International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 9(6): November-December 2019

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences

Review Article……!!!

Received: 30-10-2019; Revised: 21-11-2019; Accepted: 23-11-2019

VARIOUS THERAPIES USED IN DIABETES MELLITUS

Paragini D. Jain*, Ajinkya P. Joshi, Harshal L. Tare

TSPM'S Trimurti Institute of Pharmacy, Jalgaon, Maharashtra, India.

Keywords:

Diabetes mellitus, Gene Therapy, Blood glucose levels

For Correspondence:

Paragini D. Jain

TSPM'S Trimurti Institute of Pharmacy, Jalgaon, Maharashtra, India

E-mail:

paraginijain@gmail.com

ABSTRACT

Diabetes mellitus is a widespread disease prevalence and incidence of which increases worldwide. The introduction of insulin therapy represented a major breakthrough in type 1 diabetes; New therapeutic approaches, such as whole pancreas transplant or pancreatic islet transplant, stem cell, gene therapy and islets encapsulation, Incretin mimetics, Amylin analogues, Nanotechnology approach, Statins Therapy, Gene Therapy, Herbal Therapy, Nutrition Therapy, Peroxisome proliferator activated receptors. This Review focuses and discusses on the new approaches available for the treatment of high blood glucose levels.

INTRODUCTION :

Diabetes mellitus (DM), commonly known as diabetes, is a group of metabolic disorders characterized by a high blood sugar level over a prolonged period.

Diabetes occurs in one of the following situations:

The pancreas (an organ behind your stomach) produces little insulin or no insulin at all. Insulin is a naturally occurring hormone, produced by the beta cells of the pancreas, which helps the body use sugar for energy. Or The pancreas makes insulin, but the insulin made does not work as it should. This condition is called insulin resistance. Type 2 diabetes mellitus (T2DM) is a disease that affects more than 400 million people around the world. In 2040, there will be more than 640 million people with diabetes worldwide .

A major concern with the diabetes epidemic is the anticipated increase in mortality and morbidity related to the complications of the disease. This article reviews current and future treatments for patients with T2DM, its use in clinical practice and in special situations such as kidney failure and elderly patient, with an emphasis on agents introduced within the last decade. The aim of this review is to perform an update on the benefits and limitations of different drugs, both current and future, for the treatment of T2DM[1].

THERAPIES FOR DIABETES :

1. Pancreas transplant or Pancreatic islet transplant :

The American College of Surgeons/National Institutes of Health Organ Transplant Registry recorded 57 pancreas transplant in 55 diabeti patients from December 17, 1966 until the registry closed on June 30, 1977 . Only two patients were independent of insulin for more than one year, one a patient of Lillehei et with a pancreaticoduodenal graft, and one a patient of Gliedman etal. with a segmental graft; both died with functioning.

Patient, Selection, Immunosuppressive Treatment and Timing of Transplantation Most recipients of pancreas transplants have had far ad-vanced complications of diabetes - at a time when the risks of immunosuppression and transplantation are high. Ideally, pancreas transplantation should be performed early in the course of diabetes in order to prevent the secondary complications in the first place. Because of the uncertainty of success or failure, just the opposite has been the case. The results of pancreas transplantation could undoubtedly be improved by earlier transplantation, but not all diabetic individuals will develop secondary complications. For those patients, who, at the moment, are free of complicable the risks associated with immunosuppression may exceed the risks of secondary complications developing in the future. Even in the situation where there is abundant experience and the technical problems are largely solved, such as kidney

transplantation, conventional immunosup-pression (combination of azathioprine and prednisone with or without temporary administration of heterologous anti-lymphocyte globulin preparations) has a relatively high failure rate; the two year graft survival rate for renal allo-grafts from cadaver donors is approximately 50% [2]. Early results suggest that a new immunosuppressive drug, cyclosporin A, may reduce the rejection rate of organ allografts,but this treatment still produces generalized immunosuppression. Until specific immuno-suppression, i.e., tolerance induction, is possible in humans, pancreas transplantation will be restricted to patients who have already demonstrated their propensity to develop secondary complications or who are extremely labile in their exogenous insulin requirements.

Techniques of Clinical Pancreas Transplantation :

Pancreaticoduodenal Transplantation. The technique of pancreaticoduodenal transplantation has been described in detail . The pancreas, duodenum, an aortic patch encompassing the coeliac axis and superior mesenteric artery, and the portal vein are removed en bloc from the donor and vascular anastomoses are made to the iliac vessels of the recipient. In the pioneering series of Lillehei et al. , the duodenum was brought out as a cutaneous duodenostomy in four patients; in eight patients the duodenum was anastomosed to a Roux-en-Y jejunal loop; in one instance the papilla of Vater was used for anastomosis Bewick performed internal drainage to a Roux-en-Y jejunal loop in 3 and external drainage in 4 of 7 cases of pancreaticoduodenal transplantation. The 3 pancreaticoduodenal grafts of Connolly et al. the 2 of Merkel et al. , the 2 of Largiader , and the 1 of Alexander were all drained into a jejunal loop.

