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Review Article

Insulin delivery: what is new in the queue?

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ABSTRACT

Diabetes Mellitus (DM) is a cluster of metabolic disorders with the shared feature of hyperglycemia which may be due to discrete etiopathogenesis. India stands to be the diabetic capital of the world, second only to China. After its discovery by Banting and Best, it has been established that insulin plays a fundamental role in the management of DM. In spite of insulin being in the market for so long, what still remains a challenge is the invasive approach of its administration. Conventional pharmacotherapeutic approaches of insulin delivery that have been available over the years are insulin syringes, pumps and pens. Upcoming innovative modes of insulin delivery include oral insulin, inhaled insulin, colonic insulin delivery, transdermal insulin, intra-peritoneal insulin, intra-nasal insulin, nano-technology etc. Constant research has been going on since many years to discover a route of administration for insulin that is minimally or noninvasive, effective, safe, convenient and cost-effective for patients. If successful, alternative routes of administration could revolutionize the treatment of DM and help improve patients' quality of life.

Keywords: Diabetes Mellitus (DM), Insulin delivery

INTRODUCTION

According to the global report on Diabetes Mellitus (DM) by WHO in 2016, about 422 million adults were living with diabetes in 2014, compared to 347 million in 2013 and 108 million in 1980.[1] The global prevalence of DM has nearly doubled since 1980 (rising from 4.7% to 8.5%).[2] There were reportedly 62 million cases of DM in India in 2014.[3] India stands to be the diabetic capital of the world, second only to China.

TYPES OF DM

DM is a cluster of metabolic disorders with the shared feature of hyperglycemia which may be due to discrete etiopathogenesis. Although, it is primarily classified into two broad categories of type 1 and 2 DM, there are other categories as well such as DM due to genetic causes, drugs, infections, gestation, and maturity onset diabetes of the young (MODY). The figure below illustrates the different types of DM on the basis of etiology.

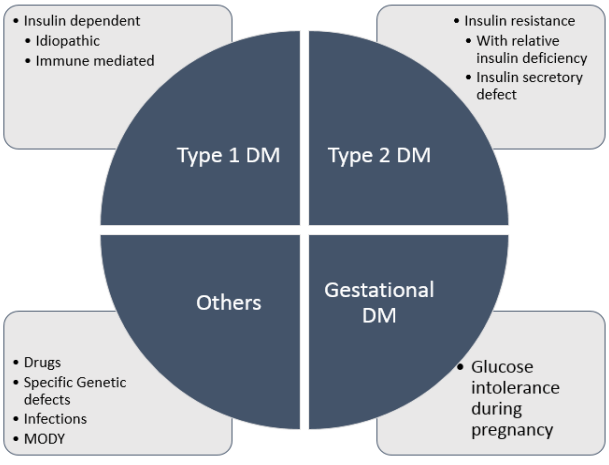

Figure 1: Types of DM.

ROLE OF INSULIN IN MANAGEMENT OF DM

Insulin is a hormone secreted from the pancreatic beta cells consisting of 2 polypeptide chains of 21 and 30 amino acid respectively, joined by disulphide bridges. After its discovery by Banting and Best, it has been established that insulin plays a fundamental role in the management of DM.[4] Although type 1 Diabetes constitutes only 5-10% of the total patients with Diabetes, it has to be kept in mind that insulin contributes profoundly in the management of type 2 Diabetes, in situations such as diabetic ketoacidosis or if the glycemic levels are not controlled by oral anti diabetic drugs.[5]

TYPES OF INSULIN

Table 1: Types of insulin analogs.

Serial No.	Type	Analogs
1.	Rapid acting	Lispro and Aspart
2.	Short acting	Regular
3.	Intermediate acting	Lente and NPH
4.	Long acting	Ultralente, Glargine, Detemir
5.	Ultralong acting	Degludec

NEED FOR NEWER DELIVERY METHODS

In spite of insulin being in the market for so long, what still remains a challenge is the invasive approach of its administration. For a person who requires around 2-3 injections per day, importunate research to meet these needs in an effortless way is crucial.

