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REVIEW

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Effectiveness, safety, and preference of transdermal insulin compared to subcutaneous insulin in the treatment of diabetes patients: a systematic review of clinical trials

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Abstract

Background Several studies were performed on transdermal (TD) insulin delivery in vitro and in vivo, and recently, the study groups included a clinical trial in humans. Therefore, this systematic review was conducted to get summary information about the effectiveness, safety, and preferability of TD insulin in comparison with subcutaneous insulin delivery.

Methods We conducted a thorough search to find studies in the databases Cochrane Library, MEDLINE via PubMed, Web of Science Core Collection, EMBASE, Scopus, Hinari, Medlib, and Magiran until January 2024. We included 18 randomized clinical trials.

Results Although there are various types of TD delivery methods, the TD insulin delivery methods that have undergone clinical trials are the TD patch, micro needle TD insulin delivery, and TD insulin jet injector. Eighteen studies were conducted on TD insulin delivery, which showed either superior or comparable effectiveness, safety, and preferability of TD insulin in comparison with SC insulin. About eleven out of eighteen studies (61.1%) showed more effective blood glucose control than SC delivery, and the remaining seven studies showed comparable effectiveness with SC delivery. Eleven studies (61.1%) showed equal tolerability of TD insulin versus SC insulin, and seven studies (38.9%) showed more tolerability of TD insulin over SC insulin. In most studies, eleven out of eighteen (61.1%) showed a higher preference for TD insulin delivery over traditional SC delivery; sixth out of eighteen (33.3%) showed equal preferability for TD insulin versus SC insulin; and only one study (5.6%) showed that TD insulin delivery was less preferable than SC insulin.

Conclusion The review revealed that clinical trials have demonstrated the effectiveness of TD insulin delivery methods such as TD patches, MN-based insulin delivery, and insulin jet injectors compared to traditional SC routes

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of administration. The studies showed the superior or comparable effectiveness of TD insulin in controlling blood glucose levels. Additionally, TD insulin delivery was found to be equally or more tolerable than SC insulin delivery in all studies. Overall, the majority of studies favored TD insulin delivery over traditional SC delivery methods, highlighting its potential as a preferred option for insulin administration.

Keywords Diabetes mellitus, Transdermal delivery, Subcutaneous delivery, Insulin, Effectiveness, Safety, Preferability

Introduction

A collection of metabolic disorders collectively known as diabetes mellitus (DM) are typified by elevated hepatic glucose synthesis and reduced glucose uptake by muscle and fat, leading to an atypical build-up of glucose in the bloodstream, all of which are caused by insufficient insulin production [1–3]. Type 1 diabetes (T1D) is caused by an autoimmune reaction that destroys β-cells in the pancreas, which prevents the body from producing enough insulin [4]. Insulin resistance and/or impaired pancreatic β-cell function are the underlying causes of long-term hyperglycemia, a characteristic of type 2 diabetes (T2D) [5]. In 2021, it was predicted that 536.6 million adults between the ages of 20 and 79 will get DM, with 90% of those cases being T2D [6]. According to a world health organization forecast, by 2040, DM is expected to affect roughly 642 million people, and it will rank seventh among all causes of death globally by 2030 [7].

For T1D, strict glucose control with multiple insulin doses is the standard of care; however, hypoglycemia is a common side effect [8]. People with DM are typically told to self-inject insulin through the subcutaneous (SC) route several times a day, which requires extensive self-management and training, with patients often needing to adjust their dosage based on glucose monitoring [9, 10]. Even though exogenous insulin is widely accessible, those who are affected by T1D are still susceptible to both acute and long-term complications because they are unable to consistently achieve euglycemia with current formulations and technologies [11, 12]. Many healthcare professionals and patients are also reluctant to start insulin therapy because of the somewhat inconvenient SC route of administration, negative side effects like weight gain, and other psychosocial factors [13–16]. Because of this, scientists have looked into less-invasive ways to administer medications based on novel pharmaceutical formulations that maintain hormone stability and guarantee therapeutic efficacy [17, 18]. When insulin is administered orally or through another novel delivery system, needle-related anxiety, injection pain, and potential infections are avoided [19, 20].

There are various novel approaches for the delivery of insulin, including inhaled insulin delivery, oral, colonic, nasal, buccal, transdermal (TD), intra-peritoneal, ocular, rectal, vaginal, etc. [7]. TD drug delivery systems (TDDDS) are appealing due to their numerous advantages, such as utilizing the large surface area of the skin for drug administration and enabling continuous insulin release to stabilize glucose levels over an extended period, thereby reducing the risk of concentration-related side effects [21–24]. Because of the benefits they provide over invasive injection and oral dosage forms, TD systems have drawn more attention and have been seen as a possible hope for managing diabetes over the past ten years [25]. Various strategies may be used to ensure skin delivery of insulin, such as using fatty acids and surfactants as chemical penetration enhancers to partially disrupt the SC barrier, although they are only effective with small molecules [26]. Moreover, utilizing a variety of penetration-enhancing techniques such as iontophoresis, lipid-based nano-delivery systems, microneedles (MNs), TD films, and patches to ensure adequate TDD of insulin [22, 24, 25]. MNs have become a more appealing alternative due to their proven utility and capacity to mitigate the drawbacks of parenteral and oral drug delivery, and they are small enough to be self-administered without causing pain or discomfort [27, 28].

