Review Article

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Insulin Analogs for Type 1 Diabetes Management

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Abstract

Type 1 diabetes is a metabolic dysfunction in which there is the autoimmune destruction of the β cells in the islet of Langerhans; thereby, there is very little or no insulin production.[1] Insulin regulates the blood glucose level in the body, and there is no known way of preventing type 1 diabetes.[35] Blood glucose homeostasis is vital to avoid further complications, and hence they need insulin analogs to mimic the same. Regular insulin has limitations on how it mimics the bolus insulin secretion. By changing the amino acid sequence in the DNA through genetic engineering, insulin analogs can have different characteristics from natural insulin, which helps overcome these shortcomings. Rapid-acting, long-acting, and mixed formulations are subcategories of insulin analogs. These can help mimic the pattern of insulin release in a healthy individual. Intravenous and subcutaneous administrations influence how fast the insulin analogs can act. The success of each analog depends on how close its action is to natural insulin. All-analog basal bonus regimens show lower glycosylated hemoglobin than all-human insulin basal bonus regimens. Generally, analogs do not have adverse side effects. Therefore, analogs have a significant role in preventing type 1 diabetes from developing into a potentially fatal disease.[9] This article even projects the prospects of insulin analogs like inhalers and oral administrations.

Keywords: diabetes, insulin, genetic engineering

1 Introduction

β cells in the islet of Langerhans are responsible for insulin production in the body.[6] α cells produce glucagon, and δ cells produce somatostatin. The β cells first create a single polypeptide chain called preproinsulin, a single peptide chain with a 24-residue signal peptide that translocates the polypeptide chain to the lumen of the rough endoplasmic reticulum.[2,3] The chain cleaves and forms proinsulin. Proinsulin then forms three disulfide bonds and is folded into the correct conformer.[4] This process takes 5-10 minutes and then is transported to the trans-Golgi network and takes around 30 minutes. Here the cellular endopeptidases called the prohormone convertases, PC1 and PC2, and the exoprotease carboxypeptidase E act on proinsulin to convert it to insulin. The endopeptidase cleaves proinsulin with the sequence B-C-A into three chains, A, B, and C.[5] The C peptide is a single fragment, whereas two disulfide bonds link A and B. The C cleaves after a pair of basic residues; lysine-64 and arginine-65, and arginine-31 and -32. Carboxypeptidase removes the basic residues. Mature insulin thus produced waits for metabolic signals and vagal nerve stimulation to exocytose the insulin into the blood.

Glutamate decarboxylase creates antibodies against proteins IA-2, IA-2β, and ZNT8 or antibodies against

insulin.[7,8] Patients with type 1 diabetes have more antibodies, which destroy β cells. Insulin obtained from the pancreas of pigs and cows is modified to insulin analogs using recombinant technology. In the beginning, insulin obtained caused

allergic reactions due to impurities present. Now, the purity has increased to around 99% by using HPLC, causing the side effects to reduce significantly.

1.1 Limitations of regular insulin

Hexamers form from regular insulin, dissociating into monomers, delaying absorption and onset of action 1/2 to 1 h. This poses the risk of postprandial hyperglycemia. Peak time is 2-3 h, so is the risk of late postprandial hypoglycemia. Hence the bolus insulin secretion is not mimicked. Adjustment of the dose according to the size of the meal is not possible. Differences in absorption rate as much as 25% can occur with a change in injection site and exercise. Hence insulin analogs have better control over the glycemic levels than regular insulin

2. Insulin analogs categorization based on how fast they act

Types of insulin analogs	Time taken for its activity to begin (min)	Time activity sustains (h)	Analogs analogs present in the category
Fast-acting	5 to 15	3 to 4	aspart,lispro,glulisine
Short-acting	30	5 to 8	regular insulin
Intermediate-acting	60-180	16-24	NPH insulin
Long-acting	60-120	24	glargine U100,detemir
Ultra-long acting	30-90	>24	Insulin glargine U300,detemir

Table.1 Classification of insulin analogs based on their activity

Rapid-acting analogs overcome the limitations of regular insulin, and long-acting ones overcome those of intermediate ones. The formation of hexamers is lesser, and dissociation of the hexamers that do happen is faster in rapid-acting analogs. They can be administered before or after meals, allowing the dose adjustment according to the meal size. Even the site of injection and exercise does not influence its pharmacokinetics.

