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Review

Type 1 and 2 diabetes mellitus: A review on current treatment approach and gene therapy as potential intervention



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ABSTRACT

Type 1 and type 2 diabetes mellitus is a serious and lifelong condition commonly characterised by abnormally elevated blood glucose levels due to a failure in insulin production or a decrease in insulin sensitivity and function. Over the years, prevalence of diabetes has increased globally and it is classified as one of the leading cause of high mortality and morbidity rate. Furthermore, diabetes confers a huge economic burden due to its management costs as well as its complications are skyrocketing. The conventional medications in diabetes treatment focusing on insulin secretion and insulin sensitisation cause unwanted side effects to patients and lead to noncompliance as well as treatment failure. Besides insulin and oral hypoglycaemic agents, other treatments such as gene therapy and induced β -cells regeneration have not been widely introduced to manage diabetes. Therefore, this review aims to deliver an overview of the current conventional medications in diabetes, discovery of newer pharmacological drugs and gene therapy as a potential intervention of diabetes in the future.

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1. Introduction

Diabetes mellitus (DM) is apparently one of the oldest diseases known to man. DM is a metabolic disease commonly characterised by an elevation of the blood glucose levels that warrant frequent monitoring and proper control. Pancreatic beta cells (β -cells) produce the hormone insulin which facilitates the absorption of glucose into the cells in order to provide energy and is also involved in a variety of other functions. DM occurs due to lack of insulin production or insulin sensitivity. It is mainly classified into many

types, however, the most common types are type 1 and type 2 DM. Type 1 DM (T1DM) is typically associated with failure in insulin production resulting from the destruction of pancreatic β -cells by T-cell-mediated autoimmunity [1]. On the other hand, type 2 DM (T2DM) is characterised by insulin resistance and reduction of insulin production. Lower life expectancy was found in T1DM compared to T2DM due to the relatively higher incidence of cardiovascular diseases and acute metabolic disorders in the former group [2]. It is important that all forms of diabetes to be diagnosed and managed at the early stage to prevent or slow down its potential complications involving other organs such as diabetic nephropathy, retinopathy, neuropathy, cardiovascular diseases and diabetic foot ulcer [3–5].

As DM is a considerable socioeconomic burden to many countries [6], scientific and technological advances play a vital role in the discovery of new treatment entities [7]. Thus, this has contributed to the establishment of new therapeutic classes including gastric inhibitory peptide (GIP) analogues, amylin analogues, incretin mimetics [8] and potential targets for drugs in the treatment of

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diabetes, namely peroxisome proliferator activated receptor (PPAR) and dipeptidyl peptidase-4 (DPP4) inhibitors [9].

Inducing β -cells regeneration through trans-differentiation or stem cells has a direct effect in improving β -cells' function and morphology [10]. However, gene therapy is recently discovered to hold great potential for diabetes management with abundant of clinical studies showing evidences of safety and efficacy for various complex diseases. Viral and non-viral gene therapy has shown promising results. For example, Adeno-associated viral (AAV) vector-based gene therapy have shown to potentiate long term glycaemic control as well as prevention of secondary complications of diabetes [11].

2. Epidemiology

DM is no longer a foreign term to the global population; it is increasingly prevalent in every country [12], regardless of the income level. Recent data estimated that 629 million people will suffer from DM by year 2049 [13]. T1DM is more prevalent in children, especially those who range from birth to 14 years old, but it can happen to individuals of any age, with an excess of male seen among young adults [14]. On the other hand, adults or obese individuals are mostly affected with T2DM, but it can occur in children too according to the recent reports [15]. Also, T2DM is denoted as the major contributor to the total diabetes population.

