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Published in:
Journal of Diabetes Science and Technology

DOI (link to publication from Publisher):
10.1177/19322968221145964

Publication date:
2024

Document Version
Accepted author manuscript, peer reviewed version

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Time for using Machine Learning for Dose Guidance in Titration of People with Type 2 Diabetes? A Systematic Review of Basal Insulin Dose Guidance

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Abbreviations: (T2D) Type 2 diabetes, (PROSPERO) International Prospective Register of Systematic Reviews, (PRISMA) Preferred Reporting Items for Systematic Reviews and Meta-analyses, (JBI) Joanna Briggs Institute, (RCT) randomized controlled trial, (HCP) healthcare professional, (DTSQ) Diabetes Treatment Satisfaction Questionnaire

Keywords: Basal insulin, dose guidance, glycemic control, insulin titration, type 2 diabetes, systematic review

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Funding Source: None

Conflict-of-Interest Disclosure: Author P.V. is head of research at the Steno Diabetes Center North Denmark, funded by the Novo Nordisk Foundation. Author M.H.J is a former Novo Nordisk employee and holds Novo Nordisk shares.

Acknowledgments: Research librarian Connie Skrubbeltrang, who provided competent assistance in the literature search

Figure and table count: 4 figures, 6 tables

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Abstract:

Background: Real-world studies of people with Type 2 Diabetes (T2D) have shown insufficient dose adjustment during basal insulin titration in clinical practice leading to suboptimal treatment. Thus, 60% of people with T2D treated with insulin do not reach glycemic targets. This emphasizes a need for methods supporting efficient and individualized basal insulin titration of people with T2D. However, no systematic review of basal inulin dose guidance for people with T2D has been found.

Objective: To provide an overview of basal insulin dose guidance methods that support titration of people with T2D and categorize these methods by characteristics, effect, and user experience.

Methods: The review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. Studies about basal insulin dose guidance, including adults with T2D on basal insulin analogs published before 07/09/2022, were included. Joanna Briggs Institute critical appraisal checklist was applied to assess risk of bias.

Results: In total, 35 studies were included, and three categories of dose guidance were identified: paper-based titration algorithms, telehealth solutions, and mathematical models. Heterogeneous reporting of glycemic outcomes challenged comparison of effect between the three categories. Few studies assessed user experience.

Conclusions: Studies mainly used titration algorithms to titrate basal insulin as telehealth or in paper format, except for studies using mathematical models. A numerically larger proportion of participants seemed to reach target using

telehealth solutions compared to paper-based titration algorithms. Exploring capabilities of machine learning may provide insights that could pioneer future research while focusing on holistic development.

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1. Introduction

Initiation of basal insulin is a complex and time-consuming task associated with clinical inertia[1–5]. Thus, approximately 60% of people with T2D treated with insulin do not reach glycemic targets[4,6–8]. Insulin titration is used when determining the optimal dose for an individual[2,4,9]. This is necessary since people with T2D vary in pancreatic insulin production and insulin resistance[9,10]. Hence, the optimal dose of basal insulin differs among people with T2D and may change over time due to, e.g., stress levels, lifestyle changes, and sickness.

Suboptimal treatment is partly caused by non-adherence to treatment and failure to initiate or intensify treatment promptly[9,11]. Lack of adjustment to insulin treatment is mainly caused by the complexity of the titration process[5]. This causes people with T2D to remain on suboptimal insulin doses, leading to less improvement in glycemic control than what could have been accomplished with an optimal dose[5,12,13]. In addition, studies based on real-world data have shown both a delay in the initiation of basal insulin and insufficient dose adjustment during titration[1,14,15]. Suboptimal insulin titration has been shown in the range of 3-12 months after initiation of active titration in clinical practice[3,6,16–19]. This elucidates that people with T2D, in some cases, have not reached glycemic target after 3+ months of active titration. Failure to achieve glycemic targets during the initial three months of titration is associated with a higher risk of failure to reach glycemic targets two years after the initiation[15]. This emphasizes the need for dose guidance supporting efficient and individualized basal insulin titration of people with T2D to provide optimal and timely treatment.

In recent years, basal insulin dose guidance has been of rapidly growing interest within international research, emphasized by increased publications on the subject.

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Despite this interest and the fact that it has been a research field for several decades, a preliminary search of the Cochrane Database of Systematic Reviews and Reviews, the International Prospective Register of Systematic Reviews (PROSPERO), and Joanna Briggs Institute (JBI) Evidence Synthesis revealed no systematic review of basal inulin dose guidance for people with T2D. Therefore, this systematic review aims to provide an overview of methods used for basal insulin dose guidance supporting titration of people with T2D and categorize these methods by characteristics, effect, and user experience.

2. Methods

2.1 Study Design

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[20]. Therefore, a protocol was registered in PROSPERO on 19/12/2021 (CRD42021289364), forming the review's basis [21].

2.2 Eligibility Criteria

Studies evaluating dose guidance methods supporting basal insulin titration of people with T2D in any setting, including participants (≤18 years) diagnosed with T2D, were considered. Studies investigating populations of mixed diabetes types without a transparent subgroup analysis or without a clear statement of diabetes types were excluded.

Studies including participants on basal-bolus regimens, human or intermediate insulin, or other injectable antidiabetic treatment were excluded.

Primary studies reporting any glycemic outcome published in English, Danish, Norwegian, or Swedish before 07/09/2022, as peer-reviewed full-text, were

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77 included. All study designs except study protocols, animal research, expert opinions,
78 and case studies were considered.

79 **2.3 Information sources and search strategy**

80 A comprehensive systematic search was performed in PubMed, Embase, and IEEE
81 by one author (C.H.N.T) with assistance from a research librarian. Citation and
82 reference searches were conducted in Google Scholar. Authors of relevant studies
83 were contacted if additional information was needed.

