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Milestones In Diabetes Research

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Abstract: Diabetes is a lifestyle disease which grows epidemically at an alarming rate. Solomon Berson and Rosalyn Yalow measured how much insulin was in a diabetic's blood which led to the discovery that some people with diabetes could still make insulin. There is Type-1 and Type-2 diabetes other than gestational diabetes . Diabetes is a mysterious illness with a wide array of complications. It has become a severe socio-economic burden on the developed and underdeveloped countries. It has been reported that half of the death is due to high blood sugar level. Despite many scientific milestones achieved in providing better healthcare facilities and in the treatment and mitigation of this disease, it still imposes a severe threat in countries with middle and low-level-income groups of population and many patients suffering from diabetes are still unable to achieve desired glycemic level. Recent explorations in drug discovery have opened new avenues in the development of new classes of drugs. Focusing on the emerging trends and advances in the field of diabetes treatment, the review will highlight the recent scientific and technological advancement in the development of newer generations of drugs or regimens over the past few decades.

Keywords: Mysterious Illness; Metabolic disorder; Diabetes; Milestones; Socio-economic burden innovative technique

INTRODUCTION

Diabetes mellitus is a chronic, life-long disorder that primarily affects the endocrine system of the body (Stein, Maloney and Pollin, 2014).Diabetes mellitus is generally characterized by hyperglycemia due to insulin secretion deficiency or a combination of insulin resistance and inadequate insulin secretion.Type-1 is also called insulin-dependent diabetes or juvenile-onset diabetes because it often begins in childhood. It is caused by pancreatic islet B cell destruction by an autoimmune process, and these persons are prone to ketoacidosis.Type-2 diabetes is the more common form that results from insulin resistance with a defect in compensatory insulin secretion and known as noninsulin-dependent or adult-onset diabetes (Holt *et al.*, 2017).About 90%of people are with type-2 diabetes. Symptoms of diabetes and its progression can lead to severe consequences and may even affect the body's internal organs. Blindness, heart attacks, kidney failure, lower limb amputation are the significant concerns associated with diabetes.Type-2 diabetes is associated with many liver disorders, including elevated liver enzymes, fatty liver disease, cirrhosis, hepatocellular carcinoma, and acute liver failure. The standardized mortality rate for cirrhosis is higher than that for cardiovascular disease in type 2 diabetes (Ezhilarasan, 2018a). Cumulative evidence generated by prior research suggests that diabetes, insulin resistance, and serum glucose are associated with the progression of hepatic fibrosis in patients with chronic liver disease (Ezhilarasan, Sokal and Najimi, 2018a).

Diabetes mellitus has known since antiquity. Descriptions have been found in the Egyptian papyri, in ancient Indian and Chinese medical literature, as well as in the work of ancient Greek and Arab physicians. In the 2nd century Aretaeus of Cappadocia provided the first accurate description of diabetes, coining the term diabetes. In contrast, in the 17th century, Thomas Willis added the term Mellitus to the disease in an attempt to describe the extremely sweet taste of the urine. The vital work of the 19th-century French physiologist Claude Bernard, on the liver's glycogenic action, paved the way for further progress in the study of the disease. In 1889, Oskar Minkowski and Joseph von Mering performed their famous experiment of removing the pancreas from a dog and producing severe and fatal diabetes. In 1921, Frederick Banting and Charles Best extended Minkowski's and Mering's experiments. They isolated insulin from pancreatic islets and administered it to patients who have type-1 diabetes, saving thus the lives of millions and inaugurating a new era in diabetes treatment (Karamanou, 2016).

With the increasing number of short term and long-term adverse events associated with conventional medicine, novel methods are explored to counteract the issue (Xu *et al.*, 2018). According to the World Health Organization(WHO), Diabetes Mellitus will be the 7th leading cause of death in 2030 (Laios *et al.*, 2012), (Mathers and Loncar, 2006). The burden of diabetes on the health care system mandates to treat those with the disease more optimally and to prevent its development (Blonde, 2005).

