

SMART INSULIN: A PROMISING INSULIN PREPARATION FOR GLYCEMIC CONTROL IN DIABETES MELLITUS

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ABSTRACT

Diabetes mellitus is a group of metabolic disorders with a number of etiologies characterized by hyperglycemia along with impairment of carbohydrate, fat and proteins metabolism. It can occur due to an imbalance of insulin secretion, insulin action or both.^[1] Hyperglycemia in diabetes is associated with micro vascular disturbances and dysfunction of eyes, kidneys, nerves and heart together with an increased risk of macro vascular disease. The criteria of diagnosis of diabetes mellitus are defined by guideline of by American Diabetes Association (ADA).^[3] Diabetes mellitus management is associated with the episodes of hypoglycemia. The hypoglycemia complications

are mainly associated in elderly and also in some cases of type I diabetes subjects. Furthermore, prolonged insulin deficiency and longer disease duration increase the risk of hypoglycemia in type II diabetes mellitus.^[2] Diabetes and its associated complications are the possible cause of morbidity and mortality worldwide. This calls for a firm action in part of its therapeutic potential. To check the increased episodes of diabetes and its associated complications, cost-effective and minimal tedious interventions are needed for its efficient management and to slow down its rate of prevalence.^[3] The epidemiological analysis of diabetes mellitus episodes enables the researchers to develop the smart insulin. Smart insulin is the best option to minimize the episodes of hypoglycemia and diabetes associated complications. Besides associated micro-vascular and macro-vascular complications with diabetes, hypoglycemia is among the most important complication in patients relying on insulin action. It is commonly prevalent in elderly population, type I diabetic subjects and

with those having co-morbidities. Subsequent episodes of hypoglycemia can also lead to deaths. Smart insulin is also known as glucose-responsive insulin that is being designed on the situation and need.^[4] It can automatically turns on when the glucose level reaches to maximum and, it can turn off when glucose level reaches to normal. This insulin could make a remarkable history and ensure for a perfect glycemic control throughout the life span.^[3] The working of smart insulin depends on the principle of sensing of glucose. When the concentration of glucose is low a signal goes to some binding element having a biodegradable material that attached to insulin molecules and it can prohibit its action. When the concentration of glucose is high the binding element attached to insulin detached and enables the insulin to perform its function.^[4]

KEYWORDS: Carbohydrate, fat and proteins metabolism

INTRODUCTION

The first globally accepted classification of diabetes mellitus was published by World Health Organization in 1980^[4] and it is modified in 1985.^[5] The American Diabetes Association (ADA) categorized diabetes into various classical forms to differentiate individuals with diabetes mellitus.

(a) Type I diabetes mellitus

Type 1 diabetes accounts for only 5-10% of diabetic people. This form of diabetes is also known as insulin dependent diabetes or juvenile onset diabetes which results from destruction of pancreatic beta cells via the cellular mediated autoimmune mechanism. The prime participants for this destruction include auto-antibodies to insulin, GAD65 and tyrosine phosphatases IA-2. Ketoacidosis may be the first symptoms that appear in diabetes patients with this class. Other classical symptoms include mild or severe hyperglycemia followed by infection and other stress.^[6]

(b) Type II Diabetes mellitus

Type 2 diabetes mellitus (T2DM) is the most common form of diabetes (>90-95% of total diabetic patients) and currently it is the major cause of morbidity and mortality. T2DM is generally viewed as a clinical syndrome with variable phenotypic expression (β - cells insufficiency and insulin resistance). However, in most instances, the exact cause seems to be polygenic in nature and is yet unknown. People with this form of diabetes are insulin resistant. Nevertheless, such patients with this form of diabetes are at a high risk of

development of macro-vascular and micro-vascular complications.^[7] The majority of patients with this form of diabetes mellitus are obese and it can lead to insulin resistance.^[8]

(c) Gestational Diabetes (GDM)

Gestational diabetes is glucose intolerance resulting in hyperglycemia with onset or first recognition during pregnancy. Insulin resistance is the main cause for GDM, as pregnancy hormones (placental) along with other unknown (fat depositions) factors bind with insulin receptors causing insulin resistance.^[11]

COMPLICATIONS OF DIABETES MELLITUS

The complications of diabetes mellitus are far less common and less severe in people who have well-controlled blood sugar levels. Acute complications include hypoglycemia and hyperglycemia, diabetic coma and nonketotic hyperosmolar coma. Chronic complications occur due to a mix of microangiopathy, macrovascular disease and immune dysfunction in the form of autoimmune disease or poor immune response, most of which are difficult to manage. Microangiopathy can affect all vital organs, kidneys, heart and brain, as well as eyes, nerves, lungs and locally gums and feet. Macrovascular problems can lead to cardiovascular disease including erectile dysfunction. Female infertility may be due to endocrine dysfunction with impaired signalling on a molecular level.^[10]