Transdermal delivery of insulin

The human body's largest organ is the skin, which is a complex mixture of mesenchymal and epithelial tissue, consisting of a stratified, multilayered epidermis, a dermis with collagen and elastic fibers, underlying SC fat, and adnexal structures like sweat glands, sebaceous glands, and hair follicles [29]. The stratum corneum, epidermis, and dermis are the three layers that make up the skin, which performs the dual roles of an active immune organ and a physical and chemical barrier against foreign invaders [30–32]. A vital barrier function of the epidermis is carried out by the stratum corneum [33, 34]. Because SC insulin administration cannot achieve the required portal-systemic insulin concentration gradient, it has limited effects on hepatic glucose suppression [35]. Insulin TD delivery is being investigated in ways such as altering skin barrier characteristics, refining formulations, increasing diffusion coefficients, and applying extra driving forces [30, 36]. The potential of TDDDS to advance medical science with cutting-edge enhancement methods is highlighted by clinical trials looking into TD delivery of macromolecules and vaccines using methods like thermal ablation and MNs [37]. Benefits of MN arrays include minimal trauma, painless delivery, accurate depth control, and different types depending on morphology [38–42]. The structure and composition

of TD patches are influenced by the particular drug and release requirements. They are made up of multiple layers that are intended to penetrate the skin and deliver medication [43].

Jet injectors also use the methods of TDDD, which have undergone clinical trials, and usually pressurize the liquid at approximately 20 MPa. To breach the stratum corneum, penetrate the skin barrier, and transport the fluid to the required depths, jet velocities of 100 m/s are required [44]. As a result, jet injections are not constrained by the rates at which various drugs diffuse; they can overcome the drawbacks of other drug delivery techniques, including ablation, iontophoresis, electroporation, sonophoresis, and MNs, although it is challenging to control the jet pressure during drug delivery [33, 45]. Because it is a non-invasive technique that provides the convenience of a TDDDS, this type of insulin delivery is appealing [36]. Therefore, the objective of this study was to synthesize the available evidence on the effectiveness, safety, and preference of TD insulin in comparison with SC insulin.

Methodology

Search strategy

A comprehensive search strategy was conducted using electronic databases, including PubMed, MEDLINE, SCOPUS, CINAHL, Web of Science, EMBASE, Google Scholar, Cochrane Library, ISI, Scopus, Medlib, Irandoc, SID, and Magiran, which were systematically searched online to retrieve related articles. The search terms will include, ((“Diabetes patient”, “Patients with diabetes mellitus”, “Type 1 diabetes”, “Type I diabetes”, “Type 2 diabetes”, “Type II diabetes”, “Type 1 and type 2 diabetes”) and (“Transdermal insulin”, “Transdermal insulin injection”, “Transdermal insulin delivery”, “Cutaneous insulin”, “Microneedle insulin”, “Insulin patch”, “jet injector insulin”) and (“Subcutaneous insulin”, “Subcutaneous insulin delivery”, “SC insulin”, “SQ insulin delivery”) and (“Effectiveness of insulin”, “Outcome of insulin”, “Safety of insulin”, “Adverse effect of insulin”, “Effectiveness and safety of insulin”, “HbA1c”, “Blood glucose”, “Postprandial blood glucose”, “Fating blood glucose”, “AUC of insulin”, “Hypoglycemia”, “preference of insulin”)). Manual searches of relevant journals and conference proceedings were also conducted. The retrieved study references were also screened and checked. The review protocol is available on PROSPERO (ID: CRD42024497023).

Eligibility criteria

The PICO approach (population, intervention, comparator/control, and outcome) was applied for this review. “P” for DM patients, “I” for TD insulin, “C” for SC insulin, and “O” for effectiveness, safety, and preference. This study included clinical trial research that compared the efficacy, safety, and preference of TD insulin compared to SC insulin and that was published in the English language under an open-access system. Reports lacking a full document, abstract, and comparison, however, were not included in the analysis. The titles, abstracts, and comprehensive full-document reviews of the articles were read to assess them.

Data extraction, management, and analysis

Each study’s authors, publication year, design, location, length of time, type of diabetes, inclusion and exclusion criteria, number of patients who finished the study, interventions, outcomes, side effects, and results were extracted, along with study characteristics and patient demographics. If mentioned in the studies, hypoglycemia, the main side effect of insulin, was also thought to be well documented. To find possibly eligible studies, the search results were independently screened by three reviewers. In cases of disagreement among reviewers, a discussion or consultation with an additional reviewer was conducted. Complete text publications from qualified research were located and evaluated for possible inclusion. We sorted the publications according to the types of TDD methods, such as TD patches, MN-based TDD, and insulin jet injectors. The outcome of various TDD methods was evaluated based on their effect on controlling blood glucose (BG), their safety, and their preferred ability by the patient.

Result

In this systematic review, we have searched a total of 1480 articles from all databases. About 271 articles were excluded because of duplication, 1034 articles were excluded because they were out of interest, and 157 articles were excluded because they did not meet the eligibility criteria. Finally, 18 articles that fulfilled the eligible criteria were systematically reviewed [Fig. 1].

Study characteristics

In this study, we included 18 studies that were done in three countries. About eight studies were conducted in the United States of America (USA) [46–53]; one study was conducted in each of the following countries: Germany [54], Israel [55], Australia [61], five studies were conducted in China [56–60], and two studies were performed in the Netherlands [62, 63]. The total sample size was 1044; from them, the maximum sample was from China (657), and the minimum sample was from Australia, which had 10 participants. Of all the studies, two were patch-based delivery, seven were microneedle-based delivery, and ten were jet injectors. The duration of the trial ranged from 3 days to 48 weeks [Table 1].