Segmental Pancreas Transplantation.

The first pancreas transplant performed was segmental , and all groups currently performing pancreas transplants use the segmental technique. With this approach the body and tail (approximately 50%) of the pancreas is removed and the splenic artery (or celiac axis) and splenic vein (or portal vein) are used for vascular anastomoses to the iliac vessels of the recipient . Either a retroperitoneal or intraperitoneal approach can be used to expose the vessels of the recipient; most transplants teams have used the former approach. Details of removal of segmental pancreas grafts from cadaver donors before or after circulatory rest have been well described. The segmental approach allows use of living related donors, since more than half of the pancreas can be removed from a normal individual without serious metabolic consequences, and the spleen will survive on the short gastric vessel. Several methods have been used to drain or suppress secretions of segmental pancreas grafts.[3]

A deliberate cutaneous fistula was created in two cases following pancreas transplantation to the neck . There were numerous complications associated with this unusual approach and the grafts were removed at 6 and 120 days respectively.

Duct ligation has been used in seven cases. Three of the grafts failed for purely technical reasons the others were rejected and were removed between 12 and 59 days after transplantation, either with or without persistent technical problems. Duct ligation does not necessarily reduce the volume of pancreatic secretions, since cut lymphatics can act as accessary ducts. All seven of the grafts were placed in the retroperitoneal area. Fluid accumulation around the pancreas or pancreatic fistulas develop.

Pancreatic graft ductoureterostomy has been performed in eight patients. In one who was nonuraemic the duct of the graft was anastomosed to the side of the reci-pient's ureter, and the ipsilateral kidney was not removed; the pancreas was rejected within a few days so the long term effect on the kidney could not be determined. In the series of Gliedman et al. the recipients' ipsilat-eral kidneys were removed and end-to-side three of seven grafts failed because of vascular complications and three others were rejected within three months; the other graft functioned and the ureteral anastomosis remained patent until the recipient died at 49 months. Since anastomosis to the ureter may require sacrifice of the kidney, this technique is probably applicable only to uraemic patients.[4]

2. Stem cell Therpy :

Embryonic stem cells (ESC) can be differentiated into insulin-producing cells by manipulating culture conditions. In-vitro differentiation of mouse ESC can generate embryoid bodies, which, after selection for nestinexpressing ESC, were stimulated to differentiate towards a cell-like phenotype. The addition of phosphoinositide kinase inhibitors promoted differentiation of larger numbers of ESC towards functional cells. Variations in ESC-culture conditions generate cells with properties of cells.3–5 With manipulation of culture conditions anduse of pax4 or pdx-1, transcription factors associated with-cell lineage6,7 yield promising results.

Stem cells derived from haemopoietic organs :Bone marrow harbours cells that can become parenchymal cells after entering the liver, intestine, skin, lung, skeletal muscle, heart muscle, and central nervous system,16 in rodent models and in human recipients of marrow or organ transplantation.17,18 In rodents, haemo-poietic organs harbour cells that can also differentiate into functional pancreatic endocrine cells. 1–2 months after bone-marrow transplantation, donor-derived cells are found in pancreatic islets of recipient mice.19 These cells express insulin and genetic markers of cells. In culture, the cells secrete insulin in response to glucose, and show

intracellular calcium fluctuations similar to normal - cells. However, only about 1–3% of the islet cells originate from the transplanted marrow . A marrow-derived cell-type with pluri- potential capacity to transdifferentiate into various pheno- types has been described.25 This or a similar cell type might be able to differentiate into pancreatic cells.[5]

Stem cells in liver and pancreas: n isolated pancreatic tissue, pancreas-resident progenitor cells might give rise to endocrine islet cells. Human and rodent pancreatic-duct cells,33,34 islet-derived cells,35,36 and exocrine tissue37 contain cells that can differentiate towards a pancreatic endocrine phenotype. These tissues,cultured and differentiated in vitro, have been transplanted and can reverse diabetes mellitus in rodents. Rodent-liver stem cells and human fetal-liver cells have been differentiated in vitro into insulin-secreting cells by culture methods and/or introduction of - -cell-specific genes. When transplanted, these cells reverse diabetes mellitus in rodents.39 Cells within liver that can differ- entiate into insulin-secreting cells after introduction of ß-cell-specific genes have also been seen in vivo after adenoviral gene-delivery into rodents that have been rescued from diabetes for long periods.