84 Unstructured searches in PubMed and Google Scholar were performed to identify
85 relevant search terms. The search was adjusted to each database. Search terms
86 included different synonyms and spellings. Search functions were applied, including
87 thesaurus, Boolean operators, phrase, truncation, free text, and advanced search
88 (Supplementary material).

89 **2.4 Selection process**

90 First, studies identified through the systematic search were uploaded to RefWorks
91 (version 2.1.0.1). Second, duplicates were removed using the functions *Exact*
92 *duplicates* and *Close duplicates*. Third, one reviewer (C.H.N.T.) screened the title
93 and abstract of the remaining studies. Fourth, studies deemed eligible were
94 retrieved in full text and assessed by one reviewer (C.H.N.T.). Doubt about the
95 studies' eligibility was resolved through discussion with co-authors. Reason for
96 exclusion of studies was recorded during full-text assessment (Supplementary
97 material). The final sample consisted of studies deemed eligible after full-text
98 assessment.

99 **2.5 Data extraction and synthesis**

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One author (C.H.N.T.) extracted data using a sheet in Microsoft Excel (2016). Extracted data included study characteristics (title, author, publication year, study design, country, sample size, and duration of study), participant characteristics (age, sex, BMI, insulin-naïve, and initial HbA1c), characteristics of the dose guidance method (setting, description of the method, and type of insulin used), and glycemic outcomes.

A narrative synthesis of extracted data was conducted, and characteristics of studies and populations were described. The narrative synthesis focused on categorizing dose guidance methods and assessing effect of the interventions and user experience according to the categorization.

2.6 Risk of bias assessment

Critical appraisal tools from JBI were applied by study design of the studies to assess risk of bias[22]. Study design was determined using Andrews and Likis, 2015[23]. One author (C.H.N.T.) assessed included studies with support from co-authors.

Before critical appraisal was performed, authors agreed on a scoring system and cut-off points per the JBI reviewers manual[24]. Studies were judged as described in Melo et al., 2018[25].

A suitable tool for simulation studies was not found from JBI; therefore, the critical appraisal tool from Fone et al., 2003[26] was used.

3. Results

3.1 Study selection

A total of 4,363 papers were found. After removing duplicates, 3,327 papers were included in title and abstract screening. Of those, 280 papers were found eligible for full-text screening. Thirty-one papers met the inclusion criteria and were included in

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the review. Four additional papers were identified through reference and citation searches. Thus, 35 articles were included in this review. The selection process is presented in Figure 1. Supplementary material contains a tabular overview of data extracted from the included studies.

Some studies seemed eligible but were excluded due to use of human insulin or basal-bolus regimen in a subgroup of participants without a transparent subgroup analysis of participants treated only with basal insulin analogs or using bolus insulin as rescue medication[13,27–29].

Figure 1. The selection process is illustrated in a PRISMA flowchart[20].

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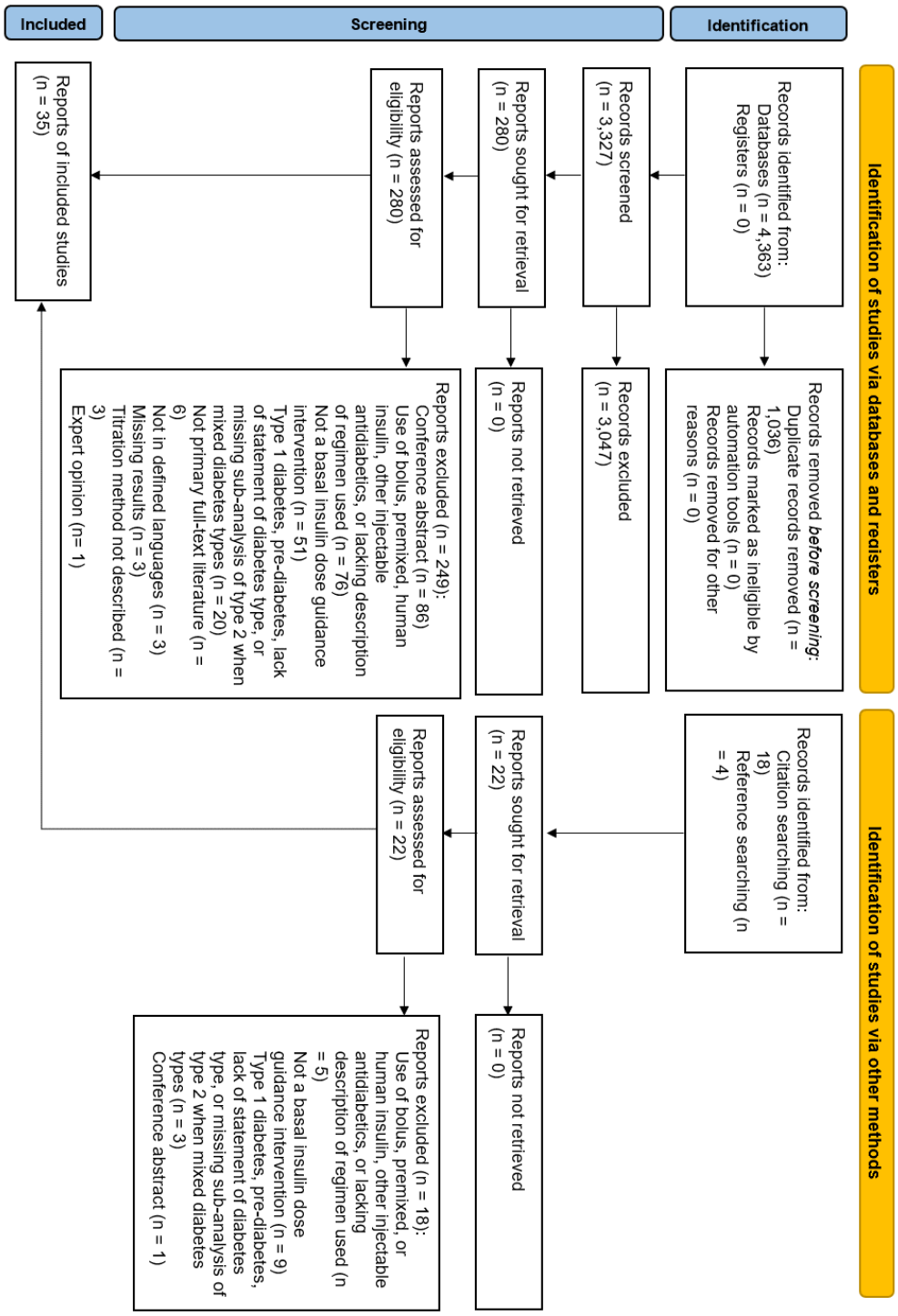