3. Risk factors

DM that occurs in childhood is most commonly type 1 and the major contributor is often an individual's inherent genetic predisposition. DM in adulthood is more likely to be type 2 and is normally attributed to sedentary lifestyle, mindless eating which involves consumption of food that is high in carbohydrates and fat and may also be linked to genetics. As T1DM is largely attributed to hereditary genes from family members, a few susceptible genes were identified to be risk factors for this type of diabetes. This includes some of the human leukocyte antigen (HLA) types. Studies shows that identical twins have a higher likelihood to develop T1DM than fraternal twins, showing a strong familial genetic predisposition. T1DM can also be triggered by environmental factors such as viral infections, low levels of vitamin D and lower exposure to ultraviolet rays. This was shown by a study on the correlation between ultraviolet B (UVB) exposure and incidence of T1DM, with the result showing an inverse relationship [16]. Several dietary and lifestyle factors also contributes to the incidence of T1DM such as childhood obesity, rapid growth of infant, older maternal age and short duration of breastfeeding [17]. Although T1DM is mainly linked to the genetic predisposition of an individual, in reality, it involves a complex interplay of genetic, immune and environmental factors that destruct the pancreatic β -cell function.

Although family history plays a role in T2DM, diet and lifestyle are the major contributors. Consumption of food high in carbohydrates but low fibre, sugary beverages and a sedentary lifestyle escalate an individual's risk for T2DM. This is because less glucose in the blood is taken up by the body to be utilised for energy production due to low level of physical activity. Hence, obesity is often linked to the increasing incidence of diabetes. Women who had gestational diabetes have a higher chance of having T2DM than women who did not experience gestational diabetes [18].

4. Pathogenesis

4.1. Type 1 diabetes mellitus

T1DM also known as insulin-dependent diabetes, is the

consequence of insulin deficiency arising from the progressive destruction of pancreatic β -cells through an autoimmune response. Histologic analysis of pancreas in a patient with T1DM showed infiltration of various immune cells including T and B lymphocytes, macrophages, dendritic cells, natural killer cells, as well as islet-reactive autoantibodies and islet-reactive T-cells in the islets of Langerhans [19].

The possibility of developing T1DM is associated with β -cells turnover or damage which leads to the release of autoantigens. In turn, β -cells auto-antigens are presented by the antigen-presenting cell (APC) to T-helper cells. In conjunction with major histocompatibility complex (MHC), APC will then migrate to the pancreatic lymph node. Autoantibodies and autoreactive T-cells will become activated in the presence of APC and they will be directed against β -cells auto-antigens [20]. These activated T-cells re-encounter cognate β -cell antigens and reactivate again, thus killing the β -cells.

Macrophages and T-cells produce cytokines namely interleukin-22 (IL-22), interferon- α (IFN- α), and tumour necrosis factor- β (TNF- β) which in turn lead to the development of T1DM [21]. They can induce an inflammatory response by producing nitric oxide synthase (NOS) that induces the formation of reactive oxygen species (ROS). ROS may disrupt the β -cells and leads to tissue destruction [22,23]. Besides that, the expression of apoptosis-inducing receptors (AIF), Fas, can be triggered by the cytokines, eventually leading to Fas-mediated apoptosis of β -cells. β -cells are also destroyed when surface ligands of Fas are in contact with effector T-cells. Effector T-cells facilitate the passage of protease granzymes through secretion of perforin molecules [19]. These granzymes kills the β -cells by allowing the passage of perforin molecules and activating nucleases in the cells. Meanwhile, the toxic effect of macrophages is associated with the action of superoxide anion and hydrogen peroxide. Macrophages produce soluble mediators such as ROS and cytokines like interleukin-1 beta (IL-1 β) and interferon-gamma (IFN- γ) by tumour necrosis factor-alpha (TNF- α) and lipopolysaccharide stimulation and eventually contribute to β -cell damage [22,23].

β -cells can undergo self-destruction when they are exposed to a certain environment. During inflammation, β -cells increase the number of MHC II and thereby present antigen to diabetogenic CD4 T-cells [22]. Also, multiple chemokines produced in β -cells infiltrate islets of Langerhans and recruit immune cells to the pancreas via chemokines receptors [24].

Both innate and adaptive immunity take part in the development of T1DM. Recent studies reveal the emergence of gut microbiota as a key player in the development of autoimmune disease which includes T1DM. Together with innate immunity, gut microbiota acts on pattern-recognition receptors (PRR) and coordinates the innate inflammatory response. PRR recognises pathogen-associated molecular patterns (PAMPs) and further induction of innate immune response results in pro-inflammatory cytokines which promote phagocytosis, autophagy and interferons activity that promote cell death. For instance, toll-like receptors (TLR) 7, TLR8, MyD88 and NLRP3 are responsible for T1DM disease predisposing [25] (Fig. 1).