Other health problems compound the chronic complications of diabetes such as smoking, obesity, high blood pressure, elevated cholesterol levels and lack of regular exercise which are accessible to management as they are modifiable. Non-modifiable risk factors of diabetic complications are type of diabetes, age of onset, and genetic factors, both protective and predisposing have been found.^[11]

Complications of diabetes mellitus are acute and chronic. Risk factors for them can be modifiable or not modifiable. Overall, complications are far less common and less severe in people with well-controlled blood sugar levels. However, (non-modifiable) risk factors such as age at diabetes onset, type of diabetes, gender and genetics play a role. Some genes appear to provide protection against diabetic complications, as seen in a subset of long-term diabetes type I survivors without complications.^[11]

RISK FACTORS OF DIABETES MELLITUS

1. Age

Type II diabetes in youth brings a much higher prevalence of complications like diabetic kidney disease, retinopathy and peripheral neuropathy than type I diabetes, though no significant difference in the odds of arterial stiffness and hypertension.^[12]

2. Poor glucose control

A 1988 study over 41 months found that improved glucose control led to initial worsening of complications but was not followed by the expected improvement in complications. In 1993 it was discovered that the serum of diabetics with neuropathy is toxic to nerves, even if its blood sugar content is normal. Research from 1995 also challenged the theory of hyperglycemia as the cause of diabetic complications. The fact that 40% of diabetics who carefully controlled their blood sugar nevertheless developed neuropathy made clear other factors were involved. In a 2013 meta-analysis of 6 randomized controlled trials involving 27,654 patients, tight blood glucose control reduced the risk for some macrovascular and microvascular events but without effect on all-cause mortality and cardiovascular mortality.^[11,12]

3. Autoimmune processes

Research from 2007 suggested that in type I diabetics, the continuing autoimmune disease which initially destroyed the beta cells of the pancreas may also cause retinopathy, neuropathy, and nephropathy. In 2008 it was even suggested to treat retinopathy with drugs to suppress the abnormal immune response rather than by blood sugar control.^[12]

4. Genetic factors

The known familial clustering of the type and degree of diabetic complications indicates, that genetics play a role in causing complications.^[12]

HYPOGLYCEMIA: A CONSEQUENCE OF INSULIN

Hypoglycemia, also known as low blood sugar, is when blood sugar decreases to below normal levels. This may result in a variety of symptoms including clumsiness, trouble talking, confusion, loss of consciousness, seizures, or death. A feeling of hunger, sweating, shakiness, and weakness may also be present. Symptoms typically come on quickly. Incidence of severe hypoglycemia even requires aid of another helping person to deliver the treatment.^[13] Hypoglycemia is a well known common side effect occurring during insulin therapy and also

remains the leading role in management of glucose control in insulin derived diabetes management. It can be counteracted by behavioral, hormonal and metabolic events. When this episode of hypoglycemia occurs in healthy subjects, the counter mechanism involves a gradual decrease in endogenous insulin release and co-release of glucagon, adrenalin (epinephrine), cortisol and growth hormone. Patients with type 1 diabetes completely depends on exogenous insulin and they can't reduce the source of endogenous insulin generation during the episodes of hypoglycemia. Hormonal responses in the episodes of hypoglycemia have prominent metabolic effects in normal populations and it can lead to increased endogenous glucose secretion.^[14]

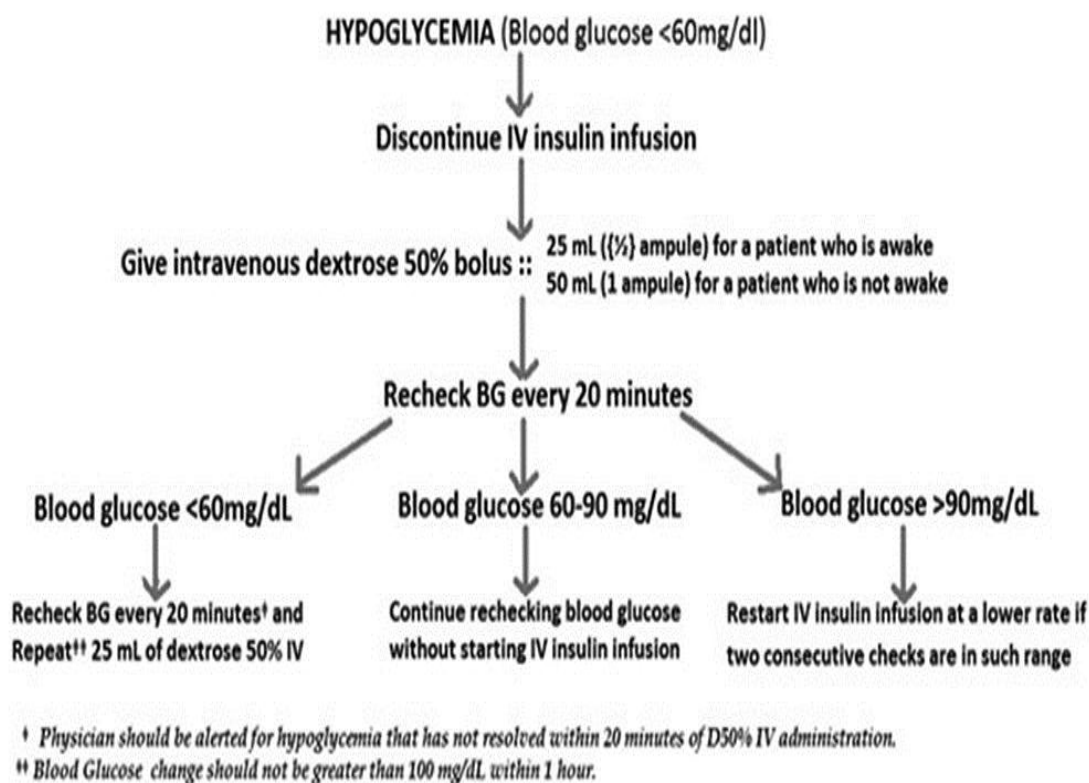
The most common cause of hypoglycemia is medications used to treat diabetes mellitus such as insulin and sulfonylureas. Risk is greater in diabetics who have eaten less than usual, exercised more than usual, or have drunk alcohol. Other causes of hypoglycemia include kidney failure, certain tumors, such as insulinoma, liver disease, hypothyroidism, starvation, inborn error of metabolism, severe infections, reactive hypoglycemia, and a number of drugs including alcohol. Low blood sugar may occur in otherwise healthy babies who have not eaten for a few hours.^[14]

