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NOVEL THERAPEUTIC APPROACHES TOWARDS TYPE 1 DIABETES MELLITUS

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ABSTRACT
Diabetes Mellitus is one of the most common endocrine diseases and prevalence of this continually rising globally. There are 65.1 million people living with diabetes in india, leads the world with largest number no of diabetes patient earning the title "Diabetes Capital of the World". Type 1 diabetes is less common than type 2, Type 1 diabetes is also known as insulin dependent diabetes mellitus (IDDM), and which is characterized by autoimmune destruction of cellular-mediated pancreatic beta cells results into total loss of insulin secretion. Recent studies have emphasizes the importance of strict glycemic control to prevent the various complications associated with diabetes mellitus. There have been ongoing improvements providing several advantages over the Conventional insulin vials and syringe. In recent years, insulin pens and insulin pumps have become increasingly user-friendly. In the view of the drawbacks of exogenous insulin therapy, a strong focus has been placed on discovery of functional cure for T1DM by beta cell replacement, Islet cell transplantation and pancreas transplantation. This all are minimally invasive cellular replacement therapy and that was developed to normalize glucose metabolism while avoiding the hypoglycemic risk of intensified exogenous insulin.

KEYWORDS: Type 1 diabetes; Insulin therapy; Insulin delivery systems; Beta cell replacement; Islet transplantation; Pancreas transplantation.

INTRODUCTION
Diabetes mellitus is a most common endocrine disorder resulting from a defect in insulin secretion, insulin action, or both.[1] Diabetes generally characterized by insulin insufficiency, negative nitrogen balance, glycosouria, and sometimes ketonaemia.[2] The prevalence of diabetes is rapidly rising globally. According to World Health Organisation (WHO) and current International Diabetes Federation Reports, worldwide prevalence of diabetes in 2013 is 382 million people expected to increase 592 million by 2035. There are 65.1 million people living with diabetes in India, leads the world with largest number no of diabetes patient earning the title "Diabetes Capital of the World".[1,3] Several different observational based studies occurred in last decades found that the prevalence of diabetes is high in urban area and is categorized under life style disorder.[3]

The word diabetes is derived from the Greek word 'diabanein' means to pass through, as excessive glucose available in urine term as 'Sweet Urine' in ancient, which leads to an increase urine production is an major symptom of diabetes. On the basis of physiology diabetes is divided into two types; Type 1 and Type 2, most people with diabetes have type 2. Type 1 diabetes is also known as insulin dependent diabetes mellitus (IDDM), often starts in childhood. But, it can start in adulthood.[4]

Epidemiology
The exact number of type 1 diabetic individuals around the world is not known but the accountability of T1D patient in India increased day by day having an incidence of 10.6 cases per year per 100,000 observed in recent studies. Currently the prevalence of diabetes in US is around 1,100,000 individuals with 35,000 new cases diagnosed each year. T1d is one of the most common endocrine and metabolic conditions among children's and adult.[5] According to national diabetes fact sheet 2011, more than 1 million people in North America is affecting by T1D. It is a second most common chronic autoimmune disease in children's and around 78,000 youth are diagnosed worldwide with type 1 diabetes annually.[6] Quality of life is hampering by various chronic complications and represents a million of annual burden on the heath care system. About 10% of T1D patient are prone to disabling and life-threatening episodes due to blood glucose imbalance. T1D generated in adults called as latent autoimmune diabetes in adults (LADA) and also referred as juvenile onset diabetes.[7]

Pathophysiology

Type 1 diabetes is characterized by an autoimmune destruction of cellular-mediated pancreatic beta cells results into total loss of insulin secretion.[8] Type 1 diabetic patient has an absolute insulin deficiency and no longer produces insulin, ultimately required insulin for survival. Cellular destruction of beta cell can vary from patient to patient.[9] Autoimmune destruction includes islet cell antibody, antibodies to glutamic acid decarboxylase, autoantibodies to insulin and antibodies to tyrosine phosphate. Beta cell destruction of pancreatic islets is prone to ketoacidosis.[10]