Basal insulin controls the blood glucose level between meal times and overnight.[33] Intermediate-acting insulin or long-acting insulin can regulate the basal

rate. Continuous infusion of rapid-acting insulin through an insulin pump can also achieve the same. Prandial insulin regulates mealtime glucose spikes. Glucose level and carbohydrate intake determine the dose of prandial insulin. The insulin pump calculates the amount needed and accordingly releases insulin. Rapid-acting or regular insulin is administered 15-30 minutes before the meal. Combining basal insulin and prandial insulin can give better results in some patients.

3. Insulin analogs differ from human insulin in terms of the amino acid sequence

Amino Acid Substitutions							
	A-Chain Position			B-Chain Position			
Insulin	A-8	A-10	A-21	B-28	B-29	B-30	B-31 B-32
regular	Thr	Ile	Asn	Pro	Lys	Thr	-
Aspart	Thr	Ile	Asn	Asp	Lys	Thr	-
Lispro	Thr	Ile	Asn	Lys	Pro	Thr	-
Glulisine	Thr	Ile	Asn	Pro	Glu	Thr	-
Glargine	Thr	Ilc	Gly	Pro	Lys	Thr	Arg
Detemir	Thr	Ile	Asn	Pro	Lys	-	Myristic acid
Degludec	Thr	Ile	Asn	Pro	Lys	-	Hexadecanedioic acid
Ala=Alanine Val=Valine Asn=Asparagine Pro=Proline Lys=Lysine Thr=Threonine Ile=Isoleucine Glu=Glutamine Gly=Glycine							

Table.2 Amino acid sequence of Insulin

4. Methods of administration

Oral administration is not yet a full-proof method since insulin breaks down into amino acids and loses activity. So it is administered subcutaneously via insulin pens with repeated usage, single-use syringes with needles, or an insulin pump.[39] Injection ports can reduce the number of skin punctures. Insulin pumps have better control over the basal and bolus insulin dosages. They are attached to a catheter or a cannula. The catheters can be a source of infection and lipodystrophy. Keeping the infusion sites clean minimizes infections.

5. Insulin Aspart

H-Phe-Val-Asn-Gln-His-Leu-Cys-Gly-Ser-His

Leu-Val-Glu-Ala-Leu-Tyr-Leu-Val-Cys-Gly

Glu-Arg-Gly-Phe-Phe-Tyr-Thr-Asp-Lys-Thr-OH

H-Gly-Ile-Val-Glu-Gln-Cys-Cys-Thr-Ser-Ile

Cys-Ser-Leu-Tyr-Gln-Leu-Glu-Asn-Tyr-Cys

Asn-OH

Fig.1 Structure of Insulin aspart[11]

The chemical formula of insulin aspart is $C_{256}H_{381}N_{65}O_{79}S_6$.[9,10,12,13] The metal ion present is Zinc with a 19.6 microgram/ml concentration. The buffer used is disodium hydrogen phosphate dihydrate with a 1.25 mg/ml concentration. The preservatives used are m-cresol and phenol with 1.72mg/ml and 1.50mg/ml concentrations. Isotonicity agents are glycerin and sodium chloride with 16mg/ml and 0.58mg/ml concentration. Its pH lies around 7.2-7.4. Manufacturing involves yeast for recombinant technology. Insulin must be changed every 48h to prevent insulin and preservative degradation. Administrations are generally done subcutaneously just before mealtimes. It can also be intravenous. Peak action occurs in around 45 to 90 minutes. The rate of blood flow, exercise, and infusion sites influence it.

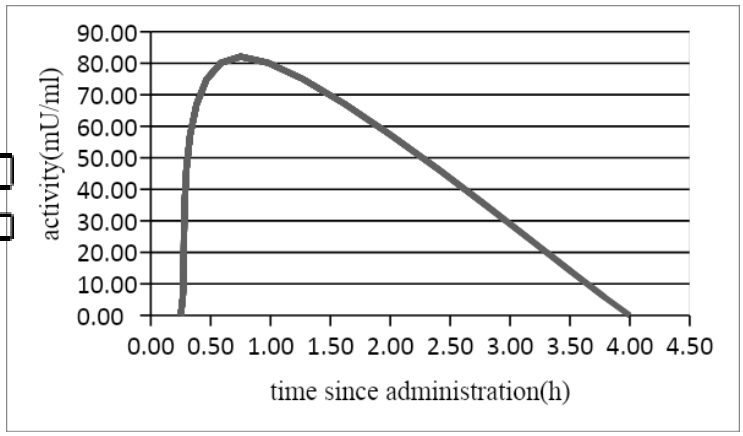

Fig.2 Pharmacokinetics of Insulin aspart[37]

It need not be refrigerated if room temperatures are under 30℃. Above this temperature, aspart degrades very quickly. At times, there is an addition of modifying protein protamine. The most common side effect is hypoglycemia. A severe side effect of low potassium levels can occur.