4.2. Type 2 diabetes mellitus

T2DM is mainly linked to insulin resistance. The latter is majorly attributed to obesity, caused by poor dietary and lifestyle habits. The sensitivity of insulin fluctuates with intake of carbohydrate-rich foods, amount of physical activity, as well as stress signals. Obese individuals contain more adipose tissues, relating to the higher secretion of hormones and other substances that may increase the fluctuation of insulin sensitivity. Circulating non-esterified fatty acids (NEFA) in obese individuals is also associated

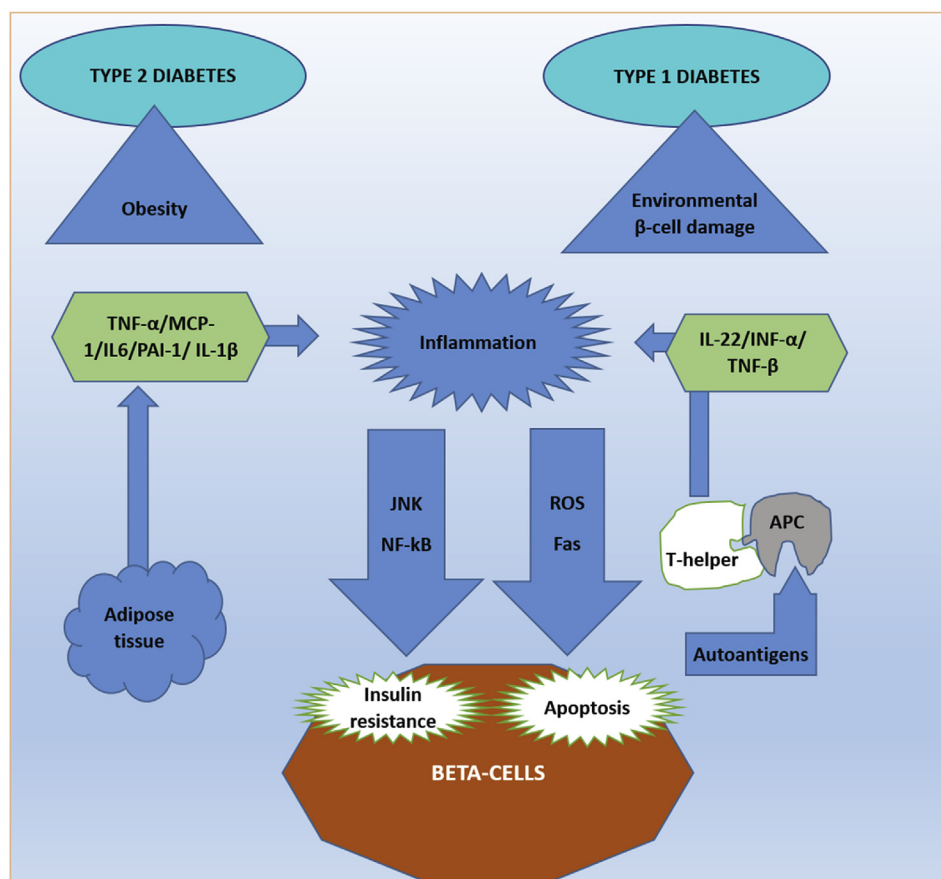


Fig. 1. Inflammation as a common factor between T1DM and T2DM which leads to β -cells destruction. In T1DM, damaged β -cells release autoantigens which presented to T-helper via APC. Active T-helper release cytokines which enhance inflammation, in turn induces ROS and Fas leading to apoptosis of β -cells. In the same manner, in T2DM, adipose tissues release cytokines which enhance inflammation and affect insulin signalling in β -cells via activating JNK and NF- κ B pathways. Antigen-presenting cell (APC), tumour-necrosis factor α and β (TNF- α /- β), monocyte chemoattractant protein-1 (MCP-1), interleukin (IL-6), interleukin-1 β (IL-1 β) and plasminogen activator inhibitor-1 (PAI-1).

with insulin resistance. A high fatty acid environment with hyperglycaemic conditions can lead to reduced insulin gene expression [26]. Impaired function of cholesterol transporter destroys β -cells through sterol accumulation and islet inflammation [27]. Lipoprotein fractions and cholesterol metabolism contribute to β -cell failure. The low-density lipoprotein (LDL) that undergo oxidation can decrease the pre-proinsulin expression in isolated β -cells while very low-density lipoprotein can induce β -cells apoptosis. On the other hand, there are experimental evidence revealing the protective effects of high-density lipoprotein (HDL) on β -cells. They impact beneficially on glucose homeostasis by increasing pancreatic β -cells function and plasma glucose disposal [28].

