

# An Overview on the Insulin Preparations and Devices

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## ABSTRACT

Insulin preparations are the mainstay in the management of type 1 along with various type 2 diabetes. Available insulin preparations are either short-acting or long-acting or mixture to mimic the physiological insulin secretion and their doses need to be individualized. Attempting to imitate normal secretion of insulin can be valuable paradigm for understanding and providing effective therapy. This review provides an outline about the composition, use, route of administration, injection site, pharmacokinetics, storage and handling of various insulin preparations. The efficacy and safety of various insulin preparations for the management of diabetes mellitus are discussed. In addition, the use and application of various insulin devices to improve adherence and provide optimum delivery are elaborated. Indeed, the patient awareness and adherence on these issues is crucial to achieve good glycemic control.

**Key words:** Short-acting insulin, Long-acting insulin, Mixture, Analogues, Handling, Devices, Diabetes.

## INTRODUCTION

Physiological insulin consists of two constituents namely basal (a relatively constant background level of insulin during the fasting and post absorptive period) and bolus (prandial spikes of insulin after eating) insulins which are the basis of administration of two different types of commercially available insulins. The key objective of insulin therapy in diabetes is to accomplish rigid blood glucose management by simulating insulin secretion of normal pancreas. In all regimens, long-acting insulins supply basal insulin, whereas short-acting ones provide postprandial requirements. Elevation of postprandial blood glucose level contributes notably to glycated hemoglobin (HbA<sub>1c</sub>) values and resulting long term complications of diabetes.<sup>1</sup> Thus, postprandial regulation of blood glucose is indispensable for optimum diabetes disease management. For a diabetic patient, bolus injections are supposed to cater approximately 10-20% of total insulin demand per day during every meal. The dose of insulin must be individualized.<sup>2</sup> Individuals

with type 1 diabetes mellitus, the average daily requirement for insulin is 0.5 to 1 unit/kg/day divided into multiple doses, with approximately 50% being delivered as basal insulin, and the remaining 50% dedicated to meal coverage. It is suggested that when insulin requirements exceed 100 units/day, efforts to shrink insulin resistance must be enforced, for example, exercise, restricting dietary carbohydrate intake, and individualizing dosage regimen.

## INSULIN PREPARATIONS

In 1921, insulin was first administered to a diabetic dog, paving the way for human insulin therapy.<sup>3</sup> All insulin preparations are currently generated by recombinant DNA technology. Doses and concentration levels of insulin preparations used in clinics are indicated in international units. Indeed, one international unit of insulin is defined as the bioequivalent of 34.7 µg of crystalline insulin. Insulin preparations consist of the

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amino acid sequence of human insulin or variations thereof (insulin analogues). Eli Lilly and Sanofi use a non-pathogenic strain of *Escherichia coli* to synthesize insulin; whereas Novo Nordisk uses *Saccharomyces cerevisiae*, or bakers' yeast.<sup>4</sup> Pharmacokinetic properties of different insulin preparations are summarized in Table 1. There is great variability in the time of onset of action, peak effect, and duration of action of insulin amongst individuals and even with repeated doses in the same individual depending on the dose size, the injection site, the exercise, the desire of circulating anti-insulin antibodies (Table 1).

### Short-acting Insulin Preparations

The regular human insulin and the rapidly acting insulin analogues are considered as short-acting formulations. Typically they are clear solutions at neutral pH and have minor amounts of zinc (for greater stability and shelf life). The insulin molecules generally exist as dimers which can join to form hexamers when two zinc ions are present in the formulation. The formed hexamers generally exhibit further stability in the presence of phenolic compounds such as phenol and meta-cresol.<sup>5</sup> Pharmacokinetic properties of different types of short-acting insulins are summarized in Table 1. Various clinical studies have indicated that the right time for preprandial administration of regular human insulin and rapid-acting insulin are 45 and 15 min before food, respectively.<sup>6</sup> In general, the quick onset of action is considered ideal as the patient can begin his food immediately after administering the dose. The storage condition of the short-acting insulin preparations are given in Table 2.

