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REVIEW ARTICLE **OPEN ACCESS**

Artificial pancreas: Substitute to defective pancreas

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ABSTRACT
Insulin hormone is synthesized by the islets of Langerhans in the pancreas which ultimately regulates the blood glucose levels in the blood. Therefore, failure in function of insulin leads to diabetes. This review recapitulates methods of stem cell technologies to produce artificial pancreas which could replace the defective and damaged pancreas. The current review discusses the problems that obstruct the pathway of artificial pancreas engineering and the possible therapies for development of an artificial pancreas
Keywords:*Artificial pancreas, Artificial pancreas tissue engineering.*

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INTRODUCTION

During the recent past years it has been observed that there are various diseases that are taking place due to lifestyle imbalances. Various diseases include hypertension, cardiovascular diseases, diabetes, etc. In this course, diet and physical work play an important role in maintaining both physical and mental state of the body[1]. For many centuries, communicable diseases are thought to be responsible for killing many populations. But taking non-communicable diseases into account, it is estimated that by the year 2020, out of ten deaths in the developing nations, seven will be due to the non –communicable diseases[2].Because diabetes is occurring at an alarming rates, it has become a major reason of concern. In the recent past, no. of patients with diabetes has risen to 422 million and has caused 1.6 million deaths as per the reports issued by World Health Organisation (WHO)[3]. With time, diabetes is considered to damage the body organs and can be a major cause for kidney failures, heart attacks, strokes, blindness and lower limb amputations. Diabetes is a chronic disease that is caused when islets cells of Langerhans in pancreas are unable to produce insulin(which is required to transform glucose into energy) to meet the body's requirement and is generally of three types[4]:

a) Type I diabetes mellitus(TIDM)
b) Type II diabetes mellitus(T2DM)
c) Gestational diabetes mellitus(GDM)

Type I diabetes is caused due to autoimmune destruction of insulin in pancreas, Type II diabetes is caused when the body uses insulin inefficiently that it produces, while gestational diabetes causes high glucose level in blood during pregnancy and is complicated to both the mother and the child[5].

Type I(T1DM) , a juvenile onset disease can occur at any age but mostly to children and infants. TIDM is characterized by destruction of islet beta cells of pancreas which causes deficiency in insulin production. By the means autoimuune destruction it is meant that body's defense system attacks the cells that produces insulin[6]. For the initiation of autoimmunity, TIDM requires various genetic factors such as human leukocytes, antigen class II genes and various environmental factors. Cellular and humoral immunity where $CD8^+$ T lymphocytes kill the beta cells causes the pathogenesis of T1DM[7]. People with Type I diabetes do not produce enough insulin to meet the requirement of body and therefore an exogenous insertion of insulin is required to mimic insulin levels during mealtimes. Patients with TIDM were used to treat with immunosuppressant agents in the past but that does not meet the requirement of beta cells which left only replacement therapy as option. Symptoms of T1DM includes: abnormal thirst and dry mouth, sudden weight loss, constant hunger, frequent urination, etc[8]. Management of Type 1

includes: daily insulin treatment, regular blood glucose monitoring , and healthy lifesyles. Plans including twice-daily insulin, or basal bolus regime.

Type II(T2DM) , an adult onset disease is most commonly found in older adults, but recently seen increasingly among children, younger adults. This type of diabetes accounts for 90% of diabetes[9].It is generally marked by insulin resistance where body does not responds to insulin. Since insulin is not able to work properly glucose levels keeps on increasing resulting in more insulin. Patients with Type II sometimes can even exhaust the pancreas which results in very less and less insulin and sometimes often leads to HYPERGLYCEMIA(high blood sugars level). Risks factors involved in Type II include overweight, unhealthy diet , overweight, etc. Oral medication are prescribed to such patients[10].

