

## INSULIN THERAPY AND IT'S NEW APPROACHES

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### ABSTRACT

Diabetes mellitus is a serious pathologic condition which is responsible for major healthcare problems worldwide. Insulin replacement therapy has been used in the clinical Management of diabetes mellitus for more than 84 years. Insulin has remained indispensable in management of diabetes mellitus since its discovery in 1921. Comparatively, a large percentage of world population is affected by diabetes mellitus, out of which approximately 5-10% with type 1 diabetes while the remaining 90% with type 2. The present mode of insulin administration is by the subcutaneous route through which insulin introduced into the body in a non-physiological manner having many challenges. Hence novel approaches for insulin delivery are being explored. Challenges that have adverse effect on oral route of insulin administration mainly includes rapid enzymatic degradation in the stomach, inactivation and digestion by proteolytic enzymes in the intestinal lumen and poor permeability across intestinal epithelium because of its high molecular weight and its lipophilicity. Approaches such as liposomes, micro emulsions, nano cubicle, insulin chewing gum and so forth have been prepared to ensure the oral delivery of insulin. Attempts have been made to achieve oral insulin delivery using various systems. Scientists have been able to protect the insulin delivery systems from acidic environment of the stomach and target it to the intestine. Limitations to the delivery of insulin have not resulted in fruitful results to date.

**KEYWORDS:** Diabetes mellitus, Liposome, Micro emulsions, Nano cubicle, Oral insulin delivery systems.

### INTRODUCTION

Insulin could be a hormone with intensive effects on metabolism and a number of other body systems (e.g. vascular compliance); Insulin causes most of the body's cells to require glucose from the blood (including liver, muscle and fat tissue cells), storing it as glycogen within the liver and muscle and stops use of fat as an energy source. When insulin is absent or low, glucose isn't preoccupied by most body cells and the body begins to use fat as an energy source (i.e. transfer of lipids from fat to the liver for metabolism as an energy source). As its level could be a central metabolic control mechanism, its status also used as a way signal to other body systems (such as organic compound uptake by body cells). it's several other anabolic effects throughout the body. When control of insulin levels fails, DM results.

Diabetes mellitus can be a standard disease and its complications are chargeable for excess morbidity and mortality, loss of independence, and reduced quality of life. DM can be a significant pathologic condition that's chargeable for major healthcare problems worldwide and costing billions of dollars annually. Diabetes develops thanks to a diminished production of insulin (in type 1) or resistance effects (in type 2 and

gestational).). Both lead to hyperglycaemia, which largely energy causes the acute signs of diabetes: excessive urine production, leading to compensatory thirst and increased fluid intake, blurred vision, unexplained weight loss, lethargy, and changes in energy metabolism. Monogenic e.g. MODY, constitute 1-5% of cases. Through more convenient drug delivery methods, pharmaceutical companies, regulatory bodies, and other government institutions can introduce better diabetes care and reduce costs related to diabetic complications caused by poor compliance." At this point, several methods of non-lar.

### Types of Diabetes

#### Diabetes Type 1

##### Overview

Diabetes type 1, also called insulin-dependent diabetes, is additionally a chronic condition within which the pancreas produces little or no insulin. Insulin also a hormone needed to permit sugar (glucose) to enter cells to supply energy. Various factors, including genetics and some viruses, may contribute to type 1 diabetes. Although type 1 diabetes usually appears during childhood or adolescence, it can develop in adults. Despite active research, type 1 diabetes has no

cure. Treatment focuses on managing glucose levels with insulin, diet, and lifestyle to prevent complications.

### Symptoms

Type 1 diabetes signs and symptoms can appear relatively suddenly and may include:

- Increased thirst
- Frequent urination
- Bed-wetting in children who previously didn't wet the bed during the night
- Extreme hunger
- Unintended weight loss
- Irritability and other mood changes
- Fatigue and weakness
- Blurred vision

When to work out a doctor Consult your doctor if you notice any of the above signs and symptoms in you or your child.

### Causes

The exact cause of type 1 diabetes is unknown. Usually, the body's own immune system — which normally fights harmful bacteria and viruses — mistakenly destroys the insulin-producing (islet, or islets of Langerhans) cells in the pancreas. Other possible causes include:

- Genetics
- Exposure to viruses and other environmental factors.

### The role of insulin

Once a big number of islet cells are destroyed, you'll produce little or no insulin. Insulin could be a hormone that comes from a gland situated behind and below the stomach (pancreas).

- The pancreas secretes insulin into the bloodstream.
- Insulin circulates, allowing sugar to enter your cells.
- Insulin lowers the number of sugar in your bloodstream.
- As your glucose level drops so does the secretion of insulin from your pancreas.

### The role of glucose

Glucose — a sugar — could be a main source of energy for the cells that form up muscles and other tissues.

- Glucose comes from two major sources: food and your liver.
- Sugar is absorbed into the bloodstream, where it enters cells with the assistance of insulin.
- Your liver stores glucose as glycogen.
- When your glucose levels are low, like once you haven't eaten in an exceedingly while, the liver breaks down the stored glycogen into glucose to stay your glucose levels within a traditional range.

In type 1 diabetes, there isn't any insulin to let glucose into the cells, so sugar builds up in your bloodstream. This could cause life-threatening complications.

### Risk factors

Some known risk factors for type 1 diabetes include:

- Family history. Anyone with a parent or sibling with type 1 diabetes contains a slightly increased risk of developing the condition.
- Genetics. The presence of certain genes indicates an increased risk of developing type diabetes.
- Geography. The incidence of type 1 diabetes tends to extend as you travel far away from the equator.
- Age. Although type 1 diabetes can appear at any age, it appears at two noticeable peaks. The primary peak occurs in children between 4 and seven years old, and therefore the second is in children between 10 and 14 years old.

### Complications

Over time, type 1 diabetes complications can affect major organs in your body, including heart, blood vessels, nerves, eyes, and kidneys. Maintaining a traditional glucose level can dramatically reduce the danger of the many complications. Eventually, diabetes complications could also be disabling or maybe life-threatening.

- Heart and vessel disease. Diabetes dramatically increases your risk of assorted cardiovascular problems, including arteries coronaries disease with hurting (angina), attack, stroke, narrowing of the arteries (atherosclerosis), and high-pressure level.
- Nerve damage (neuropathy). Excess sugar can injure the walls of the small blood vessels (capillaries) that nourish your nerves, especially within the legs. this could cause tingling, numbness, burning, or pain that typically begins at the ideas of the toes or fingers and gradually spreads upward. Poorly controlled glucose could cause you to eventually lose all sense of feeling within the affected limbs.

Damage to the nerves that affect the alimentary tract can cause problems with nausea, vomiting, diarrhoea, or constipation. For men, dysfunction could also be a difficulty.

1. Kidney damage (nephropathy). The kidneys contain lots of tiny vessel clusters that filter waste from your blood. Diabetes can damage this delicate filtering system. Severe damage can result in nephrosis or irreversible end-stage nephropathy, which needs dialysis or a kidney transplant.
2. Eye damage. Diabetes can damage the blood vessels of the retina (diabetic retinopathy), potentially causing blindness. Diabetes also increases the danger of other serious vision conditions, like cataracts and glaucoma.
3. Foot damage. Nerve damage within the feet or poor blood flow to the feet increases the danger of assorted foot complications. Left untreated, cuts and blisters can become serious infections that will ultimately require toe, foot, or leg amputation.

