Comparison between insulin delivery methods: subcutaneous, inhaled, oral, and buccal

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ABSTRACT

Diabetes mellitus is a complex and chronic metabolic disorder characterized by hyperglycemia. Part of the treatment for this condition is the administration of insulin, a protein that directly influences blood glucose levels. It is traditionally administered parenterally; however, new alternative ways for its application seek greater efficiency and less invasiveness. The objective of this article is to compare the different methods of insulin administration, taking into account new technologies. This review article provides an overview of diabetes and insulin, highlights the advantages and disadvantages of insulin delivery methods (subcutaneous, inhaled, oral, and buccal), and shows the new technologies that include biotechnological applications.

Key words: diabetes; insulin; subcutaneous; inhaled; oral; buccal.

RESUMEN

La *diabetes mellitus* es un desorden metabólico crónico y complejo, caracterizado por hiperglicemia. Parte del tratamiento para este padecimiento es la administración de insulina, proteína que influye directamente en los niveles de glucosa en sangre. Tradicionalmente esta se administra de forma parenteral; sin embargo, en la actualidad existen formas alternativas para su aplicación que buscan mayor eficacia y menos invasividad. El objetivo del presente artículo es comparar los diferentes métodos de aplicación de la insulina, tomando en cuenta las nuevas tecnologías. Este artículo de revisión ofrece una descripción general de la diabetes y la insulina, destaca las ventajas y desventajas de los métodos de administración (subcutánea, inhalada, oral y bucal) y muestra las nuevas tecnologías que incluyen aplicaciones biotecnológicas.

Palabras clave: diabetes; insulina; subcutánea; inhalada; oral; bucal.

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INTRODUCTION

Diabetes mellitus (DM) is a complex and chronic metabolic disorder characterized by hyperglycemia.[1,2] It is classified into two main types, type 1 (DM1) and type 2 diabetes (DM2).[3] DM1 is an autoimmune disease in which the pancreatic beta-cells are destroyed while DM2 is a combination of insulin resistance and a deficiency in pancreatic insulin production.[1] Between 5 and 10% of the patients suffer DM1 and 90–95% have DM2.[4]

Some of the complications of DM are retinopathy, nephropathy, and neuropathy as well as an elevated risk of suffering other illnesses like coronary, peripheral artery and cerebrovascular diseases, obesity, cataracts, erectile dysfunction, non-alcoholic fatty liver disease, and infections.[3]

Both types of DM require lifestyle changes, for instance, healthy eating and physical exercise.[5] The treatment of DM1 comprises insulin and/or insulin analogues while the management of DM2 includes oral antidiabetics, such as metformin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase-4 inhibitors, and sodium-glucose cotransporter-2 inhibitors. Insulin is necessary in DM2 in the following cases: when patients with oral antidiabetic treatment at maximum doses do not reach their glycemic control goals (HbA$_{1c}$<6.5%) in 3 months, when oral antidiabetic drugs are contraindicated, or during pregnancy.[6]

Insulin is commonly self-administered subcutaneously by patients through injections.[7] The Worldwide Injection Technique Questionnaire Study was conducted in 2014–2015 among 13,000 insulin-injecting patients from 42 countries, including Mexico. It was found that the incorrect provision of insulin through injections can cause a number of complications. Among those are unexpected hypoglycemia or glucose variability due to factors such as lipohypertrophy (30.8% of diabetic patients), poor rotation at injection sites (29.4% of diabetic patients), insulin leakage (36.9% of diabetic patients), and the reuse of needles.[8,9] To improve the optimization of insulin administration it is recommended to seek alternative insulin delivery methods.[9] Therefore, this review aims to compare subcutaneous insulin administration with inhaled, oral, and buccal delivery methods to exhibit the advantages and disadvantages of each.

INSULIN

It is a hormone that increases glucose assimilation, stimulating glycolysis and favoring glycogen synthesis in the liver and muscles.[10] It is used in patients with DM1 whose production of this hormone is null and DM2 patients with resistance to or limited production of it. Having different insulin preparations and administration methods allows patients to have greater application comfort, contributing to their well-being.

Types of insulin

Types of insulin are characterized based on their pharmacokinetic profiles, concentration, and the onset, peak and duration of action[11] (Table 1).