Pathogenesis of T1D includes genetic factors and various environmental factors including toxins, food constituents, pathogens, viral infections and drugs. Human leukocytes antigen contributes 30%-50% of genetic risk factors and it increases frequency of arising T1D.[11] Deficiency of insulin arises due to reduction in beta cell mass that leads to a failure of glucose homeostasis, as glucose can not enter into the cell and remain in the blood stream, Results into increasing blood glucose level.[12] Glycerol is converted into glucose in cell to meet cellular energy needs as well as fat is broken down through lipolysis results in releasing glycerol and free fatty acids. In type 1 diabetic patient's pancreas has no longer to produces insulin to meet body demand and it absolutely depends on exogenous insulin for survival.[13]

Autoantibodies for islet cell are detected in T1D patient, and they were first discovered by incubating sera with frozen pancreas collected from T1D patient.[14] Recent advances shows that antibodies specific for beta cell antigens increased frequently in T1D patient. Insulin Harmon release from beta cells which comprise 28%-75% of pancreatic islets, shows rapid response to alteration in blood glucose level for maintain glycemic control.[15]

Secretion of insulin is closely related to plasma glucose level and occurs mainly by two ways, basal secretion and meal related secretion. In the basal state, adequate amount of insulin is secreted from pancreatic islets of beta cells to utilize glucose produced by liver.[16] Meal leads to a sharp increasing in insulin secretion results plasma glucose level increases to maximum in 30-60minutes and turn back to basal rate within 2 hrs. American diabetes association currently classifies T1D in to 1A (immune mediated) and 1B (non-immune mediated) diabetes. About 21 million people are estimated to be affected with diabetes in US, out of this 10% of patient have 1Ai.e immune mediated T1D.[17]

Symptoms[18]

T1D generally been diagnosed on the basis of catabolic symptoms like:

- Polyuria,
- Polydispesia
- Marked hyperglycemia.
- Fatigue
- Cramps
- Constipation
- Blurred vision
- Candidiasis
- Polyphagia
- Extreme thirst and hunger
- Weight loss
- More skin and vaginal infections

Complications

Diabetes is a lifelong disorder and major cause of mortality and morbidity worldwide, which is markedly affected by day to day variations in diet, exercise, infection and stress Diabetes posse's great challenge to the world's health care system. Diabetes associated with number of long term micro and macrovascular complications like retinopathy, neuropathy and peripheral vascular insufficiencies.[19] The characterise symptoms of diabetes hyperglycemia, glycosouria, polyuria, polydypsia, polyphagia, unusual thirst, extreme weakness, extreme hunger, tiredness and unexpected weight loss. Main causes of diabetes include obesity, lack of physical work, variations in diet and life style modification.[20]

Novel Approaches

Prevalence of diabetes increases rapidly all over the world**,** needs to implement preventive measures to reduce the burden of diabetes on social economy as well as to save the life of diabetic patients by improving their life especially in case of children. The main aim of the treatment of T1D should be to achieve strict glycemic control to minimize various complications arises due to abnormal blood glucose level. Various Indian and US associations contributes their efforts in developing new strategies against diabetes.[21]

Insulin Therapy

Insulin is a Harmon secret from pancreatic duct of beta cells is necessary for carbohydrate, fat and protein metabolism. Insulin therapy is important to achieve good glycemic control to reduce long term microvasucular complications which are shown by diabetes control and complication trail (DCCT).[22] Food is converted into sugar and insulin allows sugar to pass from blood into cells for the body's energy need. Body fails to turn sugar into energy without insulin exogenous source of insulin is used to overcome the body's demand of diabetic patient as he is unable to produce insulin due to destruction of beta cells in the pancreas in T1D patient and its survival.[23] Exogenous insulin should have similar pharmacokinetic properties as the insulin secrets from pancreas of normal individual. Isolation of insulin by Banting, Best, Collip and Macleod was done in 1991 and its first clinical use in the treatment of T1D patient in 1992, this event is recorded as most dramatic event in the treatment of history of diabetes,[24,25] It gave hope to thousands of diabetes patients, prolongs their life span and allowed them to lead highly improved quality of life.