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134 **3.2 Study characteristics**

135 Seven studies were quasi-experimental design[30–36], 20 studies were randomized

136 controlled trials (RCT)[37–56], three studies were mixed method[57–59], one study was

137 qualitative design[60], one study was a cohort[61], and three studies were simulation

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design[8,10,62]. Mixed method studies were a mix of quasi-experimental and qualitative designs. The studies were published from 2006 to 2022 and enrolled 19,432 people with T2D. The length of the studies ranged from 28 days to 12 months.

The studies were conducted in 31 countries across Europa, Asia, North and South America, the Middle East, and Africa. Seven studies did not specify in which country it was conducted[8,10,32,48,55,61,62].

3.3 Participant characteristics

Characteristics of participants were similar regarding initial BMI, age, and sex distribution. The most significant difference was whether participants were insulin naïve at start-of-trial. Study population in 60% of the studies were insulin naïve[8,10,31,34,35,37,39–41,45,46,48–51,53,56–58,61,62]. In 14% of studies, the population continued basal insulin treatment initiated before the study[30,32,33,36,43], and 26% of studies included a study population of both insulin naïve and continuers[38,42,44,47,52,54,55,59,60]. Initial HbA1c, duration of diabetes, and whether the study population was insulin naïve are essential factors to consider when comparing the impact on glycemic control from dose guidance interventions[15,63–67]. All study populations had initial HbA1c above 7%, and diabetes duration ranged from 2.9-15.9 years.

3.4 Characteristics of the dose guidance methods

Twenty-one of identified dose guidance methods were developed for titration of glargine[30,32,34,36–39,41,42,44,45,47,49,51,53–56,58,61,62], three for detemir[40,48,52], five for degludec[8,10,31,43,46], one for icodec[50], and one for glargine and detemir[59]. Four studies did not specify insulin further than it was basal insulin analogs[33,35,57,60].

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Approximately 70% of the studies were in an outpatient clinic. The remaining studies were in primary care[34,35,42,51,52,61] or did not specify the setting[8,10,36,50,62].

3.4.1. Categorization of the dose guidance methods

Identified dose guidance methods were divided into three categories: paper-based titration algorithms, telehealth solutions, and mathematical models (Figure 2).

Paper-based titration algorithms reflect standard practice at the time of writing. The studies investigated algorithms with varying targets and sizes of dose adjustment carried out during in-person visits. In total, 20 studies investigated paper-based titration algorithms[32,34,36–38,40–43,46,48–53,56,58,61,62].

Telehealth solutions covered telemonitoring solutions with titration across a digital platform[30,45,54,57,59,60] and combined with home visits [35], or self-titration decision support[33,39,44,47,55]. In contrast to studies addressing paper-based algorithms, the organizational setup was altered in these studies. Interactions between participants and healthcare professionals (HCP) were primarily handled over distance via phone. In total, 12 studies investigated telehealth solutions[30,33,35,39,44,45,47,54,55,57,59,60].

Mathematical models were investigated by three studies using used compartment modeling and control theory [8,10,31]. Most of these studies did not specify the use case of the method.

Figure 2. Overview of type of dose guidance methods used in the included studies.

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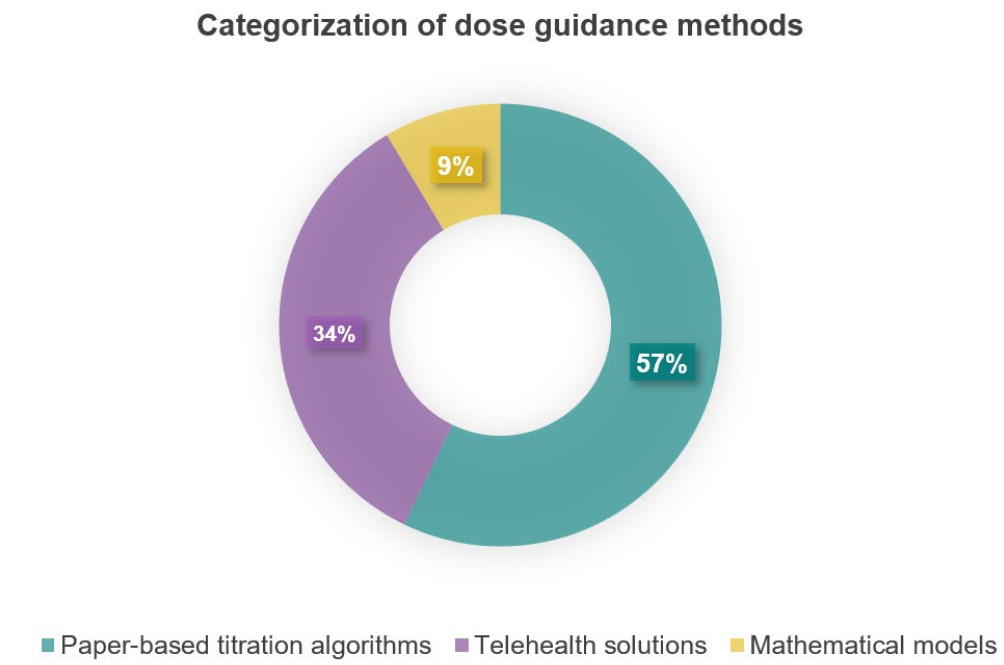
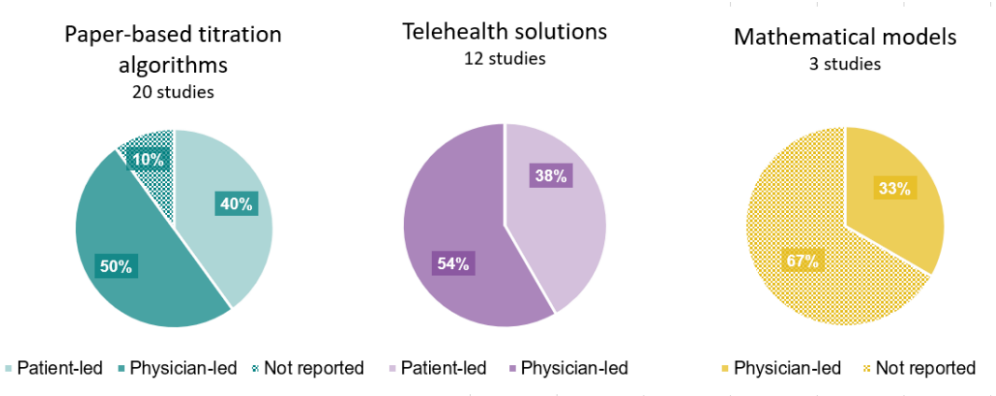