3. Incretim Mimetics:

Type 2 diabetes mellitus (T2DM) is a huge health problem globally. It affects nearly 25.8 million people in the United States.1 Over 35% of US adults 20 years or older (or 79 million Americans) are currently classified as having prediabetes, which places them at greater risk for developing diabetes. Patients diagnosed with diabetes have a much higher risk of developing heart disease, hypertension, stroke, and kidney disease. No optimal medication exists currently for the treatment of T2DM. The American Diabetes Association (ADA) recommends metformin as the preferred initial pharmacologic agent for the treatment of this disease. However, if high doses of noninsulin monotherapy are not successful at achieving a patient's goal glycated hemoglobin (A1C), then a second oral agent, a glucagonlike peptide-1 (GLP-1) receptor agonist or insulin should be added. Many patients will eventually need to have insulin added to their medication regimen. Numerous side effects exist with all medications used for the treatment of T2DM, including hypoglycemia and weight gain, as well as difficulty tolerating therapy.

Incretin Effect :

To understand how the medications affecting the incretin system work, it is necessary to first understand the incretin effect. When nondiabetic patients are given oral glucose, their insulin levels increase as much as 3 times greater than when the same patients are given IV glucose to match the plasma glucose levels seen with the oral dose. This is what is referred to as the incretin effect.

GLP-1 analogues:

At this time there are no long term studies with GLP-1 analogues to assess weight loss over long periods of time, cardiovascular outcomes, or safety. The first product, exenatide, was not FDA-approved until 2005. For these reasons, they are not considered first-line therapy. Currently, there are two GLP-1 analogues on the market, exenatide and liraglutide.[6]

Herbal Therapy :

In the last few years there has been an exponential growth in the field of herbal medicine and these drugs are gaining popularity both in developing and developed countries because of their natural origin and less side effects. Many traditional medicines in use are derived from medicinal plants, minerals and organic matter. A number of medicinal plants, traditionally used for over 1000 years named rasayana are present in herbal preparations of Indian traditional health care systems. In Indian systems of medicine most practitioners formulate and dispense their own recipes, Indian Medicinal Plants with Antidiabetic and Related Beneficial Effects.

There are many herbal remedies suggested for diabetes and diabetic complications.

***Acacia arabica*: (Babhul):**

It is found all over India mainly in the wild habitat. The plant extract acts as an antidiabetic agent by acting as secretagouge to release insulin. It induces hypoglycemia in control rats but not in alloxanized animals. Powdered seeds of Acacia arabica when administered (2,3 and 4 g/kg body weight) to normal rabbits induced hypoglycemic effect by initiating release of insulin from pancreatic beta cells.

***Allium cepa*: (onion)**

Various ether soluble fractions as well as insoluble fractions of dried onion powder show anti-hyperglycemic activity in diabetic rabbits. Allium cepa is also known to have antioxidant and hypolipidaemic activity. Administration of a sulfur containing amino acid from Allium cepa, S-methyl cysteine sulphoxide (SMCS) (200 mg/kg for 45 days) to alloxan induced diabetic rats significantly controlled blood glucose as well as lipids in serum and tissues and normalized the activities of liver hexokinase, glucose 6-phosphatase and HMG Co A reductase [18, 19]. When diabetic patients were given single oral dose of 50 g of onion juice, it significantly controlled post-prandial glucose levels[7] .

Aloe vera and Aloe barbadensis

Aloe, a popular houseplant, has a long history as a multipurpose folk remedy. The plant can be separated into two basic products: gel and latex. Aloe vera gel is the leaf pulp or mucilage, aloe latex, commonly referred to as “aloe juice,” is a bitter yellow exudate from the pericyclic tubules

just beneath the outer skin of the leaves. Extracts of aloe gum effectively increases glucose tolerance in both normal and diabetic rats . Treatment of chronic but not single dose of exudates of Aloe barbadensis leaves showed hypoglycemic effect in alloxanized diabetic rats. Single as well as chronic doses of bitter principle of the same plant also showed hypoglycemic effect in diabetic rats. This action of Aloe vera and its bitter principle is through stimulation of synthesis and/or release of insulin from pancreatic beta cells. This plant also has an anti-inflammatory activity in a dose dependent manner and improves wound healing in diabetic mice.[8]

***Azadirachta indica*: (Neem)**

Hydroalcoholic extracts of this plant showed anti-hyperglycemic activity in streptozotocin treated rats and this effect is because of increase in glucose uptake and glycogen deposition in isolated rat hemidiaphragm. Apart from having anti-diabetic activity, this plant also has anti-bacterial, antimalarial, antifertility, hepatoprotective and antioxidant effects .