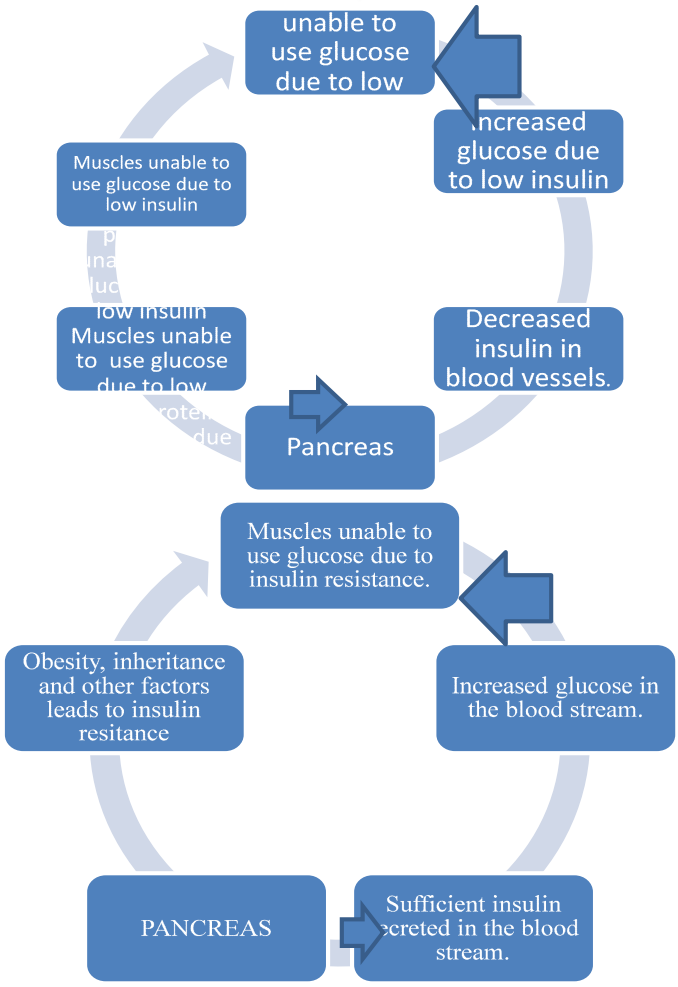


Fig: Type I and Type II diabetes mellitus (T1DM & T2DM).

BASIC INTRODUCTION TO TISSUE ENGINEERING

Tissue Engineering is an associative field that involves the principles of both life sciences and medicine and basically has three components : cells, scaffolds and signals[11].

The basic requirements of Tissue Engineering is the replacement and regeneration of damaged tissues, or organs. Or simply it is the construction of living components in the laboratory which can be further used for the replacement of damaged tissues[12].

a) Cells: The most common type of cells that are used is Stem Cell which includes both embryonic stem cells as well as adult stem cells(Mesenchymal stem cell).Stem cells are the cells that includes various types and are capable of giving rise to any types of cells in the body.
b) Scaffolds: These provides cells a structure where they interact with each other , without them cells are free floating and neither connect or interact. Scaffolds provides a medium to form a structure similar to damaged tissue which is to be replaced. Once the structure is formed scaffolds denatures.An ideal scaffolds should be: Biocompatible and Biodegradable and proper Mechanical Properties.
c) Signals: Signals can be thought as any Growth factors , or physically can be a bioreactor

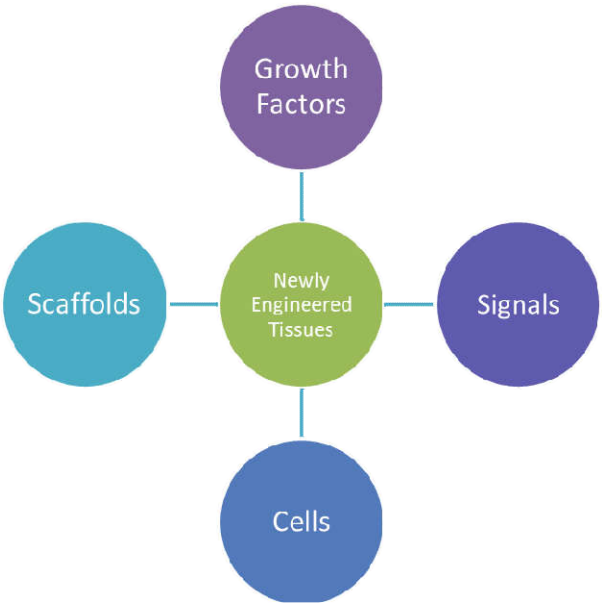
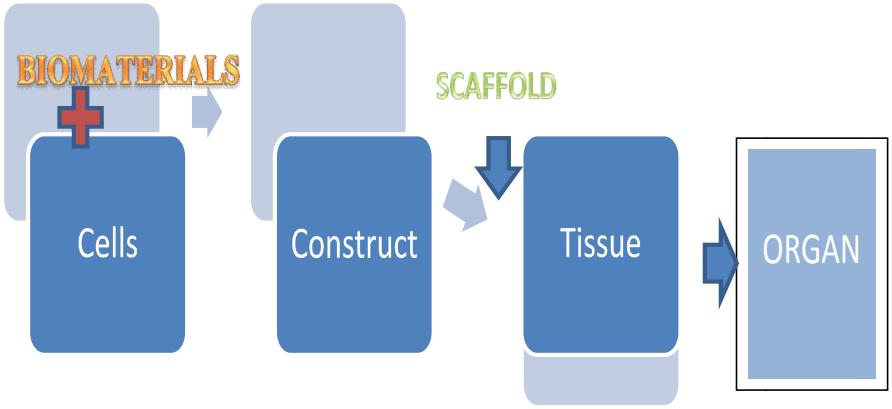


Fig.Tissue Engineering requires cells, signals, Scaffolds , and Growth Factors to produce Newly Engineered Tissues which can be used to replace damaged tissues.