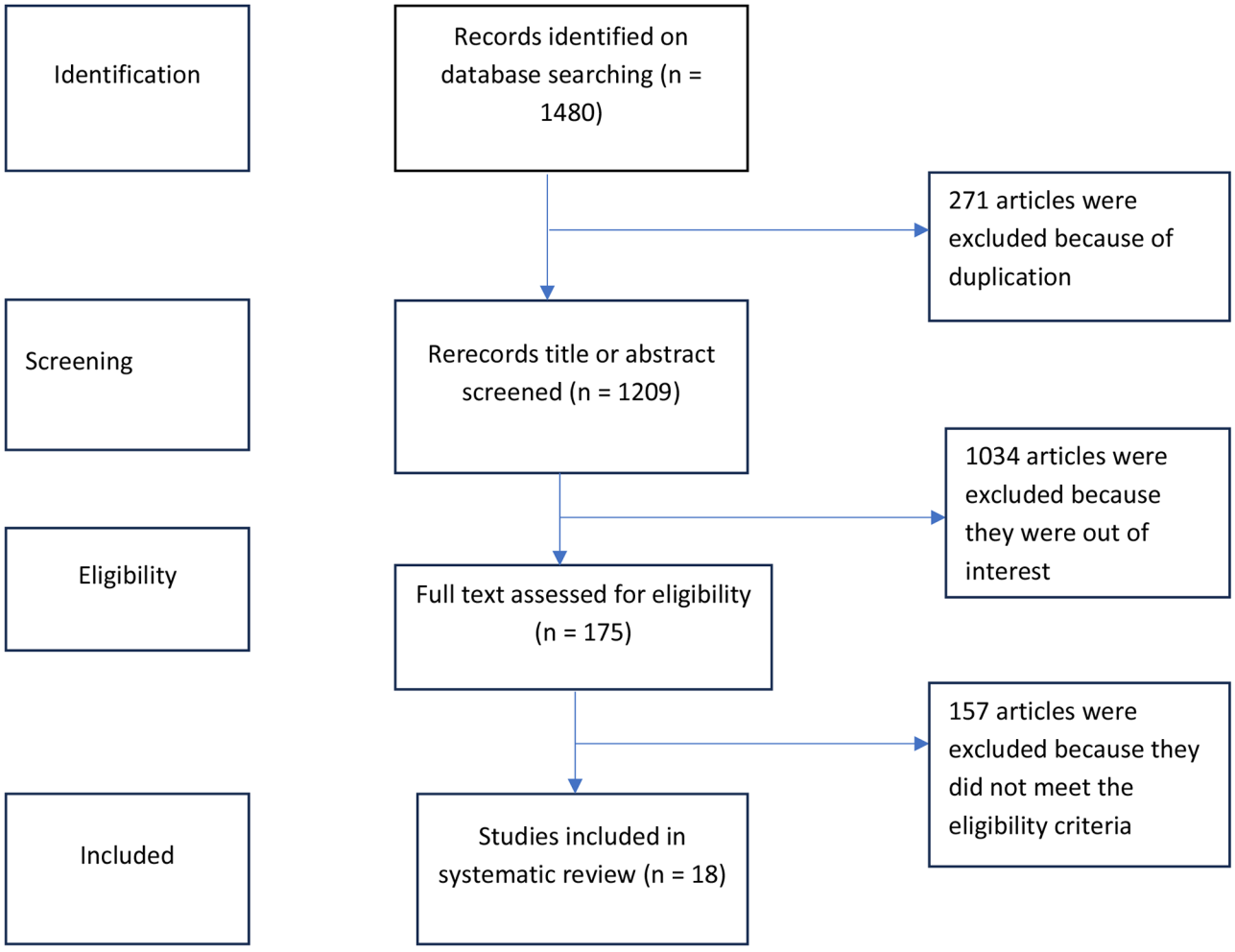

Fig. 1 PRISMA flow diagram of study selection

Effectiveness of transdermal insulin compared with subcutaneous insulin

Although there are various types of TD delivery methods, TD insulin delivery that has undergone clinical trials is the TD patch, MN TD insulin delivery, and TD insulin jet injector. All studies [46–63] showed significant effectiveness in comparison with the usual SC routes of administration. There were about two studies [46, 47] that were based on TD insulin patches; seven studies [48–54] were based on MN-based insulin delivery; and nine studies [55–63] were based on an insulin jet injector. All studies compare the effectiveness, safety, and preference of TD delivery in comparison with SC delivery. All of the studies showed either superior or comparable effectiveness of TD insulin in comparison with SC insulin. About eleven out of eighteen studies (61.1%) [49, 51, 52, 54–57, 59, 60, 62, 63] showed more effective BG control than SC delivery, and the remaining seven studies [46–48, 50, 53, 58, 59] showed comparable effectiveness with SC delivery. Most studies investigated the PH characteristics of TD insulin in comparison with SC insulin delivery, which showed rapid PK characteristics. Twelve studies found that TD insulin has more rapid PK characteristics than SC delivery.

Transdermal insulin patch

There are only two TD patch insulin deliveries that have undergone clinical trials. All of the two studies showed comparable effectiveness, as described in the following paragraphs: Bergenstal et al. [46] reported a 48-week randomized, multicenter interventional trial that compared the efficacy, safety, and self-reported outcomes of basal insulin therapy in 278 adults with T2D who initiated and managed mealtime insulin therapy with a patch pump versus an insulin pen. Glycemic control was assessed using international consensus guidelines for percentages of time in range (%TIR: >70% at 70–180 mg/dL) and time below range (%TBR: 180 mg/dL; 250 mg/dL). Both the patch and pen groups achieved recommended targets in %TIR, but with an increased %TBR.

