International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Scholarly Publisher
RS Global Sp. z O.O.
ISNI: 0000 0004 8495 2390

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ARTICLE TITLE	NEW FORMS AND TECHNOLOGIES OF INSULIN THERAPY IN TYPE 1 DIABETES - A SYSTEMATIC LITERATURE REVIEW
DOI	https://doi.org/10.31435/ijitss.4(48).2025.4479
RECEIVED	18 October 2025
ACCEPTED	14 December 2025
PUBLISHED	30 December 2025
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NEW FORMS AND TECHNOLOGIES OF INSULIN THERAPY IN TYPE 1 DIABETES - A SYSTEMATIC LITERATURE REVIEW

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ABSTRACT

Introduction: Type 1 diabetes is a chronic autoimmune disease that leads to permanent lack of insulin. In recent years, advances in insulin formulations and delivery methods have improved the ability to mimic natural insulin secretion and support better diabetes management.
Aim: The aim of this article is to review the most commonly used forms of insulin therapy and modern technologies supporting the treatment of type 1 diabetes, with attention to their effectiveness, safety, and impact on patients' quality of life.
Methods: A search of PubMed and ScienceDirect was performed for publications from January 2008 to June 2025. The review included clinical trials and review articles about insulin therapy in type 1 diabetes. Titles and abstracts were screened, full texts were analysed, and reference lists of key papers were checked.
Results: Modern insulin therapy is based on insulin analogues with different action profiles and on delivery systems such as insulin pens, pumps, and hybrid closed-loop devices. New basal and prandial analogues help improve glycaemic control and reduce complications. Automated Insulin Delivery systems increase time in range and improve daily functioning. However, problems such as variability of insulin absorption, lipodystrophy, and high costs still remain.
Conclusions: Although progress in insulin therapy has improved diabetes care, further research, better access to modern technologies, and further patient education is essential.

KEYWORDS

Insulin, Insulin Therapy, Diabetes Mellitus, Type 1, Multiple Daily Injections, Continuous Subcutaneous Insulin Infusion

CITATION

Agata Ogórek, Aleksandra Kaniak, Julia Andrzejewska, Agata Wińska, Hanna Pietruszewska, Irmina Czerepak, Izabela Majchrzak, Michał Ziemba, Klaudia Zackiewicz, Julianna Zielska. (2025) New Forms and Technologies of Insulin Therapy in Type 1 Diabetes – A Systematic Literature Review. *International Journal of Innovative Technologies in Social Science*. 4(48). doi: 10.31435/ijitss.4(48).2025.4479

Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disease leading to irreversible insulin deficiency, which makes exogenous insulin administration a mandatory part of therapy. In 2022, an estimated 8.4 million individuals worldwide were living with T1DM [1], and projections suggest that by 2040 this number may rise to 13.5-17.4 million, primarily due to environmental factors such as microbiome alterations, malnutrition, obesity, viral infections, and air pollution [2].

Review Methods

A comprehensive search of PubMed and ScienceDirect was performed, including publications from January 2008 to June 2025, with a focus on studies from the last five years. The search included clinical trials and review articles concerning insulin therapy in type 1 diabetes. The following keywords were used: insulin; insulin therapy; diabetes mellitus, type 1; multiple daily injections; continuous subcutaneous insulin infusion. Titles and abstracts were screened, then full texts of selected papers were reviewed. Reference lists of important articles were also checked. Only peer-reviewed articles in English or Polish were included. Studies not directly related to the topic, non-peer-reviewed sources, and conference abstracts without complete data were excluded.

Results

History of Insulin

The first effective insulin administration took place in 1922, and less than a year later, mass production began. Initially, insulin was obtained from the pancreases of cows and pigs. Since their molecular structure differs from human insulin by just a few amino acids, allergic reactions in patients were not uncommon [3]. A true breakthrough was the development of protamine-zinc insulins, which were the first long acting insulins. Human insulin NPH, whose structure is identical to the insulin produced by the pancreas, appeared on the market in the late 1970s. It was produced using genetic engineering Escherichia coli [3]. Over the next few years, rapid-acting and long-acting insulin analogs were developed, followed by newer generations such as ultra-rapid and ultra-long-acting formulations. At the same time, alternative insulin delivery methods appeared, including insulin pumps, which continue to be developed to this day.