4. Skin and mouth conditions. Diabetes may leave you more at risk of infections of the skin and mouth, including bacterial and fungal infections. Gum disease and dryness are more likely.
5. Pregnancy complications. High glucose levels may be dangerous for both the mother and also the baby. The danger of miscarriage, stillbirth, and birth defects increases when diabetes isn't well-controlled. For the mother, diabetes increases the danger of diabetic ketoacidosis, diabetic eye problems (retinopathy), pregnancy-induced high-pressure level, and preeclampsia.

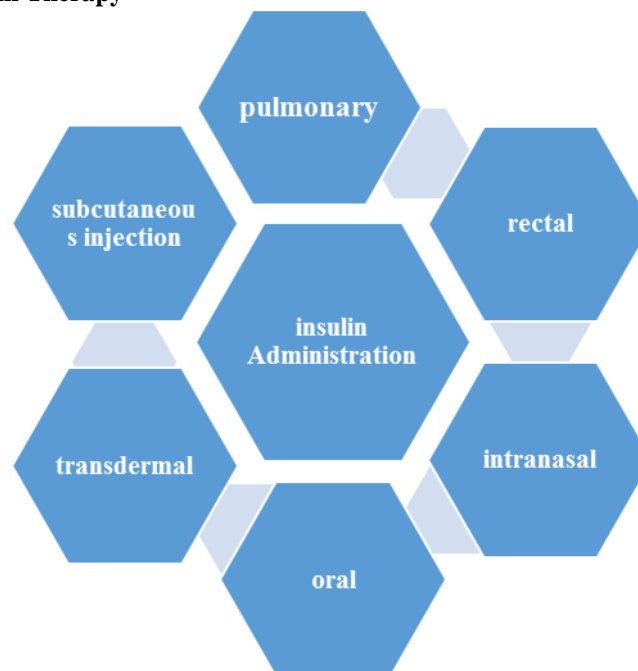
### Prevention

There's no known thanks to prevent type 1 diabetes. But researchers are performing on preventing the disease or further destruction of the islet cells in those who are newly diagnosed. Ask your doctor if you may be eligible for one in all these clinical trials, but carefully weigh the risks and benefits of any treatment available in an exceedingly trial.

A healthy lifestyle includes:

- Eating healthy foods. Choose foods lower in fat and calories and better in fibre. Specialise in fruits, vegetables, and whole grains.
- Getting active. Aim for a minimum of 30 to hr of moderate physical activity — or 15 to half-hour of vigorous aerobic activity — on most days. Take a brisk daily walk. Ride a motorbike. Swim laps. If you cannot slot in a protracted workout, spread your activity throughout the day.

### Novel Approaches In Insulin Therapy



### Approaches for Oral Insulin Delivery Systems

Generally, all peptides can't be absorbed by the GIT because of degradation by the enzymes and also less

- Losing weight. If you're overweight, losing 5 to 10 percent of your weight can reduce the danger of diabetes. to stay your weight during a healthy range, specialise in permanent changes to your eating and exercise habits. Motivate yourself by remembering the advantages of losing weight, like a healthier heart, more energy, and improved self-esteem.
- Avoiding being sedentary for long periods. Sitting still for long periods can increase your risk of type 2 diabetes. Attempt to get on my feet every half-hour and move around for a minimum of some minutes.

Sometimes medication is an option further. Metformin (Glucophage, Glumetza, others), an oral diabetes medication, may reduce the chance of type 2 diabetes. But whether or not you're taking medication, healthy lifestyle choices remain essential for preventing or managing diabetes.

### General Objectives of Diabetes Management

- To alleviate symptoms
- To correct associated health problems and to cut back morbidity, mortality and economic Costs of diabetes
- To stop the maximum amount as possible acute and long-term complications; to observe the Development of such complications and to produce timely intervention.

permeability in GIT. So, it's most vital to contemplate these parameters during the formulation of insulin oral dosage form. These following

parameters will be managed by managing the subsequent things:

1. Modification of physicochemical properties like lipophilicity and enzyme susceptibility
2. Addition of a completely unique function to macromolecules.
3. Use of improved carrier systems.

The various oral delivery systems which are attempted to deliver insulin orally either singly or in an exceedingly synergistic approach will be categorized as follows.

### Advances in Insulin Delivery

#### Needle and syringe

A common way of administering is with the needle and syringe. Syringes are available a variety of capacities (1ml, 0.5ml, 0.3ml) with different needle types. Needles have very fine points and special coating to form injections pain free.



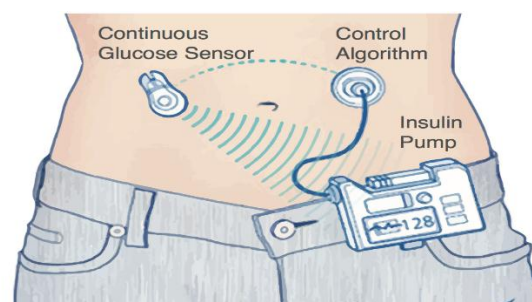
#### Insulin pens

Insulin pen injectors are a convenient and discreet way of administering insulin. They need a built-in dial that enables us to see the number of insulin to be injected, a brief needle one end and a plunger at the opposite. Insulin pens are particularly useful if we want to require premixed insulin. Insulin pens more discreet compared with vials and syringes. Insulin pens combine the insulin container and therefore the syringe into one modular unit. Insulin pens eliminate the inconvenience of carrying insulin vials and syringes and are more accurate and fewer painful. Insulin pens are user-friendly, with decreased discomfort of the injection, simple cartridge replacement, insulin-dose setting dial use and prominence of audible clicks can all affect overall dose accuracy. These are the benefits of syringes and needles. Reusable insulin pens offer a good range of benefits like their durability, eliminating the necessity for cartridge refrigeration, and providing flexibility in carrying a 3 to a five-day supply. Patient satisfaction and preference are higher with pen use compared to syringes and needles.



#### Insulin jet injectors

Insulin jet injectors offer an alternative to needles and work by sending a fine spray of insulin into the skin using a pressurized jet of air instead of a needle.



#### Insulin pump

Insulin pumps are small devices of the scale of a pager that may be attached to our belt or placed in our pocket. They're made from an insulin reservoir connected to a tube, ending in a very cannula or catheter, which is inserted under the skin of our abdomen. they will be set to deliver insulin at a slow, continuous rate throughout the day, or to release larger quantities at mealtimes or when glucose is high. The most advantage of a pump is that it closely mimics the slow but continual release of insulin by the pancreas.



#### Insulin patches

Insulin patches are currently under development, but it's difficult for insulin to be absorbed through the skin. The patch is meant to release insulin slowly and continuously. An extra dose will be administered by pulling off a tab on the patch.



### Insulin inhalers

Insulin inhalers are a new way of delivering pre-mealtime insulin. Insulin inhalers work like an asthma inhaler, but deliver dry powdered insulin into the bloodstream via the lungs. However, because the system can only be used to deliver fast-acting insulin, long-acting insulin must still be injected. Large doses are needed because only around 10 per cent of the dose actually reaches the bloodstream and that amount may vary, for instance, if you have a cold or asthma. The inhalers are not yet commercially available in Australia, but have been approved for use in the USA.