Nutrition therapy

Medical nutrition therapy (MNT) is important in preventing diabetes, managing existing diabetes, and preventing, or at least slowing, the rate of development of diabetes complications. It is, therefore, important at all levels of diabetes prevention. MNT is also an integral component of diabetes self-management education (or training). This position statement provides evidence-based recommendations and interventions for diabetes MNT. The previous position statement with accompanying technical review was published in 2002 and modified slightly in 2004 . This statement updates previous position statements, focuses on key references published since the year 2000, and uses grading according to the level of evidence available based on the American Diabetes Association evidence-grading system. Since overweight and obesity are closely linked to diabetes, particular attention is paid to this area of MNT.

The goal of these recommendations is to make people with diabetes and health care providers aware of beneficial nutrition interventions. This requires the use of the best available scientific evidence while taking into account treatment goals, strategies to attain such goals, and changes individuals with diabetes are willing and able to make. Achieving nutrition-related goals requires a coordinated team effort that includes the person with diabetes and involves him or her in the decision-making process. It is recommended that a registered dietitian, knowledgeable and skilled in MNT, be the team member who plays the leading role in providing nutrition care. However, it is important that all team members, including physicians and nurses, be knowledgeable about MNT and support its implementation.[9]

Advantages

The benefits of pancreas transplantation are clear: improved quality of life, prevention of recurrent diabetic nephropathy, freedom from exogenous insulin with euglycemia and normalization of HbA1C, less stringent dietary restrictions, less frequent blood glucose monitoring and stabilization of or improvement in secondary complications. The major disadvantages to the patient are the operative risk, the need for chronic immunosuppression, and the inherent side effects of chronic immunosuppression .

CONCLUSION

In the 21st century is found to be the most challenging health problem health problem through out the global. Through diabetes is serious health problem it can be controlled due to availability of the medication and advance approaches for the prevention and treatment of diabetes is still going on. For the management of type 1 diabetes patients need to administration insulin about 3-4 times per day throughout there lifetimes and after the blood sugar level should be monitored regularly in ordered to avoid serious complication like retinopathy and cardiovascular disease.

REFERENCES

1. ."About diabetes". World Health Organization. Archived from the original on 31 March 2014. Retrieved 4 April 2014.
2. American Diabetes Association. Diabetes Basics. Accessed 11/5/2018.
3. The National Institute of Diabetes and Digestive and Kidney Diseases. What is Diabetes? Accessed 11/5/2018.
4. American Diabetes Association. A1C and eAG. Accessed 11/5/2018.
5. World Health Organisation. Diabetes Fact Sheet Nº 312. November 2008.
6. Surabhi kavya reddy et al. Evaluation of Anti-diabetic and Anti-lipidimic Potential of Kalongi Sugar Powder Water Extract in STZ Induced Diabetic Rats. Int J Pharm Pharm Sci. 2013;5:94-96.
7. Montiel-Tellez, et al. Ec.+62G>A and g.-420C>G RETNPolymorphisms and the Risk of Developing Type 2Diabetes and Obesity: Original Research on a Mexican Population and Meta-analysis. Endocrinol Metab Syndr. 2016;5:228.
8. Sharma JN. The Role of Bradykinin System in Type 2 Diabetes. J Diabetes Metab. 2016;7:658.
9. Wong SN, et al. A Review on the Clinical Impact of Point of Care Capillary Blood Glucose Measurement in Diabetes Patients in Public Primary Care Clinics in Hong Kong. J Clin Diabetes Pract. 2016;1:105.

10. Huttada L, et al. Enhancing the Activity of Peroxisome Proliferator- Activated Receptor's (PPAR) Activity through Natural Ligand Binding in Diabetes: Substantial Computational Approach. Nat Prod Chem Res.2016;4:213.
11. Cusick M, Meleth AD, Agrón E, et al. Associations of mortality and diabetes complications in patients with type 1 and type 2 diabetes. Diabetes Care. 2005;28:617–25. doi: 10.2337/diacare.28.3.617. [PubMed] [CrossRef] [Google Scholar]
12. Mohan V, Pradeepa R. Mortality in diabetes mellitus: revisiting the data from a developing region of the world. Postgrad. Med. J. 2009;85:225–6. doi: 10.1136/pgmj.2008.075606.
13. International Diabetes Foundation. Diabetes: facts and figures [accessed 2016 Mar 22] Available from: http://www.idf.org/wdd15-guide/facts-and-figures.html.
14. Tufveson G. An experience of pancreas and islet transplantation in patients with end stage renal failure due to diabetes type I. Curr Opin Organ Transplant. 2009;14:95–102. doi: 10.1097/MOT.0b013e328320a8ff.