Another study by Bohannon et al. [47] compared the efficacy, safety, device satisfaction, and quality of life

Table 1 Characteristics of included studies

Author/country	Design/duration	Population	Intervention		Measurement	Outcomes
			Transdermal	Subcutaneous		
Bergenstal et al. [46]/ USA	Randomized, multicenter, interventional trial, 48 weeks	97 patients with T2D	IA (1/2 as basal and as mealtime)	IA (1/2 as basal and as mealtime)	Percentage of time in range, GC, HbA1c, Preference, AE	There were no noticeable differences in glycemic improvements or AE between the groups. Nonetheless, the participants preferred the patch.
Bohannon et al. [47]/ USA	Randomized, multicenter, crossover study, 6 weeks	38 patients (26 T1D and 12 T2D)	IA 200IU	IA 200IU	MDBG, AE, fructosamine, 1,5-anhydroglucitol, HBA1c, quality of life Scale	The MDBG (mean ± SE) acquired using SC and the bolus patch were identical. The groups' use of hemoglobin A1c, fructosamine, insulin, and 1,5-anhydroglucitol was similar. On the other hand, the patch demonstrated enhanced QOL, substantial device satisfaction, and good safety.
Pettis et al. [48]/ USA.	Randomized, open-label, five-way crossover study,	29 T1D patients	IL and RHI (0.125 U/kg)	IL and RHI (0.125 U/kg)	AUC, Cmax, Tmax, AE	Significantly faster uptake, Tmax, Cmax, and shorter systemic circulating duration were shown in the ID IL and ID RHI PK data. ID RHI and SC IL offered similar PPG control right before the meal. RHI and ID IL delivery were typically well tolerated.
Gupta et al. [49]/ USA	Open-label, within-subjects, controlled design.	2 patients T1 D	IL 50-U	IL 100-U	PPG AE	MNs are an effective way to lower PPG levels because they quickly increase insulin absorption and cause glucose levels to drop. Regarding the MN treatments, there were no complaints of pain or AE.
Norman et al. [50]/ USA	Repeated measures study	16 T1D patients	IL 10 to 20 U	IL 10 to 20 U	AUC, onset and offset of insulin, AE	The MN insertion pain was much less severe than the SC catheter. The insulin onset and offset times were quicker following hollow MN delivery than SC delivery.
Rini et al. [51]/ USA	Randomized clinical trial, single-center, open-label, two-period crossover study, 3 days	23 T1D patients	IA 6.8 ± 2.1 U insulin	IA 6.8 ± 2.1 U insulin	IA and BG level in serum, PPG, Tmax, AE	Tmax was found to be significantly shorter after the ID bolus infusion. The PPG response was notably less pronounced: participants' perceptions of the device were generally considered acceptable, and there were no serious AEs.
Gupta et al. [52]/USA	Open-label, within-subject, controlled design.	5 T1D	IL based on the subject's BG	IL based on the subject's BG	AUC, Cmax, Tmax, AE	ID insulin infusion using MN lowered BG faster and reached Cmax in roughly half the time compared to SC catheters. MNs were also significantly less uncomfortable than SC catheters.
Pettis et al. [53]/USA	Randomized, crossover fashion	10 healthy males	IL 10 IU	IL 10 IU	AUC, Cmax Tmax Insulin levels	Early in the postinjection period, delivery of MN ID resulted in increased fractional availability, a shorter time to reach the Cmax, and faster absorption. ID had more immediate effects on glucose uptake The relative total insulin bioavailability was similar. ID-IL delivery was generally well tolerated.
McVey et al. [54]/ Germany	Single-center, randomized, open-label, eight-period crossover study using a five-block design	22 patients T1 D, multi-week period			PPG, AUC, Cmax, Tmax, AE	The systemic availability and PK consistency of ID insulin delivery are superior to those of SC insulin delivery, which might aid in PPG control. Compared to the SC, the ID delivery was notably less painful. AE was similar, and they were well tolerated.
Kochba et al. [55]/ Israel	Single-center, pilot, open-label crossover study, 4–14 days	70, T2D	IA 0.2 U/kg	IA 0.2 U/kg	Tmax, Cmax, AUC BG, Tolerability	While the Cmax, AUC, and relative bioavailability did not differ significantly between ID and SC injections, the ID Tmax was significantly shorter. This could lead to reduced PPG excursions by ID and improved insulin coverage during meals. The ID route was well tolerated.

Table 1 (continued)

Author/country	Design/duration	Population	Intervention		Measurement	Outcomes
			Transdermal	Subcutaneous		
Ji et al. [56]/ China	Prospective, multi-center, randomized, open-label study, random, 16 weeks	427 T2DM	Insulin: 30 units/day	Insulin: 30 units/day	HbA1c, BG, Patients' satisfaction	When compared to SC injections, insulin therapy administered via a needle-free injector demonstrated a non-inferior glycemic-lowering effect and a significantly higher degree of patient satisfaction with insulin treatment. The safety profile of the needle-free injector was also superior.
Jin et al. [57]/ China	Prospective, randomized, open, cross-controlled, 8 weeks	42 patients T2D	IA	IA	FBG, PPG Pain score	Compared to SC insulin, premixed insulin delivered using a needle-free syringe results in less pain at the injection site and better FBG control.
Xing et al. [58]/ China	Multicenter, randomized, prospective, open-label, crossover study, 7–14 days,	62 T2D	IG	IG	FBG Level of Insulin AE	Using a needle-free injector can help improve patient compliance by reducing the amount of insulin needed to achieve good glycemic control as well as AE.
Wu et al. [59]/ China	self-controlled crossover study	62 T2D			FBG, AUC Satisfaction	Needle-free insulin injections were a better way to control glucose, and the patients also felt less pain.
Guo et al. [60]/ China	Randomly, 8 weeks	64 patients with T2 D	RI and IA: 20 to 150 IU daily with different cycle	RI and IA: 20 to 150 IU daily with different cycle	PPG Insulin level AUC, AE	Compared to SC injections, RI and IA injections using the jet injector resulted in noticeably lower BG. Insulin and BG levels are better managed by insulin jet injectors than by insulin pens. When delivering insulin, the jet injector conveniently functions with a high level of acceptability and tolerability.
Reutens et al. [61]/ Australia	Randomized, open-label, single-center, crossover study, 30 days	10 T1D	Based on insulin-to-carbohydrate ratios	Based on insulin-to-carbohydrate ratios	Tmax, Gluexc, AUCglu, AUCinsulin	The devices were similar in glucose excursion, AUCglu, corrected for BG, and AUCinsulin. Devices were similar for participant preference and relative injection pain.
de Wit et al. [62]/Netherlands	randomized, controlled, crossover study,	10 T1D and 10 T2D	IA	IA	PPG, Tmax Cmax, AUC, AE	When IA is administered via jet injection rather than a SC, patients with a higher body mass index experience a faster and safer correction of marked incidental hyperglycemia.
Engwerda et al. [63]/ Netherlands	Randomized, double-blind, double-dummy crossover study	12 T1D, 12 T2D	Insulin 17.6 ± 6 3.9 IU	Insulin 17.6 ± 6 3.9 IU	Cmax Tmax BG Safety	When compared to SC delivery, insulin administered by jet injection produced a noticeably lower Cmax and Tmax and a lower hyperglycemic burden during the first hour. For the next five hours, however, the jet injection did not considerably lessen the hyperglycemic burden. Patients who have trouble limiting PPG excursions may particularly benefit from improved early PPG control.