### Regular Insulin

Regular insulin is a zinc-insulin crystalline product with strength of 100 or 500 USP insulin unit/mL. To add caution against accidental use of the inappropriate strength, the products packets are color coded orange for 100 unit/mL and brown for 500 unit/mL with diagonal white strips. The major limitations of regular insulin are postprandial hypoglycemia and late postprandial hypoglycemia. This injection should be administered 30-45 min before meals.<sup>7</sup> The onset time, peak effect, and duration of regular insulin is dose dependent. It can be administered by intravenous route to treat diabetic ketoacidosis unlike other insulin analogues. Regular insulin product should not freeze and discard if it has been already frozen. There are certain precautionary measures to be taken like disposing cloudy preparation and solution where particulate matters are present. Vigorous agitation of the vial before withdrawing the

dose must be avoided otherwise potency loss, aggregate formation, or precipitation may occur. Thawing refrigerated insulin to room temperature prior to use will lower the irritation at the injection site. During storage, insulin vials should be kept in their cartons and be protected from direct light and heat. Regular insulin is absorbed quickly when injected in the deltoid or abdomen when compared to other regions like thighs and buttocks.<sup>8</sup> Regular insulin should be mixed only with neutral protamine Hagedorn (NPH) insulin in the same syringe and never use in continuous infusion insulin pumps. It is usually administered through intravenous/subcutaneous routes and is compatible with normal saline (0.9% NaCl), dextrose (5% or 10%) and 50 mmol/L (40 mEq/L) of potassium chloride. For intravenous infusion, it is diluted to a concentration of 0.05-1 unit/mL in polypropylene bags.

### Rapid-acting Insulin

The rapid-acting insulins include technosphere human insulin and three insulin analogues namely lispro, aspart and glulisine. When injected subcutaneously, these analogues rapidly dissociate into monomers and are rapidly absorbed due to their low propensity for self-aggregation. These rapid-acting insulins reach peak serum values within 1 h and have reduced duration of action in contrast to regular human insulin.<sup>9</sup> So, when used to treat glycemia after meals, the rapid-acting insulins have lower rates of hypoglycemia and greatly improved HbA<sub>1c</sub> levels compared to regular insulin. Pharmacokinetic properties of different types of rapid-acting insulins are summarized in Table 1.

### Insulin Lispro

Insulin lispro is an insulin analog wherein the proline at location B28 is reversed with the lysine at B29. It is administered as subcutaneous bolus by pen or conventional syringe or continuous subcutaneous infusion using selected external controlled infusion devices. For better dosing accuracy in pediatric patients, it should be diluted to a ratio of 1:1 or 1:2 with the sterile vehicle provided by the manufacturer.<sup>10</sup> The variations in absorption related to site of administration are smaller than regular insulin when it is used alone in the syringe. Insulin lispro injection should be dispensed in the original, unopened, multiple-dose vial, disposable injection pen, or injection cartridge supplied by the manufacturer. If the product exhibits discoloration, turbidity, or unusual viscosity, the vial or cartridge should be discarded since these changes indicate deterioration or contamination. If insulin lispro is used in an external insulin pump, the 100 units/mL infusion sets and site should be changed weekly or after exposure above 37°C. In an insulin

pump, do not mix 100 units/mL with any other insulin and do not administer 200 units/mL in an infusion pump.