The glucose level that defines hypoglycemia is variable. In people with diabetes levels below 3.9 mol/L (70 mg/dL) is diagnostic. In adults without diabetes, symptoms related to low blood sugar, low blood sugar at the time of symptoms, and improvement when blood sugar is restored to normal confirm the diagnosis. Otherwise a level below 2.8 mol/L (50 mg/dL) after not eating or following exercise may be used. In newborns a level below 2.2 mol/L (40 mg/dL) or less than 3.3 mol/L (60 mg/dL) if symptoms are present indicates hypoglycemia. Other tests that may be useful in determining the cause include insulin and C peptide levels in the blood. Hyperglycemia (high blood sugar) is the opposite condition.^[14,15]

Among people with diabetes, prevention is by matching the foods eaten with the amount of exercise and the medications used. When people feel their blood sugar is low, testing with a glucose monitor is recommended. Some people have few initial symptoms of low blood sugar and frequent routine testing in this group is recommended. Treatment of hypoglycemia is by eating foods high in simple sugars or taking dextrose. If a person is not able to take food by mouth, an injection of glucagon may help. The treatment of hypoglycemia unrelated to diabetes includes treating the underlying problem as well and a healthy diet. The term "hypoglycemia" is sometimes incorrectly used to refer to idiopathic postprandial syndrome, a

controversial condition with similar symptoms that occur following eating but with normal blood sugar levels.^[15]

MANAGEMENT OF HYPOGLYCEMIA



PREPARATIONS OF INSULIN^[15]

Insulin Preparation	Generic Name	Trade Name	Onset	Peak	Usual Effective Duration	Comments
Rapid acting	Insulin Aspart	NovLog	5-10 minutes	1-3hrs	3-5 hrs	Eat within 5-10 minutes of injecting
	Insulin Lispro	Humlog	<15 minutes	½-1 ½ hrs	2-4 hrs	Eat within 5-10 minutes of injecting
	Insulin glisine	Apidra	<15 minutes	½ -1 ½ hrs	1-2 ½ hrs	Take from 15''before to 20''after meal. May only be mixed with NPH
Short acting	Regular	HumulinR Novolin R	½ -1hrs	2-3 hrs	3-6 hrs	Humulin R is also made in U-500 strength. The onset is slower than U-100 and duration is up to 24 hrs.
Intermediate acting	NPH	Humulin N Novolin N	2-4hrs	4-10 hrs	10-16 hrs	Roll vigorously to mix. Given once or

						twice daily.
Long acting	Insulin Glargine	Lantus	1hrs	No peak	24hrs	Do not put in the same syringe with any other insulin. Usually given once daily.
	Detemir	Levemir	1-2hrs	No peak	6-23hrs, depending on dose	Do not put in the same syringe with any other insulin. May be given once or twice daily.
Combinations	70%NPH +30%Regular	Humulin 70/30 Novolin 70/30	½ -1hrs	There are 2 peaks: 2-3 hrs & 4-10hrs	10-16 hrs	Roll vigorously to mix. Do not put in the same syringe with any other insulin.
	70% Aspart Protamine + 30% Aspart	Novolog Mix 70/30	5-10 minutes	There are 2 peaks: 1-3 hrs&4-10 hrs	10-16 hrs	Eat within 5-10 minutes of injecting. Roll vigorously to mix. Do not put in the same syringe with any other insulin.
	50% Lispro Protamine +50% Lispro	Humalog 50.50	<15 minutes	There are 2 peaks: ½-1 ½ hrs &4-10 hrs	10-16 hrs	Eat within 5-10 minutes of injecting. Roll vigorously to mix. Do not put in the same syringe with any other insulin.
	75% Lispro Protamine +25% Lispro	Humalog mix 75/25	<15 minutes			Eat within 5-10 minutes of injecting. Roll vigorously to mix. Do not put in the same syringe with any other insulin.