Abbreviations: AEs: Adverse events; AUC: Area under the curve; BG: Blood glucose; Cmax: Maximum concentration; FBG: Fasting blood glucose; IA: Insulin aspart; ID: Intradermal; IL: Insulin lispro; MDBG: mean daily blood glucose; MNs: Microneedles; PK: pharmacokinetic; PPG: Postprandial glucose; RHI: Regular human insulin; SC: Subcutaneous; T1D: Type 1 diabetes; T2D: Type 2 diabetes; TBR: Time below range; TIR: Time in range; Tmax: time to reach maximum concentration

(QOL) in people with diabetes using an insulin bolus patch versus SC delivery. About 38 subjects with diabetes (26 with T1D and 12 with T2D) were randomized to a bolus-patch or SC to deliver mealtime insulin in a multicenter, 6-week crossover study. Using a bolus patch, the mean daily seven-point blood glucose was equivalent to that using SC. Hemoglobin A1c, 1,5-anhydroglucitol, fructosamine, and insulin use were similar between groups.

Microneedle-based transdermal insulin delivery

About seven clinical trials were conducted to compare the effectiveness, safety, and preference of MN-based insulin delivery in comparison with SC insulin delivery. Of them, in four (57.1%) [49, 51, 52, 54] studies, MN insulin has higher effectiveness than SC delivery, and the remaining three [48, 50, 53] show comparable effectiveness. All MN-based TD insulin delivery clinical trials also compared the PK characteristics, and all of them confirmed that MN TD insulin deliveries had more rapid PK properties than SC insulin delivery. A study by Pettis et al. [48] assessed PK and pharmacodynamic [PD] PPG in patients with type T1D after a standardized liquid meal following insulin lispro (IL) or regular human insulin (RHI) given by MN-based intradermal (ID) versus SC delivery. In this randomized, open-label, five-way crossover study, 29 patients received IL and RHI by both the SC and ID routes. The 90-min PPG for ID RHI was 14% lower than SC RHI at 17 min and 11% lower than ID RHI at 2 min. PPG did not significantly differ between ID RHI and SC IL, and ID IL and SC IL. Both ID IL and ID RHI PK data showed significantly faster uptake, Tmax, and Cmax than SC dosing.

A study by Gupta et al. [49] was carried out on two adults with T1D and evaluated bolus delivery of IL using a hollow MN compared to SC delivery. The first phase of the study indicated that MNs led to rapid insulin absorption and a reduction in BG. Bolus insulin delivery followed by consumption of a standardized meal in the second phase revealed that MNs were effective in reducing PPG levels.

Norman et al. [50] studied ID insulin delivery using a hollow MN in comparison with SC delivery. In these repeated measures study, 16 T1D children and adolescents were administered IL in SC and MN on different days. When hollow MN delivery was used instead of SC delivery, insulin onset time was 22 min faster, and offset time was 34 min faster.

Rini et al. [51] conducted a clinical trial to evaluate ID MN insulin kinetics using a randomized, single-center, open-label, two-period crossover study in T1D patients. About 28 patients received treatment during interventional visits: one SC and one ID basal/bolus infusion of insulin aspart [IA] administered over 3 days. ID-bolus infusion was associated with a significantly shorter Tmax and statistically significantly smaller intra-subject variability compared to SC infusion. The PPG response was significantly less pronounced after ID bolus: for most endpoints, ID vs. SC, differences were statistically significant within the 0–1.5 or 0–2 h period.

Gupta et al. [52] compared the PK, pain, and PPG responses of ID IL delivery via a MN versus SC in five T1D subjects. Compared to SC catheters, ID insulin infusion using MN reduced BG levels more quickly and achieved Cmax in about half the time. The use of MN for ID insulin infusion has a rapid PK, which offers great promise for better diabetes control.

Pettis et al. [53] compared the PK and PD of IL delivered via MN ID injection with SC injection in 10 healthy male volunteers who received 10 IU of IL in a randomized crossover fashion. With a quick Tmax and Cmax, MN ID delivery led to a faster absorption of IL, which was associated with faster effects on glucose uptake, more AUC, and a quicker offset of insulin action. Between the administration routes, there was no discernible difference in the relative total insulin bioavailability.