### Insulin Aspart

Insulin aspart is a single substitution of proline by aspartic acid at position B28.<sup>11</sup> Generally it is administered concomitantly with certain long-acting insulin (e.g. NPH) to meet basal insulin needs in diabetic patients.<sup>12</sup> The fixed dose combination of insulin aspart protamine with insulin aspart (70/30) is meant only for subcutaneous administration and should not be given intravenously.<sup>13</sup> To suspend the mixture in a vial immediately before use, the vial should gently roll between the hands about 10 times until the suspension appears to be evenly opaque and cloudy. Further, while mixing insulin aspart with NPH, first the insulin aspart is withdrawn and then mix with NPH and inject immediately. However, the compatibility data indicates that the insulin aspart should not be mixed with crystalline zinc insulin preparations. Fixed dose combination of insulin aspart should not mix with other analogues. Since it has a more rapid and short duration of action than regular insulin, administration should be followed by an immediate meal.<sup>14</sup> A color code has been introduced to bring down dispensing errors due to similarity in names. In addition to color code, pharmacist should use the product's name, national drug code, crosscheck formulation name and should separate the products on pharmacy shelves to evade dispensing error.

### Insulin Glulisine

Insulin glulisine is different from human insulin because the amino acid asparagine at location B3 is exchanged by lysine and the lysine in location B29 by glutamic acid. This biosynthetic product is intended for parenteral administration and possesses all required characteristics. When given through subcutaneous route 15 min prior to meal at a dose rate of 0.5-1 unit/kg/day, it exhibits a more rapid onset and shorter duration of action.<sup>15</sup> It can also be administered alone via intravenous route at a dose of 0.05-1 unit/mL in normal saline for glycemic control under medical supervision in a hospital setting.<sup>16,17</sup> It is typically used in conjunction with long-acting basal insulin or sometimes as a continuous administration by subcutaneous infusion pump. It is administered subcutaneously using a conventional insulin syringe or an injection pen. It is also given by continuous subcutaneous infusion into the abdominal wall via an external controlled infusion device. It is incompatible with dextrose or Ringer's injection. It should be mixed only with NPH insulin and when mixed, ensure that it is taken into syringe first. The

mixture must be administered immediately after mixing; such mixture should not be given intravenously. When used in an external infusion pump, insulin glulisine should not be diluted or mixed with any other insulins. The product should be stored in refrigerator between 2-8°C. If the formulation is accidentally frozen or exposed to heat (37°C), it must be discarded. Insulin glulisine formulation is stable in infusion sets up to 48 h.

### Technosphere Insulin

Technosphere insulin is a dry-powder formulation of recombinant human regular insulin that can be inhaled and absorbed through pulmonary tissue. It is a rapid-acting powder insulin, inhaled at mealtimes to improve blood glucose control in type 1 and type 2 diabetic population.<sup>18</sup> The patient should not use technosphere as a substitute for long-acting insulin and in diabetic ketoacidosis. It must be used along with long-acting insulin in type 1 diabetes. Technosphere insulin is a very small whistle-like device, prepared as a single-use color coded cartridge providing 4, 8 or 12 units soon before the meal. It is not approved in habitual smokers or who have recently stopped smoking and not proposed for use in children less than 18 years of age. It is contraindicated in asthmatic and chronic obstructive pulmonary disease patients.<sup>19</sup> Technosphere should be inhaled at the beginning of a meal as a single inhalation per cartridge using inhaler. Before putting the cartridge in the inhaler, make sure it has been at room temperature (~25°C) for at least 10 min. Precautions should be taken like not leaving cartridges in inhaler, not washing inhaler and keeping mouthpiece cover until the next dose.

### Long-acting Insulin Preparation

#### NPH

NPH is an equivalent mixture of protamine and native insulin in water for injection adjusted to pH 7.1-7.4 with phosphate buffer.<sup>20</sup> It is an opaque suspension consists of rod shaped insulin crystals with particle size <30 µm. The preparation should be free of large aggregates following moderate shaking for consistent absorption. The expiry date of the formulation is not later than 24-36 months from the date of manufacturing. NPH is packaged in 10 mL multiple dose container or in vials with strength 100 unit/mL. The usual dose range for this insulin preparation is between 10-80 unit subcutaneous. The dose controls the action profile; precisely, small doses have inferior and prior peaks and shortened duration of action, while it is opposite for large doses. In general, the absorption of NPH insulin is quick from abdominal fat, relatively slow from posterior upper arms and lateral thigh area, and slowest from superior

