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A Perspective on Recent Trends in Diabetes and its Cure

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Abstract: *Diabetes is considered as a global pandemic that afflicts millions of people all over the world. It is a major public health problem along with its social and economic connotations. There is a change in the pattern of expression of diabetes and newer risk factors are implicated as possible precipitating factors of Diabetes. Now pollution is considered to be an emerging risk factor for diabetes. About 3.2 million new cases of diabetes are reported to be pollution related and represents 14 % of new cases reported globally.*
With a vast literature flooded with diabetes research, a possible cure remains a distant dream for a diabetic patient. Therefore, in the present review the recent trends in diabetes research, care and therapy is discussed.

Key words: *Diabetes, Type I Diabetes mellitus (T1DM), Type 2 Diabetes Mellitus (T2DM), insulin pill, islet cell transplantation*

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I. Introduction

Diabetes represents a major threat to human health globally.(NCD Risk Factor Collaboration (NCD-RisC), 2016).World Health Organization (WHO) reported that the disease affected 180million people in 2006 and would reach an alarming proportion by 2040.WHO factsheet 312.

In addition to the health burden to the individuals affected, diabetes has major financial and economic implications. In 2010, it was estimated that the global expenditure on diabetes care and treatment was 418billion international dollars (ID). In 2030, this cost is predicted to rise to 561billion ID. In particular, Type 2 diabetes with its complications of nephropathy, neuropathy and retinopathy may cost 800 billion US dollars/year. (International Diabetes Federation, 2009 and Seuring et al, 2015). Pollution is one of the risk factors associated with Diabetes. (Bo-Yi Yang, Zhengmin (Min) Qian, Shanshan Li et al.2018). Therefore, in this review emerging trends in the field of Diabetes including the salient features of diagnosis, therapy and care of diabetic patients are discussed.

Updates on classification of diabetes

Brownlee 2005 and Reddy et al, (2015) indicated that early intervention is critical for avoiding diabetic complications that arise due to poor metabolic control. Prolonged metabolic derangement registered by the tissues as metabolic memory due to persistent and prolonged hyperglycemia are considered as possible biochemical phenomena that needs immediate glycemic control and therapy. For such early intervention requires a revised classification of diabetes that may help identify and categorize patients to institute proper care and therapy. The following update on classification of diabetes sets the basis for such early intervention to control the metabolic derangement.

Table 1 summarizes the sub-groupings of Diabetes which will help to design early treatment intervention possibly providing precise and practical guide-lines .

Clusters	Diabetic Types and Conditions
Cluster 1	Diabetics identical to type 1 diabetes, is severe autoimmune diabetes
Cluster 2	Severe insulin deficiency when the immune system is not involved
Cluster 3	Severe insulin resistance co-related to obesity
Cluster 4	Mild-obesity related diabetes
Cluster 5	Mild age-related diabetes

The classification categorizes patients into two categories based on whether there is absolute insulin deficiency or insulin resistance. It also focuses on the immune status of the patient, degree of obesity and

insulinresistance along with the age of the patient. The newer classification includes a cluster of patients as type 3 diabetes who exhibit cognitive impairment similar to Alzheimer Disease with greater oxidative stress that affect glucose metabolism (Boles et al, 2017 and Kandimalla et al, 2017).

Current Medications for Diabetes

Around the globe, scientists in life science, drug companies, and health service providers are trying to design treatment regimens that aim to eliminate or at least delay the appearance of the unfavorable diabetic complications. Collectively treatment targets aim to lowering insulin resistance and maintain insulin secretion. In fact, no definitive treatment plans are designed. Despite this fact, the field of diabetic research provides FDA-approved medications for treatment of diabetes including oral hypoglycemic drugs (Boles et al, 2017).

Reversal of type2 diabetes:

In a recent review White and his colleagues in 2016 discussed the reversible nature of short-duration type 2 diabetes. Hyperglycemia reversibly impairs insulin release (Kramer et al, 2010). The dual action of hyperglycemia and elevated free fatty acids have an additive effect upon insulin secretion (Carpentier et al, 2010). Deposition triglycerides for a long time seriously interferes withβ-cell function (Figure 1) in individuals with high risk of developing type 2 diabetes (Storgaard et al, 2003). Decreasing calorie supply enables the removal of accumulated lipid from the pancreas. (Lim et al, 2011,Pinnick et al, 2010).