181 Dose guidance methods covered both physician- and patient-led methods. The
182 distribution was similar for paper-based titration algorithms and telehealth
183 solutions, where most approaches based on mathematical models did not specify
184 the intended user (Figure 3).

185 **Figure 3.** Distribution of the intended user of the identified dose guidance methods
186 according to the three main categories: paper-based titration algorithms, telehealth
187 solutions, and mathematical models.



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189 Description of the dose guidance method is presented in Table 1.

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190 **Table 1.** Overview of how basal insulin was titrated in the included studies grouped

191 by the titration algorithm used.

Study	Description of dose guidance method	Category
Yuan et al. 2021[37]	2-0-2 titration algorithm according to three different fasting blood glucose targets; 70<FBG≤100, 100<FBG≤110, or 110<FBG≤126 mg/dL. Titrated based on the lowest of three consecutive fasting SMBG values.	Paper-based titration algorithm
Zhang et al. 2018[58]	Comparison of the use of a titration algorithm to reach different glycemic targets (Group 1: 70 <FBG≤100 mg/dL, Group 2: 100<FBG<110 mg/dL, and Group 3: 110<FBG≤126 mg/dL) The titration algorithm used was a modification of the 2-0-2 algorithm.	Paper-based titration algorithm
Misra et al. 2019[41]	2-0-2-4 titration algorithm as patient-led compared to physician-led. Insulin doses were titrated every three days.	Paper-based titration algorithm
McGloin et al. 2020[57]	MyMedic hub. Telemonitoring system where people with T2D were titrated	Telehealth solution

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	using a 2-0-2 titration algorithm twice weekly for three weeks and once weekly after that.	
Ngassa Pioti et al. 2022[35]	Nurse-driven and home-based telehealth intervention where participants were titrated using the 2-0-2 titration algorithm to reach the target of 72-126 mg/dL.	Telehealth solution
Seufert et al. 2019[61]	2-0-2 titration algorithm (adjusted every three days) compared to the 2-0-2-4-6-8 titration algorithm (adjusted every 3-5 days).	Paper-based titration algorithm
Kadowaki et al. 2017[43]	2-0-2 titration algorithm compared to the 2-0-2-4-6-8 titration algorithm at both fixed dosing and flexible dosing. Adjustments to insulin doses were made weekly.	Paper-based titration algorithm
Kennedy et al. 2006[49]	Comparison of usual and active insulin titration using the 2-0-2-4-6-8 titration algorithm. If fasting blood glucose was below 70 mg/dL insulin dose was decreased to the previous dose.	Paper-based titration algorithm

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Yu et al. 2020[40]	3-0-3 titration algorithm compared to the 2-4-6-8 titration algorithm. Titration was performed per three days.	Paper-based titration algorithm
Blonde et al. 2009[48]	3-0-3 titration algorithm to the target of 70-90 mg/dL compared to 79-110 mg/dL. Adjustments to insulin doses were made every three days.	Paper-based titration algorithm
Meneghini et al. 2007[52]	3-0-3 titration algorithm, where adjustments were made every three days, compared to standard-of-care, where adjustments were made at the physician's discretion.	Paper-based titration algorithm
Hsu et al. 2016[45]	Diabetes management program. Telemonitoring system where the 3-0-3 titration algorithm was used to reach the target of 79-110 mg/dL.	Telehealth solution
Philis-Tsimikas et al. 2013[46]	4-0-4 titration algorithm compared to the 4-2-0-2-4-6-8 titration algorithm. Adjustments of doses were made weekly based on one and the lowest of three	Paper-based titration algorithm

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	consecutive days of fasting SMBG measure, respectively.	
Lingvay et al. 2021[50]	Comparison of four titration algorithms: three for icodec and one for glargine. Glargine: 4-0-4 titration algorithm to target 79-130 mg/dL Icodec titration A: 21-0-21 titration algorithm to target 79-130 mg/dL Icodec titration B: 28-0-28 titration algorithm to target 79-130 mg/dL (equivalent to the titration algorithm used for glargine) Icodec titration C: 28-0-28 titration algorithm to target 70-108 mg/dL	Paper-based titration algorithm
Garg et al. 2015[51]	2-0-2-4 titration algorithm as patient-led compared to physician-led. In the physician-led titration, group doses were adjusted at each visit, whereas doses were adjusted twice weekly in the patient-led titration group.	Paper-based titration algorithm