DISADVANTAGES OF INSULIN THERAPY^[16]

1. Hypoglycemia is the most common and serious side effect of insulin.
2. An unusual ocular disturbance during the beginning of therapy is bilateral presyopia (blurry vision).
3. Dermatologic reactions to insulin can result in lipohypertrophy (insulin is lipogenic) or lipoatrophy (probably immunologically-mediated). Without proper hygiene, subcutaneous insulin injections may be complicated by infection.
4. Hypersensitivity reactions--either local or systemic

5. Immunologic analysis of anaphylaxis to some insulin preparations in some cases has revealed markedly elevated serum levels of IgE and IgG to protamine, but not to regular insulin.
6. Some experts are evaluating insulin as a possible atherogenic agent. Controversy and continued study surround the role of hyperinsulinemia as the precursor of hypertension. Insulin may stimulate heart rate in the absence of hypoglycemia.
7. Intensive insulin therapy causes an increase in body fat as a result of the elimination of glycosuria and reduction in 24-hour energy expenditure. General weight gain is associated with insulin use, sometimes presenting as edema.
8. Insulin increases the intracellular transport of phosphate, which often results in hypophosphatemia, hypokalemia and hypomagnesemia.
9. Hypoglycemia is associated with increased plasma dopamine, epinephrine, and plasma renin activity. The renal effects from insulin-induced hypoglycemia include significantly decreased renal plasma flow, glomerular filtration rate, and significantly increased urinary albumin excretion rate.
10. Due to the insulin therapy anaemia can also occur.

SMART INSULIN FOR ATTAINING PROPER GLYCEMIC CONTROL

Smart insulin (also known as glucose responsive insulin, adaptive insulin, smart insulin patch, is a promising and experimental type of insulin that automatically manages blood sugars and keeps them in the normal range in diabetics. Its purpose is to treat and prevent hyperglycemia. Smart insulin is supposed to adapt by releasing either less or more insulin relative to the level of glucose in the bloodstream to keep it stable.^[17]

The development of “*smart*” drug delivery strategies for diabetes is particularly promising given the need to vary dosage based on real-time disease state of the patient. The ultimate goal for these efforts would be to create a “*Fully Synthetic Pancreas*”, an abiotic construct that can sense elevations in blood glucose and respond with a metered dose of insulin, and/or potentially glucagon, for closed-loop therapy.^[18] However, while recreating the natural dynamics of glycemic control, complete with both peaks and troughs, represents a major challenge in the design of a sensing material. The trigger for such a therapy, glucose, is a small-molecule analyte that is present in both healthy and diseased states, though in different concentrations. An ideal system would respond quickly to elevation in blood glucose, but would promptly shut off to prevent insulin overdose. It should also not allow burst release, as

that could lead to insulin overdose and hypoglycemia immediately following administration. The management of diabetes also necessitates life-long therapy.^[19] This system helps to deliver the action without the presence of food as the normal insulin needs food for their effective action. These are among the many challenges that must be overcome in the development of a glucose-responsive insulin delivery system in order to realize the vision of a fully synthetic pancreas.

It is primarily used to treat type I diabetes but will eventually be used on type II diabetes. A constant amount would be injected every so often and it would adapt to the user's blood sugar levels. This would eliminate the need for worrying about an insulin:carb:ratio. Frequent hypo and hyperglycemia would be a thing of the past.^[20]

For many who suffer from diabetes, insulin injections can be a painful and imprecise process of keeping their blood sugar levels under control. So the new 'smart insulin' patch could do away the way diabetics keep their blood sugar levels in check.

STRUCTURE OF SMART INSULIN

The patch, created by researchers from the University of North Carolina and NC State, is a thin square covered with more than 100 tiny needles. According to researchers, the patch works fast, is simple to use and is made from biocompatible materials. The patch's tiny painless needles are packed with insulin and glucose sensing enzymes in microscopic storage units. The patch is able to release these enzymes when blood sugar levels get too high.^[21]