### Enzyme Inhibitors

Researchers have evaluated the use of protease inhibitors with an aim to slow the rate of Degradation of insulin. They hypothesized that the slow rate of degradation will increase the amount of insulin available for absorption. As discussed previously, enzymatic degradation of insulin is mediated by serine proteases trypsin, a chymotrypsin in, and thiol metalloproteinase IDE. Consequently, stability of insulin has been evaluated in the presence of excipients that inhibit the enzymes. Representative inhibitors of trypsin and a chymotrypsin include pancreatic inhibitor, soybean trypsin inhibitor camas at mesylate, and aprotinin. Inhibitors of insulin-degrading enzyme include phenanthroline, pchoromericuri benzoate, and bacitracin. Enzyme inhibitors have been associated with systemic intoxication if they are absorbed. If they are not absorbable, then the digestion of nutritive proteins may be disturbed.

### Penetration Enhancers

Permeation enhancers improve the absorption of proteins by increasing they're par cellular and Trans cellular transports. a rise in paracellular transport is mediated by modulating tight junctions of the cells, and a rise in transcellular transport is related to a rise within the fluidity of the semipermeable membrane. Permeation enhancers that constitute the previous category include calcium chelators, and people that constitute the latter category include surfactants. Calcium chelators act by inducing calcium depletion, thereby creating global changes within the cells, including disruption of actin filaments, disruption of adherent junctions, and diminished cell adhesion. Surfactants act by causing exfoliation of the intestinal epithelium, thus compromising its barrier functions. This raises questions about the toxicity and long-term clinical use of permeation enhancers. Most literature studies on the employment of those permeation enhancers have demonstrated that their enhancement is dose and time-dependent. Samples of permeation enhancers used include sodium laurate and acetyl alcohol, sodium chlorate, ethylenediaminetetraacetic acid (EDTA), and zonula occludes toxin (ZOT) clinical.

### Role of Polymer Systems

The use of polymer systems both alone and concurrent with absorption modifiers like enzyme inhibitors and permeation enhancers has been evaluated. Within the former system, the drug is released after uptake of the polymer system intact from the GIT. Within the latter system, the drug is released within the lumen before being absorbed.

### Oral Insulin Delivery Approaches

#### Hydrogels

These are cross-linked networks of hydrophilic polymers, which are ready to absorb large amounts of water and swell while maintaining their three-dimensional structure. Complexation hydrogels are suitable candidates for oral delivery of proteins and peptides thanks to their abilities to reply to changes in pH within the channel and supply protection to the drugs from the cruel environment of the channel.

#### Liposomes

Insulin-entrapped liposomes cause dose dependent hypoglycaemia. Researchers have prepared liposomes with varying composition by two methods: solvent

evaporation hydration and solvent spherule evaporation. Liposomes containing lecithin 100 mg, cholesterol 20 mg, insulin 150 units, and tween 1% v/v were found to be most effective.

### Erythrocyte

Human red blood cells have been developed as oral carrier systems for human insulin.

### Nanospheres

Damage, et.al, prepared insulin-loaded nanospheres by polymerization of isobutyl cyanoacrylate (IBCA) in an acidic medium these nanospheres displayed a mean size of 145 nm and an association rate of 1 U of insulin per milligram of the polymer. These nanospheres were dispersed in an oily medium (e.g. Miglitol 812) containing surfactant (e.g. Poloxamer 188 and deoxycholic acid) and evaluated for in vitro and in vivo degradation.

### Nano cubicle

A liquid formula that can be easily dispersed in water to produce particles named "Nano cubicle" was developed by Chung and co-workers Thiolate chitosan insulin tablets.

The efficacy of orally administered insulin has also been improved using thiolate chitosan. 2-Iminothiolane was covalently linked to chitosan and also the resulting chitosan-TBA (chitosan-4-tributylamine) conjugate exhibited  $453.5 \pm 64.1 \mu\text{mol}$  thiol groups per gram of polymer

### Oral insulin pill

Insulin administration in the form of a pill has always been an attractive concept in research. Due to numerous limitations of this mode of insulin administration, efficacy has been hard to demonstrate. Research has focused on overcoming these limitations by stabilizing the degradation, improving the permeability, and adding absorption promoters to protect the insulin as it passes through the stomach.

### Currents Routes for Insulin Delivery

The present mode of insulin administration is by the subcutaneous route by which insulin is presented to the body during a non-physiological manner. Insulin injected subcutaneously a minimum of twice on a daily basis has many inherent disadvantages include local pain, inconvenience of multiple injections, and occasional hypoglycemia as a results of the overdose, itching, allergy, hyperinsulinemia, and insulin clinical trials have shown that even of injectable insulin treatment, a big percentage of patients fail to realize lasting glycaemic control thanks to noncompliance. due to these problems, novel approaches for insulin delivery are being explored, including oral, transdermal, nasal, rectal, pulmonary, uterine, and ocular delivery yet as subcutaneous implants.

## Problems

### 1. Enzymatic degradation of insulin

The harsh environment of the alimentary canal (GIT) causes insulin to undergo degradation. This is often because digestive processes are designed to breakdown proteins and peptides with none discrimination. Insulin, therefore, undergoes enzymatic degradation by pepsin and pancreatic proteolytic enzymes like trypsin and  $\alpha$ -chymotrypsin. Overall, insulin is subjected to acid-catalyzed degradation within the stomach, luminal degradation within the intestine, and intracellular degradation. The cytosolic enzyme that degrades insulin is that the insulin-degrading enzyme (IDE). Insulin is however not subject to proteolytic breakdown by brush border enzymes. Insulin will be presented for absorption given that the enzyme attack is either reduced or defeated.

### 2. Intestinal transport of problems

Evidence of transport for insulin was negative. Morpho-cytochemical and biochemical evidence for insulin absorption was demonstrated in rat GIT. This result was achieved by direct instillation of an answer of insulin into various parts of the GIT, followed by visualization with gold markers and immune as say of the insulin within the blood. No evidence exists for the transport of insulin by the paracellular route. Researchers found that insulin is adsorbed to the apical cell wall and is internalized by endocytosis. It then reaches the basolateral cell wall via the endosomal pathway of small vesicles and is secretes into the interstitial space. Whether the internalization may be a result of the presence of insulin receptors on the surface of the epithelial cells is unclear. The presence of insulin receptors has been demonstrated in enterocytes on both the apical and basolateral sides.

### 3. Stability problems

The activity of proteins depends on the three-dimensional molecular structure. During dosage form development, proteins may be subject to physical and chemical degradation. Physical degradation involves modification of the native structure to a higher-order structure while chemical degradation involving bond cleavage ends up in the formation of a replacement product. Proteins must be characterized for change in conformation, size, shape, surface properties, and bioactivity upon formulation processing. Changes in conformation, size, and shape are often observed by the employment of spectrophotometric techniques, X-ray diffraction, differential scanning calorimetry, light scattering, electrophoresis, and gel filtration. The soundness of insulin preparations has been documented intimately, and research data on the solid-state stability of proteins in dosage forms are reviewed recently.

### Future Trends for Insulin Delivery Systems

Insulin sprays, either for the nose or mouth and oral insulin (insulin pills) are methods of insulin delivery that still be investigated. These options represent long-term possibilities for insulin delivery, as difficulties in obtaining adequate amounts of insulin within the bloodstream are yet to be overcome.

### Islet cell transplantation

This is a recently developed surgical treatment -called the Edmonton protocol - whereby islet cells from a donated human pancreas are injected into the liver of a recipient with type 1 diabetes. The transplanted cells begin to secrete insulin, while the recipient must take immunosuppressive medications for keeps to forestall rejection of the transplanted tissue. Clinical trials still establish the security and long-term effectiveness of this procedure as a way of supplying insulin.