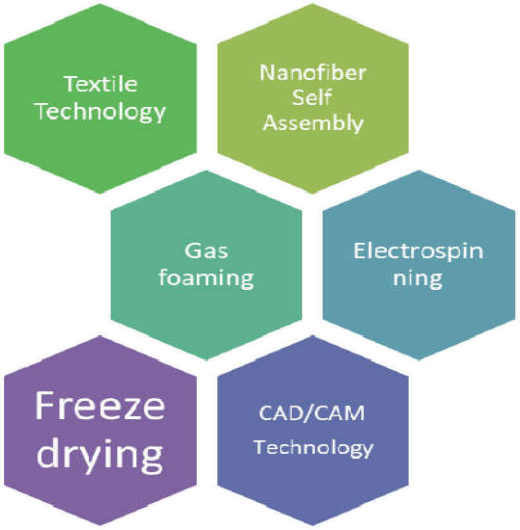


Fig.Scaffolds Preparation Techniques

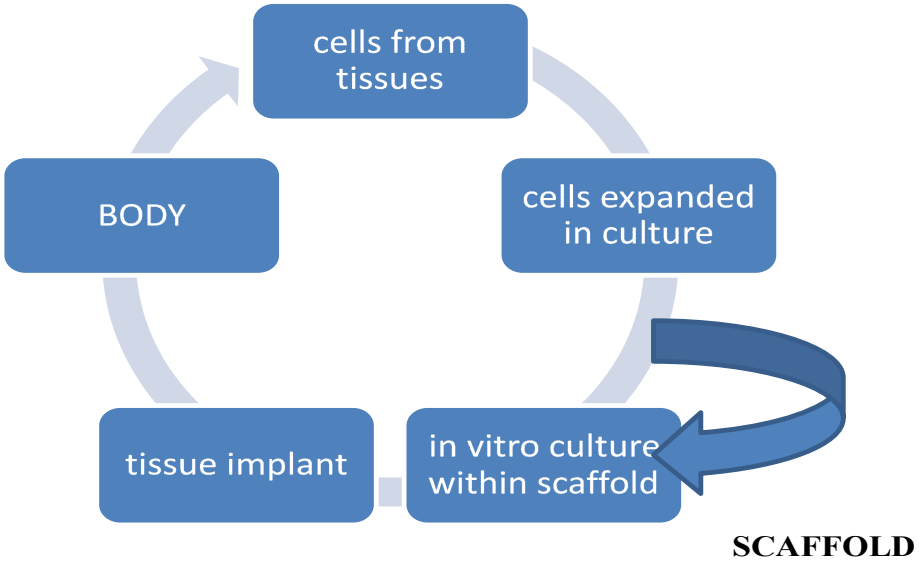


Fig. Flow chart Diagram of overall process

POLYMERS

Polymers has a wide range of applications including tissue engineering and this involves 2 categories of polymers :Natural and Synthetic polymers . Synthetic polymers are more likely to show chemical modifications and can be modified according to the requirements while natural polymers are present in abundant amount in the nature and they mimic the extra-cellular components.

Table 1.Advantages and Disadvantages of some natural polymers for Tissue Engineering[13].

Sl. No.	Polymer	Advantage	Disadvantage
1.	Collagen	a) Biocompatible b) Biodegradable	Low mechanical strength
2.	Gelatin	a) Biocompatible b) Non immunogenic & non pathogenic	Low mechanical strength
3.	Fibrin	a) Soft elasticity & Self assembly	Immunogenicity

Table 2. Advantages and Disadvantages of some synthetic polymers for Tissue Engineering.[14].

Sl. No.	Polymer	Advantage	Disadvantage
1.	PGA (Poly-glycolic acid)	Biodegradable, stable	Immunogenicity
2.	PLA (Poly-lactic acid)	Biocompatible, long half-live, Biodegradable	Hydrophobic nature
3.	PLGA (Poly-lactide-glycolic acid)	High biocompatibility, non-toxic biodegradation	Poor protein absorption

3D- BIOPRINTING

3D- Bioprinting is an emerging field that are involved in the various biomedical applications. One of the major differences between 3D- Printing and 3D-Bioprinting is that Bioprinting involves the application of living cells to form a three- dimensional structure that can be further used for implantation. Since there is a limitation of donors for transplantation, the demand for its alternatives is highly required. In order to reduce the chances of rejection, saves lives and relieve suffering , it is highly recommended to form these structures for patient's own cells[15] . The basic purpose of tissue engineering and 3D-bioprinting is the formation of scaffold that provides an environment for the cells to communicate and proliferate that can mimic the native environment of damaged organs.

