Η βιβλιογραφία επισημαίνει ότι η αντλία ινσουλίνης μπορεί να επιφέρει μέτριες, αλλά κλινικά σημαντικές βελτιώσεις σε HbA1c (περίπου 0,3–0,6%), ενώ ταυτόχρονα έχει συσχετιστεί με μειωμένα επεισόδια σοβαρής υπογλυκαιμίας και διαβητικής κετοξέωσης (DKA) σε επιλεγμένους πληθυσμούς (Heinemann et al., 2018b). Ωστόσο, η αντλία από μόνη της δεν εξαλείφει το βασικό πρόβλημα της «ανοιχτού βρόχου» θεραπείας, δηλαδή ότι η λήψη αποφάσεων παραμένει κυρίως στον ασθενή. Οι απαιτήσεις για ρύθμιση παραμέτρων (βασικά προφίλ, αναλογίες υδατανθράκων, συντελεστές διόρθωσης) παραμένουν υψηλές, ενώ τεχνικά προβλήματα (π.χ. απόφραξη σετ, αποκόλληση καθετήρα) μπορούν να οδηγήσουν σε ταχεία εμφάνιση υπεργλυκαιμίας και κετοξέωσης, λόγω της απουσίας μακράς δράσης ινσουλίνης (Heinemann et al., 2018b).

1.6.2. CGM έναντι SMBG: από τη στιγμιαία μέτρηση στη δυναμική παρακολούθηση

Η συνεχής καταγραφή γλυκόζης (continuous glucose monitoring, CGM) αποτελεί μία από τις σημαντικότερες τεχνολογικές καινοτομίες στη διαχείριση του ΣΔ1. Τα CGM συστήματα μετρούν γλυκόζη στο διάμεσο υγρό ανά περίπου 5 λεπτά, παρέχοντας συνεχές προφίλ γλυκαιμίας, τάσεις μεταβολής, ειδοποιήσεις υπο- και υπεργλυκαιμίας, καθώς και μετρικές, όπως ο χρόνος εντός στόχου (time in range, TIR) (Freckmann, 2020). Σε αντίθεση με την SMBG, η CGM επιτρέπει όχι μόνο την καταγραφή της τρέχουσας γλυκόζης, αλλά και την πρόβλεψη της πορείας της, γεγονός που ενισχύει την πρόληψη υπογλυκαιμίας και βελτιώνει την καθημερινή λήψη αποφάσεων. Η κλινική σημασία αυτής της μετάβασης είναι ιδιαίτερα εμφανής σε πληθυσμούς υψηλού κινδύνου, όπως άτομα με μειωμένη επίγνωση υπογλυκαιμίας ή ιστορικό σοβαρών επεισοδίων (Freckmann, 2020). Η μελέτη HypoDE, όπως συνοψίζεται και στο άρθρο

του Freckmann, ανέδειξε ότι η χρήση real-time CGM (rtCGM) μπορεί να μειώσει σημαντικά την υπογλυκαιμία, με αναφερόμενη μείωση της συχνότητας επεισοδίων κατά 72% σε σύγκριση με SMBG σε ενήλικες με ΣΔ1 και προβληματική υπογλυκαιμία (Freckmann, 2020). Παράλληλα, δεδομένα από τυχαιοποιημένες κλινικές δοκιμές δείχνουν ότι η CGM μπορεί να βελτιώσει την HbA1c και σε νεότερους πληθυσμούς. Στην τυχαιοποιημένη μελέτη του JAMA σε εφήβους και νεαρούς ενήλικες με ΣΔ1, η ομάδα CGM παρουσίασε μείωση HbA1c σε 26 εβδομάδες, με προσαρμοσμένη διαφορά -0,37% έναντι της ομάδας SMBG (Laffel et al., 2020). Ιδιαίτερο ενδιαφέρον παρουσιάζει το γεγονός ότι η CGM δεν αποτελεί μόνο εργαλείο «αριθμητικής» βελτίωσης του ελέγχου, αλλά και μέσο μείωσης ψυχολογικών παραμέτρων όπως το άγχος για υπογλυκαιμία, η διαβητική δυσφορία και το αντιλαμβανόμενο φορτίο αυτοδιαχείρισης (Freckmann, 2020). Παρόλα αυτά, η αποτελεσματικότητα της CGM εξαρτάται σε μεγάλο βαθμό από την εκπαίδευση και τη σωστή αξιοποίηση των δεδομένων. Η ανασκόπηση του Yoo και συνεργατών υπογραμμίζει ότι η CGM μπορεί να έχει περιορισμένη επίδραση στην HbA1c, όταν χρησιμοποιείται χωρίς δομημένη εκπαίδευση, ενώ η προσθήκη εκπαιδευτικών παρεμβάσεων ενισχύει σημαντικά την αποτελεσματικότητα (Yoo & Kim, 2020).

1.6.3. Sensor-augmented pump (SAP): συνδυασμός αντλίας και CGM

Η επόμενη εξέλιξη μετά την απλή χρήση αντλίας ή CGM είναι η λεγόμενη «αντλία με αισθητήρα» (sensor-augmented pump, SAP), όπου τα δεδομένα CGM εμφανίζονται στην αντλία και ο χρήστης προσαρμόζει χειροκίνητα τις δόσεις. Ο συνδυασμός αυτός προσφέρει σαφή πλεονεκτήματα σε σχέση με την απλή αντλία, καθώς παρέχει καλύτερη εικόνα της γλυκαιμίας, ιδιαίτερα νυχτερινά (Heinemann et al., 2018b). Επιπλέον, αρκετά SAP συστήματα ενσωματώνουν λειτουργίες διακοπής βασικής ινσουλίνης, όταν η γλυκόζη είναι χαμηλή (low glucose suspend) ή όταν προβλέπεται ότι θα γίνει χαμηλή (predictive low glucose suspend, PLGS), μειώνοντας έτσι τον κίνδυνο σοβαρής υπογλυκαιμίας (Heinemann et al., 2018b). Ωστόσο, παρά τις βελτιώσεις, τα SAP παραμένουν κατά βάση συστήματα «ημι-αυτοματοποιημένα», όπου ο χρήστης εξακολουθεί να έχει τον κύριο ρόλο στη ρύθμιση, ιδιαίτερα στα γεύματα (Heinemann et al., 2018b).

1.6.4. Συστήματα κλειστού βρόχου: από την υποβοήθηση στην αυτοματοποίηση

Τα συστήματα κλειστού βρόχου (closed-loop systems, CLS), γνωστά και ως «τεχνητό πάγκρεας», αποτελούν την πλέον προηγμένη τεχνολογική προσέγγιση στη διαχείριση του ΣΔ1. Ο πυρήνας τους είναι η αυτοματοποιημένη προσαρμογή της βασικής ινσουλίνης μέσω αλγορίθμου, με βάση τα δεδομένα CGM, με στόχο τη διατήρηση της γλυκόζης εντός εύρους στόχου (Heinemann et al., 2018b). Στην παρούσα κλινική πραγματικότητα, τα περισσότερα εμπορικά συστήματα είναι υβριδικού κλειστού βρόχου (hybrid closed-loop, HCL), δηλαδή απαιτούν από τον χρήστη να δηλώνει γεύματα και να χορηγεί γευματικές δόσεις, ενώ ο αλγόριθμος ρυθμίζει αυτόματα την βασική ινσουλίνη και συχνά χορηγεί μικρές διορθωτικές δόσεις (Heinemann et al., 2018b). Η τυχαιοποιημένη κλινική δοκιμή 6 μηνών σε ενήλικες με ΣΔ1 (Diabetes Care) ανέδειξε σημαντικά οφέλη του HCL έναντι της συνήθους φροντίδας (που περιλάμβανε SMBG). Συγκεκριμένα, ο χρόνος εντός στόχου (70–180 mg/dL) αυξήθηκε από περίπου 55% σε 69,9% στο τέλος της μελέτης, με διαφορά περίπου 14,8 ποσοστιαίων μονάδων έναντι της ομάδας ελέγχου (McAuley et al., 2020).

Σημαντικό εύρημα είναι ότι η βελτίωση του TIR παρατηρήθηκε τόσο σε συμμετέχοντες που ήταν ήδη σε αντλία, όσο και σε όσους ήταν σε MDI κατά την ένταξη, γεγονός που υποστηρίζει ότι το HCL μπορεί να προσφέρει κλινικά οφέλη, ανεξάρτητα από την προηγούμενη τεχνολογική εμπειρία (McAuley et al., 2020). Επιπλέον, το HCL συσχετίστηκε με μειώσεις τόσο στην υπεργλυκαιμία, όσο και στην υπογλυκαιμία, ενώ η βελτίωση ήταν πιο έντονη τη νύχτα, στοιχείο που συνάδει και με μικρότερες μελέτες (McAuley et al., 2020). Συνολικά, οι Heinemann et al. επισημαίνουν ότι τα HCL συστήματα εμφανίζουν σταθερά και επαναλαμβανόμενα οφέλη σε διαφορετικές ηλικιακές ομάδες (παιδιά, εφήβους, ενήλικες), με βελτίωση του TIR και μείωση του κινδύνου υπογλυκαιμίας χωρίς αύξηση ανεπιθύμητων συμβάντων (Heinemann et al., 2018b).

1.6.5. Closed-loop έναντι SAP: συγκριτικά δεδομένα

Καθώς οι τεχνολογίες εξελίσσονται, η συγκριτική αξιολόγηση του κλειστού βρόχου έναντι των SAP συστημάτων αποκτά ιδιαίτερη σημασία. Στη συστηματική ανασκόπηση, επισημαίνεται ότι τόσο τα CLS, όσο και τα SAP μπορούν να βελτιώσουν τον γλυκαιμικό έλεγχο, ωστόσο τα CLS εμφανίζουν γενικά ανώτερη αποτελεσματικότητα, καθώς μειώνουν το θεραπευτικό φορτίο και αυξάνουν το TIR μέσω αυτοματοποιημένων προσαρμογών (Alamoudi et al., 2024). Οι συγγραφείς

αναφέρουν ότι το κλινικό πλεονέκτημα των CLS δεν αφορά μόνο αριθμητικούς δείκτες, αλλά και δείκτες ικανοποίησης, καθώς μειώνεται η ανάγκη συνεχών χειροκίνητων παρεμβάσεων (Alamoudi et al., 2024).

1.6.6. Οικονομική διάσταση: κόστος και αποδοτικότητα των τεχνολογιών

Η ενσωμάτωση τεχνολογιών όπως η CGM και τα HCL συστήματα συνοδεύεται από αυξημένο άμεσο κόστος (συσκευές, αναλώσιμα, αισθητήρες, εκπαίδευση). Ωστόσο, η οικονομική αξιολόγηση είναι πολυπαραγοντική, καθώς τα πιθανά οφέλη περιλαμβάνουν μείωση επειγόντων περιστατικών, λιγότερες νοσηλείες, και μείωση μακροχρόνιων επιπλοκών (Jiao et al., 2022). Η συστηματική ανασκόπηση των Jiao και συνεργατών αξιολόγησε τη σχέση κόστους-αποτελεσματικότητας της CGM έναντι SMBG σε ΣΔ1, με βάση 19 οικονομικές μελέτες από 11 χώρες. Τα περισσότερα μοντέλα χρησιμοποίησαν Markov προσεγγίσεις και υπολόγισαν ICER (incremental cost-effectiveness ratio) ανά QALY (quality-adjusted life year). Οι εκτιμήσεις ICER για CGM κυμάνθηκαν περίπου από $18,734 έως $99,941 ανά QALY, ενώ οι περισσότερες μελέτες κατέληξαν ότι η CGM είναι cost-effective με βάση τα αντίστοιχα thresholds κάθε χώρας (Jiao et al., 2022). Ιδιαίτερα σημαντικό είναι ότι η αποδοτικότητα αυξάνεται, όταν η CGM εφαρμόζεται σε πληθυσμούς με υψηλότερο κίνδυνο υπογλυκαιμίας ή υποβέλτιστο γλυκαιμικό έλεγχο, καθώς σε αυτές τις ομάδες το όφελος σε QALYs είναι μεγαλύτερο και το ICER χαμηλότερο (Jiao et al., 2022). Σχετικά με τα HCL συστήματα, η ίδια ανασκόπηση εντόπισε λιγότερες μελέτες (μόλις τρεις), ωστόσο και οι τρεις έδειξαν χαμηλότερα ICER και υψηλότερα QALY gains σε σχέση με SAP, γεγονός που αποδίδεται στη συνδυαστική επίδραση μείωσης HbA1c και μείωσης σοβαρών υπογλυκαιμικών επεισοδίων (Jiao et al., 2022).

1.6.7. Αναδυόμενες προσεγγίσεις: closed-loop σε MDI και αλγοριθμική υποστήριξη

Παρότι η τεχνολογική εξέλιξη έχει επικεντρωθεί κυρίως σε αντλίες, τα τελευταία χρόνια εμφανίζονται καινοτόμες προσεγγίσεις που επιχειρούν να εισάγουν «κλειστό βρόχο» και σε σχήματα MDI. Χαρακτηριστικό παράδειγμα αποτελεί η ερευνητική εφαρμογή reinforcement learning (RL) για προσαρμογή bolus δόσεων σε ασθενείς με MDI, χρησιμοποιώντας δεδομένα πραγματικού χρόνου από αισθητήρες γλυκόζης. Στη μελέτη των Jaloli και Cescon, το RL μοντέλο έδειξε βελτίωση του TIR και μείωση της γλυκαιμικής μεταβλητότητας σε in silico πληθυσμούς, σε σύγκριση με open-loop συμβατική θεραπεία (Jaloli & Cescon, 2023). Αν και πρόκειται για

προκλινική/υπολογιστική αξιολόγηση και όχι κλινική εφαρμογή, το εύρημα αυτό είναι ενδεικτικό της τάσης προς «αλγοριθμοποίηση» της θεραπείας, με στόχο την επέκταση των οφελών της αυτοματοποίησης και σε ασθενείς που δεν χρησιμοποιούν αντλία (Jaloli & Cescon, 2023).

Συνοψίζοντας, η συμβατική θεραπεία με MDI και SMBG εξακολουθεί να αποτελεί την πιο διαδεδομένη θεραπευτική προσέγγιση διεθνώς, ωστόσο έχει σαφείς περιορισμούς λόγω της αποσπασματικής παρακολούθησης, της υψηλής ανάγκης χειροκίνητων αποφάσεων και της αδυναμίας πρόβλεψης γλυκαιμικών τάσεων. Η μετάβαση σε αντλία ινσουλίνης μπορεί να βελτιώσει την ευελιξία και να μειώσει την HbA1c σε επιλεγμένους ασθενείς, όμως δεν επιλύει πλήρως την πολυπλοκότητα της καθημερινής διαχείρισης (Jaloli & Cescon, 2023).

Η CGM αναδεικνύεται ως τεχνολογία-κλειδί, καθώς βελτιώνει τόσο την HbA1c, όσο και τον TIR, ενώ μειώνει υπογλυκαιμικά επεισόδια, ιδιαίτερα σε πληθυσμούς υψηλού κινδύνου (Freckmann, 2020; Laffel et al., 2020).Τα SAP συστήματα προσφέρουν μια ενδιάμεση λύση, όμως η πιο μετασχηματιστική εξέλιξη φαίνεται να είναι τα HCL/CLS συστήματα, τα οποία παρέχουν σταθερή αύξηση TIR, μειώνουν τις διακυμάνσεις και μετατοπίζουν σημαντικό μέρος της διαχείρισης από τον ασθενή στον αλγόριθμο (Heinemann et al., 2018b; McAuley et al., 2020). Τέλος, η οικονομική αξιολόγηση δείχνει ότι οι τεχνολογικές παρεμβάσεις, παρά το αυξημένο αρχικό κόστος, είναι συχνά cost-effective μακροπρόθεσμα, ειδικά όταν στοχεύουν σε πληθυσμούς με αυξημένο κίνδυνο υπογλυκαιμίας ή κακής ρύθμισης (Jiao et al., 2022).

Η εξέλιξη των τεχνολογιών διαχείρισης του Σακχαρώδους Διαβήτη Τύπου 1 (ΣΔ1) έχει οδηγήσει σε σημαντική αλλαγή παραδείγματος στη θεραπευτική προσέγγιση, καθώς η παραδοσιακή αυτοπαρακολούθηση γλυκόζης (SMBG) και οι πολλαπλές ημερήσιες ενέσεις ινσουλίνης (MDI) έχουν πλέον σε μεγάλο βαθμό συμπληρωθεί ή αντικατασταθεί από συστήματα συνεχούς παρακολούθησης γλυκόζης (CGM), αντλίες ινσουλίνης (CSII), sensor-augmented pump (SAP) και, πιο πρόσφατα, από συστήματα αυτοματοποιημένης χορήγησης ινσουλίνης ή κλειστού βρόχου (closed-loop) (Freckmann, 2020). Παρότι η HbA1c εξακολουθεί να αποτελεί τον παραδοσιακό κύριο δείκτη αξιολόγησης του γλυκαιμικού ελέγχου, η σύγχρονη βιβλιογραφία αναγνωρίζει ότι η HbA1c δεν αποτυπώνει επαρκώς κρίσιμες παραμέτρους, όπως η συχνότητα και διάρκεια υπογλυκαιμίας, οι ενδοημερήσιες διακυμάνσεις και η γλυκαιμική μεταβλητότητα (Yoo & Kim, 2020; Toschi et al., 2020). Η ευρεία χρήση της CGM ανέδειξε νέους δείκτες, όπως ο χρόνος εντός στόχου (Time in Range, TIR), ο χρόνος

κάτω από το εύρος στόχου (Time Below Range, TBR) και ο συντελεστής μεταβλητότητας (%CV), οι οποίοι επιτρέπουν πολυπαραμετρική αξιολόγηση της ποιότητας της ρύθμισης και της ασφάλειας της θεραπείας (Lazar et al., 2023; Yoo & Kim, 2020).

Παρά τα σημαντικά δεδομένα υπέρ της αποτελεσματικότητας της CGM και των συστημάτων κλειστού βρόχου, η υπάρχουσα βιβλιογραφία παρουσιάζει ετερογένεια ως προς: (α) τον τύπο της τεχνολογικής παρέμβασης (rtCGM, iscCGM, SAP, hybrid closed-loop), (β) το θεραπευτικό υπόβαθρο (MDI έναντι αντλίας), (γ) τις ηλικιακές ομάδες (έφηβοι, νεαροί ενήλικες, ενήλικες), καθώς και (δ) τα χρησιμοποιούμενα καταληκτικά σημεία, τα οποία συχνά εστιάζουν μονοδιάστατα στη HbA1c και λιγότερο σε δείκτες CGM που περιγράφουν τη μεταβλητότητα και τον κίνδυνο υπογλυκαιμίας (Freckmann, 2020; Lazar et al., 2023).

Επιπλέον, αν και οι τυχαιοποιημένες ελεγχόμενες δοκιμές (randomized controlled trials, RCTs) αποτελούν το ισχυρότερο επίπεδο τεκμηρίωσης για την αξιολόγηση θεραπευτικών παρεμβάσεων, δεν είναι πάντα σαφές σε ποιο βαθμό τα οφέλη της CGM και των συστημάτων αυτοματοποιημένης χορήγησης ινσουλίνης μεταφράζονται σε κλινικά σημαντική βελτίωση τόσο της HbA1c, όσο και των δεικτών γλυκαιμικής σταθερότητας και ασφάλειας, ιδιαίτερα σε διαφορετικούς πληθυσμούς και θεραπευτικά σχήματα (Heinemann et al., 2018b; Laffel et al., 2020). Στο πλαίσιο αυτό, κρίνεται αναγκαία μια συστηματική ανασκόπηση που να συνθέτει τα διαθέσιμα δεδομένα από RCTs και να αξιολογεί συγκριτικά τις επιδράσεις των τεχνολογιών, αυτών όχι μόνο στη HbA1c, αλλά και σε βασικούς δείκτες CGM (TIR, TBR, GV, %CV), οι οποίοι αντανακλούν πιο ολοκληρωμένα την ποιότητα του γλυκαιμικού ελέγχου (Lazar et al., 2023; Toschi et al., 2020; Yoo & Kim, 2020).

Σκοπός της παρούσας συστηματικής ανασκόπησης είναι να αξιολογηθεί, σε άτομα με Σακχαρώδη Διαβήτη Τύπου 1, η επίδραση της συνεχούς παρακολούθησης γλυκόζης (CGM) και των συστημάτων αυτοματοποιημένης χορήγησης ινσουλίνης (αντλία/closed-loop) στη μεταβολή της HbA1c και σε δείκτες γλυκαιμικού ελέγχου, σε σύγκριση με συμβατική θεραπεία (π.χ. SMBG, MDI) ή/και με λιγότερο αυτοματοποιημένα τεχνολογικά σχήματα (π.χ. αντλία χωρίς closed-loop, SAP), μέσω σύνθεσης δεδομένων από τυχαιοποιημένες ελεγχόμενες δοκιμές.

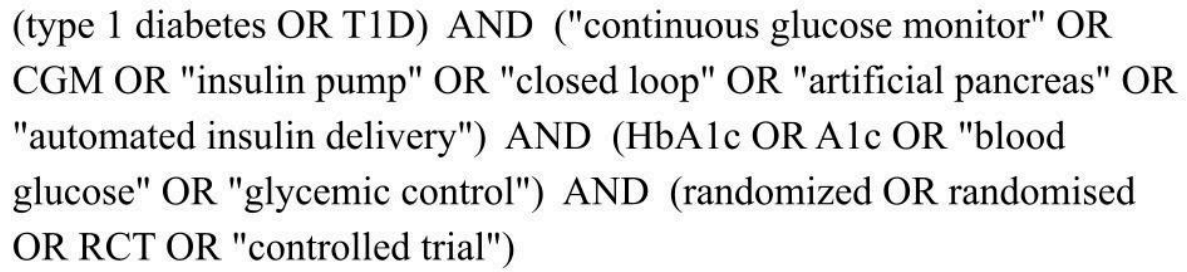
ΚΕΦΑΛΑΙΟ 2

ΜΕΘΟΔΟΣ

Κύριο μέλημα της παρούσας συστηματικής ανασκόπησης ήταν η αξιολόγηση της αποτελεσματικότητας της χρήσης συστημάτων κλειστού βρόχου χορήγησης ινσουλίνης (closed-loop insulin pumps) σε άτομα με σακχαρώδη διαβήτη τύπου 1, σε σύγκριση με τη συνήθη θεραπεία ινσουλίνης (multiple daily injections - MDI ή μη closed-loop αντλίες ινσουλίνης), αναφορικά με τις κύριες εκβάσεις της γλυκαιμικής ρύθμισης. Οι βασικές εκβάσεις που εξετάστηκαν ήταν η γλυκοζυλιωμένη αιμοσφαιρίνη (HbA1c) και οι δείκτες γλυκόζης αίματος, όπως αυτοί αναφέρονται στις πρωτογενείς μελέτες.

Η συστηματική αναζήτηση πραγματοποιήθηκε σε τρεις ηλεκτρονικές βάσεις δεδομένων, Medline, Excerpta Medica Database (EMBASE), και CENTRAL, ακολουθώντας τις κατευθυντήριες οδηγίες PRISMA 2020 για τη διενέργεια και αναφορά συστηματικών ανασκοπήσεων (Page et al., 2021). Στην ανασκόπηση συμπεριλήφθηκαν αποκλειστικά τυχαιοποιημένες κλινικές δοκιμές (Randomized Controlled Trials - RCTs) που αφορούσαν άτομα με σακχαρώδη διαβήτη τύπου 1 και συνέκριναν συστήματα closed-loop με τυπική θεραπεία ινσουλίνης (MDI ή συμβατικές αντλίες χωρίς αλγόριθμο κλειστού βρόχου).

Για τη διασφάλιση της αξιοπιστίας και της αναπαραξιμότητας της αναζήτησης, παρατίθεται το search string της βάσης PubMed, σύμφωνα με τις οδηγίες PRISMA-S (Rethlefsen et al., 2021)(εικόνα 1). Η συνολική στρατηγική αναζήτησης σχεδιάστηκε με βάση τους κύριους όρους του PICO και περιλάμβανε συνδυασμούς λέξεων-κλειδιών και ελεγχόμενων όρων (MeSH/Emtree), όπως “type 1 diabetes”, “closed-loop”, “artificial pancreas”, “hybrid closed loop”, “insulin pump”, “multiple daily injections”, “HbA1c”, και “glucose”.



Εικόνα 1: Διατύπωση της στρατηγικής αναζήτησης (search string) που χρησιμοποιήθηκε για την αναζήτηση στη βάση δεδομένων PubMed, στοχεύοντας σε τυχαιοποιημένες ελεγχόμενες μελέτες που αφορούν της χρήσης συστημάτων κλειστού βρόχου χορήγησης ινσουλίνης (closed-loop insulin pumps) σε άτομα με σακχαρώδη διαβήτη τύπου 1, σε σύγκριση με τη συνήθη θεραπεία ινσουλίνης (multiple daily injections - MDI ή μη closed-loop αντλίες ινσουλίνης), αναφορικά με τις κύριες εκβάσεις της γλυκαιμικής ρύθμισης όπως γλυκοζυλιωμένη αιμοσφαιρίνη (HbA1c) και οι δείκτες γλυκόζης αίματος σύμφωνα με τα κριτήρια PRISMA-S (Rethlefsen et al., 2021).

Δεν ορίστηκε χρονικό όριο αναζήτησης στην εύρεση μελετών για την συγκέντρωση μεγαλύτερου όγκου αποτελεσμάτων, ενώ ο γλωσσικός περιορισμός ορίστηκε σε αποκλειστικά αγγλόφωνες δημοσιεύσεις. Επίσης, αποκλείστηκαν μελέτες που δεν ήταν RCTs, μελέτες παρατήρησης, περιγραφικές μελέτες, ανασκοπήσεις, καθώς και μελέτες που αφορούσαν σακχαρώδη διαβήτη τύπου 2 ή άλλες μορφές διαβήτη. Πιο συγκεκριμένα το PICOT του ερευνητικού ερωτήματος ήταν:

- P: Άτομα με σακχαρώδη διαβήτη τύπου 1
- I: Χρήση συστημάτων κλειστού βρόχου χορήγησης ινσουλίνης (closed-loop insulin pumps).
- C: Συνήθη θεραπεία ινσουλίνης (multiple daily injections - MDI ή μη closed-loop αντλίες ινσουλίνης).
- O: Η μεταβολή της γλυκοζυλιωμένης αιμοσφαιρίνη (HbA1c) και της γλυκόζης στο αίμα.

- Τ: Τυχαιοποιημένες κλινικές δοκιμές (RCTs)

Τα αποτελέσματα της αναζήτησης εισήχθησαν στο λογισμικό διαχείρισης αναφορών Systematic Review Accelerator, όπου πραγματοποιήθηκε αφαίρεση διπλότυπων μελετών τόσο μέσω του εργαλείου, όσο και χειροκίνητα (Clark et al., 2020). Στη συνέχεια, πραγματοποιήθηκε έλεγχος σε επίπεδο τίτλου και περίληψης.

Οι μελέτες που πληρούσαν τα κριτήρια μετά τον αρχικό έλεγχο εισήχθησαν στο λογισμικό Mendeley για τη διαχείριση των πλήρων κειμένων και ακολούθησε έλεγχος πλήρους κειμένου (Clark et al., 2020). Η διαδικασία επιλογής των μελετών καταγράφηκε αναλυτικά σε διάγραμμα ροής σύμφωνα με τις οδηγίες PRISMA 2020 (Page et al., 2021), όπου παρουσιάζεται ο αριθμός των μελετών που εντοπίστηκαν, αποκλείστηκαν (με αιτιολόγηση) και τελικά συμπεριλήφθηκαν. Μετά την τελική επιλογή, οι εναπομείνασες μελέτες παρουσιάστηκαν σ’ ένα αρχείο excel για λόγους εύκολης μορφοποίησης. Ο πίνακας που δημιουργήθηκε αποτελεί το περιεχόμενο του παραρτήματος (Παράρτημα 1). Για πρακτικούς λόγους κάθε σελίδα περιλαμβάνει τα στοιχεία από 1 κλινική μελέτη. Τα στοιχεία των μελετών που μελετήθηκαν περιλάμβαναν χαρακτηριστικά δείγματος (ηλικία, φύλο, διάρκεια νόσου), χαρακτηριστικά παρέμβασης (τύπος closed-loop συστήματος, διάρκεια παρέμβασης), ομάδα σύγκρισης (MDI ή non closed-loop pump), καθώς και τα αποτελέσματα που σχετίζονταν με HbA1c και μετρήσεις γλυκόζης.

2.1 Συστηματική ανασκόπηση

Η ενσωμάτωση τεκμηριωμένων προσεγγίσεων στην κλινική πράξη προϋποθέτει τον συνδυασμό των καλύτερων διαθέσιμων επιστημονικών δεδομένων με την κλινική εμπειρία και τις προτιμήσεις του ίδιου του ασθενούς. Από τις πλέον αξιόπιστες πηγές τεκμηρίωσης θεωρούνται οι τυχαιοποιημένες ελεγχόμενες μελέτες (RCTs) και οι συστηματικές ανασκοπήσεις (Impellizzeri & Bizzini, 2012). Η συστηματική ανασκόπηση αποτελεί μια ειδική μορφή βιβλιογραφικής ανασκόπησης, στην οποία εφαρμόζονται προκαθορισμένες, αναπαραγώγιμες και διαφανείς μεθοδολογίες για την αναζήτηση, συλλογή, αξιολόγηση και ανάλυση των διαθέσιμων στοιχείων από τη διεθνή βιβλιογραφία. Μέσω αυτής της διαδικασίας, επιδιώκεται η ανίχνευση και επιλογή των μελετών με τη μεγαλύτερη μεθοδολογική εγκυρότητα και αξιοπιστία (Grant & Booth, 2009). Κεντρικός στόχος μιας συστηματικής ανασκόπησης είναι να παρέχει μια συνολική και αμερόληπτη εικόνα της υπάρχουσας επιστημονικής γνώσης, ακολουθώντας προκαθορισμένο πρωτόκολλο που μειώνει τον κίνδυνο συστηματικού σφάλματος. Το πρωτόκολλο αυτό, καθορίζει με σαφήνεια το ερευνητικό ερώτημα, τα κριτήρια ένταξης και αποκλεισμού των μελετών, τη στρατηγική αναζήτησης, καθώς και τις μεθόδους ανάλυσης και παρουσίασης των αποτελεσμάτων (Grant & Booth, 2009). Η χρήση του μοντέλου PICO (Population, Intervention, Comparison, Outcome) συμβάλλει στην αυστηρή διατύπωση του ερευνητικού ερωτήματος και στην εστιασμένη αναζήτηση της βιβλιογραφίας, διασφαλίζοντας ότι η ανασκόπηση απαντά σε συγκεκριμένα κλινικά ερωτήματα. (Bearman & Dawson, 2013).

Μια συστηματική ανασκόπηση στοχεύει στη συγκέντρωση και ανάλυση όλων των διαθέσιμων μελετών που απαντούν σε ένα συγκεκριμένο ερευνητικό ερώτημα, σύμφωνα με προκαθορισμένα κριτήρια ένταξης και αποκλεισμού. Η διαδικασία περιλαμβάνει τη συστηματική αναζήτηση, την αξιολόγηση της ποιότητας των εντοπισμένων μελετών και την ανάλυση των αποτελεσμάτων τους. Για την ενίσχυση της αξιοπιστίας και της επιστημονικής τεκμηρίωσης των ευρημάτων, οι συστηματικές ανασκοπήσεις εστιάζουν κατά κύριο λόγο σε τυχαιοποιημένες ελεγχόμενες δοκιμές (RCTs), οι οποίες θεωρούνται η ισχυρότερη μορφή πρωτογενούς έρευνας στην ιεραρχία των επιστημονικών δεδομένων (Ahn & Kang, 2018). Η συστηματική ανασκόπηση χρησιμοποιείται ευρέως σε διάφορους τομείς της ιατρικής και της υγείας, συμβάλλοντας στην εξαγωγή αξιόπιστων, συγκρίσιμων και υψηλής ποιότητας συμπερασμάτων από τον μεγάλο όγκο δημοσιευμένων δεδομένων. Η συστηματική

ανασκόπηση είναι μια διαφανής, αντικειμενική και αναπαραγώγιμη διαδικασία, η οποία αποσκοπεί στη συλλογή, αξιολόγηση και σύνοψη όλων των σχετικών μελετών που απαντούν σε ένα συγκεκριμένο ερευνητικό ερώτημα. (Ahn & Kang, 2018).

Η συγκεκριμένη εργασία ασχολήθηκε με την χρήση συστημάτων κλειστού βρόχου χορήγησης ινσουλίνης (closed-loop insulin pumps) σε άτομα με με σακχαρώδη διαβήτη τύπου 1, σε σύγκριση με τη συνήθη θεραπεία ινσουλίνης (multiple daily injections - MDI ή μη closed-loop αντλίες ινσουλίνης) παρατηρώντας την μεταβολή της γλυκοζυλιωμένης αιμοσφαιρίνη (HbA1c) και της γλυκόζης στο αίμα. Έτσι, η μηδενική υπόθεση της συγκεκριμένης συστηματικής ανασκόπησης σχηματίζεται ως εξής :

H0: Η χρήση συστημάτων κλειστού βρόχου χορήγησης ινσουλίνης δεν υπερέχει της συνήθους θεραπείας ινσουλίνης ως προς τη βελτίωση της γλυκαιμικής ρύθμισης σε άτομα με σακχαρώδη διαβήτη τύπου 1, όπως αυτή αποτυπώνεται μέσω της γλυκοζυλιωμένης αιμοσφαιρίνης (HbA1c) και των δεικτών γλυκόζης αίματος, σύμφωνα με τα διαθέσιμα δεδομένα της βιβλιογραφίας.

H1: Η χρήση συστημάτων κλειστού βρόχου χορήγησης ινσουλίνης (closed-loop insulin pumps) είναι εξίσου ή περισσότερο αποτελεσματική σε άτομα με σακχαρώδη διαβήτη τύπου 1 σε σύγκριση με τη συνήθη θεραπεία ινσουλίνης (multiple daily injections ή μη closed-loop αντλίες), όσον αφορά τη βελτίωση της γλυκαιμικής ρύθμισης, όπως αυτή εκφράζεται μέσω της μείωσης της γλυκοζυλιωμένης αιμοσφαιρίνης (HbA1c) και της βελτίωσης των δεικτών γλυκόζης αίματος.

Η αποδοχή ή απόρριψη της μηδενικής υπόθεσης θα προκύψει μέσω της συστηματικής ανάλυσης των διαθέσιμων τυχαιοποιημένων κλινικών δοκιμών, και θα συμβάλει στην αξιολόγηση της αποτελεσματικότητας των συστημάτων closed-loop σε σύγκριση με τις συμβατικές μεθόδους χορήγησης ινσουλίνη.

2.2 Αξιολόγηση των δεδομένων

Για τη συστηματική και αναπαραγώγιμη καταγραφή των πληροφοριών που απαιτούνται για την αξιολόγηση των μελετών που εντάχθηκαν στην παρούσα συστηματική ανασκόπηση, δημιουργήθηκε φύλλο συλλογής δεδομένων σε αρχείο μορφής .xlsx. Σ' αυτό το σημείο πρέπει να υπογραμμισθεί ότι το αρχείο excel δημιουργήθηκε όχι για την εξαγωγή δεδομένων, αλλά για τη συλλογή τους και την απεικόνιση τους μ' εναν ευανάγνωστο κι οργανωμένο τρόπο. Η συλλογή των δεδομένων από τις τυχαιοποιημένες κλινικές δοκιμές οδήγησε στις παρακάτω κατηγορίες:

Χαρακτηριστικά της μελέτης:

- Πρώτος συγγραφέας και έτος δημοσίευσης
- Αριθμός NCT
- Σχεδιασμός μελέτης (π.χ. τυχαιοποιημένη ελεγχόμενη δοκιμή)
- Χώρα
- Αριθμός κέντρων διεξαγωγής
- Τυφλοποίηση
- Τυχαιοποίηση
- Κριτήρια ένταξης και αποκλεισμού των συμμετεχόντων
- Τυχόν δηλωθείσα χρηματοδότηση
- Διάρκεια της μελέτης (enrolment period)

Χαρακτηριστικά παρέμβασης:

- Περιγραφή της παρέμβασης χορήγησης ινσουλίνης με σύστημα κλειστού βρόχου.
- Τυπική θεραπεία χορήγησης ινσουλίνης.
- Δόση
- Οδός χορήγησης
- Συχνότητα χορήγησης

Χαρακτηριστικά συμμετεχόντων:

- Συνολικός αριθμός συμμετεχόντων

- Αριθμός συμμετεχόντων στο υβριδικό σύστημα κλειστού βρόχου (n)
- Αριθμός συμμετεχόντων στη συμβατική χορήγηση ινσουλίνης (n)
- Ηλικία (ομάδα υβριδικού συστήματος κλειστού βρόχου)

Εκβάσεις:

- Πρωτεύουσες έκβασεις
- Δευτερεύουσες εκβάσεις
- Στόχος ινσουλίνης TIR (Time in range)
- Γλυκοζυλιωμένη αιμοσφαιρίνη A1c (HbA1c)

Η συστηματική καταγραφή αυτών των δεδομένων επέτρεψε τη συγκριτική αξιολόγηση των μελετών και την αξιολόγηση της ομοιογένειας των παρεμβάσεων και των εκβάσεων, διευκολύνοντας την περαιτέρω ανάλυση των αποτελεσμάτων της ανασκόπησης.