6. Insulin lispro

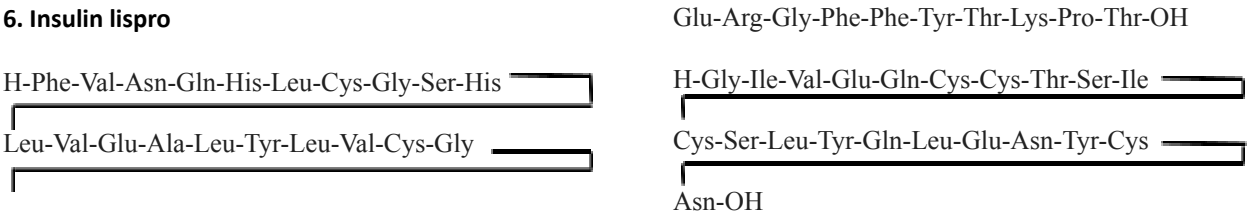

Fig.3 Structure of Insulin lispro

The chemical formula is $C_{257}H_{389}N_{65}O_{77}S_6$.[15] The exchange of amino acids lysine and proline at the terminal ends causes it to behave like insulin-growth factor 1. This exchange also blocks the formation of insulin dimers and hexamers while not altering the receptor binding. It increases the active postprandial insulin.

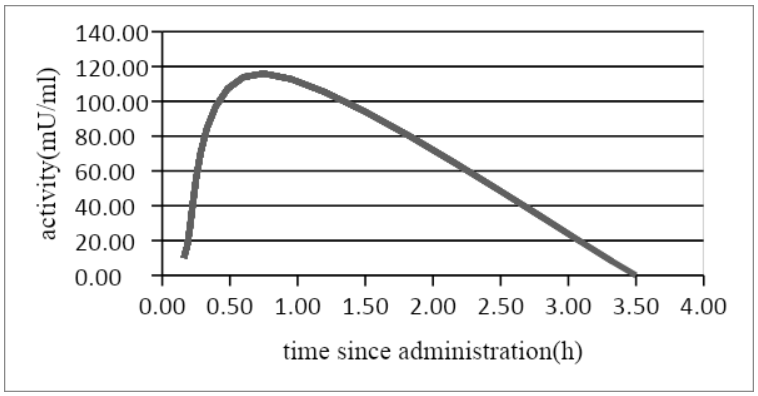

Fig.4 Pharmacokinetics of Insulin lispro[37]

Common side effects include hypoglycemia and hypokalemia. Serious side effects include anaphylaxis and hypersensitivity. It is contraindicated during hypoglycemia or hypersensitivity to its components.

7. Insulin glulisine

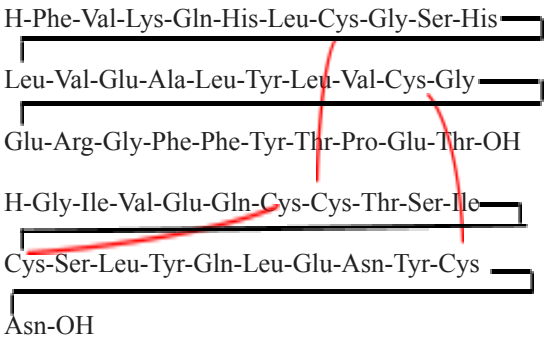

Fig.5 Structure of Insulin glulisine[16]

The chemical formula is $C_{258}H_{384}N_{64}O_{78}S_6$.[17] Subcutaneous administrations are standard before mealtimes, but they could be given intravenously in extreme hyperglycemia. The most common side effect is hypoglycemia.