Technologies in 3D-Bioprinting involves construction of a porous structure similar to unconventional scaffolds through which nutrients and media can reach to the cells . A blueprint is created using a software system followed by toolpath planning and finally a 3D- bioprint[16].

Major Components of Bio-printing is: Bio-ink, Bio-paper and Bio-printer.

Steps involved in 3D Bioprinting are:[17].

i) In a biopaper gel, bioink spheroids are printed into layers.

ii) To build an object, additional layers were added.
iii) Biopaper dissolves after bioink spheroids fuses.
iv) Finally, a living tissue is formed.

DIABETES: EARLY TREATMENTS AND RECENT ADVANCEMENT

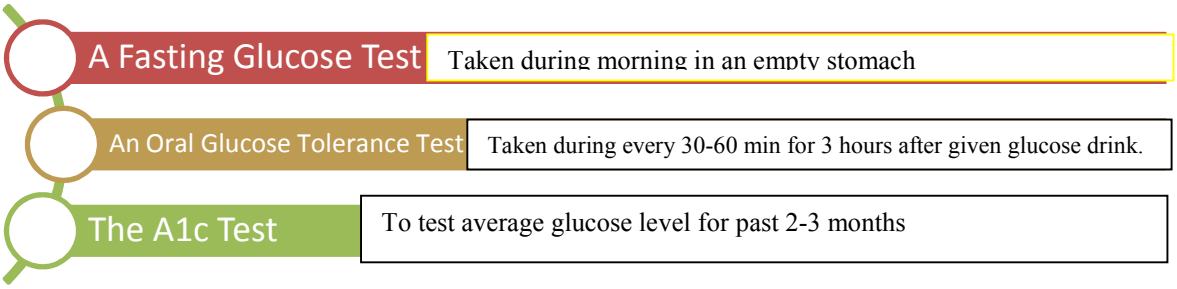
Diabetes happens when body is unable to produce enough insulin or is unable to process enough insulin, and this leads to increase in sugar levels in blood. Managing sugar levels is quite challenging but ongoing research in this field has made possible to led a life free from diabetes[18].

Earlier, patients with Type 1 diabetes had life risks for several months. But introduction of insulin into human body has reduced this risks. Although there is no proper cure for diabetes , but recent advancements has led to improve the condition and provides longer lives[19]. Along with certain medications, it is preferred to have a consultancy with nutritionist, this helps the patients to have an active and balanced lifestyles.

Diabetes patients have to take insulin outside either in the form of injections or with the help of continuous pump. Dosage varies depending on the amount of sugar levels present. But this is not the permanent solution [20]. Thus, a method should be opted that can reduce the dependency of taking insulin from outside the body.

DIAGNOSIS FOR DIABETES:[21].

The amount of sugar present is examined by three different tests. However, doctors sometimes re-examined the test to ensure the perfect results. These tests include:



A PERMANENT SOLUTION : A FUNCTIONAL PANCREATIC CONSTRUCT:

Although there are various treatments available for diabetes, each has its own implications. Therefore, the sight has been shifted to an permanent solution which include bioartificial pancreas. However, there are various changes in the advancement of bioartificial pancreas. These approaches include polymer-based scaffolds, encapsulation, bioprinting , organ decellularization.[22].

One of the major problem with pancreatic tissue engineering lies in the organ itself, as the pancreas has both exocrine and endocrine functions which include ductal and acinar cells in exocrine portions and Islets of Langerhans in endocrine portion of Pancreas. Multiple cell types need to be considered during islet grafting among which (beta-cells) has more dominant roles[23]. As islets requires much more blood supply than any other compartment of Pancreas ,it is important to have a continuous blood supply for its survival. This construct would reduce the dependency of taking insulin outside the body.Therefore , beta cell replacement is an effective method for diabetes patients[24].

CONCLUSION

There are numerous of difficulties that come across in the construction of artificial pancreas which includes:

a) The choice of cell types
b) Culture environment
c) Scaffold processing
d) Site of implantation

The choice of cell types include xenogenic, allogenic and various other sources like :Embroyonic stem cells, MSC. Allogenic and Xenogenic cells have proven to be shown successful results, but due to their post – isolation instability has lead to the use of stem cells.

Once the appropriate cell type is chosen, the next step is to have a proper culture environment ,i.e, either to culture the cells individually or with other types of cells. Transplanting the beta-cells alone are proved to shown only limited results while transplanting the beta-cells with other cells like Mesenchymal stem cells, or fibroblasts have shown better stability , as well as better functionality.

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