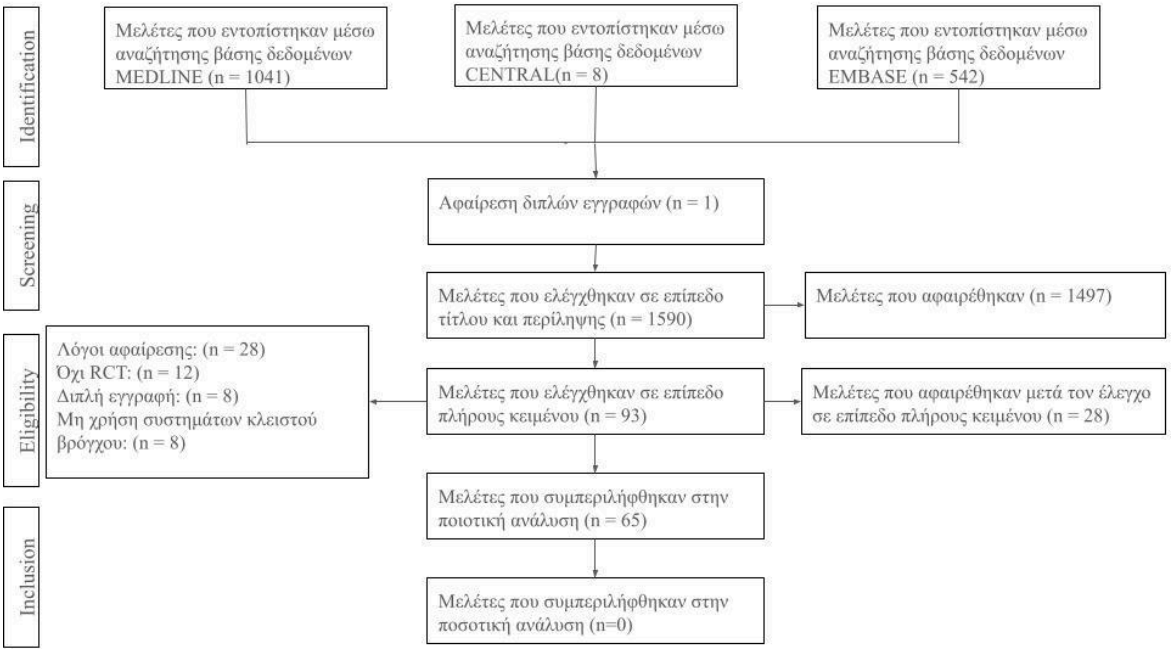
ΚΕΦΑΛΑΙΟ 3

ΑΠΟΤΕΛΕΣΜΑΤΑ

Για την ανεύρεση των κατάλληλων μελετών, ακολουθήθηκε μια συστηματική και αναπαραγώγιμη διαδικασία, σύμφωνα με τις κατευθυντήριες οδηγίες του PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Page et al., 2021). Η αναζήτηση πραγματοποιήθηκε σε τρεις ηλεκτρονικές βάσεις δεδομένων, Medline, Excerpta Medica Database (EMBASE), και CENTRAL. Οι βάσεις αυτές επελέγησαν λόγω της ευρείας κάλυψης που προσφέρουν στη διεθνή βιβλιογραφία της ιατρικής, της νοσηλευτικής και των συναφών επιστημών υγείας.

Από τη διαδικασία αυτή προέκυψε αρχικά ένας συνολικός αριθμός 1.591 δυνητικά σχετικών εγγράφων, τα οποία εξήχθησαν σε αρχείο τύπου .ris, κατάλληλο για περαιτέρω επεξεργασία μέσω εργαλείων διαχείρισης αναφορών και συστηματικών ανασκοπήσεων. Στη συνέχεια, το σύνολο των εγγράφων εισήχθη στο εργαλείο Systematic Review Accelerator (SRA) (Clark et al., 2020), το οποίο χρησιμοποιήθηκε για την αυτόματη και χειροκίνητη απομάκρυνση διπλοτύπων. Συγκεκριμένα, το εργαλείο εντόπισε 1 διπλότυπη μελέτη, η οποία αφαιρέθηκε αρχικά με τη βοήθεια των αυτοματοποιημένων προτάσεών του. Επιπλέον, πραγματοποιήθηκε χειροκίνητος έλεγχος, στον οποίο επανεξετάστηκε το σύνολο των τίτλων και περιλήψεων για ενδεχόμενα υπολειπόμενα διπλότυπα που δεν ανιχνεύθηκαν αυτόματα, διασφαλίζοντας τη μέγιστη ακρίβεια στη διαδικασία. Ακολούθως, οι 1.590 μοναδικές μελέτες υποβλήθηκαν σε έλεγχο σε επίπεδο τίτλου και περίληψης. Κατά τη διαδικασία αυτή, αξιολογήθηκε η συνάφεια κάθε μελέτης με βάση τα εκ των προτέρων καθορισμένα κριτήρια ένταξης και αποκλεισμού, όπως είχαν διατυπωθεί στο σκέλος της μεθοδολογίας της ανασκόπησης. Μετά την ολοκλήρωση του αρχικού αυτού ελέγχου, 93 μελέτες κρίθηκαν επιλέξιμες για περαιτέρω αξιολόγηση σε επίπεδο πλήρους κειμένου. Οι πλήρεις μελέτες ανακτήθηκαν και διαβάστηκαν προσεκτικά, προκειμένου να διαπιστωθεί εάν πληρούσαν τα τελικά κριτήρια ένταξης για την ένταξή τους στη συστηματική ανασκόπηση. Από τη διαδικασία αυτή, 65 μελέτες πληρούσαν πλήρως τα κριτήρια και εντάχθηκαν στην τελική ποιοτική ανάλυση των αποτελεσμάτων. Η πλήρης διαδικασία ελέγχου σε επίπεδο πλήρους κειμένου πραγματοποιήθηκε στο λογισμικό διαχείρισης αναφορών Mendeley (MacMillan, 2012). Η διαδικασία επιλογής τεκμηριώνεται με διάγραμμα ροής PRISMA, που παρουσιάζει με διαφάνεια όλα τα στάδια αναζήτησης, επιλογής και ένταξης των μελετών στην παρούσα συστηματική

ανασκόπηση Prisma 2020 (Page et al., 2021) (εικόνα 2).



Εικόνα 2: Διάγραμμα ροής PRISMA (PRISMA flowchart) της διαδικασίας επιλογής μελετών (Page et al., 2021). Απεικονίζεται η ροή των μελετών που ανακτήθηκαν από τις τρεις βάσεις δεδομένων (EMBASE, CENTRAL, MEDLINE), η αφαίρεση διπλότυπων, ο έλεγχος σε επίπεδο τίτλου, περίληψης και πλήρους κειμένου, καθώς και οι λόγοι αποκλεισμού. Τελικά, 65 μελέτες κρίθηκαν κατάλληλες και συμπεριλήφθηκαν στην ποιοτική ανάλυση της συστηματικής ανασκόπησης.

3.1.Συλλογή των δεδομένων και χαρακτηριστικά μελετών

Η συλλογή κι αξιολόγηση δεδομένων πραγματοποιήθηκε από τις μελέτες που τελικά συμπεριλήφθηκαν στη συστηματική ανασκόπηση, όπως αυτές καταγράφονται στο αρχείο δεδομένων. Το τελικό σύνολο περιλάμβανε 65 κλινικές δοκιμές που σύγκριναν συστήματα hybrid closed-loop έναντι standard insulin therapy. Οι μελέτες παρουσίαζαν αξιοσημείωτη ετερογένεια ως προς το σχεδιασμό, τη διάρκεια παρακολούθησης, το μέγεθος δείγματος και τα χαρακτηριστικά των συμμετεχόντων, ωστόσο διατηρούσαν συγκρίσιμη βασική δομή παρέμβασης/ελέγχου, δεδομένου ότι το κύριο ερευνητικό ερώτημα αφορούσε την αποτελεσματικότητα της αυτοματοποιημένης ινσουλινοθεραπείας σε σχέση με τις συμβατικές πρακτικές.

Αναφορικά με τον σχεδιασμό, το μεγαλύτερο ποσοστό των μελετών ήταν τυχαιοποιημένες ελεγχόμενες δοκιμές με crossover σχεδιασμό (n=39), ενώ 25 μελέτες είχαν κλασικό parallel-group RCT σχεδιασμό. Επιπλέον, καταγράφηκε μία μελέτη με 3-way crossover σχεδιασμό. Σε όλες τις δοκιμές το πρωτόκολλο χαρακτηριζόταν ως open-label, στοιχείο που θεωρείται αναμενόμενο στη συγκεκριμένη κατηγορία παρεμβάσεων, καθώς η χρήση αντλίας ινσουλίνης, αισθητήρα CGM και αλγορίθμου ελέγχου καθιστά πρακτικά δύσκολη την τυφλοποίηση τόσο των συμμετεχόντων, όσο και των ερευνητών. Η προσέγγιση αυτή συναντάται συστηματικά σε μεγάλες κλινικές δοκιμές του πεδίου, όπως εκείνες των Beck et al. (2022) και Kruger et al. (2022), καθώς και σε παλαιότερες μελέτες ανάπτυξης/επιβεβαίωσης κλειστών βρόχων (Breton et al., 2020).

Ως προς τη γεωγραφική κατανομή, οι μελέτες προέρχονταν από ευρύ φάσμα χωρών, με σαφή υπερεκπροσώπηση των Ηνωμένων Πολιτειών (n=16) και σημαντική παρουσία ευρωπαϊκών χωρών, όπως το Ηνωμένο Βασίλειο (n=6). Παράλληλα, αρκετές δοκιμές είχαν πολυεθνικό χαρακτήρα, γεγονός που υποδηλώνει την αυξανόμενη διεθνή ερευνητική δραστηριότητα στον τομέα των αυτοματοποιημένων συστημάτων ινσουλίνης και επιτρέπει την εξαγωγή συμπερασμάτων με μεγαλύτερη εξωτερική εγκυρότητα. Σε ορισμένες περιπτώσεις, η γεωγραφική κατανομή αναφερόταν με μεγαλύτερη λεπτομέρεια, όπως σε μελέτες που διεξήχθησαν σε διαφορετικές περιοχές του Ηνωμένου Βασιλείου (England, Scotland, Northern Ireland), όπως η μελέτη των Lee et al. (2024), ενώ σε άλλες δηλωνόταν γενικά ως multi-center.

Το συνολικό μέγεθος δείγματος που εξήχθη από τις 65 μελέτες ανήλθε σε 4.705 συμμετέχοντες. Παρατηρήθηκε σημαντική διακύμανση στον αριθμό των συμμετεχόντων ανά δοκιμή, με το μικρότερο δείγμα να περιλαμβάνει 10 άτομα και το

μεγαλύτερο 326. Η διάμεση τιμή του μεγέθους δείγματος ήταν περίπου 41 συμμετέχοντες ανά μελέτη, γεγονός που αντανακλά ότι μεγάλο μέρος της βιβλιογραφίας περιλαμβάνει μικρές έως μεσαίου μεγέθους δοκιμές, συχνά crossover, οι οποίες είναι μεθοδολογικά κατάλληλες για τεχνολογικές παρεμβάσεις, όπου ο κάθε συμμετέχων μπορεί να λειτουργεί ως δικό του control. Παράλληλα, στο σύνολο υπήρχαν και μεγάλες πολυκεντρικές δοκιμές με parallel σχεδιασμό, οι οποίες συνεισέφεραν σημαντικά στον συνολικό αριθμό συμμετεχόντων και αποτελούν συχνά τη βάση για κατευθυντήριες οδηγίες και κλινική υιοθέτηση (Beck et al., 2022; Kruger et al., 2022).

Η διάρκεια παρακολούθησης των δοκιμών εμφάνισε επίσης μεγάλη ετερογένεια, με συχνότερες διάρκειες τους 6 μήνες, τις 13 εβδομάδες και τις 26 εβδομάδες. Τα δεδομένα έδειξαν ότι σημαντικό ποσοστό των μελετών εστίαζε σε χρονικά πλαίσια 3 έως 6 μηνών, τα οποία θεωρούνται επαρκή για να καταγραφούν σταθερές μεταβολές σε μετρικές CGM και HbA1c. Παράλληλα, υπήρχαν βραχυχρόνιες μελέτες διάρκειας λίγων ημερών ή εβδομάδων, οι οποίες ήταν κυρίως crossover και στόχευαν περισσότερο στην τεχνολογική αξιολόγηση, την ασφάλεια ή την απόδοση του αλγορίθμου σε ελεγχόμενες συνθήκες. Αντίθετα, σε ειδικούς πληθυσμούς υπήρξαν δοκιμές σημαντικά μεγαλύτερης διάρκειας, όπως στην περίπτωση εγκύων με σακχαρώδη διαβήτη τύπου 1, όπου η παρακολούθηση απαιτεί μεγαλύτερο χρονικό εύρος, ώστε να αποτυπωθεί η επίδραση κατά την κύηση (Lee et al., 2024).

Σε επίπεδο πληθυσμού, τα κριτήρια ένταξης και αποκλεισμού ήταν γενικά συνεπή με τη διεθνή πρακτική για κλινικές δοκιμές κλειστού βρόχου. Οι περισσότερες μελέτες περιλάμβαναν άτομα με σακχαρώδη διαβήτη τύπου 1, με προϋπόθεση προηγούμενης χρήσης αντλίας ή/και CGM σε αρκετές περιπτώσεις, ενώ συχνά υπήρχαν περιορισμοί που σχετίζονταν με τη συμμόρφωση, την ικανότητα χρήσης τεχνολογίας και την απουσία σοβαρών συννοσηροτήτων. Παρότι ο βασικός πληθυσμός στόχευε σε ενήλικες ή/και εφήβους, στο σύνολο των μελετών εντοπίστηκαν και ειδικές υποομάδες, όπως έγκυες γυναίκες (Lee et al., 2024) ή ηλικιακά περιορισμένα δείγματα ενηλίκων, όπως η δοκιμή των Matejko et al. (2022) που περιλάμβανε άτομα 26–60 ετών. Η ύπαρξη τέτοιων υποομάδων είναι κρίσιμη, διότι αναδεικνύει ότι η βιβλιογραφία δεν εξετάζει μόνο την "μέση" κλινική εικόνα, αλλά επιχειρεί να διερευνήσει και την αποτελεσματικότητα σε πληθυσμούς υψηλότερου κινδύνου ή ιδιαίτερων απαιτήσεων.

Η παρέμβαση στις μελέτες περιγραφόταν ως hybrid closed-loop insulin delivery, βασισμένη σε συνεχή έγχυση ινσουλίνης μέσω αντλίας, σε συνδυασμό με συνεχή

καταγραφή γλυκόζης και αλγοριθμική ρύθμιση της βασικής ινσουλίνης. Οι συγκριτικές ομάδες αναφέρονταν συνολικά ως standard insulin therapy, με διαφοροποιήσεις ανάλογα με το πρωτόκολλο της κάθε δοκιμής. Στις περισσότερες περιπτώσεις, η standard θεραπεία περιλάμβανε είτε αντλία με manual ρυθμίσεις, είτε συμβατική διαχείριση με CGM χωρίς αυτοματοποίηση. Παρότι το αρχείο δεν παρείχε πάντα λεπτομερή τεχνική ανάλυση των αλγορίθμων, ήταν σαφές ότι ο πυρήνας της σύγκρισης παρέμενε σταθερός: αυτοματοποιημένη ρύθμιση έναντι μη αυτοματοποιημένης διαχείρισης.

Οι εκβάσεις που εξήχθησαν ήταν σε μεγάλο βαθμό συγκρίσιμες μεταξύ των μελετών, με τις μετρικές συνεχούς καταγραφής γλυκόζης να κυριαρχούν. Το time in range (TIR) και συναφείς δείκτες (όπως time above range και time below range) αποτελούσαν τις συχνότερες εκβάσεις, γεγονός που ευθυγραμμίζεται με τη σύγχρονη τάση της βιβλιογραφίας να αξιολογεί την ποιότητα γλυκαιμικού ελέγχου μέσω δυναμικών δεικτών και όχι αποκλειστικά μέσω HbA1c. Παράλληλα, η HbA1c παρέμεινε σημαντική έκβαση, είτε ως πρωτεύον είτε ως δευτερεύον καταληκτικό σημείο, ειδικά στις μεγαλύτερης διάρκειας δοκιμές, όπως στις Beck et al. (2022) και Kruger et al. (2022). Σε αρκετές μελέτες καταγράφηκε επίσης συγκεκριμένος glucose target ως κεντρικό σημείο αξιολόγησης, ενισχύοντας την εικόνα ότι οι δοκιμές αυτές δεν περιορίζονταν μόνο στη μείωση μέσων τιμών, αλλά στοχεύουν στη βελτιστοποίηση της κατανομής της γλυκόζης εντός κλινικά αποδεκτών ορίων.

Τέλος, από την συλλογή δεδομένων προέκυψε ότι η χρηματοδότηση ήταν συχνά παρούσα και καταγεγραμμένη, είτε μέσω δημόσιων ερευνητικών φορέων, είτε μέσω υποστήριξης από τη βιομηχανία τεχνολογίας διαβήτη, όπως παροχή εξοπλισμού και συσκευών. Η πληροφορία αυτή θεωρείται κρίσιμη, καθώς μπορεί να σχετίζεται με πιθανούς κινδύνους μεροληψίας ή συγκρούσεις συμφερόντων και αποτελεί βασικό στοιχείο στη συνολική αξιολόγηση της ποιότητας των μελετών (Beck et al., 2022; Matejko et al., 2022). Το σύνολο των δεδομένων που συλλέχθησαν περιγράφεται στο Παράρτημα 1. Πιο αναλυτικά, στο παράρτημα κάθε σελίδα απεικονίζει και μία διαφορετική τυχαιοποιημένη κλινική δοκιμή με αναλυτικά τα χαρακτηριστικά της παρέμβασης, του πληθυσμού, της μελέτης και τις εκβάσεις.

3.2. Ανάλυση

Η συνολική σύνθεση των διαθέσιμων τυχαιοποιημένων ελεγχόμενων δοκιμών καταδεικνύει με συνέπεια ότι τα συστήματα αυτοματοποιημένης χορήγησης ινσουλίνης, συμπεριλαμβανομένων των hybrid closed-loop (HCL), advanced hybrid closed-loop (AHCL) και πλήρως κλειστού βρόχου συστημάτων (bionic pancreas), προσφέρουν ουσιαστική βελτίωση του γλυκαιμικού ελέγχου σε άτομα με σακχαρώδη διαβήτη τύπου 1 σε σύγκριση με τη συμβατική θεραπεία ή τη sensor-augmented pump (SAP). Το πλέον σταθερό και επαναλαμβανόμενο εύρημα είναι η αύξηση του χρόνου εντός στόχου (Time in Range, 70–180 mg/dL), συνοδευόμενη από μείωση της υπεργλυκαιμίας, χωρίς παράλληλη αύξηση της υπογλυκαιμίας.

Σε ενήλικες υπό ελεύθερες συνθήκες διαβίωσης, η day-and-night χρήση closed-loop συστημάτων οδήγησε σε σημαντική αύξηση του TIR συγκριτικά με SAP, τόσο σε βραχυχρόνια, όσο και σε μελέτες μεγαλύτερης διάρκειας, με παράλληλη μείωση της μέσης γλυκόζης και του χρόνου άνω του στόχου (Leelarathna et al., 2014; Thabit et al., 2015). Η βελτίωση αυτή διατηρήθηκε σε πολυκεντρικές μελέτες διάρκειας 3–6 μηνών, όπου η προσαρμοσμένη διαφορά υπέρ του closed-loop κυμάνθηκε σε διψήφιες ποσοστιαίες μονάδες ως προς το TIR (Brown et al., 2019). Αντίστοιχα, σε μελέτες πραγματικών συνθηκών με εμπορικά συστήματα, όπως το DBLG1 και το Omnipod 5, παρατηρήθηκαν σημαντικές αυξήσεις του TIR και ουσιαστικές μειώσεις της HbA1c, ιδίως σε άτομα με υποβέλτιστο αρχικό έλεγχο (Benhamou et al., 2019; Renard et al., 2019).

Ιδιαίτερη κλινική σημασία έχει το γεγονός ότι το όφελος είναι πιο έντονο σε άτομα με υψηλή αρχική HbA1c. Σε πληθυσμούς με HbA1c ≥8%, η μετάβαση από MDI ή συμβατική αντλία σε AHCL οδήγησε σε μειώσεις HbA1c που ξεπερνούσαν το 1%, με ταυτόχρονη σημαντική αύξηση του TIR (Choudhary et al., 2022; Christensen et al., 2025). Αντίθετα, σε καλά ρυθμισμένους ενήλικες με ήδη υψηλό TIR υπό SAP, η αύξηση του TIR ήταν μικρότερη ή μη στατιστικά σημαντική, αν και παρατηρήθηκε μείωση της υπογλυκαιμίας (Pinsker et al., 2022). Το εύρημα αυτό υποδηλώνει ότι το απόλυτο μέγεθος του οφέλους εξαρτάται από το baseline επίπεδο ελέγχου κι ότι τα συστήματα κλειστού βρόχου έχουν μεγαλύτερη σχετική κλινική επίδραση σε υπορρυθμισμένους ασθενείς (Pinsker et al., 2022).

Ένα από τα πλέον συνεπή μοτίβα μεταξύ των μελετών είναι η εντονότερη βελτίωση κατά τη νυχτερινή περίοδο. Η overnight ή day-and-night χρήση closed-loop οδήγησε σε σημαντική

αύξηση του νυχτερινού TIR και σε μείωση τόσο της νυχτερινής υπεργλυκαιμίας όσο και της υπογλυκαιμίας (Brown et al., 2017; Nimri et al., 2013). Η "νυχτερινή επαναφορά" σε σταθερότερο γλυκαιμικό προφίλ φαίνεται να συμβάλλει και στη βελτίωση του συνολικού 24ώρου, υποδηλώνοντας ότι ο σταθερός έλεγχος σε περιβάλλον χωρίς γευματικές διακυμάνσεις αποτελεί κεντρικό μηχανισμό δράσης των αλγορίθμων (Brown et al., 2017; Nimri et al., 2013).

Όσον αφορά την υπογλυκαιμία, τα δεδομένα συγκλίνουν στο ότι η αύξηση του TIR δεν επιτυγχάνεται εις βάρος της ασφάλειας. Σε πολλές μελέτες ο χρόνος <70 mg/dL μειώθηκε σημαντικά με closed-loop ή παρέμεινε μη διαφοροποιημένος έναντι SAP, τεκμηριώνοντας μη κατωτερότητα ως προς την υπογλυκαιμία (Wadwa et al., 2023). Σε πληθυσμούς υψηλού κινδύνου για υπογλυκαιμία, το όφελος ήταν πιο εμφανές, με σημαντική μείωση δεικτών, όπως ο Low Blood Glucose Index (Anderson et al., 2019). Παρά ταύτα, σε συγκρίσεις έναντι συστημάτων με ήδη ενσωματωμένο μηχανισμό αναστολής, λόγω χαμηλής γλυκόζης (threshold suspend), η επιπλέον μείωση υπογλυκαιμίας ήταν μικρότερη ή μη ανιχνεύσιμη, γεγονός που υποδηλώνει ότι το συγκριτικό σύστημα επηρεάζει το παρατηρούμενο μέγεθος οφέλους (Renard et al., 2019).

Σε ειδικούς πληθυσμούς, τα αποτελέσματα παρουσιάζουν ιδιαίτερο ενδιαφέρον. Σε μικρά παιδιά, συμπεριλαμβανομένων ηλικιών κάτω των 6 ετών, τα συστήματα HCL αύξησαν σημαντικά το TIR και μείωσαν την υπεργλυκαιμία χωρίς αύξηση υπογλυκαιμίας, παρά τη μεγαλύτερη ενδοημερήσια μεταβλητότητα της ηλικιακής αυτής ομάδας (Wadwa et al., 2023; Ware et al., 2022). Σε εφήβους με υπορρύθμιση, οι αυξήσεις στο TIR ήταν εντυπωσιακές, με παράλληλη μείωση της υπεργλυκαιμίας, ενώ η HbA1c δεν διαφοροποιήθηκε πάντα στατιστικά σημαντικά (Isganaitis et al., 2021). Ποιοτικά δεδομένα σε εφήβους που χρησιμοποίησαν πλήρως κλειστό βρόχο ανέδειξαν σημαντική μείωση του καθημερινού φορτίου αυτοδιαχείρισης και βελτίωση της αντιλαμβανόμενης ποιότητας ζωής (Kadiyala et al., 2025). Στην εγκυμοσύνη, όπου οι γλυκαιμικοί στόχοι είναι αυστηρότεροι, τα δεδομένα δείχνουν διαφοροποίηση ανάλογα με το baseline επίπεδο ελέγχου. Στη μελέτη AiDAPT, η χρήση HCL οδήγησε σε σημαντική αύξηση του χρόνου εντός του εγκυμοσύνης-ειδικού εύρους στόχου και μείωση της HbA1c (Lee et al., 2025). Αντίθετα, στη CRISTAL δεν παρατηρήθηκε διαφορά στον συνολικό TIR, αλλά καταγράφηκε σημαντική μείωση της υπογλυκαιμίας και βελτίωση του νυχτερινού ελέγχου (Benhalima et al., 2024). Στην πρώιμη λοχεία, το κύριο όφελος αφορούσε τη μείωση της υπογλυκαιμίας, ενώ σε παρακολούθηση έως 6 μήνες μετά τον τοκετό παρατηρήθηκε συνολική βελτίωση του TIR (Donovan et al., 2023; Lee et al., 2025). Σε ηλικιωμένους με ΣΔ1, τα δεδομένα υποδεικνύουν σημαντική

αύξηση του TIR και ουσιαστική μείωση της νυχτερινής υπογλυκαιμίας, χωρίς σημαντικές διαφορές στην HbA1c, πιθανώς λόγω ήδη ικανοποιητικού baseline ελέγχου (Boughton et al., 2022; Harold Henrison Chiu & Jun-Sing Wang, n.d.). Η συγκεκριμένη ομάδα αποτελεί ιδιαίτερης σημασίας πληθυσμό, δεδομένου του αυξημένου κινδύνου σοβαρής υπογλυκαιμίας.

Ως προς την ασφάλεια, η συνολική εικόνα είναι καθησυχαστική. Τα επεισόδια σοβαρής υπογλυκαιμίας και διαβητικής κετοξέωσης ήταν σπάνια και συχνά σχετίζονταν με τεχνικά προβλήματα (π.χ. αποτυχία infusion set) κι όχι με αποτυχία του αλγορίθμου (Bionic Pancreas Research Group et al., 2022; Brown et al., 2017). Η πλειονότητα των μελετών δεν ανέφερε αύξηση σοβαρών ανεπιθύμητων ενεργειών σε σύγκριση με τη συμβατική θεραπεία.

Επιπλέον, δεδομένα πραγματικής κλινικής πρακτικής σε μεγάλο αριθμό χρηστών υποστηρίζουν ότι η επίτευξη στενότερων γλυκαιμικών στόχων (Time in Tight Range) είναι εφικτή με συνεπή χρήση και κατάλληλες ρυθμίσεις, με συσχέτιση μεταξύ υψηλότερου TITR και χαμηλότερου GMI (Choudhary et al., 2022). Η παρατήρηση αυτή ενισχύει τη μετατόπιση από την αποκλειστική στόχευση της HbA1c προς μια πολυπαραμετρική αξιολόγηση της ρύθμισης.

Συνολικά, η σύνθεση των δεδομένων υποστηρίζει ότι τα συστήματα αυτοματοποιημένης χορήγησης ινσουλίνης προσφέρουν σταθερά κλινικά σημαντική βελτίωση του γλυκαιμικού προφίλ σε ευρύ φάσμα πληθυσμών με ΣΔ1. Το όφελος είναι πιο έντονο σε άτομα με υποβέλτιστο έλεγχο, αλλά παραμένει ορατό και σε καλά ρυθμισμένους ασθενείς μέσω βελτίωσης της ασφάλειας. Η αύξηση του TIR και η μείωση της υπεργλυκαιμίας αποτελούν τα πλέον συνεπή ευρήματα, ενώ η υπογλυκαιμία είτε μειώνεται, είτε δεν αυξάνεται. Η ετερογένεια ως προς το μέγεθος του οφέλους αντικατοπτρίζει διαφορές στο baseline προφίλ, στη διάρκεια των μελετών, στο επίπεδο αυτοματοποίησης και στο συγκριτικό σύστημα, χωρίς όμως να αναιρεί τη γενική σύγκλιση των αποτελεσμάτων υπέρ της αυτοματοποιημένης ινσουλινοθεραπείας ως αποτελεσματικής και ασφαλούς στρατηγικής διαχείρισης του ΣΔ1.

ΚΕΦΑΛΑΙΟ 4

ΣΥΖΗΤΗΣΗ

Η παρούσα συστηματική ανασκόπηση είχε ως στόχο την αξιολόγηση της αποτελεσματικότητας της συνεχούς καταγραφής γλυκόζης (CGM) και των συστημάτων αυτοματοποιημένης χορήγησης ινσουλίνης (hybrid/closed-loop) σε άτομα με Σακχαρώδη Διαβήτη Τύπου 1 (ΣΔ1), σε σύγκριση με τη συμβατική θεραπεία ή λιγότερο αυτοματοποιημένα τεχνολογικά σχήματα. Η ανάλυση των δεδομένων από 65 τυχαιοποιημένες ελεγχόμενες δοκιμές ανέδειξε με συνέπεια ότι οι τεχνολογικές παρεμβάσεις υπερέχουν ως προς τη βελτίωση της ποιότητας και της σταθερότητας του γλυκαιμικού ελέγχου, με ιδιαίτερα έντονη την επίδραση των συστημάτων κλειστού βρόχου στον χρόνο εντός στόχου (Time in Range, TIR), στη μείωση της υπεργλυκαιμίας και στον περιορισμό της γλυκαιμικής μεταβλητότητας, χωρίς παράλληλη αύξηση του κινδύνου υπογλυκαιμίας.

Ένα από τα σημαντικότερα ευρήματα της ανασκόπησης είναι η σταθερή και κλινικά ουσιαστική αύξηση του TIR με τη χρήση συστημάτων κλειστού βρόχου. Η μετατόπιση του ενδιαφέροντος από τη μονοδιάστατη αξιολόγηση της HbA1c προς πολυπαραμετρικούς δείκτες CGM αντικατοπτρίζει τη σύγχρονη κατανόηση της δυναμικής φύσης του ΣΔ1. Ο TIR έχει συσχετιστεί με μειωμένο κίνδυνο μικροαγγειακών επιπλοκών και οξέων απορρυθμίσεων, γεγονός που ενισχύει τη σημασία της αύξησής του ως θεραπευτικού στόχου. Σε αντίθεση με τη HbA1c, η οποία αποτυπώνει έναν μέσο όρο γλυκαιμίας και μπορεί να αποκρύπτει σημαντικές διακυμάνσεις, ο TIR αντανακλά με μεγαλύτερη ακρίβεια την καθημερινή εμπειρία του ασθενούς και τη λειτουργική σταθερότητα της ρύθμισης (El Malahi et al., 2022; Yoo & Kim, 2020).

Παράλληλα, τα δεδομένα της ανασκόπησης υποδεικνύουν ότι η βελτίωση της υπεργλυκαιμίας μέσω των αυτοματοποιημένων συστημάτων δεν συνοδεύεται από αύξηση της υπογλυκαιμίας. Το εύρημα αυτό είναι ιδιαίτερα σημαντικό, καθώς διαχρονικά η εντατικοποίηση της ινσουλινοθεραπείας συνδεόταν με αυξημένο υπογλυκαιμικό κίνδυνο, περιορίζοντας την επιθετική επίτευξη γλυκαιμικών στόχων. Η δυνατότητα των συστημάτων κλειστού βρόχου να προσαρμόζουν δυναμικά τη βασική ινσουλίνη με βάση δεδομένα σε πραγματικό χρόνο φαίνεται να αμβλύνει το παραδοσιακό αυτό θεραπευτικό δίλημμα, επιτυγχάνοντας καλύτερη ισορροπία μεταξύ αποτελεσματικότητας και ασφάλειας, όπως έχει αναδειχθεί και σε μελέτες όπως η HypoDE Trial (Heinemann et al., 2018b).

Η βελτίωση της HbA1c που καταγράφηκε σε αρκετές από τις συμπεριλαμβανόμενες μελέτες ενισχύει περαιτέρω τη συνολική εικόνα υπεροχής των τεχνολογικών παρεμβάσεων, αν και το μέγεθος της μείωσης ποίκιλε ανάλογα με τα αρχικά επίπεδα ρύθμισης, την ηλικιακή ομάδα και τον βαθμό συμμόρφωσης. Όπως έχει τεκμηριωθεί στη μελέτη των Laffel et al. (2020), η αποτελεσματικότητα της CGM εξαρτάται σε μεγάλο βαθμό από τη συστηματική χρήση της συσκευής, ιδιαίτερα σε εφήβους και νεαρούς ενήλικες, όπου η συμμόρφωση αποτελεί συχνά πρόκληση. Συνεπώς, τα τεχνολογικά οφέλη δεν είναι αυτόματα, αλλά προϋποθέτουν εκπαίδευση, υποστήριξη και ενεργό συμμετοχή του ασθενούς (Laffel et al., 2020).

Ιδιαίτερη σημασία αποκτά και η μείωση της γλυκαιμικής μεταβλητότητας (glycemic variability, GV), η οποία καταγράφηκε σε σημαντικό αριθμό μελετών. Η GV έχει συσχετιστεί με οξειδωτικό stress, ενδοθηλιακή δυσλειτουργία και αυξημένο καρδιαγγειακό κίνδυνο (Lazar et al., 2023; Suh & Kim, 2015), ενώ η αυξημένη μεταβλητότητα συνδέεται και με υψηλότερο υπογλυκαιμικό φορτίο. Η μείωση του συντελεστή μεταβλητότητας (CV), ιδιαίτερα κάτω από το όριο του 36%, θεωρείται ένδειξη σταθερότερου γλυκαιμικού προφίλ και χαμηλότερου κινδύνου υπογλυκαιμίας (Toschi et al., 2020). Τα ευρήματα της παρούσας ανασκόπησης είναι συνεπή με τα δεδομένα αυτά, υποδεικνύοντας ότι οι τεχνολογικές παρεμβάσεις δεν βελτιώνουν μόνο τους μέσους δείκτες, αλλά και τη σταθερότητα της ρύθμισης.

Πέραν των καθαρά μεταβολικών παραμέτρων, η χρήση CGM και συστημάτων κλειστού βρόχου φαίνεται να επηρεάζει και το θεραπευτικό φορτίο. Η μείωση της ανάγκης για συνεχείς χειροκίνητες παρεμβάσεις και η παροχή προγνωστικών ειδοποιήσεων μπορεί να ενισχύει το αίσθημα ασφάλειας και να μειώνει τη διαβητική δυσφορία. Ωστόσο, ζητήματα όπως η «κόπωση από alarms», τα τεχνικά προβλήματα, η ανάγκη συνεχούς φορετής συσκευής και το κόστος αποτελούν παράγοντες που επηρεάζουν τη μακροχρόνια αποδοχή (Freckmann, 2020). Επομένως, η επιτυχής ενσωμάτωση των τεχνολογιών στην κλινική πράξη απαιτεί όχι μόνο τεχνική επάρκεια αλλά και ψυχοκοινωνική υποστήριξη.

Από την άποψη της πολιτικής υγείας, τα αποτελέσματα της ανασκόπησης έχουν σημαντικές προεκτάσεις. Αν και το αρχικό κόστος των συστημάτων CGM και closed-loop είναι υψηλότερο σε σχέση με τη συμβατική θεραπεία, η πιθανή μείωση των νοσηλειών λόγω σοβαρής υπογλυκαιμίας ή διαβητικής κετοξέωσης, καθώς και η πρόληψη χρόνιων επιπλοκών, ενδέχεται να καθιστούν τις τεχνολογίες αυτές αποδοτικές σε μακροπρόθεσμο ορίζοντα. Η αξιολόγηση κόστους-αποτελεσματικότητας καθίσταται ιδιαίτερα κρίσιμη, ειδικά σε συστήματα υγείας με περιορισμένους πόρους και ανισότητες πρόσβασης. Η ερμηνεία των

ευρημάτων πρέπει να γίνει υπό το πρίσμα ορισμένων περιορισμών. Υπήρχε ετερογένεια μεταξύ των μελετών ως προς τη διάρκεια παρακολούθησης, τα χρησιμοποιούμενα τεχνολογικά συστήματα και τα συγκριτικά σχήματα. Επιπλέον, οι περισσότερες δοκιμές είχαν σχετικά βραχυπρόθεσμο ορίζοντα, γεγονός που δεν επιτρέπει ασφαλή συμπεράσματα για τη μακροπρόθεσμη επίδραση στις χρόνιες επιπλοκές. Τέλος, οι συμμετέχοντες σε τυχαιοποιημένες δοκιμές συχνά παρουσιάζουν υψηλότερη συμμόρφωση σε σχέση με τον γενικό πληθυσμό, γεγονός που μπορεί να υπερεκτιμά την αποτελεσματικότητα σε πραγματικές συνθήκες.

Συνολικά, τα ευρήματα της παρούσας συστηματικής ανασκόπησης υποστηρίζουν ότι η ενσωμάτωση της CGM και των συστημάτων αυτοματοποιημένης χορήγησης ινσουλίνης στη διαχείριση του ΣΔ1 συνιστά ουσιαστική μετατόπιση παραδείγματος, με έμφαση όχι μόνο στη μείωση της HbA1c, αλλά στη συνολική ποιότητα και ασφάλεια του γλυκαιμικού ελέγχου. Υπό την προϋπόθεση κατάλληλης εκπαίδευσης, εξατομίκευσης και ισότιμης πρόσβασης, οι τεχνολογικές παρεμβάσεις φαίνεται να αποτελούν πλέον κεντρικό άξονα στη σύγχρονη θεραπευτική στρατηγική του ΣΔ1, προσεγγίζοντας περισσότερο από κάθε προηγούμενη προσέγγιση τον στόχο μιας σταθερής και ασφαλούς γλυκαιμικής ρύθμισης.

ΚΕΦΑΛΑΙΟ 5

ΣΥΜΠΕΡΑΣΜΑΤΑ

Η παρούσα συστηματική ανασκόπηση καταδεικνύει ότι η συνεχής καταγραφή γλυκόζης και κυρίως, τα συστήματα αυτοματοποιημένης χορήγησης ινσουλίνης τύπου hybrid/closed-loop προσφέρουν σαφή κλινικά οφέλη στη διαχείριση του Σακχαρώδους Διαβήτη Τύπου 1. Η αύξηση του χρόνου εντός στόχου, η μείωση της υπεργλυκαιμίας και ο περιορισμός της γλυκαιμικής μεταβλητότητας επιτυγχάνονται χωρίς αντίστοιχη αύξηση του κινδύνου υπογλυκαιμίας, γεγονός που ενισχύει την ασφάλεια της θεραπείας. Παράλληλα, η αξιοποίηση δεικτών της CGM επιτρέπει μια πιο ολοκληρωμένη και ρεαλιστική αποτίμηση της γλυκαιμικής ρύθμισης σε σύγκριση με την αποκλειστική χρήση της HbA1c, αναδεικνύοντας τη σημασία μιας πολυπαραμετρικής προσέγγισης στην καθημερινή κλινική πράξη.

