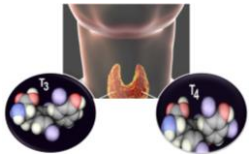

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Brief analysis of Therapeutic Approaches of Type 1 Diabetes Mellitus along with Diagnosis and Screening Methods

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ABSTRACT: *Diabetes is an endocrine system disease which is characterized by abnormal elevated glucose levels. Type I Diabetes Mellitus (T1DM) is an autoimmune disorder with early onset, whereas Type 2 Diabetes Mellitus (T2DM) is non-autoimmune form with late onset. Small and large artery complications are the two main categories of diabetes mellitus long term complications. Overproduction of superoxide by the mitochondrial electron transport chain (ETC), leading to oxidative stress, occurs because of pathogenic effects of hyperglycemia. New vessels are fragile and hyper permeable in case of retinopathy in T1DM. T1DM is known to be occurred by beta cell destruction which leads to hyperglycemia and insulin scantiness. In phase 3 T1DM is normally diagnosed, the stage at which the disorder has led to life threatening condition known as diabetic ketoacidosis. To minimize the possibility of serious complication it is necessary to diagnose autoimmunity which is present during first years of life through early screening or by using diagnostic tools. Measuring fasting blood glucose or standard OGTT's are performed for screening of phase 2 T1DM in the persons which have 1 or more autoantibodies targeting β-cell. The management of type 1 diabetes mellitus is necessary to encourage healthy lifestyle and to control glycaemia conditions in order to avoid severe complication. Pharmacological approaches are the most widely used method for the treatment of T1DM including injectable insulin and sodium glucose cotransporter 2 (SGLT2) inhibitors, Gene therapy and stem cell-based therapies. These are supposed to help in providing life-time freedom from T1DM but there is still a room for debate in this regard.*

Keyword: *Autoimmune disorder, Ketoacidosis, Autoantibodies, Gene*

INTRODUCTION

Diabetes is an endocrine system disease which is characterized by abnormal elevated glucose levels. It is among the most common disease. It is estimated that by 2045 diabetes will affect about

693 million adults globally (Cho et al., 2018). It is a chronic metabolic disease which is the consequence of complete or relative deficiency of insulin. It is divided into two main types: Type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). T1DM is an autoimmune disorder with early onset, whereas T2DM is non-autoimmune form with late onset. Besides this classical classification there are subtypes too which includes monogenic diabetes (may be neonatal diabetes or maturity- onset diabetes of the young MODY), gestational diabetes, and latent autoimmune diabetes (Ahlqvist et al., 2018). T1DM is due to the T-cell mediated self-destruction of β cells (insulin secreting islet) present in the pancreas (Liu et al., 2016) T1DM etiology is complicated. Environment is also found to have a critical role in development of T1DM along with genetics (Jerram and Leslie, 2017). Many factors play a crucial role in type 1 diabetes mellitus progression as shown in Fig. 1. With advancement of technology and continuous efforts of researchers, genes playing a crucial role in T1DM development have been identified. By using gene therapy approach, manipulation of these genes can provide a more comprehensive management of the disease or ever treat T1DM (Cole and Florez, 2020). Stem cell therapy provides a new outlook for T1DM treatment and it can overcome many shortcomings of conventional therapies. They promote the repair as well as regeneration of β cells. But the stem cell therapy has numerous hurdles in its way as tumor genesis, and autoimmune attack (Zhou et al., 2022).

Polydipsia, polyphagia, weight loss, and blurred vision are some common symptoms of hyperglycemia. However, many long-term complications can be the consequence of uncontrolled diabetes.

Long Term Complications

Insulin therapy is shown to be involved in decreasing the likelihood of ketoacidosis and several other metabolic diseases linked with T1DM (Nathan et al., 2014). Microvascular and macrovascular complications are the two main categories of diabetes mellitus long term complications. Neuropathy, retinopathy, and nephropathy fall into the microvascular complications associated with diabetes.

Macrovascular complications demonstrate cerebrovascular disease peripheral artery disease, and coronary

heart disease. These are not only limited to diabetes and can occur due to several other reasons however the individuals suffering from T1DM can develop these conditions.