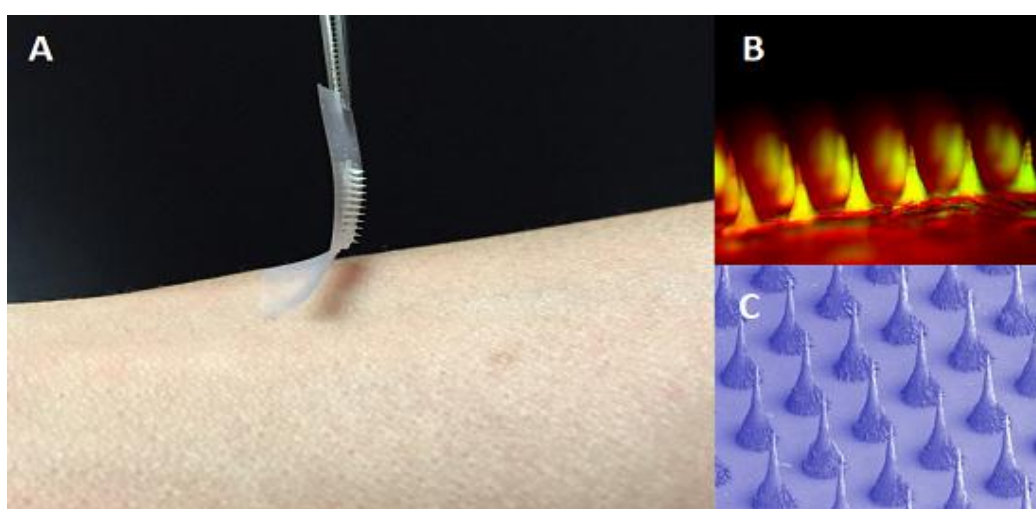


Figure 1: A- Smart insulin patch, B- Fluorescent image of the microneedle patch with insulin tagged in green, C-Scanning electronic microscopy image.

Smart Insulin !!

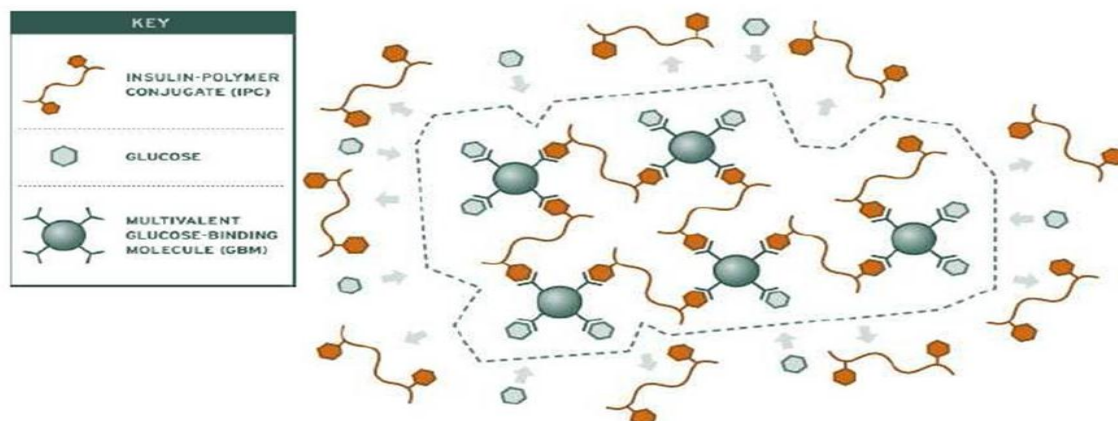


Figure 2.

FORMULATION OF SMART INSULIN

Smart insulin is basically a combination of biodegradable polymer and insulin.

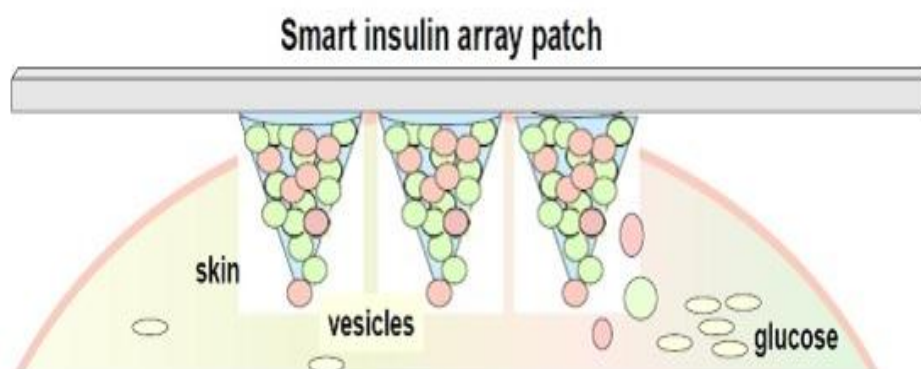


Figure 3. The smart insulin patch (microneedle array patch) (simplified representation)

A working group of North Carolina State University (UNC) has developed a promising delivery system so called “smart insulin patch” (array of tiny needles) which could be placed anywhere on the body to detect and deliver insulin according to changes in the glucose concentrations. Therefore, a perfect glucose-responsive insulin delivery system might be a game-changer for patients with diabetes.^[22]

Smart insulins behave like alarm call centers, sensing increases in glucose levels with subsequent release of insulin. These approaches generally integrate a glucose sensing or conversion module and a sensing/conversion activated insulin releasing module. Three classic strategies are often utilized comprising different glucose-sensing moieties: glucose oxidase (GO_x), glucose-binding protein (GBP, i.e. Con A) and glucose-binding molecules

(GBM, i.e. phenylboronic acid (PBA)) for achieving glucose triggers. A variety of formulations, such as bulk hydrogels, microgels, emulsion based nanoparticles, and self-assembled vesicles have been developed to respond to glucose concentration changes by structural transformations such as swelling, shrinking, degrading or dissociating in order to promote the release of insulin.^[23] Some innovative strategies are developed for formulating smart insulins.