Lipid interacts with incretin hormones, particularly GLP-1, by down regulating their receptors and altering the downstream cAMP signalling, thereby having a negative impact on incretin signalling that promotes insulin secretion and β -cells survival [29]. Moreover, fatty acids can potentiate inflammatory toxicity by activating inflammatory pathways directly, as adipose tissues are crucial in producing inflammatory mediators such as TNF- α , MCP-1, IL-6, IL-1 β and PAI-1. For example, TNF- α acts as pro-inflammatory cytokine which mediates insulin resistance through distributing insulin receptor substrate (IRS) proteins by enhancing serine phosphorylation on IRS-1. Moreover, TNF- α initiates c-Jun NH2-terminal kinase (JNK) and Nuclear factor- κ B (NF- κ B) signalling pathways. Both pathways will then induce serine phosphorylation of IRS-1 at Ser 307, causing insulin resistance [30]. They increase

inflammatory cytokines and immune cells that consequently result in islet inflammation in the pancreas of T2DM *in vivo*. Meanwhile in high fat feeding *in vitro*, the production of macrophage migration inhibitory factor (MIF) of islets was increased which directed the β -cells to lipotoxic cell death [31]. Lipids also affect insulin sensitivity via increasing the accumulation of intracellular diacylglycerols, a triacylglycerol product which has a negative impact on insulin signalling. Furthermore, lipids enhance protein kinase C proteins which play a main role in inhibiting insulin signalling transduction [32]. Saturated fatty acids (SFAs) activate Toll-like receptor 4 (TLR4), which in turn mediated insulin resistance-associated inflammation by upregulating the expression of I κ B kinase (IKK), NF- κ B transcription factors and pro-inflammatory mediators in adipose tissue macrophages [30]. Altogether, it is clear that inflammation is involved in the pathogenesis of both T1DM and T2DM (Fig. 1).

5. Therapeutic approaches

5.1. Gene therapy

Currently, viral techniques such as lentivirus, adenovirus and AAV as well as non-viral techniques such as liposomes and naked DNA have been used for insulin gene delivery into different tissues, for example, pancreas, liver, adipocytes and muscle [33]. Interestingly, intestinal cells such as enteroendocrine K-cells showed many similarities with pancreatic β -cells, it produces glucose-dependent insulinotropic polypeptide (GIP), and contains prohormone

convertases which are crucial for proinsulin processing [34]. As a result, many researchers attempted to manipulate K-cells *in vitro* to produce and release insulin; however, the implantation of these cells failed to safely reverse diabetes. Surprisingly, transgenic mice which modified to express insulin under the GIP promoter after using streptozotocin (STZ) to induce diabetes, showed normal levels of glucose. This indicated that K-cells produced insulin in sufficient amount to maintain glucose homeostasis [35]. Gene therapy approach has been introduced recently for the management of DM based on the co-expression of both insulin and glucokinase genes in skeletal muscles through adeno-associated viral (AAV) vectors. It is evident that normoglycemic could be achieved by long-term efficacy of diabetes gene therapy without the supply of exogenous insulin [11]. AAV vectors cause mild immune response and infect both dividing and dormant cells without integrating the genome of host cell. These features make AAV vectors as the best candidate for gene therapy. In the study, AAV vectors encoded with insulin and glucokinase genes are introduced into the skeletal muscles of STZ-induced diabetic mice and dogs. Co-expression of two genes enhances the translocation of GLUT4 and glucokinase enzyme which facilitates glucose uptake into engineered muscle cells. Expression of glucokinase enzyme alleviates the phosphorylation of glucose to glucose-6-phosphate in engineered skeletal muscle. Besides, it acts as the glucose sensor which senses blood glucose levels and reflects the amount of insulin produced to attain normoglycemia [36].