Pharmacology of Insulin

Short-acting insulins

Short-acting insulins, also called regular or neutral insulins, are human insulin preparations produced via recombinant DNA technology. The onset of action occurs approximately 30 minutes after injection, the peak between 2-4 hours, and a total duration time lasts 5-8 hours [4]. This profile often leads to a risk of postprandial hyperglycemia, when insulin action may not cover glucose absorption after meals. It is also associated with an increased likelihood of hypoglycemia during the peak of insulin activity. For many years, regular insulins played a main role in intensive insulin therapy. However, with the development of newer insulin analogues, their use has become less common. Currently, regular insulin is used in specific situations when intravenous administration is necessary, for example, in diabetic ketoacidosis, hyperglycemic-hyperosmolar states, perioperative management, and other critical conditions [5].

Intermediate-acting insulins

NPH insulins are intermediate-acting insulins and the first generation of basal insulins. Protamine added to the insulin molecule slows its absorption and prolongs duration of action to 18-26 hours [6]. However, the significant peak of activity increases the risk of hypoglycemia, especially at night. Nowadays they are still occasionally used in clinical practice due to economic reasons [7]. Rapid-Acting Insulins (RAA)

Modification of specific amino acids in the human insulin molecule resulted in the creation of fast-acting insulin analogues with better solubility and absorption after subcutaneous injection [5]. Moreover, their formulations include zinc ions and phenolic compounds, which stabilize the preparation and prevent denaturation and aggregation in the vial [8]. Insulins such as lispro, aspart, and glulisine have very similar pharmacokinetic and pharmacodynamic profiles [8, 9]. Their onset of action begins approximately 10-20 minutes after injection, peaks at around 1-2 hours, and the total duration of action ranges from 3 to 5 hours.Studies have shown that all three analogues are equally effective and safe, and minor differences – such as the slightly faster onset of action of glulisine - are not clinically significant [9]. RAAs are used in both multiple daily injections (MDI) and insulin pump therapy, and their efficacy and safety have been confirmed in various populations, including children, pregnant women, and individuals using CSII (Continuous Subcutaneous Insulin Infusion) [10].

Ultra-Rapid-Acting Insulins

Ultra-rapid-acting insulins (URAA), such as faster aspart (Fiasp) and ultra-rapid lispro (URLi), represent the next generation of prandial insulin analogs. Through addition of nicotinamide, l-arginine, treprostinil, or citrate, these insulins have even faster absorption from subcutaneous tissue and earlier onset of action compared to classic RAAs [11]. URAAs achieve higher plasma concentrations within the first 30 minutes after injection and more similarly reflect natural insulin secretion after meals [12]. Clinical trials have shown that URAAs provide better postprandial glucose control, with average levels 12–18 mg/dL lower at 1 and 2 hours post-meal, while maintaining comparable safety and efficacy to RAAs [2]. Their biggest advantage is the ability to administer them immediately before or even after starting a meal, which increases therapeutic flexibility. However, benefits in terms of HbA1c reduction or fewer hypoglycemic episodes compared to RAAs have not yet been clearly proved [13].

Table 1. Pharmacological characteristics of selected insulin analogs, including onset, peak, duration of action, mechanisms of action, hypoglycemia risk, and available commercial formulations.

Parameter	Glargine U-100	Glargine U-300	Detemir	Degludec
Onset of action	1-2 h	3-4 h	1-2 h	1 h
Peak activity	3–4 h after injection	12–16 h after injection	6–8 h after injection	no distinct peak
Total duration	Up to 24 h	Up to 36 h	Up to 24 h	> 42 h
Mechanism of prolonged action	Precipitation in subcutaneous tissue	Formation of a concentrated subcutaneous depot	Formation of dihexamers and strong albumin binding	Formation of multihexamers in subcutaneous tissue and partial albumin binding
Risk of hypoglycemia	Low	Lower vs Glargine U-100	Lower vs Glargine U-100	Lowest among long-acting analogs
Example products	Lantus	Toujeo	Levemir	Tresiba

Long-Acting and Ultra-Long-Acting Insulins

Long-acting basal insulins are characterized by delayed onset and prolonged duration of activity. Their primary role is to maintain stable blood glucose levels between meals and during the night. Because of their slow onset and lack of rapid response to postprandial hyperglycemia, these insulins are used in combination with short- or rapid-acting formulations. Unlike RAAs, which have very similar pharmacokinetic characteristics, the choice of a specific basal insulin preparation has greater therapeutic significance. Differences in duration of action, presence of activity peaks, and individual variability can significantly impact treatment results and the risk of hypoglycemia [14].