Subcutaneous injection has been only rout of delivery of insulin in diabetic patient since last 75 years. Recently numerous attempts have been made as alternative routes for systemic insulin administration,[26] Use of syringes for delivery of insulin by subcutaneous route is the most common method of choice that is easy to read and operate. Intravenous administration of insulin was initially introduced in 1974. Insulin absorption from the subcutaneous tissue can changes, depending upon the site of injection, exercise, dose, timing, and depth used results into variability in insulin action on glycemic control,[27] Commercially insulin is derived from animal sources like bovine & porcine, pork pancreas or manufactured chemically identical to human insulin by recombinant DNA technology and this were main types of insulin's available from last 80 years.[28]

New promising preparations of Insulin is available includes, short-, intermediate-, long-acting and ultra fast-acting analogue. That may be injected separately or mixed in the same syringe.[29]

Rapid-acting insulin analogues (insulin lispro, insulin aspart) have ability to absorb quickly when injected subcutaneously due to its non aggregating property. In comparison with regular insulin they have an onset of action with higher peak. Rapid- acting insulin analogues should be injected 5 to 15 minutes before a meal as if they can administered after meal not show effect on glycemic control. They have peak activity in 30-90 minutes and effectively last two to four hour. Intermediate acting insulin's consist of regular insulin modified by adding zinc (lente) or neutral protomine Hagedom (NPH) that allows it to be absorb in the body more slowly reaching peak plasma concentration approximately in 6 to 7 hours with duration of action of 12-14 hours and concentration usually need to be given twice in a day to provide cover for the entire 24 hours. Recently, production of lente and ultralente insulin was discontinued because of their decreasing market shares. Regular insulin released slowly from the subcutaneous tissue as it forms hexamer in solution. Therefore it has relatively delayed peak and long duration of action. Human long-acting insulin (ultra-lente, insulin glargine) has duration of action of approximately up to 18-20 hours, but its Absorption is highly variable. Novel ultra-long acting basal insulin i.e Insulin degludec is almost identical in structure except for the last amino acid deleted from the B-chain to human insulin. After subcutaneous injection it forms soluble multihexamers, resulting in an ultra-long action with half life more than 24 hours.[28,29,30]

Newer insulin's including long acting basal insulin analogue called insulin degludec and ultra fast acting human insulin Linjeta™.

Insulin Degludec

It is novel ultra long acting basal insulin is an almost identical in structure to human insulin. After subcutaneous injection it forms soluble multihexamers. Results into ultra long action profile having half life more than 24 h. It was studied that it has comparable response as insulin deludec as an ultra-long acting profile by using injections three times a week. Most of the exploratory studies in T1D have shown insulin degludec is to be with reduced rates of hypoglyacemia and comparable glyacemic control to long acting insulin glargine., once daily administration of Insulin degludec with mealtime insulin aspart is basal-bolus therapy for T1D.[31]

VIAject™

It is recombinant human insulin having ultra fast onset of action and was reported to have less intrasubject variability. Various pharmacokinetic and pharmacodyanemic studies shows that the onset of action of VIAject is much greater than that of insulin lispro and human soluble insulin.[32]

Insulin Delivery Devices

Insulin is delivered most commonly by subcutaneous injections using insulin syringes**.** The main drawback of this method is due to invasive nature of insulin; new ways of insulin administration are developed such as infusion pumps, and sharp needles, supersonic injectors and pens, to overcome this problem.[33]

Insulin Pump

Insulin pump is a medical device and was developed to avoid repetitive subcutaneous injections. Low dose of continuous subcutaneous infusion (CSII) was first given in 1978.CSII referees insulin pump system as it simulate the physiology of insulin secretion except bypassing the liver.[34] For some patients, insulin pumps are a vital alternative to multiple daily injections. Insulin pump was available since the late 1970s but was widely used in pediatric patients mainly after year 2000.various Factors, such as increased sensitivity to insulin, irregular lifestyle, smaller size, and the need for smaller doses of insulin make insulin pump therapy a useful treatment option in very young children. An estimated 300,000 people use insulin pumps worldwide. Recent physician survey research has shown that significantly fewer pumps are used in Europe than in other countries; only 1.3 per cent of type 1 diabetics in the UK compared to 20 per cent in the US [33, 35]. With the use of insulin pump risk of diabetic eye disease decreased by up to 76 per cent, kidney complications were reduced by up to 56 per cent and nerve disease was reduced by up to 60 per cent. Thus Pumps are more precise compared to insulin syringes or pens. Precise insulin doses can be helpful in the treatment of insulin sensitive patients, such as those with type 1 diabetes.[36]