**Table 1: Pharmacokinetic properties of insulin preparations.**

Insulin Preparations	Onset of action (h)	Peak effect (h)	Duration of action (h)
<b>Short-acting (clear)</b>			
Regular insulin	0.5-1	1-3	6-10
Insulin lispro	0.25-0.5	0.5-1.0	3-5
Insulin aspart	0.17-0.33	0.5-1.0	4-5.3
Insulin glulisine	0.25-0.41	0.5-1.0	4-6.3
Technosphere insulin	<0.25	0.5-1.5	2-3
<b>Long-acting (clear)</b>			
NPH	1-2	6-14	16-24
Insulin detemir	3-4	6-8	6-24
Insulin glargine	1-2	Flat	24
Insulin degludec	1-2	Flat	42
<b>Mixtures (cloudy)</b>			
Isophane/regular insulin 70/30, 50/50	0.5-1	2-12	18-24
NPL/lispro mix 75/25	5 min	7-12	1-24

NPH: neutral protamine Hagedorn, NPL: neutral protamine lispro

buttocks area.<sup>21</sup> Patients should be cautious for initial signs of frosting or clumping of this insulin, as it shows a noticeable loss of potency. This form of insulin must not be administered through intravenous route. Since the active ingredient is in the precipitate, vial should be gently agitated to assure a uniform mixture for accurate measurement of each dose. This may be done by slowly swirling or carefully shaking or inverting the vial several times before withdrawal of each dose. Vigorous shaking should be avoided because this results in foaming, which impede with accurate measurement of a dose. To prevent clogging at the tip of the needle, NPH should be injected rapidly (<5 sec) subcutaneous. Thawing refrigerated insulin to room temperature prior to use will decrease irritation at the injection site. The storage condition of the long-acting insulin preparations are given in Table 2. Unopened vials of suspensions and prefilled syringes should be refrigerated between 2-8°C and should not be subjected to freezing (<2°C) or exposed to heat (>30°C) or sunlight. Pharmacokinetic properties of long-acting insulins are summarized in Table 1.

### Insulin Detemir

In this insulin analogue, the threonine at position B30 has been detached and myristic acid (a 14-C fatty acid chain) is attached to the lysine at position 29.<sup>22</sup> Insulin detemir is administered by subcutaneous injection once or twice daily using a conventional insulin syringe or injection pen. The property of self-association and protein binding is responsible for slow absorption and long duration. The onset of action of this basal insulin ranges from

3-4 h and peak observed between 6-8 h.<sup>23</sup> The duration of action of insulin detemir is dose dependent. When administered at low dose (0.1-0.2 unit/kg), the duration ranges 5-12 h, moderate dose (0.6 unit/kg), ~20 h and at high dose (>0.6 unit/kg), duration of action ranges between 22-24 h. Insulin detemir cannot be acutely mixed with either regular insulin or the rapid-acting insulin analogues. The extended duration of action of soluble insulin detemir is due to slow systemic absorption by virtue of strong self-association and albumin binding. When administered once a day, the dose should be given with the evening meal or at bed time. However, it has been administered once a day in the morning in type 2 diabetic patients. The switching from NPH to insulin detemir is 1:1 with minor alterations if necessary by monitoring the glucose.<sup>24</sup>

### Insulin Glargine

Insulin glargine is different from normal insulin, as the asparagine is changed by glycine at amino acid 21 of the insulin A chain, and two arginine residues are added to the carboxyl terminal of the B chain. When insulin glargine formulation (pH of 4.0 to maintain solubility) is injected into subcutaneous tissue, it is neutralized and forms microprecipitates at the injection site. In general, this insulin analogue is not mixed with other insulins and preferably use an additional syringe to avoid the possibility of contamination which in turn may cause loss of efficacy. The onset of action begins within 1-2 h and duration of basal insulin secretion extends up to 24 h.<sup>25</sup> Since it contributes only to basal secretion, it is frequently used in combination with other insulins or

Table 2: Storage conditions for insulin preparations.