Glargine

Glargine is a human insulin analog modified to reduce solubility at the injection site. The drug precipitates in subcutaneous tissue, which slows its absorption into the bloodstream. Glargine is classified by concentration into two forms: U100 and U300. Glargine U100 is the classical preparation, active for up to 24 hours without a distinct activity peak. Glargine U300 is three times more concentrated than U100 and forms a tightly compacted depot upon subcutaneous injection, from which insulin is released more slowly and steadily [14]. This results in a prolonged, up to 36 hours, and more stable action profile. The EDITION 3 and 4 studies, along with a meta-analysis by Joshi et al. (2023), found no significant differences in HbA1c when using glargine U300 compared to U100, but they did confirm a reduction in hypoglycemic episodes, especially at night [15, 16]. Detemir

Insulin detemir differs from other basal analogs in its mechanism of action. The attached fatty acid chain allows for reversible binding to albumin, both at the injection site and in the bloodstream, which slows down absorption. Its effect can last up to about 24 hours, but the exact duration depends on the dose [18]. In some patients, maintaining stable insulin levels may require two daily injections [14]. It should also be remembered that conditions such as hypoalbuminemia can alter detemir's pharmacokinetics by increasing the amount of free insulin. In such cases, insulin starts to act earlier and the risk of hypoglycemia is higher. It may be necessary to adjust the dose or use a different basal insulin that is not dependent on plasma albumin level [19].

Degludec

Insulin degludec is a modern, long-acting insulin with a very stable and even effect. After being injected under the skin, it forms large structures (multihexamers) that slowly release insulin into the bloodstream. The gradual release is controlled by the slow separation of zinc ions. Because of this, degludec works for more than 42 hours and doesn't have a clear peak of activity [14]. This makes injections once a day sufficient, at any

flexible time [20]. Clinical studies, including BEGIN and SWITCH 1, have shown that degludec provides similar HbA1c control to insulin glargine, but with a lower risk of hypoglycemia, especially at night [21, 22].

Once-weekly insulins

Once-weekly insulins are the newest type of basal insulins analogues, designed to reduce the number of injections required by patients. A representative of this group is icodec, whose structure has been modified by the addition of a fatty acid chain and changes in amino acids [23, 24]. This modification led to reduction of enzymatic degradation and insulin receptor affinity, enabling strong, reversible binding to albumin. As a result drug is slowly released into the circulation, so the concentration profile remains flat and stable. Half-life of icodec is 8.2 days and concentrations are proportional to the administered dose [25]. In the ONWARDS 6 study in patients with type 1 diabetes, HbA1c reduction was similar between icodec and degludec, but the incidence of hypoglycemia was higher in the icodec group (19.9 vs. 10.4 episodes per patient-year in the degludec group) [26]. Limiting basal insulin dosing to once-weekly injections facilitates patient compliance [23, 24], however, this therapy requires closer glycemic monitoring due to the higher risk of hypoglycemia [27]. Icodec received a positive opinion from the CHMP/EMA in March 2024 and was approved for marketing in the European Union in May 2024 [28].

Efsitora alfa (basal Fc insulin, BIF) is also a once-weekly insulin. Its half-life is extended to approximately 17 days due to the addition of the Fc fragment of human IgG2 via a short peptide linker [25]. Efsitora alfa is currently in Phase III clinical trials (QWINT-1–5 program), including studies in both type 2 and type 1 diabetes [29]. Results of phase II trials confirmed good dose tolerability, with a glycemic profile and incidence of hypoglycemia comparable to daily basal analogues. Efsitora alfa has not yet been approved for use in any country. Both the EMA/CHMP and FDA are waiting for full data from the Phase III trials and safety analyses before making any regulatory decisions [30].