Our department is passionate about research we have published numerous high quality articles in this domain over the past years (Abraham *et al.*, 2005; Devaki, Sathivel and BalajiRaghavendran, 2009; Neelakantan *et al.*, 2010, 2015; Arja *et al.*, 2013; Ramshankar *et al.*, 2014; Sumathi *et al.*, 2014; Surapaneni and Jainu, 2014; Surapaneni, Priya and Mallika, 2014; Ramamoorthi, Nivedhitha and Divyanand, 2015; Manivannan *et al.*, 2017; Ezhilarasan, 2018b; Ezhilarasan, Sokal and Najimi, 2018b; J *et al.*, 2018; Ravindiran and Praveenkumar, 2018; Malli Sureshbabu *et al.*, 2019; Mehta, Deeksha, Tewari, Gupta, Awasthi, Singh, Pandey, Chellappan, Wadhwa, Collet, Hansbro, Kumar, *et al.*, 2019; Krishnaswamy *et al.*, 2020; Samuel, Acharya and Rao, 2020; Sathish and Karthick, 2020)

The article aims to review Milestones in Diabetes Research.

INSULIN THERAPY

It was discovered by the University of Toronto in 1921.Insulin therapy is an important and critical part of treatment for people with type 1 diabetes and also for type 2 diabetes. The target of the insulin therapy is to keep blood sugar levels within a target range. Insulin is injected in the fat under your skin using a syringe, insulin pen or insulin pump tubing (Davidson, 2015).

Conventional insulin:

It is a therapeutic regimen for treatment of diabetes mellitus which contrasts with the newer significant intensive insulin therapy. This older method which is prior to the development of home blood glucose monitoring is still in use (Willms and Boustani, no date).It is of Insulin injections of a mixture of regular and intermediate acting insulin.

Newer insulin:

Novel long and short acting insulin analogues,so called designer insulin.It was developed through genetic engineering in the 1990.It had paved the way for more physiological insulin therapy that have increased stability,less variability and selective action in treatment ('Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group', 1998).

Advances in Insulin Therapy:

The recent advances in novel insulin therapy for diabetic treatment includes newer injectable formulations, artificial pancreas systems, oral, transmucosal, and transdermal dosage forms.

Continuous Subcutaneous Infusion of Insulin:

The administration of insulin by continuous subcutaneous infusion of insulin (CSII) has great advantages in terms of permitting the programmed timing of insulin levels. At present, insulin pumps are available, which permit preprogrammed delivery of basal insulin profiles as well as quick premeal infusion of bolus insulin doses. Insulin pumps typically deliver insulin through an indwelling subcutaneous catheter, which must be changed every 48-72 hours. Modern insulin pumps have proven safe and effective in a wide variety of type 1 and type 2 diabetic patients, representing all ages and education levels, and are very well accepted by patients (Duckworth *et al.*, 1998). Implanted pumps have also been developed. The implanted pumps deliver insulin directly into the peritoneal cavity and then to the portal venous system, thus allowing a first pass in the liver before the peripheral circulation, similar to that of normal physiological pancreatic insulin (Boivin, Belicar and Melki, 1999).

Artificial pancreas:

Artificial pancreas is also known as an integrated closed-loop control, this system utilises real-time feedback from continuous glucose monitoring, to continuously adjust insulin administration via an insulin pump (continuous subcutaneous insulin infusion) depending on blood glucose levels.The system consists of a continuous glucose monitoring, linked wirelessly to an insulin infusion pump, which delivers insulin in accordance to an algorithm, automatically (Duckworth *et al.*, 1998; Breton *et al.*, 2012).This method mimics physiological pancreatic β-cell function to a certain extent, and reduces the risk of hypoglycaemia.It is minimally invasive as the electrode is implanted in the subcutaneous tissue and measures glucose electrochemically (Favero *et al.*, 2015).