Rapid-acting and insulin bolus

The application of insulin bolus (rapid-acting insulin together with basal insulin and food) provides flexibility in the dosage.[11] Its onset action is at 0.5–1 h, with a peak action at 2–4 h

TABLE 1. Onset of action, maximum effect, and action duration of insulin preparations after subcutaneous injection.

TYPE OF INSULIN	START	MAXIMUM PEAK	DURATION
RAPID ACTING INSULIN			
Aspart insulin	10–20 min	40–50 min	3–5 h
Lispro insulin	15–30 min	30–90 min	3–5 h
Glulisine insulin	20–30 min	30–90 min	1–2.5 h
SHORT-ACTING INSULIN			
Regular insulin	30–60 min	2–5 h	5–8 h
INTERMEDIATE ACTION INSULIN			
Isophane insulin (NPH)	1–2 h	4–12 h	18–24 h
LONG-ACTING INSULIN			
Insulin glargine	1–1,5 h	None	20–24 h
Insulin detemir	1–2 h	6–8 h	Up to 24 h
Insulin degludec	1–2 h	None	> 24 h

and an activity duration of 6–8 h. It can be accompanied by different methods to accelerate its absorption; however, research is trying to improve its mechanism of action.[12,13] It can be administered before, during or after meals, and the dose can be adjusted based on carbohydrate consumption.[11]

Short-acting or concentrated insulin

It is two to five times more concentrated than its commonly used counterpart. It is used in patients who have severe insulin resistance or consume steroid-type medications. Its peak of action corresponds to the type of insulin concentrated and can range from 30 min to over 1 h. It is useful in patients who require more than 200 units a day.[11,14]

Intermediate-acting insulin

Intermediate-acting insulin analogues have an onset action between 1 and 2 h, with a maximum action of 6–10 h and an activity duration of 10–16 h. The rate of absorption is reduced by adding protamine to the preparation.[13]

Long-acting or basal insulin

It is an ideal option for patients with DM2 just starting their treatment. It is usually injected at night, every 24 h and suppresses hepatic glucose production. It generates a better glycemic control with minimal side effects, resulting in optimal plasma insulin concentrations.[15] It is administered independently of food intake, and patients should continue to receive the established dose upon reaching normal glucose levels.[12]

METHODS OF INSULIN ADMINISTRATION

To date, insulin methods of administration have been limited mainly to subcutaneous injections and parenteral pumps.[12] Then, research is looking for alternative administration methods that allow the gradual improvement of diabetes management to increase patient compliance and reduce invasiveness.[16] These methods include inhalable forms that use microspheres[17], closed-loop delivery systems with insulin pumps[18], and oral forms associated with microencapsulation techniques (Figure 1).