Insulin preparations	Storage Conditions		
	Unopened (RT below 30 °C)	Unopened (refrigerated)	Opened (RT below 30 °C)
<b>Regular Insulin</b>			
10 mL/3 mL vial	42 days	Until expiry date	42 days
<b>Insulin Lispro</b>			
10 mL/3 mL vial	28 days	Until expiry date	28 days/refrigerated or RT
3 mL cartridge, 3 mL Kwik pen prefilled (100/200 unit/mL)	28 days	Until expiry date	28 days RT (Do not refrigerate)
<b>Insulin Aspart</b>			
10 mL	28 days	Until expiry date	28 days/refrigerated or RT
3 mL cartridge, 3mL NovoLog®, Flexpen® prefilled, Novolog® Penfill®	28 days	Until expiry date	28 days RT (Do not refrigerate)
<b>Insulin Glulisine</b>			
10 mL vials	28 days	Until expiry date	28 days/refrigerated or RT
3 mL SoloStar® prefilled pen	28 days	Until expiry date	28 days RT (Do not refrigerate)
<b>Technosphere insulin (Foil packages)</b>	10 days	30 days	3 days
<b>NPH</b>			
10 mL/3 mL vial	31 days	Until expiry date	31 days/refrigerated or RT
3 mL Pen	14 days	Until expiry date	14 days RT (Do not refrigerate)
<b>NPH and Regular Insulin</b>			
10 mL/3 mL vial	31 days	Until expiry date	31 days/refrigerated or RT
3 mL Pen, 3mL Humulin N Pen Prefilled-Kwik Pen	14 days	Until expiry date	14 days RT (Do not refrigerate)
<b>Insulin Detemir</b>			
10 mL/3 mL vial	42 days	Until expiry date	42 days/refrigerated or RT
3 mL Flex Pen	42 days	Until expiry date	42 days RT (Do not refrigerate)
<b>Insulin Glargine</b>			
10 mL	28 days	Until expiry date	28 days/refrigerated or RT
3 mL Prefilled-SoloSTAR® Pen	28 days	Until expiry date	28 days RT (Do not refrigerate)
<b>Insulin Degludec</b>			
3 mL TRESIBA®, U-100 FlexTouch	56 days	Until expiry date	56 days/refrigerated or RT
3 mL pre-filled pen, 3 mL TRESIBA®	56 days	Until expiry date	56 days/refrigerated or RT
U-200 FlexTouch®, 3 mL pre-filled pen	56 days	Until expiry date	56 days/refrigerated or RT
<b>Mixtures</b>			
Humulin® 70/30, Humulin® 50/50, 10 mL/3 mL	31 days	Until expiry date	31 days/refrigerated or RT
Humalog® Mix50/50™, Humalog® Mix75/25™	31 days	Until expiry date	31 days/refrigerated or RT
10 mL vial/3 mL vial, 3 mL KwikPen (prefilled)	10 days	Until expiry date	10 days RT (Do not refrigerate)

RT - Room temperature

occasionally with oral antidiabetic drugs. When converting twice daily NPH insulin to once daily insulin glargine, one should consider to reduce the initial dose of NPH insulin by ~20% from the overall daily dose in the initial first week and modify later according the patients response. However, converting single dose NPH insulin to once daily insulin glargine, no change in initial dose is recommended. Higher strength preparation (300 unit/mL) has been approved by the US Food and Drug Administration (FDA).<sup>26</sup> It is also available as prefilled pen with dose strength 450 unit/1.5 mL.