Συνολικά, τα διαθέσιμα δεδομένα υποστηρίζουν ότι οι τεχνολογικές παρεμβάσεις αποτελούν πλέον βασικό άξονα της σύγχρονης θεραπευτικής στρατηγικής στον ΣΔ1 κιι όχι απλώς συμπληρωματική επιλογή. Η αποτελεσματικότητά τους, ωστόσο, εξαρτάται από την ορθή εκπαίδευση, τη συστηματική χρήση και την εξατομίκευση της εφαρμογής τους, καθώς κι από τη διασφάλιση ισότιμης πρόσβασης. Η ενσωμάτωσή τους στα συστήματα υγείας έχει τη δυναμική να βελτιώσει ουσιαστικά τόσο τα γλυκαιμικά αποτελέσματα, όσο και την ποιότητα ζωής των ασθενών, συμβάλλοντας σε μια πιο ασφαλή και σταθερή μακροχρόνια διαχείριση της νόσου.

5.1. Προτάσεις για μελλοντική έρευνα

Παρά την αυξανόμενη τεκμηρίωση υπέρ της συνεχούς καταγραφής γλυκόζης και των συστημάτων αυτοματοποιημένης χορήγησης ινσουλίνης, παραμένουν σημαντικά ερευνητικά ερωτήματα που απαιτούν περαιτέρω διερεύνηση. Καταρχάς, είναι αναγκαίες μακροχρόνιες προοπτικές μελέτες που να αξιολογούν την επίδραση των τεχνολογικών παρεμβάσεων στην εμφάνιση και εξέλιξη μικροαγγειακών και μακροαγγειακών επιπλοκών. Η πλειονότητα των διαθέσιμων τυχαιοποιημένων δοκιμών έχει σχετικά περιορισμένη διάρκεια παρακολούθησης, γεγονός που δεν επιτρέπει ασφαλή συμπεράσματα για τις μακροπρόθεσμες κλινικές εκβάσεις. Επιπλέον, απαιτείται περαιτέρω διερεύνηση της επίδρασης της μείωσης της γλυκαιμικής μεταβλητότητας και της αύξησης του χρόνου εντός στόχου σε «σκληρά» κλινικά καταληκτικά σημεία.

Εξίσου σημαντική είναι η ανάγκη για μελέτες πραγματικού κόσμου (real-world evidence), οι οποίες θα αποτυπώνουν τη χρήση των τεχνολογιών σε καθημερινές συνθήκες κλινικής πρακτικής και όχι μόνο στο πλαίσιο αυστηρά ελεγχόμενων πρωτοκόλλων. Η συμμόρφωση, η διατήρηση της χρήσης σε βάθος χρόνου, οι ψυχοκοινωνικοί παράγοντες και οι ανισότητες στην πρόσβαση αποτελούν κρίσιμες μεταβλητές που δεν αποτυπώνονται επαρκώς στις κλασικές κλινικές δοκιμές. Παράλληλα, απαιτείται στοχευμένη έρευνα σε ειδικούς πληθυσμούς, όπως παιδιά προσχολικής ηλικίας, ηλικιωμένοι με συννοσηρότητες, έγκυες γυναίκες και άτομα με χαμηλό κοινωνικοοικονομικό επίπεδο, προκειμένου να διασφαλιστεί η γενικευσιμότητα των ευρημάτων.

Τέλος, ιδιαίτερη έμφαση θα πρέπει να δοθεί σε μελέτες κόστους-αποτελεσματικότητας και ανάλυσης επιπτώσεων στα συστήματα υγείας. Η αυξανόμενη τεχνολογική πολυπλοκότητα συνοδεύεται από υψηλότερο αρχικό κόστος, κι η τεκμηρίωση της μακροπρόθεσμης οικονομικής αποδοτικότητας είναι απαραίτητη για τη διαμόρφωση βιώσιμων πολιτικών αποζημίωσης και καθολικής πρόσβασης. Παράλληλα, η μελλοντική έρευνα θα μπορούσε να εστιάσει στη βελτίωση των αλγορίθμων αυτοματοποίησης, στην ενσωμάτωση τεχνητής νοημοσύνης για εξατομικευμένη πρόβλεψη γλυκαιμικών μεταβολών και στην ανάπτυξη συστημάτων με μικρότερο θεραπευτικό φορτίο και υψηλότερη εργονομία. Μέσα από αυτές τις κατευθύνσεις, η τεχνολογία μπορεί να εξελιχθεί περαιτέρω προς ένα ολοένα και πιο εξατομικευμένο και ασφαλές μοντέλο διαχείρισης του ΣΔ1.

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ΠΑΡΑΡΤΗΜΑ

Χαρακτηριστικά των μελετών, της παρέμβασης, του πληθυσμού και των εκβάσεων της εκάστοτε μελέτης όπως αυτα προέκυψαν από την διαδικασία εξαγωγής δεδομένων.

Trial 1
Lee et al. 2024
ISRCTN56898625

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
Lee et al. 2024	ISRCTN56898625	Randomised Controlled Trial (RCT)	United Kingdom	Multi-center	No (open-label)	Yes (1:1)	Yes National Institute for Health Research (NIHR) (UK)	1. Between 18 and 45 years of age 2. Type 1 diabetes for at least 12 months' duration 3. Viable pregnancy confirmed by ultrasound, up to 13 weeks and 6 days' gestation 4. On intensive insulin therapy (three or more injections/day or insulin pump). This included sensor-augmented insulin pumps and hybrid closed-loop systems other than CamAPS FX 5. Willingness to use the study devices throughout the trial 6. HbA1c level ≥ 48 mmol/mol (≥ 6.5%) at booking (first antenatal contact) and ≤ 86 mmol/mol (≤ 10%) at point of randomisation. A CGM or Libre GMI ≥ 48 mmol/mol (≥ 6.5%) or ≤ 86 mmol/mol (≤ 10%) was used if laboratory HbA1c could not be obtained37 7. Provided written informed consent 8. Had access to an e-mail account	1. Non-type 1 diabetes 2. Other physical or psychological disease which was likely to interfere with the normal conduct and interpretation of the study results, as judged by the site investigator 3. Current treatment with drugs known to interfere with glucose metabolism (e.g. high-dose corticosteroids) 4.Known or suspected insulin allergy 5. Advanced nephropathy (estimated glomerular filtration rate < 45), severe autonomic neuropathy, uncontrolled gastroparesis or severe proliferative retinopathy, as judged by the site investigator 6. Target glycaemia or very high HbA1c that is first antenatal HbA1c < 48 mmol/mol (< 6.5%) and HbA1c > 86 mmol/mol (> 10%). Those with HbA1c > 86 mmol/mol (> 10%) may participate if they achieve HbA1c ≤ 86 mmol/mol (≤ 10%) before randomisation 7. Total daily insulin dose > 1.5 units/kg suggesting severe insulin resistance 8. Severe visual or hearing impairment 9. Unable to speak and understand English

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Dana Diabecare RS + Dexcom G6 + CamAPS FX an insulin pump + a continuous glucose monitor (CGM) + a computer-based model predictive control (MPC) algorithm	an insulin pump + a continuous glucose monitor (CGM)	51 weeks max (from 13 weeks and 6 days' gestation up to 24 weeks post partum)	Continuous insulin infusion	124 women	62 women	62 women	Pregnant women between 18 and 45 years of age	The difference between the intervention and control groups in percentage time spent in the pregnancy glucose target range (3.5–7.8 mmol/l) as measured by continuous glucose monitoring from 16 weeks' gestation until delivery.	1. Overnight time in range time above range (> 7.8 mmol/l) 2. Glycated haemoglobin A1c 3. Safety outcomes (diabetic ketoacidosis 4. Severe hypoglycaemia 5. Adverse device events 6. Psychosocial functioning obstetric 7. Neonatal outcomes	The percentage of time that maternal glucose levels were within target range was higher with closed-loop than standard insulin therapy: **Closed-loop:** 68.2 ± 10.5 vs **Control group:** 55.6 ± 12.5 (mean-adjusted difference 10.5 percentage points, 95% confidence interval 7.0 to 14.0; p < 0.001).	Lower glycated haemoglobin A1c favouring closed-loop (−0.31%, 95% confidence interval −0.50 to −0.12%; p < 0.002)

Trial 2
B. Matejko et al. 2022
NCT04616391

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
B. Matejko et al. 2022	NCT04616391	Randomised Controlled Trial (RCT)	NA	2 centers	No (open-label)	Yes (1:1)	Yes Medtronic supplied MiniMed 780G insulin pumps Guardian 3 Link transmitters Guardian Sensors 3 Transmitter Docks Accu-Chek Guide Link glucometers.	1. Age 26 - 60 years at time of screening a clinical diagnosis of type 1 diabetes for 2 years or more as determined via medical record or source documentation by an individual qualified to make a medical diagnosis 2. Willing to participate in a study for the specified duration 3. Willing to perform ≥ 4 finger stick blood glucose measurements daily 4. Willing to perform required sensor calibrations 5. Willing to wear the system continuously throughout the study 6. Glycosylated hemoglobin (A1C) value less than 10.0% at time of screening visit 7. Treated with MDI 8. Willing to perform at least 4 BGM/day, when on MDI 9. At least communicative level of English to be able to understand the pump interface	1. Previous treatment with CSII/CGM 2. Usage of ultra-rapid insulins, e.g. FIASP 3. Concurrent illness 4. Laboratory abnormalities, or medications that might affect study participation, 5. Current pregnancy 6. Renal impairment 7. Hemoglobin A1c value above 10%

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
MiniMed 780G an insulin pump + a continuous glucose monitor (CGM) + a computer-based model predictive control (MPC) algorithm	MDI (multiple daily injections) + self-monitoring blood glucose (BGM)	14 weeks	Continuous insulin infusion	41 participants	20 participants	21 participants	Individuals aged 26–60 years	The primary objective was to evaluate whether the MiniMed 780G AHCL system improves glycemic control and QoL perception in adult individuals with T1DM and naive to CSII and CGM technologies.	1. Time spent in the hyperglycemic, euglycemic and hypoglycemic ranges 2. Glycemic variability 3. HbA1c 4. QoL	Time spent with glucose levels in target range: **AHCL group:** increased from 69.3 ± 12.3% at baseline to 85.0 ± 6.3% at 3 months **Control group:** remained unchanged (treatment effect 21.5% [95% CI 15.7, 27.3]; P < 0.001). The time with levels below range (<70 mg/dL): **AHCL group:** decreased from 8.7 ± 7.3% to 2.1 ± 1.7% **MDI+BGM group:** remained unchanged (treatment effect −4.4% [95% CI −7.4, −2.1]; P < 0.001).	Lower HbA1c levels in AHCL group (treatment effect −0.6% [95% CI −0.9, −0.2]; P = 0.005)

Trial 3
R. W. Beck et al. 2022
NCT04200313

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
R. W. Beck et al. 2022	NCT04200313	Randomised Controlled Trial (RCT)	USA	Multi-center	No (open-label)	Yes (2:2:1)	Yes NIDDK - National Institute of Diabetes and Digestive and Kidney Diseases	1. Clinical diagnosis of T1D for at least one year and using insulin for at least 1 year 2. Diabetes managed using the same regimen (either pump or MDI, with or without CGM) for ≥ 3 months 3. Age ≥ 6 years old Exception: the initial 5-participant test run will be limited to >18 years old 4. Current use of a CGM, or if not a CGM user, at least 3 blood glucose meter tests daily on average over the last 4 weeks (according to judgment of investigator if meter is not available). 5. Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial 6. For participants <18 years old, living with one or more parent/legal guardian knowledgeable about emergency procedures for severe hypoglycemia. 7. For participants >18 years old who live alone, participant has a relative or acquaintance who lives within 30 minutes of participant and is willing to be contacted to check on participant if study staff feel that participant may be experiencing a medical emergency and can't be reached. 8. Investigator believes that the participant can safely use the iLet and will follow the protocol The investigator will take into account the participant's HbA1c level, compliance with current diabetes management, and prior acute diabetic complications. For this reason, there is no upper limit on HbA1c specified for eligibility. 9. If a GLP-1 agonist or pramlintide is being used, participant must be willing to discontinue use while the iLet BP system is being used, including the randomized trial and extension study.	1. Unable to provide informed consent (e.g. impaired cognition or judgment) 2. Unable to safely comply with study procedures and reporting requirements (e.g. impairment of vision or dexterity that prevents safe operation of the bionic pancreas, impaired memory) 3. Unable to speak and read English • For pediatric participants, both caregivers and participants must be able to speak and read English 4. Plan to change usual diabetes regimen in the next 3 months This would include changing from MDI to pump. pump to MDI, change in insulin automation delivery system, starting a CGM if not previously used, changes in drug therapy specifically for glucose control except for changes in one insulin analog to another. 4. Changes in insulin dose, carb ratio, sensitivity factor and basal rate profile are allowed. 5. Current use of non-FDA approved closed-loop or hybrid closed-loop insulin delivery system 6. Use of Apidra as the pre-study rapid-acting insulin analog and unwilling to switch to lispro or aspart for the duration of the study 7 Known hemoglobinopathy (sickle cell trait is not an exclusion) 8. Current participation in another diabetes-related clinical trial 9. History of cystic fibrosis, pancreatitis, or other pancreatic disease, including pancreatic tumor or insulinoma, or history of complete pancreatectomy 10. Electrically powered implants (e.g. cochlear implants, neurostimulators) that might be susceptible to RF interference 11. Established history of allergy or severe reaction to adhesive or tape that must be used in the study 12. Current use of SGLT2 inhibitors or a sulfonylurea drug (use more than 3 months prior to enrollment is acceptable) • If using GLP1 agonist, pramlintide, or metformin drugs must be on a stable dose for 3 months prior to enrollment (and as per inclusion criterion #8, must be willing to discontinue use of GLP-1 agonist or pramlintide while using the iLet BP system during the RCT and the extension phase). 13. Pregnant (positive urine hCG), breast feeding, plan to become pregnant in the next 3 months, or sexually active without use of contraception 14. For adults >18 years old, most recent (must be within the last 2 years) eGFR <30 ml/min OR currently in renal failure on dialysis • If no eGFR is available for an adult participant during the last 2 years, one must be obtained to confirm eligibility 15. Presence of a medical condition or use of a medication that, in the judgment of the investigator, clinical protocol chair, or medical monitor, could compromise the results of the study or the safety of the participant. Conditions to be considered by the investigator may include the following: • Alcohol or drug abuse • Use of prescription drugs that may dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder decision making during the period of participation in the study • Coronary artery disease that is not stable with medical management, including unstable angina, angina that prevents moderate exercise (e.g. climbing a flight of stairs) despite medical management, or within the last 12 months before screening a history of myocardial infarction, percutaneous coronary intervention, enzymatic lysis of a presumed coronary occlusion, or coronary artery bypass grafting • Congestive heart failure with New York Heart Association (NYHA) Functional Classification III or IV • History of TIA or stroke in the last 12 months • Untreated or inadequately treated mental illness • History of eating disorder within the last 2 years, such as anorexia, bulimia, or diabulemia or omission of insulin to manipulate weight • History of intentional, inappropriate administration of insulin leading to severe hypoglycemia requiring treatment 16. Employed by, or having immediate family members employed by Beta Bionics, or being directly involved in conducting the clinical trial, or having a direct supervisor at place of employment who is also directly involved in conducting the clinical trial (as a study investigator, coordinator, etc.); or having a first-degree relative who is directly involved in conducting the clinical trial

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
iLet® bionic pancreas (insulin-only) + Rapid-acting insulin analogs (lispro and aspart)+ real-time CGM (Dexcom G6 CGM sensor) iLet® bionic pancreas (insulin-only) + Ultra-rapid–acting insulin aspart (Fiasp®) + real-time CGM (Dexcom G6 CGM sensor)	Standard care insulin delivery (MDI or pump therapy) + real-time CGM (Dexcom G6 CGM sensor)	13 weeks	Continuous insulin infusion	275 adult participants	**219 BP participants** 107 BP-A/L participants 114 (BP-F) participants	54 (SC) participants	Adult (≥18 years)	The primary outcome is superiority for Bionic-pancreas group vs the Standard-care group regarding the hemoglobin A1c at 13 weeks	1. The percentage of time that the glucose level as measured by the CGM was below 54 mg per deciliter (3.0 mmol per liter) 2. The mean glucose level 3. The percentage of time with the glucose level in the range of 70 to 180 mg per deciliter (3.9 to 10.0 mmol per liter) 4. The percentage of time with the glucose level above 180 mg per deciliter 5. The percentage of time with the glucose level above 250 mg per deciliter (13.9 mmol per liter) 6. The glucose-level standard deviation 7. The percentage of time with the glucose level below 70 mg per deciliter 8. The percentage of time with the glucose level below 54 mg per deciliter, to be tested for superiority 9. The glucose coefficient of variation.	The percentage of time that the glucose level as assessed by CGM was below 54 mg per deciliter was noninferior in the bionic-pancreas group as compared with the standard-care group.	The glycated hemoglobin level: **Bionic-pancreas group:** decreased from 7.9% to 7.3% **Standard-care group:** did not change (was at 7.7% at both time points) (mean adjusted difference at 13 weeks, −0.5 percentage points; 95% confidence interval [CI], −0.6 to −0.3; P<0.001)

Trial 4
D. Kruger et al. 2022
NCT04200313

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
D. Kruger et al. 2022	NCT04200313	Randomised Controlled Trial (RCT)	USA	Multi-center	No (open-label)	Yes (2:1)	Yes NIDDK - National Institute of Diabetes and Digestive and Kidney Diseases	1. Clinical diagnosis of T1D for at least one year and using insulin for at least 1 year 2. Diabetes managed using the same regimen (either pump or MDI, with or without CGM) for ≥ 3 months 3. Age ≥ 6 years old Exception: the initial 5-participant test run will be limited to >18 years old 4. Current use of a CGM, or if not a CGM user, at least 3 blood glucose meter tests daily on average over the last 4 weeks (according to judgment of investigator if meter is not available). 5. Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial 6. For participants <18 years old, living with one or more parent/legal guardian knowledgeable about emergency procedures for severe hypoglycemia. 7. For participants >18 years old who live alone, participant has a relative or acquaintance who lives within 30 minutes of participant and is willing to be contacted to check on participant if study staff feel that participant may be experiencing a medical emergency and can't be reached. 8. Investigator believes that the participant can safely use the iLet and will follow the protocol The investigator will take into account the participant's HbA1c level, compliance with current diabetes management, and prior acute diabetic complications. For this reason, there is no upper limit on HbA1c specified for eligibility. 9. If a GLP-1 agonist or pramlintide is being used, participant must be willing to discontinue use while the iLet BP system is being used, including the randomized trial and extension study.	1. Unable to provide informed consent (e.g. impaired cognition or judgment) 2. Unable to safely comply with study procedures and reporting requirements (e.g. impairment of vision or dexterity that prevents safe operation of the bionic pancreas, impaired memory) 3. Unable to speak and read English • For pediatric participants, both caregivers and participants must be able to speak and read English 4. Plan to change usual diabetes regimen in the next 3 months This would include changing from MDI to pump. pump to MDI, change in insulin automation delivery system, starting a CGM if not previously used, changes in drug therapy specifically for glucose control except for changes in one insulin analog to another. 4. Changes in insulin dose, carb ratio, sensitivity factor and basal rate profile are allowed. 5. Current use of non-FDA approved closed-loop or hybrid closed-loop insulin delivery system 6. Use of Apidra as the pre-study rapid-acting insulin analog and unwilling to switch to lispro or aspart for the duration of the study 7 Known hemoglobinopathy (sickle cell trait is not an exclusion) 8. Current participation in another diabetes-related clinical trial 9. History of cystic fibrosis, pancreatitis, or other pancreatic disease, including pancreatic tumor or insulinoma, or history of complete pancreatectomy 10. Electrically powered implants (e.g. cochlear implants, neurostimulators) that might be susceptible to RF interference 11. Established history of allergy or severe reaction to adhesive or tape that must be used in the study 12. Current use of SGLT2 inhibitors or a sulfonylurea drug (use more than 3 months prior to enrollment is acceptable) • If using GLP1 agonist, pramlintide, or metformin drugs must be on a stable dose for 3 months prior to enrollment (and as per inclusion criterion #8, must be willing to discontinue use of GLP-1 agonist or pramlintide while using the iLet BP system during the RCT and the extension phase). 13. Pregnant (positive urine hCG), breast feeding, plan to become pregnant in the next 3 months, or sexually active without use of contraception 14. For adults >18 years old, most recent (must be within the last 2 years) eGFR <30 ml/min OR currently in renal failure on dialysis • If no eGFR is available for an adult participant during the last 2 years, one must be obtained to confirm eligibility 15. Presence of a medical condition or use of a medication that, in the judgment of the investigator, clinical protocol chair, or medical monitor, could compromise the results of the study or the safety of the participant. Conditions to be considered by the investigator may include the following: • Alcohol or drug abuse • Use of prescription drugs that may dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder decision making during the period of participation in the study • Coronary artery disease that is not stable with medical management, including unstable angina, angina that prevents moderate exercise (e.g. climbing a flight of stairs) despite medical management, or within the last 12 months before screening a history of myocardial infarction, percutaneous coronary intervention, enzymatic lysis of a presumed coronary occlusion, or coronary artery bypass grafting • Congestive heart failure with New York Heart Association (NYHA) Functional Classification III or IV • History of TIA or stroke in the last 12 months • Untreated or inadequately treated mental illness • History of eating disorder within the last 2 years, such as anorexia, bulimia, or diabulemia or omission of insulin to manipulate weight • History of intentional, inappropriate administration of insulin leading to severe hypoglycemia requiring treatment 16. Employed by, or having immediate family members employed by Beta Bionics, or being directly involved in conducting the clinical trial, or having a direct supervisor at place of employment who is also directly involved in conducting the clinical trial (as a study investigator, coordinator, etc.); or having a first-degree relative who is directly involved in conducting the clinical trial

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
iLet® bionic pancreas (insulin-only) + Rapid-acting insulin analogs (lispro / aspart)+ real-time CGM (Dexcom G6 CGM sensor)	Standard-of-care (SC) control group continued their pre-study subcutaneous insulin delivery + real-time CGM: Multiple daily injections [MDI] An insulin pump without automation of insulin delivery An insulin pump with predictive low glucose suspend feature, or an insulin pump as part of an HCL system)	13 weeks	Continuous insulin infusion	161 adult participants	107 participants	54 (SC) participants	Adult (≥18 years)	The primary outcome is superiority for Bionic-pancreas group vs the Standard-care group regarding the hemoglobin A1c at 13 weeks	CGM metrics were secondary outcomes including: • Mean glucose • Time in range 70–180 mg/dL (TIR), • Time >180 mg/dL • Time >250 mg/dL • Time <70 mg/dL • Time <54 mg/dL, • Standard deviation • Coefficient of variation.	1. Mean time in range 70-180 mg/dL (TIR) increased by 11% (2.6 h/d) 2. Mean CGM glucose was reduced by 16 mg/dL with BP compared with SC (P < 0.001).	Mean HbA1c decreased: BP: from 7.6% ± 1.2% at baseline to 7.1% ± 0.6% at 13 weeks versus SC: 7.6% ± 1.2% to 7.5% ± 0.9% (adjusted difference = -0.5%, 95% confidence interval -0.6% to -0.3%, P < 0.001).

Trial 5
M. D. Breton et al., 2020
NCT03844789

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
M. D. Breton et al., 2020	NCT03844789	Randomised Controlled Trial (RCT)	USA	4 centers	No (open-label)	Yes (3:1)	Yes Tandem Diabetes Care + NIDDK	1. Clinical diagnosis, based on investigator assessment, of type 1 diabetes for at least one year and using insulin for at least 6 months 2. Familiarity and use of a carbohydrate ratio for meal boluses. 3. Age ≥ 6 and ≤ 13 years old 4. Weight ≥25 kg and ≤140 kg 5. For females, not currently known to be pregnant If female and sexually active, must agree to use a form of contraception to prevent pregnancy while a participant in the study. A negative serum or urine pregnancy test will be required for all females of child-bearing potential. Participants who become pregnant will be discontinued from the study. Also, participants who during the study develop and express the intention to become pregnant within the timespan of the study will be discontinued. 6. Living with one or more parent/legal guardian knowledgeable about emergency procedures for severe hypoglycemia and able to contact emergency services and study staff. 7. Willingness to suspend use of any personal closed loop system that they use at home for the duration of the clinical trial once the study CGM is in use 8. Investigator has confidence that the participant can successfully operate all study devices and is capable of adhering to the protocol 9. Willingness to switch to lispro (Humalog) or aspart (Novolog) if not using already, and to use no other insulin besides lispro (Humalog) or aspart (Novolog) during the study for participants using the t:slim X2. This includes: o Participants randomized to Control IQ o Participants on the SC group on MDI treatment that will be provided a Tandem pump to switch to CSII o Participates that are already in CSII randomized to SC during the extension phase when transition to Control IQ 10. Total daily insulin dose (TDD) at least 10 U/day 11. Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial 12. Participant and parent(s)/guardian(s) willingness to participate in all training sessions as directed by study staff.	1. Concurrent use of any non-insulin glucose-lowering agent other than metformin (including GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas). 2. Hemophilia or any other bleeding disorder 3. A condition, which in the opinion of the investigator or designee, would put the participant or study at risk (specified on the study procedure manual) 4. Participation in another pharmaceutical or device trial at the time of enrollment or during the study 5. Employed by, or having immediate family members employed by Tandem Diabetes Care, Inc., or having a direct supervisor at place of employment who is also directly involved in conducting the clinical trial (as a study investigator, coordinator, etc.); or having a first-degree relative who is directly involved in conducting the clinical trial

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
t:slim X2 insulin pump with Control-IQ Technology + Dexcom G6 CGM	Sensor-augmented pump (Dexcom G6; personal pump or t:slim X2 with predictive low-glucose suspend)	16-week treatment period	Continuous insulin infusion	101 participants	78 participants	23 participants	6–13 years	% time in range 70–180 mg/dL (CGM) over 16 weeks	• % time >180 • mean glucose • HbA1c at 16 weeks • % time <70 • % time <54 • % time >250 • Coefficient of variation • Safety (severe hypoglycemia, DKA)	Time that the glucose level was in the target range of 70 to 180 mg per deciliter • In the closed-loop group: increased from 53±17% at baseline to 67±10% (the mean over 16 weeks of treatment) • In the control group: from 51±16% to 55±13% with a mean adjusted difference of 11 percentage points (95% confidence interval [CI], 7 to 14; P<0.001)	Regarding the glycated hemoglobin level at 16 weeks the mean adjusted between-group difference was −0.4 percentage points which did not meet the threshold for statistical significance. (95% CI, −0.9 to 0.1; P=0.08)

Trial 6
L. E. Donovan et al., 2025
NCT04902378

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
L. E. Donovan et al., 2025	NCT04902378	Randomised Controlled Trial (RCT)	Australia, Canada	Multi-center	No (open-label)	Yes (1:1)	Yes University of Calgary; in-kind donations from Tandem Diabetes Care and Dexcom	1. Between 18 and 45 years of age (inclusive) 2. A diagnosis of type 1 diabetes, as defined by Diabetes Canada, for at least 12 months 3. A viable singleton pregnancy confirmed by ultrasound, less than 14 weeks gestation 4. Currently on intensive insulin therapy (≥ 3 injections, or Continuous subcutaneous insulin infusion (CSII) 5. Willingness to use the study devices throughout the trial 6. A1c ≥ 6.2% and <10% measured any time during pregnancy prior to enrollment 7. Able to provide informed consent 8. Have access to email	1. Non-type 1 diabetes 2. Current treatment with drugs known to interfere with glucose metabolism as judged by the investigator such as high dose systemic corticosteroids 3. Known or suspected allergy to insulin 4. Women with nephropathy (estimated glomerular filtration rate [eGFR] <45), severe autonomic neuropathy, uncontrolled gastroparesis or severe proliferative retinopathy, as judged by the investigator, that is likely to interfere with the normal conduct of the study and interpretation of study results 5. Total daily insulin dose <8 or >250 units/day at screening 6. Severe visual or hearing impairment, as judged by the investigator to impact treatment compliance 7. Unable to communicate effectively in English or French as judged by the investigator 8. Current use of Tandem Control IQ, DIY looping system, 670G in Auto Mode, or alternate closed-loop system as judged by the investigator 9. Any reason judged by the investigator that would likely interfere with the normal conduct of the study and interpretation of study results

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Tandem t:slim X2 with Control-IQ + Dexcom G6 CGM	MDI + real-time CGM (RT-CGM)	13 weeks (from 16 weeks to 34 weeks gestation)	Continuous (pump) / MDI	91 participants	46 participants	45 participants	Pregnant women between 18 and 45 years of age	% time in range/day (3.5–7.8 mmol/L) from 16 to 34 weeks by CGM	• Time above range • Time below range • Mean glucose • Variability • Maternal hypoglycemia • Psychosocial outcomes • Maternal & neonatal outcomes • Severe hypoglycemia • DKA • Device-related adverse events	The mean percentage of time spent in the pregnancy-specific glucose range from 16 to 34 weeks' gestation was in the closed-loop group: 65.4% and in the standard care group: 50.3% (mean adjusted difference, 12.5 [95% CI, 9.5-15.6] percentage points; P < .001).	The closed-loop system resulted in a significantly lower HbA1c, with a mean adjusted difference of - 0.4 percentage points (95% CI, 0.5-0.3) percentage points compared to standard care.

Trial 7
Heuvel et al., 2024
NCT04235504

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
Heuvel et al., 2024	NCT04235504	Randomised Controlled Trial (RCT)	Germany, United Kingdom	5 centers	No (open-label)	Yes (1:1)	Yes Medtronic International Trading Sàrl	1.Subject is age ≥ 18 years old at time of screening 2. Subject has a clinical diagnosis of Type 1 diabetes for ≥ 2 years prior to screening as determined via source documentation 3. On MDI therapy (defined as ≥ 3 insulin injections per day and/or a basal/bolus regimen) ≥ 2 years prior to screening 4. Subject has been followed and treated by the investigator at this investigational site for at least 3 months prior to screening and subject has already undergone local educational therapeutic programs. 5.Subject is using: -Flash Glucose Monitoring (FGM) for ≥ 3 months with a daily average number of scans ≥ 5 over and with sensor readings > 70% of time over the previous month prior to screening (based on sensor usage from the download summary report of the FGM system over 30 days prior to screening) Or -Continuous Glucose Monitoring (CGM) for ≥ 3 months with a frequency of sensor use ≥ 70% of the time over the previous month prior to screening (based on download summary report from the CGM system over 30 days prior to screening). 6. Subject has a glycosylated hemoglobin (HbA1c) ≥ 8.0% (64 mmol/mol) at time of screening visit (as processed by a Central Lab). 7. Subject is willing to take or switch to one of the following insulins: -Humalog™ (insulin lispro injection) -NovoLog™ (insulin aspart) 8. Subject must have a minimum daily insulin requirement (Total Daily Dose) of ≥ 8 units and a maximum of 250 units. 9. Subject is willing to upload data from the study pump and meter, must have Internet access and a compatible computer system that meets the requirements for uploading the study pump data at home. 10. Subject is willing and able to sign and date informed consent, comply with all study procedures and wear all study devices, as required during the study.	1. Subject has untreated Addison's disease, thyroid disorder, growth hormone deficiency, hypopituitarism or definite gastroparesis, per investigator judgment. 2. Subject is using pramlintide, DPP-4 inhibitor, GLP-1 agonists/mimetics, metformin, SGLT2 inhibitors at time of screening. 3. Subject has had renal failure defined by creatinine clearance <30 ml/min, as assessed by local lab test ≤ 12 months before screening or performed at screening at local lab, as defined by the creatinine-based Cockcroft or MDRD equations. 4. Subject is planning to switch from FGM to CGM therapy during the 6 months study phase. Note: Subject randomized to Control Arm should remain on their current FGM or CGM therapy during the study phase and will be switched to AHCL during the continuation phase. 5. Subject has a history of hearing or vision impairment hindering perception of glucose display and alarms, or otherwise incapable of using the study devices, per investigator judgment. 6. Women of child-bearing potential who have a positive pregnancy test at screening or plan to become pregnant during the course of the study. 7. Females who are sexually active and able to conceive will be excluded if they are not using an effective method of contraception and do not agree to continue using an effective method of contraception for the duration of the study, per investigator judgment. 8. Subject has any unresolved adverse skin conditions in the area of sensor placement (e.g. psoriasis, dermatitis herpetiformis, rash, Staphylococcus infection). 9. Subject is actively participating in an investigational study (drug or device) wherein he/she has received treatment from an investigational study drug or device in the last 2 weeks before enrollment into this study, as per investigator judgment. 10. Subject is currently abusing illicit drugs, marijuana, alcohol or prescription drugs (other than nicotine), per investigator judgment. 11. Subject has any other disease or condition that may preclude the patient from participating in the study, per investigator judgment. 12. Subject is legally incompetent, illiterate or vulnerable person. 13. Research staff involved with the study.

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Medtronic MiniMed 670G v4.0 investigational AHCL + Guardian Sensor 3	MDI + RT-CGM	6 months	Continuous (pump) / MDI	13 participants	8 participants	5 participants	Adult (≥18 years)	The difference in the mean HbA1c change (6 months - baseline) between the AHCL and the MDI + CGM arm	• TIR Between 70-180 mg/dL • Time in Hyperglycemic Range • Hypoglycemic Events	Participants in the AHCL group spent a significantly greater percentage of time with SG levels between 70 and 180 mg/dL (3.9-10.0 mmol/L) than those in the MDI + RT-CGM group AHCL group : TIR: 73.6% MDI + RT-CGM group : 46.4% (model-based treatment effect = 28.8 percentage points; 95% CI = 12.3 to 45.3 percentage points; P = .0035).	The mean (SD) change from baseline in HbA1c was in the AHCL group : −1.70 percentage points (1.04 percentage points) and in the MDI + RT-CGM group : −0.60 percentage points (1.26 percentage points) resulting in a model-based treatment effect of −1.08 percentage points (95% CI = −2.17 to 0.00 percentage points, P = .0508) in favor of the AHCL group

Trial 8
P. Choundary et al., 2022
NCT04235504

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
P. Choundary et al., 2022	NCT04235504	Randomised Controlled Trial (RCT)	France, Germany, and the UK	Multi-center	No (open-label)	Yes (1:1)	Yes Medtronic International Trading Sàrl	1. Subject is age ≥ 18 years old at time of screening 2. Subject has a clinical diagnosis of Type 1 diabetes for ≥ 2 years prior to screening as determined via source documentation 3. On MDI therapy (defined as ≥ 3 insulin injections per day and/or a basal/bolus regimen) ≥ 2 years prior to screening 4. Subject has been followed and treated by the investigator at this investigational site for at least 3 months prior to screening and subject has already undergone local educational therapeutic programs. 5. Subject is using: -Flash Glucose Monitoring (FGM) for ≥ 3 months with a daily average number of scans ≥ 5 over and with sensor readings > 70% of time over the previous month prior to screening (based on sensor usage from the download summary report of the -FGM system over 30 days prior to screening) Or -Continuous Glucose Monitoring (CGM) for ≥ 3 months with a frequency of sensor use ≥ 70% of the time over the previous month prior to screening (based on download summary report from the CGM system over 30 days prior to screening). 6. Subject has a glycosylated hemoglobin (HbA1c) ≥ 8.0% (64 mmol/mol) at time of screening visit (as processed by a Central Lab). 7. Subject is willing to take or switch to one of the following insulins: Humalog™ (insulin lispro injection) NovoLog™ (insulin aspart) 8. Subject must have a minimum daily insulin requirement (Total Daily Dose) of ≥ 8 units and a maximum of 250 units. 9. Subject is willing to upload data from the study pump and meter, must have Internet access and a compatible computer system that meets the requirements for uploading the study pump data at home. 10. Subject is willing and able to sign and date informed consent, comply with all study procedures and wear all study devices, as required during the study.	1. Subject has untreated Addison's disease, thyroid disorder, growth hormone deficiency, hypopituitarism or definite gastroparesis, per investigator judgment. 2. Subject is using pramlintide, DPP-4 inhibitor, GLP-1 agonists/mimetics, metformin, SGLT2 inhibitors at time of screening. 3. Subject has had renal failure defined by creatinine clearance <30 ml/min, as assessed by local lab test ≤ 12 months before screening or performed at screening at local lab, as defined by the creatinine-based Cockcroft or MDRD equations. 4. Subject is planning to switch from FGM to CGM therapy during the 6 months study phase. Note: Subject randomized to Control Arm should remain on their current FGM or CGM therapy during the study phase and will be switched to AHCL during the continuation phase. 5. Subject has a history of hearing or vision impairment hindering perception of glucose display and alarms, or otherwise incapable of using the study devices, per investigator judgment. 6. Women of child-bearing potential who have a positive pregnancy test at screening or plan to become pregnant during the course of the study. 7. Females who are sexually active and able to conceive will be excluded if they are not using an effective method of contraception and do not agree to continue using an effective method of contraception for the duration of the study, per investigator judgment. 8. Subject has any unresolved adverse skin conditions in the area of sensor placement (e.g. psoriasis, dermatitis herpetiformis, rash, Staphylococcus infection). 9. Subject is actively participating in an investigational study (drug or device) wherein he/she has received treatment from an investigational study drug or device in the last 2 weeks before enrollment into this study, as per investigator judgment. 10. Subject is currently abusing illicit drugs, marijuana, alcohol or prescription drugs (other than nicotine), per investigator judgment. 11. Subject has any other disease or condition that may preclude the patient from participating in the study, per investigator judgment. 12. Subject is legally incompetent, illiterate or vulnerable person. 13. Research staff involved with the study.

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
AHCL system (MiniMed 780G)	MDI + isCGM (intermittently scanned continuous glucose monitoring)	6 months	Continuous (pump) / MDI	82 participants	41 participants	41 participants	Adult (≥18 years)	The between-group difference in mean HbA1c change from baseline to 6 months in the intention-to-treat population using AHCL therapy and those using multiple daily injections of insulin plus isCGM.	• TIR Between 70-180 mg/dL • Time in Hyperglycemic Range • Hypoglycemic Events	Participants regarding time in range (70-180 mg/dL) from baseline to the end of the 6-month study phase on AHCL therapy experienced a 26.7% increase compared to those on MDI + isCGM	Mean HbA1c had decreased in the AHCL group: 1·54% (SD 0·73) - from 9·00% to 7·32% in the MDI + CGM : 0·20% (0·80) - from 9·07% to 8·91% (model-based difference -1·42%, 95% CI -1·74 to -1·10; p<0·0001).