McVey et al. [54] examined the PK and PD effects of IL delivered by SC delivery versus MN-based ID delivery. A total of 22 individuals with T1D participated in the study, which used an eight-arm full crossover block design. The insulin PK endpoints demonstrated faster ID availability than SC insulin. SC administration revealed slight, statistically noteworthy variations in the secondary PD effect.

Jet injector-based transdermal insulin delivery

About nine clinical trials were conducted based on insulin TD jet injectors; most of them (77.8%) [55–57, 59, 60, 62, 63] showed higher effectiveness than SC insulin, and the remaining studies [58, 61] showed comparable effectiveness with SC insulin delivery. Kochba et al. [55] conducted a pilot open-label crossover study at a single center with 17 T2D patients to confirm insulin PK may be improved by ID injection. The Tmax for ID injection was significantly shorter than that of SC injection, but the Cmax was not significantly different. The groups' median insulin AUC was the same. In patients with T2D, ID insulin injection administered via a jet injector showed a better PK profile than conventional SC administration, better insulin coverage during meals, and fewer PPG excursions might result from this.

Ji et al. [56] carried out a study to compare the effects of insulin treatment with a SC delivery and a needle-free insulin injector (NFII) on glucose-lowering effect, tolerability, patient satisfaction, and compliance in patients with T2D. In a prospective, multicenter, randomized, open-label study, 427 patients were enrolled for 16 weeks of treatment. The adjusted mean HbA1c reduction from baseline at week 16 was 0.55% in the NFII group, which

was statistically superior and non-inferior to the HbA1c reduction in the SC group.

Jin et al. [57] conducted a study to explore the effect of using a NFII on BG control and well-being index in 42 patients with early-onset T2D using IA. The FBG of the NFII group was lower than that of the SC group. The amount of insulin in the NFII group was lower than that in the SC group, but there was no statistically significant difference. NFII is effective in controlling FBG in patients with early-onset T2D and is less painful at the injection site.

Xing et al. [58] assessed the safety and effectiveness of a NFI in comparison with SC insulin in Chinese T2D patients receiving basal insulin therapy in a multicenter, prospective, randomized, open-label crossover study that included about 62 patients for seven to fourteen days. The FBG control attained by the patients in the SC and insulin NFII groups was comparable. Nonetheless, the NFI group needed less insulin than the SC group to reach the desired FBG level.

Wu et al. [59] demonstrated that both needle injection and NFI can raise HbA1c in T2D patients. About 62 T2D patients received insulin in a self-controlled cross-over study. When patients received NFI instead of needle injections, their BG levels were higher during fasting and post-breakfast. The AUC, or daily blood glucose fluctuation, did decrease during NFI periods. During the NFI period, patients received a lower dose of fast-acting insulin than when they received needle injections. In hospitalized T2D patients undergoing intensive glycemic control, insulin injections without needles provided better glycemic control.

Guo et al. [60] conducted a study to investigate the efficacy of an insulin jet injector and an insulin pen in the treatment of 60 T2D patients treated with RHI and IA in four successive test cycles. RHI and IA administration by the jet injector showed significant decreases in plasma glucose levels as compared to the pen injection. PPG excursions at the time points of 0.5 to 3 h were lower in the jet-treated patients than the pen-treated ones. Postprandial plasma insulin levels were markedly higher in the jet-treated patients than the pen-treated ones. However, the area under the glucose curve in the pen-treated patients was significantly increased as compared to the jet-treated ones. The efficacy of the insulin jet injector in treating T2D patients is superior to that of the insulin pen in regulating plasma glucose and insulin levels.

Reutens et al. [61] carried out an open-label, randomized, crossover pilot study to assess the device preference and tolerability of SC IA delivery and jet injector delivery. Two meal tolerance tests were administered to ten T1D participants one week apart. The results of this small pilot study showed that the devices showed similar glucose excursion, the area under the glucose concentration-time curve for 0–240 min corrected for baseline glucose level, and insulin absorption over the 240-min span.

De Wit et al. [62] conducted a study to determine the effectiveness of jet injection in comparison with SC delivery. A randomized, controlled crossover study was conducted with ten adult patients with T1D and ten with T2D who were overweight. The jet injection significantly decreased the time to peak insulin levels and the hyperglycemic burden during the first two hours. When patients with diabetes who are overweight or obese are given insulin injections, their marked hyperglycemia is corrected more quickly by a jet injection.

Engwerda et al. [63] compared the PK and PD profiles of insulin administration by jet injection versus SC delivery in patients with 12 T1D and 12 T2D patients who received IA by jet injection or by SC in a randomized, double-blind, double-dummy crossover study. When insulin was administered by jet injection, Tmax was shorter, and the hyperglycemic burden was lower during the first hour. For the next five hours, however, the jet injection did not considerably lessen the hyperglycemic burden. Patients with T1D and T2D saw a significant, if modest, decrease in PPG as a result of the significantly faster absorption of insulin following administration by a jet injector. Patients who have trouble controlling PPG excursions may particularly benefit from the enhanced early PPG control.

Safety and participant preference of transdermal insulin in comparison with subcutaneous insulin

As for effectiveness, all studies showed either TD insulin delivery had equal tolerability or more tolerability. Eleven studies (61.1%) [47, 51–57, 61–63] showed equal tolerability of TD insulin versus SC insulin, and seven studies (38.9%) [46, 48–50, 58–60] showed more tolerability of TD insulin over SC insulin. Most studies, eleven out of eighteen (61.1%) [46–50, 52, 54–56, 58, 60] showed a higher preference for TD insulin delivery over traditional SC delivery; sixth out of eighteen (33.3%) [51, 53, 57, 59, 61, 62] showed equal preferability for TD insulin versus SC insulin; and only one study (5.6%) [63] showed that TD insulin delivery was less preferable than SC insulin.