Oral insulin: The intensive goal of exogenous insulin therapy is via oral administration, because of its numerous advantages.Initially,oral delivery of insulin enters the portal circulation and reaches the liver before entering the

systemic circulation. This resembles the pathway of physiologically secreted insulin, resulting in inhibition of glucose production by the liver and avoidance of peripheral hyperinsulinaemic effects (Costa *et al.*, 2020).

Transmucosal insulin:
Transmucosal insulin delivery includes buccal, pulmonary (inhaled), nasal, ocular, as well as rectal routes (Senel and Hincal, 2001). These routes are common in that they involve insulin absorption/transport across mucosal surfaces into the bloodstream.

Transdermal insulin:
It is the method of delivering insulin into the bloodstream in a non invasive way through the skin surface into the underlying capillary network. This method of delivery is convenient, which would lead to better patient convenience . However, the stratum corneum layer which is the outermost surface of the skin acts as the main barrier for transdermal delivery, which only allows small lipophilic molecules to be absorbed. Many methods have been developed to overcome this barrier (Fonseca *et al.*, 2020). Additionally, new drug carriers can also aid transdermal insulin transport (e.g. nano- and microparticles, lipid vesicles).

ORAL HYPOGLYCEMIC AGENTS
Anti diabetic medication which are used to reduce blood glucose level especially in type 2 diabetes is known as oral hypoglycemic agents(OHA) (Madsen *et al.*, 2019).These drugs act by different mechanisms either by increasing the insulin release or by improving the peripheral resistance.

Sulfonylureas:
The first Sulfonylureas were developed in the 1950s.The drugs work by increasing the release of insulin from the pancreas (Sola *et al.*, 2015).First-generation drugs include acetohexamide, carbutamide, chlorpropamide, glycyclamide,metahexamide, tolazamide and tolbutamide whereas Second-generation drugs include glibenclamide,glibornuride, gliclazide, glipizide, gliquidone, glisoxepide and glyclopyramide.Despite the great number of anti-diabetic agents currently available in clinical practice, sulfonylureas are still frequently used due to their lower cost, to the possibility of mono-dosing and to the presence of an association with metformin in the same tablet.In patients suffering from inadequate glycemic control, sulfonylureas can rapidly achieve significant improvement when added to metformin.

Meglitinides:
The class of drugs used to treat diabetes type 2.Medications in this class include Prandin (repaglinide) and Starlix (nateglinide).They bind to an ATP-dependent K+ channel on the cell membrane of pancreatic beta cells but have a weaker binding affinity and faster dissociation from the binding site, which increases the concentration of intracellular potassium, which causes the electric potential in the membrane to become more positive. This depolarization opens voltage-gated Ca2+ channels (Kennedy *et al.*, 2020). The rise in intracellular calcium leads to increased fusion of insulin granula in the cell membrane, and therefore increase in secretion of proinsulin.

Biguanides:
The novel drug came into existence in the late 1950s. Metformin is the only biguanide currently available in most countries for diabetes treatment.Glucophage (metformin) and Glucophage XR (metformin extended-release) are well-known forms of these drugs (Sharma *et al.*, 2019).It works by preventing the production of glucose in the liver and by improving the body's sensitivity towards insulin and reducing the amount of sugar absorbed by the intestines to treat type-2diabetes (Bridges *et al.*, 2016).Biguanides do not affect the output of insulin unlike other hypoglycemic agents

Thiazolidinediones:
The drug is also known as glitazones.Pioglitazone and rosiglitazone are the drugs that come under this class.It can be used on its own as a monotherapy or as combination treatment with either a sulphonylurea or metformin, or insulin.It works by reducing the body’s resistance to insulin, and effectively improves the blood glucose control.The drug was developed in the 1990s (Nesto *et al.*, 2003).

Alpha Glucosidase Inhibitors:
There are two medications in this group of drugs which are acarbose and miglitol . The drugs work by competitive and reversible inhibition of the intestinal enzymes. They slow the digestion of carbohydrates and delay glucose absorption (Derosa and Maffioli, 2012). This results in slower rise in blood glucose levels after meals and also effectively throughout the day.