Trial 9
I. Capel et al., 2014
NCT01614496

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
I. Capel et al., 2014	NCT01614496	Randomised Controlled Trial (RCT)-crossover	Spain	1 center	No (open-label)	NA	Yes Medtronic International Trading Sàrl	Type 1 Diabetes Insulin pump treatment Undetectable C-Peptide	Autonomous system neuropathy

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
pRBA (closed-loop[CL]) + CGM	CSII pattern (open-loop [OL]) + CGM	2 consecutive nights	Continuous insulin infusion	10 participants	10 participants	10 participants	Adult (≥18 years)	Time spent with glucose in TIR 3.9–8.0 mmol/L	• Median time in hypoglycemi • Hypoglycemic events	The time spent in target range (3.9–8.0 mmol/L) was increased to 95.8% for closed-loop therapy compared to 66.6% with conventional open-loop	NA

Trial 10
Lee et al. 2024
ISRCTN56898625

Study characteristics									
Author-year	NCT Number	Study Design	Country	Centers	Blinding	Randomisation NA - crossover trials	Funding	Inclusion criteria	Exclusion criteria
Lee et al. 2024	ISRCTN56898625	Randomised Controlled Trial (RCT)	England, Scotland and Northern Ireland.	Multi-center	No (open-label)	Yes (1:1)	Yes National Institute of Health and Care Research (NIHR)	1. Between 18 and 45 years of age 2. Type 1 diabetes for at least 12 months' duration 3. Viable pregnancy confirmed by ultrasound, up to 13 weeks and 6 days' gestation 4. On intensive insulin therapy (three or more injections/day or insulin pump). This included sensor-augmented insulin pumps and hybrid closed-loop systems other than CamAPS FX 5. Willingness to use the study devices throughout the trial 6. HbA1c level ≥ 48 mmol/mol (≥ 6.5%) at booking (first antenatal contact) and ≤ 86 mmol/mol (≤ 10%) at point of randomisation. A CGM or Libre GMI ≥ 48 mmol/mol (≥ 6.5%) or ≤ 86 mmol/mol (≤ 10%) was used if laboratory HbA1c could not be obtained37 7. Provided written informed consent 8. Had access to an e-mail account	1. Non-type 1 diabetes 2. Other physical or psychological disease which was likely to interfere with the normal conduct and interpretation of the study results, as judged by the site investigator 3. Current treatment with drugs known to interfere with glucose metabolism (e.g. high-dose corticosteroids) 4.Known or suspected insulin allergy 5. Advanced nephropathy (estimated glomerular filtration rate < 45), severe autonomic neuropathy, uncontrolled gastroparesis or severe proliferative retinopathy, as judged by the site investigator 6. Target glycaemia or very high HbA1c that is first antenatal HbA1c < 48 mmol/mol (< 6.5%) and HbA1c > 86 mmol/mol (> 10%). Those with HbA1c > 86 mmol/mol (> 10%) may participate if they achieve HbA1c ≤ 86 mmol/mol (≤ 10%) before randomisation 7. Total daily insulin dose > 1.5 units/kg suggesting severe insulin resistance 8. Severe visual or hearing impairment 9. Unable to speak and understand English

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	Standard insulin therapy	Duration of trial	Dosing frequency	Total number of participants (n)	Number of participants in hybrid closed-loop system (n)	Number of participants in standard insulin delivery	Age group	Primary endpoint	Secondary endpoint	Glucose target	Glycated haemoglobin A1c
CamAPS FX-based hybrid closed-loop system	(MDI) or insulin pumps (CSII)	from 16 weeks' gestation until delivery (24 weeks)	Continuous (pump) / MDI	124 women	62 women	62 women	Pregnant women between 18 and 45 years of age	The difference between the intervention and control groups in percentage time spent in the pregnancy glucose target range (3.5–7.8 mmol/l) from 16 weeks' gestation until delivery.	• Overnight time in range • Time above range (> 7.8 mmol/l) • Glycated haemoglobin A1c • Safety outcomes such as: diabetic ketoacidosis severe hypoglycaemia adverse device events • Psychosocial functioning obstetric and neonatal outcomes.	The percentage of time that maternal glucose levels were within target range was higher with closed-loop than standard insulin therapy: in closed-loop : 68.2 ± 10.5 and in the control group : and 55.6 ± 12.5 (mean-adjusted difference 10.5 percentage points, 95% confidence interval 7.0 to 14.0; p < 0.001).	Lower glycated haemoglobin A1c favouring closed-loop (−0.31%, 95% confidence interval −0.50 to −0.12%; p < 0.002)

Trial 11
A. Boucsein et al., 2024
ACTRN12622001454763

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
A. Boucsein et al., 2024	ACTRN12622001454763	Randomised Controlled Trial (RCT)-crossover	Australia, New Zealand	Multi-center	No (open-label)	NA	Yes Otago Southland Diabetes Research Trust Rotary New Zealand Spinal Cord Society NZ University of Otago Medtronic Lions Clubs District 202F University of Otago	1. Male or female aged 7 – 25 years inclusive. 2. Type I diabetes as per the American Diabetes Association Classification, diagnosed at least 1 year prior to Study Day 1. 3. Current HbA1c level of greater than or equal to 8.5% (69mmol/mol). 4. Minimum daily insulin requirement of greater than or equal to 8 units of insulin/day. 5. Willing and able to adhere to the study protocol. 6. Access to the internet and a computer system that meets requirements for uploading the study pump.	1. Previous use of closed loop technology prior to Baseline visit. 2. Previous significant adverse event at investigator discretion that precludes the participant safely using advanced diabetes technology/sensors e.g., unable to wear glucose sensors due to prior cutaneous adverse events. 3. Use of a medication indicative of moderate/severe diabetes complications (ACE inhibitors and statins are permitted). 4. Use of systemic glucocorticoids within 2 weeks prior to the Baseline visit. 5. Current use of Metformin, SGLT-2 or GLP-1 medications. 6. History or current evidence of severe psychiatric disorder, uncontrolled seizure disorder, renal impairment or cardiovascular disease (including uncontrolled hypertension), that in the opinion of the Investigator would limit study involvement or be a safety issue. 7. For diabetic retinopathy (DR) or other visual impairment, the following criteria apply: A. Nil or Minimal retinopathy (less than or equal to R1/M1) – no restriction on study entry. To follow established ISPAD screening guidelines as below. B. If Grade 1 / Mild retinopathy (R2/M2) and HbA1c less than 10% (86mmol/mol) – no restriction to study entry. C. If Grade 1 / Mild retinopathy (R2/M2) and HbA1c equal to or greater than 10% (86mmol/mol) – DR screening to be performed during the study pre-screening phase (not greater than 4 weeks prior to initiation of blinded CGM). If subject remains at Grade 1 / Mild retinopathy (R2/M2) and frequency of screening is equal to or more than 1 year (indicating less clinical concern), subject meets inclusion. If subject has progressed to Moderate (Grade 2) or Severe (Grade 3) DR, to be excluded as per below exclusion criteria. D. Absolute exclusion: Any DR classed as Moderate (Grade 2) or Severe (Grade 3) non-proliferative retinopathy (known as equal to or more than R3/M3) is exclusive. NB: ISPAD guidelines (2022) for who needs retinopathy screening to be followed while in study care. These are: Screening from age 11 years with 2-5years diabetes duration. Subsequent monitoring frequency 2-3 yearly (or as locally recommended/available). E. History of severe visual impairment (which in the opinion of the Investigator would limit their successful involvement), is exclusive. 8. If female, is pregnant or plans to become pregnant while participating in the study. A positive urine pregnancy test at Screening is exclusionary. 9. Any clinically significant concomitant disease or condition that could interfere with, or for which the treatment of might interfere with, the conduct of the study, or that would, in the opinion of the investigator, pose an unacceptable risk to the subject in this study.

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
AHCL system (MiniMed 780G) + (CGM) components (Guardian 4 Sensor and Guardian 4 transmitter, and Medtronic's newest Synergy CGM system)	MDI or continuous subcutaneous insulin infusion therapy) + will undergo 2 weeks of blinded CGM (Guardian 3 sensor and transmitter CGM system) at the end of the RCT phase (weeks 11-13).	3 months	Continuous (pump) / MDI	80 participants	37 participants	43 participants	Children and youth (between 7 - 27 years)	Glycaemic control as measured by glycated hemoglobin (HbA1C) from blood samples.	• Glycaemic control as measured by percentage of time in range (3.9 – 10mmol/L), by way of CGM data analysis. • Glycaemic outcomes via CGM data for % CGM time below 3.0mmol/L • Glycaemic outcomes via CGM data for % CGM time below 3.9mmol/L • Glycaemic outcomes via CGM data for % CGM time above 10.0mmol/L • Glycaemic outcomes via CGM data for % CGM time above 13.9mmol/L	Patients in the AHCL group spent on average 8.4 hours more in the target glucose range of 70 to 180 mg/dl than those in the control group.	At 13 weeks, the mean (±SD) glycated hemoglobin decreased - in the AHCL group : from 10.5±1.9% to 8.1±1.8% -in the control group : 10.4±1.6% to 10.6±1.8% (remained relatively consistent) (baseline-adjusted between-group difference, -2.5 percentage points; 95% confidence interval [CI], -3.1 to -1.8; P<0.001).

Trial 12
M. B. Christensen et al. 2025
NCT04914910

Study characteristics									
Author-year	NCT Number	Study Design	Country	Centers	Blinding	Randomisation NA - crossover trials	Funding	Inclusion criteria	Exclusion criteria
M. B. Christensen et al. 2025	NCT04914910	Randomised Controlled Trial (RCT)-crossover	Denmark	Single-center	No (open-label)	NA	Yes Partly funded by an unrestricted grant from Medtronic A/S.	1. Age 18-75 years 2. Type 1 diabetes ≥2 years. 3. HbA1c >=58 mmol/mol 4. Insulin pump treatment ≥12 months 5. CGM or isCGM use ≥6 months 6. Novorapid use ≥1 week 7. Carbohydrate counting and use of the insulin pump bolus calculator for most snacks and meals. 8. Carbohydrate intake >80 grams per day (assessed by review of intake recorded in the insulin pump during the 2 weeks prior to the screening visit)	1. Breast-feeding, pregnancy or planning to become pregnant. 2. Use of anti-diabetic medicine (other than insulin), corticosteroids or other drugs affecting glucose metabolism during the study period or within 30 days prior to study start. 3. Use of hybrid closed-loop systems 4. Daily use of paracetamol (acetaminophen) 5. Alcohol or drug abuse. 6. Severe cardiac disease or retinopathy contraindicating HbA1c <53 mmol/mol. 7. Other concomitant medical or psychological condition that according to the investigator's assessment makes the person unsuitable for study participation. 8. Lack of compliance with key study procedures at the discretion of the investigator. 9. Unacceptable adverse events at the discretion of the investigator.

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	Standard insulin therapy	Duration of trial	Dosing frequency	Total number of participants (n)	Number of participants in hybrid closed-loop system (n)	Number of participants in standard insulin delivery	Age group	Primary endpoint	Secondary endpoint	Glucose target	Glycated haemoglobin A1c
(AID) Automated insulin delivery - MiniMed 780G system	Insulin pump + CGM/isCGM	14 weeks	Continuous insulin infusion	40 participants	20 participants	20 participants	Adult (18-75 years)	The primary endpoint was change in time in range (TIR: 3·9-10·0 mmol/L) from baseline to week 14.	• The secondary outcomes were : • The difference in the change in time above range (TAR; > 10.0 mmol/L, > 13.9 mmol/L) • Time below range (TBR; < 3.9 mmol/L, < 3.0 mmol/L) • Mean sensor glucose (SG) • Standard deviation (SD) of mean SG • Coefficient of variation (CV) • HbA1c • Body weight and total daily insulin dose (TDD).	-In the AID group: TIR increased by 18.7% -In the UC group: TIR remained unchanged (95% confidence interval [CI] = 14.5, 22.9%) (P < .0001)	Hemoglobin A1c -In the AID group : decreased by 10.0 mmol/mol (95% CI = 7.0, 13.0 mmol/mol) (0.9% [95% CI = 0.6%, 1.2%]) -In the UC group : but remained unchanged (P < .0001)

Trial 13
Lee et al. 2023
ISRCTN56898625

Study characteristics									
Author-year	NCT Number	Study Design	Country	Centers	Blinding	Randomisation NA - crossover trials	Funding	Inclusion criteria	Exclusion criteria
Lee et al. 2023	ISRCTN56898625	Randomised Controlled Trial (RCT)	United Kingdom England Northern Ireland Scotland	Multi-center	No (open-label)	Yes (1:1)	Yes National Institute for Health Research (NIHR) (UK)	1. Between 18 and 45 years of age (inclusive) 2. A diagnosis of type 1 diabetes (T1D), as defined by WHO (a chronic condition in which the pancreas produces little or no insulin by itself, characterized by deficient insulin production and a requirement for daily administration of insulin), for at least 12 months 3. A viable pregnancy confirmed by ultrasound, up to 13 weeks and 6 days gestation 4. Currently on intensive insulin therapy (≥3 injections or CSII). This includes women using sensor augmented pumps and/or hybrid closed-loop systems other than CamAPS FX. 5. Willingness to use the study devices throughout the trial 6. HbA1c level ≥48 mmol/mol (≥6.5%) at booking (first antenatal contact) and ≤86 mmol/mol (≤10%) at point of randomization. A CGM or Libre GMI (glucose management indicator) ≥48 mmol/mol (≥6.5%) or ≤86 mmol/mol (≤10%) may also be used. 7. Able to provide informed consent 8. Have access to email	1. Non-type 1 diabetes 2. Any other physical or psychological disease which, in the opinion of the investigator, is likely to interfere with the normal conduct and interpretation of the study results e.g. untreated coeliac disease or untreated hypothyroidism 3. Current treatment with drugs known to interfere with glucose metabolism as judged by the investigator such as high dose systemic corticosteroids, non-selective beta-blockers and MAO inhibitors 4. Known or suspected allergy against insulin 5. Women with advanced nephropathy (eGFR <45), severe autonomic neuropathy, uncontrolled gastroparesis or severe proliferative retinopathy, as judged by the investigator, that is likely to interfere with the normal conduct of the study and interpretation of study results 6. Very good or very poor glycaemic control i.e. first antenatal HbA1c <48mmol/mol (<6.5%) and current HbA1c >86mmol/mol (>10%). A CGM or Libre GMI (glucose management indicator) <48 mmol/mol (<6.5%) or >86 mmol/mol (>10%) may also be used. Women who enter pregnancy with HbA1c or GMI >86 mmol/mol (>10%) may participate if they achieve HbA1c or GMI ≤86 mmol/mol (≤10%) before randomization. 7. Total daily insulin dose ≥1.5 IU/kg at recruitment. 8. Severe visual or hearing impairment. 9. Unable to speak and understand English.

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	Standard insulin therapy	Duration of trial	Dosing frequency	Total number of participants (n)	Number of participants in hybrid closed-loop system (n)	Number of participants in standard insulin delivery	Age group	Primary endpoint	Secondary endpoint	Glucose target	Glycated haemoglobin A1c
CamAPS FX app (closed-loop), Dexcom G6 continuous glucose monitor	Standard open-loop insulin pump therapy + CGM	24 weeks	Continuous insulin infusion	124 women	61 participants	63 participants	Pregnant women between 18 and 45 years of age	Percentage of time spent with glucose levels between 3.5-7.8 mmol/L based on CGM levels between 16 weeks gestation and delivery. Data for the intervention group will be collected as part of the data collection from the AiD closed-loop system. Data for the control group will be collected using software provided by the CGM manufacturer.	1. The time spent with CGM glucose levels above and below target range (TAR>7.8mmol/L, TBR<3.5mmol/L), mean CGM glucose and CGM glucose variability measures (CV, SD) 2. The frequency and severity of hypoglycaemia episodes defined as CGM glucose levels TBR <3.5 mmol/L (level 1 hypoglycaemia) and TBR <3.0 mmol/L (level 2 hypoglycaemia) for at least 15 min. Distinct episodes must be separated for at least 30 min. 3. The international consensus targets for glycaemic assessment; TIR 3.5-7.8 mmol/L >70% (16hr 48 min), TAR >7.8mmol/L <25% (6 h), TBR <3.5 mmol/L <4% (1 h), and TBR <3.0 mmol/L <1% (15 min) 4. The Low Blood Glucose Index (LBGI) and High Blood Glucose Index (HBGI) measures 5. Where possible, blood samples will be collected at baseline, 24-26 weeks, 34-36 weeks for HbA1c testing to assess the change in the maternal level. Samples will be stored for further metabolic studies (optional). 6. CGM glucose levels during the first (<12 weeks 6 days gestation), second (13-27 weeks 6 days gestation) and third trimesters (28 weeks until delivery) 7. CGM glucose levels during the 24 h (midnight to midnight) and overnight time 23.00-07.00	The mean percentage of time that the maternal glucose level was in the target range was -In the closed-loop group: 68.2±10.5% -In the standard-care group: 55.6±12.5% (mean adjusted difference, 10.5 percentage points; 95% confidence interval [CI], 7.0 to 14.0; P<0.001)	Lower glycated hemoglobin levels favouring closed-loop (difference, −0.31 percentage points; 95% CI, −0.50 to −0.12)

Trial 14
J. Ware et al., 2022
NCT02925299

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
J. Ware et al., 2022	NCT02925299	Randomised Controlled Trial (RCT)	United Kingdom United States	Multi-center	No (open-label)	Yes (1:1)	Yes National Institute of Diabetes and Digestive and Kidney Diseases.	1. Age ≥6 and <19 years 2. Type 1 diabetes as defined by WHO (51) for at least 1 year [WHO definition: 'The aetiological type named type 1 encompasses the majority of cases with are primarily due to beta-cell destruction, and are prone to ketoacidosis. Type 1 includes those cases attributable to an autoimmune process, as well as those with beta-cell destruction for which neither an aetiology nor a pathogenesis is known (idiopathic). It does not include those forms of beta-cell destruction or failure to which specific causes can be assigned (e.g. cystic fibrosis, mitochondrial defects, etc.).'] 3. Use of an insulin pump for at least 3 months, with good knowledge of insulin self-adjustment by subject or caregiver as judged by the investigator 4. Using U-100 rapid acting insulin analogues insulin Aspart or Lispro only 5. Willing to perform regular finger-prick blood glucose monitoring, with at least 4 blood glucose measurements per day day 6. Screening HbA1c ≥ 7.0% (53 mmol/mol) and ≤10 % (86mmol/mol) based on analysis from local laboratory 7. Literate in English 8. Willing to wear glucose sensor Willing to wear closed-loop system at home Willing to follow study specific instructions Willing to upload pump and CGM data at regular intervals Access to WiFi. Lives with someone who is trained to administer intramuscular glucagon and is able to seek emergency assistance	1. Living alone 2. Current use of any closed-loop system 3. Any other physical or psychological disease likely to interfere with the normal conduct of the study and interpretation of the study results as judged by the investigator 4. Untreated coeliac disease, adrenal insufficiency, or untreated thyroid disease 5. Current treatment with drugs known to interfere with glucose metabolism, e.g. systemic corticosteroids, non-selective beta-blockers and MAO inhibitors etc. 6. Known or suspected allergy to insulin 7. Clinically significant nephropathy (eGFR < 45ml/min) or on dialysis, neuropathy or active retinopathy (defined as presence of maculopathy or proliferative changes) as judged by the investigator 8. Recurrent incidents of severe hypoglycaemia (>1 episode) during the previous 6 months (adolescents: severe hypoglycaemia is defined as an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions including episodes of hypoglycaemia severe enough to cause unconsciousness, seizures or attendance at hospital; children: severe hypoglycaemia is defined as an event associated with a seizure or loss of consciousness) 9. Recurrent incidents of diabetic ketoacidosis (>1 episode) during previous 6 months 10. Unwilling to avoid regular use of acetaminophen 11. Lack of reliable telephone facility for contact 12. Total daily insulin dose ≥ 2 IU/kg/day 13. Total daily insulin dose < 15 IU/day 14. Pregnancy, planned pregnancy, or breast feeding 15. Severe visual impairment 16. Severe hearing impairment 17.Seizure disorder 18. Medically documented allergy towards the adhesive (glue) of plasters or unable to tolerate tape adhesive in the area of sensor placement 19. Serious skin diseases (e.g. psoriasis vulgaris, bacterial skin diseases) located at places of the body, which potentially are possible to be used for localisation of the glucose sensor) 20. Illicit drugs abuse 21. Subject is currently abusing prescription drugs 22. Alcohol abuse 23. Use of pramlintide (Symlin), or other non-insulin glucose lowering agents including sulphonylureas, biguanides, DPP4-24. Inhibitors, , GLP-1 analogues, SGLT-1/ 2 inhibitors at time of screening 25. Shift work with working hours between 10pm and 8am 26. Sickle cell disease, haemoglobinopathy, or has received red blood cell transfusion or erythropoietin within 3 months prior to time of screening 27. Eating disorder such as anorexia or bulimia 28. Employed by Medtronic Diabetes or with immediate family members employed by Medtronic Diabetes

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Closed-loop in the USA is FlorenceM (Medtronic 640G pump and Guardian3 sensor) Closed-loop in the UK is FlorenceX (DANA pump and Dexcom sensor)	Standard open-loop insulin pump therapy + CGM	6 months	Continuous insulin infusion	133 participants	65 participants	68 participants	Adults aged ≥6 and <19 years	The primary outcome is the centralised measurement of glycated haemoglobin (HbA1c) at 6 months. [Time Frame: HbA1c will be taken at baseline, 3 and 6 months]	• Time spent in the target glucose range (3.9 to 10mmol/l) (70 to 180mg/dl) [Time Frame: 6 months] • Time spent below target glucose (3.9mmol/l)(70mg/dl) [Time Frame: 6 months] • Time spent above target glucose (10.0 mmol/l) (180 mg/dl) [Time Frame: 6 months] • Mean and standard deviation or percentiles sensor glucose [Time Frame: 6 months] • Coefficient of variation of glucose levels [Time Frame: 6 months] • Time with glucose levels < 3.5 mmol/l (63 mg/dl) [Time Frame: 6 months] • Time with glucose levels <3.0 mmol/l (54 mg/dl) [Time Frame: 6 months] • Time with glucose levels in significant hyperglycaemia (glucose levels > 16.7 mmol/l) (300mg/dl) [Time Frame: 6 months]	Time with glucose in target range of 3·9–10·0 mmol/L was 6·7 percentage points (95% CI 2·2 to 11·3; p=0·0043) higher in the closed-loop group.	At 6 months, HbA1c was lower in the closed-loop group than in the control group (between-group difference -3·5 mmol/mol (95% CI -6·5 to -0·5 [-0·32 percentage points, -0·59 to -0·04]; p=0·023) Specifically, Mean HbA1c decreased from 66 mmol/mol (SD 8; 8·2% [SD 0·7]) at baseline to 60 mmol/mol (12; 7·6% [1·1%]) at 6 months compared with a smaller change in the control group (from 67 mmol/mol [8; 8·3% [0·7]] at baseline to 64 mmol/mol [8; 8·1% [0·8]] at 6 months).

Trial 15
D. Elleri et al., 2013
NCT01074801

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
D. Elleri et al., 2013	NCT01074801	Randomised Controlled Trial (RCT)-crossover	Cambridge University Hospital, London and Norwich	3 centers	No (open-label)	NA	Yes National Institute of Diabetes and Digestive and Kidney Diseases	1. The subject is between 12 and 18 years of age (inclusive) 2. The subject has had type 1 diabetes, as defined by WHO for at least 1 year or is confirmed C-peptide negative 3. The subject will have been on insulin pump for at least 3 months, with good knowledge of insulin self-adjustment 4. HbA1c ≤ 12% based on analysis from central laboratory	1. Non-type 1 diabetes mellitus including those secondary to chronic disease 2. Any other physical or psychological disease likely to interfere with the normal conduct of the study and interpretation of the study results 3. Current treatment with drugs known to interfere with glucose metabolism such as systemic corticosteroids, non-selective beta-blockers and MAO inhibitors 4. Known or suspected allergy against insulin 5. Subjects with clinical significant nephropathy, neuropathy or proliferative retinopathy as judged by the clinician Total daily insulin dose >= 2 IU/kg Postmenarchal girls who are pregnant or intending to become pregnant or are breastfeeding Any coexisting cardiac and respiratory condition (including asthma)

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Closed-loop system	Standard pump therapy	36 hours	Continuous insulin infusion	24 adolescents	12 adolescents	12 adolescents	Young people aged 12–18 years	The primary outcome measure is time spent with plasma glucose concentration in the target range (3.9-10.0 mmol/L) between 24:00 on Day 1 to 08:00 on Day 3.	Secondary outcomes include: (i) Total and basal insulin delivery between 24:00 on Day 1 and 08:00 on Day 3 (36 hours) (ii) CGM glucose levels between 24:00 on Day 1 and 08:00 on Day 3 (36 hours)	Closed-loop basal insulin delivery increased percentage time when glucose was in the target range (median 84% [interquartile range 78–88%] vs. 49% [26–79%], P = 0.02) Plasma glucose levels were in the target range 100% of the time on 17 of 24 participants during closed-loop insulin delivery at night	Time in target ≥70% threshold was recorded in all subjects during closed-loop basal insulin delivery, whereas during conventional pump therapy, only one third of participants presented a comparable outcome. If extrapolated to long-term control, the improved glucose levels could represent a ≥1% fall in HbA1c

Trial 16
E. Renard et al., 2019
NCT02509429

Study characteristics									
Author-year	NCT Number	Study Design	Country	Centers	Blinding	Randomisation NA - crossover trials	Funding	Inclusion criteria	Exclusion criteria
E. Renard et al., 2019	NCT02509429	Randomised Controlled Trial (RCT)	France	4 centers	No (open-label)	NA	NA	1. Age from 7 to 12 2. Puberty status at Prader 1 3. Diabetes diagnosed according to WHO criteria since more than 1 year 4. Fasting plasma C-peptide level <0.2 ng/ml for a fasting blood glucose level < 180 mg/dl 5. At least one positiveness for plasma antibodies against pancreatic islets: IAA, IA2, GAD, ICA or ZnT8, since diagnosis of diabetes 6. Treatment of diabetes by insulin pump since more than 6 months 7. HbA1c level below 8.5% 8. Trained in carbohydrate counting 9. Lack of any associated disease or therapy (except insulin) affecting glucose metabolism 10. Willingness to follow all study procedures 11. Informed consent signed by patient and parent or legally responsible party 12. Patient must be affiliated or beneficiary of a social medical insurance	1. Unwillingness of one parent or the legally responsible party to be present during all study procedures 2. Expected use of acetaminophen-containing drugs 3. Any disease or therapy (except insulin) affecting glucose metabolism during previous month 4. Impaired cognitive or psychological abilities which may result in defective adherence to study procedures 5. Active enrollment in another clinical trial or participation in a study within 30 days or participation in previous studies resulting in a cumulated annual income which would exceed 4500 €

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	Standard insulin therapy	Duration of trial	Dosing frequency	Total number of participants (n)	Number of participants in hybrid closed-loop system (n)	Number of participants in standard insulin delivery	Age group	Primary endpoint	Secondary endpoint	Glucose target	Glycated haemoglobin A1c
Artificial Pancreas system - Insulin therapy with Control-to-Range algorithm	Standard Insulin Pump Therapy - Insulin therapy withThreshold Low Glucose Suspend	48 hour	Continuous insulin infusion	24 Children	NA	NA	Children 7-12 years old	Time spent with blood glucose <70 mg/dl from 22:00 to 08:00, over two consecutive nights	• Percent time spent with blood glucose <70mg/dl over two consecutive days (48h) • Percent time spent with blood glucose level in 70-180 mg/dl range • Percent time spent with blood glucose level in 80-150 mg/dl range from 22:00 to 08:00 over two consecutive nights • Percent time spent with blood glucose level in 70-180 mg/dl range over two consecutive days (48h) • Mean blood glucose level from 22:00 to 08:00, over two consecutive nights • Mean blood glucose level over two consecutive days (48h) • Number of needed interventions by the patients, the parents, and by the investigational team, to treat hypoglycemia during 65 hours of each investigational session • Number of needed interventions by the patients, the parents, and by the investigational team, to fix issues related to the functioning of the insulin delivery system during 65 hours of each investigational session • Score of the Artificial Pancreas Acceptance Questionnaire at time of inclusion (at Visit 2) and 5 to 6 weeks after inclusion (i.e at Visit 4) • Score of the Hypo Fear Survey at time of inclusion (at Visit 2) and 5 to 6 weeks after inclusion (i.e at Visit 4)	Overnight (22:00-08:00) per cent CGM time below 3.9 mmol/L (primary outcome) was similar between artificial pancreas & standard insulin pump therapy Time in ranges 3.9 to 10.0 and 3.9 to 7.8 mmoL/L and mean CGM were all significantly improved with CL (P < 0.001). These results were confirmed over the whole 48 hour.	NA

Trial 17
PY Benhamou et al., 2019
NCT02987556

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
PY Benhamou et al., 2019	NCT02987556	Randomised Controlled Trial (RCT)	France	Multi-center	No (open-label)	Yes (1:1)	Yes French Innovation Fund, Diabeloop.	1. Type 1 diabetic patient for at least two years 2. Patient treated by external insulin pump for at least 6 months 3. Patient with HbA1c ≤ 10%; dosage of less than 4 months done in analysis laboratory medical or equivalent. 4. Patient requiring a daily dose of insulin ≤ 50 units 5. Patient domiciled in an area with Global System for Mobile Communication (GSM) 6. Not isolated patient, not living alone, or having a person "resource" living nearby and having a phone and the key of its place of residence 7. Patient not envisaging a journey outside France during the "closed-loop" period 8. Patient aged over 18 years 9. Patient affiliated to Social Security 10. Patient who agreed to participate in the study and who signed an informed consent	1. Patient with any serious illness that may impair study participation 2. Patient having a treatment known to have a significant interference on the glycemia. 3. Patient enjoying a measure of legal protection 4. Pregnant woman or likely to be

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
DIABELOOP System (closed-loop)	Usual System (open-loop)	12-weeks periods separated by a Wash-out period of at least one month	Continuous insulin infusion	68 participants	33 participants	35 participants	Adult (≥18 years)	Percentage of time spent in the tight glycemic control area 70-180 mg/dl continuously measured for 12 weeks	• Percentage of time spent in the glycemic range 70-180 mg/dl, 80-140 mg/dl and in blood glucose >180 mg/dL during nights and during 24 hours for 12 weeks [Time Frame: During 24 hours for 12 weeks] • Measurement of HbA1c at the onset and at the end of each period of treatment [Time Frame: During 12 weeks for each period of treatment] Dosage of HbA1c every 3 months • Average blood glucose levels throughout the full period [Time Frame: During 12 weeks for each period of treatment] measurement of glucose by CGM • Calculated risks of hypo- and hyperglycemia (LBGI, HBGI) throughout the full period during 12 weeks [Time Frame: Throughout the full period during 12 weeks] • Total supplies of insulin during tests [Time Frame: During 12 weeks for each period] • Number of hyper-glycemic events defined by American Diabetes Association	The proportion of time that the glucose concentration was within the target range was - significantly higher in the DBLG1 group (68·5% [SD 9·4] than - the sensor-assisted pump group (59·4% [SD 10·2]; mean difference 9·2% [95% CI 6·4 to 11·9]; p<0·0001)	NA

Trial 18
M. Tauschmann et al., 2018
NCT02523131

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
M. Tauschmann et al., 2018	NCT02523131	Randomised Controlled Trial (RCT)-crossover	United Kingdom United States	Multi-center	No (open-label)	NA	Yes JDRF, NIHR, and Wellcome Trust.	1. The subject is at least 6 years or older [with equal proportion of youth (6 to 21 years) and adults (22 years and older)] 2. The subject has type 1 diabetes, as defined by WHO for at least 1 year or is confirmed C-peptide negative 3. The subject will have been an insulin pump user for at least 3 months, with good knowledge of insulin self-adjustment as judged by the investigator 4. The subject is treated with one of the rapid acting insulin analogues (insulin Aspart, Lispro or Glulisine) 5. The subject is willing to perform regular capillary blood glucose monitoring, with at least 4 blood glucose measurements taken every day 6. Screening HbA1c ≥ 7.5% (58.5mmol/mol) and ≤ 10 % (86mmol/mol) based on analysis from local laboratory or equivalent [with equal proportion of subjects above and below HbA1c 8.5% (69mmol/mol)] 7. The subject is literate in English 8. The subject is willing to wear glucose sensor 9. The subject is willing to wear closed loop system at home 10. The subject is willing to follow study specific instructions 11. The subject is willing to upload pump and CGM data at regular intervals 12. The subject is willing to restrict alcohol consumption to ≤ 2 units per day throughout the study period 13. Female subjects of child bearing age should be on effective contraception and must have a negative urine-HCG pregnancy test at screening. 14. The subject lives with someone who is trained to administer intramuscular glucagon and is able to seek emergency assistance. 15. The subject has access to WIFi at home.	1. Non-type 1 diabetes mellitus including those secondary to chronic disease 2. Subject using real-time CGM on regular basis in preceding 3 months 3. Any other physical or psychological disease likely to interfere with the normal conduct of the study and interpretation of the study results as judged by the investigator 4. Untreated coeliac disease or thyroid disease or subject is being treated for hypothyroidism at time of screening 5. Current treatment with drugs known to interfere with glucose metabolism, e.g. systemic corticosteroids, non-selective beta-blockers and MAO inhibitors etc. 6. Known or suspected allergy to insulin 7. Subjects with clinically significant nephropathy (eGFR < 45ml/min) or on dialysis, neuropathy or active retinopathy (defined as presence of maculopathy or proliferative changes) as judged by the investigator 8. Adults: one or more episodes of severe hypoglycaemia as defined by American Diabetes Association (33) in preceding 6 months; Youth: recurrent incidents of severe hypoglycaemia during the previous 6 months (Adults and adolescents: severe hypoglycaemia is defined as an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions including episodes of hypoglycaemia severe enough to cause unconsciousness, seizures or attendance at hospital; children: severe hypoglycaemia is defined as an event associated with a seizure or loss of consciousness); 9. Random C-peptide > 100pmol/l with concomitant plasma glucose >4 mmol/l (72 mg/dl) 10. Regular use of acetaminophen 11. Lack of reliable telephone facility for contact 12. Total daily insulin dose ≥ 2 IU/kg/day 13. Total daily insulin dose < 15 IU/day 14. Pregnancy, planned pregnancy, or breast feeding 15. Severe visual impairment 16. Severe hearing impairment 17. Significantly reduced hypoglycaemia awareness in subjects 18 year and older (screening Gold score > 4) 18. Subjects using implanted internal pace-maker 19. Patients with medically documented allergy towards the adhesive (glue) of plasters or Subject is unable to tolerate tape adhesive in the area of sensor placement 20. Serious skin diseases (e.g. psoriasis vulgaris, bacterial skin diseases) located at places of the body, which potentially are possible to be used for localisation of the glucose sensor) 21. Subject is currently abusing illicit drugs 22. Subject is currently abusing prescription drugs 23. Subject is currently abusing alcohol 24. Subject is using pramlintide (Symlin) at time of screening 25. Subject has elective surgery planned that requires general anaesthesia during the course of the study 26. Subject is a shift worker with working hours between 10pm and 8am 27. Subject has a sickle cell disease, haemoglobinopathy; or has received red blood cell transfusion or erythropoietin within 3 months prior to time of screening 28. Subject plans to receive red blood cell transfusion or erythropoietin over the course of study participation 29. Subject diagnosed with current eating disorder such as anorexia or bulimia 30. Subject plans to use significant quantity of herbal preparations (use of over the counter herbal preparation for 30 consecutive days or longer period during the study) or significant quantity of vitamin supplements (four times the recommended daily allowance used for 30 consecutive days or longer period during the study) during the course of their participation in the study

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Hybrid closed-loop system therapy	Sensor-augmented pump therapy	12 weeks	Continuous insulin infusion	86 participants (42 youth and 42 adults)	46 participants	46 participants	Participant (≥6 years)	Time spent in the target glucose range from 3.9 to 10.0 mmol/l (70 to 180mg/dl) based on CGM glucose levels in both arms for the 12 week intervention phase	• HbA1c at the end of treatment period [Time Frame: HbA1c will be taken at the end of 12-week study intervention.] • Time spent below target glucose (3.9mmol/l)(70mg/dl) [Time Frame: 12 week intervention phase] • Time spent above target glucose (10.0 mmol/l) (180 mg/dl) [Time Frame: 12 week intervention phase] • Average of glucose levels [Time Frame: 12 week intervention phase] • The time with glucose levels < 3.5 mmol/l (63mg/dl) and <2.8 mmol/l (50mg/dl) [Time Frame: 12 week intervention phase] • The time with glucose levels in the significant hyperglycaemia (glucose levels > 16.7 mmol/l) (300mg/dl) [Time Frame: 12 week intervention phase] • Total, basal and bolus insulin dose [Time Frame: 12 week intervention phase] • AUC of glucose below 3.5mmol/l (63mg/dl) [Time Frame: 12 week intervention phase] • Standard deviation of glucose levels [Time Frame: 12 week intervention phase] • Coefficient of variation of glucose levels [Time Frame: 12 week intervention phase] • Number of pump suspend events [Time Frame: 12 week intervention phase] • Change of body weight from screening to end of study [Time Frame: 12 week intervention phase]	The proportion of time that glucose concentration was within the target range was in the closed-loop group (65%, SD 8) - significantly higher compared with the control group (54%, SD 9) (mean difference in change 10·8 percentage points, 95% CI 8·2 to 13·5; p<0·0001).	In the closed-loop group, HbA1c was reduced from a screening value of 8·3% (SD 0·6) at screening to 8·0% (SD 0·6) after the 4-week run-in and to 7·4% (SD 0·6) after the 12-week intervention period. In the control group, the HbA1c values were 8·2% (SD 0·5) at screening 7·8% (SD 0·6) after run-in and 7·7% (SD 0·5) after intervention Reductions in HbA1c percentages were significantly greater in the closed-loop group compared with the control group (mean difference in change 0·36%, 95% CI 0·19 to 0·53; p<0·0001).