Transdermal insulin patch

One study of TD patch insulin delivery showed comparable tolerability between TD insulin delivery and SC insulin delivery, while the other study showed TD insulin delivery had more tolerability than SC insulin delivery. All TD patch studies were preferable to SC insulin delivery. Bergenstal et al. [46] found that more satisfied patients preferred using the patch, felt less constrained, recommended the patch to others, and felt free to manage their diabetes with the patch over the pen. Their safety was also comparable. Bohannon et al. [47] showed

subjects preference for bolus-patch over SC delivery. Both delivery methods had comparable safety, with a similar incidence of non-severe hypoglycemia for both methods.

Microneedle-based transdermal insulin delivery

About four studies (57.1%) [48–51] of MN TD insulin delivery were well tolerable over SC insulin delivery, while three studies (42.9%) [52–54] showed comparable tolerability of MN-based TD insulin delivery versus SC insulin delivery. Moreover, most MN-based TD insulin deliveries (71.4%) [48–50, 52, 54] were preferable over SC insulin delivery, and only two studies (28.6%) [51, 53] showed comparable preferability of both delivery methods by patients. A study by Pettis et al. [48] found comparable AEs for both methods of administration. Both of them showed no serious AEs such as headaches, diarrhea, hypoglycemia, or edema, which occurred in three to four patients. Their equal tolerability may implicate their comparable acceptability and preferability.

Gupta et al. [49] found that patients indicated that all MN insulin deliveries were less painful than catheter-based deliveries, which indicated their preference for this method of administration. Subjects indicated a mild tingling sensation during MN delivery, which they attribute to the relatively fast delivery flow rate. Norman et al. [50] found less insertion pain when a single, hollow MN device was used for ID insulin delivery. Pain relief could increase insulin delivery compliance and preference. Rini et al. [51] also investigated that there was no bias in AEs between treatment routes, and ID was safe compared to SC delivery. Pain scores were low for both routes. Patients found infusion set insertion equally acceptable and preferable for both routes.

Gupta et al. [52] found better patient acceptance, which is consistent with the minimally invasive nature of MNs. Additionally, MN caused a lot less pain than catheters. Pettis. et al. [53] showed that all participants experienced safe and well-tolerated ID delivery. During the study, no significant AE was recorded in both methods of delivery, and patients showed comparable preference between both methods of insulin delivery. McVey et al. [54] showed ID delivery preferability and minor variations in pain perception based on route. The number of hypoglycemic events and time in hypoglycemic and hyperglycemic ranges did not significantly differ between routes. No significant AEs were reported in both methods of delivery.

Jet injector-based transdermal insulin delivery

Six Jet injector-based TD insulin delivery studies (66.7%) [55–57, 60–63] showed comparable tolerability with SC insulin, while three insulin Jet injector studies (33.3%) [58–60] showed good tolerability over SC insulin delivery. High preferability of jet injector TD insulin delivery over SC insulin delivery was demonstrated by four studies (44.4%) [55, 56, 58, 60], four studies (44.4%) [57, 59, 60, 62] showed equal preferability, and one study (11.1%) [63] showed less preferability of jet injector-based insulin delivery over SC insulin delivery. Kochba et al. [55] investigated no significant difference in insertion pain and AEs between ID and SC injections. ID is more preferable to SC delivery. Ji et al. [56] showed that there was no significant difference in compliance rates between groups due to similar injection miss rates, although they preferred NFII. After 16 weeks, NFII patients had higher treatment satisfaction than SC patients. The incidence of hypoglycemia and unexpected adverse events was similar between groups.

Jin et al. [57] found that pain scores were lower with needle-free syringes vs. SC delivery, and skin bleeds were similar in both groups. They showed comparable preferability in both delivery methods. Xing et al. [58] investigated patients who reported feeling more at ease using the NFI due to its comparable acceptability and ease of use. Additionally, using a NFI considerably lessened their anxiety and pain about injections. Wu et al. [59] found that similar levels of patient satisfaction were reported for the two types of injection devices, both of which were above the general satisfaction threshold. When needle injections were avoided, the level of pain was substantially less than when they were administered.

Guo et al. [60] found that jet-treated patients had no fear about their administration, which showed their preferability for jet injection. They had comparable AEs, and no serious AEs were observed. Reutens et al. [61] investigated and found that no significant AEs were observed and there were no reports of bruises at the device application site. Participants liked using both devices equally. de Wit et al. [62] showed most mild to moderate AEs were related to hyperglycemia, like thirst, polyuria, and nausea, which resolved when glucose levels dropped. Preferability, ease of use, and pain/discomfort levels were comparable between the jet injector and pen. Engwerda et al. [63] found that there were no differences in the need for exogenous glucose, timing, or amount between the jet injector and pen. Pain levels and tolerance were similar. Contrary to all studies, this study showed the preferability of SC insulin delivery.

Discussion

All of the studies demonstrated significant effectiveness, or at the very least, showed comparability with respect to the traditional SC delivery methods. About eleven out of eighteen studies (61.1%) [49, 51, 52, 54–57, 59, 60, 62, 63] showed more effective BG control than SC delivery, and the remaining seven studies [46–48, 50, 53, 58, 59] showed comparable effectiveness with SC delivery. One

key finding was that the majority of studies (61.1%) demonstrated superior BG control with TD insulin compared to SC delivery. This suggests that TD insulin may offer better glycemic control for individuals with diabetes. Additionally, the remaining studies showed comparable effectiveness between TD and SC insulin, indicating that TD delivery is at least as effective as SC administration.