DPP-4 inhibitors:

Dipeptidyl peptidase-4 inhibitors are also known as gliptins, they are usually prescribed for patients with type 2 diabetes who does not responded well to drugs such as metformin and sulfonylureas (Zhang *et al.*, 2019).Medicines in this class include sitagliptin, saxagliptin, linagliptin, and alogliptin.DPP-4 inhibitors will lower high blood glucose levels and also block the action of DPP-4, an enzyme which destroys the hormone incretin.

Incretin Mimetics:
The drugs also commonly known as GLP-1receptors agonists or GLP-1 analogues,Drugs in the incretin mimetic class include exenatide ,liraglutide ,sitagliptin,saxagliptin, alogliptin and linagliptin.These drugs are given if tablet medications for diabetes cannot be controlled .They bind to GLP-1 receptors and release glucose dependent insulin (Cernea and Raz, 2011).Incretins help the body produce more insulin only when it is needed and reduce the amount of glucose being produced by the liver when it is not needed.

SGLT-2 inhibitors:
Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors. SGLT2 inhibitors are a class of prescription medicines that are FDA-approved for use with diet and exercise to lower blood sugar in adults with type 2 diabetes. Medicines in the SGLT2 inhibitor class include canagliflozin, dapagliflozin, and empagliflozin.The drugs are also known as gliflozins (Deerochanawong *et al.*, 2019).SGLT2 inhibitors work by preventing the kidneys from reabsorbing glucose back into the blood and hence the glucose level in the blood is reduced.

RECENT TRENDS IN THE MANAGEMENT OF DIABETES
Nanotechnology application in diabetes:
Nanotechnology has recently gained importance in diabetes research over the past few decades. This branch of science deals with nano-size particles which includes nanomaterials, nanostructures, nanoparticle design.Recent advances in nanotechnology have emerged as promising alternate strategies for management of diabetes (Veiseh *et al.*, 2015).For example,implantable nanosensors are being developed for continuous new nanoparticle based imaging approaches that quantify subtle changes in beta cell mass can facilitate early diagnosis and nanotechnology based insulin delivery methods are being exposed as novel therapies.Plant induced zinc oxide and silver nanoparticles act as potent antidiabetic agents (Karthiga, Rajeshkumar and Annadurai, 2018; Rajeshkumar, Kumar, *et al.*, 2018).Selenium as a hypoglycemic cofactor has remarkable antioxidant and curative effects against DM. In addition, Se nanoparticles have been confirmed able to produce the hypoglycemic effect analogous to that of insulin (Menon *et al.*, 2018).Techniques for nanomedicine includes insulin replacement therapies, B-cell imaging, Glucose sensors,Glucose-sensing molecules, Artificial Pancreas (DiSanto, Subramanian and Gu, 2015).

Stem cell therapy:
In T2DM, Most studies used autologous bone marrow mononuclear cells or autologous or allogeneic mesenchymal stem cells from various sources.Advance effects are mild and mostly intervention related (Farooq *et al.*, 2018).Current efforts aimed at generating a sustainable source of human stem cell derived insulin producing islet cells for cell transportation and to protect such cells via immune modulation and encapsulation strategies.The milestones of stem cell research was laid in 2004 by university of Pittsburgh.They developed insulin producing beta cells from virus by extracting two genes (Solis *et al.*, 2019).It is believed that Stem cell therapy can open new avenues for providing a permanent solution for the patients with T1DM. Even T2DM, the patients can also get a permanent cure as well. However, various researches are ongoing to counteract this issue and it can be assumed that in future, it will be possible to generate islet cells from patients' own existing cells to avoid rejection during transplants (Wang *et al.*, 2015).