SUBCUTANEOUS INSULIN
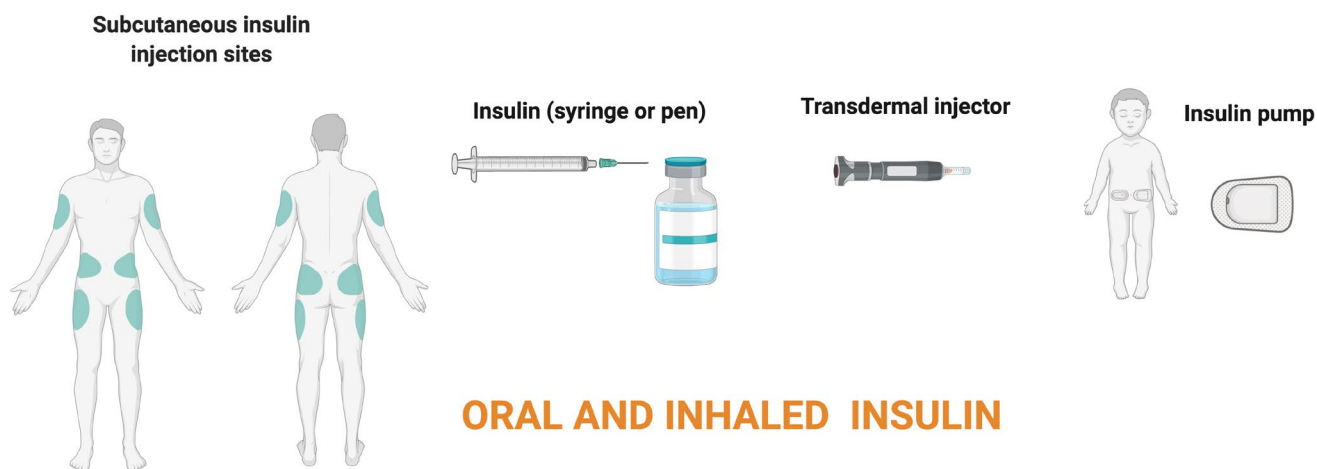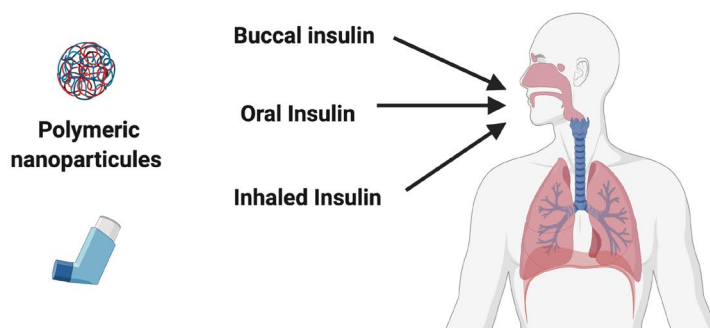
ORAL AND INHALED INSULIN

FIGURE 1. Most common routes for insulin administration.

Subcutaneous insulin

It is the conventional administration route. Preferred injection sites include the abdomen (except a 2-inch radius around the navel), arms, thighs, and buttocks because of their high rates of absorption. The injection site should be rotated to prevent lipohypertrophy or lipoatrophy.[19] This delivery method uses syringes, pens, jet injectors, and pumps.

Syringes

Syringes used for insulin injections are marked in insulin units and have 0.3, 0.5, 1, or 2 ml of capacity while needles vary in length. The patient's injection technique needs to be reviewed periodically by a physician. Recommendations that diminish painful injections are not injecting cold insulin, not changing the direction of the needle, avoiding needle reuse, keeping the muscles of the area relaxed, and puncturing the skin quickly.[19,20]

Insulin pens

Available in disposable forms[21] and in durable reusable forms, these devices use cartridges instead of vials. There are low-dose pens that deliver insulin in half-unit increments.[19] The dose is set by rotating the knob of the pen.[21] It is recommended to leave the needle applied for at least 5 s after the knob of the pen is all the way down to make sure the delivery is complete.[19] They are used by 80–90% of European patients. Nowadays, "smart" pens provide dose calculation and have tracking features.[21]

Insulin jet injectors

They inject insulin as a fine stream into the skin, without a needle.[19] They deliver insulin at a high velocity (usually >100m/s) across the skin in the subcutaneous tissue and, unlike injections, they dispense the insulin over a larger area.[22]

Insulin pump

It is a small, computerized device that delivers insulin through a thin tube that passes under the skin. It releases insulin the way the body would naturally, with a constant flow throughout the day and night, called basal insulin, and an additional dose at mealtime, called a bolus. More than a million patients currently use this treatment modality.[23] It improves administration control, reducing the risk of long-term complications. It is part of closed-loop treatment systems, in which subcutaneous insulin infusion and devices that continuously monitor glucose levels are connected to generate an automatic response.[24]

Inhaled insulin

It proposes the absorption of insulin through the pulmonary system. The distant lung presents a large, highly perfused surface area that allows for a rapid absorption of small particles into systemic circulation.[25] Inhaled insulin evades hepatic metabolism and enzymatic degradation in the gastrointestinal (GI) tract, and it prevents painful and invasive procedures. It might be ineffective in patients with respiratory problems.[26] Inhaled insulin was the first reported alternate route of administration that was successful. However, the cost and contraindications made it commercially unsuccessful.[27] In 2014, the FDA approved an inhaled form of insulin in technospheres administered via a compact inhaler device. This method consists of a dry powder insulin formulation absorbed into a carrier, namely technospheres, that are propelled into the deep lung.[28]