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Sethi et al. 2022[36]	Using the 2-0-2-4 titration algorithm to reach HbA1c<7%. The frequency of dose adjustments was made at least weekly and not more than every 3–4 days unless required for safety.	Paper-based titration algorithm
Ji et al. 2020[53]	2-0-2-4-6 titration algorithm at a standard starting dose (0.2 U/kg) or a higher starting dose (0.3 U/kg).	Paper-based titration algorithm
Bajaj et al. 2016[44]	LTHome/MyStar WebCoach. Decision support system for self-titration using the 4-2-0-2-4 titration algorithm to the target 90-130 mg/dL.	Telehealth solution
Davies et al. 2019[55]	MyStar DoseCoach. Decision support system for self-titration using the 4-2-0-2-4 titration algorithm to reach the 90-130 mg/dL target.	Telehealth solution
Kim et al. 2010[47]	Decision support system for self-titration using the 4-2-0-2-4-6 titration algorithm to the target 79-119 mg/dL.	Telehealth solution

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Hu et al. 2021[39]	Self-titration decision support program. One in-person visit was followed by five phone calls where insulin dose adjustments were made if needed, along with empowering coaching from a nurse. Otherwise, the participants self-titrated. Titration algorithm used: 6-4-2-0-2-4-6 to target 79-110 mg/dL.	Telehealth solution
Levy et al. 2018[59]	Mobile Insulin Titration Intervention (MITI). Telemonitoring system where participants were titrated using the 2-1-0-2-3-4-5 titration algorithm through weekly phone calls.	Telehealth solution
Rogers et al. 2019[60]	MITI. Telemonitoring system where participants were titrated using the 2-1-0-2-3-4-5 titration algorithm through weekly phone calls to reach the target of 79-130 mg/dL.	Telehealth solution
Levy et al. 2015[54]	MITI. Telemonitoring system where participants were titrated using the 2-1-0-	Telehealth solution

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	2-3-4-5 titration algorithm through weekly phone calls.	
Bae et al. 2022[38]	Comparison of the INSIGHT and EDITION titration algorithm. INSIGHT: titrate by one unit/day. EDITION: titrate by three units per three days.	Paper-based titration algorithm
Yale et al. 2017[42]	Comparison of the paper-based titration algorithm INSIGHT and EDITION. In the INSIGHT group, insulin was titrated by one unit/day. In the EDITION group, insulin was titration by three units per three days based on median pre-breakfast SMBG values of the last three days.	Paper-based titration algorithm
Hasan et al. 2018[34]	ADA/EASD consensus titration algorithm of 2009. Increased with two units every three days until target (70-130 mg/dL)	Paper-based titration algorithm

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	reached. If fasting blood glucose is >180 mg/dL, increase by four units every three days; if fasting blood glucose is <70 mg/dL, reduce by four units or 10% if >60 units.	
Larsen et al. 2010[33]	Electronic diary app to support self-titration by increasing dose by two units every three days if two of the previous three days' fasting SMBG measures >121 mg/dL and no readings were <72 mg/dL.	Telehealth solution
Sieber et al. 2020[62]	Comparison of three paper-based titration algorithms. Group 1: titrate by two units per three days to target 90-130 mg/dL. Group 2: titrate by four units per three days and by six units if blood glucose if >180 mg/dL to target 90-130 mg/dL. Group 3: titrate by two units per three days to target 110-150 mg/dL	Paper-based titration algorithm

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Pfützner et al. 2016[32]	Comparison of four paper-based titration algorithms. 1) Target: 90-130 mg/dL. Increase dose by two units every three days. 2) Target: 90-130 mg/dL. Increase the dose by four units every three days if blood glucose is >180 mg/dL, then increase by two units. 3) Target: 110-150 mg/dL. Increase dose by two units every three days. 4) Target: 70-100 mg/dL. Increase dose two units every three days.	Paper-based titration algorithm
Ishii et al. 2021[56]	Comparison of physician and patient-led titration algorithm. Physician-led: 0-1-2-3-4 and decrease according to the physician's discretion. Patient-led: 1-0-1. The frequency of dose adjustments was not specified.	Paper-based titration algorithm

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Tamez-Pérez et al. 2021[30]	MyDoseCoach. A combination of a mobile app and a web portal suggested basal insulin dose adjustments every three days based on a titration algorithm: 10% increase if SMBG>180 mg/dL, 5% increase if 140<SMBG<180 mg/dL, no change if 79<SMBG<140, 5% decrease if 70<SMBG<79 mg/dL, 10% decrease if SMBG<70 mg/dL.	Telehealth solution
Aradóttir et al. 2021[31]	Titration was performed using a linear dose-response algorithm. Day 1-4: No insulin. Day 5-9: 10 U insulin. Day 10: Evaluation of whether 10U is sufficient or if the dose should be adjusted with 0.2 U/kg. Day 15: The dose estimation algorithm used CGM data from day 1-14, and 75% of the estimated dose was given to the participant. Day 20-84: titration using stepwise algorithm until target (72-108 mg/dL) reached.	Mathematical model

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Krishnamoorthy et al. 2021[10]	Model-free titration approach using recursive least square-based extremum seeking control.	Mathematical model
Aradóttir et al. 2019[68]	A model predictive control-based dose guidance algorithm.	Mathematical model

Table 1 elucidates that all identified dose guidance methods, except in Krishnamoorthy et al., 2021[10] and Aradóttir et al., 2019[8], used titration algorithms to titrate basal insulin either in a digital tool or in paper-based format. Aradóttir et al., 2021[31] mixed the use of a mathematical model with use of a paper-based titration algorithm. Titration algorithms varied considerably among included studies, as approximately 18 algorithms were used. However, similar titration algorithms were found in studies investigating paper-based titration algorithms and telehealth solutions, e.g., the 2-0-2 titration algorithm.