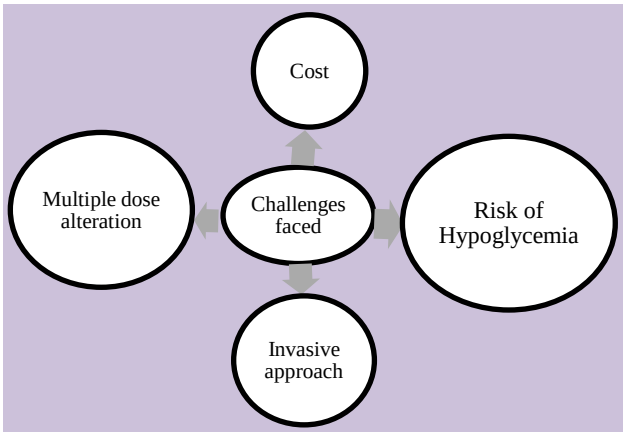

Figure 2: Challenges faced with the current delivery methods.

CURRENT PHARMACOTHERAPEUTIC APPROACHES AVAILABLE

Insulin syringes

Insulin administration through syringes has been the most conventional way so far which has been adorned in numerous ways from making them lighter to the introduction of microfine needles to reduce pain. Depending upon the manufacturer, the insulin syringes are caliberated with various capacities such as 0.3, 0.5, 1, and 2 ml.[6] Needle lengths and gauge may also be variable. However, even though now we have light syringes with microfine needles, the biggest obstacle is that the patient may not be able to switch between the manufacturers in case of travel and mixing of insulin is complicated via this technique.

Insulin pumps

Insulin pumps or continuous subcutaneous insulin infusion (CSII) has been evolving very rapidly since its introduction into the market. It has enabled the patients to achieve adequate glycemic control. Although initially, it requires training, but once learnt it is definitely a boon. It helps in accurate delivery of doses depending upon the requirement and helps in the improvement of quality of life.

Nevertheless, these modern devices are not devoid of adverse effects. A prospective study done by Wheeler BJ et al for a 16 week period concluded that maximum adverse effects were due to either pump malfunction or infusion site/set failures.[7] The other adverse effects were primarily related to user or education related issue. Due to inadequate large scale studies done prior to the launch of such products, and discrepancies in the regulatory system in the US and Europe, there is an imperative need to alter and standardise such an approach to overcome the many adverse effects of this approach.[8]

Implantable Bio Micro Electro Mechanical Systems (BioMEMS) have enticed numerous patients at the consumer level. These pumps have been designed to release a particular dose of insulin following detection of any change in glucose level.

Insulin pens

Insulin injections using vial and syringe are limited by difficulty and imprecision in preparing the insulin dose.[9] These issues led to the development of insulin pens. The first insulin pen was manufactured by NovoNordisk in 1985. The newer insulin pens are reusable, more accurate and equipped with safety features such as audible clicks with each dose to improve accuracy and reduce the chances of human errors.[10]

There are two pen systems, durable and prefilled:

- Durable pen uses a replaceable insulin cartridge. When the insulin cartridge is empty, the empty cartridge is disposed of and a new one is inserted in the pen.
- Prefilled pen is entirely disposable. The pen comes pre-filled with insulin, and when the insulin

cartridge or reservoir is empty, the entire unit is discarded.

As such insulin pens are more accurate, convenient, less painful and patient friendly but associated with higher cost in comparison with vial and syringe.[11-13]

NOVEL DRUG DELIVERY SYSTEMS

Insulin has forever been the treatment of choice in patients suffering from type 1 diabetes. However, in spite of its discovery years ago we are still handicapped by its route of administration. So far, subcutaneous injections of insulin have been the conventional approach among the patients. Nonetheless, various researchers have come up with new formulations of insulin which can be inhaled.

Alternative routes of insulin administration (ARIA) have been a subject of research in the last few decades. The need to ease the insulin administration by dodging of injections has been the foremost aim. But with the advent of painless needles and adequate pricing of this method, it has become extremely challenging for the pharmaceutical industry to come up with formulations which can guarantee a market success and also be adequately priced to be affordable by the society. The withdrawal of inhaled insulin is one such example where the company had to endure extravagant financial losses due to its failure in the antidiabetic market.[14]