Trial 19
S. A. McAuley et al., 2022
NA

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
S. A. McAuley et al., 2022	NA	Randomised Controlled Trial (RCT)-crossover	Australia	NA	No (open-label)	NA	Yes JDRF (Juvenile Diabetes Research Foundation) the Diabetes Australia Research Program St Vincent's Hospital (Melbourne) Research Endowment Fund	• Age ≥60 years • Type 1 diabetes (consistent with ADA classification) for ≥10 years, as judged by the Investigator • Using insulin pump therapy (≥1-year pump experience), with established insulin delivery settings • Treated with a rapid-acting insulin analogue • HbA 1c ≤10.5% (≤91 mmol/mol) • Able to use the study devices (with or without caregiver assistance, though able to troubleshoot independently during device use) • English language proficiency • Internet and cellular phone coverage at home • Understands study protocol; willing and able to meet all protocol requirements	• Non-type 1 diabetes (including diabetes secondary to chronic disease) • Use of closed-loop insulin delivery within the past 3 months • Nephropathy with eGFR <30 mL/min/1.73m2, measured within past 3 months, or on dialysis • Use of any glucose-lowering agent other than insulin within the past 3 months • Corticosteroid medication within the past 3 months (or anticipated during the study period) • Inability to tolerate adhesives in the area of sensor placement (e.g. due to skin disease, intolerance to adhesives) • Untreated coeliac disease or other malabsorption • Uncontrolled thyroid disease • Clinically significant gastroparesis • Haemoglobinopathy, sickle cell disease, or has received red blood cell transfusion or erythropoietin within past 3 months • Uncontrolled hypertension (blood pressure: diastolic >100 mmHg or systolic >160 mmHg) • History of myocardial infarction, severe uncontrolled heart failure, unstable angina, transient ischemic attack, stroke, or thromboembolic disease in the past 3 months • Visual or hearing impairment precluding use of the study devices • Clinical diagnosis of moderate or severe dementia • Any severe or unstable physical or psychological condition which, as judged by the Investigator, could compromise the ability to meet protocol requirements or interpretation of study results

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Closed-loop therapy	Sensor-augmented pump therapy	4 months	Continuous insulin infusion	30 participants	15 participants	15 participants	Adult (≥60 years)	Time in range (TIR; 3.9–10.0 mmol/L).	• Functional ability • Katz ADLs • Lawton-Brody Instrumental ADLs • Frailty • FRAIL scale • Mini Nutritional Assessment • Sarcopenia SARC-F 1 • Walking speed (m/sec) • Grip strength* • Physical Activity • Diabetes-related ambulance attendances Diabetes-related hospitalizations Incident falls Incident delirium Incident pressure sores Incident infections Cognitive functioning outcomes Montreal Cognitive Assessment (MoCA) Mini-Mental State Assessment (MMSE) Verbal IQ – National Adult Reading Test Executive functioning: Trails Making Task B Psychomotor speed Symbol Digit Modalities Test Trails Making Task A Grooved pegboard (dominant) Grooved pegboard (non-dominant)	The mean TIR during the closed-loop stage : 75.2% (6.3) the sensor-augmented pump stage : 69.0% (9.1) (difference 6.2 percentage points [95% CI 4.4, 8.0]; P <0.0001) All prespecified CGM metrics favored closed loop over sensor-augmented pump; benefits were greatest overnight.	There was no significant difference in HbA1c between closed-loop versus sensor-augmented pump stages (7.3% [IQR, 7.1-7.5] (56 mmol/mol [54-59]) vs. 7.5% [7.1-7.9] (59 mmol/mol [54-62]), respectively; P = 0.13)

Trial 20
E. Isganaitis et al., 2019
NCT03563313

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
E. Isganaitis et al., 2019	NCT03563313	Randomised Controlled Trial (RCT)-crossover	United States	Multi-center	No (open-label)	NA	Yes University of Virginia Jaeb Center for Health Research National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Tandem Diabetes Care, Inc. DexCom, Inc. Roche Diagnostics GmbH	1. Clinical diagnosis, based on investigator assessment, of type 1 diabetes for at least one year and using insulin for at least 1 year. 2. Familiarity and use of a carbohydrate ratio for meal boluses. 3. Age ≥14.0 years old. 4. For females, not currently known to be pregnant. If female and sexually active, must agree to use a form of contraception to prevent pregnancy while a participant in the study. A negative serum or urine pregnancy test will be required for all females of child-bearing potential. Participants who become pregnant will be discontinued from the study. Also, participants who during the study develop and express the intention to become pregnant within the timespan of the study will be discontinued. 5. For participants <18 years old, living with one or more parent/legal guardian knowledgeable about emergency procedures for severe hypoglycemia and able to contact the participant in case of an emergency. 6. Willingness to suspend use of any personal CGM for the duration of the clinical trial once the study CGM is in use. 7. Willingness to use a regular insulin pump during the study with no automatic insulin adjustment based on glucose level when assigned to participate in an SAP group 8. Investigator has confidence that the participant can successfully operate all study devices and is capable of adhering to the protocol. 9. Willingness to switch to lispro (Humalog) or aspart (Novolog) if not using already, and to use no other insulin besides lispro (Humalog) or aspart (Novolog) during the study. 10. Total daily insulin dose (TDD) at least 10 U/day. 11. Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial.	1. Concurrent use of any non-insulin glucose-lowering agent other than metformin (including GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas). 2. Hemophilia or any other bleeding disorder. 3. A condition, which in the opinion of the investigator or designee, would put the participant or study at risk. 4. Participation in another pharmaceutical or device trial at the time of enrollment or during the study. 5. Employed by, or having immediate family members employed by Tandem Diabetes Care, Inc. or TypeZero Technologies, LLC, or having a direct supervisor at place of employment who is also directly involved in conducting the clinical trial (as a study investigator, coordinator, etc.); or having a first-degree relative who is directly involved in conducting the clinical trial.

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Closed loop system (t:slim X2 with Control-IQ Technology & Dexcom G6 CGM for 6 months)	Sensor-augmented pump (SAP) will use an insulin pump with no automated insulin delivery and a study CGM (Dexcom G6)	26 weeks	Continuous insulin infusion	168 participants	112 participants	56 participants	Participant (≥14 years)	The primary outcome is time in target range 70-180 mg/dL measured by CGM in CLC group vs. SAP group.	• CGM-measured % above 180 mg/dL • CGM Mean Glucose • HbA1c at 26 Weeks • CGM Time Below 70 • CGM Time Below 54 • CGM Time in Range 70-140 mg/dL • Coefficient of Variability • Standard Deviation of CGM • CGM Time Below 60 • LBGI • CGM Hypoglycemia Events • CGM Time >250 • CGM Time >300 • HBGI • Number of Participants With HbA1c <7.0% at 26 Weeks • Number of	Time in range (TIR) increased by 13% with CLC versus decreasing by 1% with SAP (adjusted treatment group difference = +13% [+3.1 h/day]; 95% confidence interval [CI] 9–16, P < 0.001),	The mean adjusted difference in HbA1c after 6 months was 0.30% in CLC versus SAP (95% CI −0.67 to +0.08, P = 0.13).

									Participants With HbA1c <7.5% at 26 Weeks • Number of Participants With HbA1c Improvement From Baseline to 26 Weeks >0.5% • Number of Participants With HbA1c Improvement From Baseline to 26 Weeks >1.0% • HbA1c Relative Improvement From Baseline to 26 Weeks >10% • Number of Participants With HbA1c Improvement From Baseline to 26 Weeks >1.0% or HbA1c <7.0% at 26 Weeks HbA1c improvement from baseline to 26 weeks >1.0% or HbA1c <7.0% at 26 weeks • HFS-II • Hyperglycemia Avoidance Scale • Diabetes Distress Scale • Hypoglycemia Confidence Scale • INSPIRE Survey Scores • System Usability Scores (SUS) • Technology Acceptance Questionnaire • Total Daily Insulin • Basal:Bolus Insulin Ratio • Weight • BMI		

Trial 21
A. Dauber et al., 2013
NCT01421225

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
A. Dauber et al., 2013	NCT01421225	Randomised Controlled Trial (RCT)-crossover	United States	Single-center	No (open-label)	NA	NA	1. Age < 7 years old 2. Type 1 Diabetes (as diagnosed by outpatient endocrinologist) with duration greater than 6 months 3. Treated with insulin pump therapy for greater than 6 weeks	1. Any other chronic medical condition 2. Weight below 10 kg as this is the minimal required weight for the amount of blood being drawn

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Closed-loop Insulin Pump therapy	Standard Insulin Pump Therapy	48 hour	Continuous insulin infusion	10 children	10 children	10 children	6 Months to 7 Years (Child)	Time spent within target glucose range based on the glucose meter measurements between 10 PM and 8 AM. The target range is 110-200 mg/dl as this is the American Diabetes Association defined target overnight range for this age group.	• Peak post-prandial blood sugar between 8 AM and noon • The number of interventions for hypoglycemia between 10 PM - 8 AM • Blood glucose levels were documented at 12 pm just prior to being served lunch	A trend toward a higher mean nocturnal time within target range was noted for closed- versus open-loop therapy * not reaching statistical significance (5.3 vs. 3.2 h, P = 0.12)	NA

Trial 22
K. Benhalima et al., 2024
NCT04520971

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
K. Benhalima et al., 2024	NCT04520971	Randomised Controlled Trial (RCT)	Belgium Netherlands	Multi-center	No (open-label)	Yes (1:1)	Yes Diabetes Liga Research Fund and Medtronic	1. Women with type 1 diabetes (T1DM), diagnosed with T1DM at least 1 year before pregnancy 2.Age 18-45 years 3. A singleton pregnancy confirmed by b-HCG in blood and/or ultrasound-confirmed gestational age up to 11 weeks and 6 days. 4. Treated with intensive insulin treatment (either MDI or insulin pump). A closed-loop system can only be used in manual mode. 5. Have a booking HbA1c (measurement taken at the first antenatal clinic visit after confirmed pregnancy) level ≤10%. 6. Participants need to speak and understand Flemish, French or English and have e-mail access.	1. The use of a closed-loop insulin delivery system in auto mode. 2. A twin (multiple) pregnancy 3. A physical or psychological disease likely to interfere with the conduct of the study (based on the evaluation by the treating physician) 4. Medications known to interfere with glucose metabolism 5. An insulin dose of ≥1.5 units/kg 6. Known allergy to adhesives due to infusion set and/or CGM

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
AHCL therapy (MiniMed 780G)	(MDI) or insulin pumps (CSII)	28 - 40 weeks	Continuous (pump) / MDI	95 women	46 women	49 women	Pregnant women between 18 and 45 years of age	The primary outcome was proportion of time spent in the pregnancy-specific target glucose range (3·5-7·8 mmol/L), measured by CGM at - 14-17 weeks - 20-23 weeks - 26-29 weeks - 33-36 weeks	Key secondary outcomes were overnight time in target range, and time below glucose range (<3·5 mmol/L) overall and overnight	The mean proportion of time spent in the target range (averaged over four time periods) - in the AHCL therapy group: 66·5% (SD 10·0) compared with - in the standard insulin therapy group : 63·2% (12·4) (adjusted mean difference 1·88 percentage points [95% CI -0·82 to 4·58], p=0·17)	NA

Trial 23
J. Y. Kim et al., 2024
KCT0008398

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
J. Y. Kim et al., 2024	KCT0008398	Randomised Controlled Trial (RCT)-crossover	South Korea	Multi-center	No (open-label)	Yes (1:1)	Yes Korea Medical Device Development Fund supported by the Ministry of Science Ministry of Science and ICT Ministry of Trade, Industry and Energy Ministry of Health and Welfare Ministry of Food and Drug Safety	Adults aged 19-69 years with type 1 diabetes who had HbA1c levels of <85.8 mmol/mol (<10.0%) were eligible	NA

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
On-body automated insulin delivery (AID) system	On-body sensor-augmented pump (SAP)	12 weeks	Continuous insulin infusion	104 participants	53 participants	51 participants	Adults aged 19-69 years	The primary outcome was the percentage of time in range (TIR), blood glucose between 3.9 and 10.0 mmol/l, as measured by continuous glucose monitoring.	NA	The mean (±SD) TIR increased over the 12 week trial period - in the intervention group : from 62.1±17.1% at baseline to 71.5±10.7% and - in the control group : from 64.7±17.0% to 66.9±15.0% (difference between the adjusted means: 6.5% [95% CI 3.6%, 9.4%], p<0.001)	HbA1c decreased -in the intervention group : from 50.9±9.9 mmol/mol (6.8±0.9%) at baseline to 45.9±7.4 mmol/mol (6.4±0.7%) after 12 weeks and -in the control group : from 48.7±9.1 mmol/mol (6.6±0.8%) to 45.7±7.5 mmol/mol (6.3±0.7%) (difference between the adjusted means: -0.7 mmol/mol [95% CI -2.0, 0.8 mmol/mol] (-0.1% [95% CI -0.2%, 0.1%]), p=0.366)

Trial 24
YM Luijf et al., 2013
NA

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
YM Luijf et al., 2013	NA	Randomised Controlled Trial (RCT)-3 way crossover	Italy United Kingdom France Netherlands	Multi-center	No (open-label)	NA	NA	Main inclusion criteria included age <18 years and T1DM treated with CSII with a rapid-acting insulin analog for atleast 3 months	Main exclusion criteria included pregnancy and use of medicationsthat significantly impact glucose metabolism

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
-Closed-loop therapy with the algorithm of the Universities of Pavia and Padova with a Safety Supervision Module developed at the Universities of Virginia and California at Santa Barbara (international artificial pancreas [iAP]) -Closed-loop therapy with the algorithm of University of Cambridge (CAM)	Conventional CSII - open loop (OL)	3 24-h admissions (duration of intervention 23 h)	Continuous insulin infusion	48 participants	48 participants	48 participants	Adult (≥18 years)	Main outcome measures included time spent in target (glucose levels between 3.9 and 8.0 mmol/L or between 3.9 and 10.0 mmol/L after meals)	NA	Time spent in the target range was similar in CL and OL OL: 62.6% iAP : 59.2% CAM : 58.3%	NA

Trial 25
L. Leelarathna et al., 2014
NCT01666028

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
L. Leelarathna et al., 2014	NCT01666028	Randomised Controlled Trial (RCT)-crossover	United States Austria Germany	3 centers	No (open-label)	NA	NA	1. The subject has type 1 diabetes as defined by WHO 2. The subject is 18 years of age or older 3. The subject will have been on an insulin pump for at least 3 months currently using insulin Aspart, with good knowledge of insulin self-adjustment including carbohydrate counting HbA1c ≤ 10 % based on analysis from local laboratory 4. The subject is willing to perform regular finger-prick blood glucose monitoring, with at least 6 measurements per day during the 7 day home phase of the study 5. The subject is willing to wear closed-loop system at home and at work place 6. The subject is willing to follow study specific instructions 7. The subject is literate in English 8.Female subjects of child bearing age should be on effective contraception and must have a negative urine-HCG pregnancy test at screening. In addition in Germany, women of childbearing potential must use a highly effective method of birth control, which is defined as those which result in a low failure rate (i.e. less than 1% per year) and must use two independent methods of contraception, e.g. diaphragm and spermicide-coated condom.	1. Non-type 1 diabetes mellitus 2. Any other physical or psychological disease or condition likely to interfere with the normal conduct of the study and interpretation of the study results 3. Current treatment with drugs known to have significant interference with glucose metabolism, such as systemic corticosteroids, as judged by the investigator 4. Known or suspected allergy against insulin 5. Subjects with clinically significant nephropathy, neuropathy or proliferative retinopathy as judged by the investigator 6. Significantly reduced hypoglycaemia awareness as judged by the investigator 7. Total daily insulin dose more than 2 IU/kg/day 8. Subject is pregnant or breast feeding or planning pregnancy in near future (within next 3 months) 9. Severe visual impairment 10. Severe hearing impairment 11. Subjects using implanted internal pacemaker 12. Lack of reliable telephone facility for contact

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Automated closed-loop insulin delivery	Sensor-augmented insulin pump therapy (SAP)	8-day period (first day at the clinical research facility followed by 7 days at home)	Continuous insulin infusion	17 participants	17 participants	17 participants	Adult (≥18 years)	The primary end point was the time when sensor glucose was in target range between 3.9 and 10.0 mmol/L during the 7-day home phase as recorded by CGM	Secondary outcomes are : • the time spent with glucose levels above target, as recorded by CGM and other CGM-based metrics • the time spent with glucose levels below target, as recorded by CGM and other CGM-based metrics and for the stay at the clinical research facility: • time spent in the target range • above the target range as measured by plasma glucose. • below the target range as measured by plasma glucose	During the home phase, the percentage of time when glucose was in target range was significantly higher during closed-loop compared with SAP (median 75% [interquartile range 61-79] vs. 62% [53-70], P = 0.005) Increased time in target was observed during both daytime (P = 0.017) and nighttime (P = 0.013)	NA

Trial 26
L. Bally et al., 2017
NCT02727231

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
L. Bally et al., 2017	NCT02727231	Randomised Controlled Trial (RCT)-crossover	Austria United Kingdom	2 centers	No (open-label)	Yes (1:1)	Yes Swiss National Science Foundation JDRF UK National Institute for Health Research Cambridge Biomedical Research Centre and Wellcome Strategic Award	1. The subject has type 1 diabetes as defined by WHO 2. The subject is 18 years of age or older 3. The subject will have been on an insulin pump for at least 6 months with good knowledge of insulin self-adjustment including carbohydrate counting 4. The subject is treated with one of the rapid acting insulin analogues (Insulin Aspart, Insulin Lispro or Insulin Glulisine) 5. HbA1c <7.5% (58mmol/mmol) based on analysis from central laboratory or equivalent 6. The subject is willing to perform regular finger-prick blood glucose monitoring, with at least 6 measurements per day 7. The subject is willing to wear closed-loop system at home and at work place 8. The subject is willing to follow study specific instructions 9. The subject is willing to upload pump and CGM data at regular intervals 10.Female subjects of child bearing age should be on effective contraception and must have a negative urine-HCG pregnancy test at screening.	1. Non-type 1 diabetes mellitus 2. Any other physical or psychological disease or condition likely to interfere with the normal conduct of the study and interpretation of the study results 3. Current treatment with drugs known to have significant interference with glucose metabolism, such as systemic corticosteroids, as judged by the investigator 4. Known or suspected allergy against insulin 5. Subjects with clinically significant nephropathy, neuropathy or proliferative retinopathy as judged by the investigator 6. Significantly reduced hypoglycaemia awareness as judged by the investigator 7. More than one episode of severe hypoglycaemia as defined by American Diabetes Association in preceding 6 months (Severe hypoglycaemia is defined as an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions). 8. Random C-peptide > 100pmol/l with concomitant plasma glucose >4 mM(72 mg/dl) Total daily insulin dose > 2 IU/kg/day 9. Subject is pregnant or breast feeding or planning pregnancy in near future (within next 3 months) 10. Severe visual impairment 11. Severe hearing impairment 12. Subjects using implanted internal pacemaker 13. Lack of reliable telephone facility for contact 14. Subject not proficient in English (UK) or German (Austria) 15. Subjects who are living alone Additional exclusion criteria specific for Austria: Positive results on urine drug screen (amphetamines/metamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates). Positive alcohol breath test.

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Closed-loop system	Usual insulin pump therapy	4 weeks	Continuous insulin infusion	29 participants	29 participants	29 participants	Adult (≥18 years)	The primary outcome was the proportion of time when sensor glucose concentration was in target range (3·9-10·0 mmol/L) over the 4 week study period	• Time spent above and below the target glucose range from 3.9 to 10.0 mmol/l based on subcutaneous glucose monitoring (CGM) during the 4 weeks of home stay. • Average,standard deviation and coefficient of variation of glucose levels during 4 weeks of home periods • The time with glucose levels < 3.5 mmol/l and <2.8 mmol/l during 4 weeks of home periods • The time with glucose levels in the significant hyperglycaemia,(glucose levels > 16.7 mmol/l during 4 weeks of home periods • Low Blood Glucose Index • The "Area Under the Curve" below 3.5 mmol/l during 4 weeks home periods • Between 24 hour period variability: Coefficient of variation of CGM glucose between 24 hour periods (midnight to midnight) • Time spent with CGM glucose concentration in range 3.9-10.0mmol/L • Time spent with CGM glucose concentration in the target range (3.9-10.0mmol/L) • Total, basal and bolus insulin dose during 4 weeks of home periods • Safety evaluation will comprise the number of episodes of hypoglycaemia, significant ketonemia (> 3.0mmol/l)as well as nature and severity of any other adverse events 5 months • Utility evaluation is the percentage of closed-loop operation time during use at home, and when CGM was available	The proportion of time when sensor glucose concentration was in target range during closed-loop delivery compared was 10·5 percentage points higher (95% CI 7·6-13·4; p<0·0001) with usual pump therapy (65·6% [SD 8·1] when participants used usual pump therapy vs 76·2% [6·4] when they used closed-loop)	NA

Trial 27
M. Tauschmann t al., 2016
NCT01873066

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
M. Tauschmann t al., 2016	NCT01873066	Randomised Controlled Trial (RCT)-crossover	United Kingdom	Single-center	No (open-label)	NA	NA	1. The subject is between 10 and 18 years of age (inclusive) 2. The subject has type 1 diabetes, as defined by WHO for at least 1 year or is confirmed C-peptide negative 3. The subject/carer will have been an insulin pump user for at least 3 months, with good knowledge of insulin self-adjustment as judged by the investigator 4. The subject/carer is willing to perform regular finger-prick blood glucose monitoring, with at least 4 blood glucose measurements taken every day 5. HbA1c between 7.0% and 11.0 % (53 to 97mmol/mol) based on analysis from central laboratory or equivalent 6. The subject is literate in English 7. The subject is willing to wear closed-loop system at home and at school / college / work 8. The subject is willing to follow study specific instructions	1. Non-type 1 diabetes mellitus including those secondary to chronic disease 2. Any other physical or psychological disease or condition likely to interfere with the normal conduct of the study and interpretation of the study results as judged by the investigator. 3. Current treatment with drugs known to have significant interference with glucose metabolism, such as systemic corticosteroids, as judged by the investigator 4. Known or suspected allergy against insulin 5. Subjects with clinically significant nephropathy, neuropathy or proliferative retinopathy as judged by the investigator 6. Significantly reduced hypoglycaemia awareness as judged by the investigator 7. Total daily insulin dose ≥ 2 IU/kg/day 8. Total daily insulin dose <10 IU/day 9. Reduced hypoglycaemia awareness 10. Pregnancy, planned pregnancy or breast feeding 11. Severe visual impairment 12. Severe hearing impairment 13. Subjects using implanted internal pacemaker 14. Lack of reliable telephone facility for contact

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Hybrid closed-loop system	Sensor-augmented pump (SAP) therapy	42 days	Continuous insulin infusion	12 adolescents	12 adolescents	12 adolescents	10 - 18 years of age	The proportion of time spent in the target glucose range from 3.9 to 10.0 mmol/l based on CGM	• The proportion of time spent above and below the target glucose (3.9 to 10.0 mmol/l) based on CGM • The proportion of time with glucose levels < 3.5 mmol/l and <2.8 mmol/l based on CGM • The proportion of time with glucose levels in significant hyperglycaemia, as based on CGM (glucose levels > 16.7 mmol/l)	The proportion of time when the sensor glucose level was in the target range (3.9-10 mmol/L) was increased during closed-loop insulin delivery compared with sensor-augmented pump therapy (72 vs. 53%, P < 0.001; primary end point)	NA

Trial 28
T. Biester et al., 2019
NCT03767790

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
T. Biester et al., 2019	NCT03767790	Randomised Controlled Trial (RCT)-crossover	Israel Slovenia Germany	3 centers	No (open-label)	NA	NA	1. Subject with Type 1 diabetes (>1yr since diagnosis) 2. Insulin infusion pump therapy for at least 3 months 3. Patients whom uses continuous glucose sensor for at least 2 weeks(for segment 5) or will undergo run-in period of 2 weeks of glucose sensor wear before continue to baseline assessment (only for patients participating at segment 3 and 4) 4. Age ≥ 10 years until 65 years 5. HbA1c at inclusion ≥ 6.5 and <10 6. Patients willing to follow trail instructions 7. Patients live with at least one other adult person (segment 3, 5, and 6 only) 8. BMI Standard Deviation Score - below the 97th percentile for age(in segment 5 and 6 BMI SDS - below the 95th percentile for age) 9. An internet connection at patient's home (only for patients participating at segment 3 and 6) 10. Patients with care givers who are capable of operating a computer based system	1. Concomitant diseases that influence metabolic control 2. Participation in any other interventional study 3. Known or suspected allergy to trial products 4. Any significant diseases or conditions including psychiatric disorders and substance abuse that, in the opinion of the investigator, is likely to affect the subject's ability to complete the study, or compromise patient safety 5. Diabetic ketoacidosis in the past 1 month. 6. Severe hypoglycemia resulting in seizure or loss of consciousness in the month prior to enrollment. 7. Current use of oral glucocorticoids or other medications, which in the judgment of the investigator would be a contraindication to participation in the study. 8. Subject is participating in another drug or device study that could affect glucose measurements or glucose management.

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
MD-Logic closed-loop system (DreaMed GlucoSitter)	Sensor-augmented pump (SAP) therapy	60 hours during the weekend	Continuous insulin infusion	10 participants	10 (cross-over)	10 (cross-over)	Age ≥ 10 years until 65 years	The primary endpoint was percentage of glucose values between 70 and 180 mg/dL.	• Percentage of time spent in the target range,defined as sensor glucose level within 63 to 140 mg/dl (3.5 to 7.8 mmol/l)and between 70 to 140 mg/dl(3.9 to 7.8 mmol/L) • Percentage of time spent in the target range, defined as sensor glucose level within 80 to 120 mg/dl (3.5 to 7.8 mmol/l) • Average (SD) of blood glucose levels • Percentage of time spent below 60 mg/dl and below 70 mg/dl • Percentage of time spent above 140, 180, 250 mg/dl (7.8, 10, 13.9 mmol/l) • Glucose variability • Control Variability Grid Analysis (CVGA) • Number of hypoglycemic events below 60 and 70 mg/dl (3.3, 3.9 mmol/l) • The percentage of nights mean overnight sensor glucose levels was within 90-140mg/dl (5-7.8 mmol/l) • Postprandial peak blood glucose and 2 hours postprandial blood glucose (segment 4 and 6 only)	A significant increase in the percentage of time within target range (70-180 mg/dL) (66.6% vs 59.9%, P = 0.002) was observed with the closed-loop system vs control weekends with unchanged percentage of time below 70 mg/dL (2.3% vs 1.5%, P = 0.369)	NA

									• Artificial Pancreas technical performance, defined as the total frequency of failures • Analysis of the number of sensor data point not received to the artificial pancreas device divided by the total number of possible data points to be received. • Percent time of active closed-loop control defined as the number of minutes the MD-Logic system was functioning properly (computation of insulin infusion, and insulin actually delivered) divided by the maximum number of minutes the MD-Logic system should have been active (as per protocol) • Comparison of paired data points between capillary glucose level and Continuous Glucose Monitoring • The time spent in hypoglycemia below 50 mg/dl (2.8 mmol/l) • The number of hypoglycemic events below 60 and 50 mg/dl • The time sensor glucose level spent within 70 to 140 mg/dl (3.9 to 7.8 mmol/l) • The time spent in hyperglycemia above 240 mg/dl (13.3 mmol/l) • Patient's diabetes treatment satisfaction • Acceptance and use intention of an Artificial Pancreas for participant and for parents • Fear of hypoglycemia using questionaire • Satisfaction with Artificial Pancreas using questionaire • Average percentage of overnight operation of the closed-loop control • Percentage of time spent below 50, 60, 70 mg/dl • Number of hypoglycemic events below 50, 60, 70 mg/dl • Percentage of time spent above 180, 250 mg/dl • Number of readings below 70 mg/dl • Automatic Caller System (ACS) technical performance and number of accurate alerts • Number of research team intervention • HbA1c • Number of awake bouts per night Number of awake bouts per night as measured by Actigraph • Total wake up time per night as measured by Actigraph		

Trial 29
M B Abraham et al., 2021
ACTRN12616000753459

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
M B Abraham et al., 2021	ACTRN12616000753459	Randomised Controlled Trial (RCT)	Australia	Multi-center	No (open-label)	Yes (1:1)	Yes National Health and Medical Research Council Juvenile Diabetes Research Foundation Medtronic Telethon Kids Institute National Health and Medical Research Council Clinical Trials Centre, University of Sydney	1. Type 1 diabetes (diagnosis consistent with American Diabetes Association Classification of Diabetes Mellitus) diagnosed at least 1 year ago 2. Fasting C peptide less than 0.1nmol/L (in the absence of hypoglycaemia) 3. Insulin regimen either: Multiple daily injections (MDI) more than 4 injections per day (greater than 3 rapid-acting insulin and 1 long-acting insulin), or insulin pump therapy (CSII) established for greater than 3months. 4. Aged 12- less than 25years 5. HbA1c less than 10.5% 6. Living in an area with internet and cellular phone coverage 7. English speaking	1. Chronic kidney disease (eGFR <45mL/min/1.73m2) 2. Use of any non-insulin glucose-lowering agent within the past 3 months 3 Oral or injected steroid use within the past 3 months 4. Pregnancy, or planned pregnancy within study period 5. Uncontrolled coeliac disease (not following a gluten free diet), or other untreated malabsorption 6 Uncontrolled thyroid disease 7. Clinically-significant gastroparesis 8. Uncontrolled hypertension (DBP >100 mmHg and/or SBP >160 mmHg) 9. History of myocardial infarction, severe uncontrolled heart failure, unstable angina, transient ischaemic attack (TIA), stroke, or thromboembolic disease in the past 3 months. 10. Poor visual acuity precluding use of the investigational technology 11 Inability or unwillingness to meet protocol requirements (including carbohydrate-counting, CGM use as per allocated study group only). 12. Severe or unstable medical or psychological condition which, in the opinion of the investigator, would compromise the ability to meet protocol requirements

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Medtronic MiniMed™ 780G AHCL insulin pump	Continuous subcutaneous insulin infusion or multiple daily insulin injections with or without CGM	6 months	Continuous (pump) / MDI	135 participants	67 participants	68 participants	Patients aged 12 -25 years	The primary outcome was the percentage of time in range (TIR) within a glucose range of 70 to 180 mg/dL, measured by 3-week masked CGM collected at the end of the study in both groups	Glycaemic (All CGM data as per i) a - i below will be analysed over 24hrs, daytime hours (0600 – 2400), and night time hours (0000 – 0600)) A sub analysis of Hybrid closed loop (HCL) vs. Multiple daily injection (MDI) and HCL vs. insulin pump therapy (CSII) is planned. i. CGM data: This outcome will be measured with a continuous glucose monitor, that is uploaded onto Medtronic software. a. % CGM Time <2.8 mmol/L b. % CGM Time <3.3 mmol/L c. % CGM Time <3.9 mmol/L d. % CGM Time 3.9-7.8 mmol/L e. % CGM Time >10.0 mmol/L f. % CGM Time >13.9 mmol/L g. % CGM Time >16.7 mmol/L h. Standard Deviation and Coefficient of Variation of CGM values i. Mean CGM glucose Timepoint [1]- Continuous glucose monitoring (CGM) data will be collected in three time blocks; baseline (3 weeks CGM), 13 weeks (2 weeks CGM) and 26 weeks (3 weeks CGM) post randomisation.	TIR -in the HCL group : from a mean (SD) of 53.1% (13.0%) at baseline to 62.5% (12.0%) at the end of the study -in the control group : from 54.6% (12.5%) to 56.1% (12.2%) with a mean adjusted difference between the 2 groups of 6.7% (95% CI, 2.7%-10.8%; P = .002)	NA

Trial 30
E. Renard et al., 2024
ACTRN12616000753459

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
E. Renard et al., 2024	ACTRN12616000753459	Randomised Controlled Trial (RCT)	United States France	Multi-center	No (open-label)	Yes (2:1)		1. Age at time of consent 18-70 years of age; 2. Diagnosed with type 1 diabetes for at least 1 year. Diagnosis is based on investigator's clinical judgment; 3. On pump therapy for at least ≥3 months prior to screening and familiar with pump therapy concepts such as basal and bolus insulin delivery, and carbohydrate counting. Participants using automated insulin delivery devices, including devices with predictive low glucose suspend, in the 3 months prior to screening, will be excluded from participating; 4. HbA 1c 7.0-11.0% (53-97mmol/mol) by point-of-care taken at screening visit; 5. Willing to use and obtain U-100 insulin: (either insulin aspart (Novolog, NovoRapid), or insulin lispro (Humalog, Admelog)), as the primary insulin treatment; 6. Must have a smartphone that supports the Dexcom app download and participants must be willing to use the app throughout the study; 7. Investigator has confidence that the participant can safely operate all study devices and can adhere to the protocol; 8. Willing to wear the system continuously throughout the study; and 9. Willing and able to sign the Informed Consent Form.	1. Any medical condition, such as untreated malignancy, unstable cardiac disease, unstable or end- stage renal failure, eating disorders, or other conditions which in the opinion of the investigator, would put the participant at an unacceptable safety risk; 2. History of severe hypoglycemia in the past 6 months; 3. History of diabetes-related ketoacidosis in the past 6 months, unrelated to an intercurrent illness or infusion set failure; 4. Blood disorder or dyscrasia within 3 months prior to screening, including use of hydroxyurea, which in the investigator's opinion could interfere with determination of glycated hemoglobin; 5. Currently on systemic steroids or intends to receive systemic steroid treatment in the next 6 months, including stable treatment for adrenal insufficiency. Inhaled, ophthalmic, topical, joint injection, and other locally applied steroids are allowed; 6. Unable to tolerate adhesive tape or has any unresolved skin condition in the area of sensor or pump placement; 7. Use of non-insulin anti-hyperglycemic medication other than metformin, in the 12 weeks prior to the Baseline Visit. Participants taking metformin should remain on a steady dose during study participation; 8. Pregnant or lactating, or is a woman of childbearing potential and not on acceptable form of birth control (acceptable forms of contraception include abstinence, barrier methods such as condoms, hormonal contraceptives, intrauterine device, surgical sterilization such as tubal ligation or hysterectomy, or vasectomized partner); 9. Participation in another clinical study using an investigational drug or device within 30-days or 5 half-lives (whichever is longer) prior to screening, or intends to participate in any other study during this study period; or 10. Unable to follow clinical protocol for the duration of the study or is otherwise deemed unacceptable to participate in the study per the investigator's clinical judgment. 11. Participant is an employee of Insulet, an Investigator or Investigator's study team, or immediate family member of any of the aforementioned

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Tubeless Omnipod 5 automated insulin delivery (AID) system	Usual home care: insulin pump + CGM	13 weeks	Continuous insulin infusion	194 participants	132 participants	62 participants	Adults aged 18-70 years	The primary outcome was a treatment group comparison of time in range (TIR) (70-180 mg/dL) during the trial period.	The secondary glycemic outcomes, which were tested in a hierarchical order to maintain the type I error rate at 5.0%, were •percentage of time <54 mg/dL (noninferiority with a 1.0% margin) •percentage of time >180 mg/dL, •mean glucose •change from baseline in HbA1c and •percentage of time <70 mg/dL during the 13-week trial period	TIR during the trial was 4.2h/day higher in the intervention compared with the control group (mean difference 17.5% [95% CI 14.0%, 21.1%]; P < 0.0001)	The intervention group had a greater reduction in HbA1c from baseline compared with the control group intervention group : (mean ± SD -1.24 ± 0.75% [-13.6 ± 8.2 mmol/mol] vs. control group : -0.68 ± 0.93% [-7.4 ± 10.2 mmol/mol], respectively; P < 0.0001

Trial 31
M. Lei et al., 2025
NA

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
M. Lei et al., 2025	NA	Randomised Controlled Trial (RCT)-crossover	China	NA	No (open-label)	Yes (1:1)	Yes Noncommunicable Chronic Diseases National Science and Technology Major Project Diabetes mellitus research fund program from Shanghai Medical and Health development foundation	Adults with T1DM Aged 18-75 years Glycated haemoglobin (HbA1c) 7%-11% (53-97 mmol/mol) and Who have never used AID previously	NA

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Android-version hybrid OS-AID (AAPS)	Sensor-augmented insulin pump (SAP)	26 weeks	Continuous insulin infusion	28 participants	28 participants	28 participants	Adults aged 18-75 years	The primary endpoint was the percentage of time in range (TIR, 70-180 mg/dL [3.9-10.0 mmol/L]) during the final two weeks of each treatment phase.	NA	The percentage of TIR (70-180 mg/dL [3.9-10.0 mmol/L]) during the AAPS phase was AAPS phase : 75.6 ± 10.3% SAP phase : 60.4 ± 15.1% significantly higher than the one observed during the SAP phase ($p < 0.01$)	NA

Trial 32
T. Battelino et al., 2025
NCT05574062

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
T. Battelino et al., 2025	NCT05574062	Randomised Controlled Trial (RCT)-crossover	Finland Italy Slovenia United Kingdom	Multi-center	No (open-label)	Yes (1:1)	Yes Medtronic	1. Aged 2 - 6 years at time of screening 2. Has a clinical diagnosis of type 1 diabetes for ≥ 6 months prior to screening as determined via medical record or source documentation by an individual qualified to make a medical diagnosis 3. Is on MDI therapy or CSII with or without CGM prior to screening 4. Has a glycosylated hemoglobin (HbA1c) < 11% (97 mmol/mol) at time of screening visit as processed by a Local Lab 5. Is using or willing to switch to one of the following commercialized available insulins: Humalog (insulin lispro injection) and NovoLog (insulin aspart). 6. Must have a minimum daily insulin requirement (Total Daily Dose) of ≥ 6 units 7. Parent(s)/legal guardian(s) willing to upload data from the pump system, must have Internet access, a compatible computer or mobile phone that meets the requirements for uploading the study pump data at home. 8. Is living with one or more parent(s)/legal guardian(s) knowledgeable about emergency procedures for severe hypoglycemia and able to contact emergency services and study staff. 9. Investigator has confidence that the parent(s)/legal guardian(s) can successfully operate all study devices and is capable of adhering to the protocol 10. Subject and parent(s)/legal guardian(s) willingness to participate in all training sessions as directed by study staff. 11. Subject's parent/legal guardian must be willing and able to provide written informed consent.	1. Has Addison's disease, growth hormone deficiency, coeliac disease, hypopituitarism or definite gastroparesis, untreated thyroid disorder, or poorly controlled asthma, per investigator judgment. 2. Is using any anti-diabetic medication other than insulin at the time of screening or plan of using during the study (e.g. pramlintide, DPP-4 inhibitor, GLP-1, agonists/mimetics, metformin, SGLT2 inhibitors). 3. Has taken any oral, injectable, or intravenous (IV) glucocorticoids within 8 weeks from time of screening visit, or plans to take any oral, injectable, or IV glucocorticoids during the course of the study. 4. Has had renal failure defined by creatinine clearance <30 ml/min, as assessed by local lab test ≤6 months before screening or performed at screening at local lab, as defined by the creatinine-based Cockcroft, CKD-EPI or MDRD equations. 5. Has any unresolved adverse skin conditions in the area of sensor placement (e.g. psoriasis, dermatitis herpetiformis, rash, Staphylococcus infection). 6. Is under Control IQ or CamAPS FX or other advanced hybrid closed loop therapy (e.g. DIY, MiniMed 780G) in the previous 3 months before enrollment. Note: For the continuation phase only, subjects using MiniMed 780G can be enrolled. 7. Is actively participating in an investigational study (drug or device) wherein he/she has received treatment from an investigational study drug or device in the last 2 weeks before enrollment into this study, as per investigator judgment. 8. Has any other disease or condition that may preclude the patient from participating in the study, per investigator judgment. 9. History of >1 DKA event not related to illness or initial diagnosis in the last 3 months. 10. Parent(s)/legal guardian(s) are part of research staff involved with the study. 11. Parent(s)/legal guardian(s) are illiterate