Oral insulin

It has been since the discovery of insulin, a very desired aim.[29] It is the friendliest way of administering insulin, the one that most closely mimics physiological insulin delivery, increasing portal insulin concentration via intestinal absorption.[30] However, apart from the innate physical instability, oral insulin faces various physiological challenges, such as chemical and enzymatic degradation in the GI tract, intrinsic poor oral absorption, and rapid systemic clearance, resulting in low bioavailability and insufficient therapeutic effect.[16] The development of nanotechnology has offered hope to increase its efficacy. Several nanoparticles composed of biodegradable polymers, such as chitosan, alginate, mucin, yeast, liposomes, polymeric nanovesicles, and polymeric hydrogels have been developed for the microencapsulation of insulin.[12,30]

Chitosan is an optimal oral administration vehicle[31] derived from the alkaline deacetylation of chitin.[32] It is used as a drug delivery system due to its degree of acetylation and its molecular weight, which affect its aqueous solubility and hydrophobicity. Chitosan microparticles increase their solubility under acidic conditions, benefiting drug delivery in the GI tract. Its natural mucoadhesive properties and its ability to transiently open epithelial tight junctions and make it a great candidate for intestinally absorbed, orally administered drugs.[31,32]

Another recently developed vehicle are yeast-alginate microcapsules (YMC).[33] This method commonly employs

Saccharomyces cerevisiae to incorporate differentially charged insulin peptides[34], in a way that the YMC are able to open tight junctions and enter the systemic circulation through M cell-mediated endocytosis.[35] Additionally, in order to inhibit the action of the acidic environment in the stomach, alginate is used as a coating agent to efficiently deliver YMC to their absorption site.[36]

Other organic and inorganic polymeric compounds have also been tested for the same purpose. These include dextran-based and PLGA-based (poly(lactic-co-glycolic acid)) microparticles. Dextran has been used to encapsulate insulin-polyanion complexes, improving drug entrapment and loading efficiency, facilitating mucoadhesiveness, and improving GI permeability. However, the layer-by-layer method proposed is complex, costly, and time-consuming.[16,37] On the other hand, PLGA has been proposed as a potential microcarrier of insulin, due to its biocompatibility and biodegradability. Nonetheless, up to date hydrophobic PLGA has been proven unsuccessful to encapsulate hydrophilic insulin, generating loss of stability and loading efficiency.[16]

Buccal insulin

It presents some of the advantages of oral insulin, besides, it increases drug bioavailability because it bypasses enzymatic degradation in the GI tract and hepatic metabolism.[38] It is generally presented in the form of mucoadhesive buccal films.[27] The buccal mucosa has ready accessibility, high tissue permeability, high vascularization, and increased rate of cell growth, which reduces cytotoxic effects related to high drug concentration.[39] However, with hydrophilic peptides like insulin, the speed of diffusion through buccal tissue is not considered to be fast enough when compared to subcutaneous injection. Thus, buccal delivery films must usually be integrated with permeation enhancers that effectively loosen junctions between epithelial cells to increase transbuccal drug delivery.[38] The design, mechanism, and disintegration times of different mucoadhesive films varies widely in the literature. They are normally composed of film forming polymers, plasticizers, stabilizers, colorant, sweeteners, and flavors.[40] The main component, after the insulin peptides, is the polymers, which must exhibit good adhesive properties and enhance permeability of the active ingredient.[38] Several polymers have been suggested, with chitosan standing out for exhibiting similar properties as those found in oral insulin.[39] Glycan-coated gold nanoparticles (GNP) have shown promising results in clinical trials.[27] Alternatively to films, aerosolized short-acting buccal insulin products have been proposed, and are currently being clinically tested.[30]

ADVANTAGES AND DISADVANTAGES OF INSULIN DELIVERY SYSTEMS

Syringes. The incorrect use of injections, including lack of injection site rotation and reuse of needles[9,20], can cause skin hyperpigmentation, induration[41], and lipohypertrophy, the latter characterized by thickened fatty lumps in the subcutaneous tissue of the area where multiple insulin injections were applied[42]. In turn, this can increase the levels of unexplained hypoglycemia, originate uncontrolled glycated hemoglobin, and increase insulin costs.[20,21] The erroneous application of the injections in a few cases can cause lipoatrophy, a rare complication that consists of scarring lesions due to an immunological reaction to insulin or the excipients added to its formulation[43]. The errors mentioned above apply for the use of pens as well.[20]