1.) Oral insulin

Microspheres

Insulin being a large peptide molecule cannot be delivered via oral route due to its enzymatic degradation by gastric acid as well as due to the decrease passage through the tightly bound cells in the epithelial lining.[15] This results in a bioavailability of less than 1-2%.[16] In order to overcome this obstacle various approaches have been tried so far. One of them involved preparation of lipoidal dispersion of insulin in fatty acid such as palmitic acid in order to enhance the permeation of the drug across the mucosal barrier.[17] Another approach tried is enteric coated capsules. A study by Elka Touitou et al, conducted an experiment on rats to evaluate the bioavailability of insulin incorporated in gelatin capsules coated with polyacrylic polymer.[18]

Nanoparticles

Nanoparticles of various drugs encapsulated in polymeric substances such as chitosan, dextran, hyaluronic acid etc. have been tried so far, but not successfully for insulin so far.[27] Complexes of N-Arginine Chitosan and N-histidine-chitosan have been found to shield the encapsulated insulin peptide molecule from degradation by various proteolytic enzymes and also enhance the permeability across cells in in vitro studies.[28]

Nano particles can be either nanospheres or nanocapsules.

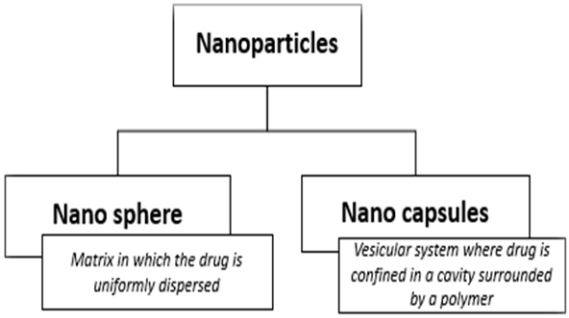

Figure 3: Classification of nanoparticles.

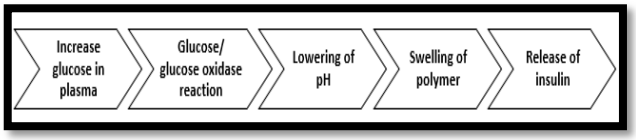

Figure 4: Release of insulin from a nanoparticle.

Difference between microparticles and nanoparticles is mention in Table 2.[19]

Table 2: Difference between micro particles and nanoparticles.

Sr. No.	Features	Microparticles	Nanoparticles
1	Size	Micrometers	Nanometers
2	Duration of action	Longer	Shorter (since they are cleared faster from the site of action)
3	Ability to embolise	Tend to emblise	No embolisation
4	Cell uptake	Can be delivered to selective cells where uptake is done by phagocytosis because of their large size	Can be delivered to all cell types because the uptake is by pinocytosis
5	Crossing of physiological barriers	Cannot cross physiological barriers	Can cross physiological barriers

2.) Inhaled insulin

The nasal mucous membrane is highly vascular and therefore a good target for systemic absorption of any drug, provided it is non irritant to the mucosa. In a proof

of concept study done by Skyler et al, in 73 patients, pre-prandial administration of inhaled insulin has said to achieve adequate glycaemic control.[20]

A dry powder formulation of recombinant human insulin, in a dose of 1-3mg was approved in the United States and the European Union, for patients of type 1 or type 2 diabetes.[21] It was shown to have an antihyperglycaemic effect comparable to that of the subcutaneous injections, except it has a rapid onset of action.[22] Although a minute fall in FEV1 was observed in the patients after approximately 12 weeks of administration of inhaled insulin, it was considered to be safe for upto 4 years.[23] Another aspect of this conundrum regarding its applicability, was its use in patients of asthma and COPD. An article by Mudaliaret al suggested the need of a higher dose of inhaled insulin in order to overcome the barrier of narrow airways in patients of asthma and a highly unpredictable absorption in cases of COPD patients.[24] It clearly stated the need of further studies to evaluate the overall effects. However, due to insufficient market sales, it was withdrawn from the market, incurring losses to its parent company. Recently a new formulation has been approved in 2014 by another company. It has been introduced with the aim of primarily reducing the number of hypoglycemic episodes as compared to the injectable preparations and providing prandial insulin coverage.[25] It differs from the earlier preparation because of its distinctive excipient fumaryldiketopiperazine which enhances the delivery of insulin in the lungs and resulting in a rapid action.[26] It is clearly evident that if this method works, it will be highly acceptable by the masses because of its non-invasive technique of delivery.