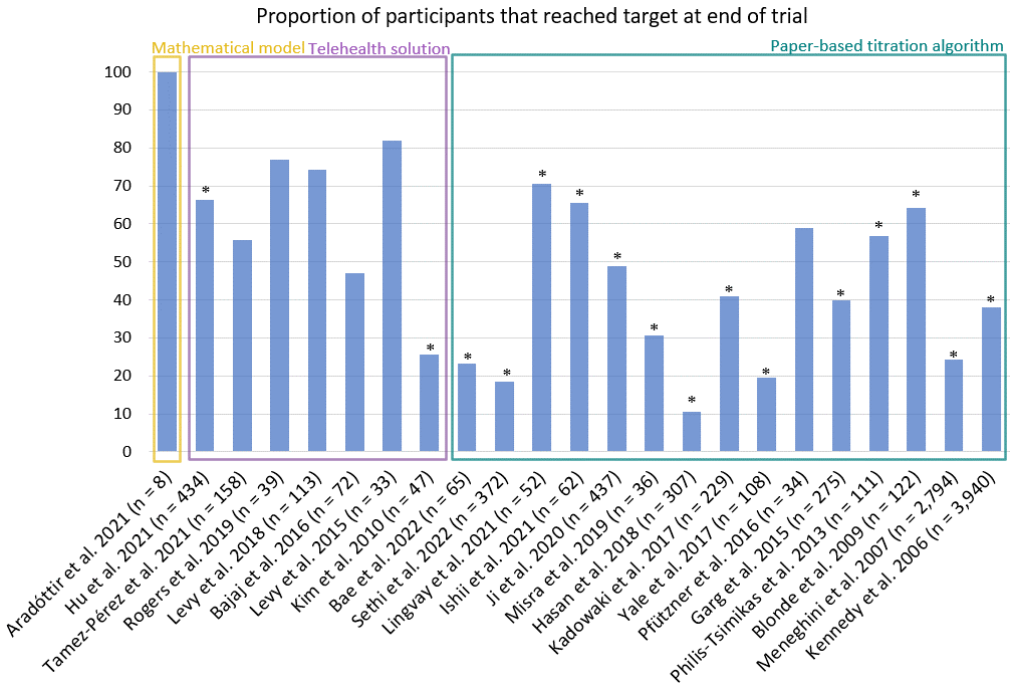
3.4.2. Effect of the dose guidance methods

Studies reported very heterogeneous glycemic outcomes (Supplementary material). The most frequently reported outcome was proportion of participants reaching glycemic target. However, this target differed among studies. Some studies used HbA1c<7% as target, while others used fasting blood glucose within a specific range. The difference in how target was defined made it challenging to compare effect across studies. To enable a comparison to some degree to elucidate tendencies in effect across different dose guidance methods, an overview of the proportion of participants reaching target is presented in Figure 4. Approximately 23% of studies

 https://doi.org/10.1177/19322968221145964

did not report proportion of participants reaching target at end-of-trial[8,10,33,40,45,57,58,62].

Figure 4. Summary of the proportion of participants that reached a predefined glycemic target. Only studies that reported target as either fasting blood glucose within the target of 79-130 mg/dL, 90-130 mg/dL, or 72-108 mg/dL or HbA1c<7% (marked with *) is included in this figure.



Aradóttir et al., 2021[31] reported that all participants reached target with a mean time to target of 44 days (n=8).

The mean proportion of participants reaching target in studies investigating telehealth solutions was 61±20% when considering both targets and 46±29% when only considering HbA1c targets. The mean for paper-based titration algorithms was 41±19% in both cases. This may indicate a tendency for a numerically larger proportion of participants titrated using telehealth solutions to reach target compared to paper-based titration algorithms.

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Among these studies, few reported time-to-target. None of the studies about paper-based titration algorithms reported time-to-target. Three studies about telehealth solutions reported mean time-to-target, which ranged from 20-66 days[30,54,59]. It should be noted that two of these studies investigated the same telehealth solution[54,59]. Since few studies have reported time-to-target, it is relevant to consider the mean study duration within the three categories to get an indication of time used to reach target. The mean duration of studies addressing paper-based titration algorithms was 22±9 weeks, 16±6 weeks for studies addressing telehealth solutions, and 11±2 weeks for studies addressing mathematical models, of which most were simulations. On average, study duration of studies investigating paper-based titration algorithms was twice as long as for mathematical models and six weeks longer than telehealth studies.

3.4.3. User experience of the dose guidance methods

User experience was investigated by 14 studies, of which 11 studies[36,38,41,42,44,45,51,54–57] reported outcomes from standardized questionnaires (e.g., Diabetes Treatment Satisfaction Questionnaire (DTSQ)), three studies[35,57,60] reported outcomes from interviews, and three studies[35,58,59] reported outcomes from non-standardized questionnaires. Studies addressing mathematical models did not investigate user experience.

The studies reporting baseline changes in the DTSQ scores showed varying results (Supplementary material). For telehealth solutions, the change ranged from 0.8-10.1 and from 0.1 to 11.7 for paper-based titration algorithms. This revealed no apparent difference in the change of DTSQ score between the two methods.

From non-standardized questionnaires and interviews, HCPs and people with T2D found telehealth solutions convenient and appropriate for titration of basal

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insulin[35,57,59,60]. Two of these studies investigated the same telehealth intervention[59,60]. People with T2D found it convenient to have fewer in-person interactions while maintaining contact with HCP via phone. In Rogers et al., 2019[60], HCPs found telehealth intervention could reduce the burden of titration. McGloin et al., 2020[57] elucidated an increased workload among HCPs caused by a large amount of generated data.