On the other hand, gene therapy for the management of diabetes is performed using humanised liver mouse model. Li et al. used AAV sero-type 2 (AAV2) as a medium to be transfected with pancreatic and duodenal homeobox 1 (*pdx-1*) gene, which can be called as insulin promoter factor 1 for the development and maturation of the pancreatic β -cells [37]. The presence of green fluorescent protein expression has confirmed that the *PDX1* gene in the liver will secrete insulin ectopically in order to have glycaemic control. From the study, high glucose content in STZ-induced diabetic mice has reduced by the treatment of AAV-*pdx-1* gene. Another gene which defined the endocrine fate of the pancreas development is neurogenin 3 (*Ngn3*) [38]. Transfection of hepatic cells by adenovirus which contained *Ngn3* leads to insulin production and trans-differentiation of oval cell population [39]. *NeuroD1* introduction into the liver of STZ-induced diabetic mice resulted in upregulation of downstream and upstream of pancreatic transcription factors, including *Pax4*, *Pax6*, *Ngn3*, *Nkx6.1* and *Nkx2.2* without remarkable hepatitis or hepatotoxicity [40,41]. Moreover, in primary duct cells, *NeuroD1* has the strongest effect in inducing insulin expression in comparison to *Ngn3*, *pdx-1*, and *Pax4* [42]. Ideal DNA construct would be targeting promoters in other cells, for example, cell type of choice such as liver-type pyruvate kinase (L-PK), glucose 6-phosphatase (G6Pase), phosphoenolpyruvate carboxykinase (PEPCK), S-14, albumin and insulin-like growth factor binding protein-1 (IGFBP-1). Promoting these genes in the liver as hepatic insulin gene therapy showed insulin secretion but the secretion is weak due to their weak promoting activity in comparison to strong constitutive promoters like cytomegalovirus [43]. For example, L-PK used to promote insulin expression in liver, this modification resulted in glucose-responsiveness and was able to restore normoglycemia for up to one month. The only limitation is the inhibition of this promoter by insulin. However, S14 and albumin could be used to avoid this feedback [44].

Non-viral introduction via intravenous injection of insulin fragments with plasmid DNA. Injection of this plasmid into the liver and muscles of STZ-induced diabetic rats, showed normoglycemia for one week and thirty weeks, respectively. The short period of expression in liver injection solved by the utilising DNA transposon

system, as the gene introduced into the host chromosome. While the co-injection of plasmid DNA containing insulin with furin, lead to considerable active insulin within muscle [45].

Introducing human insulin gene into pancreatic or liver cells through *ex vivo* transfection then autologous graft showed a positive effect on pigs as the insulin secretion, hyperglycaemia and diabetic complications remarkably improved for more than 47 weeks [46]. This improvement did not continue as gene silencing happened, however, the mechanism of this silencing is not understood. Another successful approach is through injecting lentivirus vector which carries human modified insulin gene into the portal system of diabetic rats' liver. Surprisingly, this method allows liver cells to sense glucose, in turn, synthesize, release and store human insulin as a response [47].