Insulin Delivery Methods

Insulin pens are the main tool for insulin therapy in patients with type 1 diabetes, providing ease of use and high dosing precision. Each pen consists of an insulin cartridge and a thin, single-use needle, allowing for subcutaneous administration of precise doses, often accurate to 0.5 units [31]. Recent innovations are pens that can connect to smartphones via Bluetooth, which automatically record the information of each dose and transfer this data to a mobile application [14, 32]. Continuous Subcutaneous Insulin Infusion is a method that best imitates the physiology of the pancreas. Insulin is delivered via a continuous basal infusion while allowing for the administration of prandial or correction boluses. The CSII system consists of a portable pump with a replaceable reservoir for rapid-acting insulin and a thin infusion set with a cannula inserted subcutaneously, usually into abdominal subcutaneous tissue. In the study by Liu et al. (2022) published in Frontiers in Public Health, CSII was associated with improved glycemic outcomes compared to MDI in patients with DM1. CSII users had a higher median time in range (TIR) (67.2% vs. 57.2%), lower estimated HbA1c (6.9% vs. 7.5%), and experienced less hypoglycemic episodes [33]. Other studies, such as the COMISAIR Study [34], indicate that the use of Continuous Glucose Monitoring (CGM) has a bigger influence on glycemic outcomes than the method of insulin delivery itself. However, the effectiveness of insulin delivery methods such as CSII depends on the patient's commitment to the device, use of CGM, and close collaboration with the diabetes care team. Barriers to using this technology include unequal access between healthcare systems and the high costs of the equipment [14].

The latest invention in pump-based insulin therapy, already available to patients, is the Automated Insulin Delivery system (AID), also known as hybrid closed-loop systems. These forms of therapy integrate an insulin pump, CGM and a control algorithm. The system automatically adjusts basal insulin delivery based on glucose levels. More advanced models can even independently administer correction boluses in case of hyperglycemia [3, 14]. Studies have shown that the use of AID increases TIR by an average of 15-30%, reduces the incidence of hypoglycemia, and leads to lower HbA1c values [35] Nitschke et al., 2025). Compared to traditional pump therapy, AID provides better glucose stability and reduced fluctuations. All currently available AID systems use rapid-acting insulin analogs and are compatible with selected CGM sensors [35]. Users report improved quality of life and reduced therapeutic decision fatigue [32, 36]. However, this new technology is quite expensive and patients need to be properly trained [37]. The development of AID systems is considered a step toward full automation of diabetes management. Moreover, ongoing studies are investigating bihormonal systems that, in addition to insulin, also deliver glucagon [36].

The Impact of Injection Site and Administration Technique on Absorption

The site of insulin injection significantly influences its absorption and pharmacological action, and therefore glycemic control. These differences result from variations in tissue vascularization at different injection sites, as well as the characteristics of each insulin preparation [38]. Injecting rapid-acting analogues into the abdominal area accelerates absorption and shortens the onset of action compared to the thigh or buttock [38]. These changes also apply to basal insulins - injecting insulin in areas with greater blood supply may lead to faster absorption, earlier peak action, and a shorter duration of drug activity, which increases the risk of nocturnal hypoglycemia. An exception is insulin degludec, whose unique structure allows the formation of stable multi-hexamers in subcutaneous tissue. These complexes slowly release active insulin monomers, independent of local blood flow. Studies have confirmed that of all basal insulins, degludec has the most stable profile, regardless of injection site [39]. The depth of insulin administration is also a significant factor. In patients with excess adipose tissue, injection into the subcutaneous layer may delay the drug's absorption and onset of action [38]. The situation is different in the case of intramuscular injection - the higher degree of vascularization of muscles compared to adipose tissue causes faster absorption [38]. Chronic insulin injections into the same sites stimulate the development of dermatological complications known as lipodystrophy, which includes lipoatrophy and lipohypertrophy [39]. Lipoatrophy is the localized loss of adipose tissue, leading to rapid and unpredictable insulin absorption. Thanks to the high purity of modern insulin preparations, this condition is now relatively rare. Lipohypertrophy, on the other hand, is characterized by localized hypertrophy of adipose tissue resulting from repeated injections and the associated microtrauma. It has been proved that injecting insulin into lipohypertrophic areas prolongs absorption time and reduces peak serum concentrations [40]. This results in glycemic instability and higher values of HbA1c. Patients with lipohypertrophy often require higher insulin doses, however, achieving stable metabolic control remains difficult. Proper injection technique, regularly switching injection sites help prevent this complication. It is also important to avoid injecting into areas with skin changes. [40].