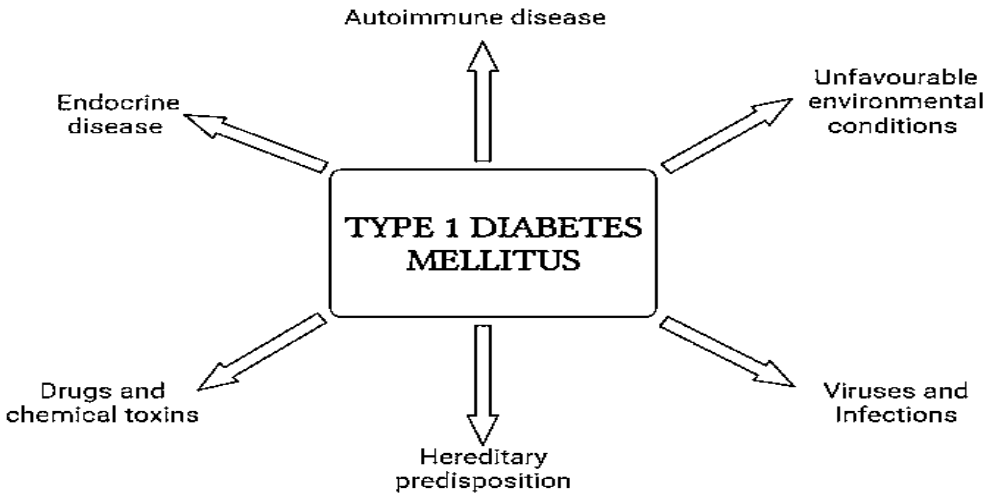

Fig. 1. Different factors shown to have a role in T1DM development (image is created Bio render)

Diagnosis

T1DM is known to be occurred by beta cell destruction which leads to hyperglycemia and insulin scantiness. Rapid appearance of hyperglycemia symptoms includes weight reduction, polydipsia, abdominal symptoms, headaches, and ketoacidosis that normally occur in young children (Care, 2019). More than 95% of recently diagnosed diabetic patients look for medical assistance and help due to appearance of symptoms while a few numbers of diabetic patients are diagnosed and identified by routine screening of glucose levels or through the autoantibodies detection. A diagnostic criterion irrespective of type of diabetes and age of onset according to American Diabetes Association (ADA) 2016 for diabetic individuals was dependent upon evidence of uncommon glucose metabolism (Seo et al., 2020). A diagnosis of autoimmune T1DM conducted if there is existence of autoantibodies targeting β cell. Patients having neonatal diabetes may be affected with type 1 diabetes mellitus but have rare monogenic kinds of diabetes (Flanagan et al., 2014).

Differentiating T1DM and T2DM

Differentiating between individuals having T1DM with those suffering from T2DM is not an uncomplicated and effortless process. T1DM occur in childhood and about 20% to 40% children affected with T1DM are obese or overweight. Family history may be sometimes responsible to determine whether an individual have T1DM. The average Body Mass Index of infants and adults affected with type 1 diabetes mellitus is lesser than infants and adolescents enduring T2DM. The occurrence of ketoacidosis is also higher in T1DM as compared to T2DM. Approximately 30% of African population has ketosis at disease onset due to hyperglycemia-induced βcell toxicity that ultimately leads to decreased endogenous insulin levels and C- peptide. However, level of C-peptide (insulin production marker) may be less at the time of disease T2DM onset.

Screening

During phase 3 T1DM is normally diagnosed, the stage at which the disorder has led to life threatening condition known as diabetic ketoacidosis. To minimize the possibility of serious complication it is necessary to diagnose autoimmunity which is present during first years of life through early screening or by using diagnostic tools. Measuring fasting blood glucose or standard OGTT's is performed for screening of phase 2 T1DM in persons having 1 or more autoantibodies targeting β-cell (Ekoe et al., 2018). Factors responsible for the continuation towards single autoantibodies to multiple autoantibodies, to dysglycemia and from dysglycemia to type 1 diabetes mellitus have been recognized in TrailNet analysis (Xu et al., 2016). In Bavaria and Germany in the month of February a study was commenced on healthy 2-5 years age children using ELISA (an immunological technique) to detect autoantibodies (GAD65, IA2 and ZNT8 autoantibodies) in capillary blood samples. None of the children developed ketoacidosis who were detected with T1DM and suggested through psychological assessment that families of children who were screened have no enhanced distress (Raab et al., 2016).

Prevention

T1DM includes two kinds of prevention. Primary prevention of type 1 diabetes mellitus can be done in infants who have elevated genetic risk through

insulin treatment and diet modification before emergence of islet-targeting autoantibodies. Primary prevention in neonate, who had an increased chance or probability of insulin autoantibodies development, executed by administration of high-dose of oral insulin (Bonifacio et al., 2015). This work accomplished with twenty-five infants having age between 2-7 years were found to show negative results for islet-targeting autoantibodies, and had increase-probability HLA genotypes as well as a family history with T1DM.

Table 1. Secondary prevention trails on nicotinamide, insulin, and immunosuppressive drugs with their phase, and outcome (Cho et al., 2018)

Trails Studies	Drug	Phase	Outcome
DPT-1	Oral insulin	3	No effect
DIPP	Intranasal insulin	3	No effect
ENDIT	Oral modified-release nicotinamide	3	No effect

Management

The management of type 1 diabetes mellitus is necessary and goal is to encourage healthy lifestyle and to control glycaemia conditions in order to avoid severe complications, guidelines have been issued for management as both hypoglycemia and hyperglycemia complications are organ specific (American Diabetes Association, 2016). Management includes therapeutic and pharmacological approaches.