3.) Transdermal Insulin

Transdermal approach involves application of adhesive patches on intact skin which deliver the drug at a constant rate into the systemic circulation. It consists of a drug reservoir and a patch with the priming dose and a micropore membrane which releases slowly at a predetermined rate. It has certain disadvantages such as skin irritation and unpredictable absorption from different skin types which can pose as a major problem in certain patients. Also, the patient may be unaware of the patch getting displaced at any point of time

4.) Microgel thin films

The use of alginate dextran sulfate is limited due to its size which makes it unstable. However, it helps in preventing the degradation of insulin in the GIT. Thus various researches have been trying to modify the present size or come up with new entities to overcome this drawback. One such technique tried by Ana C. Santos included emulsification followed by ultrasonification which resulted in the formation of nanoparticles. This size conferred stability to the insulin without significant alteration in its activity.[29] Poly micro gel thin films impregnated with insulin when subjected to adequate amount of heat results in release of bursts of insulin which can be controlled such that a constant plasma level can be achieved for a month.[30]

5.) Colonic insulin delivery

Colon is ideally not suited for absorption processes for drugs but it has certain advantages over small intestine like, long transit time, lower levels of peptidases (prevent destruction of peptides) and higher responsiveness to permeation enhancers. Accordingly, it has been under extensive investigation as a possible strategy to improve the oral bioavailability of peptide and protein drugs. In a review by Maroni et al, oral delivery systems for colonic release of insulin which were devised according to microflora, pH and time-dependent strategies have been explained.[31] Bioavailability and pharmacological availability data are generally still far from being reliable in terms of magnitude, onset, duration and above all, consistency for this route of administration and it is under investigation. There is still a long way to go before these products will be available in the market.

6.) Intra-peritoneal insulin delivery

Intravenous and subcutaneous route of insulin delivery are associated with peripheral hyperinsulinemia and considered nonphysiological. Direct delivery of insulin in the portal vein mimics the high portal insulin concentration. This route of insulin delivery has been investigated since the 1970s.[32] The pump is implanted beneath the subcutaneous tissue in the lower abdomen under general anesthesia. From this subcutaneous pocket, the peritoneum is opened, and the tip of the catheter is carefully inserted and directed towards the liver. After implantation, the pump reservoir is refilled in the outpatient clinic transcutaneously at least every 3 months, depending on the individual insulin requirement.[33] Clinical trials have shown safety and efficacy of intraperitoneal insulin delivery.[34,35]

Limitations of this route

Invasive, may be associated with subcutaneous infections, cannula blockage, higher cost, portal-vein thrombosis and peritoneal infection.[36]

7.) Intra - nasal insulin

In theory, intranasal delivery has several advantages over oral (bypass GI peptidases), subcutaneous (noninvasive and painless) and inhalation route (no issue with lung function) which makes this route attractive for the delivery of insulin.[37] However, intranasal delivery has shortcomings such as limited permeability of a large molecule through the nasal mucosa and rapid mucociliary clearance resulting in variable absorption.[37]

Nasal insulin preparations have bioavailability of about 15-25% with the onset of action ~10-20 min.[38,39] The

substances such as bile salt, surfactant and fatty acid derivatives are being investigated to enhance mucosal permeability of insulin but they increase the risks for local irritation, nasal secretion, sneezing or burning sensation.[39,40]

Nasal insulin crosses the blood brain barrier hence it has a hypothesized effect on memory function.[41] In a randomized placebo controlled trial with 104 adults with amnestic mild cognitive impairment or mild to moderate Alzheimer's disease were randomized to receive either placebo or 20 IU or 40 of intranasal insulin. Treatment with intranasal insulin improved memory, preserved caregiver-rated functional ability and preserved general cognition without any significant hypoglycemic event. These improvements in cognitive functions were correlated with changes in the Aβ42 level and in the tau protein-to-Aβ42 ratio in cerebrospinal fluid.[42] Based on this; large randomized controlled trials are ongoing to evaluate the usefulness of this agent for the treatment of Alzheimer's disease.

CONCLUSION

Constant research has been going on since many years to discover a route of administration for insulin that is minimally or noninvasive, effective, safe, convenient and cost-effective for patients. Each route and delivery device has its own advantages and disadvantages. If successful, alternative routes of administration could revolutionize the treatment of DM and help improve patients' quality of life.