Insulin Dosage

The total daily dose (TDD) of insulin in individuals with type 1 diabetes is calculated using a conversion factor of 0.4-1.0 units per kilogram of body weight per day. Basal insulin should constitute 30–50% of the TDD, while prandial insulin should account for the remaining portion [7]. MDI therapy, basal insulin is administered once or twice daily. Prandial insulin is used before meals and for correcting elevated blood glucose levels. The dose is determined individually based on the type and amount of food consumed, pre-meal glucose levels, planned physical activity, and trends observed through continuous glucose monitoring [7]. Many patients experience an early morning increase in insulin requirements [14]. This is related to the effects of insulin-antagonizing hormones and should be considered when adjusting basal or prandial doses. Moreover, in specific circumstances, such as infections, menstruation, or periods of rapid growth, a temporary increase in insulin doses may be necessary to maintain proper glycemic control. [7].

Problems Related to Insulin Therapy

Insulin resistance (IR), which is commonly associated with type 2 diabetes, can also affect patients with type 1 diabetes. It tends to increase with age and weight gain. In DM1 IR manifests as a significant increase in daily insulin requirements and large fluctuations in glycemia [41]. Studies show that IR is a stronger predictor of coronary artery calcification severity than hyperglycemia alone, and increases the risk of cardiovascular complications. [42]. Currently, there is no ideal diagnostic test for IR in type 1 diabetes. In clinical practice, markers such as eGDR (estimated glucose disposal rate), calculated from waist circumference, the presence of hypertension, HbA1c level and the triglyceride to HDL cholesterol ratio, are used [41]. The classic HOMA-IR index is not applicable in people who do not produce endogenous insulin. Treatment of insulin resistance in type 1 diabetes requires a comprehensive approach, with lifestyle modification as the cornerstone [41]. If lifestyle changes are insufficient, off-label use of metformin may be helpful. Studies have shown that it reduces total insulin requirements and improves the lipid profile[43]. Second-line treatment options are medications like GLP-1 receptor agonists, which reduce body weight and postprandial glucose levels, and SGLT2 inhibitors, which further increase insulin sensitivity. However, their use requires monitoring of ketone body levels due to the increased risk of ketoacidosis. Collaboration with diabetes treatment specialists, dietitians and physiotherapists, as well as the use of continuous glucose monitoring, allows for appropriate insulin doses and reduces the risk of complications [41].

New Routes of Administration

Afrezza, an ultra-rapid-acting inhaled insulin, was approved by the FDA in June 2014 as the first alternative to injections in the United States [14, 43, 44]. The drug has a form of dry powder administered via an inhaler in doses of 4, 8, or 12 units, which can be combined but not divided [45]. After inhalation, insulin molecules reach the lung alveoli, reaching peak serum concentrations within 12–15 minutes [43]. The total duration of action is up to 2–3 hours, so Afrezza always requires co-administration of a long-acting basal insulin.. The product is contraindicated in patients with chronic obstructive pulmonary disease (COPD), uncontrolled asthma, and active smokers. Spirometry must be performed before initiation of the therapy [44]. Despite initial optimism, Afrezza did not gain the expected popularity. Consistent dosing, need for lung function tests, and reimbursement issues limited the drug's widespread use [3]. To this day, it is available only in the United States and has not found widespread use in clinical practice [43].

Continuous intraperitoneal insulin infusion (CIPII) means administration of insulin directly into the peritoneal cavity via an implanted port or pump. The insulin is absorbed through the peritoneal membrane and enters the portal circulation, reaching peak action within 15 minutes [45]. In patients who fail to achieve glycemic control with standard treatment, CIPII allows for reductions in HbA_1c, reduction of hypoglycemia episodes and lowers overall insulin requirements [46]. Additionally, this method has a beneficial effect on the GH-IGF-I axis, potentially reducing the risk of microangiopathy. However, CIPII is an expensive and rarely used therapy, available primarily in specialized centers [45]. It requires surgical intervention and regular device maintenance and carries risks of complications such as port infections or catheter blockage [45, 46]. Therefore, CIPII is recommended when other diabetes treatment methods are ineffective, and the risk of complications is lower than the risk associated with the intraperitoneal therapy itself [46].