Gene therapy

It has been known that T1DM occur due to the under expression of many genes. It is not feasible to modulate and activate these genes by using surgical instruments therefore, gene therapy seems to be the most feasible way to manage or cure T1DM (Mallol et al., 2017). When the IGF1 coding gene sequence was transferred to non-obese diabetic NOD mice, it was proved that expression of IGF1 gene can lessen T1DM progression (Chellappan et al., 2018). A simple schematic diagram of gene transfer is shown in Fig. 2. For insulin gene delivery in various tissues like muscle, pancreas and liver, viral techniques such as AVV and adenovirus along with non-viral techniques including naked DNA and liposomes are used. For proinsulin processing,

pancreatic beta-cells are important as they form glucose-dependent insulinotropic polypeptide (GIP), and have prohormone convertases which show similarity with intestinal cells. The implantation of K-cells for the reversal of diabetes invitro to produce and generate insulin failed by many researchers. The transgenic mice are modified and altered to express and form insulin by making use of streptozotocin (STZ) so that it can generate diabetes under the influence of GIP promoter, release normal level of glucose. Thus, to maintain a normal glucose homeostasis, these K cells produce insulin in adequate amount. Based on co-expression of glucokinase and insulin genes through AVV, gene therapy has been high lightened as therapeutic management method of diabetes mellitus. It is observable that by using long-term efficient diabetic gene therapy normal glycaemia conditions could be attained without usage of exogenous insulin (Jaén et al., 2017). AVV vectors are considered best candidate for gene therapy as they infect dormant as well as proliferating cells without inserting into the genome of host. In a study, the insulin and glucokinase genes encoded on AVV vectors incorporated in the diabetic dogs and cats. Uptake of glucose in engineered myocytes (muscle cells) is facilitated by the translocation of glucokinase enzyme and GLUT4 accelerated by co-expression of these two genes. In engineered skeletal muscle cells, glucokinase enzymes cause glucose phosphorylation into glucose 6-phosphate (G6P). However, this enzyme can also detect the blood glucose level (Romer and Sussel, 2015). For T1DM management, gene therapy is implemented by humanized liver mouse model usage. PDX1 gene having secreted insulin that is present in the liver is found to have glycaemia control. This was confirmed by the detection method involving the green fluorescent protein (GFP) presence. Elevated glucose level in STZ-induced diabetic mice has decreased when AAV-PDX-1 gene was treated. Inducing genes like glucose 6-phosphatase (G6Pase), phosphoenolpyruvate carboxykinase (PEPCK), S-14, albumin and insulin like growth factor binding protein-1 (IGFBP-1), and liver-type pyruvate kinase (L-PK) in the liver for gene therapy manifested weak discharge of insulin due to less strong activity in promotion as in comparison with less

weak promoters for example cytomegalovirus (CMV) (Handorf et al., 2015). Plasmid DNA carrying tiny patches or fragments of insulin intravenously injected for non-viral introduction showed normoglycemia for seven days and 210 days into STZ-induced diabetic rats' the liver and muscle. As the gene is introduced into host chromosome by making use of DNA transposon system the short time expression of liver injection is solved. However, plasmid DNA with insulin containing furin when co-injected they cause active insulin in muscle.

Stem cell therapy for T1MD

In 1966 Dr. Richard Lillehei successfully performed transplantation of pancreas with the advent of modern technology islet transplantation was introduced and it was first even done in 1974. Unfortunately, due to the scarcity of donors there was hurdle islet transplantation. As human pluripotent stem cells (hPSCs) have emerged as the long-term management tool in many diseases, therefore several studies have been done for islet organoids or insulin producing cells' (IPCs) in vitro generation (Shapiro et al., 2017).

Human embryonic stem cells (hESCs), adult stem cells, human induced pluripotent stem cells (hiPSCs), and differentiated cells taken from developed tissues are used from in vitro generation of islet organoids or IPCs. All these cells are able to undergo trans differentiation into insulin producing cells (IPCs) (Rickels and Robertson, 2019).