### Insulin Degludec

It is an ultra-long-acting (42 h) insulin analogue, where B-30 threonine is deleted and B-29 conjugated to hexadecanedioic acid.<sup>27</sup> The long duration of action is due to the multihexamers depot formed at the injection site and slow release of monomers. The mixture product is a combination of insulin degludec and insulin aspart (70/30) for subcutaneous injection. Another insulin degludec product is a fixed ratio combination of insulin degludec and glucagon-like peptide 1 agonist, liraglutide. It is available as degludec-100 unit/mL in combination with 3.6 mg/mL of liraglutide solution for injection.<sup>28</sup>

### Mixtures of Insulins

Pharmacokinetic properties of various mixtures of insulins are summarized in Table 1. The mixture shows rapid onset and intermediate duration of action (~1 day). Stable premixed insulins (70% NPH and 30% regular) are accessible to diabetic patients having problem in mixing insulins. Patients are advised to not to modify this combination ratio by additionally mixing NPH or regular insulin. The fixed combinations are generally administered twice daily, with the morning and evening meal. Dose is determined based on blood glucose values and precisely individualized to attain optimum therapeutic effect. Premixed combinations of neutral protamine lispro (NPL) and insulin lispro (75/25 and 50/50) have a more prompt onset of glucose-lowering effect in comparison to 70% NPH/30% regular human insulin mixture and is usually administered within 15 min before or after having a meal.<sup>29</sup> The fixed combination exhibits 2 phases of absorption. The initial phase represents insulin lispro and its rapid onset of action; the ensuing phase demonstrates the prolonged action of insulin protamine suspension. Premixed mixture maintains a superior control for diabetic patients, who generally take a mixture of short and long-acting insulins.<sup>30</sup> When compared to 70 NPH/30 regular, 75/25 NPL, lispro exhibited lesser postprandial blood glucose levels as well as no significant variation between the noon and

overnight glucose levels. Moreover, insulin NPL suspension was formulated as a substitute to mixtures using NPH insulin. However, there are reports which suggest the NPH insulin was not stable for couple of weeks, when combined with lispro insulin.<sup>31</sup> A similar 70% insulin aspart protamine/30% insulin aspart is also available. Insulin degludec is available as 70% insulin degludec/30% insulin aspart and is injected once or twice a day. The storage condition of mixtures are given in Table 2.

## DEVICES

### Insulin Pens

Injection pens are extensively used over traditional vial and syringe method for insulin administration, worldwide. They are available in both disposable devices as well as reusable devices with replaceable prefilled cartridges with either 150 or 300 unit/mL.<sup>32</sup> Currently, cartridges of insulin preparations such as lispro, aspart, and glargine are existing for reusable pens. Similarly, disposable prefilled pens are available for regular insulin (U100 and U500) and most of the insulin preparations. In addition, various pen needle sizes (29, 31, and 32 gauges) and lengths are available to suit the patient requirement. However, it is recommended to evade the same injection site and rotate the site to overcome absorption related issues caused by lipohypertrophy. Studies have demonstrated that the insulin pens offer better glycemic control, avoids hypoglycemia, improves patient adherence, persistence, preference and quality of life compared to traditional insulin delivery. Injection pens may also improve accuracy of insulin delivery and is more convenient and ideal for visually impaired or neurologically impaired, pediatric or unskilled patients thereby improving compliance and therapeutic outcomes. Other advantages include portability and ease of use. Latest programmable insulin pen devices have the capacity to set patient specific doses and dosing schedule. Switching from insulin vials and syringes to prefilled insulin analogue devices reduce health care expense, emergency room visits, and reduce interval of stay and physician visits.

### Continuous Subcutaneous Insulin Infusion (Insulin Pumps)

Insulin pumps are also widely used in diabetes management which require careful handling. Various insulin pumps are currently available in the market. Typically, they are external open-loop system generally simulates basal-bolus of normal physiologic insulin delivery.<sup>33</sup> The pump is a small device which consists of an insulin