Intervention characteristics				Participant characteristics				Outcomes				
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**	
Yes Medtronic	Advanced Hybrid Closed Loop (AHCL) therapy (MiniMed 780G system in Auto Mode)	Predictive low-glucose suspend (780G system in Manual Mode with SBL activated)	26 weeks	Continuous insulin infusion	98 participants	98 participants	98 participants	Children 2-6 years old	The primary endpoint was the between-treatment difference for auto mode versus manual+SBL mode in the percentage of time in range (TIR, 70-180 mg/dL), expressed as the least-squares mean difference adjusted for sequence effect and run-in TIR, and assessed for non-inferiority (margin 7·5 percentage points)	Secondary endpoints were : - the adjusted between-treatment difference in mean HbA1c at the end of each 12-week period assessed for non-inferiority (margin 0·4 percentage points) and - the adjusted between-treatment difference in mean TIR and HbA1c assessed for superiority.	Mean TIR was 58·1% (SD 14·3) in the run-in phase in auto mode : 68·3% (6·9) in manual+SBL mode : 58·3% (12·5) (adjusted between-treatment difference 9·9 percentage points [95% CI 8·0 to 11·7]; non-inferiority met for the primary endpoint with superiority for auto mode)	Mean HbA1c was 7·53% (SD 0·96; 58·8 mmol/mol [SD 10·5]) in auto mode : 7·00% (0·53; 53·0 mmol/mol [5·8]) in manual+SBL mode : 7·61% (0·91; 59·7 mmol/mol [9·9]) (between-treatment difference: -0·61 percentage points [95% CI -0·76 to -0·46; non-inferiority met with superiority for auto mode)

Trial 33
B. P. Kovatchev et al., 2020
NCT04142229

Study characteristics									
Author-year	NCT Number	Study Design	Country	Centers	Blinding	Randomisation NA - crossover trials	Funding	Inclusion criteria	Exclusion criteria
B. P. Kovatchev et al., 2020	NCT04142229	Randomised Controlled Trial (RCT)-crossover	United States	Single-center	No (open-label)	Yes (1:1)	NA	1. Type 1 diabetes for at least one year 2. Using insulin for at least 1 year 3. An insulin pump for at least 6 months 4. Willingness to switch to lispro (Humalog) or aspart (Novolog) if using glulisine (Apidra)	A medical condition or being been treated with medications that might interfere with the study

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	Standard insulin therapy	Duration of trial	Dosing frequency	Total number of participants (n)	Number of participants in hybrid closed-loop system (n)	Number of participants in standard insulin delivery	Age group	Primary endpoint	Secondary endpoint	Glucose target	Glycated haemoglobin A1c
E-N CLC / 24-7 CLC Evening and Overnight Closed-Loop Control=SAP during day and CLC starting at dinner and continuing overnight 24/7 Closed-Loop Control=24-hour Day and Night Closed Loop Control	Sensor-augmented pump (SAP)	32 weeks	Continuous insulin infusion	93 participants	93 participants	93 participants	Adults aged 18-70 years	Overnight CLC achieved by USS+SAP(d) (also known at Evening-Night CLC) will be superior to SAP alone in terms of reduced incidence and risk for hypoglycemia overnight without deterioration in hemoglobin A1c. Outcomes will be stratified by Hemoglobin A1c < 7.5% vs ≥7.5% and time of day. Overnight CLC achieved by USS+SAP(d) (also known as Evening-Night CLC) will be superior to SAP alone in terms of reduced incidence and risk for hypoglycemia overnight without deterioration in hemoglobin A1c. Outcomes will be stratified by Hemoglobin A1c < 7.5% vs ≥7.5% and time of day.	• Time in target range 70-180 mg/dL measured by CGM • Time in hyperglycemia range >180 mg/dL measured by CGM • Mean glucose measured by CGM overall in mmol/L • Index measure of low blood glucose risk. This is an index that indicates risk of hypoglycemia with low values indicating lower risk of hypoglycemia (particularly values 1 or lower) • Index measure of high blood glucose risk • Percentage time <70mg/dL measured by CGM in three study phases combining Group A and B • Hemoglobin A1c after each 8 weeks study session by Group A and Group B	Compared to SAP, E-N CLC reduced overall time <70mg/dL from 4.0% to 2.2% () resulting in an absolute difference of 1.8% (95%CI: 1.2-2.4%), p<0.0001	Overall reduction in HbA1c from 7.4% at baseline to 7.1% at the end of study, resulting in an absolute difference of 0.3% (95% CI: 0.1-0.4%), p<0.0001

Trial 34
C K Boughton et al., 2023
NCT04977908

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
C K Boughton et al., 2023	NCT04977908	Randomised Controlled Trial (RCT)-crossover	United Kingdom	Single-center	No (open-label)	Nαι (Group A/B sequence)	NA	1. The participant has type 1 diabetes as defined by WHO for at least 1 year 2. The participant is 18 years of age or older 3. The participant will have been on an insulin pump for at least 6 months with good knowledge of insulin self-adjustment 4. The participant is treated with one of the rapid acting or ultra-rapid acting insulin analogues (Insulin Aspart, faster acting insulin Aspart, Insulin Lispro, ultra-rapid Lispro insulin or Insulin Glulisine) 5. HbA1c ≥8.0% (64 mmol/mol) based on analysis from local laboratory 6. The participant is willing to wear closed-loop devices 7. The participant is willing to follow study specific instructions 8. Female participants of child bearing age should using effective contraception and must have a negative urine-HCG pregnancy test at screening.	1. Any physical or psychological disease or condition likely to interfere with the normal conduct of the study and interpretation of the study results 2. Known or suspected allergy against insulin 3. Total daily insulin dose > 2 IU/kg/day 4. Use of a closed-loop system within the past 30 days 5. Participant is pregnant or breast feeding or planning pregnancy within next 12 months 6. Severe visual impairment 7. Severe hearing impairment 8. Lack of reliable telephone facility for contact 9. Participant not proficient in English

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Fully closed-loop with ultrarapid insulin lispro (CamAPS HX system)	Insulin pump therapy with CGM	16 weeks	Continuous insulin infusion	26 participants	26 participants	26 participants	Adult (≥18 years)	Time spent in the target glucose range from 3.9 to 10.0 mmol/l (70 to 180mg/dl) based on continuous glucose monitoring (CGM)	• Time spent above target glucose (10.0 mmol/l) (180 mg/dl) based on CGM • Time spent below target glucose (3.9mmol/l) (70mg/dl) based on CGM • Average of sensor glucose levels • Standard deviation and coefficient of variation of CGM glucose levels • Time with glucose levels < 3.0 mmol/l (54mg/dl) based on CGM • Time with glucose levels >13.9 mmol/l (250mg/dl) and > 16.7 mmol/l) (300mg/dl) • Glycated haemoglobin measured at the end of the treatment period • Total, basal, and bolus insulin dose	The proportion of time glucose was in range (primary end point 3.9-10.0 mmol/L) was higher during closed-loop than during pump with CGM (mean ± SD 50.0 ± 9.6% vs. 36.2 ± 12.2%, mean difference 13.2 percentage points [95% CI 9.5, 16.9], P < 0.001)	NA

Trial 35
N. Kadiyala et al., 2025
NCT05653050

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
N. Kadiyala et al., 2025	NCT05653050	Randomised Controlled Trial (RCT)-crossover	United Kingdom	2 centers	No (open-label)	NA	NA	1. The participant has type 1 diabetes as defined by WHO for at least 1 year 2. The participant is aged 13 to 19 years (inclusive) (Phase 2) 3. The participant will have been on an insulin pump for at least 3 months with good knowledge of insulin self-adjustment 4. The participant is treated with one of the rapid acting or ultra-rapid acting insulin analogues (Insulin Aspart, faster acting insulin Aspart, Insulin Lispro, ultra-rapid Lispro insulin or Insulin Glulisine) 5. HbA1c ≥7.5% (58mmol/mol) based on analysis from local laboratory 6. The participant is willing to wear closed-loop devices 7. The participant is willing to follow study specific instructions 8. Female participants of child bearing age must have a negative urine-HCG pregnancy test at screening and should be using effective contraception if sexually active.	1. Any physical or psychological disease or condition likely to interfere with the normal conduct of the study and interpretation of the study results 2. Known or suspected allergy against insulin 3. Total daily insulin dose more than or equal to 2 IU/kg/day 4. Use of a closed-loop system within the past 30 days 5. Participant is pregnant or breast feeding or planning pregnancy within next 12 months 6. Severe visual impairment 7. Severe hearing impairment 8. Lack of reliable telephone facility for contact 9. Participant not proficient in English

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Fully closed-loop (CamAPS HX) with Fiasp	Standard nonautomated insulin pump therapy with CGM	16 weeks	Continuous insulin infusion	24 participants	24 participants	24 participants	Participants aged 13 to 19 years	The primary endpoint was the percentage of time with sensor glucose was in the target range between 3.9 and 10.0 mmol/L during the eight-week study periods	Secondary endpoints included : - percentage of time spent at glucose levels <3.0 mmol/L - percentage of time spent at glucose levels <3.9 mmol/L - percentage of time spent at glucose levels >10.0 mmol/L - percentage of time spent at glucose levels >13.9 mmol/L, - percentage of time spent at glucose levels >16.7 mmol/L - mean sensor glucose - glucose variability measured by the standard deviation (SD) and coefficient of variation (CV) of sensor glucose levels - HbA1c and - insulin metrics (total, basal, and bolus amounts).	The percentage of time glucose was in target range (primary endpoint 3.9-10.0 mmol/L) was higher during FCL than during pump with CGM use -FCL : 45.2% ± 7.2% (mean ± standard deviation [SD]) -CGM : 32.3% ± 12.8% (mean ± standard deviation [SD]) mean difference 12.9 percentage points, 95% confidence interval [CI] 8.5 to 17.3, P < 0.001)	There was no difference in HbA1c after FCL compared with pump with CGM (median:71 mmol/mol (8.6%) vs. 74 mmol/mol (8.9%), P = 0.227)

Trial 36
M. B. Abraham et al., 2025
NA

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
M. B. Abraham et al., 2025	NA	Randomised Controlled Trial (RCT)	United States	Multi-center	No (open-label)	Yes (1:1)	Yes Juvenile Diabetes Research Foundation (JDRF) Australia Type 1 Diabetes Clinical Research Network a Special Research Initiative of the Australian Research Council National Health and Medical Research Council	1. Participants aged between 12 and 25 years 2. Type 1 diabetes for more than a year 3. Fasting C-peptide of <0.1 nmol/L 4. Mean HbA1c over 6 months and 5. Recent HbA1c >8.5% (65 mmol/mol) on CSII with or without CGM (CSII ± CGM).	1. Use of any form of closed-loop system 2. Experienced severe diabetic ketoacidosis (DKA) in the 6 months prior to the screening visit 3. Had used any noninsulin glucose-lowering agent within the preceding 3 months 4. Commenced CGM in the 3 months prior to the screening visit 5. Had uncontrolled celiac or thyroid disease or clinically significant gastroparesis 6. Pregnancy or planned pregnancy 7. Unable or unwilling to meet protocol requirements 8. Being in an unstable medical or psychological condition which, in the opinion of the treating physician and/or investigator, would compromise the ability to meet protocol requirements.

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Advanced hybrid closed-loop system	CSII ± CGM	6 months	Continuous insulin infusion	42 participants	21 participants	21 participants	Participants aged between 12 and 25 years	The primary outcome was the 24-week between-group difference in HbA1c	Secondary outcomes included : -CGM metrics from masked CGM and -Psychological measures (youth-reported problem areas in diabetes [PAID], quality of life, anxiety, depression, and hypoglycemia fear) assessed using validated questionnaires.	AHCL increased time in range 70-180 mg/dL (difference 19.1%; 95% CI 11.1 to 27.1)	The mean (SD) HbA1c was : with AHCL : 8.8 (1.1)% or 73 (12) mmol/mol with CSII ± CGM : 9.9 (1.2)% or 85 (13.1) mmol/mol with mean adjusted group difference of -0.77% (95% CI -1.45 to -0.09) or -8.4 mmol/mol (-15.8 to -1.0); P = 0.027

Trial 37
H Thabit et al., 2015
NCT01961622 & NCT01778348

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
H Thabit et al., 2015	NCT01961622 & NCT01778348	Randomised Controlled Trial (RCT)-crossover	For adults Austria Germany United Kingdom For children & adolescents United Kingdom	Multi-center	No (open-label)	NA	NA	For adults 1. The subject has type 1 diabetes as defined by WHO 2. The subject is 18 years of age or older 3. The subject will have been on an insulin pump for at least 6 months with good knowledge of insulin self-adjustment including carbohydrate counting 4. The subject is treated with one of the rapid acting insulin analogues (Insulin Aspart, Insulin Lispro or Insulin Glulisine) 5. HbA1c ≥7.5% (58mmol/mmol) and ≤ 10% (86 mmol/mmol) based on analysis from central laboratory or equivalent 6. The subject is willing to perform regular finger-prick blood glucose monitoring, with at least 6 measurements per day 7. The subject is willing to wear closed-loop system at home and at work place 8. The subject is willing to follow study specific instructions 9. The subject is willing to upload pump and CGM data at regular intervals 10. Female subjects of child bearing age should be on effective contraception and must have a negative urine-HCG pregnancy test at screening. In addition in Germany, women of childbearing potential must use a highly effective method of birth control, which is defined as those which result in a low failure rate (i.e. less than 1% per year) and must use two independent methods of contraception, e.g. diaphragm and spermicide-coated condom For children & adolescents 1. The subject is between 6 and 18 years of age (inclusive) 2. The subject has type 1 diabetes, as defined by WHO for at least 1 year or is confirmed C-peptide negative 3. The subject will have been an insulin pump user for at least 3 months, with good knowledge of insulin self-adjustment as judged by the investigator 4. The subject is willing to perform regular finger-prick blood glucose monitoring, with at least 4 blood glucose measurements taken every day 5. HbA1c ≤ 10 % based on analysis from central laboratory or equivalent 6. The subject is literate in English	For adults 1. Non-type 1 diabetes mellitus 2. Any other physical or psychological disease or condition likely to interfere with the normal conduct of the study and interpretation of the study results 3. Current treatment with drugs known to have significant interference with glucose metabolism, such as systemic corticosteroids, as judged by the investigator 4. Known or suspected allergy against insulin 5. Subjects with clinically significant nephropathy, neuropathy or proliferative retinopathy as judged by the investigator 6. Significantly reduced hypoglycaemia awareness as judged by the investigator 7. More than one episode of severe hypoglycaemia as defined by American Diabetes Association (31) in preceding 6 months (Severe hypoglycaemia is defined as an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions). 8. Random C-peptide > 100pmol/l with concomitant plasma glucose >4 mM(72 mg/dl) 9. Total daily insulin dose > 2 IU/kg/day 10. Subject is pregnant or breast feeding or planning pregnancy in near future (within next 3 months) 11. Severe visual impairment 12. Severe hearing impairment 13. Subjects using implanted internal pacemaker 14. Lack of reliable telephone facility for contact 15. Subject not proficient in English (UK) or German (Germany and Austria) 16. Subjects who are living alone For children & adolescents 1. Non-type 1 diabetes mellitus including those secondary to chronic disease 2. Untreated celiac disease 3. Any other physical or psychological disease likely to interfere with the normal conduct of the study and interpretation of the study results as judged by the investigator 4. Current treatment with drugs known to interfere with glucose metabolism, e.g. systemic corticosteroids, non-selective beta-blockers and MAO inhibitors etc. 5. Known or suspected allergy against insulin 6. Subjects with clinical significant nephropathy, neuropathy or proliferative retinopathy as judged by the investigator 7. Total daily insulin dose ≤ 2 IU/kg/day 8. Total daily insulin dose < 10 IU/day 9. Pregnancy, planned pregnancy, or breast feeding 10. Severe visual impairment 11. Severe hearing impairment 12. Subjects using implanted internal pace-maker

Intervention characteristics				Participant characteristics				Outcomes				
Hybrid closed-loop system	Standard insulin therapy	Duration of trial	Dosing frequency	Total number of participants (n)	Number of participants in hybrid closed-loop system (n)	Number of participants in standard insulin delivery	Age group	Primary endpoint	Secondary endpoint	Glucose target	Glycated haemoglobin A1c	
Yes JDRF	Closed-loop system	Sensor-augmented pump therapy (open-loop)	24 weeks	Continuous insulin infusion	58 participants	Day and night by 33 adults and Overnight by 25 children and adolescents.	58 participants	Participants aged 6 years old and older	The primary end point was the proportion of time that the glucose level was between 70 mg and 180 mg per deciliter for adults and between 70 mg and 145 mg per deciliter for children and adolescents.	For adults • Measure of average glycaemic control during study period • Total, basal and bolus insulin dose during 90 days of home periods • Safety evaluation will comprise the number of episodes of hypoglycaemia, significant ketonemia (> 3.0mmol/l)as well as nature and severity of any other adverse events • Utility evaluation is the frequency and duration of use of the closed-loop system at home and time between failures of closed-loop system components • Time spent above and below the target glucose 3.9 to 10.0 mmol/l, during the 90 days of home periods • Average,standard deviation and coefficient of variation of glucose levels during 90 days of home periods • The time with glucose levels < 3.5 mmol/l and <2.8 mmol/l during 90 days of home periods • The time with glucose levels in the significant hyperglycaemia,(glucose levels > 16.7 mmol/l during 90 days of home periods • Low Blood Glucose Index during 90 days of home periods • Duration of periods when sensor glucose values was below 3.5mmol/l for at least 20 minutes • The "Area Under the Curve" below 3.5 mmol/l during 90 days home periods • Between 24 hour period variability: Coefficient of variation of CGM glucose between 24 hour periods (midnight to midnight) • Glucose concentration in the target range (3.9-10.0mmol/L), and above and below target range based on adjusted CGM • Time spent with CGM glucose concentration in the target range (3.9-8.0mmol/L), Mean CGM glucose levels, The AUC below	Among adults, the proportion of time that the glucose level was in the target range was 11.0 percentage points (95% confidence interval [CI], 8.1 to 13.8) greater with the use of the closed-loop system day and night than with control therapy (P<0.001) Among children and adolescents, the proportion of time with the nighttime glucose level in the target range was higher during the closed-loop phase than during the control phase (by 24.7 percentage points; 95% CI, 20.6 to 28.7; P<0.001)	NA

										3.5mmol/l, CV of CGM glucose levels, Coefficient of variation of CGM glucose between nights and Total insulin dose during overnight period between 23:00 and 08:00 • Time spent with CGM glucose concentration in the target range (3.9-10.0mmol/L), Mean CGM glucose levels, The AUC below 3.5mmol/l, CV of CGM glucose levels, Coefficient of variation of CGM glucose between days and Total insulin dose during day period between 08:00 to 23:00 For children and adolescents • The proportion of nights when glucose levels drop below 3.5 mmol/l for 20 minutes or longer, as recorded by CGM • Time spent above and below the target glucose (3.9 to 8.0 mmol/l) based on CGM • The time with glucose levels in the significant hyperglycaemia range (glucose levels > 16.7 mmol/l) as recorded by CGM • Metabolic control assessed by HbA1c • Average and standard deviation of glucose levels, as recorded by CGM • The time with glucose levels < 3.5 mmol/l as recorded by CGM • The time with glucose levels in the widened target range, as recorded by CGM (glucose levels ≥ 3.9mmol/l to ≤ 10.0mmol/l) • Low Blood Glucose Index (LBGI), as recorded by CGM • Standard deviation of the glucose rate of change, as recorded by CGM • Overnight insulin dose • Total daily insulin dose • Episodes of symptomatic hypoglycaemia		

Trial 38
N. Nanayakkara etal., 2024
ACTRN12620001191987

Study characteristics									
Author-year	NCT Number	Study Design	Country	Centers	Blinding	Randomisation NA - crossover trials	Funding	Inclusion criteria	Exclusion criteria
N. Nanayakkara etal., 2024	ACTRN12620001191987	Randomised Controlled Trial (RCT)-crossover	Australia	Single-center	No (open-label)	NA	Yes Ypsomed Australia Pty Ltd Baker Heart and Diabetes Institute	• Type 1 diabetes greater than or equal to 6 months duration • Adults age greater than or equal to 18 years • Insulin pump therapy greater than or equal to 6 months duration • HbA1c less than 10.0%	• Pregnancy • Current use of real time CGM in the previous 3 months • Hospitalization for severe hypoglycaemia or ketoacidosis in the past 6 months • Chronic kidney disease (eGFR < 45 mL/min/1.73m2) • Planned international travel during the study period • Oral hypoglycaemic agents or non insulin injectable agents within past 4 weeks

Intervention characteristics				Participant characteristics				Outcomes				
Hybrid closed-loop system	Standard insulin therapy	Duration of trial	Dosing frequency	Total number of participants (n)	Number of participants in hybrid closed-loop system (n)	Number of participants in standard insulin delivery	Age group	Primary endpoint	Secondary endpoint	Glucose target	Glycated haemoglobin A1c	
Yes Ypsomed Australia Pty Ltd Baker Heart and Diabetes Institute	Hybrid Closed loop Android Artificial Pancreas System	Usual pump	8 weeks	Continuous insulin infusion	20 participants	20 participants	20 participants	Adult (≥18 years)	Percentage of CGM time in target range (3.9-10.0 mmol/L) with AndroidAPS vs conventional pump therapy as measured by masked CGM (iPro®2) in the final week of 4 week-study arm	• Percentage of CGM time in target range (3.9-10.0 mmol/L) with AndroidAPS vs conventional pump therapy as measured by masked CGM (iPro®2) in the final week of 4 week-study arm. • Mean sensor glucose value with AndroidAPS compared vs conventional pump therapy as measured by masked CGM (iPro®2) in the final week of 4 week-study arm. • Percentage of CGM time in hypoglycaemia range (< 3.9 mmol/L) with AndroidAPS compared vs conventional pump therapy as measured by masked CGM (iPro®2) in the final week of 4 week-study arm. • Percentage of CGM time in clinically significant hypoglycaemia range (< 3.0 mmol/L) with AndroidAPS vs conventional pump therapy as measured by masked CGM (iPro®2) in the final week of 4 week-study arm. • Percentage of CGM time in hyperglycaemia range (> 10.0 mmol/L) with AndroidAPS vs conventional pump therapy as measured by masked CGM (iPro®2) in the final week of 4 week-study arm. • Percentage of CGM time in significant hyperglycaemic range (> 13.9 mmol/L) with AndroidAPS vs conventional pump therapy as measured by masked CGM (iPro®2) in the final week of 4 week-study arm. • Parameters of Glycaemic variability will be assessed by measuring standard deviation of the mean (SD) , co-efficient of variation (CV) and Mean Amplitude of	The change in TIR from baseline for AAPS compared with stand-alone pump therapy was 18.6% (11.4-25.9), (P < .001), TIR 76.6% ± 11.7%, 58.0% ± 15.6%, for AAPS and stand-alone pump, respectively	NA

										Glycaemic Excursion (MAGE) with AndroidAPS vs conventional pump therapy as measured by masked CGM (iPro®2) in the final week of 4 week-study arm. • Number of symptomatic episodes of hypoglycaemia with AndroidAPS vs conventional pump therapy as reported by participants and documented in their study diary. • Entire duration (week 1-4) for each of the intervention and control periods. • Number of severe adverse events (severe hypoglycaemic and diabetic ketoacidosis) with AndroidAPS vs conventional pump therapy as reported by the participant or determined by the study team. • Average total daily dose of insulin with AndroidAPS vs conventional pump therapy as per uploaded insulin pump data. • Change in body weight with AndroidAPS compared with conventional pump therapy as measured by study team. Body weight will be measured by digital scale. • Treatment satisfaction with AndroidAPS compared with conventional pump therapy as assessed by Diabetes Treatment Satisfaction Questionnaire (DTSQ) • Diabetes distress with AndroidAPS compared with conventional pump therapy as assessed by Problem Areas in Diabetes (PAID) • Fear of hypoglycaemia with AndroidAPS compared with conventional pump therapy as assessed by Hypoglycaemia Fear Survey-II short form • Hypoglycaemia awareness with AndroidAPS compared with conventional pump therapy as assessed by Clarke hypoglycaemia awareness survey.		

Trial 39
S M Anderson et al., 2019
NCT02302963

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
S M Anderson et al., 2019	NCT02302963	Randomised Controlled Trial (RCT)	United States	2 centers	No (open-label)	Yes (1:1)	Yes NIH NIDDK	1. Aged 12–70 years 2. Type 1 diabetes on insulin for ≥1 year 3. On insulin pump therapy for ≥6 months 4. HbA1c <10.0% (86 mmol/mol) (if HbA1c <6.0% [42 mmol/mol] then total daily insulin had to be ≥0.5 U/kg). 5. Subjects had a risk of hypoglycemia or hypoglycemia unawareness as defined by any of the following: (1) Clarke Hypoglycemia Perception Awareness questionnaire score of ≥415 (2) average daily risk range (ADRR) >40 as assessed from SMBG readings from the prior month16 (3) low blood glucose index (LBGI) >2.5 as assessed from SMBG from the prior month17 or LBGI >1.1 as assessed from 1 week of continuous glucose monitoring (CGM) readings18 (4) no recognition of hypoglycemia until the glucose is <60 mg/dL (<3.3 mmol/L) and no adrenergic symptoms at glucose of 60 mg/dL (3.3 mmol/L) (shakiness, palpitations, diaphoresis) Additional eligibility criteria included the ability to speak and read English Use basic technology such as a cell phone Current use of an insulin-to-carbohydrate ratio Access to Internet or cell phone service in the subject's local environment Willingness to maintain uninterrupted availability via personal cell phone Willingness to perform SMBG testing four to six times daily (before meals, bedtime, before driving, before exercise, and as indicated) Living with a diabetes care partner ≥18 years old	1. Admission for diabetic ketoacidosis in the 12 months prior to enrollment. 2. Severe hypoglycemia resulting in seizure or loss of consciousness in the 3 months prior to enrollment. 3. Hematocrit less that the lower limit of normal for the assay. 4. Pregnancy, breast-feeding, or intention of becoming pregnant over time of study procedures 5. If female and sexually active, must agree to use a form of contraception to prevent pregnancy while a participant in the study. A negative urine pregnancy test will be required for all premenopausal women who are not surgically sterile. 5. Subjects who become pregnant will be discontinued from the study. 6. Conditions which may increase the risk of induced hypoglycemia such as: known coronary artery disease, congestive heart failure, history of any cardiac arrhythmia (benign premature atrial contractions and premature ventricular contractions allowed), history of seizure disorder, history of cerebrovascular event or transient ischemic attack, hypoglycemia-induced migraine within the last 6 months, or neurological disease. 7. Cystic fibrosis 8. A known medical condition that in the judgment of the investigator might interfere with the completion of the protocol such as the following examples: o Inpatient psychiatric treatment in the past 6 months for either the subject or the subject's diabetes care partner o Presence of a known adrenal disorder o Abnormal liver function tests (transaminase >3 times the upper limit of normal); testing required for subjects taking medications known to affect liver function or with diseases known to affect liver function o Abnormal renal function test results (estimated GFR <60 mL/min/1.73m2); testing required for subjects with diabetes duration of greater than 5 years post onset of puberty o Active gastroparesis o If on antihypertensive, thyroid, anti-depressant or lipid lowering medication, lack of stability on the medication for the past 2 months prior to enrollment in the study o Uncontrolled thyroid disease (TSH undetectable or >10 mIU/L); testing required within 3 months prior to admission for subjects with a goiter, positive antibodies, or who are on thyroid hormone replacement, and within one year otherwise o Current or recent abuse of alcohol or recreational drugs by patient history o Infectious process not anticipated to resolve prior to study procedures (e.g. meningitis, pneumonia, osteomyelitis) o Any skin condition in the area of insertion that prevents safe sensor or pump placement (e.g. bad sunburn, pre-existing dermatitis, intertrigo, psoriasis, extensive scarring, cellulitis) o Diagnosed with celiac disease and not currently following a gluten free diet 9. A recent injury to body or limb, muscular disorder, use of any medication, any carcinogenic disease, or other significant medical disorder if that injury, medication, or disease in the judgment of the investigator will affect the completion of the protocol 10. Current use of any of the following drugs and supplements: o Any medication being taken to lower blood glucose, such as Pramlintide, Metformin, GLP-1 Analogs such as Liraglutide, and nutraceuticals intended to lower blood glucose o Beta blockers o Oral glucocorticoids o Pseudoephedrine o Any other medication that the investigator believes is a contraindications to the subject's participation

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Hybrid CLC (HCLC)	Sensor-augmented pump (SAP) therapy	4 weeks	Continuous insulin infusion	42 participants	21 participants	21 participants	Participants aged 18-70 years	Reduction in hypoglycemia during the study on USS Virginia versus SAP as assessed by: LBGI from CGM during 1 week of baseline blinded use versus during the last week of intervention.	1. Reduction in hypoglycemia during the study on USS Virginia versus SAP as assessed by: CGM time <70 mg/dL and <50 mg/dL by retrofitted CGM and SMBG trace during a 24 hour period and the overnight period (11PM – 7AM) from 1 week of baseline blinded use versus the last week of intervention. 2. Improvement in counterregulatory response to hypoglycemia at baseline versus follow-up as assessed by: - Peak epinephrine - Epinephrine area under the curve (AUC) - Epinephrine increase over baseline 3. Improvement in hypoglycemia awareness at baseline versus follow-up as assessed by: - Hypoglycemia symptom ratings - Clarke Hypoglycemia Perception Awareness and Fear of Hypoglycemia scores 4. Improvement in glycemic control at baseline versus the last week of intervention as assessed by: - Time within target (70-180 mg/dL) over a 24 hour period. - Time within target (80-140 mg/dL) in the overnight period (11PM – 7AM) - Distribution of wake-up glucose levels at 7AM	Percent time within the target range 70-180 mg/dL (3.9-10 mmol/L) increased on HCLC (67.8% ± 13.5% to 78.2% ± 10%) but decreased on SAP (65.6% ± 12.9% to 59.6% ± 16.5%) P < 0.001	NA

Trial 40
C K Boughton et al., 2022
NCT04025762

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
C K Boughton et al., 2022	NCT04025762	Randomised Controlled Trial (RCT)-crossover	United Kingdom Austria	Multi-center	No (open-label)	NA	NA	1. Age 60 years and above 2. Type 1 diabetes as defined by WHO for at least 1 year or confirmed C-peptide negative 3. On insulin pump for at least 3 months with good knowledge of insulin self-adjustment 4. Treated with one of the U-100 rapid acting insulin analogues only (insulin Aspart, Lispro, Faster insulin Aspart but not Glulisine) 5. Willing to perform regular capillary blood glucose monitoring 6. HbA1c ≤ 10% (86 mmol/mmol) based on analysis from central laboratory or equivalent 7. Literate in English 8. Having a care partner who is aware of the subject's location and is trained to administer intramuscular glucagon and able to seek emergency assistance 9. Willing to wear closed-loop system at home and at work place 10. Willing to follow study specific instructions 11. Willing to upload pump and CGM data at regular intervals 12. Has access to WiFi	1. Non-type 1 diabetes mellitus 2. Use of a closed-loop system within the last 30 days 3. Any other physical or psychological disease or condition likely to interfere with the normal conduct of the study and interpretation of the study results 4. Use of any glucose-lowering agent (such as Pramlintide, Metformin, GLP-1 analogs) in the 3 months prior to enrolment or any use of SGLT2 inhibitors 5. Untreated coeliac disease, adrenal insufficiency or hypothyroidism 6. Known or suspected allergy against insulin 7. More than one episodes of severe hypoglycaemia as defined by American Diabetes Association in preceding 6 months 8. Random C-peptide > 200pmol/l with concomitant plasma glucose >4 mmol/l (72 mg/dl) 9. Lack of reliable telephone facility for contact 10. Total daily insulin dose >/= 2 IU/kg/day 11. Total daily insulin dose < 15 IU/day 12. Severe visual impairment 13. Severe hearing impairment 14. Medically documented allergy towards the adhesive (glue) of plasters or unable to tolerate tape adhesive in the area of sensor placement 15. Serious skin diseases (e.g. psoriasis vulgaris, bacterial skin diseases) located at places of the body, which could potentially be used for localisation of the glucose sensor) 16. Subject is currently abusing illicit drugs 17. Subject is currently abusing prescription drugs 18. Subject is currently abusing alcohol 19. Subject has elective surgery planned that requires general anaesthesia during the course of the study 20. Subject is a shift worker with working hours between 10pm and 8am 21. Subject has a sickle cell disease, haemoglobinopathy; or has received red blood cell transfusion or erythropoietin within 3 months prior to time of screening 22. Subject plans to receive red blood cell transfusion or erythropoietin over the course of study participation 23. Subject diagnosed with current eating disorder such as anorexia or bulimia 24. Subject plans to use significant quantity of herbal preparations (use of over the counter herbal preparation for 30 consecutive days or longer period during the study) or significant quantity of vitamin supplements (four times the recommended daily allowance used for 30 consecutive days or longer period during the study) known to affect glucose metabolism and/or blood glucose levels during the course of their participation in the study 25. Subject not proficient in English (UK), or German (Austria)

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Hybrid closed-loop (CamAPS FX, CamDiab, Cambridge, UK)	Sensor-augmented pump (SAP)	32 weeks	Continuous insulin infusion	37 participants	37 participants	37 participants	Adult (≥60 years)	The primary endpoint was the proportion of time sensor glucose was in target range between 3·9 and 10·0 mmol/L	•HbA1c at the End of the 16 Week Intervention Period (mmol/Mol) •Proportion of Time Spent Below Target Glucose (3.9mmol/l) (70mg/dl) Based on CGM During the 16 Week Intervention Period (%) •Proportion of Time Spent Above Target Glucose (10.0 mmol/l) (180 mg/dl) Based on CGM During the 16 Week Intervention Period (%) •Average (mmol/L) of CGM Glucose Levels During the 16 Week Intervention Period •Proportion of Time With Glucose Levels < 3.5 mmol/l (63mg/dl) Based on CGM During the 16 Week Intervention Period (%) •Proportion of Time With Glucose Levels in the Significant Hyperglycaemia (Glucose Levels > 16.7 mmol/l) (300mg/dl) Based on CGM During the 16 Week Intervention Period (%) •Total Daily Insulin Dose During the 16 Week Intervention Period (Units/Day) •Standard Deviation (mmol/L) of CGM Glucose Levels During the 16 Week Intervention Period •Proportion of Time With Glucose Levels < 3.0 mmol/l (54mg/dl) Based on CGM During the 16 Week Intervention Period (%)	The proportion of time with glucose between 3·9 and 10·0 mmol/L was significantly higher -in the closed-loop group : 79·9% [SD 7·9] compared to - the SAP group :71·4% [13·2] difference 8·6 percentage points [95% CI 6·3 to 11·0]; p<0·0001)	NA

Trial 41
D. Kariyawasam et al., 2022
NCT03671915

Study characteristics									
Author-year	NCT Number	Study Design	Country	Centers	Blinding	Randomisation NA - crossover trials	Funding	Inclusion criteria	Exclusion criteria
D. Kariyawasam et al., 2022	NCT03671915	Randomised Controlled Trial (RCT)-crossover	France Belgium	Multi-center	No (open-label)	Yes (1:1)	Yes Diabeloop	1. Prepubescent children (Gender: both) aged between 6 to 12 years old (Tanner stage 1) at time of screening 2. Type 1 diabetes as defined by WHO for at least 1 year or confirmed C peptide negative 3. An insulin pump user for at least 3 months. 4. Subject having a Glycosylated hemoglobin (HbA1c) blood value < 9% at time of screening visit-based on analysis from local laboratory within 3 months. 5. Subject having a minimum daily insulin requirement (Total Daily Dose) of greater than or equal to 8 units. 6. Subject and his parent/guardian willing to spend 3-overnight in hospital. 7. Subject willing to wear the system continuously throughout the study 8. Subjects and his parent/guardian must be able to speak and be literate in French or Flemish as verified by the investigator	1. Children who are in pubertal stage 2. Subject has a history of 2 or more episodes of severe hypoglycemia, which resulted in any the following during the 6 months prior to screening: - Medical assistance (i.e. Paramedics, Emergency Room (ER) or Hospitalization) - Coma - Seizures 3. Subject having sever DKA in the 6 months prior to screening visit. 4. Known or suspected allergy against insulin 5. Any other physical or psychological disease, or medication likely to interfere with the conduct of the study and interpretation of the study results as judged by the investigator. 6. Subject is unable to tolerate tape adhesive around the sensor or pump placements 7. Subject has a cardiovascular condition which the investigator determines should exclude the subject, i.e. ventricular rhythm disturbance, hypertrophic cardiomyopathy 8. Subject having took any oral, injectable, or intravenous (IV) glucocorticoids within 8 weeks from time of screening visit, or plans to take any oral, injectable, or IV glucocorticoids during the study.