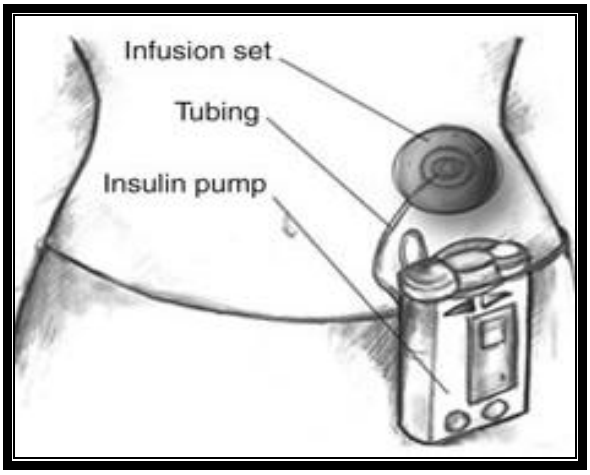

Fig. 1: Insulin Pump Systeam.

Insulin pump device is designed to provide a continuous supply of insulin and it can be individualized and adjusted as per the needs of the patient. The pump is a small mechanical battery driven device that worn outside the body, which continuously delivers insulin directly into the body through a very thin, soft, flexible tube or needle inserted under the skin of abdomen or leg. The pumps weigh about 400 g and their size is approximately that of a pager .A tiny electric motor controlled by a microprocessor slowly drives a plunger into an insulin reservoir holding 2–3ml of insulin. Infusion sets are designed to be inserted at a 90° or a 30-45° angle to the surface of the skin. Most people use lispro, aspart, or glulisine insulin in the pump reservoir. These fast analogs are used for both basal and prandial insulin need.[37] The commonly available insulin pumps are Disetronic Medical Systems Inc (StPaul, Minnesota); MiniMed Technologies (Sylmar, California); and Animas (Frasier, Pennsylvania). Patients with pumps often monitor their glucose six to eight times a day. The insulin pump is an open-loop system that has two concurrent modes of insulin delivery and it can be finely tailored to achieve tight glycemic control in the fed and fasting states: they are; continuously through basal infusion and intermittently through bolus insulin delivery.[34]

Advantages of insulin pump

Insulin pump is an advantageous treatment for diabetic patient as it allows people with diabetes to adjust insulin intake easily to keep glucose levels within a near-normal range. A pump can help patients avoid hyperglycemia, which can cause long-term complications and lead to ketoacidosis (causing coma or death if left untreated), and hypoglycemia. Insulin pump is closely related to healthy pancreas by continuous delivery of insulin.[38]

LIMITATIONS

Basic problem with insulin pumps is the potential alteration of the administered insulin by motion, contact with pump surfaces and changes in temperature. Insulin forms aggregated macromolecules that have reduced insulin activity and tend to precipitate in the catheter, causing obstruction.[39]

Insulin PEN

Insulin pens are pen shaped devices that contains an insulin cartridge or reservoir for insulin and are intended for single person use. These are designed to permit self-injection. Insulin pens were introduced in the 1985s, and now are used for some inpatient s.c. injections in many hospitals. It has become extremely popular throughout the world and in some countries, near 70% to 90% of all insulin is delivered by pen devices [40]. The devices are intended for s.c. insulin administration by a health care professional or self-administration by a patient. Insulin pens are designed to be used multiple times, using a new needle for each injection, for a single person. Insulin pens must never be used for more than one person. The pen may be disposable with a prefilled reservoir or reusable with a replaceable prefilled cartridge.[41] Disposable pens contain multiple doses and are discarded when empty or when the maximum time recommended by the manufacturer after the first use has elapsed. A new needle should be used for each injection, blood Regurgitation into the insulin cartridge can occur after injection which creates a risk of blood borne pathogen transmission if the pen is used for more than one person, even when the needle is changed.[35]

The choice of selecting insulin pen will be determine by the type of insulin. The basic steps of using insulin pen are: insulin must be at room temperature. If it's pre-mixed insulin, gently roll the insulin pen ten times to resuspend the insulin. Then attach the needle to the pen. Select the specific dose by dialing after that hold the pen against the skin. By depressing the button, inject the dose in the skin by holding it in position for at least 10 seconds. After that carefully remove the needle from injection and replace it with the cover of pen.[39,42]