Gene therapy:
It comprises a mechanism of either altering or changing the genetic material present inside the cell.The rationale behind the occurrence of the disease or disorder is the defective genes, which are eventually rectified by the gene therapy.Gene therapy is basically of 2 types; One is Somatic gene therapy and the other is Germ-line gene therapy (Kaufmann *et al.*, 2013).
Gene therapy has certainly flourished in reversing faster high blood glucose levels (Yechoor and Chan, 2005).Preventive, adjunctive and curative are those three tactics involved to approach of gene therapy for diabetes,where both the former one initially introduces the auto-immune pathogenesis of Type-I DM, while the latter one involves the synthesizing and secretion of insulin by activating the islet neogenesis (Olson *et al.*, 2008).

Statins therapy: new advancements:
The benchmark for the development and uses of statins for T2DM patients came into existence in 2017, when FDA approved the combination of dapagliflozin and saxagliptin, an SGLT2 and DPP-4 inhibitor. It was indicated as an adjunct therapy to diet and exercise and helped in improving glycemic control in adults,reducing body

weight and blood pressure in patients with T2D mellitus (Dey, 2017).Other statins approved by FDA was Semaglutide (Ozempic) which was indicated as once-weekly as subcutaneous injection to treat T2DM which has shown significant effect in decreasing HbA1C levels, the benefit risk of these class "statins" is still to be established (Sampson, Linton and Fazio, 2011).

Diet and Nutrition:
Dietary and nutrition are one of the most important factors in the management and prevention of T2DM.It has been known that dietary habits and lifestyle changes have become a significant role in the increasing incidence of diabetes over the past few decades. This trend is mostly seen in the developing countries where most of the population lacks basic nutritional requirements for sustenance (Mohammadi, 2015). Thus, it becomes a major concern for those patients who are being treated with conventional medicine but still unable to achieve desired glycemic goals. Thus, for this reason American Diabetes Association (ADA) started various Patient support programmes to make people around to be aware of the importance of diet and nutrition to treat diabetes along with the term "medical nutrition therapy" and the calorie requirement in a individual with moderate level of activity is around 30–35 kcal/kg/day and on the another hand it is 20–30 kcal/kg/day for obese individual. It was also postulated that in order to reduce weight by 1 pound/week, the individual calorie intake should not exceed 500 calories/day (Gojo *et al.*, 2007).

NEW PATHWAYS FOR BETTER EXPLORATIONS TOWARDS DIABETES
Role of RHOA/ROCK1 related transcriptional pathway in diabetes:
In diabetes mellitus, due to the high glucose level, advanced glycation end products due to endothelial damage and vascular leakage is revered by inhibition of RhoA/ROCK1 pathway (Massey *et al.*, 2003). It has been reported that Rho kinase is involved in the endothelial dysfunction (in T1DM) which leads to intensification of oxidative stress and production of increased oxygen reactive species (Gheena and Ezhilarasan, 2019) . This might also act as a precursor for development of diabetes related complications. To counteract this issue, the treatment with RhoA/ROCK1 inhibitors may also be used as one of the potential therapeutic candidates for prevention and treatment of diabetes and also shows secondary benefits by reducing oxidative stress and high apoptosis due to elevated levels of glucose (Rikitake and Liao, 2005).

Role of AMPK in diabetes:
Activation of AMPK (Activated protein kinase) plays a crucial role in better achieving glycemic control in uncontrollable diabeticsAdenosine-5-monophosphate activated protein kinase (AMPK) is a mainstay enzymatic protein comprises of serine-threonine kinase. It is considered as a main regulator in maintaining the homeostatic environment in the levels of glucose and lipid metabolism.Dysfunction of AMPK induces the progression of type-2 DM and results in development of insulin resistance. Whereas, stimulation of AMPK can either inhibit or regulate insulin resistance in patients with type-2 DM (Hardie, 2013).Due to the exploration of this pathway, development of two leading anti-diabetic drugs namely, metformin and rosiglitazone was established which mainly exert its anti-diabetic effects on it (Hardie, 2013; Castaño, Novials and Párrizas, 2019).Thus, the development of new molecules triggering anti-diabetic effect involving the AMPK pathway, may bring about desired results to achieving glycemic levels in patients with type-2 DM.