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	Standard insulin therapy	Duration of trial	Dosing frequency	Total number of participants (n)	Number of participants in hybrid closed-loop system (n)	Number of participants in standard insulin delivery	Age group	Primary endpoint	Secondary endpoint	Glucose target	Glycated haemoglobin A1c
Diabeloop for Kids DBL4K hybrid closed-loop system	Sensor-augmented insulin pump therapy	72-h in-patient period was followed by a 6-week home phase	Continuous insulin infusion	21 participants	21 participants	21 participants	Children 6-12 years old	The primary outcome, assessed in the intention-to-treat population, was the mean proportion of time spent in hypoglycaemia (3·9 mmol/L [<70 mg/dL]) during the hospital phase	• Sensor mean glucose over the 72-h, in the overnight (defined as 23:00 to 07:00) and during the home study phase for the French centers, in closed-loop and open-loop session • Coefficient of variation (SD/Mean %) • Standard deviation (SD mg/dl) of the glucose rate of change as recorded by the CGM • Low Blood Glucose Index (LBGI) and high blood glucose Index (HBGI) • Percentage of sensor time in glucose range 70-140 mg/dl • Percentage time in glucose levels in the widened target range 70-180 mg/dl • Fasting blood glucose, mg/dl (mmol/L) • Sensor time spent in glucose levels below 54 mg/dl, 60 mg/dl • Sensor time spent in glucose levels below 54 mg/dl, 60 mg/dl, and 70 mg/dl • Number of severe Hyperglycemic events as well as the number of subjects experiencing sever hypoglycemia • Time spent in glucose levels above 180 mg/dl, 250 mg/dl, 300 mg/dl • Severe Diabetic Ketoacidosis (DKA) events • Percentage of time closed-loop active • Total daily dose of insulin • Subject's perception in terms of life-style change, satisfaction and diabetes management	NA	NA

Trial 42
S. K. Garg et al., 2023
NCT02748018

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
S. K. Garg et al., 2023	NCT02748018	Randomised Controlled Trial (RCT)	United States Canada	Multi-center	No (open-label)	Yes (1:1)	Yes Medtronic	1. Subject is age 2-80 years at time of screening US, Canada, Australia and New Zealand: Subjects 2-80 years of age will be allowed to enroll in the post approval study. Europe: Only subjects ≥7 years of age are allowed to enroll in the post-market study. 2. Subjects who are 2-21 years are determined by the investigator to have the appropriate, requisite support (family, caregiver or social network) to successfully participate in this study 3. Subject must have a minimum daily insulin requirement (Total Daily Dose) of equal to or greater than 8 units/day 4. Subjects who are determined by the investigator to be psychologically sound in order to successfully participate in this study 5. Subject has been diagnosed with type 1 diabetes for at least three months Note: Determination of classification for diabetes will be based on American Diabetes Association Clinical Practice Guidelines accounting for several patient characteristics such as: age of onset, patient's weight or BMI, history of diabetic ketoacidosis, history of therapy management, if available in the medical records. 6. Subject must be on one of the following management therapies: -Multiple daily injections defined by use of rapid analogue with meals and approved long acting analogue (e.g. detemir or glargine) with or without CGM -Insulin pump therapy with or without CGM 7. Subject is willing to perform ≥ 4 finger stick blood glucose measurements daily 8. Subject is willing to perform required study procedures 9. Subject is willing to wear the system continuously throughout the study for at least 80% of the time. 10. Subject is willing to upload data at least weekly from the study pump/meter, must have Internet access and a computer system that meets the requirements for uploading the study pump/meter for data collection 11. Subject must be willing to use the study glucose meter system (i.e. along with study meter strips). 12. If subject has celiac disease, it has been adequately treated as determined by the investigator 13. Subject with the diagnosis of myocardial infarction, unstable angina, coronary artery bypass surgery, coronary artery stenting, transient ischemic attack, cerebrovascular accident, angina, congestive heart failure, ventricular rhythm disturbances or thromboembolic disease, within 1 year of screening, will be included in the study with the consent of the Investigator 14. Subject is willing to take one of the following insulins and can financially afford to use either of the 2 insulin preparations throughout the course of the study (i.e. co-payments for insulin with insurance or able to pay full amount) Humalog® (insulin lispro injection) NovoLog® (insulin aspart)	1. Subject participated in any Closed Loop study in the past. 2. Subject is unable to tolerate tape adhesive in the area of sensor placement 3. Subject has any unresolved adverse skin condition in the area of sensor placement (e.g., psoriasis, rash, Staphylococcus infection) or area of infusion set placement 4. Women of child-bearing potential who have a positive pregnancy test at screening or plan to become pregnant during the course of the study 5. Subject is being treated for hyperthyroidism at time of screening 6. Subject has an abnormality (out of reference range) in thyroid-stimulating hormone (TSH) at time of screening visit. TSH is not required for subjects 2-13 years of age. 7. Subject has taken any oral, injectable, or IV glucocorticoids within 8 weeks from time of screening visit, or plans to take any oral, injectable, or IV glucocorticoids during the course of the study. 8. Subject is actively participating in an investigational study (drug or device) wherein he/she has received treatment from an investigational study drug or investigational study device in the last 2 weeks 9. Subject is currently abusing illicit drugs or marijuana 10. Subject is currently abusing prescription drugs 11. Subject is currently abusing alcohol 12. Subject is using pramlintide (Symlin), SGLT2 inhibitors, GLP agonists, biguanides, DPP-4 inhibitors or sulfonylureas at time of screening 13. Subject is using hydroxyurea at the time of screening or plans to use it during the study 14. Subject has a history of visual impairment which would not allow subject to participate in the study and perform all study procedures safely, as determined by the investigator 15. Subject has a sickle cell disease, hemoglobinopathy; or has received red blood cell transfusion or erythropoietin within 3 months prior to time of screening 16. Subject plans to receive red blood cell transfusion or erythropoietin over the course of study participation 17. Subject diagnosed with current moderate to severe eating disorder such as anorexia or bulimia 18. Subject has been diagnosed with chronic kidney disease requiring dialysis or resulting in chronic anemia 19. Subjects who are currently being actively treated for cancer. 20. Subject who is designated as a research staff member for this study

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
MiniMed™ 670G hybrid closed loop (HCL)	Multiple daily injections (MDI), SAP, or CSII comparator	6 months	Continuous (pump) / MDI	302 participants	151 participants 2–17 years : 78 participants and 18–80 years : 73 participants	151 participants 2–17 years : 77 participants and 18–80 years : 74 participants	Participants aged 2–80 years	Change in A1C for Group 1 (baseline A1C >8.0%) from baseline to the end of study and difference in the end of study percentage of time spent below 70 mg/dL (%TBR <70 mg/dL) for Group 2 (baseline A1C ≤8.0%) to show superiority of HCL intervention versus control	Secondary effectiveness endpoints were change in A1C and %TBR <70 mg/dL for Group 2 and Group 1, respectively, to show noninferiority of HCL intervention versus control	NA	Significant mean (95% confidence interval) change in A1C was observed for both Group 1 : (-0.8% [-1.1% to -0.4%], P < 0.0001) and Group 2 : (-0.3% [-0.5% to -0.1%] P < 0.0001)

Trial 43
T. v. d. Berge et al., 2022
NA

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
T. v. d. Berge et al., 2022	NA	Randomised Controlled Trial (RCT)-crossover	NA	Single-center	No (open-label)	NA	NA	NA	NA

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Advanced hybrid closed-loop (AHCL)	Treatment as usual: CSII ± CGM	2 weeks of SAP - Sensor-augmented pump 8 weeks of PLGM - Predictive low-glucose management 8 weeks of HCL - Hybrid closed loop	Continuous insulin infusion	38 participants	38 participants	38 participants	Children aged 2-6 & 7-14 years	The percentage of time in range (TIR) of 70-180 mg/dl	• Other continuous glucose sensor metrics • HbA1c • Patient-related outcomes (DISABKIDS questionnaire, Fear of Hypoglycaemia Survey) • Safety events	High rate of TIR target (>70%) achievement with : HCL in preschool (88%) and school children (50%), with average times in Auto Mode of 93% and 87%, respectively. Preschool children achieved a mean TIR of 73% ± 6% (+8% vs. SAP, +6% vs. PLGM) and school children 69% ± 8% (+15% vs. SAP and + 14% vs. PLGM)	HbA1c improved from 7.4% ± 0.9% to 6.9% ± 0.5% (P = .0002)

Trial 44
U. Schierloh et al., 2019
NCT02099409

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
U. Schierloh et al., 2019	NCT02099409	Randomised Controlled Trial (RCT)-crossover	Luxembourg	Single-center	No (open-label)	NA	Yes EU Framework 7 Programme	1. Children aged between 6 and 12 years 2. Type 1 diabetes for at least 6 months 3. On insulin pump treatment for at least 6 months 4. HbA1c below 11% (below 96.72 mmol/mol)	1. Another type of diabetes than type 1 2. Physical or psychological disease likely to interfere with an appropriate conduct of the study 3. Current drug therapy knowing to interfere with glucose metabolism

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Overnight closed-loop insulin delivery	Sensor augmented pump therapy	2 nights (1 night in-patient stay and at home per treatment condition)	Continuous insulin infusion	15 participants	15 participants	15 participants	Children aged 6 - 12 years	Time spent in normal glucose range (mg/dl)	Glucose variability (excursions in mg/dl) Time spent in low glucose range (< 60 mg/dl) Time spent in low glucose range (<70 mg/dl) Time spent in high glucose range (>180mg/dl)	Blood glucose levels did not vary between conditions (mean difference 0.76 mmol/l; t(13) = 1.24, p = .12, d = 0.37)	NA

Trial 45
R. Nimri et al., 2014
NCT01238406

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
R. Nimri et al., 2014	NCT01238406	Randomised Controlled Trial (RCT)-crossover	Germany Israel Slovenia	NA	No (open-label)	NA	NA	1. Subject with Type 1 diabetes (>1yr since diagnosis) 2. Insulin infusion pump therapy for at least 3 months 3. Patients whom uses continuous glucose sensor for at least 2 weeks(for segment 5) or will undergo run-in period of 2 weeks of glucose sensor wear before continue to baseline assessment (only for patients participating at segment 3 and 4) 4. Age ≥ 10 years until 65 years 5. HbA1c at inclusion ≥ 6.5 and <10 6. Patients willing to follow trail instructions 7. Patients live with at least one other adult person (segment 3, 5, and 6 only) 8. BMI Standard Deviation Score - below the 97th percentile for age(in segment 5 and 6 BMI SDS - below the 95th percentile for age) 9. An internet connection at patient's home (only for patients participating at segment 3 and 6) 10. Patients with care givers who are capable of operating a computer based system	1. Concomitant diseases that influence metabolic control 2. Participation in any other interventional study 3. Known or suspected allergy to trial products 4. Any significant diseases or conditions including psychiatric disorders and substance abuse that, in the opinion of the investigator, is likely to affect the subject's ability to complete the study, or compromise patient safety 5. Diabetic ketoacidosis in the past 1 month. 6. Severe hypoglycemia resulting in seizure or loss of consciousness in the month prior to enrollment. 7. Current use of oral glucocorticoids or other medications, which in the judgment of the investigator would be a contraindication to participation in the study. 8. Subject is participating in another drug or device study that could affect glucose measurements or glucose management.

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Closed-loop insulin delivery with MD-Logic Artificial Pancreas (MDLAP) system	Sensor-augmented pump (SAP)	12 weeks	Continuous insulin infusion	24 participants	24 participants	24 participants	Participants aged 12-43 years	The primary end point was time spent with sensor glucose levels below 70 mg/dL (3.9 mmol/L) overnight.	NA	Closed-loop nights significantly increased the percentage of time spent in the target range of 70-140 mg/dL (P = 0.003) compared with nights when the SAP therapy was used	NA

Trial 46
R. Nimri et al., 2017
NA

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
R. Nimri et al., 2017	NA	Randomised Controlled Trial (RCT)-crossover	NA	3 centers	No (open-label)	NA	NA	NA	NA

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Closed-loop system	Sensor-augmented pump (SAP)	8 consecutive nights	Continuous insulin infusion	75 participants	75 participants	75 participants	NA	Primary endpoints were time spent with glucose levels below 70 mg/dL and percentage of nights in which mean overnight glucose levels were within 90 to 140 mg/dL.	NA	The percentage of individual nights with a mean overnight glucose level in target was significantly greater (75 [42, 75] and 50 [25,75], respectively; P = .008) The time spent in target range was increased by a median of 28% (P = .001), with the same amount of insulin (10.69 [7.28, 13.94] and 10.41[6.9, 14.07], respectively; P = .087)	NA

Trial 47
M. Reddy et al., 2015
NA

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
M. Reddy et al., 2015	NA	Randomised Controlled Trial (RCT)-crossover	NA	NA	No (open-label)	NA	Yes Wellcome Trust	1. Age 18-75 years 2. Duration of diabetes >1 year 3. Fasting c-peptide <0.2 nmol/l 4. Treatment with CSII for >6 months 5. HbA1c <8.5% (69 mmol/mol)	1. Recurrent severe hypoglycemia 2. Pregnancy or planning pregnancy 3. Breastfeeding 4. Enrolment in other clinical studies 5. Active malignancy or being under investigation for malignancy 6. Informed written consent was obtained.

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Closed-loop insulin delivery system - Bio-inspired Artificial Pancreas (BiAP)	Open-loop visit (standard insulin pump therapy)	48 hours	Continuous insulin infusion	12 participants	12 participants	12 participants	Participants aged 18-75 years	Percentage time spent in sensor glucose target range (3.9-10.0 mmol/l)	Secondary outcomes were : • percentage time in euglycemia (3.9-7.8 mmol/l) • hypoglycemia (<3.9 mmol/l) • hyperglycemia (>10.0 mmol/l) • mean sensor • glucose • insulin dose delivered • glycemic risk measures of low blood glucose index (LBGI) and high blood glucose index (HBGI). We calculated all glycemic outcomes for the whole time period and the overnight period Other secondary outcomes included : • intercorrelations between metabolic analytes during closed-loop and open-loop control	The median (IQR) percentage time in target did not differ between closed-loop and open-loop (71% vs 66.9%, P = .9) The percentage time in target was higher when all meals were announced during closed-loop compared to no or partial meal announcement (65.7% [53.6-80.5] vs 45.5% [38.2-68.3], P = .12)	NA

Trial 48
S. J. Russell et al., 2022
NCT04200313

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
\	NCT04200313	Randomised Controlled Trial (RCT)	United States	Multi-center	No (open-label)	Yes (2:1)	Yes National Institute of Diabetes and Digestive and Kidney Diseases	1. Clinical diagnosis of T1D for at least one year and using insulin for at least 1 year 2. Diabetes managed using the same regimen (either pump or MDI, with or without CGM) for ≥ 3 months 3. Age ≥ 6 years old Exception: the initial 5-participant test run will be limited to >18 years old 4. Current use of a CGM, or if not a CGM user, at least 3 blood glucose meter tests daily on average over the last 4 weeks (according to judgment of investigator if meter is not available). 5. Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial 6. For participants <18 years old, living with one or more parent/legal guardian knowledgeable about emergency procedures for severe hypoglycemia. 7. For participants >18 years old who live alone, participant has a relative or acquaintance who lives within 30 minutes of participant and is willing to be contacted to check on participant if study staff feel that participant may be experiencing a medical emergency and can't be reached. 8. Investigator believes that the participant can safely use the iLet and will follow the protocol. The investigator will take into account the participant's HbA1c level, compliance with current diabetes management, and prior acute diabetic complications. For this reason, there is no upper limit on HbA1c specified for eligibility. 9. If a GLP-1 agonist or pramlintide is being used, participant must be willing to discontinue use while the iLet BP system is being used, including the randomized trial and extension study.	1. Unable to provide informed consent (e.g. impaired cognition or judgment) 2. Unable to safely comply with study procedures and reporting requirements (e.g. impairment of vision or dexterity that prevents safe operation of the bionic pancreas, impaired memory) 3. Unable to speak and read English • For pediatric participants, both caregivers and participants must be able to speak and read English 4. Plan to change usual diabetes regimen in the next 3 months This would include changing from MDI to pump. pump to MDI, change in insulin automation delivery system, starting a CGM if not previously used, changes in drug therapy specifically for glucose control except for changes in one insulin analog to another. Changes in insulin dose, carb ratio, sensitivity factor and basal rate profile are allowed. Current use of non-FDA approved closed-loop or hybrid closed-loop insulin delivery system Use of Apidra as the pre-study rapid-acting insulin analog and unwilling to switch to lispro or aspart for the duration of the study Known hemoglobinopathy (sickle cell trait is not an exclusion) Current participation in another diabetes-related clinical trial History of cystic fibrosis, pancreatitis, or other pancreatic disease, including pancreatic tumor or insulinoma, or history of complete pancreatectomy Electrically powered implants (e.g. cochlear implants, neurostimulators) that might be susceptible to RF interference Established history of allergy or severe reaction to adhesive or tape that must be used in the study Current use of SGLT2 inhibitors or a sulfonylurea drug (use more than 3 months prior to enrollment is acceptable) • If using GLP1 agonist, pramlintide, or metformin drugs must be on a stable dose for 3 months prior to enrollment (and as per inclusion criterion #8, must be willing to discontinue use of GLP-1 agonist or pramlintide while using the iLet BP system during the RCT and the extension phase). Pregnant (positive urine hCG), breast feeding, plan to become pregnant in the next 3 months, or sexually active without use of contraception For adults >18 years old, most recent (must be within the last 2 years) eGFR <30 ml/min OR currently in renal failure on dialysis • If no eGFR is available for an adult participant during the last 2 years, one must be obtained to confirm eligibility Presence of a medical condition or use of a medication that, in the judgment of the investigator, clinical protocol chair, or medical monitor, could compromise the results of the study or the safety of the participant. Conditions to be considered by the investigator may include the following: Alcohol or drug abuse Use of prescription drugs that may dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder decision making during the period of participation in the study Coronary artery disease that is not stable with medical management, including unstable angina, angina that prevents moderate exercise (e.g. climbing a flight of stairs) despite medical management, or within the last 12 months before screening a history of myocardial infarction, percutaneous coronary intervention, enzymatic lysis of a presumed coronary occlusion, or coronary artery bypass grafting Congestive heart failure with New York Heart Association (NYHA) Functional Classification III or IV History of TIA or stroke in the last 12 months Untreated or inadequately treated mental illness History of eating disorder within the last 2 years, such as anorexia, bulimia, or diabulemia or omission of insulin to manipulate weight History of intentional, inappropriate administration of insulin leading to severe hypoglycemia requiring treatment Employed by, or having immediate family members employed by Beta Bionics, or being directly involved in conducting the clinical trial, or having a direct supervisor at place of employment who is also directly involved in conducting the clinical trial (as a study investigator, coordinator, etc.); or having a first-degree relative who is directly involved in conducting the clinical trial

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Bionic pancreas treatment with insulin aspart or insulin lispro	Any insulin-delivery method with unblinded, real-time CGM	13 weeks	Continuous insulin infusion	326 participants	219 participants	107 participants	Participants aged 6-79 years	The primary outcome was the glycated hemoglobin level at 13 weeks	The key secondary outcome was the percentage of time that the glucose level as assessed by continuous glucose monitoring was below 54 mg per deciliter; the prespecified noninferiority limit for this outcome was 1 percentage point.	NA	The glycated hemoglobin level : -in the bionic-pancreas group: decreased from 7.9% to 7.3% and did not change -in the standard-care group : did not change (was at 7.7% at both time points) (mean adjusted difference at 13 weeks, -0.5 percentage points; 95% confidence interval [CI], -0.6 to -0.3; P<0.001)

Trial 49
R. Nimri et al., 2014
NCT01726829

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
R. Nimri et al., 2014	NCT01726829	Randomised Controlled Trial (RCT)-crossover	Germany Israel Slovenia	NA	No (open-label)	NA	NA	1. Subject with Type 1 diabetes (>1yr since diagnosis) 2. Insulin infusion pump therapy for at least 3 months 3. Patients whom used continuous glucose sensor previously 4. Age at inclusion ≥ 10 years and ≤ 65 years 5. HbA1c at inclusion ≥ 7 and <10 6. Patients willing to follow study instructions 7. Patients live with at least one other adult person 8. BMI SDS(Standard Deviation Score) - below the 97th percentile for age 9. An internet connection at patient's home 10. Patients with care givers who are capable of operating a computer based system	1. Concomitant diseases that influence metabolic control 2. Participation in any other interventional study 3. Known or suspected allergy to trial products 4. Any significant diseases (such as preexisting seizures or epilepsy) or conditions including psychiatric disorders and substance abuse that in the opinion of the investigator is likely to affect the subjects ability to complete the study or compromise patients safety 5. Diabetic ketoacidosis in the past 1 month 6. Severe hypoglycemia resulting in seizure or loss of consciousness in the month prior to enrollment. 7. Current use of oral glucocorticoids or other medications, which in the judgment of the investigator would be a contraindication to participation in the study 8. Female subject who is pregnant or planning to become pregnant within the planned study duration

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
MD-Logic AP closed-loop system	Sensor-augmented pump (SAP)	8 nights	Continuous insulin infusion	15 participants	15 participants	15 participants	Participants aged 10-65 years	Primary endpoints were the time spent with glucose levels below 70 mg/dL and the percentage of nights in which the mean overnight glucose levels were within 90-140 mg/dL	• The time sensor glucose level spent within 70-140 mg/dl • The number and frequency of hypoglycemic events below 63, 79 mg/dl • The time sensor glucose level spent above 140, 180 mg/dl • The area under the curve <63, <70, >140, >180 mg/dl • Glucose variability • The total insulin dose during the overnight period • Artificial pancreas technical performance defined as total frequency of technical failures • Artificial pancreas technical performance defined as total frequency of lost or inaccurate sensor records • Percentage of time of active closed loop control • Fear of Hypoglycemia questionnaire • Acceptance questionnaire • Artificial Pancreas Satisfaction Questionnaire	The percentage of individual nights in which mean overnight glucose level was within 90-140 mg/dL was 67 (33, 88), and 50 (25, 75), under closed-loop and control nights, respectively, with no statistical difference	NA

Trial 50
R. J. Kaur et al., 2022
NCT04142229

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
R. J. Kaur et al., 2022	NCT04142229	Randomised Controlled Trial (RCT)-crossover	United States	2 centers	No (open-label)	NA	NA	1. Clinical diagnosis, based on investigator assessment, of type 1 diabetes for at least one year and using insulin for at least 1 year 2. Using an insulin pump for at least 3 months at the time of screening. Insulin pump use includes use of automated features, to include predictive or threshold low-glucose suspend or hybrid closed-loop with or without a Dexcom sensor. 3. Familiarity and use of a carbohydrate ratio for meal boluses. 4. Age ≥18.0 years old 5. HbA1c < 10.5%, as performed by point of care or central laboratory testing. HbA1c will be assessed at the screening visit, or if already completed within 2 weeks of the screening visit, the prior lab value may be used in lieu of repeating this assessment. 6. For females, not currently known to be pregnant. If female and sexually active, must agree to use a form of contraception to prevent pregnancy while a participant in the study and up to one month afterwards. A negative serum or urine pregnancy test will be required for all females of child-bearing potential. Participants who become pregnant will be discontinued from the study. Also, participants who during the study develop and express the intention to become pregnant within the timespan of the study will be discontinued. 7. Willingness to switch home pump to PLGS or full manual mode if using hybrid - Investigator has confidence that the participant can successfully operate all study devices and is capable of adhering to the protocol. 8. Willingness to switch to lispro (Humalog) or aspart (Novolog) if not using already, and to use no other insulin besides lispro (Humalog) or aspart (Novolog) during the study. 9. Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial.	1. Use of an unapproved closed-loop insulin delivery system within 2 weeks before screening or during the study is not allowed. 2. Have a blood pressure at screening outside the range of 160 mmHg systolic blood pressure and/or greater than 100 mmHg for diastolic blood pressure (if repeated measurements are within this range, the patient may be included in the study) 3. Have coronary artery disease that is not stable with medical management, including unstable angina, angina that prevents moderate exercise despite medical management, or within the last 12 months before screening a history of myocardial infarction, percutaneous coronary intervention, enzymatic lysis of a presumed coronary occlusion, or coronary artery bypass grafting 4. Concurrent use of Afrezza or any non-insulin glucose-lowering agent other than metformin (including GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas). 5. Hemophilia or any other bleeding disorder 6. A condition, which in the opinion of the investigator or designee, would put the participant or study at risk, to include: -Pregnancy, or planning pregnancy within 1 month of completing the clinical trial. -Allergy or hypersensitivity to hydrocortisone, or any component of the formulation -Presence of a known adrenal disorder -Systemic fungal infections -Active infection of any kind, or at risk of infection (susceptibility to infection) from known immunosuppression or underlying immunosuppressed condition -Idiopathic thrombocytopenia purpura (ITP) -Varicella -Glaucoma or other chronic ocular condition that could be adversely affected by steroids (e.g., cataracts, increased ocular pressure from other causes, exophthalmos) -Hypertension requiring treatment with one or more antihypertensive medications -Congestive heart failure -Current treatment for a seizure disorder -Mental incapacity, unwillingness or language barriers precluding adequate understanding or co-operation, including subjects not able to read or write -Known coronary artery disease -Active gastroparesis -Cystic fibrosis -Uncontrolled thyroid disease (TSH undetectable or > 10 mIU/L) -Known abuse of alcohol -A recent injury to body or limb, muscular disorder, use of any medication, any carcinogenic disease, or other significant medical disorder if that injury, medication or disease in the judgment of the investigator will affect the completion of the protocol -Current use of a beta blocker medication -Laboratory results: HbA1c > 10.5% Abnormal liver or renal function (Transaminase >2 times the upper limit of normal, creatinine> 1.5 mg/dL) Labs drawn at screening visit or within three months prior to screening (for other purposes) will suffice for enrollment purposes Subject has skin conditions that, in the determination of the investigator, would preclude wearing the study devices (infusion set and sensor), in the abdomen. Examples include but are not limited to: psoriasis, burns, scaring, eczema, tattoos, and significant hypertrophy at sites of device wear; any known allergy to medical adhesives. Currently on long-term treatment using prednisone or other steroid If subject had been on short term treatment of prednisone, defer enrollment until underlying condition and prednisone treatment have resolved. Allergy to study drug, food or other study material. Clinically significant physical examination, laboratory test, or vital sign abnormality. Exposure to any investigational drug within 30 days. History of malignancy within the 5 years before screening (other than basal cell carcinoma). 7. Participation in another pharmaceutical or device trial at the time of enrollment or during the study 8. Having a direct supervisor at place of employment who is also directly involved in conducting the clinical trial (as a study investigator, coordinator, etc.); or having a first-degree relative who is directly involved in conducting the clinical trial

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Insulin use with Zone Model Predictive Control (zone-MPC) AID system	Sensor-augmented pump (SAP)	4 weeks	Continuous insulin infusion	14 participants	14 participants	14 participants	Adult (≥18 years)	Time in target glucose range 70-180 mg/dL measured by CGM to determine safety and efficacy of the integrated system	• Change in glucose levels with stress induction sessions (mg/dL) • Change in insulin requirements with stress induction • Analysis of EDA to verify stress detection and correlation to glucose changes, both during the stress sessions and in the outpatient setting • Percent time within the target range of 70-180 mg/dl postprandial within 5 hours following meals • Glucose < 70 mg/dL Percent time GGM glucose < 70 mg/dL • Glucose < 54 mg/dL Percent time GGM glucose < 54 mg/dL • Glucose > 180 mg/dL Percent time GGM glucose > 180 mg/dL • Glucose > 250 mg/dL Percent time GGM glucose > 250 mg/dL • The total number of serious adverse events during the clinical trial • The total number of serious adverse events related to the study device use during the clinical trial • The total number of adverse device effects (ADE) during the clinical trial • The total number of unanticipated adverse device effects (UADE) during the clinical trial • Salivary cortisol assessment (nmol/l) during psychologic and physiologic stress induction • EDA Measurement of psychologic and physiologic stress from the Empatica E4 Watch • Trier Social Stress Test (TSST) score at end of each test induction • Socially evaluated cold-pressor test (SECPT) score at end of each test induction	During the 2-week AID use TIR was 74.4% (vs. SAP 63.1%, P = 0.001) and overnight TIR was 78.3% (vs. SAP 63.1%, P = 0.004)	NA

Trial 51
J. E. Pinsker et al., 2022
NCT04436796

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
J. E. Pinsker et al., 2022	NCT04436796	Randomised Controlled Trial (RCT)-crossover	United States	5 centers	No (open-label)	NA	Yes National Institutes of Health	1. Clinical diagnosis, based on investigator assessment, of type 1 diabetes for at least one year and using insulin for at least 1 year 2. Using an insulin pump for at least 3 months (which may include use of automated features) 3. Familiarity and use of a carbohydrate ratio for meal boluses 4. Age ≥18.0 years old 5. For females, not currently known to be pregnant. If female and sexually active, must agree to use a form of contraception to prevent pregnancy while a participant in the study. A negative serum or urine pregnancy test will be required for all females of child-bearing potential. Participants who become pregnant will be discontinued from the study. Also, participants who during the study develop and express the intention to become pregnant within the timespan of the study will be discontinued. 6. If using a personal CGM, willingness to use a Dexcom G6 CGM and discontinue personal CGM use during the study 7. Willing not to begin use of, or not to continue use of if currently using, a personal AID (closed loop control) system during the study; note if the system offers an open-loop mode or can be switched to a PLGS mode that is compatible with the Dexcom G6, the system may be used during the study in these modes only 8. Willingness to switch to lispro (Humalog) or aspart (Novolog) if not using already, and to use no other insulin besides lispro (Humalog) or aspart (Novolog) during the study 9. Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial, and not to use Afrezza during the trial 10. Investigator believes that the participant can successfully and safely operate all study devices and is capable of adhering to the protocol	1. Use of Afrezza or any non-insulin glucose-lowering agent other than metformin (including GLP-1 agonists, DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas) unless participant is willing to discontinue during the trial. 2. Two or more episodes of DKA requiring an emergency room visit or hospitalization in the past 6 months 3. Two or more episodes of severe hypoglycemia with seizure or loss of consciousness in the last 6 months 4. Hemophilia or any other bleeding disorder 5. A medical or other condition that in the opinion of the investigator could create a safety concern for the participant or put the study at risk. History of frequent severe hypoglycemia or history of frequent severe hyperglycemia and/or ketosis, without emergency room visit or hospitalization, due to poor diabetes self-management may be disqualifying per investigator judgment 6. Participation in another pharmaceutical or device trial at the time of enrollment or during the study

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Automated insulin delivery	Sensor-augmented pump (SAP)	26 weeks	Continuous insulin infusion	35 participants	35 participants	35 participants	Adult (≥18 years)	Primary outcome was sensor glucose time-in-range 70–180 mg/dL, with noninferiority in percent time below 54 mg/dL as a hierarchical outcome.	• CGM-measured mean glucose (mg/dL) • CGM time > 180 mg/dL • CGM time > 250 mg/dL • CGM time < 70 mg/dL • CGM time < 54 mg/dL (Superiority) • CGM measured glucose variability measured with the coefficient of variation (CV) • CGM-measured % in range 70-140 mg/dL • CGM measured glucose variability measured with the standard deviation (SD) • CGM time < 60 mg/dL • Low blood glucose index (LBGI) by CGM with higher index	Mean time-in-range 70-180 mg/dL was with SAP : 66% versus AID : 69% (mean adjusted difference +2% [95% confidence interval: -1% to +6%], P = 0.22)	NA

									indicating higher risk of hypoglycemia. LBGI ≤ 1.1 is associated with minimal risk of hypoglycemia, 1.1 < LBGI ≤ 2.5 is associated with a low risk of hypoglycemia, 2.5 < LBGI ≤ 5.0 is associated with a moderate risk of hypoglycemia, and LBGI > 5.0 is associated with high risk of hypoglycemia. • CGM time > 300 mg/dL • High Blood Glucose Index (HBGI) is a measure of Hyperglycemic Risk based on frequency and severity of hyperglycemic events. HBGI < 4.5 is associated with lower risk of hyperglycemia, 4.5 < HBGI < 9 is associated with a moderate risk of hyperglycemia and HBGI > 9 is associated with high risk of hyperglycemia • Hemiglobin A1c measured after completing each study arm 13 weeks • Number of participants HbA1c <7.0% after completing each study arm • Number of participants HbA1c <7.5% after completing each study arm • Diabetes Distress Scale for adults has 28 items rated on a 6 point Likert scale that ranges from 1 (not a problem) to 6 (a very serious problem). The total score is the mean of the sum of responses and ranges from 1 to 6 where a higher score indicates greater degrees of diabetes distress. • The GMSS for Type 1 Diabetes contains four subscales as well as a total scale. For this measure, total scale is reported. To calculate the total scale (higher scores indicate greater satisfaction): Mean of all items 1-15 (reverse code items: 2-7, 9, 11-13, and 15) which are all scored on a 5 point scale (1-5) (Minimum Total Scale Score is 1, Maximum Total Scale Score is 5) • Hypoglycemia Confidence Scale has 20 items which are rated on a 4-point Likert Scale ranging from 1 (not confident at all) to 4 (very confident) with higher scores indicating higher confidence in dealing with		

									hypoglycemia. A single score is computed by calculating the mean of the sum of all items and ranges from 1 to 4. • The INSPIRE questionnaire assesses user expectations and experiences with Insulin Delivery Systems: Perceptions, Ideas, Reflections, Expectations (INSPIRE). Survey total scores are computed by calculating the mean of the sum of all item ratings then multiplying the mean by 25 to scale the score to a range from 0 to 100. Higher scores indicate a more positive perception of insulin delivery systems. Items are rated on a 5 point Likert scale ranging from 0 (strongly disagree) to 4 (strongly agree). The Adult survey has 22 items, the Teens/Adolescents survey has 17 items and the Parent survey has 21 items. • System Usability Scores (SUS)-composite score from 0 to 100 with higher scores indicate better perceived usability • Total Daily Insulin (units) • Basal: bolus insulin ratio		

Trial 52
S. A. Brown et al., 2017
NCT02131766 and NCT02008188

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
S. A. Brown et al., 2017	NCT02131766 and NCT02008188	Randomised Controlled Trial (RCT)-crossover	United States Italy	4 centers	No (open-label)	NA	Yes National Institutes of Health Grants University of Virginia and Grant Mayo Clinic the Urdang Family Fund (to Y.C.K.); the JDRF	1. Clinical diagnosis, based on investigator assessment, of type 1 diabetes for at least one year and using insulin for at least 1 year and an insulin pump for at least 6 months - Criteria for documented hyperglycemia (at least 1 must be met): i. Fasting glucose ≥126 mg/dL ii. Two-hour Oral Glucose Tolerance Test (OGTT) glucose ≥200 mg/dL iii. HbA1c ≥6.5% documented iv. Random glucose ≥200 mg/dL with symptoms v. No data at diagnosis is available but the participant has a convincing history of hyperglycemia consistent with diabetes. - Criteria for requiring insulin at diagnosis (1 must be met): i. Participant required insulin at diagnosis and continually thereafter ii. Participant did not start insulin at diagnosis but upon investigator review likely needed insulin (significant hyperglycemia that did not respond to oral agents) and did require insulin eventually and used continually iii. Participant did not start insulin at diagnosis but continued to be hyperglycemic, had positive islet cell antibodies - consistent with latent autoimmune diabetes in adults (LADA) and did require insulin eventually and used continually 2. Age ≥21 to <65 years 3. HbA1c <10.0% 4. For females, not currently known to be pregnant If female and sexually active, must agree to use a form of contraception to prevent pregnancy while a participant in the study. A negative urine pregnancy test will be required for all premenopausal women who are not surgically sterile. Subjects who become pregnant will be discontinued from the study. 5. Demonstration of proper mental status and cognition for the study 6. Currently using insulin-to-carbohydrate ratio to calculate meal bolus sizes 7. Ability to access the Internet and upload CGM data via the DexCom company software during the data collection period. 8. Willingness to remain within approximately 30 miles radius of study site during the day time hours of Visit 4. 9. An understanding of and willingness to follow the protocol and sign the informed consent -Additional Inclusion Criteria for UVA subjects only who participate in the 5 days at-home portion -Availability of a significant other or family member committed to participating in all training activities, knowledgeable at all times of the participant's location, and being present and available to provide assistance when system is being used at night -Commitment to maintaining uninterrupted availability via cell phone and avoiding any overnight travel for the duration of the period of time using the closed-loop system at home. -Access to internet and cell phone service at home	1. Admission for diabetic ketoacidosis in the 12 months prior to enrollment 2. Severe hypoglycemia resulting in seizure or loss of consciousness in the 12 months prior to enrollment 3. History of a seizure disorder (except hypoglycemic seizure), unless written clearance is received from a neurologist 4. Coronary artery disease or heart failure, unless written clearance is received from a cardiologist 5. Cystic fibrosis 6. A known medical condition that in the judgment of the investigator might interfere with the completion of the protocol such as the following examples: -Inpatient psychiatric treatment in the past 6 months -Presence of a known adrenal disorder -Abnormal liver function test results (Transaminase >2 times the upper limit of normal); testing required for subjects taking medications known to affect liver function or with diseases known to affect liver function -Abnormal renal function test results (calculated GFR <60 mL/min/1.73m2); testing required for subjects with diabetes duration of greater than 5 years post onset of puberty -Active gastroparesis -If on antihypertensive, thyroid, anti-depressant or lipid lowering medication, lack of stability on the medication for the past 2 months prior to enrollment in the study -Uncontrolled thyroid disease (TSH undetectable or >10 mIU/L); testing required within three months prior to admission for subjects with a goiter, positive antibodies, or who are on thyroid hormone replacement, and within one year otherwise -Abuse of alcohol or recreational drugs -Infectious process not anticipated to resolve prior to study procedures (e.g. meningitis, pneumonia, osteomyelitis). -Uncontrolled arterial hypertension (Resting diastolic blood pressure >90 mmHg and/or systolic blood pressure >160 mmHg). -Oral steroids -Uncontrolled microvascular complications such as current active proliferative diabetic retinopathy defined as proliferative retinopathy requiring treatment (e.g. laser therapy) in the past 12 months. 7. A recent injury to body or limb, muscular disorder, use of any medication, any carcinogenic disease, or other significant medical disorder if that injury, medication or disease in the judgment of the investigator will affect the completion of the protocol 8. Basal Rates <0.01 units/hour. 9. Current use of the following drugs and supplements: -Acetaminophen -Any medication being taken to lower blood glucose, such as Pramlintide, Metformin, glucagon-like peptide (GLP)-1 Analogs such as Liraglutide, and nutraceuticals intended to lower blood glucose -Beta blockers -Any other medication that the investigator believes is a contraindication to the subject's participation

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Closed-loop system	Sensor-augmented pump (SAP)	5 nights	Continuous insulin infusion	40 participants	40 participants	40 participants	Participants aged 21 to <65 years	The percentage of time spent in the target range (70 to 180 mg/dL measured using a continuous glucose monitor).	• Mean glucose level, mg/dL - Overall, 24 h - 07:00 (waking up) - 23:00 (bedtime) • Time spent in range for 24 h, % - <50 mg/dL - <60 mg/dL - <70 mg/dL - >180 mg/dL - >250 mg/dL - >300 mg/dL - 80–140 mg/dL • Time spent in range, overnighta, % -70–180 mg/dL - <50 mg/dL - <60 mg/dL - <70 mg/dL - >180 mg/dL - >300 mg/dL • Glucose variability • Coefficient of variation for glucose overnighta, % • LBGI overnighta • HBGI overnighta	The time in the target range (70 to 180 mg/dL) significantly improved in CLC vs SAP over 24 hours (78.3% vs 71.4%; P = 0.003) and overnight (85.7% vs 67.6%; P < 0.001)	Better, albeit modest, reduction in the HbA1c compared with that achieved after 2 months of SAP (−0.3% vs −0.2%; P = 0.047)