### Insulin nano pump

The nano pump could be a powerful device and has many possible applications within the medical field. The primary application of the pump, introduced bibliotic, is Insulin delivery. The pump injects Insulin to the patient's body in a very constant rate, balancing the quantity of sugars in his or her blood. The pump can even administer small drug doses over long period of your time. Gene therapy two recent reports describe research into gene therapy for various aspects of diabetes. These reports are within the forefront of what is going to little doubt be ongoing and exciting research arising from the decoding of the human genome. Scientists have identified a gene called SHIP2 that appears to control insulin. Such findings make SHIP2 a possible gene therapy target for the treatment of type 2 diabetes geared toward improving the individual insulin regulation. A protein that blocks the overgrowth of blood vessels within the eye is being studied as possible gene therapy for diabetic retinopathy. A recent study showed that treatment with the protein, called pigment epithelium-derived factor, or PEDF, prevented excessive new vessel formation in an animal model of retinopathy. It should even be accustomed treat devolution.

### Marketed Product

#### Marketed Products

- **Fiasp (pro)**  
Generic name: insulin as part
- **Novo log mix 70/30 flex pen**  
Generic name: insulin as part protamine
- **Humulin R (pro)**  
Generic name: insulin regular
- **Relion**  
Generic name: insulin isophane

- **Humalog mix**

Generic name: insulin lispro

- **Apidra**

Generic name: insulin glulisine

- **Lantus**

Generic name: insulin glargine

- **Exubera**

Generic name: insulin inhalation/rapid acting

- **Levemir**

Generic name: insulin detemir

### Animal Source Of Insulin

Animal insulin was the primary style of insulin to be administered to humans to manage diabetes. Animal insulin springs from cows and pigs. Until the 1980s, animal insulin was the sole treatment for insulin-dependent diabetes. Nowadays the employment of animal insulin has largely been replaced by human insulin and human analogy insulin, however, animal insulin remains available on prescription.

### How is animal insulin produced?

As the name suggests animal insulin is taken from the pancreases of animals, usually pigs (porcine or pork insulin) and cows (bovine or beef insulin). The insulin is purified which reduces the possibility of the insulin user developing a reaction to the insulin.

### Can animal insulin be prescribed?

Animal insulin, under the name Hyperon, is being produced by Wockhardt UK and is available on prescription.

### What types of animal insulin are available?

Animal insulin's are available in 3 differing kinds of action and duration, short-acting, intermediate, and long-acting: short-acting: Hypurin Porcine Neutral, Hypurin Bovine Neutral Intermediate-acting: Hypurin Porcine Isophane, Hypurin Bovine Isophane Long-acting: Hypurin Bovine Lente, Hypurin Bovine PZI (protamine zinc insulin) Premixed: Hypurin Porcine 30/70.

### What are premixed animal insulins?

Premixed animal insulins combine a ratio of short-acting and intermediate insulin. As an example, Hypurin Porcine consists of 30% short-acting and 70% intermediate-acting insulin.

### How quickly do animal insulins act?

Short-acting animal insulin starts to act from about half-hour after injecting, with their peak action occurring between 3 and 4 hours after injecting. The duration is up to eight hours. Intermediate-acting animal insulin takes about 4 to six hours to begin acting, has its peak activity between 8 and 14 hours, and encompasses a duration of up to 24 hours.

### Benefits And Disadvantages Of Animal Insulin

There is some controversy over the advantages and drawbacks of animal insulin compared with human insulin. There's reported evidence to suggest that human insulin's may cause behavioural changes, lethargy, often feeling unwell, and loss of hypo symptoms that aren't recognized when using animal insulin. However, no research has been administrated to produce conclusive evidence to either backup or dismiss the claim. a drawback of animal insulin is within the peak activity time. The height activity period for short-acting insulin occurs up to three to 4 hours after injecting which may make the timing of meals in relevancy injections tougher than with human and particularly analogue insulin's.

### Marine Source Of Insulin

Pandey and associates found that bacteria related to the marine sponge, Aka coralliphaga, produced an outsized number of glycosidase inhibitors. Imada also reported several enzyme inhibitors and other bioactive compounds from marine actinomycetes (e.g., Streptomyces.).

Streptomyces corchorusii subsp. Rhodomarinus showed interesting  $\alpha$ -amylase inhibition, while another Streptomyces strain (Streptomyces sp.) collected at a depth of roughly 100 m from Otsu chi Bay in Iwate Prefecture, was found to provide two novel compounds, Pyro statins A and B, with specific inhibitory activity against N-acetyl-glucosaminidase.

In addition to bacteria, cyanobacteria, and actinomycetes, marine fungi have also been screened for possible anti-diabetic bioactivities. Bioassay-guided investigation of

the culture broth obtained from the marine-derived fungus *Cosmospora* sp. SF-5060, isolated from intertidal sediment collected at Gejae Island (Korea), dropped at the invention of the compound Aqua statin A with potent inhibitory activity against the enzyme PTP1B.

Microalgae have also been screened for his or her anti-diabetic activity. Microalgae are photosynthetic eukaryotes that constitute one among the main components of marine and freshwater phytoplankton. Recent advances in aquatic biotechnology have identified a series of microalgal species with promising anti-diabetes properties (Table 1). In 2010, Sun and associates evaluated the anti-glycation activities of 20 microalgae during different growth phases. The green microalgae *Chlorella* sp. and diatom *Nietzsche laevis* exhibited the very best inhibitory effects against the formation of total AGEs, especially pentosidine and N $\epsilon$ -Carboxymethyllysine. Using HPLC and gas chromatography analyses, Sun and associates revealed that carotenoids (e.g., neoxanthin, violaxanthin, antheraxanthin, and lutein) contributed to the strong antiglycation capacities in *Chlorella* sp., whereas the linoleic, arachidonic and eicosapentaenoic (EPA) fatty acids contributed to the identical bioactivity in *Nietzsche laevis*. In 2011, Sun and associates tested the anti-glycoxidative properties of various extracts (each extract had different concentrations of the carotenoid astaxanthin) of *Chlorella zofingiensis*. They showed that extracts rich in astaxanthin exhibited higher antioxidant abilities yet as stronger antiglycation capacities, suggesting that this microalga will be a beneficial food supplement and a possible preventive agent for diabetic patients.

**Table 1: Summary of tested microorganisms and possible compounds chargeable for the observed anti-diabetes properties (Advanced glycation end-products are reported with AGE, the protein tyrosine phosphatase 1B with PTP1B and not available with N.A.). Main active species names are reported in red.**

Species	Possible Compounds	Tested Activity
500 freshwater and marine cyanobacteria	N.A.	$\alpha$ -glucosidase inhibition
Bacteria	N.A.	$\alpha$ -amylase and $\alpha$ -glucosidase inhibition
Actinomycetes <i>Streptomyces corchorusii</i>	N.A.	$\alpha$ -amylase inhibition
Actinomycetes <i>Streptomyces</i> sp.	Pyrostatins A and B	N-acetyl-glucosaminidase inhibition
Fungus <i>Cosmospora</i> sp.	Aquastatin A	PTP1B Inhibition
Three clones of the microalgae <i>Chlorella pyrenoidosa</i> , <i>Chlorella protothecoides</i> , three clones of <i>Chlorella vulgaris</i> , four clones of <i>Cryptocodinium cohnii</i> , <i>Nietzsche laevis</i>	Carotenoids, linoleic acid, arachidonic acid, eicosapentaenoic acid	AGE formation inhibition
Microalgae <i>Chlorella zofingiensis</i>	Astaxanthin	AGE formation inhibition
Microalgae <i>Chlorella protothecoides</i> , <i>Chlorella zofingiensis</i> , <i>Nietzsche laevis</i>	Astaxanthin, lutein and eicosapentaenoic acid	AGE formation inhibition
Microalgae <i>Chlorella pyrenoidosa</i>	N.A.	Antioxidant potential, $\alpha$ -amylase and $\alpha$ -glucosidase inhibition
Microalgae <i>Isochrysis galbana</i> , <i>Nannochloropsis oculata</i>	Docosahexaenoic and Eicosapentaenoic acids	Clinical values and intestinal inflammation in



		rats
Microalgae <i>Attheya longicornis</i> , <i>Chaetoceros socialis</i> , <i>Chaetoceros furcellatus</i> , <i>Skeletonema marinoi</i> and <i>Porosira glacialis</i>	N.A.	PTP1B Inhibition
Several microalgae	N.A.	PTP1B Inhibition