The working group of UNC creates “glucose response cells” to realize a combination of fast responsiveness and long-term persistence.

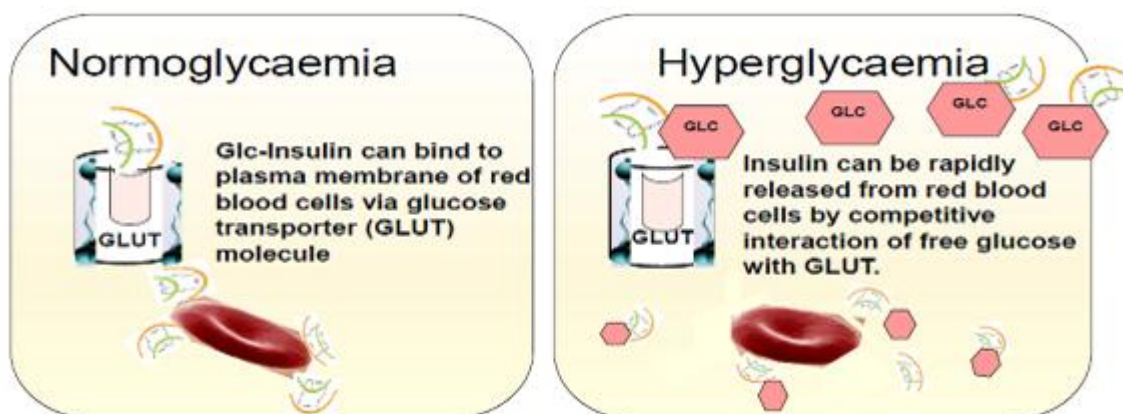


Figure 4. Glucose responsive red blood cells (simplified representation).

1. An innovative strategy to overcome the use of synthetic materials has been generated by the integration of red blood cells (RBC) and glucose derivative-modified insulin (Glc-Insulin). After being conjugated with glucosamine, insulin can efficiently bind to red blood cells by interacting with glucose transporter (GLUT) on plasma membranes.^[24] The reversible binding between glucose derivative-modified insulin (Glc-Insulin) and GLUT can enable a fast insulin release from the cellular carrier in the setting of hyperglycaemia. The delivery vehicle can be further simplified utilizing injectable polymeric nanocarriers coated with red blood cell membrane and loaded with Glc-Insulin. This approach could be simply integrated with a microneedle-array patch.

There remains the challenge to demonstrate a desirable insulin delivery system, which combines ease of use, high drug capacity loading for longer use, fast responsiveness and excellent biocompatibility.^[25]

2. Most glucose-responsive formulations that incorporated glucose oxidase (GO_x) involve pH sensitive materials based on the enzymatic oxidation of glucose to gluconic acid. Local

decline of pH associated with increasing blood glucose levels promote the insulin release through either by degradation or protonation. Nevertheless, these systems are limited because of the challenge of rapidly switching the physiological pH *in vivo*.^[26]

3. The working group of UNC has presented a closed-loop, glucose-responsive insulin delivery system by integrating hydrogen peroxide (H₂O₂)-responsive polymeric vesicles with a transcutaneous microneedle array patch to sense glucose and release insulin across the skin layer. Vesicles are microscopic vesicles that enclose a volume with a molecularly thin membrane. The membranes are generally self-directed assemblies of amphiphilic molecules with dual hydrophilic-hydrophobic characteristics. Utilizing polymeric vesicles, water-soluble insulin has been encapsulated into the inner cavity which has a high loading capacity. In the setting of hyperglycaemia glucose will diffuse across the membrane and interact with GO_x in the cavity, which leads to the oxidation of glucose to gluconic acid, simultaneously generating H₂O₂. By virtue of the generated H₂O₂, the copolymer becomes water soluble with leading to disassembly of the polymeric vesicles and the subsequent release of the preloaded insulin. This formulation demonstrated both *in vitro* and *in vivo* glucose-mediated disassembly, releasing the encapsulated insulin under hyperglycaemic conditions with rapid responsiveness, without insulin release in normoglycaemic conditions.^[27]