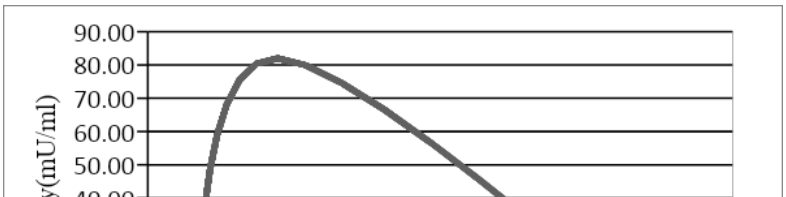

Fig.6 Pharmacokinetics of Insulin glulisine[37]

8. Regular insulin

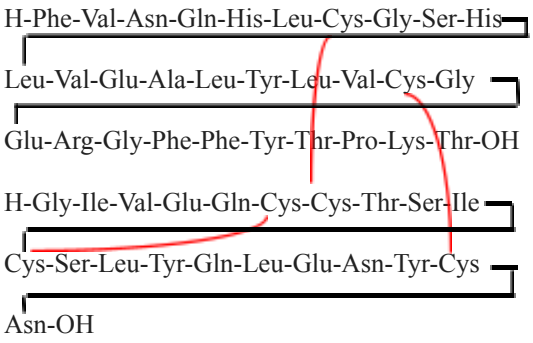

Fig.7 Structure of Regular insulin[18]

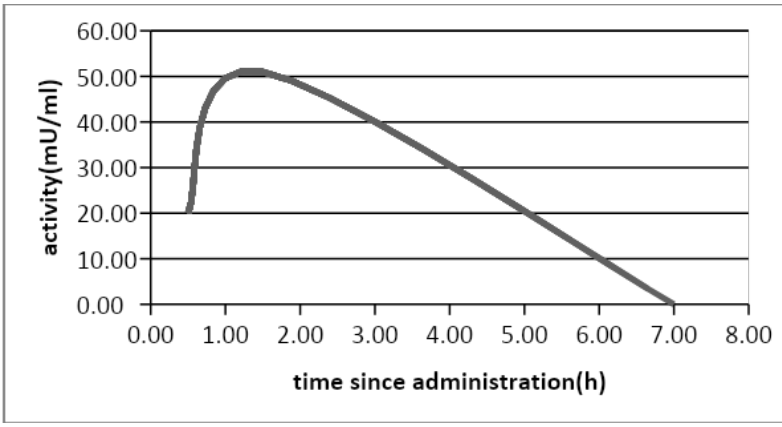

Fig.8 Pharmacokinetics of Regular insulin[37]

The chemical formula is $C_{257}H_{383}N_{65}O_{77}S_6$.[34] Conversion of insulin from the pancreas of pigs and cows into the human version forms regular insulin. Generally, administrations are subcutaneous but also intramuscular or intravenous at times. Manufacturing uses Escherichia coli and recombinant technology. Its primary use is in treating diabetic ketoacidosis and hyperosmolar hyperglycemic states. Sometimes it is administered in higher concentrations. Also, NPH insulin is administered in combination with regular insulin to increase the activity speed. Common side effects include hypoglycemia.

9. Insulin detemir

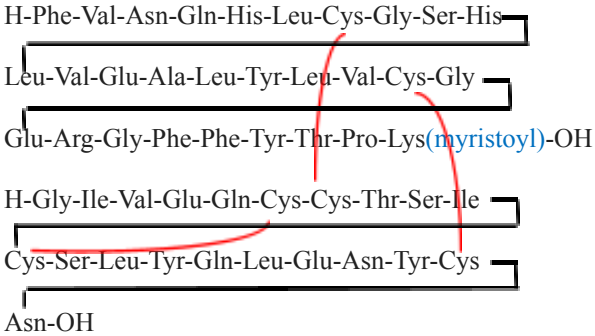

Fig.9 Structure of insulin detemir[19]

The chemical formula is $C_{267}H_{402}N_{64}O_{76}S_6$. [20,36,41] The administrations are subcutaneous. The myristic acid bonded to lysine binds with the albumin present in the blood. This results in faster absorption. The activity begins after its dissociation from the complex. The bioavailability is 60%. Insulin detemir causes an increase in glucose uptake by the tissues and reduces the

production of glucose by the liver. Its elimination half-life is 5-7 hours.