### Marine Microorganisms With Anti-Diabetes Properties

In the last 15 years, several marine microorganisms have also been screened for possible anti-diabetes properties, e.g., macroalgae, seagrasses, sponges, corals, sea anemones, fishes, salmon skin, a shark fusion protein still as fish and shellfish wastes (Table 2).

Table 2

Anti-diabetes screening of microorganisms for bioactive compounds and their mechanisms of action (Advanced glycation end products are reported with AGE, the protein tyrosine phosphatase 1B with PTP1B and glycogen synthase kinase 3 $\beta$  with GSK-3 $\beta$ ).

Macroalgae are consumed as a readily available food especially among coastal communities for hundreds of years, when their nutritional properties and composition were still unknown. Currently, macroalgae are adopted as a part of a healthy lifestyle in several countries and are consumed entirely or are used as extracts or food additives.

Several red, brown and green macroalgae have shown anti-diabetes properties (e.g., *Rhodomela confervoides*, *Ecklonia cava*, *Palmaria*, *Alaria* and *Ascophyllum*). A bromophenol, 3,4-dibromo-5-(2-bromo-3,4-dihydroxy-6-(ethoxymethyl)benzyl)benzene-1,2-diol isolated from the red alga *Rhodomela confervoides*, and also its synthetic analogue 3,4-Dibromo-5-(2-bromo-3,4-dihydroxy-6-(isopropoxymethyl)benzyl)benzene-1,2-diol (HPN), have potent PTP1B inhibitory action in vitro. HPN also significantly decreased plasma glucose, serum triglycerides and total cholesterol during a mouse model. Two other bromophenols, 2, 4, 6-tribromophenol and a pair of, 4-dibromophenol, purified from the red alga *Grateloupia elliptica* showed inhibition against brewer's yeast  $\alpha$ -glucosidase and against *Bacillus stearothermophilus*  $\alpha$ -glucosidase. Additionally, both compounds inhibited rat-intestinal sucrase and maltase. Besides inhibition against PTP1B and  $\alpha$ -glucosidase, some bromophenols also inhibit aldose reductase, the primary enzyme of the polyol pathway chargeable for fructose formation from glucose. As an example, bromophenols from the red alga *Symphyclocladia latiuscula* have aldose reductase inhibitory activity and will be utilized in the treatment of complications of diabetes, like eye and nerve damage in type-2 diabetes patients. Phenolic extracts of the red alga *Palmaria* sp. showed inhibitory effects on  $\alpha$ -amylase activity, while, in another study, protein hydrolysates from *Palmaria palmata* showed potential anti-diabetes properties, i.e., dipeptidyl peptidase IV inhibitory activity. Other samples of seaweeds that have shown interesting

anti-diabetes properties are *Cladophora rupestris*, able to significantly inhibit  $\alpha$ -glucosidase and  $\alpha$ -amylase in vitro, *Derbesia marina* and *Symphyclocladia latiuscula*, able to inhibit PTP1B in vitro, and *Laminaria angustata* Kjellman var. *longissima* (in particular its natural sodium alginate), able to reduce blood sugar levels in Winstar rat model. Sharifuddin and colleagues reviewed beneficial roles of seaweeds for diabetes prevention and management. They highlighted the healthy nutritional composition which will benefit diabetic patients: as an example, unsaturated fatty acids, dietary fibers moreover as bioactive compounds (see review).

Fucoanthin, a characteristic carotenoid present in brown seaweeds (and also in some microalgae like diatoms), is taken into account a treasure from the ocean. D'Orazio et al. demonstrated that fucoxanthin and its metabolites prevented the event of diabetes through down-regulation of mRNA levels of inflammatory mediators, like TNF- $\alpha$  and IL-6, during a model of obese/diabetic mice. Additionally, fucoxanthin promoted the recovery of blood sugar uptake to muscle by the up-regulation of glucose transporter 4, which is additionally associated with the anti-diabetic effects. For these reasons, fucoxanthin is considered a possible anti-obesity and anti-diabetic functional food with no known side effects.

Marine sponges are considered as a superb source of marine natural products since the 1950s, with about 4851 compounds described thus far, contributing to almost 30% of all marine natural products discovered up to now. Several sponges show anti-diabetes properties, e.g., inhibition of GSK-3 $\beta$ ,  $\alpha$ -glucosidase, PTP1B, dipeptidyl peptidase IV or protection of the beta pancreatic cells. A sesquiterpene named palinurin, found within the sponge *Ircinia dendroides*, and a phenylmethylene hydantoins, from the sponge *Hemimycale Arabica*, showed GSK-3 $\beta$  inhibitory activity. In 2007, a patent was published on GSK-3 $\beta$  inhibitors from the marine sponges *Ircinia dendroides*, *Ircinia variabilis* and *Ircinia oros* collected from the sea.

Callyspongynic acid, isolated from sponge *Callyspongia truncata* inhibited  $\alpha$ -glucosidase and therefore the  $\alpha$ -galactosylceramide ( $\alpha$ -GalCer) from the sponge *Agelas mauritanus* induced protection of pancreatic  $\beta$  cells, whereas aqueous extracts of the sponge *Xetospongia muta* inhibited dipeptidyl peptidase IV activity in in vitro models. Inhibitory effects on the enzyme PTP1B are reported for a polybromodiphenyl ether from the Indonesian marine sponge *Lamellodysidea herbacea* and for the terpene Dysidine, from the sponge *Dysidea* sp that has recently entered pre-clinical trials for the

treatment of type-2 diabetes. Dysidine was found for the primary time during a sponge at Lahdu (San).

Species	Compounds/Extracts	Mechanism of Action
Red algae <i>Rhodomela confervoides</i>	3,4-dibromo-5-(2-bromo-3,4-dihydroxy-6-(ethoxymethyl) benzyl) benzene-1,2-diol	PTP1B inhibition
Red algae <i>Grateloupia elliptica</i>	2,4,6-tribromophenol and 2,4-dibromophenol	$\alpha$ -glucosidase, sucrase and maltase inhibition
Red algae <i>Symphyclocladia latiuscula</i>	Bromophenols	Aldose reductase inhibition
Red algae <i>Palmaria</i> sp.	Phenolic extracts	$\alpha$ -amylase inhibition

### Natural Remedies

Many common herbs and spices are claimed to own a glucose lowering properties that make them useful for people with or at high risk of type 2 diabetes. A number of clinical studies are allotted in recent years that show potential links between herbal therapies and improved blood sugar control, which has led to a rise in people with diabetes using these more 'natural' ingredients to assist manage their condition.