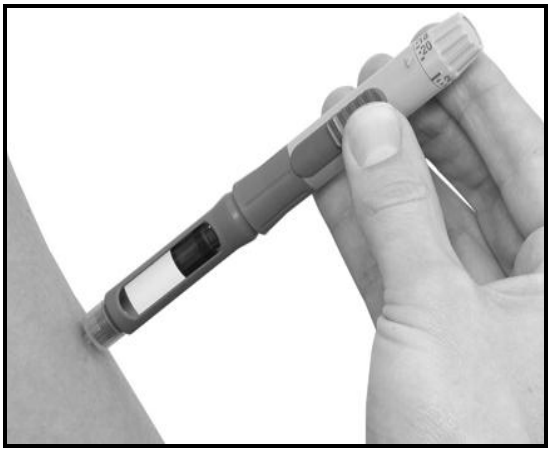

Fig. 2: Insulin pen.

Table 1: Advantages of insulin pen devices over conventional insulin syringes

- More convenient delivery of insulin
- Better quality of life
- More accurate dosing

- More discreet
- More flexibility
- Less pain because of small gauge needles are used.
- Simpler for specific population to use.

LIMITATIONS OF INSULIN PENS

With some advantages insulin pen has some limitations as the maximum dose of most insulin pens is 60 to 80 units with compare to syringe they are 100 units. Patients who use single injection given by insulin pen cannot mix their own insulin formulations [42].

Beta Cell Replacement and Regeneration

During the progression of diabetes, Beta cells undergo many complex changes and these are beyond the scope of this review. Beta cells are able to store and secrete insulin in an efficient manner to keep glucose levels in the normal range in presence of meals and exercise.[43] In type 1 diabetes autoimmune destruction of beta cell can occur ultimately results in to markedly decrease in insulin production leads to various complications to overcome this problem new strategy has been developed.[44] For long term treatment of T1D Traditional stem cell therapy is not likely to be effective. β-cell mass and function could be preserved and/or restored in at least three different ways: replacing damaged β-cells by direct stem cell differentiation, modifying the pancreatic microenvironment allowing endogenous β-cell regeneration and abrogating the autoimmune response to β-cells.[45]

Replenishment of lost beta cells or their product insulin is the key of treating T1D. Beta cells do not undergo proliferation frequently as they have long life span. Proliferation of beta cells is one of the dynamic processes which involve the intrinsic pathways which is very difficult to understood.[46] It was recently reviewed that only a small group of beta cells will regain the potential to proliferate under particular conditions Beta cell replacement therapy is a process that involves implantation of cells having ability to secret insulin a protective barrier into the body. From the last two decades, much effort has been made into increasing beta cell regeneration so that the new insulin producing cells can replenish the lost beta cells.[47] Human embryonic stem cells become fully mature beta cells and there is expectation that it can be similarly directed to induce pluripotent stem (iPS) cells. IPS cells can also be generated from diabetic patients to allow studies of the pathogenesis and genomics of the disease. In the same way mesenchymal stem cells and Human cord blood-derived stem cells (CB-SCs) modulate in vitro immune activity as it can be used to improve markers and alter immune function in non obese diabetic mice (NOD) of T1D. CB-SCs have been shown to modulate the immune function of derived pancreatic islet b cell-specific pathogenic T cell clones in co-culture of T1D patient [48]. Some of the animal model studies suggest that CB-Sc treatment may allow the pancreas to generate the sufficient population of beta cell without stem cell transplantation. For in vivo replacement there is some alternative approaches of beta cells include finding ways to enhance the replication of existing beta cells and stimulating neogenesis. Beta cells can replicate through out the life but at slow rate and the beta cell mass normally fluctuates in response to environmental and physiological changes. This replication can be stimulate with the help of two category of factors or hormone, first category include cyclin D1/D2, glucagon-like peptide (GLP-1), cyclin dependent kinase 4 (CDK4), gastrin, keratinocyte, betacellulin (BTC) and long lasting homolog. The second category includes other mitogenic factors such as hepatocyte growth factor (HGF) and vascular endothelial growth factor (VEGF) and. Also the artificial increase in beta cell mass with replication can be stimulated by pregnency and diabetogenic stimuli, such as glucose and free fatty acids.[49]