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REFERENCES

1. Mukherjee B, Paul P, Choudhury A, Bhattacharya S, Maji R, Dutta L. Variation of pharmacokinetic profiles of some antidiabetic drugs from nanostructured formulations administered through pulmonary route. Curr Drug Metab. 2015.
2. Global report on diabetes WHO Library Cataloguing-in-Publication Data. ISBN;978:92-4.
3. Kaveeshwar SA, Cornwall J. The current state of diabetes mellitus in India. Australas Med J. Australasian Medical Journal. 2014;7(1):45-8.
4. Rosenfeld L. Insulin: discovery and controversy. Clin Chem. 2002;48(12):2270-88.
5. Al-Tabakha MM, Arida AI. Recent challenges in insulin delivery systems: a review. Indian J Pharm Sci. Medknow Publications; 2008;70(3):278-86.
6. Insulin Administration. Diabetes Care. 2003;26(11):3080-6.
7. Wheeler BJ, Heels K, Donaghue KC, Reith DM, Ambler GR. Insulin pump-associated adverse events in children and adolescents- a prospective study. Diabetes Technol Ther. 2014;16(9):558-62.
8. Heinemann L, Fleming GA, Petrie JR, Holl RW, Bergenstal RM, Peters AL. Insulin pump risks and benefits: a clinical appraisal of pump safety standards, adverse event reporting and research needs. A joint statement of the European Association for the Study of Diabetes and the American Diabetes Association Diabetes Technology W. Diabetologia. 2015;58(5):862-70.
9. Selam JL. Evolution of diabetes insulin delivery devices. J Diabetes Sci Technol. Diabetes Technology Society. 2010;4(3):505-13.
10. Penfornis A, Personeni E, Borot S. Evolution of Devices in Diabetes Management. Diabetes Technol Ther. 2011;13(S1):S93-102.
11. Xue L, Mikkelsen KH. Dose accuracy of a durable insulin pen with memory function, before and after simulated lifetime use and under stress conditions. Expert Opin Drug Deliv. 2013;10(3):301-6.
12. Garg S, Bailey T, DeLuzio T, Pollom D. Preference for a new prefilled insulin pen compared with the original pen. Curr Med Res Opin. 2011;27(12):2323-33.
13. Pfützner A, Bailey T, Campos C, Kahn D, Ambers E, Niemeyer M, et al. Accuracy and preference assessment of prefilled insulin pen versus vial and syringe with diabetes patients, caregivers, and healthcare professionals. Curr Med Res Opin. 2013;29(5):475-81.
14. Heinemann L. New ways of insulin delivery. Int J Clin Pract Suppl. 2010;(166):29-40.
15. Carino GP, Mathiowitz E. Oral insulin delivery1Abbreviations: GI, gastrointestinal; IDDM, insulin-dependent diabetes mellitus; IU, international units; NIDDM, non-insulin-dependent diabetes mellitus; PIN, phase inversion nanoencapsulation; ZOT, zona occludens toxin.1. Adv Drug Deliv Rev. 1999;35(2-3):249-57.
16. Pauletti GM, Gangwar S, Knipp GT, Nerurkar MM, Okumu FW, Tamura K, et al. Structural requirements for intestinal absorption of peptide drugs. J Control Release. 1996;41(1-2):3-17.
17. Mesiha M, Plakogiannis F, Vejosoth S. Enhanced oral absorption of insulin from desolvated fatty acid-sodium glycocholate emulsions. Int J Pharm. 1994;111(3):213-6.
18. Touitou E, Rubinstein A. Targeted enteral delivery of insulin to rats. Int J Pharm. 1986;30(2-3):95-9.
19. Kohane DS. Microparticles and nanoparticles for drug delivery. Biotechnol Bioeng. 2007;96(2):203-9.
20. Skyler JS, Cefalu WT, Kourides IA, Landschulz WH, Balagtas CC, Cheng SL, et al. Efficacy of inhaled human insulin in type 1 diabetes mellitus: a randomised proof-of-concept study. Lancet. Elsevier; 2001;357(9253):331-5.
21. Strack TR. Inhaled human insulin. Drugs of Today. 2006;42(4):207.
22. Dunn C, Curran MP. Inhaled human insulin (Exubera): a review of its use in adult patients with diabetes mellitus. Drugs. 2006;66(7):1013-32.