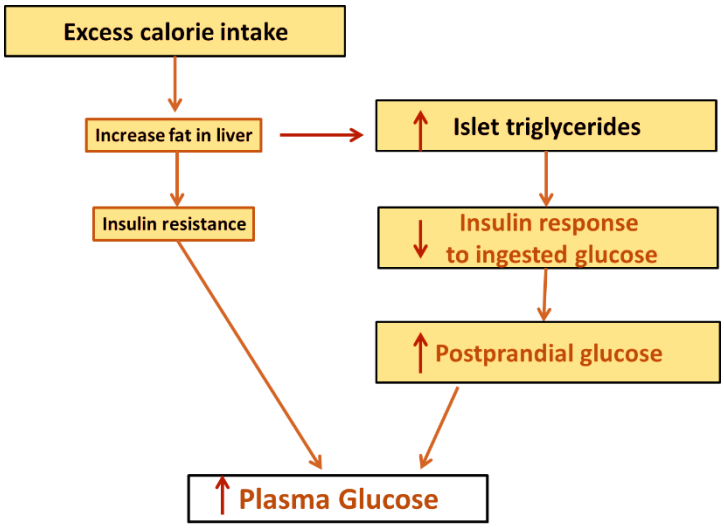

Figure 1—During chronic high calorie intake accompanied by insulin insensitivity in muscles, the increased insulin rates will induce lipogenesis of the excess calorie of carbohydrates promoting storage fat. This will gradually induce the storage of fat in the liver over long periods of time and promote insulin insensitivity in the liver which at the end caused a mild elevation in blood sugar, as illustrated in Whitehall II study (Tab´aket al, 2009). Subsequently, insulin secretion will rise to maintain normal levels of plasma glucose. The increased insulin levels will bring about a self-reinforcing vicious cycle. By time the higher levels VLDL triglyceride will be exported to peripheral tissue including pancreatic islet cells with subsequent stress on endoplasmic reticulum resulting in dedifferentiation β-cells and low glucose-induced insulin secretion. The figure is redrawn from Taylor (2008 and 2018).

During exposing the rat insulinoma β-cells to oleate caused the appearance of storage vacuoles in the cytosol, whereas palmitic acid leads to expansion of the endoplasmic reticulum(Fig.2 A and B) (Pinnick et al, 2010).

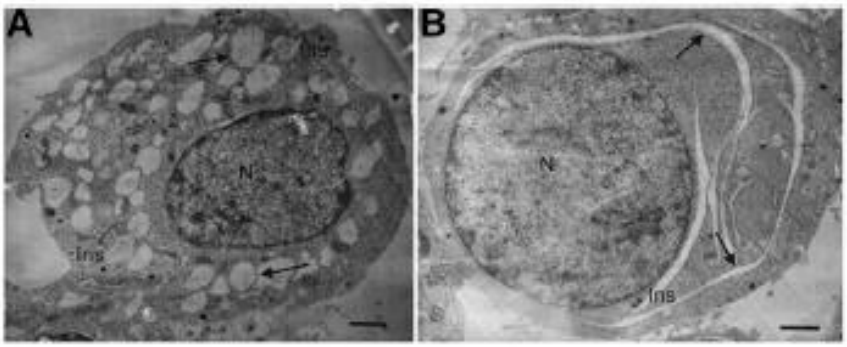

Figure 2—Interaction of fatty acids withβ-cell ultrastructure and function. A: rat insulinoma cells exposed to 0.33 mmol/L oleic acid. Oval-shaped vacuoles in the cytosol (arrows) indicate deposition of Triglycerides. B: The same cell type exposed to 0.33 mmol/L palmitic acid. Splits of triglycerides formed in the cytosol close to the endoplasmic reticulum (arrows). Original photomicrographs adopted from Pinnick et al, (2010).

This is explained by the presence of markers of endoplasmic reticulum stress in human β-cells from individuals with type 2 diabetes (Laybuttet al, 2007). Exposingβ-cells to physiologic mixture of saturated and unsaturated fatty acids lowers insulin release, and upon removal of fatty acid from the medium, the rate of insulin release returned back after 24 hours (Pinnick et al, 2010).

Recently White et al, (2016) concluded that β-cells lose differentiation characteristics, including glucose-evoked insulin release, under metabolic stress. Dedifferentiation of β-cells resulted from long-term excess nutrient consumption is reversible. Weight loss in subjects allowed restoration of glucose-evoked insulin release and helped to reduce elevated intra- pancreatic triglyceride content. However, in type 2 diabetes of duration more than ten years, the cellular dedifferentiation could not be reversed (Taylor et al, 2019).

Type 2 diabetes nowadays is considered as reversible condition exposed to continuous calorie overload in predisposed subjects. Losing function and the end-differentiatedβ-cell phenotype can be restored by marked loss of body weight (White et al, 2016). Beyond 10 years of diabetic duration, theβ-cell dedifferentiation form accepted irreversible loss of insulin release and the marked weight loss have low ability reverse the condition. Despite type 2 diabetes is considered as a progressive, nonreversible disease, many scientists and clinical doctors now believe that it could be effectively treated with a low carbohydrate diet program.

Insulin pill instead of injectable insulin

The oral administration of the drugs has the advantages of ease of administration, high patient compliance, and cheap industrial costs. However, because of variety gastrointestinal barriers against drug absorption, Oral administration becomes inconvenient way of protein drug delivery. For instance, insulin is available as medication for type 1 diabetes management. It is currently administered as a sub cutaneous injection but has the disadvantage of lack of patient adherence due to pain and needle phobia associated with injections (Fu et al, 2009). Developing oral insulin product could make patients enjoy in taking their medication which would be reflected on the life quality of diabetics over the globe (Banerjee et al, 2017).