Development of pancreatic beta-cell lines has progressed slowly in recent years from rodent or human origin. Current experiments for ex vivo expansion of beta cells and in vitro differentiation of embryonic and adult stem cells into insulin producing beta-cell phenotypes led to promising results.[50] Advantage of encapsulated beta cell is that they can maintain the blood glucose level and secrete the correct amount of insulin in diabetic patient as well as their barrier can protect them from being destroy by the autoimmune system. It also helps to prevent lifelong administration of powerful and toxic immunosuppressive drug.[51] Human ES cells are derived from the innermost cell layer of the blast cyst. These cells are then give rise to all differentiated cells in the adult through a series of cell fate choices which involve self-renewal and differentiation. Therefore they can theoretically be differentiated into pancreatic beta-cells as well as any other definitive cell type.[52]

Another approach to produce more β-cells has involved differentiating Mesenchymal Stem Cells (MSCs) into functional β-cells, seems to be a promising way for overcoming autoimmunity in T1D, because of their Transdifferentiation towards various cell lines. Powerful immunomodulatory effects of the MSCs to treat graft-versus-host diseases have been demonstrated by recent clinical trials. MSCs are known to differentiate into osteocyte, chondrocyte, and adipocyte natively; MSCs could transdifferentiate insulin-producing cells under certain circumstances.[53]

A simple protocol can induce murine bone marrow-derived MSC differentiation into insulin-secreting cells and this differentiated cells contained insulin-secretory granules, after glucose stimulation they secreted mature insulin. This kind of cells when transplanted into diabetic mice results into reduction of blood glucose levels [54]. They are also effective in inhibiting proliferation of CD4 and CD8 T cell. Differentiated cells have expressed a broad pancreatic β-cell genetic profile levels when transplanted to streptozotocin (STZ)-induced diabetic mice which released high levels of insulin in response to

glucose stimulation in vitro and reduced blood glucose level.[55]

Mesenchymal stem cells produce two types of soluble factors with distinct functions. Various immunosuppressive factors such as Indoleamine 2, 3-dioxygenase (IDO) and Prostaglandin E (PGE)-2 prevented the autoimmune destruction of pancreatic beta cells by reversing the activation of hyper-reactive T cells, while the trophic factors such as HGF and VEGF created a Suitable environment for proliferation beta cell [56]. Several studies have shown that pancreatic ductal cell differentiation and existing β-cells' self-duplication are the main mechanisms by which pancreatic β-cells could be replenished in humans and animals. MSCs secrete various bioactive growth factors which help to provide support for injured tissue to develop the microenvironment to induced local precursor proliferation and differentiation with improving damage tissue irrigation and prevent parenchymal cell apoptosis. MSCs also have immunosuppressive and anti-inflammatory properties as they secrete anti-inflammatory cytokines and form cell to cell inhibitory interactions; which could promote immunological tolerance.[57]

Islet Cell Transplantation

Islet cell transplantation is an attractive option of cell based therapy in T1D patient. Islets are nothing but the tiny clusters of endocrine cells scattered throughout the pancreas that includes insulin producing beta cells and often called as pancreatic islets.[57] A strong focus has been placed on discovery of function lure for T1D by endocrine cell replacement to avoid high risk of hypoglycaemic events associated with whole organ pancreas transplantation. Precutaneous islet transplantation dose not required a large abdominal incision and critical surgery; hence it is a less invasive cellular replacement therapy than others.[58]

The largest data pool on ICT and summarized results of islet allograft transplant performed at three European centre, two Australian centers and 32 north American medical centers between 1999 and 2008, repressed by the national institute of diabetes, digestive and kidney disease.[59] This report encompassed 828 islet infusions in 412 allograft recipient. ICT is considered as suitable therapy for T1D and procedure has been performed since the publication of the Edmonton Protocol in 2000 that use a low dose immunosuppressive therapy without glucocorticoid drug, as well as improved islet preparation, and infuse a minimum islet mass of 9,000 islets-equivalents per kilogram (IEq/kg) of body weight and improves results for maintenance of normal blood glucose level as well as insulin independence.[60]