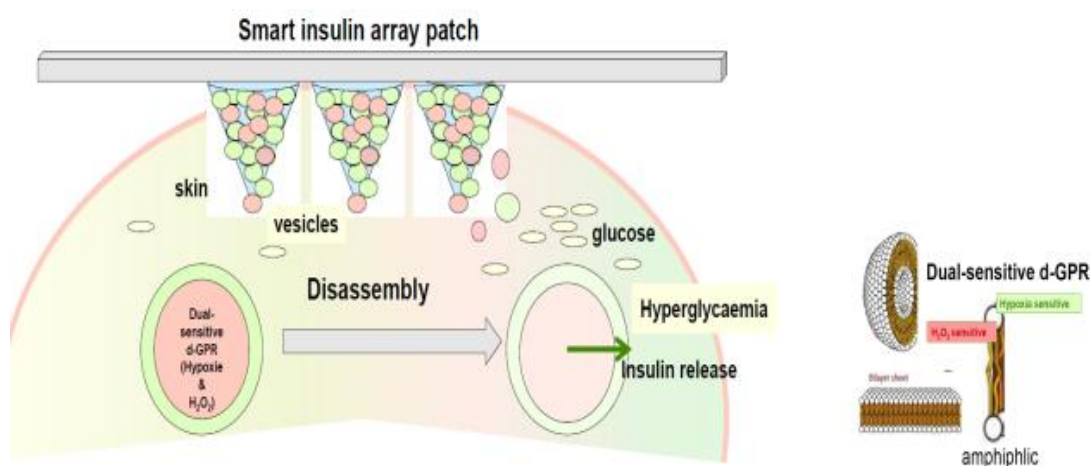


Figure 5. Glucose-responsive insulin delivery system using hypoxia and H₂O₂-responsive polymersome vesicles loading with microneedle-array patches.

As rapid H₂O₂ accumulation may lead to local inflammation, the active glucose-responsive insulin delivery system has been further exploited utilizing polymersome vesicles sensitive to both hypoxia and H₂O₂ (smart insulin patch). These polymersome-based vesicles (dual

sensitive d-GRP) were able to eliminate excess H_2O_2 and to reduce tissue inflammation while maintaining the activity of GO_x . Furthermore, these vesicles can be integrated within a cross-linked hyaluronic acid-based (natural substance) microneedle–array patch to achieve convenient, painless and continuous administration of insulin with high biocompatibility. In vivo experiments indicated that this enhanced smart insulin patch was highly effective in providing tight blood glucose regulation in diabetic mice and showed minimal side effects regarding inflammation. For potential translation of this microneedle array patch-based formulation in to clinical use, efforts associated with further enhancement of loading capability and bioavailability are expected.^[28]

These promising innovative strategies will require further investigations in early clinical development. Long-term goal is to develop a smart insulin patch that patients would only have to change every few days. If these patches will work in patients with diabetes it might prove to be a game changer in insulin treatment of patients with diabetes mellitus.

PHARMACOLOGY OF SMART INSULIN PATCHES

Since its discovery and isolation, exogenous insulin has resulted dramatically change in the prognosis for patients with diabetes. Nowadays, novel insulin analogues have improved pharmacokinetic profiles mirroring endogenous basal and prandial insulin secretion more closely. However, despite advances in insulin formulations and in closed loop systems combined with advanced continuous glucose-monitoring systems and external insulin infusion pumps, glucose control still remains a challenge. Patients with diabetes do not achieve their glycaemic targets and hypoglycaemia continues to be the major hurdle for intensification of insulin therapy. The advantageous scientific technology associated with smart insulin is self regulating release and non release depends on glucose concentration at a specific range to certain level by recognizing plasma –molecular indicator. Smart insulin is also known as glucose-responsive insulin that is being designed on the situation and need.^[29] It automatically turns on when the glucose level reaches to maximum and, it turn off when glucose level reaches to normal. This insulin could make a remarkable history and ensure for a perfect glycemic control throughout the life span. The mechanism depends on the principle of sensing of glucose. When the concentration of glucose is low a signal goes to some binding element having biodegradable material that attached to insulin molecules and prohibits its action. During high glucose concentration the binding element attached to insulin detached and enables the insulin to perform its function. Insulin unlocks glucose entry to cells

and it can deliver the energy. The flexibility and innovative technology to control and self-regulate the insulin secretion as with glucose level high and low smart insulin become a best managing tool over hypoglycemia (low blood sugar).^[28]

CLINICAL TRIALS OF SMART INSULIN

Smart Insulin has started clinical (human) trials and the trial started in November 2014. The clinical trial was under the name MK-2640. The trial itself has a fairly complex design. It's two trials combined into one. Part 1 is a group of 7 different "panels" (dosing regimens) given to healthy people. Part 2 is a comparison of regular insulin to MK-2640 in people who have had type-1 diabetes for at least a year. All of this involves 58 people and is expected to be done by July 2015.^[30] Most of the data they are collecting is "pharmacokinetic" meaning they are measuring how much of the drug is available in the body at any given time. How quickly it "washes out" of the body and so on. They will also be looking for adverse events and also patient drop outs caused by adverse effects. Three-part Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of MK-2640 in Healthy Participants (Part I) and Participants With Type 1 Diabetes Mellitus (Parts II and III) (MK-2640-001).^[29,30]

PURPOSE

The purpose of Part I of this study is to evaluate the safety and tolerability of intravenous (IV) doses of MK-2640 in healthy participants and to obtain preliminary plasma pharmacokinetic profiles of MK-2640. The purpose of Parts II and III of this study is to evaluate the safety and tolerability of IV doses of MK-2640 and regular human insulin (RHI), and to evaluate the pharmacokinetic and pharmacodynamic profile of MK-2640 and RHI in participants with type 1 diabetes mellitus (T1DM). Part II will be initiated only if Part I general safety, tolerability and other observed data are supportive of progression to Part II. Part III will be initiated only if Parts I and II general safety, tolerability and other observed data are supportive of progression to Part III.^[30]

Study design: Randomised control trial.