Only the study by Zhang et al., 2018[58] reported qualitative findings on the use of paper-based titration algorithms. The study found a gap between preferences of people with T2D and HCPs when choosing a titration algorithm. People with T2D preferred simple and easy-to-use algorithms. In contrast, HCPs preferred algorithms recommended by guidelines with higher perceived efficacy in lowering blood glucose levels and were known to the HCP.

3.5 Critical appraisal of the studies

Table 2-6 shows the results of critical appraisal of the included studies.

Table 2. Summary of critical appraisal assessed by JBI Critical Appraisal Checklist for Randomized Controlled Trials. U = Unclear, + = Yes, and - = No. Question 3: Red marks visual inspection of between-group differences in baseline characteristics of the population to determine if the groups were similar, and green marks studies that performed statistical tests for the difference between groups. Question 9: Red marks intention-to-treat analysis was carried out but did not describe how lost-to-follow-up was handled. Green indicates that intention-to-treat analysis was carried out with an explanation of how lost-to-follow-up was handled.

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	Risk of bias

Thomsen CHN, Hangaard S, Kronborg T, Vestergaard P, Hejlesen O, Jensen MH.
Time for Using Machine Learning for Dose Guidance in Titration of People With Type 2 Diabetes? A Systematic Review of Basal Insulin Dose Guidance.
J Diabetes Sci Technol. 2022 Dec 23:19322968221145964.
 https://doi.org/10.1177/19322968221145964

Yuan et al., 2021[37]	+	+	+	-	-	-	+	+	+	+	+	+	+	Low
Bae et al., 2021[38]	U	+	+	-	-	-	+	+	+	+	+	+	+	Moderate
Hu et al., 2021[39]	+	U	+	-	-	-	+	+	-	+	+	+	+	Moderate
Lingvay et al., 2021[50]	U	+	+	-	-	-	+	+	+	+	+	+	+	Moderate
Ishii et al., 2021[56]	+	U	U	-	-	+	+	+	-	+	+	+	+	Moderate
Yu et al., 2020[40]	U	U	+	-	-	-	+	-	-	+	+	-	+	High
Ji et al., 2020[53]	U	U	+	-	-	+	+	+	-	+	+	+	+	Moderate
Misra et al., 2019[41]	U	+	+	-	-	-	+	+	-	+	+	-	+	Moderate
Davies et al., 2019[55]	U	U	+	-	-	-	+	-	+	+	+	-	+	High
Yale et al., 2017[42]	U	U	+	-	-	-	+	+	+	+	+	-	+	Moderate
Kadowaki et al., 2017[43]	U	U	+	-	-	-	+	-	+	+	+	+	+	Moderate
Bajaj et al., 2016[44]	U	U	+	-	-	-	+	-	+	+	+	+	+	Moderate
Hsu et al., 2016[45]	U	U	+	-	-	-	+	+	+	+	+	+	+	Moderate
Garg et al., 2015[51]	+	+	+	-	-	-	+	-	+	+	+	+	+	Moderate
Levy et al., 2015[54]	+	+	+	-	-	-	+	+	+	+	+	+	+	Low
Philis-Tsimikas et al., 2013[46]	U	U	+	-	-	-	+	+	+	+	+	+	+	Moderate
Kim et al., 2010[47]	+	U	U	-	-	-	+	+	-	+	+	+	+	Moderate
Blonde et al., 2009[48]	U	U	+	-	-	-	+	+	+	+	+	+	+	Moderate
Meneghini et al. 2007[52]	U	U	+	-	-	-	U	-	-	+	+	+	+	High
Kennedy et al., 2006[49]	U	U	+	-	-	-	+	+	-	+	+	+	+	Moderate

Table 3. Summary of critical appraisal assessed by JBI Critical Appraisal Checklist for Quasi-experimental studies, including assessment of the qualitative part of mixed-methods studies. U = Unclear, + = Yes, and - = No. Question 2: red marks visual

276 inspection of between-group differences in baseline characteristics of the

277 population to determine if the groups were similar.

Study	1	2	3	4	5	6	7	8	9	Risk of bias
Tamez-Pérez et al., 2021[30]	+	+*	+	-	+	-	+	+	+	Low
Aradóttir et al., 2021[31]	+	+*	+	-	+	+	+	+	-	Low
McGloin et al., 2020[57] m	+	+*	U	U	+	+	U	+	+	Moderate
Zhang et al., 2018[58] m	+	+	+	+	+	-	U	U	+	Moderate
Levy et al., 2018[59]	+	+*	+	-	+	+	+	+	+	Low
Hasan et al., 2018[34]	+	+*	+	-	+	-	+	+	+	Low
Pfützner et al., 2016[32]	+	U	+	U	-	+	+	+	U	Moderate
Larsen et al., 2010[33]	+	+*	+	-	+	+	+	+	+	Low
Ngassa Piotie et al., 2022[35]	+	+*	+	-	+	+	+	+	+	Low
Sethi et al., 2022[36]	+	+*	+	-	+	+	+	+	-	Low

278 [m] Mixed method study.

279 * Single-arm study.

280 **Table 4.** Summary of critical appraisal assessed by JBI Critical Appraisal Checklist for

281 qualitative studies, including assessment of the qualitative part of mixed-methods

282 studies. U = Unclear, + = Yes, and - = No.

Study	1	2	3	4	5	6	7	8	9	10	Risk of bias
McGloin et al., 2020[57] m	+	+	+	+	+	-	-	+	+	+	Low
Rogers et al., 2019[60]	-	U	U	U	U	-	-	+	+	+	High
Zhang et al., 2018[58] m	U	U	U	U	U	-	-	U	+	U	High

283 [m] Mixed method study.