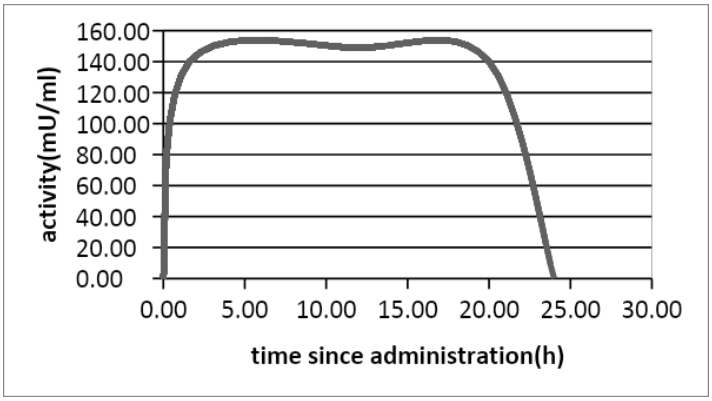

Fig.10 Pharmacokinetics of Insulin detemir[37]

10. Insulin glargine

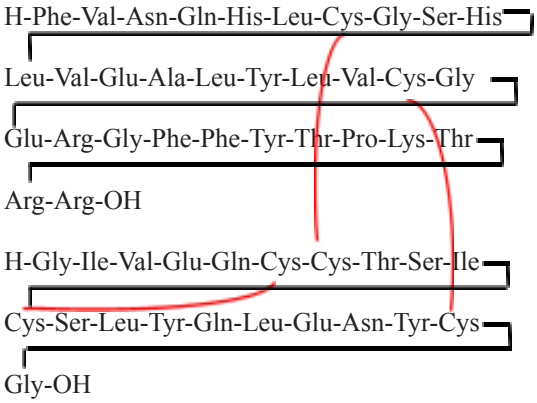

Fig.11 Structure of insulin glargine

The chemical formula is $C_{267}H_{404}N_{72}O_{78}S_6$.[21,22,23] The administrations are subcutaneous. Glargine is stable at pH 4 but precipitates at neutral pH. Neutral conditions cause slower absorption of insulin. The arginine residues alter the isoelectric point from 5.4 to 6.7. This change allows subcutaneous injections of clear solution. Microcrystals present slowly release insulin into the blood, causing uniform and prolonged insulin action. Like insulin detemir, it causes an increase in glucose uptake by the tissues and reduces glucose production by the liver. Glycine protects the amide linkage of arginine in acidic conditions. Like insulin detemir, it causes an increase in glucose uptake by the tissues and reduces glucose production by the liver.

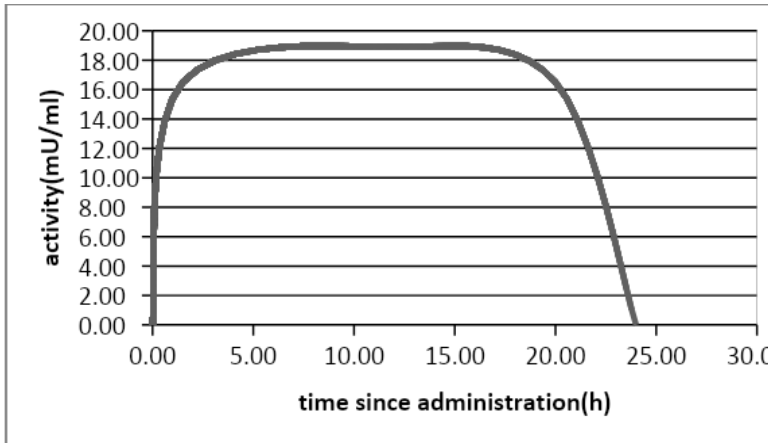

Fig.12 Pharmacokinetics of Insulin glargine[37]

The most common side effect is hypoglycemia. A severe side effect of hypokalemia can occur.

11. Neutral Protamine Hagedorn insulin (NPH)

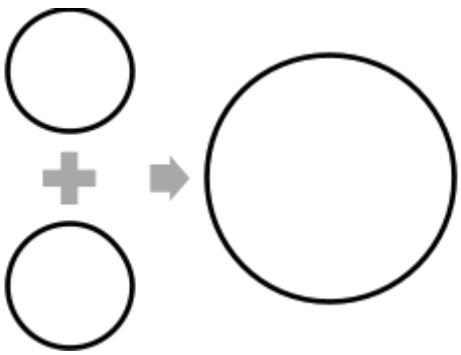

Fig.13 Preparation of NPH Insulin

Neutral Protamine Hagedorn is made by mixing regular insulin and protamine with Zinc and phenol in equal proportions to maintain a neutral pH so that the formation of crystals occurs.[38] The administrations are subcutaneous, generally twice a day.