### What herbal therapies are available?

Plant-based therapies that are shown in some studies to possess anti-diabetic properties include: Aloe Vera, Bilberry extract, Bitter melon, Cinnamon, Fenugreek, Ginger, Okra while such therapies are commonly utilized in ayurvedic and oriental medicine for treating serious conditions like diabetes, many health experts within the west remain sceptical about their reported medical benefits. In fact, because certain herbs, vitamins, and supplements may interact with diabetes medications (including insulin) and increase their hypoglycaemic effects, it's often argued that the employment of natural therapies could reduce blood sugars to dangerously low levels and lift the chance of other diabetes complications.

Whatever your intended reasons for using these specific herbs, you need to always discuss your plans along with your doctor and diabetes healthcare team first to confirm they're safe for your condition and determine an acceptable dose.

### Further Herbal Therapies

The herbs and plant derivatives listed below are employed traditionally by native people within the treatment of diabetes, within the areas within which they grow. Many suffer from an inadequate cognitive content.

### Allium

Allium sativum is more commonly referred to as garlic and is believed to supply antioxidant properties and micro-circulatory effects. Although few studies have directly linked allium with insulin and blood sugar levels, results are positive. Allium may cause a discount in blood sugar, increase secretion, and slow the degradation of insulin Limited data is offered however, and further trials are needed.

### Bauhinia Forficata and Myrcia Uniflora

Bauhinia forficata grows in South American, and is employed in Brazilian herbal cures. This plant has been mentioned as 'vegetable insulin'. Myrcia uniflora is additionally widely employed in South America. Studies utilizing the herbs as tea infusions suggest that their hypoglycaemic effects are overrated.

### Coccinea Indica

Coccinea indica is also known as the 'ivy gourd' and grows wild across the Indian subcontinent. Traditionally employed in ayurvedic remedies, the herb has been found to contain insulin-mimetic properties (i.e.; it mimics the function of insulin). Significant changes in glycaemic control have been reported in studies involving coccinea indicant, and experts believe that it should be studied further.

### Ficus Carica

Ficus carican, or fig-leaf, is well-known as a diabetic remedy in Spain and South-western European, but its active component is unknown. Some studies on animals suggest that fig-leaf facilitates glucose uptake. The efficacy of the plant is, however, still yet to be validated within the treatment of diabetes.

### Ginseng

Ginseng may be a collective name for a spread of various plant species. In some studies utilizing herb, decreases in fasting blood sugar were reported. Varieties include Korean ginseng, Siberian ginseng, herb, and Japanese ginseng.

### Preventive Measures

- Cut Sugar and Refined Carbs
- From Your Diet
- Work Out Regularly
- Drink Water as Your Primary Beverage
- Lose Weight If You're Overweight or Obese
- Quit Smoking
- Follow a Very-Low-Carb Diet
- Watch Portion Sizes
- Avoid Sedentary Behaviours
- Eat a High-Fibre Diet
- Optimize Vitamin D Level

### Herbs For Rejuvenation Of Islet Cells

Regeneration therapy is additionally getting used and is certainly a worthwhile therapeutic goal with alluring possibilities to ameliorate diabetes and lessen its complications many scientists and researchers are working tirelessly to reinforce somebody's aptitude to regenerate beta cells by using gene therapy, which involves delivering to the pancreas cellular factors known to reinforce cell growth and regeneration. Though, pancreas has regenerative potential in embryonic, neonatal and adult life. However, this potential doesn't seem to assist during progression of diabetes. The diabetic environment, via hyperglycaemia, changes the lipid profile and, including glycaemic and high fat diet, precipitates the disease thus, preventing regenerative processes. Effective management of diabetes could be a pivotal global need that's yet to be established. Human pancreases conjure 65-80% of the cells within the islets that are distributed throughout the exocrine parenchyma of the gland. Every pancreatic islet contains ~1,000 endocrine cells of which 75% are insulin-producing beta-cells. Beta cells ( $\beta$  cells) are a sort of cell within the pancreas located within the islets of Langerhans. Insulin is produced by the beta-cells of the pancreatic islets in response to an increment in blood sugar level within the endoplasmic reticulum and is processed to the biologically active form inside the secretary granules. The granules are small membrane-bound secretary granules with a diameter of ~0.35  $\mu$ m cell dysfunction could be a characteristic of both type 1 and kind 2 diabetes. In type 1 diabetes, beta cells insulin-producing cells found within the pancreas are destroyed, while in type 2 diabetes, they will not produce enough insulin to. Pancreatic  $\beta$  cells are plastic cells that alter their mass in response to physiological (pregnancy) and pathophysiological (obesity or insulin resistance) states. It's been shown that  $\beta$  cell volume in obese humans without diabetes is 50% more than that in normal lean subjects and increases in islet mass occur during pregnancy in humans suggesting that human islets are capable of expanding their mass in response to metabolic demands, although much lower compared with mice. The amount of functionally intact beta cells within the islet organ is of decisive importance for the event of diabetes. The full cell mass reflects the balance between the renewal and loss of those cells. Gorry et al. suggested that the regeneration of islets of beta cells following the destruction by alloxan could also be the first reason behind the recovery of alloxan injected guinea pigs from the effect of the drug. Various plant extracts and herbal biomolecules, because of their hypoglycaemic effects, may offer similar degree of efficacy without many worrying side effects. Herbs and their bioactive compounds attenuate carbohydrate metabolism and hyperglycaemia; improve pancreatic cell function and insulin secretion even before the advent of insulin injections and other pharmaceutical preparations, people relied heavily upon herbs to treat diabetes. More than 1200 plants have been used in the treatment of diabetes mellitus According to WHO, plant-

based traditional system of medicine is still the mainstay of about 75–80% of the world population, mainly in the developing countries, for primary healthcare because of better cultural acceptability, compatibility with the human body and lesser side effects. Plants and herbs have been tested for their hypoglycaemic properties, mainly due to different concentration of polyphenols and other phytochemical and a limited number of studies have been conducted in this direction so far, and a lot more have yet to be explored and proved. This review will throw light on the beta cell regenerating capacity of some plants.

### **Azadirachta indica**

It is known as neem in many countries of the world. It is a large evergreen tree, belongs to the family Meliaceae. It is believed to have originated from Assam and Burma in South Asia and grows well in tropical and sub-tropical regions around the world with ability to withstand many adverse environmental conditions such as drought, infertile soil, stony, shallow or acidic soil *Azadirachta indica* is very efficacious in its antihyperglycaemic effect. Regeneration of pancreatic islet cells of Langerhan, was observed in rats pre-treated with alloxan. The antidiabetic property of *Azadirachta indica* extract maybe related either to the ability of the extract to stimulate insulin production or ability of extract to generate beta cells to carry out function. Beta cell regenerating potential of *Azadirachta indica* (Neem) extract in diabetic rats has been proved). Aqueous extract of *Azadirachta indica* can rebuild the destroyed beta cells and acini cells in diabetes induced rats. The pancreatic beta cells are involved in the insulin production, while acini cells produce alpha amylase enzyme which is normally channelled in to gastro intestinal tract as part of pancreatic juice for the digestion of polysaccharides in diet. Damage to acini cells results in leakage of enzymes into blood and may raise its concentration in blood serum. The potential of an *Indica* leaves extract was also observed to attenuate islet lesions associated with established diabetes

### **Pumpkin**

Pumpkin is a widely grown vegetable; belongs to family cucurbitacin and incredibly rich in beta carotene, some B vitamins, fibre. The phytochemicals found in *C. Ficifolia* may favourably affect insulin and glucose levels in laboratory diabetes. A positively effect of *C. Ficifolia* on the distribution and number of pancreatic  $\beta$  cells in the diabetic rats was also observed by many scientists. Xia and Wang divided diabetic rats and normal rats into two groups, one group (control) was fed a normal diet and the other fed the normal diet supplemented with the pumpkin extract for 30 days and they found that plasma insulin levels in the diabetic rats receiving pumpkin extract were restored to 95 percent of insulin levels in normal healthy animals. Additionally, the number of active beta cells in the treated animals was restored to 92 percent of trigonallin and nicotinic acid, caused significant reductions in blood glucose, cholesterol and

triglycerides, indicating improvement in the diabetic condition. Trigonalin is considered as beta cells rejuvenator.