Primary Outcome Measures^[31]

- Number of participants who experienced an adverse event [Time Frame: Up to 30 days].
- Pharmacokinetic parameter: steady state plasma concentration (C_{ss}) [Time Frame: 30 minutes of interval].

- Pharmacokinetic parameter: area under the plasma concentration curve from time 0 to infinity.
- Pharmacokinetic parameter: clearance (CL) [Time Frame: Part I: final 30 minutes of each infusion rate; Parts II and III: final 30 minutes of each interval].
- Pharmacokinetic parameter: volume of distribution (Vd) [Time Frame: Part I: final 30 minutes of each infusion rate; Parts II and III: final 30 minutes of each interval].
- Pharmacokinetic parameter: plasma apparent terminal half-life [Time Frame: Part II: following 9 hour infusion; Part III: following 7 hour infusion].
- Pharmacodynamic parameter: steady-state glucose infusion-rate (GIR) in Part II [Time Frame: Part II: during the final 60 minutes of the infusion].

Secondary Outcome Measures^[31]

- Number of participants with anti-drug antibody (ADA) formation [Time Frame: Up to 30 days following last dose].

Criteria^[31]

Inclusion Criteria (Part I)

- healthy male or healthy female of non-child bearing potential
- in good health
- is a non-smoker and/or has not used nicotine or nicotine containing products (e.g., nicotine patch) for at least approximately 3 months

Inclusion Criteria (Parts II and III)

- male or female of non-child bearing potential
- has T1DM for at least 12 months
- on stable doses of insulin
- in good health
- is a nonsmoker and/or has not used nicotine or nicotine-containing products (e.g., nicotine patch) for at least approximately 3 months

Exclusion Criteria

- is mentally or legally incapacitated.
- has a history of clinically significant endocrine (except T1DM for Part II subjects), gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal,

respiratory, genitourinary or major neurological (including stroke and chronic seizures) abnormalities or diseases

- is positive for hepatitis B surface antigen, hepatitis C antibodies or human immunodeficiency virus (HIV)
- has a history of cancer (malignancy)
- has a history of significant multiple and/or severe allergies, or has had an anaphylactic reaction or significant intolerance to prescription or non-prescription drugs or food, had major surgery, donated or lost 1 unit of blood within 4 weeks
- has participated in another investigational trial within 4 weeks prior to the screening visit

Exclusion Criteria (Parts II and III)

- has a history of diabetic ketoacidosis in the last 6 months.
- has had one or more severe hypoglycemic episodes associated with hypoglycemic seizures, comas or unconsciousness within 2 weeks prior to dosing
- has used systemic (intravenous, oral, inhaled) glucocorticoids
- has a history of hypersensitivity to pharmacologic insulins or to any of the inactive ingredients in regular human insulin, or to any E. coli-derived drug products.

ADVANTAGES OF SMART INSULIN^[32]

-It could result in blood glucose levels within range during the day and no more worrying about low or high blood sugar.

-It automatically responds to changing blood glucose levels.

-It eliminates multiple daily injections and meal planning.

-It can be used safely and widely and effectively by all diabetics.

- To control over the arising cases of hypoglycemia rather taking insulin directly via injections.

DISADVANTAGES OF SMART INSULIN^[32]

-It can't sense changes in glucose and release insulin nearly as fast as pancreatic beta cells do.

- Sometimes it can cause allergic reactions.

CONCLUSION

Hypoglycemia is an important limiting factor in strict glycemic management of diabetes mellitus especially in insulin controlled environment. The choice of smart insulin in an effective approach for the management of insulin responsive hypoglycemia in diabetes and

maintain good glycemic control. Smart insulin is a promising treatment option for people with diabetes that, if successful, could result in blood glucose levels remaining within range during the day, and no more worrying about low or high blood sugar. Scientists worldwide are working on administering smart insulin in different forms such as capsules and patches. But in research human testing of smart insulin is not scheduled for several years.^[33]

Smart insulin work in the body by automatically reacting to blood sugar fluctuations as the same as normal insulin producing cells in people without diabetes. It would therefore take the hassle out of consistently managing blood sugar levels and also enable tighter blood glucose control. If the smart insulin ultimately proves successful it could be revolutionary for treating diabetes.

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