Smart insulins are modern therapeutics designed to automatically regulate their activity based on blood glucose levels. The mechanism of action relies on integration with glucose-sensitive molecules or carriers that release or activate insulin only in response to elevated blood glucose levels, remaining inactive in conditions of normal or low glycemia. The most promising smart insulin system currently is NNC2215, a project developed by Novo Nordisk in collaboration with scientists from the University of Bristol [47]. A so-called "molecular switch" is added to the insulin molecule, consisting of a glucose-binding macrocycle and a glucoside. In the condition of normoglycemia or hypoglycemia, the glucoside stabilizes the insulin structure in an inactive form.. When glucose levels rise, the glucoside is replaced by glucose, which changes the molecule's conformation and activates the insulin. Animal model studies have shown that NNC2215 effectively lowers glucose levels during hyperglycemia without causing hypoglycemia.In vitro, it demonstrates a 3.2-fold increase in insulin receptor affinity with increasing glucose levels from 3 to 20 mmol/l, confirming a rapid response [47]. Although preclinical studies are promising, none of the so-called "smart" insulins have yet been approved for use. The main obstacles are the difficulty of maintaining the stability of these molecules in the body, the risk of allergic reactions, and problems with precisely matching the insulin release rate to the needs of an individual patient.

Guidelines of Diabetes Associations: ADA, NICE, EASD, PTD

The ADA 2025 Standards of Care recommend the use of ultra-rapid-acting and rapid-acting insulin analogues instead of human insulin due to a more physiological action profile [7]. The 2021 ADA/EASD consensus considers URAAs as an alternative to RAAs, but does not indicate their superiority, due to the lack of evidence of a more effective reduction in HbA_1c levels and hypoglycemia episodes [48]. Both the ADA and ADA/EASD consensus allow the use of inhaled insulin as an alternative prandial insulin form for patients in the U.S. The Polish Diabetes Association (PTD) and the UK's NICE (NG17) recommend the use of rapid-acting insulin analogues before meals, without distinguishing URAA as a separate and better therapeutic category [49, 50]. Similarly, ADA guidelines recommend the use of basal insulin analogues, because of their more stable pharmacokinetic profile and lower risk of hypoglycemia compared to NPH insulin. Particular attention was paid to the flat action profile of the glargine U-300 and degludec, which allows for more flexible dosing. NICE guidelines differ slightly in this approach recommending detemir administered twice daily as the first-choice basal insulin. As alternatives, they suggest once-daily glargine U-100 or detemir, and in situations of high risk for nocturnal hypoglycemia, degludec. The Polish Diabetes Association, in its 2024 guidelines, recommended the use of basal insulin analogues due to their advantages in reducing hypoglycemia and improving quality of life, without explicitly highlighting ultra-long-acting formulations [50]

Weekly insulins icodec and efsitora have not yet been included in the current guidelines of the ADA, EASD, or NICE. However, their clinical trial results suggest that soon they may be added to diabetic treatment options. According to the ADA/EASD consensus, insulin delivery should be tailored to the needs of each

patient, but hybrid closed-loop systems are the most effective. The ADA 2025 Standards of Care do not recommend insulin pumps for all patients, but do highlight CSII therapy with CGM - especially as part of AID systems - as the better choice.

Conclusions and discussion

The evolution of insulin therapy involves not only improving medications, but also better tailoring treatment to the individual needs of each patient. The effectiveness of diabetes treatment currently depends on the type of insulin used, its administration method and the use of modern technologies. The future of type 1 diabetes treatment lies in further automation, the development of new formulations and delivery methods, and the growing importance of education and patient collaboration. All of these elements have the potential to significantly improve treatment outcomes and patient quality of life.

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Acknowledgments: Not applicable
Informed Consent: Not applicable.
Ethical approval: Not applicable.
Funding: This study received no external funding.
Conflicts of Interest: The authors declare no conflicts of interest.
Data and materials availability: All data associated with this work are present in the paper.

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