5.2. Diabetic therapy targeting β -cells and β -cells regeneration

5.2.1. Trans-differentiation

Drugs for diabetic treatment nowadays mostly focus on sensitising the β -cells to produce insulin mainly to lower blood glucose. However, these medicines carry unwanted side effects which lead to studies of other alternative treatments. Bonner-Weir et al. showed that upon β -cells depletion in diabetes, increased proliferation of remaining β -cells contributes to β -cell regeneration [48]. This statement was then suggested by several injury models of insulin-producing cells, which also leads to the concern of studies in β -cells neogenesis from other cell types [49]. Recently, researchers work on therapy which induces β -cells regeneration by using different kinds of cells. Researchers believe in the ability of β -cells regeneration through pancreatic progenitor cells trans-differentiation in the pancreas [50]. Trans-differentiation is explained as a conversion process from a differentiated cell to other cells. It relies on cell reprogramming, to regenerate new β -cells from pancreatic progenitor cells of adult pancreas [51]. Pancreatic exocrine cells, for example, acinar cell and ductal epithelial cell are chosen as the most relevant cells for β -cells regeneration because of the properties of pancreatic lineage as well as their differentiation potential. There are assumptions that β -cells neogenesis from pancreatic progenitor cells can happen in pancreatic ducts after childbirth. There are also researches proved that β -cells can be raised in the adult pancreas ductal tissue [50]. Ductal cells can self-transdifferentiate to β -cells when there is depletion of β -cell from duct ligation-induced injury. Nevertheless, it is controversial to the more recent studies applying labelling experiments of the ductal lineage that fail to prove duct-derived β -cell formation [36]. According to Kopinke and Murtaugh, there is no evidence of postnatal endocrine specification of progenitor ductal cells in healthy mice after birth [52]. Moreover, donor organs shortage and immune-suppressants limit its clinical applications as all studies used animal models instead of a real human microenvironment. Besides pancreatic progenitor cells trans-differentiation to β -cells, there are studies done related to the ability of α -cells for conversion into β -cells by applying β -cells ablation model in zebrafish, but further studies are required [53]. Another example of trans-differentiation is the ability of glucagon secreting α -cells to differentiate into β -cells. Furthermore, pancreatic δ -cells can transdifferentiate into β -cells which only occurs in juveniles.

5.2.2. Stem cells

Limitations of trans-differentiation of pancreatic progenitor cells have prompted to studies of alternative β -cell sources, for example, embryonic stem cells (ESCs). Throughout embryonic development, the pancreatic epithelium containing multipotent progenitors will grow into other pancreatic cell types such as ductal, endocrine and exocrine lineages [54]. The main problem of

this alternative is the usage of human stem cell during the embryonic stage. This raises the ethical issue, undoubtedly, becomes a limitation. To overcome this limitation, induced pluripotent stem cells (iPSCs) were produced through somatic cell nucleus reprogramming [55]. iPSCs have similar properties to ESCs. iPSCs can be produced by small molecules and ribonucleic acids. iPSCs match genetically with most patients, therefore preventing immune reactions. iPSCs have a slight difference as compared to ESCs which increases possibilities of applying patient-specific cell replacement therapy [56]. These alternative sources contain limitless pluripotency and expansion capacity for differentiation into all sorts of cells in the germ layer. iPSCs obtained from pancreatic duct cells of the human are generated by applying several factors such as Klf4, lenti-Oct3/4, Sox2 and c-Myc, named hiPSCs [57]. These hiPSCs showed equal levels of specific ESCs markers, which immediately differentiate into 3 germ layers where hiPSCs forms an embryoid body [58]. Recent studies reported protocols which significantly yielded β -cells which express similarly to β -cells isolated from human [59]. After its transplantation into diabetic mice, within 2 weeks, the new stem cell derived β -cells secreted insulin in response to high glucose and maintains the normoglycemic level. This yield enhances the potential of applying ESC or iPSCs as β -cell replacement therapies for the diabetic patients in future [60]. Nevertheless, ESCs and iPSCs differentiation impose multiple stages and different factors need to be taken into consideration. Besides that, clinical trials of the differentiation protocols are time consuming while undifferentiated ESCs and iPSCs carry tumorigenesis risk [61]. The obstacles have limited the application of ESCs and iPSCs for diabetes treatment. Interestingly, pancreatic progenitor cells (PPCs) can somehow defeat the limitations faced by ESCs and iPSCs due to the presence of pancreatic lineage [50].

There are many studies mentioning the advantages of mesenchymal stem cells (MSCs) therapy in diabetic through immunomodulatory mechanisms. A microenvironment is created where β -cells are regenerated while destructive T-Helper1 (Th1) cells are partially suppressed [62]. In these studies, the researchers agreed that there is an improvement in hyperglycaemia control. However, it is more preferable that MSCs therapy to be utilised with other treatment approaches. Strong histologic evidence advocates that undifferentiated MSCs do not regenerate new β -cells directly [53]. Moreover, the media obtained from MSC culture generated effective therapeutic results upon injection into diabetic mice [63]. This strategy provides a successful therapy because of its cell-free nature, as a result it prevents the issues of autoimmunity and oncogenesis. Wrapping up, if the collection techniques are optimised, MSC media could be used together with other standard and well-established therapies to lower insulin dependence or alongside transplant of insulin producing cells derived from other pluripotent sources [64].