Insulin pens. Compared with syringes, insulin pens have long term advantages for glycemic control, cause less hypoglycemia events, increase dose accuracy, and are the preferred insulin administration method. They are easier to use[44], induce less pain[45], reduce the injection force required, have a shorter needle length, are more discreet[46], and improve adherence.[19] Some pens incorporate mechanisms to store the dose, time, and date of previous insulin injections.[46]

Insulin jet injectors. They do not use needles, so they are ideal for patients who cannot use syringes or with needle phobias[47]; however, they form a hole in the skin.[48] One possible advantage is the faster absorption of rapid-acting insulin because it decreases postprandial glycemia in diabetic patients.[47] Its disadvantages are a relatively high cost[19,48] and a probable traumatization of the skin. Because of this, they should not be a routine option for patients.[19] Compared with insulin pens, insulin jet injectors have a faster flow rate and a larger area of local subcutaneous absorption. A drawback of jet injectors is the post administration "wetness" of the skin because it can be contaminated with dust or other impurities if it is not taken care of.[49]

Insulin pump. It reduces the number of injections while patients require a puncture every 2 or 3 days compared to daily injections. It is more precise as the sensing of glycemic indexes allows a more adequate and effective administration. It is flexible and allows the patient to adjust the doses depending on their caloric intake. It automatically calculates insulin bolus doses for corrections using glucose measurements from the patient's finger and allows data to be stored, which can be used for patient analysis.[50,51] The main disadvantage of this method is its high cost as well as the fact that the pump only delivers rapid-acting insulin and cannot deliver insulin bolus; however, it does allow dose

adjustments according to patient needs. It can lead to skin damage in case of trauma or mishandling and the risk of developing ketoacidosis in case of poor function.[50,52]

Inhaled insulin. It has a high absorption rate that mimics the bioavailability observed in subcutaneous insulin. Licensed options on the market have not yet achieved success over traditional administration methods.[27] Earlier versions of these devices tended to be bulky, difficult to use, and costly since nebulizer replacements tended to have a short lifespan.[26] Even in newer products, their implementation with diabetic patients has been low given the limitations found in patients with diminished respiratory capacity.[11,28]

Oral insulin. It is probably one of the most effective, less invasive and patient-friendly routes on the market. However, the inherent instability of insulin has proven to be a great obstacle in its development. It is perhaps the best route to mimic the physiological excretion of insulin, due to the fact it is absorbed into the portal system and distributed in the same route. However, the acidic conditions in the GI tract in conjunction with hepatic metabolism contribute to a less than desired bioavailability in the systemic circulation. Oral delivery systems technology vary widely in nature and mechanisms, creating diverse factors that might interfere with the desired absorption rate.[53]

Buccal insulin. Buccal insulin poses similar advantages to those of oral insulin, additionally increasing absorption through the highly vascularized buccal mucosa, and avoiding acidic, enzymatic, and hepatic degradation through direct absorption into the systemic circulation. One of its obstacles is the development of highly permeable polymers that allow a high rate of absorption through the oral mucosa. Also, many factors may alter drug function, including food consumption, variable saliva secretion, and hot or cold beverage intake. Finally, adverse effects must be considered, such as the risk of swallowing or low compliance due to below average palatability.[54] Table 2 shows a summary of the advantages and disadvantages of buccal insulin.

DISCUSSION

Many attempts have been made to introduce less invasive, patient-friendly, and more efficient modes of insulin administration. Still, the scientific evidence and the variety of socioeconomic factors presented in this review have promoted the use and overall acceptance of subcutaneous administration as the golden standard for diabetes insulin therapy. The side effects and disadvantages of this method tend to be sidelined just by the overall effectiveness of this route. No other route has been able to recreate this effectiveness or bioavailability, nor has it been able to cope with the economic factors that interfere with its development, production, and marketing. It is inferred that this apparent standstill in insulin administration innovation is closer to an end than it has ever been. In this context, this review has centered on analyzing and understanding the different innovations that have transcended from basic science to potential clinical applications in the treatment of diabetes, especially where insulin therapy is concerned.