#### **Curcuma longa (Turmeric)**

Curcuma is a rhizome belongs to family Zingiberaceae. Curcumin, the naturally occurring yellow pigment is the main active ingredient of *Curcuma longa*, has been shown to possess antioxidant, anti-tumor, and anti-inflammatory properties. Radicals' activity in streptozotacin induced diabetic rats. They further reported that the pancreatic islets regeneration in response to treatment of diabetic rats could be attributed to the anti-inflammatory and antioxidant effects of curcumin and thus creates a favourable and systemic environment to foster islet neogenesis. Curcumin has also been demonstrated in prevention of isolated beta cell death and dysfunction induced by STZ. It is generally accepted that beta-cells have a finite life span and dying beta-cells are continuously replaced by new ones.

#### **Gymnema sylvestre (family Asclepiadaceae)**

It is a woody climber that grows in tropical forests of the central and southern parts of India, where it has been used as a treatment for diabetes mellitus since ancient times. The administration of *Gymnema sylvestre* extract to diabetic animals not only results in improved glucose homeostasis, but also regeneration of beta cells in the pancreas. A methanol extract of *Gymnema sylvestre* leaf and callus showed anti-diabetic activities through regenerating  $\beta$ -cells. Leaf and optimum callus extracts contains gymnemic acid. The gymnemic acid of leaf and callus extracts significantly increases the regeneration of  $\beta$ -cells in treated rats, when compared with the standard diabetic rats. Aqueous extract of *G. sylvestre* has been reported to cause reversible increases in intracellular calcium and insulin secretion in mouse and human  $\beta$  cells with type 2 diabetes. Regeneration of the cells in the pancreas might raise the insulin levels.

#### **Momordica charantia L (Bitter guard)**

It is also known as bitter melon, a member of the Cucurbitaceae family is a tropical plant currently distributed across the globe. *Momordica charantia* increases the healthy regeneration of  $\beta$  cells in the pancreas, hence, increasing the secretion of insulin from the pancreas. Signs of regeneration of  $\beta$  cells, potentiating insulin secretion from surviving  $\beta$  cells of the islets of Langerhans and decrease of blood glucose have been reported following consumption of bitter guard.

#### **Pterocarpus marsupium (Roxb)**

(Indian kino tree, bijasar) belongs to the family Leguminosae. Heart wood, leaves, flowers, bark, and gum are commonly used plant parts. *Pterocarpus marsupium* is widely grown in India, Nepal, and Sri Lanka. *P. marsupium* was found to reverse the damage to the beta cells and truly repopulate the islets causing an almost complete restoration of normal insulin secretion

which has been attributed to the flavonoid content within the plant. Besides eliciting a robust antidiabetic property, *Pterocarpus marsupium* is reported to be effective against obesity, hyperlipidemia and, inflammation and also reported as, antioxidative, antitumorigenic and antiulcerative. A methanolic extract of tree when supplemented for 7 and 14 days to STZ-diabetic rats showed normalization of streptozotocin-distressed serum glucose by correcting glycosylated hemoglobin (HbA1c), serum protein, insulin, alkaline and acid phosphatase, and albumin levels.

#### **Salvadora oleoides Decne (salvadoraceae family)**

It is an oil-yielding multipurpose and medicinal tree and commonly known as meethajal in India. It can grow in arid and alkaline conditions. It has been documented that *Salvadora oleoides* feeding can increase regeneration of beta cells, insulin secretion and consequently decrease of blood glucose concentration (58). The ethanolic extract of *Salvadora oleoides* in euglycemic rats produced significant decrease in blood glucose level. The hypoglycaemic effect may be due to increased secretion of insulin from the  $\beta$  cells of the pancreas. *Stevia rebaudina* is commonly known as sweet leaf and belong to family asteraceae. The natural sweetener stevioside, promotes regeneration of pancreatic cells, a property that helps in improving insulin production. Kosta and Tiwari observed that oral administrations of *Stevia rebaudina* extract normalized the blood glucose levels and decreased the weight in STZ induced diabetic mice. They also observed significant restoration in the islet  $\beta$  cells dysfunction structure in SR treated diabetic mice respectively. The glycoside stevioside present in *Stevia rebaudina* exerts antihyperglycaemic, insulinotropic, and glucagonostatic actions in the type 2 diabetic GK rat. The natural sweeteners stevioside and steviol stimulate insulin secretion via a direct action on the  $\beta$ -cells of pancreatic islet.

#### **Syzygium cumini Jamun**

It is an evergreen tropical tree within the phanerogam family Myrtaceae. *Syzygium cumini* is native to the Indian Subcontinent and adjoining regions of geographic region. The bark, the fruit, the seed likewise because the leaves are utilized within the treatment of insulin dependent DM (IDDM). *Syzygium cumini* can stimulate cell regeneration by the proliferation of its precursor cells within the epithelial duct.

#### **Genes Involved Rejuvenation of Islet Cells Dysfunctional pancreas in diabetes**

Insulin, a key polypeptide hormone secreted by the pancreas, targets several tissues for the employment of glucose and thus maintains the glucose homeostasis. Type 2 diabetes (T2DM) develops from a mix of genetic and purchased factors (such as changes in metabolic homeostasis) that impair  $\beta$ -cell function on one side, and tissue insulin sensitivity on the other<sup>2, 3</sup>. Normally,  $\beta$ -cell mass can adapt to changes in metabolic

homeostasis. Recurrence of those changes in metabolism creates a stress on pancreas often predating the on-set of T2DM by a few years. This pancreatic stress causes  $\beta$ -cell mass expansion, through enhanced proliferation and neogenesis. The progression from this stress condition to a state of diabetes is inevitably related to a decrease within the  $\beta$ -cell mass. This  $\beta$ -cell loss arises thanks to a rise in  $\beta$ -cell apoptosis, which clearly outweighs replication and neogenesis. The war against diabetes through the event of recent drugs is an ongoing continuous process<sup>5</sup>. With the technological advancement, efforts are being made to rejuvenate the pancreatic cells or create artificial pancreas. Pancreatic rejuvenation can happen either thanks to proliferation of existing  $\beta$ -cells or differentiation of progenitor cells to  $\beta$ -cells<sup>6</sup> (figure), or thanks to decrease in  $\beta$ -cell apoptosis.