Trial 53
M. D. DeBoer et al., 2017
NCT02750267

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
M. D. DeBoer et al., 2017	NCT02750267	Randomised Controlled Trial (RCT)-crossover	United States Italy	Single-center	No (open-label)	NA	NA	1. Clinical diagnosis of type 1 diabetes, -The diagnosis of type 1 diabetes is based on the investigator's judgment -C peptide levels and antibody determinations are not required 2. Daily insulin therapy for ≥ 12 months 3. Insulin pump therapy for ≥ 3 months 4. Age ≥5 - ≤8 years old 5. Avoidance of acetaminophen-containing medications (i.e. Tylenol) while wearing the continuous glucose monitor. 6. Willingness to wear a continuous glucose sensor and physiological monitor for the duration of the study	1. Diabetic ketoacidosis in the past month 2. Hypoglycemic seizure or loss of consciousness in the past 3 months 3. History of seizure disorder (except for hypoglycemic seizure) 4. History of any heart disease including coronary artery disease, heart failure, or arrhythmias 5. Cystic fibrosis 6. Current use of oral glucocorticoids, beta-blockers or other medications, which in the judgment of the investigator would be a contraindication to participation in the study. 7. History of ongoing renal disease (other than microalbuminuria). 8. Subjects requiring intermediate or long-acting insulin (such as NPH, Detemir or Glargine). 9. Subjects requiring other anti-diabetic medications other than insulin (oral or injectable). 10. Presence of a febrile illness within 24 hours of admission or acetaminophen use while wearing the CGM. The subject may be rescheduled for Research House/Hotel Admission if these criteria are not met. The study subject will not participate in the trial if these conditions are met. 11. Medical or psychiatric condition that in the judgment of the investigator might interfere with the completion of the protocol such as: -Inpatient psychiatric treatment in the past 6 months -Uncontrolled adrenal insufficiency

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
the UVa AP using the DiAs Control Platform software with child-resistant lock-out screens (followed as an out-patient admission)	Usual insulin pump+continuous glucose monitor (CGM) care	68 - 72 hours	Continuous insulin infusion	12 participants	12 participants	12 participants	Young children 5-8 years old	Percent of Sensor Glucose Readings Between 70-180 mg/dL - All subjects have CGM output analyzed and compared between time on closed-loop system and time on usual care period	• Percent of Time Sensor Glucose Readings Are <70 mg/dL • Percent of Time Sensor Glucose Readings Are >150 mg/dL • Percent of Time Sensor Glucose Readings Are >180 mg/dL • Percent of Time Sensor Glucose Readings Are >250 mg/dL • Percent of Time Sensor Glucose Readings Are >400 mg/dL • Distribution of Sensor and Meter Glucose Values (Maximum, Minimum, Median, Interquartile Range, Mean, Standard Deviation) • Distribution of Sensor and Meter Glucose Values (Maximum) • Distribution of Sensor and Meter Glucose Values (Minimum) • Distribution of Sensor and Meter Glucose Values (Median/Interquartile Range) • Mean BG (as Measured by CGM) • Hypoglycemia Area Under the Curve <60 • Hypoglycemia Area Under the Curve <70 mg/dL • Hyperglycemia Area Under the Curve >180 • Hyperglycemia Area Under the Curve >250 mg/dL • Incidence of Hypoglycemia Per Subject, Defined by Handheld Meter Glucose <70 mg/dL • End of Night Blood Glucose	Compared to home care, the AP admission resulted in increased time with blood glucose (BG) 70-180 mg/dL (73% vs. 47%) P < 0.001 after adjustment for activity.	NA

Trial 54
L. H. Messer et al., 2022
NCT04200313

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
L. H. Messer et al., 2022	NCT04200313	Randomised Controlled Trial (RCT)	USA	Multi-center	No (open-label)	Yes (2:1)	NA	1. Clinical diagnosis of T1D for at least one year and using insulin for at least 1 year 2. Diabetes managed using the same regimen (either pump or MDI, with or without CGM) for ≥ 3 months 3. Age ≥ 6 years old Exception: the initial 5-participant test run will be limited to >18 years old 4. Current use of a CGM, or if not a CGM user, at least 3 blood glucose meter tests daily on average over the last 4 weeks (according to judgment of investigator if meter is not available). 5. Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial 6. For participants <18 years old, living with one or more parent/legal guardian knowledgeable about emergency procedures for severe hypoglycemia. 7. For participants >18 years old who live alone, participant has a relative or acquaintance who lives within 30 minutes of participant and is willing to be contacted to check on participant if study staff feel that participant may be experiencing a medical emergency and can't be reached. 8. Investigator believes that the participant can safely use the iLet and will follow the protocol The investigator will take into account the participant's HbA1c level, compliance with current diabetes management, and prior acute diabetic complications. For this reason, there is no upper limit on HbA1c specified for eligibility. 9. If a GLP-1 agonist or pramlintide is being used, participant must be willing to discontinue use while the iLet BP system is being used, including the randomized trial and extension study.	1. Unable to provide informed consent (e.g. impaired cognition or judgment) 2. Unable to safely comply with study procedures and reporting requirements (e.g. impairment of vision or dexterity that prevents safe operation of the bionic pancreas, impaired memory) 3. Unable to speak and read English • For pediatric participants, both caregivers and participants must be able to speak and read English 4. Plan to change usual diabetes regimen in the next 3 months This would include changing from MDI to pump. pump to MDI, change in insulin automation delivery system, starting a CGM if not previously used, changes in drug therapy specifically for glucose control except for changes in one insulin analog to another. 4. Changes in insulin dose, carb ratio, sensitivity factor and basal rate profile are allowed. 5. Current use of non-FDA approved closed-loop or hybrid closed-loop insulin delivery system 6. Use of Apidra as the pre-study rapid-acting insulin analog and unwilling to switch to lispro or aspart for the duration of the study 7 Known hemoglobinopathy (sickle cell trait is not an exclusion) 8. Current participation in another diabetes-related clinical trial 9. History of cystic fibrosis, pancreatitis, or other pancreatic disease, including pancreatic tumor or insulinoma, or history of complete pancreatectomy 10. Electrically powered implants (e.g. cochlear implants, neurostimulators) that might be susceptible to RF interference 11. Established history of allergy or severe reaction to adhesive or tape that must be used in the study 12. Current use of SGLT2 inhibitors or a sulfonylurea drug (use more than 3 months prior to enrollment is acceptable) • If using GLP1 agonist, pramlintide, or metformin drugs must be on a stable dose for 3 months prior to enrollment (and as per inclusion criterion #8, must be willing to discontinue use of GLP-1 agonist or pramlintide while using the iLet BP system during the RCT and the extension phase). 13. Pregnant (positive urine hCG), breast feeding, plan to become pregnant in the next 3 months, or sexually active without use of contraception 14. For adults >18 years old, most recent (must be within the last 2 years) eGFR <30 ml/min OR currently in renal failure on dialysis • If no eGFR is available for an adult participant during the last 2 years, one must be obtained to confirm eligibility 15. Presence of a medical condition or use of a medication that, in the judgment of the investigator, clinical protocol chair, or medical monitor, could compromise the results of the study or the safety of the participant. Conditions to be considered by the investigator may include the following: • Alcohol or drug abuse • Use of prescription drugs that may dull the sensorium, reduce sensitivity to symptoms of hypoglycemia, or hinder decision making during the period of participation in the study • Coronary artery disease that is not stable with medical management, including unstable angina, angina that prevents moderate exercise (e.g. climbing a flight of stairs) despite medical management, or within the last 12 months before screening a history of myocardial infarction, percutaneous coronary intervention, enzymatic lysis of a presumed coronary occlusion, or coronary artery bypass grafting • Congestive heart failure with New York Heart Association (NYHA) Functional Classification III or IV • History of TIA or stroke in the last 12 months • Untreated or inadequately treated mental illness • History of eating disorder within the last 2 years, such as anorexia, bulimia, or diabulemia or omission of insulin to manipulate weight • History of intentional, inappropriate administration of insulin leading to severe hypoglycemia requiring treatment 16. Employed by, or having immediate family members employed by Beta Bionics, or being directly involved in conducting the clinical trial, or having a direct supervisor at place of employment who is also directly involved in conducting the clinical trial (as a study investigator, coordinator, etc.); or having a first-degree relative who is directly involved in conducting the clinical trial

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
iLet Bionic Pancreas (BP) System with insulin aspart or insulin lispro	Standard care insulin delivery plus real-time continuous glucose monitoring	13 weeks	Continuous (pump) / MDI	164 participants	112 participants	53 participants	Youth 6-17 years	The primary outcome was HbA1c at 13 weeks	CGM metric 1. The percentage of time that the glucose level as measured by the CGM was below 54 mg per deciliter (3.0 mmol per liter) 2. The mean glucose level 3. The percentage of time with the glucose level in the range of 70 to 180 mg per deciliter (3.9 to 10.0 mmol per liter) 4. The percentage of time with the glucose level above 180 mg per deciliter 5. The percentage of time with the glucose level above 250 mg per deciliter (13.9 mmol per liter) 6. The glucose-level standard deviation 7. The percentage of time with the glucose level below 70 mg per deciliter 8. The percentage of time with the glucose level below 54 mg per deciliter, to be tested for superiority 9. The glucose coefficient of variation.	Over 13 weeks mean time in range (TIR) 70-180 mg/dL increased by 10% (2.4 h per day) and mean CGM glucose was reduced by 15 mg/dL with BP compared with SC (P < 0.001)	Mean HbA1c BP : decreased from 8.1% ± 1.2% at baseline to 7.5% ± 0.7% at 13 weeks versus SC : 7.8% ± 1.1% at both baseline and 13 weeks (adjusted difference = -0.5%, 95% CI -0.7% to -0.2%, P < 0.001)

Trial 55
B. P. Kovatchev et al., 2020
NCT02985866

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
B. P. Kovatchev et al., 2020	NCT02985866	Randomised Controlled Trial (RCT)	USA	Multi-center	No (open-label)	Yes (1:1)	NA	1. Clinical diagnosis, based on investigator assessment, of type 1 diabetes for at least one year and using insulin for at least 1 year 2. Use of an insulin pump for at least 6 months 3. Age ≥14 years old 4. HbA1c level <10.5% at screening 5. For females, not currently known to be pregnant 6. Willingness not to add glucose-lowering agents (such as Pramlintide, Metformin, GLP-1 analogs, SGLT2 inhibitors) during the study 7. Willingness, if not assigned to the closed-loop group, to avoid use of any closed-loop control system for the duration of the clinical trial 8. Willingness to suspend use of any personal CGM for the duration of the clinical trial once the unblinded study CGM is in use 9. Willingness to establish network connectivity on at least a weekly basis either via local Wifi network or via a study-provided cellular service 10. Currently using no insulins other than one of the following rapid-acting insulins at the time of enrollment: insulin lispro (Humalog), insulin aspart (Novolog), or insulin glulisine (Apidra) 11. Investigator has confidence that the subject can successfully operate all study devices and is capable of adhering to the protocol 12. For subjects less than 18 years old, living with one or more parent/legal guardian (referred to subsequently as diabetes care partner) committed to participating in study training for emergency procedures for severe hypoglycemia and able to contact the subject in case of an emergency	1. Medical need for chronic acetaminophen 2. Use of any glucose-lowering agent (such as Pramlintide, Metformin, GLP-1 analogs, SGLT2 inhibitors) in the 3 months prior to enrollment 3. Hemophilia or any other bleeding disorder 4. A condition, which in the opinion of the investigator or designee, would put the participant or study at risk including any contraindication to the use of any of the study devices per FDA labeling 5. Participation in another pharmaceutical or device trial at the time of enrollment or during the study 6. Use of a closed-loop system within the last month prior to enrollment 7. Employed by, or having immediate family members employed by

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Control-to-Range (CTR) closed-loop (CL)	Sensor-augmented pump (SAP)	3 months	Continuous insulin infusion	127 participants	65 participants	62 participants	Participant (≥14 years)	-Time Below 70 mg/dL CGM-measured % time below 70 mg/dL - 1st co-primary outcome (superiority) -Time Above 180 mg/dL CGM-measured % time above 180 mg/dL - 2nd co-primary outcome (noninferiority)	• Time Below 54 mg/dL • Time Below 60 mg/dL • Time in Range 70-180 mg/dL • Time in Range 70-140 mg/dL • Time Above 250 mg/dL • Time Above 300 mg/dL • Coefficient of Variation	NA	NA

Trial 56
J. Ware et al., 2022
NCT03784027

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
J. Ware et al., 2022	NCT03784027	Randomised Controlled Trial (RCT)-crossover	Luxembourg Austria Germany United Kingdom	Multi-center	No (open-label)	NA	Yes European Commission's Horizon 2020 Framework Programme JDRF	1. Age between 1 and 7 years (inclusive) (Luxembourg and Austria) 2. Age between 2 and 7 years (inclusive) (Germany and UK) 3. Type 1 diabetes as defined by WHO for at least 6 months [WHO definition: 'The aetiological type named type 1 encompasses the majority of cases which are primarily due to beta-cell destruction, and are prone to ketoacidosis. Type 1 includes those cases attributable to an autoimmune process, as well as those with beta-cell destruction for which neither an aetiology nor a pathogenesis is known (idiopathic). It does not include those forms of beta-cell destruction or failure to which specific causes can be assigned (e.g. cystic fibrosis, mitochondrial defects, etc.).'] 4. Insulin pump user (with or without continuous glucose monitoring or flash glucose monitoring system) for at least 3 months, with subject/carer good knowledge of insulin self-adjustment as judged by the investigator 5. On sensor-augmented pump as standard clinical care (extension phase only) 6. Treated with rapid or ultra-rapid acting insulin analogue 7. Subject/carer is willing to perform regular finger-prick blood glucose monitoring, with at least 2 blood glucose measurements taken every day 8. Screening HbA1c ≤ 11% (97mmol/mol) on analysis from local laboratory 9. Willing to wear glucose sensor 10. Willing to wear closed loop system 24/7 during intervention arm 11. The subject/carer is willing to follow study specific instructions 12. The subject/carer is willing to upload pump and CGM data at regular intervals	1. Physical or psychological disease likely to interfere with the normal conduct of the study and interpretation of the study results as judged by the investigator 2. Untreated coeliac disease or thyroid disease based on local investigations prior to study enrolment 3. Current treatment with drugs known to interfere with glucose metabolism, e.g. systemic corticosteroids 4. Use of closed loop insulin delivery within the past 2 months 5. Known or suspected allergy to insulin 6. Carer's lack of reliable telephone facility for contact 7. Subject/carer's severe visual impairment 8. Subject/carer's severe hearing impairment 9. Medically documented allergy towards the adhesive (glue) of plasters or subject is unable to tolerate tape adhesive in the area of sensor placement 10. Serious skin diseases (e.g. psoriasis vulgaris, bacterial skin diseases) located in parts of the body which could potentially be used for localisation of the glucose sensor) 11. Sickle cell disease, haemoglobinopathy; or has received red blood cell transfusion or erythropoietin within 3 months prior to time of screening 12. Plan to receive red blood cell transfusion or erythropoietin over the course of study participation 13. Subject/carer not proficient in English (UK, Germany, Austria, Luxembourg) or German (Germany, Austria, Luxembourg) or French (Luxembourg)

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Closed-loop system - CamAPS FX	Sensor-augmented pump (SAP) + CGM	32 weeks	Continuous insulin infusion	74 particiants	74 participants	74 participants	Children 1 to 7 years of age	The primary end point was the between-treatment difference in the percentage of time that the sensor glucose measurement was in the target range (70 to 180 mg per deciliter) during each 16-week period	Key secondary end points included : - the percentage of time spent in a hyperglycemic state (glucose level, >180 mg per deciliter) - the glycated hemoglobin level - the mean sensor glucose level and - the percentage of time spent in a hypoglycemic state (glucose level, <70 mg per deciliter)	The percentage of time with the glucose level in the target range was 8.7 percentage points higher during the closed-loop period than during the control period (95% confidence interval [CI], 7.4 to 9.9) (P<0.001)	NA

Trial 57
H. R Murphy et al., 2017
NCT03563313

Study characteristics									
Author-year	NCT Number	Study Design	Country	Centers	Blinding	Randomisation NA - crossover trials	Funding	Inclusion criteria	Exclusion criteria
H. R Murphy et al., 2017	NCT03563313	Randomised Controlled Trial (RCT)-crossover	United States	2 centers	No (open-label)	NA	Yes Diabetes UK (UK) National Institute for Health Research (NIHR) (UK)	1. Signed informed consent obtained before study-related activities. Study-related activities are any procedure that would not have been performed during standard medical care. 2. The participant is between 16 and 44 years of age (inclusive), female only 3. The participant has type 1 diabetes (T1DM), as defined by World Health Organisation (WHO) for at least 12 months and has had a viable singleton pregnancy confirmed by ultrasound 4. The participant has been commenced on insulin pump therapy during or prior to pregnancy 5. The participant is able and willing to use a real time continuous sensor	1. Non-type 1 diabetes mellitus including those secondary to chronic disease 2. Any other physical or psychological disease likely to interfere with the normal conduct of the study and interpretation of the study results such as coeliac disease or untreated hypothyroidism 3. Current treatment with drugs known to interfere with glucose metabolism such as systemic corticosteroids, non-selective beta-blockers and monoamine oxidase (MAO) inhibitors 4. Known or suspected allergy against insulin 5. Women with clinically significant nephropathy, neuropathy or proliferative retinopathy as judged by the investigator 6. Documented gastroparesis 7. Very poor glycaemic control i.e. HbA1c greater than or equal to 10% 8. Significant obesity, i.e., body mass index (BMI) at booking greater than 35 kg/m^2 9. Total daily insulin dose greater than 1.5 IU/kg at booking 10. Women who have conceived with in vitro fertilisation (IVF) or assisted reproductive techniques

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	Standard insulin therapy	Duration of trial	Dosing frequency	Total number of participants (n)	Number of participants in hybrid closed-loop system (n)	Number of participants in standard insulin delivery	Age group	Primary endpoint	Secondary endpoint	Glucose target	Glycated haemoglobin A1c
Closed-loop system	Conventional continuous subcutaneous insulin infusion (CSII)	24 h on two occasions - at 19 weeks' gestation - at 23 weeks' gestation	Continuous insulin infusion	12 women	12 women	12 women	Pregnant women between 16 and 44 years of age	Plasma glucose time in target Percentage of time in target (63–140 mg/dL)	• Plasma glucose outcomes Mean plasma glucose (mg/dL) SD of plasma glucose (mg/dL) • Hypoglycemia Percentage of time hypoglycemic <63 mg/dL Percentage of time hypoglycemic ≤50 mg/dL Percentage of time hypoglycemic ≤45 mg/dL Symptomatic hypoglycemia Episodes >45–54 mg/dL Episodes >36–45 mg/dL Episodes <36 mg/dL LBGI* 2.4 (0.9–3.5) • Hyperglycemia Percentage of time hyperglycemic >140 mg/dL Percentage of time hyperglycemic ≥180 mg/dL High blood glucose index • PAEE (kJ/kg) • Insulin Insulin infusion (units/h) SD insulin infusion rate Plasma insulin concentration	Plasma glucose time in target was comparable for closed-loop and conventional CSII (median [interquartile range]: 81 [59-87] vs. 81% [54-90]; P = 0.75)	NA

Trial 58
D Elleri et al., 2014
NCT01629277

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
D Elleri et al., 2014	NCT01629277	Randomised Controlled Trial (RCT)-crossover	United Kingdom	4 centers	No (open-label)	NA	Yes National Institute of Diabetes and Digestive and Kidney Diseases	1. Aged 12-18 years 2. Type 1 diabetes diagnosed for > 1 year 3. Insulin pump treatment for at least 3 months 4. HbA1c between 8 and 12% 5. Subject willing to perform reduction/omission of meal insulin boluses during clinical studies	1. Non-type 1 diabetes mellitus 2. Physical or psychological disease likely to interfere with the normal conduct of the study 3. Current treatment with drugs known to interfere with glucose metabolism 4. Known or suspected allergy against insulin 5. Subjects with clinical significant nephropathy, neuropathy or proliferative retinopathy 6. Total daily insulin dose >= 2 IU/kg/day 7. Pregnancy, planned pregnancy, or breast feeding

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Closed-loop system	Conventional insulin pump therapy	Two 24-hour duration	Continuous insulin infusion	12 participants	12 participants	12 participants	Youth aged 12-18 years	The primary outcome was time spent with plasma glucose in the target range (3.9–10 mmol/l) between 19:00 hours on day 1 and 18:00 hours on day 2	Secondary analyses were additionally evaluated : -plasma glucose after dinner (19:00 hours on day 1 to 02:00 hours on day 2) -plasma glucose after lunch (12:30–18:00 hours on day 2) Results are presented as median (interquartile range [IQR]) or mean (s.d.) values	Plasma glucose levels were in the target range of 3.9-10 mmol/l for a median [interquartile range (IQR)] of 74 (55,86)% of the time during closed-loop therapy with meal announcement and for 62 (49,75)% of the time during conventional therapy (p = 0.26)	NA

Trial 59
B. P. Kovatchev et al., 2014
NCT01714505 & NCT01727817 & NCT01742741

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
B. P. Kovatchev et al., 2014	NCT01714505 & NCT01727817 & NCT01742741	Randomised Controlled Trial (RCT)-crossover	United States Italy France	Multi-center	No (open-label)	NA	Yes JDRF Artificial Project National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases	1. Adults (ages 21–65 years) 2. Clinical diagnosis of type 1 diabetes 3. Experienced insulin pump users 4. HbA1c of 6–9% 5. Predefined insulin pump parameters for basal rates, carbohydrate ratios, and correction factors 6. Proper mental status/cognition	1. Recent history of diabetic ketoacidosis or severe hypoglycemia 2. Pregnancy, breast feeding, or intention of becoming pregnant (females); 3. Uncontrolled arterial hypertension 4. Conditions that may increase the risk of hypoglycemia or infections

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Closed-loop system	Open loop system - Conventional continuous subcutaneous insulin infusion (CSII)	Two 40-hour duration	Continuous insulin infusion	18 participants	18 participants	18 participants	Participants aged 21 to <65 years	The primary objective of the study was to estimate the effect size of hypoglycemia risk reduction on CLC versus open loop (OL; defined as CGM-augmented insulin pump treatment) in an outpatient setting	Secondary objectives included : - comparing markers of frequency of hypoglycemia - time within the target range of 3.9–10 mmol/L - average glycemic control on CLC versus OL	Slight decrease in percentage of time in the target range of 3.9-10 mmol/L (66.1 vs. 70.7%) (8.9 vs. 8.4 mmol/L; P = 0.04) on CLC versus OL.	NA

Trial 60
S A McAuley et al., 2020
ACTRN12617000520336

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
S A McAuley et al., 2020	ACTRN12617000520336	Randomised Controlled Trial (RCT)	Australia	Multi-center	No (open-label)	Yes (1:1)	Yes JDRF Australia T1DCRN National Health and Medical Research Council (NHMRC)	1. Type 1 diabetes 2. Insulin delivered via either multiple daily (basal and bolus) injections, or via insulin pump (for at least 3 months) 3. HbA1c <= 10.5%	1. Chronic kidney disease (eGFR <45mL/min/1.73m2) 2. Current use of real-time CGM 3. Use of non-insulin glucose-lowering agent in the past 3 months 4. Steroid use (oral or injected) within past 3 months 5. Pregnancy

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Hybrid closed-loop system	Standard insulin therapy - insulin pump / MDI	26 weeks	Continuous (pump) / MDI	120 participants	61 participants	59 participants	Adult (≥18 years)	The primary outcome was masked CGM time in range (TIR; 70–180 mg/dL) during the final 3 weeks	Secondary glucose outcomes included: the proportion of time that glucose was above and below thresholds the proportion of time that glucose was outside the target range mean glucose glucose SD coefficient of variation (CV) HbA1c	TIR increased in HCL group HCL group: increased from (baseline) 55% (13%) to (26 weeks) 70% (10%) the control group remaiin unchanged: (baseline) 55% (12%) and (26 weeks) 55% (13%) (difference 15% [95% CI 11, 19]; P < 0.0001)	HbA1c was lower in HCL therapy than in standard insulin therapy group (median [95% CI] difference -0.4% [-0.6, -0.2]; -4 mmol/mol [-7, -2]; P < 0.0001)

Trial 61
S.A. Brown et al., 2019
NCT03563313

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
S.A. Brown et al., 2019	NCT03563313	Randomised Controlled Trial (RCT)	United States	Multi-center	No (open-label)	Yes (2:1)	Yes National Institute of Diabetes and Digestive and Kidney Diseases	1. Clinical diagnosis, based on investigator assessment, of type 1 diabetes for at least one year and using insulin for at least 1 year. 2. Familiarity and use of a carbohydrate ratio for meal boluses. 3. Age ≥14.0 years old. 4. For females, not currently known to be pregnant. If female and sexually active, must agree to use a form of contraception to prevent pregnancy while a participant in the study. A negative serum or urine pregnancy test will be required for all females of child-bearing potential. Participants who become pregnant will be discontinued from the study. Also, participants who during the study develop and express the intention to become pregnant within the timespan of the study will be discontinued. 5. For participants <18 years old, living with one or more parent/legal guardian knowledgeable about emergency procedures for severe hypoglycemia and able to contact the participant in case of an emergency. 6. Willingness to suspend use of any personal CGM for the duration of the clinical trial once the study CGM is in use. 7. Willingness to use a regular insulin pump during the study with no automatic insulin adjustment based on glucose level when assigned to participate in an SAP group 8. Investigator has confidence that the participant can successfully operate all study devices and is capable of adhering to the protocol. 9. Willingness to switch to lispro (Humalog) or aspart (Novolog) if not using already, and to use no other insulin besides lispro (Humalog) or aspart (Novolog) during the study. 10. Total daily insulin dose (TDD) at least 10 U/day. 11. Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial.	1. Concurrent use of any non-insulin glucose-lowering agent other than metformin (including GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas). 2. Hemophilia or any other bleeding disorder. 3. A condition, which in the opinion of the investigator or designee, would put the participant or study at risk. 4. Participation in another pharmaceutical or device trial at the time of enrollment or during the study. 5. Employed by, or having immediate family members employed by Tandem Diabetes Care, Inc. or TypeZero Technologies, LLC, or having a direct supervisor at place of employment who is also directly involved in conducting the clinical trial (as a study investigator, coordinator, etc.); or having a first-degree relative who is directly involved in conducting the clinical trial.

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Closed-loop system	Sensor-augmented pump (SAP)	6 months	Continuous insulin infusion	168 participants	112 participants	56 participants	Participants aged 14-71 years	The percentage of time that the blood glucose level was within the target range of 70 to 180 mg per deciliter (3.9 to 10.0 mmol per liter), as measured by continuous glucose monitoring	• Percentage of time that the glucose level was >180 mg per deciliter • Mean glucose level • Glycated hemoglobin level • Percentage of time that the glucose level was <70 mg per deciliter or <54 mg per deciliter [3.0 mmol per liter])	The mean (±SD) percentage of time that the glucose level was within the target range -in the closed-loop group: increased from 61±17% at baseline to 71±12% during the 6 months and -in the control group: remained unchanged at 59±14% (mean adjusted difference, 11 percentage points; 95% confidence interval [CI], 9 to 14; P<0.001)	The mean adjusted difference in glycated hemoglobin level after 6 months was -0.33 percentage points (95% CI, -0.53 to -0.13; P = 0.001) favouring closed-loop

Trial 62
R Nimri et al., 2013
NCT01238406

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
R Nimri et al., 2013	NCT01238406	Randomised Controlled Trial (RCT)-crossover	Slovenia Germany Israel	3 centers	No (open-label)	NA	NA	1. Age ≥ 10 yr 2. T1DM diagnosed for more than 1 yr 3. Current use of CSII therapy for at least 3 months 4. A1c at inclusion ≥7 and <10%, 5. BMI (body mass index) below the 97th percentile for age	1. Patients with a concomitant disease affecting metabolic control or any other medical condition that could compromise their safety during the trial were 2. Patients with a known or suspected allergy to the trial products or who had participated in another study involving drugs that could affect glucose measurements or glucose management

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Closed-loop insulin delivery by MDLAP	Continuous subcutaneous insulin infusion (CSII)	2 overnight sessions	Continuous insulin infusion	12 participants	12 participants	12 participants	Participant (≥10 years)	The number of hypoglycemic events below 63 mg/dL	• Percentage of time spent in the target range defined as sensor glucose level within 63–140 mg/dL • Percentage of time spent above and below target • Percentage of time spent in the tight normal range defined as sensor glucose level within 80–120 mg/dL [average (SD) and median glucose levels]	The percentage of time spent in the near normal range of 63-140 mg/dL was significantly higher in the overnight closed-loop sessions than during CSII therapy in the overnight closed-loop sessions : [76% (54-85)] in the CSII therapy : [29% (11-44)] [p = 0.02, median (interquartile range)]	NA

Trial 63
R. P. Wadwa et al., 2023
NCT04796779

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
R. P. Wadwa et al., 2023	NCT04796779	Randomised Controlled Trial (RCT)	United States	3 centers	No (open-label)	Yes (2:1)	Yes National Institute of Diabetes and Digestive and Kidney Diseases	1. Clinical diagnosis, based on investigator assessment, of type 1 diabetes for at least 6 months and using insulin for at least 6 months 2. Familiarity and use of a carbohydrate ratio for meal boluses. 3. Age ≥2 and <6 years old 4. Living with one or more parent/legal guardian knowledgeable about emergency procedures for severe hypoglycemia and able to contact emergency services and study staff. 5. Investigator has confidence that the parent can successfully operate all study devices and is capable of adhering to the protocol 6. Willingness to switch to lispro (Humalog) or aspart (Novolog) if not using already, and to use no other insulin besides lispro (Humalog) or aspart (Novolog) during the study for participants using a study-provided Tandem pump during the study. • Study will not be providing insulin; therefore, participants will need to have access to either lispro or aspart 7. Total daily insulin dose (TDD) at least 5 U/day 8. Body weight at least 20 lbs. 9. Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial (see section 2.3) 10. Participant and parent(s)/guardian(s) willingness to participate in all training sessions as directed by study staff. 11. Parent/guardian proficient in reading and writing English.	1. Concurrent use of any non-insulin glucose-lowering agent (including Glucagon-like peptide-1 [GLP-1] agonists, Symlin, Dipeptidyl peptidase-4 [DPP-4] inhibitors, Sodium-glucose Cotransporter-2 (SGLT-2) inhibitors, sulfonylureas). 2. Hemophilia or any other bleeding disorder 3. History of >1 severe hypoglycemic event with seizure or loss of consciousness in the last 3 months 4. History of >1 DKA event in the last 6 months not related to illness, infusion set failure, or initial diagnosis 5. History of chronic renal disease or currently on hemodialysis 6. History of adrenal insufficiency 7. Hypothyroidism that is not adequately treated 8. Use of oral or injectable steroids within the last 8 weeks 9. Known, ongoing adhesive intolerance 10. Plans to receive blood transfusions or erythropoietin injections during the course of the study 11. A condition, which in the opinion of the investigator or designee, would put the participant or study at risk (specified in the study procedure manual) 12. Currently using any closed-loop system, or using an insulin pump that is incompatible with use of the study CGM 13. Participation in another pharmaceutical or device trial at the time of enrollment or during the study 14. Employed by, or having immediate family members employed by Tandem Diabetes Care, Inc., or having a direct supervisor at place of employment who is also directly involved in conducting the clinical trial (as a study investigator, coordinator, etc.); or having a first-degree relative who is directly involved in conducting the clinical trial

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Closed-loop system of insulin delivery	Standard care (an insulin pump or multiple daily injections of insulin plus a CGM)	13 weeks	Continuous insulin infusion	102 children	68 children	34 children	Children 2-6 years old	The percentage of time that the glucose level was in the target range of 70 to 180 mg per deciliter, as measured by continuous glucose monitoring	• The percentage of time that the glucose level was above 250 mg per deciliter or below 70 mg per deciliter • The mean glucose level • The glycated hemoglobin level • Safety outcomes	The mean (±SD) percentage of time that the glucose level was within the target range increased from baseline during the 13-week follow-up period in the closed-loop group in the closed-loop group: from 56.7±18.0% at baseline to 69.3±11.1% during the 13-week follow-up period in the standard-care group: from 54.9±14.7% at baseline to 55.9±12.6% during the 13-week follow-up period (mean adjusted difference, 12.4 percentage points [equivalent to approximately 3 hours per day] 95% confidence interval, 9.5 to 15.3; P<0.001)	The glycated hemoglobin level was improved favoring the closed-loop system

Trial 64
J. Kropff et al., 2015
NCT02153190

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
J. Kropff et al., 2015	NCT02153190	Randomised Controlled Trial (RCT)-crossover	France Italy Netherlands	3 centers	No (open-label)	NA	Yes European Commission	1. Age ≥ 18 et < 70 years old 2. Having diabetes according to WHO criteria for at least 6 months, and Type 1 diabetes according to ADA criteria 3. Under basal-bolus insulin therapy using an external insulin pump for at least 3 months 4. BMI < 35 kg/m² 5. Willing to wear a CGM device for the whole duration of the study, except during washout period, combined with the DiAs platform during the evening and night-time for 2 months 6. Trained in carbohydrate counting 7. HbA1c > 7.5 % and < 10% 8. If on antihypertensive, thyroid, anti-depressant or lipid lowering medication, stability on the medication for at least 1 month prior to study inclusion 9. Willing to undergo all study procedures 10. Informed consent signed	1. Pregnancy or breast feeding, or intention to be pregnant during the study duration 2. Use of a medication that significantly impacts glucose metabolism, e.g. steroids 3. Uncontrolled hypertension with resting blood pressure over 140/90 mmHg 4. Patient plans to go abroad during the trial period 5. Patient is expected to be out-of-home in the evening and during night time (e.g. shift-workers, etc.) more than 25% of a study period 6. Patient does not hold any nearby party for assistance if needed 7. Patient with severe hypoglycemia including coma, mental confusion and/or convulsions requesting IV glucose injection or glucagon injection during the last year. 8. Presence of any malignant disease, unless considered as cured for more than 10 years 9. History of acute cardiovascular event during the prior year 10. History of diabetic keto-acidosis during the prior 6 months 11. Renal insufficiency with creatinin > 150 µmol/L 12. Impairment of liver status estimated from ASAT/ALAT plasma levels > 2x upper limits of normal values 13. Impaired cognitive or psychological abilities which may result in defective adherence to study conditions

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Artificial Pancreas system	Sensor-augmented pump (SAP)	4 months	Continuous insulin infusion	34 participants	34 participants	34 participants	Adults aged 18-69 years	The percentage of time spent in the target glucose concentration range (3·9-10·0 mmol/L) from 2000 to 0800 h	• The percentage of time spent in the target range (3·9–10·0 mmol/L) over 24 h • Early morning (0600–0700 h) blood glucose concentration • Mean blood glucose • Percentage of time spent below 3·9 mmol/L (hypoglycaemia) and above 10·0 mmol/L(hyperglycaemia) • Daily insulin use • Change in HbA1c • Percentage of time spent in closed-loop control (defi ned as the actual time spent in closed loop compared with maximum theoretical use)	During 2000-0800 h, the mean time spent in the target range was higher with AP than with SAP use: 66·7% versus 58·1% (paired difference 8·6% [95% CI 5·8 to 11·4], p<0·0001)	Decrease in mean HbA1c during the AP period was significantly greater than during the control period (-0·3% vs -0·2%; paired difference -0·2 [95% CI -0·4 to -0·0], p=0·047)

Trial 65
M. Tauschmann et al., 2016
NCT01873066

Study characteristics									
Author-year	**NCT Number**	**Study Design**	**Country**	**Centers**	**Blinding**	**Randomisation NA - crossover trials**	**Funding**	**Inclusion criteria**	**Exclusion criteria**
M. Tauschmann et al., 2016	NCT01873066	Randomised Controlled Trial (RCT)-crossover	United Kingdom	Single-center	No (open-label)	NA	Yes National Institute of Diabetes and Digestive Kidney Diseases JDRF National Institute for Health Research Cambridge Biomedical Research Centre Wellcome Strategic Award	1. The subject is between 10 and 18 years of age (inclusive) 2. The subject has type 1 diabetes, as defined by WHO for at least 1 year or is confirmed C-peptide negative 3. The subject/carer will have been an insulin pump user for at least 3 months, with good knowledge of insulin self-adjustment as judged by the investigator 4. The subject/carer is willing to perform regular finger-prick blood glucose monitoring, with at least 4 blood glucose measurements taken every day 5. HbA1c between 7.0% and 11.0 % (53 to 97mmol/mol) based on analysis from central laboratory or equivalent 6. The subject is literate in English 7. The subject is willing to wear closed-loop system at home and at school / college / work 8. The subject is willing to follow study specific instructions	1. Non-type 1 diabetes mellitus including those secondary to chronic disease 2. Any other physical or psychological disease or condition likely to interfere with the normal conduct of the study and interpretation of the study results as judged by the investigator. 3. Current treatment with drugs known to have significant interference with glucose metabolism, such as systemic corticosteroids, as judged by the investigator 4. Known or suspected allergy against insulin 5. Subjects with clinically significant nephropathy, neuropathy or proliferative retinopathy as judged by the investigator 6. Significantly reduced hypoglycaemia awareness as judged by the investigator 7. Total daily insulin dose ≥ 2 IU/kg/day 8. Total daily insulin dose <10 IU/day 9. Reduced hypoglycaemia awareness 10. Pregnancy, planned pregnancy or breast feeding 11. Severe visual impairment 12. Severe hearing impairment 13. Subjects using implanted internal pacemaker 14. Lack of reliable telephone facility for contact

Intervention characteristics				Participant characteristics				Outcomes			
Hybrid closed-loop system	**Standard insulin therapy**	**Duration of trial**	**Dosing frequency**	**Total number of participants (n)**	**Number of participants in hybrid closed-loop system (n)**	**Number of participants in standard insulin delivery**	**Age group**	**Primary endpoint**	**Secondary endpoint**	**Glucose target**	**Glycated haemoglobin A1c**
Hybrid closed-loop system	Sensor-augmented pump (SAP)	42 days	Continuous insulin infusion	12 adolescents	12 adolescents	12 adolescents	Adolescents between 10 and 18 years of age	The proportion of time that sensor glucose was in the target range (3.9-10 mmol/L; primary end point	• Mean sensor glucose concentrations • Glucose variability • Time spent at glucose levels 3.9 mmol/L (hypoglycemia) and .10.0 mmol/L (hyperglycemia) • Insulin delivery	The proportion of time that sensor glucose was in the target range (3.9-10 mmol/L; primary end point) was increased during the closed-loop intervention compared with sensor-augmented insulin pump therapy by 18.8 ± 9.8 percentage points (mean ± SD; P < 0.001)	NA