It is a complex procedure that consists of pancreas procurement and preservation, islet cell processing, islet infusion and an immunosuppressive regimen after transplantation. This procedure often used especially after accumulating evidence in rodents that viable and physiologically functioning islets cells could be extracted from the donor pancreas, it may be purified from the exocrine component of the pancreas, and infused in the portal vein of diabetes induced rat, achieving stable euglycemia.[61] Also in the 1970s, Evidence of the effectiveness of islet transplantation was accrued when pilot centers worldwide introduced the clinical practice of islet auto transplantation. Islet cell transplantation may be performed alone, in combination with renal transplantation, or following kidney transplantation. In general, pancreatic islet cells may begin to function immediately after transplantation.[62]

The genesis of ICT may be traced after Clinical experience with human islet transplantation began in the late 1970s and early 1980. ICT need for life-long immunosuppressive therapy for stem cell derived islets. There are two ways for pancreatic IT; first is allo-transplantation and second is auto transplantation and need very potent immunosuppressive regimen to prevent immune-mediated rejection, as islets are targeted for both alloimmune and auto immune responses.[63] According to USFDA allogenic islet cell transplantation is somatic cell therapy and requires premarket approval as well as Autologous islet transplantation is proposed in conjunction with pancreatectomy for patients with chronic pancreatitis. The outcome of islet auto transplantation depends on the yield of islets which is obtained at the end of the process of digesting, excising, and purifying the pancreas. University of Alberta group published that 7 out of 7 diabetic patients became insulin independent after allogeneic cell transplantation in 2000. And the protocol of this publication was made and called as Edmonton protocol. After publication of this protocol no. of clinical allogeneic ICT has increased.[64]

Transplant is complex procedure which firstly involves procurement and preservation of pancreas, as doner pancreata are carefully procured with maintaining surface temperature of pancreas and then preserve in solution such as two-layer oxygenated perfluorocarbons solution. Islets are isolated and purified from explanted pancreas by enzymatic digestion with mechanical agitation, followed purification on density gradient. Isolation of islets from Islet culture takes sufficient time for extensive viability and functionality of islets prior to transplantation.[65] Islet cell product obtain from culture are injected intraportally or intraperitoneally in to hepatic portal vein under local anesthesia by a manual syringe with minor surgical risk as well as using minimally invasive radiology (ultrasound and fluoroscopic) techniques after elimination of most of the acinar tissue.[66]

The advantage of islet cell transplantation deliver from simple route of administration that does not require major surgical procedures also it can be performed on an outpatient basis under local anesthesia, under the supervision of a trained interventional radiologist, and

can be repeated several times without major discomfort to the patient. The problem of immune rejection seen with islet transplant can also be overcome by genetic manipulation of the islets in vitro to resist immune attack before encapsulation, either by reducing potential islet immunogens, or by expressing immunomodulators.[67]

ICT is also associated with some clinically relevant risks, which includes; intraperitoneal or liver subcapsular bleeding occurring with an incidence as high as 13%. Partial portal vein thrombosis complications obtained in about 5% IST along with complete portal venous thrombosis.[58,65]

Pancreas Transplantation

The pancreas is an organ located in the abdomen behind the bowel; consist of 2 different types of tissue having different functions. About 2-3 % of the Pancreas consists of endocrine tissue which is cluster of cells secrets special substance called as hormones into the blood and insulin is one of the most important hormones among them that regulate the absorption of sugar (glucose) into cells.[68] Most of the pancreas is a gland that secrets special juice rich in digestive enzymes that helps in digestion of food we eat. Type 1 diabetes results when pancreas can't make enough insulin, causing sugar to rise to dangerous levels. Pancreas transplant is a widely viable option with the purposes of to produce complete insulin independence, resolve the various diabetes related complications and improve the quality of life hence it requires a dedicated and experienced team.[69]