### $\beta$ -Cell proliferation

Islets regeneration refers to a rise in  $\beta$ -cell mass by proliferation and replication of existing islet cells. Several mouse studies here shown that  $\beta$ -cells don't proliferate, however, lineage tracing studies have confirmed that human  $\beta$ -cells proliferate and

provides rise to a population of progenitor/stem cell. Various genes and transcription factors are involved during this process viz. Reg (Regenerating islets derived proteins), Sox9, Hnf-6, NeuroD1, Neurogenin-3 and Netrin-1 (Table I). Besides these genes, certain peptides or their analogues like glucagon like peptide-1/exendin-4 are involved in islet regeneration. These observations are confirmed by using dipeptidyl peptidase (DPP) IV inhibitor sitagliptin in mice. So far, five REG proteins are reported in humans that belong to Reg gene family. a number of the members of this family are implicated in  $\beta$ -cell replication and/or neogenesis as shown in *in vivo* studies using transgenic and knockout mice. These also preserve the  $\beta$ -cell mass in autoimmune type 1 diabetes. This Reg family of genes are expressed in both young and old mice that were subjected to partial pancreatectomy<sup>18</sup>. In isolated rat islets, Reg1 mRNA levels were significantly increased by glucose, amino acids, foetal serum or specific growth factors like insulin, somatotropin and platelet-derived growth factors (PDGF). PDGF receptor signaling controls age-dependent  $\beta$ -cell proliferation in mouse and human pancreatic islet cells.

**Table I. Genes involved in beta cell proliferation.**

Genes proteins	Functions
Reg gene family (RegI, II, III $\alpha$ , III $\beta$ , III $\gamma$ )	Increase islets cell size and density, Regeneration of pancreas
Sox9	Stimulates proliferation and survival of pluripotent progenitors.
Hnf-6	Essential for maintenance of Ngn3 expression.
Neurog3 (Ngn-3) Or Neurogenin-3	Initiates endocrine differentiation and activates NeuroD1.
NeuroD1/BETA-2	It is required for normal pancreatic development and glucose homeostasis.
Netrin-1	Involves in islets regeneration.

### Transcription factors in $\beta$ -cell proliferation

Certain transcription factors (Sox9, Hnf-6, Ngn-3 and NeuroD1) are found to be involved within the proliferation of  $\beta$ -cells. SOX9 is that the first specific marker and maintenance factor of multi-potential progenitors during pancreatic organogenesis. SOX9, within the embryonic pancreas stimulates proliferation and prevents apoptosis of pluripotent progenitor cells. It controls pancreatic progenitor cell maintenance by modulating Notch signal transduction. The phenotypic alterations within the Sox9-deficient pancreas shows a striking resemblance to the pancreatic defects related to mutations in components of the Notch signalling pathway, thus establishing a possible link between Sox9 and therefore the notch signal transduction pathway for somatic cell maintenance. The hepatocyte nuclear factor 6 (Hnf-6), homeodomain-containing transcription factor, is a vital regulator of endocrine development. HNF6 is expressed in early pancreatogenesis all told endodermally derived cells, but isn't detected in differentiated endocrine cells at late-gestation. Hnf-6 null mice embryos showed impaired endocrine differentiation and perturbed duct

morphogenesis during embryogenesis. Additionally to defects in endocrine development, Hnf-6 null embryos showed defects in duct development. Loss of Hnf-6 from Ngn-3 expressing cells didn't affect  $\beta$ -cell function or glucose homeostasis suggesting that Hnf-6 is dispensable for later events of endocrine differentiation. These data confirm that HNF6 has both early and late functions within the developing pancreas and is crucial for maintenance of Ngn-3 expression and proper channel morphology<sup>32</sup>. NeuroD1, a downstream target of Ngn-3, carries on the endocrine differentiation programme initiated by Ngn3 and participates within maintenance of the differentiated phenotype of the mature islet cells<sup>33</sup>. During pancreatic endocrine development, Ngn-3 acts early to see endocrine cell fate, while NeuroD1 directs endocrine cell differentiation. At early stage of life, mice lacking a functional NeuroD1 (also called as BETA2) gene exhibit a striking reduction within the number of insulin-producing  $\beta$ -cells and did not develop mature islets with a marked hyperglycaemia. Attempts to rescue the diabetic phenotype by administration of insulin were unsuccessful, suggesting that the mutant animals were

unable to reply to insulin, became insulin resistant, or perhaps contained additional defects. Thus BETA-2 is required for the expansion of the pancreatic  $\beta$ -cells population, still as other islet cell types which are involved within the development of endocrine cells into islets of Langerhans. Netrins are laminin-like diffusible chemotactic proteins involved in pancreatic morphogenesis and play a task within the regulation of duct cell and foetal islet cell migration. In adult rat pancreas, Netrin-1 mRNA was practically undetectable. After duct ligation, its expression was very low within the head a part of the pancreas whereas it absolutely was strongly upregulated within the tail part at 3rd, 5th and 7th day of post-ligation with the utmost expression on day 536. Netrin-1 mRNA was found to be expressed by islet cells and exocrine cells with ductal characteristics. These observations suggest that Netrin-1 plays a task in pancreatic morphogenesis, both prenatally and within the regenerating adult rat pancreas.

#### Tran's differentiation of pancreas

Islet neogenesis specifically refers to a rise in  $\beta$ -cell mass via Tran's differentiation of adult pancreatic stem cells, putatively found within the ductal epithelium or acinar

tissue. Trans-differentiation involves within the conversion of alpha or delta cells of the pancreas into insulin producing  $\beta$ -cells. Various genes/proteins contribute to the present process. These include INGAP, Gastrin, MafA, Pdx-1, Foxa2, Nkx2.2, Nkx6.1, Pax4, etc.

#### Inhibition of $\beta$ -cell apoptosis

Under normal circumstances, apoptosis is extremely regulated to keep up normal physiological function of the cells. In diabetes, during excess stress, the pancreatic cells not only undergo apoptosis but also become necrotic and are unable to secrete insulin. A study conducted by Butler ET al<sup>61</sup> indicated that increased apoptosis instead of decreased neogenesis/proliferation can be the most mechanism resulting in reduced  $\beta$ -cell mass in T2DM. Thus, decrease within the rate of apoptosis itself, may increase the  $\beta$ -cell mass via proliferation. Several genes/proteins are involved in pancreatic apoptosis and their functions are summarized in Table II. Perforin (pore forming protein) may be a cytolytic protein, initiating apoptosis by inducing minimal semipermeable membrane damage while effectively releasing.

**Table II. Genes involved in inhibition of beta cell apoptosis.**

Genes/proteins	Functions
<i>Pdx-1</i> Granzymes	Possesses anti-apoptotic activity that helps facilitate the maintenance of $\beta$ -cell mass. A serine protease, that activates Bid (a pro-apoptotic factor) essential for death-receptor induced apoptosis of islets.
Caspase-3	Principle executioner of apoptosis.
<i>BIRC5 (Survivin)</i>	Bifunctional role, controlling both proliferation and inhibition of apoptosis
<i>Bcl-2</i>	Survival genes that suppresses apoptosis.
C-Myc	Induces extensive apoptosis in pancreatic $\beta$ -cells.
Thioredoxin-interacting protein (TXNIP)	It is a pro-apoptotic factor that plays an essential role in glucose toxicity-induced $\beta$ -cell apoptosis.
Huntingtin-interacting protein 14 (HIP-14)	Prevents apoptosis and regulates insulin secretion in $\beta$ -cells.
Bace-2	Negative regulator of $\beta$ -cell mass.

#### CONCLUSION

Diabetes is now become very common disease which is spreading worldwide rapidly due to poor life style. Insulin is one of the best therapies for treatment of diabetes mellitus and in above research study we learn about novel approaches and future trends of insulin therapy and herbal and marine sources of insulin successfully. It is important to have knowledge about insulin therapy. Therefore, above review study on 'NOVEL APPROACHES OF INSULIN THERAPY' carried out.

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