Table 5. Summary of critical appraisal assessed by JBI Critical Appraisal Checklist for cohorts. U = Unclear, + = Yes, and - = No.

Study	1	2	3	4	5	6	7	8	9	10	11	Risk of bias
Seufert et al., 2019[61]	+	+	+	-	-	+	+	+	U	U	U	Moderate

Table 6. Summary of critical appraisal assessed by the checklist in Fone et al. 2003(26) for simulation studies. Scores that can be given to a question; 0, 1, or 2 (poor to good). Overall indicated the overall score; A, B, C, or D (high to low risk of bias).

Study	1	2	3	4	5	6	7	8	9	10	Overall
Krishnamoorthy et al., 2021[10]	2	2	1	2	2	1	1	1	1	1	B
Sieber et al., 2020[62]	2	2	2	1	2	1	1	1	1	2	B
Aradóttir et al., 2019[68]	1	2	1	2	2	1	2	1	2	1	B

4. Discussion

4.1 Summary of evidence

The review aimed to provide an overview of dose guidance methods supporting basal insulin titration of people with T2D and categorize these according to characteristics, effects, and user experience. Overall results showed three categories of methods: paper-based titration algorithms, telehealth solutions, and mathematical models. Most studies investigated implementations of paper-based titration algorithms. Studies investigating digital solutions for basal insulin titration for people with T2D were limited to simple telehealth solutions and, in one case, a mathematical model embedded into a decision support system. In summary, all

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studies used titration algorithms either in paper form or digital, except for the mathematical models.

Similar findings are seen in Deerochanawong et al., 2017[19], which highlighted use of paper-based titration algorithms and telehealth solutions when investigating titration of insulin glargine 100 U/mL in an Asian population. However, use of mathematical models was not reported. Furthermore, Kerr et al., 2022[69] found indications for improved glycemic control when using digital solutions to manage T2D treatment compared to standard of care. This is further supported by Hangaard et al., 2021[70], which found a significant improvement in HbA1c when using telemedicine among people with T2D. These studies did not focus on basal insulin titration but overall treatment of people with T2D. However, it is feasible to assume that a similar effect may be seen using telemedicine for titrating basal, which aligns with the tendency observed in this review.

User experience was not investigated thoroughly by included studies. Yet, common characteristics were the wish of people with T2D for simple and easy-to-use solutions and HCPs' attention to effect on workload. Concerning telehealth solutions, HCPs, in some cases, uttered concern about increased data being generated compared to standard practice affecting workload[57]. None of the studies investigating mathematical models looked at user experience. Consideration of user experience when developing methods for basal insulin dose guidance is essential to ensure a holistic solution aimed at the intended end-user and thereby to secure effect in a real-world setting[71]. Especially considering solutions aimed at people with T2D due to known issues of non-adherence to treatment[72,73].

4.2 Strengths and limitations

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The broad scope and comprehensive literature strengthen the present systematic review. However, relevant studies may have been overlooked since the search was limited to use of basal insulin analogs and English, Danish, Norwegian, and Swedish language.

The heterogeneity of reported glycemic outcomes and differences in study design complicated comparison of effect.

Validity of the review is weakened since mainly one reviewer screened the search results. To minimize this effect, co-authors were continuously consulted to clarify doubts about inclusion of studies and during critical appraisal. Furthermore, the review was strengthened since the structured search was performed with assistance from a research librarian, ensuring a thorough search.

4.3 Implications for future research

Mathematical models were limited to three studies which were mainly evaluated through simulation. Expect a study by Aradóttir et al., 2021[31] where the solution was tested on eight participants showing promising results. Limited use of mathematical models may be due to the complex nature of T2D and heterogeneity of the population caused by varying insulin sensitivity and production. This complicates modelling of insulin's effect on blood glucose. The modelling task is further complicated by the limited available information about people with T2D. Glucose measures are typically performed using glucometers, and frequency of these measures varies depending on the individual in question.

In contrast, people with type 1 diabetes more often use continuous glucose monitoring to measure blood glucose, enabling more thorough insight into blood

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glucose levels throughout the day[74–76]. Similar challenges have been recognized by studies addressing mathematical models[10,68].

New technologies enabling improved data collection might ease some challenges in modeling insulin's effect on blood glucose levels for people with T2D using mathematical models. Kerr et al., 2022[69] highlight that new technology that supports improved data capturing may facilitate better treatment support when combined with dose recommendation software. Furthermore, addition of automated data-driven dose guidance might help rectify the increased workload for HCP that, in some cases, has been reported when introducing new technology[77].

At the time of writing, machine learning methods used for problems related to T2D have focused on detection or prediction of hypoglycemic events, blood glucose levels, and optimal bolus insulin dosing[78]. In the future, exploring the capability of machine learning methods for basal insulin dose guidance for people with T2D may provide insight into the field that could pioneer future research.

5. Conclusions

Three basal insulin dose guidance categories aimed at people with T2D were identified: paper-based titration algorithms, telehealth solutions, and mathematical models. Compared to paper-based titration algorithms, a numerically larger proportion of participants reached a predefined target using telehealth solutions.

Few studies investigated user experience. Some studies underlined a possible increase in workload when using telehealth solutions due to increased data. However, it was found that people with T2D preferred simple and easy-to-use solutions and fewer in-person visits.

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Future work might benefit from exploring the capabilities of machine learning methods for basal insulin dose guidance for people with T2D, focusing on a simple and easy-to-use method that does not increase the workload for HCPs.

Acknowledgments

The authors thank research librarian Connie Skrubbeltrang for competent assistance in the literature search.

Conflict of interest

Author P.V. is head of research at Steno Diabetes Center North Denmark, funded by the Novo Nordisk Foundation.

Author M.H.J is a former Novo Nordisk employee and holds Novo Nordisk shares.

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