Type 1diabetic patient shows lack of insulin producing ability due to self destruction of insulin producing islets. Such a patient can be given further source of islets by pancreas transplantation. It is life-enhancing, but not life-saving procedure. At 16 December 1996, first pancreas was transplanted and after that approximately 12,000 transplants have been performed worldwide.[64] Initial result of this experiment had showed very poor graft survival rates; less than 5% of grafts survived after six months. According to the international pancreas transplant registry (IPTR), approximately 3500 patients worldwide have received pancreas transplant over the last 4 yeas among them 2500 patients are received simultaneous kidney-pancreas transplants. In 2009, more than 23,000 patients in the United States received a pancreas transplant.[70]

A pancreas transplant is a surgical procedure to place a healthy pancreas from a donor into a patient whose pancreas no longer functions properly. Exocrine pancreas transplantation is a standard treatment of choice in diabetic patients which are complicated with end stage renal disease. Pancreas transplant is often done in conjugation with kidney transplant.[17] There is several type of pancreas transplants o the basis of diabetic condition; some people may have pancreas transplant alone (PTA), those patients suffering from diabetic neuropathy will often receive simultaneous pancreas-kidney (SPK) transplant, similar procedure include pancreas after kidney (PAK) and kidney after pancreas (KAP) transplant. Pancreas transplantation required lifelong Immunosuppression to prevent alloimmune rejection of the organ or graft. Immunosuppression protocols had to be adjusted in such a way to prevent graft rejection while not being so strong as to damage the beta cells.[66] From early year of pancreas transplantation, only azathioprine and prednisone were used but such regimen was not adequate for prevention of immune rejection to overcome this problem Minnesota antilymphocyte globulin added in treatment with triple therapy by cyclosporine, azathioprine and prednisone for induction or maintenance of Immunosuppression. The elimination of steroids was one of the important stepping stone in anti-rejection therapy. For maintenance Immunosuppression, perhaps the best current regimen is prednisolone free or rapidly steroid tapering regimens which consist of tacrolimus and Mycophenolate mofetil combinations.[71]

Future Directions in Type 1 Diabetes Mellitus

Due to a shortage of available donor pancreas, alternative sources of islets are of keen interest. Engineered insulinoma cell may become a viable alternative for transplantation. Other potential alternative sources of islets are being explored and these include

Xenogenic islet cells (humanized pig islet cells)

Expansion and transdifferentiation of pancreatic duct cells

Fetal pancreatic stem cells and beta cell precursors

Engineering other Cells to Produce Insulin (beta cell Copy Cats)

In last few years a new era has dawned, exploring the ability to engineer non-islet cells to produce insulin through forced expression of the insulin gene. So far duodenal K cells, hepatocytes and pituitary cells have been successfully transfected. Most of the time glucose was able to cause release of insulin in these systems. However, insulin delivery should be modulated in response to changing periods of food intake (feeding/fasting), and exercise. Unless such Regulation is ensured, these approaches will not likely be applicable to humans. The fact that experiments have been successful in generating surrogate beta cells is a major step forward (123-125). The pancreatic and duodenal home box gene 1 (PDX-1) encodes protein that is central to pancreatic development and insulin gene expression. Recombinant transfer of PDX-1 to the livers of mice led to an increase in immunoreactive insulin levels by reprogramming hepatocytes causing them to acquire a beta cell phenotype.[17]

Immunotherapy in T1d

In T1D immune system attacks insulin-producing pancreatic beta cells and the immunopreventation results in to either reserve the autoimmune attack or prevent the appearance of autoimmunity in healthy individuals it also aims to preserve the beta cell mass and halt beta cell

destruction. There are some future directions in TD immunotherapy [62].

Vaccination with high-affinity binding lingads
Delivery of multiple epitopes from multiple antigens
Monoclonal antibodies to recognize Autoantigen
The use of non-depleting Anti-CD8 and Anti-CD4 Antibodies

CONCLUSION

Diabetes is one of the most common metabolic endocrine disorders worldwide. Recent developments in insulin therapy have potential for minimizing some of the negative aspects of current methods. Insulin pens and pumps offer many benefits to people with diabetes who use insulin. As diabetes is a major health problem there have been extraordinary recent advances in our understanding and the remarkable development of scientific methods in cell biology and immunotherapy. Beta cell regeneration is a current aspect in treatment of T1D with great advances. Due to shortage of available donor pancreas, alternative source of islets are of keen interest along with artificial pancreas. In this review, we have described some of these advances and future directions.

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