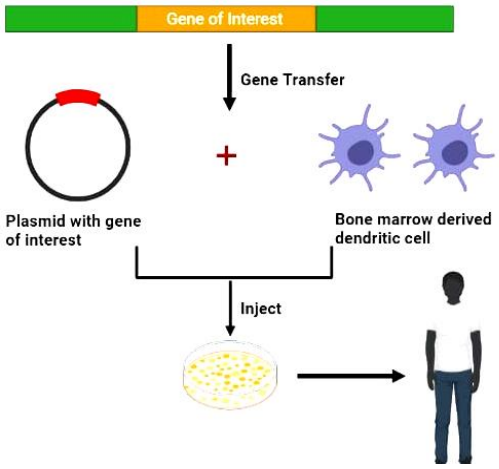

Fig. 2. Basic method of Gene Therapy (image is created Bio render)

Almost all the methods and ways aiming for the generation of IPCs are based on those protocols that imitate the development of normal pancreas. After the generation of IPCs, it is made sure that IPCs express normal β cells' particular biological markers. These markers can identify final differentiation status including MAFA (transcription factor of basic leucine zipper nature, expressed in matured β cells and is not expressed in different pancreatic progenitors), PDX1/NKX 6.1M, and NEUROD1 (Yabe et al., 2017). Moreover, the surety of specific functional characters of β cells is also considered like secretion of C-peptide, and glucose-stimulated insulin secretion (GSIS) (Russ et al., 2015). When IPCs or islet organoids are implanted into immunodeficient diabetic animals or diabetic patients, they should be able to counter changes in blood glucose level and generate suffice amount of insulin and ultimately do the reversal of hyperglycemia (Tao et al., 2019). The results of clinical trials regarding TIDM stem cell therapy is discontented (Hwang et al., 2019). Additionally, many ethical as well as technical queries are still unanswered and are open to debate. Five aspects that contribute to major issue are : (1) method for the in vitro generation of mature and functional β- cells in larger amount from human pluripotent stem cells (hPSCs); (2) protection of introduced insulin producing cells from immune system attack; (3) ways to ameliorate the efficiency of differentiation of insulin producing cells (IPCs) from hPSCs; (4) desired types of cells' sufficient generation for the clinical transplantation; and (5) establishment of thorough independence of insulin (Zhou et al., 2022). In spite of all these hurdles, the utilization of stem cell therapy in T1DM management is the most progressive and up to the minute approach for Type 1 diabetes mellitus.

Pharmacological Approaches

Treatment options for T1DM are limited as injectable insulin is the most used and recommended treatment. But it can induce hypoglycemia which can maximize the chance of heart diseases. Sodium glucose cotransporter 2 (SGLT2) inhibitors are the most advance oral anti-hyperglycemic medications class (Heerspink et al., 2016). The benefit of them is that they do not increase the risk of hypoglycemia. They have been approved by US Food and Drug

Administration (FDA) for the treatment of type 2 diabetes mellitus. It has been proposed that SGLT2 inhibitors can be used for the treatment of T1DM, although FDA has not approved those (Song et al., 2016). Inhibition of SGLT2 in the kidney's early proximal tubules is the primary mechanism of action (Vallon et al., 2017). Several trails about safety and efficacy of SGLT2 inhibitors for the treatment of T1DM are still in progress in different regions of the worlds (Henry et al., 2015). In order to achieve accurate glycaemia control, the diabetic patients may require multiple therapies, while the choice of pharmacological agents to be used by diabetic patients depends upon its, side effects, advantages, price, glucose level decreasing ability as well as dosage. These pharmacological agents include insulin, biguanides, thiazolidinediones, sulfonylureas, analogues of glucagon-like peptide 1 (GLP-1), and inhibitors of dipeptidyl peptidase-4 (DPP4) etc.

CONCLUSION

Diabetes mellitus is the multifactorial disease. Environmental factors in addition to genetic factors have been found to have a role in progress of diabetes mellitus. The disease is divided into several types. Symptoms vary from patients to patients and screening methods mainly include measuring fasting glucose level. In type 1 diabetes mellitus, the main way of treatment and management is injectable insulin whereas several other methods have been developed which includes; Sodium glucose co-transported-2 (SGLT2) inhibitors, thiazolidinediones, Sulfonylureas, biguanides, Dipeptidyl peptidase-4 (DPP4) inhibitors, and glucagon-like peptide 1 (GLP-1) analogues. Gene therapies also made its way in curing and managing type 1 diabetes mellitus as several genes have been discovered that play a role in progression as well as advancement of type 1 diabetes mellitus. Several strategies have been developed and opted in this regard but still there is a room for more advance study and practice. Stem cell-based therapy for type 1 diabetes mellitus management is also the ray of hope. Several clinical trials are still in progress but there is an anticipation that stem cell therapy can provide the insulin independence. Despite this, the whole world is looking to gene therapy and stem cell-based therapies as the most reliable and effective method for curing and regulating of type 1 diabetes mellitus.

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AUTHORS CONTRIBUTION

SR guided and supervised the authors. IF, SA, and RT were involved in data analysis, content editing, and manuscript preparation. All authors have read and approved the final manuscript.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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