A team of Harvard researchers utilized a novel approach with insulin pill, dispersing insulin in a liquid made of choline (nutrient) and geranic acid, commonly found in cardamom. When the insulin pill administered to rats, their blood glucose decreased to around half their initial value, but returned back to a higher level four hours afterwards. The marked fall in blood sugar indicates that the choline/geranic acid liquid protected the insulin from being digested and facilitated the passage of insulin into circulation (Banerjee et al, 2017). The oral administration of insulin mimics a physiological response and reaches the liver where it is regulated to secrete physiological levels of insulin in the circulation. It is well known that type 1 diabetes caused by T cell-mediated autoimmune damage of insulin-producing β-cells results in a complete deficiency of insulin (Donath and Halban, 2004).

Exogenous insulin represents the 1st line treatment choice for type 1 Diabetes. Despite of the advantages of using insulin in diabetes management, unfavorable complications exist due to the lack of absolute adjustment of blood glucose values within the normal ranges.

Transplantation of human cadaveric islets to replace the damagedβ-cells in type 1 diabetics is one of current choices for treating those patients, the topic is elegantly reviewed by Shahjalal and colleagues (2018). Islet transplants maintain euglycemia, and absolutely solve the problem of insulin deficiency in the long term which is reflected on the life quality of the individuals Barton et al, (2010).

Despite its promising potential, it is faced by various obstacles including the scarcity of donors compared to the huge number of diabetics, low yield of transplantable islets from cadaveric pancreases, and finally the requirement for immunosuppressive therapy to avoid graft rejection (Shapiro et al, 2006).

Stem cell therapy for type 1 diabetes

Due to the difficulties facing islet transplantation, finding alternative source of surrogate cells become necessity. Additionally, the extractedβ-cells from one cadaveric pancreas are limited and cannot maintain glycemic control in one diabetic patient (White et al, 2009). Because of all these reasons, it is necessary to find alternatives of β-cells to treat the rising number of diabetics. Human pluripotent stem cells (hPSCs), including human embryonic stem cells (hESC) and induced pluripotent stem cells (hiPSC), are alternative choice to solve the problem ofβ-cells scarcity because of their ability to differentiate into pancreaticβ-like cells from hPSCs as well as other endocrine cells of the islets (Russ et al, 2015). Shahjalal et al, (2018) concluded that, despite of many obstacles currently limit the use of hESC/iPSC-derived cells in cell replacement therapies, priority should be given to high risk groups of type 1 diabetes.

ViaCyteis a USA company work to develop islet cell replacement therapies which aim to overcome the scarcity of islet donors and the need for long-term use of immune-suppressive drugs to avoid graft rejection. ViaCyte's PEC-Direct and PEC-Encap (VC-01) products offer a potential "functional cure" for patients with type 1 diabetes and insulin-dependent type 2 diabetes. (ViaCyte's 2017, Dominguez-Bendala 2016)

ViaCyte's encapsulated islet cell technology developed for treatment of type1 diabetes. This method has proved elevated survival rates for a period of two years in humans.The PEC-Encap product is a unique stem cell therapy that involves a sac which encapsulates human islet cells grown in vitrousing human pancreatic progenitor cells (PEC-01). The PEC-Encap products are implanted into diabetics, where they differentiate to functional pancreatic islet tissue that possesses glucose-induced insulin-producing β-cells. The encapsulation device has the advantage of protecting the islet cells from the attack by the immune system. The current technology has been designed to mimic the job oft he pancreas in healthy subject in an attempt to cure type 1 diabetics (Cooper-Jones B and Ford C, 2017).

Due to the increased numbers of diabetic conditions, the authors suggested that the use the PEC-Direct product will be prioritized for the treatment of individuals with high-risk type 1 diabetes including; individuals with impaired awareness of low blood glucose values (hypoglycemia unawareness), subjects exposed to severe fluctuations of blood glucose (glycemic liability) and/or frequent and severe episodes of decreased blood glucose (hypoglycemic episodes).

The preliminary findings from the STEP ONE clinical trial showed that the implanted ViaCyte's encapsulated cells survived and matured into islet-like tissue capable of secreting insulin and glucagon. Additionally, cells survived and proliferate for prolonged periods. In addition to showing high survival rates, the application was shown to be safe and well tolerated by participants. Although the study showed a significant success, more research and development is required to improve engraftment of pancreatic endocrine cells. (The American Diabetes Association, 2018).

II. Conclusion:

Diabetes is one of the major non-communicable diseases. Still is there is no single permanent cure for the disease as it is a multifactorial disease. Diet, drugs, islet cell transplantation and stem cell therapy are areas that are trying to find a remedy for diabetic patients. Diet control seemed to help reduce pancreatic triglyceride content and insulin release. Control of diabetes and its complications not only will alleviate the sufferings of the patients but also help the economy by cutting short the enormous amounts of funds being utilized for diabetic research, diagnosis, care and therapy. The growing number of patients with complications of diabetes have become major concern for Diabetologists. Therefore an urgent need is felt for early intervention and care of diabetic patients. The present review gives a perspective by reviewing the recent trends in diabetes, its classification, diagnosis, and therapeutic options.

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