23. Hegewald M, Crapo RO, Jensen RL. Pulmonary function changes related to acute and chronic administration of inhaled insulin. Diabetes Technol Ther. Mary Ann Liebert, Inc. 2 Madison Avenue Larchmont, NY 10538 USA. 2007;9(1):S93-101.
24. Mudaliar S, Henry RR. Inhaled Insulin in Patients with Asthma and Chronic Obstructive Pulmonary Disease. Diabetes Technol Ther. Mary Ann Liebert, Inc. 2 Madison Avenue Larchmont, NY 10538 USA. 2007;9(1):S83-92.
25. Nuffer W, Trujillo JM, Ellis SL. Technosphere insulin (Afrezza): A new, inhaled prandial insulin. Ann Pharmacother. 2015;49(1):99-106.
26. Ledet G, Graves RA, Bostanian LA, Mandal TK. A second-generation inhaled insulin for diabetes mellitus. Am J Health Syst Pharm. 2015;72(14):1181-7.
27. Fonte P, Araújo F, Silva C, Pereira C, Reis S, Santos HA, et al. Polymer-based nanoparticles for oral insulin delivery: Revisited approaches. Biotechnol Adv. 2015;33:1342-54.
28. Abbad S, Zhang Z, Waddad AY, Munyendo WLL, Lv H, Zhou J. Chitosan-Modified Cationic Amino Acid Nanoparticles as a Novel Oral Delivery System for Insulin. J Biomed Nanotechnol. 2015;11(3):486-99.
29. Santos AC, Cunha J, Veiga F, Cordeiro-da-Silva A, Ribeiro AJ. Ultrasonication of insulin-loaded microgel particles produced by internal gelation: impact on particle's size and insulin bioactivity. Carbohydr Polym. 2013;98(2):1397-408.
30. Nolan CM, Serpe MJ, Lyon LA. Thermally Modulated Insulin Release from Microgel Thin Films. Biomacromolecules. American Chemical Society; 2004;5(5):1940-6.
31. Maroni A, Zema L, Del Curto MD, Foppoli A, Gazzaniga A. Oral colon delivery of insulin with the aid of functional adjuvants. Adv Drug Deliv Rev. 2012;64(6):540-56.
32. Botz CK, Leibel BS, Zingg W, Gander RE, Albisser AM. Comparison of peripheral and portal routes of insulin infusion by a computer-controlled insulin infusion system (artificial endocrine pancreas). Diabetes. 1976;25(8):691-700.
33. van Dijk PR. CIPII Intraperitoneal insulin. Diapedia.org; 2016.
34. Renard E. Insulin delivery route for the artificial pancreas: subcutaneous, intraperitoneal, or intravenous? Pros and cons. J Diabetes Sci Technol. 2008;2(4):735-8.
35. Gin H, Renard E, Melki V, Boivin S, Schaepelynck-Bélicar P, Guerci B, et al. Combined improvements in implantable pump technology and insulin stability allow safe and effective long term intraperitoneal insulin delivery in type 1 diabetic patients: the EVADIAC experience. Diabetes Metab. 2003;29(6):602-7.
36. Kumareswaran K, Evans ML, Hovorka R. Closed-loop insulin delivery: towards improved diabetes care. Discov Med. 2012;13(69):159-70.
37. Yaturu S. Insulin therapies: Current and future trends at dawn. World J Diabetes. Baishideng Publishing Group Inc. 2013;4(1):1-7.
38. Leary AC, Stote RM, Cussen K, O'brien J, Leary WP, Buckley B. Pharmacokinetics and Pharmacodynamics of Intranasal Insulin Administered to Patients with Type 1 Diabetes: A Preliminary Study. Diabetes Technol Ther. 2006;8(1):81-8.
39. Illum L. Nasal drug delivery - Recent developments and future prospects. J Control Release. 2012;161(2):254-63.
40. Stote R, Marbury T, Shi L, Miller M, Strange P. Comparison pharmacokinetics of two concentrations (0.7% and 1.0%) of Nasulin, an ultra-rapid-acting intranasal insulin formulation. J Diabetes Sci Technol. 2010;4(3):603-9.
41. Benedict C, Frey WH, Schiöth HB, Schultes B, Born J, Hallschmid M. Intranasal insulin as a therapeutic option in the treatment of cognitive impairments. Exp Gerontol. 2011;46(2-3):112-5.
42. Craft S, Baker LD, Montine TJ, Minoshima S, Watson GS, Claxton A, et al. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. Arch Neurol. 2012;69(1):29-38.

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