Role of Activin in diabetes:
The role of activins and related TGFβ family in the management of regulation of blood sugar levels via pancreatic β-cell in animal models. Also, confirmed that Activin A is expressed in islet cells of pancreas and acts as insulin secretion enhancing agent during the release of glucose in the body and clinical implications of cardio-vascular events in T2DM patients was confirmed (Ofstad *et al.*, 2013).

Antisense Oligonucleotide Therapy in Diabetic Retinopathy:
Diabetes damages the small blood vessels throughout the body, including the retina. Lipids, proteins, DNA damage, Glutathione, catalane and superoxide dismutase are various biomarkers of oxidative stress in diabetes mellitus. Oxidative stress induced complications of diabetes includes stroke, diabetic neuropathy, diabeticretinopathy and diabetic nephropathy.Diabetic retinopathy occurs when these tiny blood vessels leak blood and other fluids. This causes the retinal tissue to swell, resulting in cloudy or blurred vision.Second-generation antisense oligonucleotides, such as iCo-007, may offer a significant advantage in the treatment of diabetic retinopathy by downregulating the signal pathways of multiple growth factors that seem to play a critical role in the process of ocular angiogenesis and vascular leakage. Benefits of such molecules are expected to include the specificity of the kinase target and an extended half-life, resulting in less frequent intravitreal drug administration, resistance to molecule degradation (Mehta, Deeksha, Tewari, Gupta, Awasthi, Singh, Pandey, Chellappan, Wadhwa, Collet, Hansbro, Rajesh Kumar, *et al.*, 2019)

PLANT BASED DRUGS FOR FOR DIABETES

Even with significant advances and trends in modern medicine and therapeutic agent development, the search for effective antidiabetic drugs remains challenging. Few plants are found to have antioxidant activity. Hence it can be used in the treatment of diabetes mellitus.

Coumarins are secondary metabolites found widely in nature plants. The search for coumarins against diabetes and its complications, either isolated from traditional medicine or chemically synthesized, has been constantly expanding.The cellular and molecular mechanisms involved in Coumarin includes protecting pancreatic beta cells from damage, improving abnormal insulin signaling, reducing oxidative stress/inflammation, activating AMP-activated protein kinase (AMPK), inhibiting α-glucosidases and ameliorating diabetic complications (Perumalsamy *et al.*, 2018).On the other hand, leaf extract of *Caralluma fimbriata* has been reported to reduce blood glucose (Anitha and Ashwini, 2017; Ashwini, Ezhilarasan and Anitha, 2017). Similarly, *Acacia catechu*, also known as Katha, has been used for many years by the local healers to treat diabetic patients. It is Potential antidiabetic cum anti-dyslipidemic (Ezhilarasan, Lakshmi, Nagaich, *et al.*, 2017),(Ezhilarasan, Lakshmi, Vijayaragavan, *et al.*, 2017). With increased age, blood sugar levels, DMFT values, dental caries are increased in diabetic patients.Dental caries can be reduced by traditional sources like *Azadirachta indica* where bark and leaf extract of neem is most effectively used in preventing cavities and gum disease. Mouthwash containing Neem is a remedy of choice for tooth decay, oral infections, and prevents bleeding and sore gums. Twigs of Neem trees are used as chewing sticks by people earlier in India (Lakshmi *et al.*, 2015). In addition, *B. oleracea* extracts attenuated the adverse effect of diabetes on malondialdehyde, glutathione, and superoxide dismutase activity as well as catalase activity and total antioxidant capacity of diabetes (Rajeshkumar, Agarwal, *et al.*, 2018).

CONCLUSION

Diabetes has now become a challenging health issue across the globe. Since years, development of therapeutic advancements and technological upgrades have been constantly looked upon to keep a check on the management of diabetes. These advancements and development in new therapeutic options has enabled patients to manage the disease in a much more cost effective way which makes easily achievable glycemic goals. Combinations of lifestyle changes and diet along with these technological and therapeutic advancements may contribute towards the management of diabetes in a much more effective manner.

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