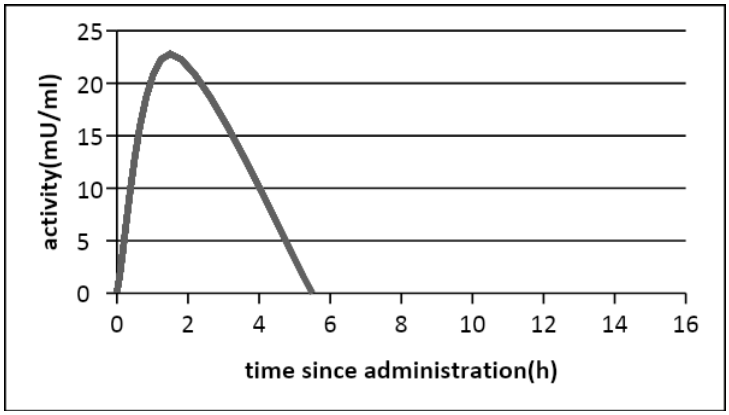

Fig.14 Pharmacokinetics of NPH Insulin[37]

Solutions premixed with regular insulin are also available. The most common side effect is hypoglycemia.

12. Insulin degludec

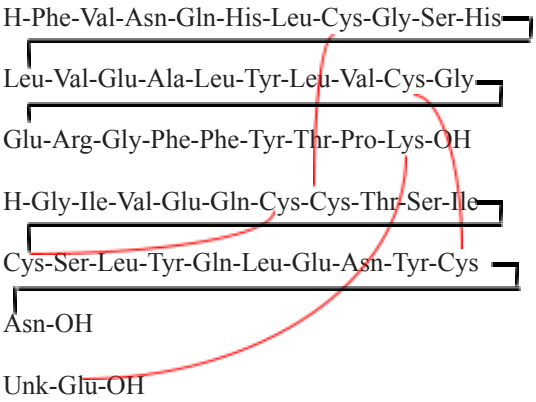

Fig.15 Structure of insulin degludec[24]

The chemical formula is $C_{274}H_{411}N_{65}O_{81}S_6$.[25] The administration is subcutaneous once daily. The Thapsic acid allows the formation of multi-hexamers in the subcutaneous tissues, which induce slow insulin release. Insulin degludec has very efficient control over glycemic levels but poses a higher risk of hypoglycemia.

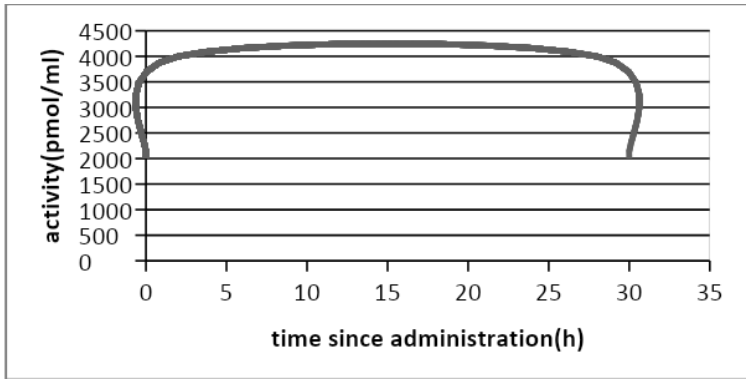

Fig.16 Pharmacokinetics of Insulin degludec[37]

13. Prospects of insulin analogs

Administrations of insulin analogs are intravenous and subcutaneous, which creates a risk of lipodystrophy. An attempt to manufacture insulin inhalers is in process.[27] To date, inhalers have been only effective if additional intravenous and subcutaneous administrations are needed to keep the glycemic levels under control. It is contraindicated for those with asthma and smoking problems. Research is still ongoing to make this a success. Even oral administration of insulin is a vision for the future since the insulin would go through the liver and, in turn, be more effective.[28,29] However, unfortunately, insulin breaks down in the gastric acid and is ineffective. Scientists are striving to make insulin

pills gastro-resistant and give patients' lives more quality. Even glucose-responsive insulin analogs are a booming area that focuses on feedback mechanisms regulating insulin release.[30] Apart from only manufacturing insulin analogs, even stem cell therapy involving mesenchymal stem cells can regenerate the β cells of islet of Langerhans.[31,32] These are a few possibilities to improve type 1 diabetic management in the near future.[26]

14. Conclusion

Insulin analogs have different pharmacokinetics and pharmacology, which allow the mimicking of basal and bolus insulin and glycemic levels. If the benefits outweigh the demerits for a given patient, they can improve their quality of life. Research is still ongoing to see if analogs with better control and with different ways of administering can be made. To conclude, insulin analogs are great help for type 1 diabetic treatment.

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