In recent years, biotechnological innovation has helped the introduction of new technologies that allow the development of oral and buccal routes. Even though still far away from being as accepted as traditional subcutaneous methods, these routes hold the potential for being more patient friendly, reliable, and able to fully recreate the physiological excretion of insulin. Nevertheless, the advancement of these methods still has a lot of distance to cover, going from prototypes to actual licensed administration methods. Buccal and oral forms are not the only proposed alternative methods of administration. Inhalable forms, and alternate subcutaneous forms, such as insulin pumps, have also been developed, and some of them are currently available on the market. These methods, even though less preferable than the ideal non-invasive oral or buccal methods, have paved the way to wider development and interest from the pharmaceutical companies to introduce alternative attractive methods of insulin therapy in the diabetes market. Overall, it is our opinion that even though traditional subcutaneous methods are still the golden standard in diabetes treatment, the current and constant scientific innovation will eventually provide the effectiveness, efficiency, reliability, and patient friendliness needed for the future success and overall acceptance of the alternative methods discussed in this review, and many other more that are still unthought of.

CONCLUSION

Subcutaneous insulin is the only option for the treatment of type 1 diabetes and the use of insulin improves glycemic control in patients with type 2 diabetes. Therefore, the deep knowledge of the different types of insulin as well as the advantages and disadvantages of the routes of administration is the basis for the physician to determine the most appropriate treatment. In this context, it is imperative that research continues focusing on new biotechnological options to obtain more effective, safe, and less invasive treatments to help improve the patient's quality of life.

CONFLICT OF INTEREST

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TABLE 2. Advantages and disadvantages of insulin delivery methods.

METHODS	ADVANTAGES	DISADVANTAGES
SUBCUTANEOUS		
Syringes	• The most used • Less expensive than pens, jet injectors, and pumps • Can mix two insulins	• Frequently erroneous self-injections • Hyperpigmentation • Indurations • Lipohypertrophy • More painful than pens, jet injectors, and pumps • Needle phobia • Less accurate than pens • Decreased adherence
Insulin pen	• Compared to syringes: • Less painful • Easier to use • Improved adherence • Increased dose accuracy • Fewer hypoglycemia events • Long term advantages in glycemic control	• Frequently erroneous self-injections • Hyperpigmentation • Indurations • Lipohypertrophy • Needle phobia • More expensive than syringes • Cannot mix two insulins
Insulin jet injector	• Less painful than syringes and pens • No needles • Faster absorption of rapid-acting insulin • Reduced risk of transmitting diseases	• Relatively high cost • Probable traumatization of the skin • Keeping skin dry after the application is necessary
Insulin pump	• Less injections than syringes • More accurate • Lower risk of complications • More flexible release • Adaptable to the patient's needs	• High cost • Needle phobia • Risk of developing diabetic ketoacidosis in case of malfunction • Possible skin damage • Time-consuming pump replacement
INHALED		
Insulin inhaler device	• Large surface area for absorption • Perfused epithelial cells assure high bioavailability • Highly permeable and thin barrier • Most enzymatic and hepatic metabolism bypassed • Non-invasive efficient route	• Not recommended for patients with respiratory problems • Cough, allergic reactions and long-term damage to the lungs • Lack of long-term adverse effects studies • Bioavailability compromised by variable respiratory factors
ORAL		
Oral insulin	• The least invasive • The physiological release of insulin mimicked • Increased compliance • Easy to use • Reduced cases of hyperinsulinemia	• Low pH, enzymatic activity, and hepatic metabolism and decreased final bioavailability • Varied technology mechanisms creating variability in the absorption and intestinal permeability
Buccal insulin	• High patient acceptability • Low degree of acidic, enzymatic or hepatic degradation • Highly vascularized buccal mucosa allowing direct access to systemic circulation • Easy to use	• Low permeability of mucosa requiring specialized polymers and agents • Drug effectivity altered by saliva secretions, food consumption, and beverage temperature • Compliance affected by low palatability

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