Although there are various types of TD insulin delivery methods, the ones that have undergone clinical trials are the TD patch, MN TD insulin delivery, and transdermal insulin jet injector. Furthermore, the study investigated the PK characteristics of TD insulin and found that TD delivery methods generally have more rapid PK profiles compared to SC administration. This suggests that TD insulin may lead to quicker absorption and onset of action, which could be beneficial for managing BG levels effectively. Overall, the findings suggest that TD insulin delivery methods have shown promising results in clinical trials.

The studies demonstrate improved effectiveness, safety, and preferability with TD insulin administration, indicating the potential for this innovative delivery approach to be introduced to the market. Recent research has explored alternative delivery methods to replace the traditional SC route, with several studies highlighting the benefits of TD insulin delivery. There were various promising clinical trials that provided alternative routes of insulin to prevent traditional SC delivery. Akbari et al. (2016) conducted a systematic review and meta-analysis comparing the safety and efficacy of oral insulin delivery to the SC route. The meta-analyses revealed that there were no significant differences between oral and SC insulin in terms of regulating HbA1c, FBG, 1- and 2-hour PPG levels, or insulin Cmax and Tmax. This systematic review and meta-analysis suggest that oral insulin is generally comparable to SC insulin in terms of glycemic efficacy and safety [64]. In comparison with TD insulin delivery, which is often considered more convenient, preferable, and potentially less invasive, the findings from Akbari et al.'s study suggest that both oral and SC insulin delivery methods offer similar effectiveness and safety profiles.

As for effectiveness, in the studies reviewed, most of them (11 out of 18) demonstrated either equal tolerability or more tolerability of TD insulin compared to SC insulin. This suggests that patients may experience fewer adverse effects or discomfort with TD insulin delivery, making it a more acceptable option for some individuals. Specifically, eleven studies showed equal tolerability between TD and SC insulin, indicating that TD insulin is at least as well-tolerated as SC insulin in terms of side effects, injection site reactions, and overall patient comfort. Additionally, seven studies reported greater tolerability of TD insulin than SC insulin, indicating that TD insulin may offer a more favorable experience for patients in terms of tolerability and acceptance.

The preference for TD insulin delivery over traditional SC delivery was also assessed in the studies. Most of the studies (11 out of 18) showed a higher preference for TD insulin delivery, suggesting that patients may prefer the convenience, ease of use, and potentially reduced invasiveness of TD insulin administration. On the other hand, six studies reported equal preferability for TD insulin versus SC insulin, indicating that some patients may not have a strong preference for one method over the other. Only one study showed that TD insulin delivery was less preferable than SC insulin. This outlier suggests that individual preferences and experiences with different insulin delivery methods can vary among patients.

The potential advantages of TD insulin, such as improved tolerability, higher preference among patients, and potentially enhanced convenience, make it a promising alternative to traditional SC insulin administration. Further research and clinical trials are needed to confirm these findings and explore the long-term benefits and outcomes of TD insulin delivery in diabetes management. Besides that, TD systems have the advantage of reducing dosing frequency as drugs are released at a predetermined rate and controlling blood glucose levels over a prolonged period of time, contributing to better patient compliance [65].

In addition to their superior effectiveness and safety, TD insulin delivery should preferably be highly considered because improved patient compliance would ultimately lead to reduced healthcare costs for diabetes patients due to the potential lower frequency of hypo- and hyperglycemic events and related hospitalizations. As indicated previously, MN has been used to extract interstitial fluid from human subjects to successfully detect glucose levels [66]. Further research and clinical trials are needed to confirm these findings and explore the long-term benefits of TD insulin delivery for individuals with diabetes. To ensure the reliability and dependability of the results and enable stronger inferences to be made, a larger sample size is essential. To increase the generalizability of the findings, a more varied study sample must be assembled, comprising people with various socioeconomic, ethnic, and geographic backgrounds. Additionally, examining the safety and effectiveness of the alternate delivery method in distinct patient subgroups, such as children, the elderly, or individuals with certain comorbidities, will offer important information on its generalizability to a range of demographics. To guarantee the safety and effectiveness of this delivery mechanism over time, it is important to investigate any potential problems and effects over time. Finally, carrying out comparative analyses that assess this method's efficacy in comparison to conventional delivery methods

will facilitate a thorough comprehension of its advantages and disadvantages, ultimately contributing to evidence-based decision-making.

Conclusion

This is the first systematic review of the effectiveness, safety, and preference of TD insulin delivery in comparison with SC insulin delivery, considering clinical trials. Although for many years the only choice of insulin delivery was SC delivery, in recent years there have been various novel-based studies on oral and TD insulin delivery. These TD-based insulin delivery methods found that TD insulin delivery methods were the best alternative because most of them were more effective, safe, and preferable over SC delivery. If they are not more effective, safe, and preferable, at least they are equally effective, safe, and preferable with SC insulin delivery. By considering this, further clinical trials should be conducted with a larger sample size to ensure the effectiveness and safety of this type of delivery, ultimately making it a practical and accessible option for patients.

Abbreviations

AEs	Adverse events
AUC	Area under the curve
BG	Blood glucose
Cmax	Maximum concentration
DM	Diabetes mellitus
FBG	Fasting blood glucose
IA	Insulin aspart
ID	Intradermal
IL	Insulin lispro
MDBG	Mean daily blood glucose
MNs	Microneedles
NFII	Needle-free insulin injector
PD	Pharmacodynamic
PK	Pharmacokinetic
PPG	Postprandial glucose
QOL	Quality of life
RHI	Regular human insulin
SC	Subcutaneous
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TBR	Time below range
TDDDS	Transdermal drug delivery systems
TIR	Time in range
Tmax	Time to reach maximum concentration

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