reservoir, the program chip, the keypad, and the display screen. This small plastic encased computer device allows the patient to program the insulin amount (up to 300 units) to release in periodic intervals. The device is usually placed in pocket and the tubing is inserted subcutaneously, which allows the insulin delivery. The most suitable site for continuous insulin infusion is the abdomen, although other regions like thigh is also used. One should remember to change the reservoir, tubing and infusion set on 2-3 days in a sterile environment. Usually, the pump is programmed to control the basal delivery for a day, but can be altered if necessary. However, the bolus amount will be calculated by the system based on the carbohydrate intake entered by the user. In general, the use of the new rapid-acting insulin analogues with continuous subcutaneous insulin infusion has shown better glycemic control and improved therapeutic outcomes by decreasing the rate of postprandial hyperglycemic episodes with very few hypoglycemic events. A high accuracy insulin pump is an ideal choice for children with type 1 diabetes as they require very low basal rates. Indeed, the use of insulin pump in young adults, children and adolescents with type 1 diabetes results in low risk of hypoglycemia, diabetic ketoacidosis while improved the glycemic control. Several studies showed moderate improvement in HbA<sub>1c</sub> level when insulin pumps are used, compared to multiple daily insulin injections. However, the cost for insulin therapy by this device is relatively expensive. Insulin pump has safety alarms for low battery, reminder to check postprandial blood glucose, to alter the site of infusion as well as to replenishment of the insulin reservoir.<sup>34</sup> This system also provides indication if there is any obstruction in infusion line or if there is any mechanical snags happen with the pump. There is also an additional auto-off feature which can be set if the patients have not used or turn on for long period. This is definitely an advantage as it will disable the pump to prevent further administration of insulin. It is recommended that the patient may change the injection site every 2-3 days or when the blood glucose level is above 240 mg/dL for two tests in succession, for better efficiency of pumps. It has been suggested that continuous subcutaneous insulin infusion be continued in case of intraoperative procedure below 2 h but can be changed by an infusion of regular insulin in patients who had longer surgical operation.<sup>35</sup> Additionally, if the user include the quantity of carbohydrate consumed in the food as well as present blood glucose value, the device will determine the right dose of insulin. New insulin pumps do have an additional “insulin on board” characteristic that regulates blood glucose correction dose by considering residual activity of earlier

bolus doses. In addition, there is great interest in using the data obtained from continuous glucose monitoring systems to automatically deliver insulin by continuous subcutaneous insulin infusion pump.

### Closed Loop Systems

Continuous subcutaneous glucose sensing is another approach used in the field of plasma glucose management in diabetic patients.<sup>36</sup> A typical real time glucose responsive insulin delivery which contain glucose sensing and insulin administration is developed as closed loop system. This offers a promising treatment option in type 1 diabetes and improve the quality of life. Attempts are already initiated to make this system of clinical use in type 2 patients. Optimized glycemic control without hypoglycemia is a major advantage of closed loop system. The fundamental aspect of this technology is based on an integrated loop system with a continuous monitor, a control algorithm and insulin pump.<sup>37</sup> The autonomous delivery of insulin is based on serum glucose level and post prandial elevation of glucose. Thus it mimics physiologic insulin release from pancreas (artificial pancreas) in response to serum glucose level. Limitations reported by this system include inaccuracy and reliability of constant glucose sensing which in turn postpone the insulin delivery as well as inter- and intra-patient variability. Telemedicine close loop system integrates physiologic sensors, mobile technologies with patient/physician application presents a remote sensing for diabetes management.<sup>38</sup>

### CONCLUSION

Diabetic investigations are now transforming from preliminary controlled in-patient settings to crucial real-world outpatient environment. Continued development of novel diabetic technologies must focus on patient-centered needs and improve clinical outcomes for a broad spectrum of diabetic population. Continued improvements in continuous glucose monitoring technology facilitated both direct benefits to the care of type 1 diabetic patients and paved the way toward the development of emerging artificial pancreas systems. In near future, insulin devices may feature intelligent timer, super bolus for better carbohydrate coverage and faster corrections. It may also account for exercise, provide meaningful suggestions, and carry out pattern spotting, analysis and direct communication capabilities.

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ABBREVIATIONS

**DNA:** Deoxyribonucleic acid; **NPH:** Neutral protamine Hagedorn; **HbA<sub>1c</sub>:** Glycated hemoglobin.

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