Bone marrow stem cells (BMSC) used to replace damaged β -cells, but it produces low levels of insulin. Fortunately, adipose tissue has low immunogenicity, higher immunomodulatory and have the ability to produce more stem cells than bone marrow [65]. Furthermore, adipose-derived stem cells (ADSCs) characterised by its simple isolation procedure, easy accessibility and the capacity of the stem cells proliferation is not affected by patients age [66]. In a study, ADSCs differentiated into insulin-producing cells (IPCs), then IPCs was injected into the pancreas of STZ rats. The histological analysis revealed induction of the pancreatic regeneration process with many dilated congested blood capillaries and diffused proliferated islet cells. Interestingly, the pancreas of IPCs rats appeared similarly to the control and there was no remarkable difference in the serum glucose when IPC transplanted group compared with control (diabetic-free) group. Collectively, the transplantation of differentiated IPCs improved the morphology and function of Islet

cells in diabetic rats. More studies have done to confirm the capability of ADSCs in ameliorating T2DM in rats. ADSCs infusion could restore islet β -cells and improve hyperglycaemia through islet angiogenesis enhancement, reduce cell apoptosis and improve insulin sensitivity [67]. Another report revealed that using of human eyelid adipose tissue-derived stem cells gave rise to increased human insulin and c-peptide levels in type 2 diabetic mice and decreased IL-6, triglyceride and free fatty levels in type 2 diabetic mice model [68]. A first trial of inducing BM-MSC to differentiate into IPCs, was done by applying adenoviral vectors coding for mouse pdx-1 and Xie et al. induced human BM-MSCs. Produced IPCs showed a capacity to liberate insulin in a glucose-dependent manner [69,70]. Many studies compared between umbilical cord (UC)-MSCs especially Wharton's jelly-derived MSCs (WJ-MSCs), and BM-MSCs, they concluded that WJ-MSCs showed a superiority in differentiation potential towards a mature β -cell phenotype than that in BM-MSCs [71]. In addition, WJ-MSCs revealed greater capacity of mRNA expression of insulin and C-peptide than BM-MSCs [64]. Consequently, ADSCs could be a propitious therapeutic strategy to patients with T1DM and T2DM if its safety and effectiveness are confirmed [66].

Human placenta-derived MSC (PD-MSC) also attracted scientist due to their ability to produce insulin. A pilot study tested the effect of PD-MSC after intravenous injection for 10 T2DM patients. Data revealed a significant decrease of glycosylated haemoglobin in all the 10 patients, and the levels of insulin and C-peptide were higher than those prior treatments. Furthermore, no development of side effects such as chills, liver damage, fever and immune rejection, and the cardiac and renal functions were improved [72].

5.2.3. Enhancing self-replication of β -cells

Promoting β -cell replication or expansion by β -cells self-replication can be considered as one diabetic therapy in future too. β -cells were quiescent during infancy [49]. However, β -cells can still replicate under certain conditions, for example, obesity and pregnancy [73,74]. The proliferative capacity is age-dependent and varies with different species. One of the methods to induce regeneration of β -cell is to focus on the pathways regulating β -cell proliferation. Respective receptors activation enhances signalling through ERK signalling pathway. Glucose, glucagon-like peptide-1 (GLP-1), as well as insulin was proven to have the ability in activating mitogenic signalling by PI3K/Akt/mTOR pathway. Signals of glucose via calcineurin/NFAT and ERK pathways and signalling through GLP-1 provoke the generation of cAMP for β -cells proliferation [75]. Various circulating factors which include GLP-1 from intestinal cells, osteoblast-derived hormone, osteocalcin and thyroid hormone have been identified to pro-proliferate β cells. Furthermore, MAPK and PI3K/Akt pathways regulate β -cell proliferation. ERK1/2 phosphorylation-mediated MAPK pathway has become the main mitogenic pathway which discrete regulation of β -cell function from proliferation metabolically because ERK1/2 phosphorylation is not participated in the secretion of insulin [76]. MAPK pathway also influences mitogenic effect of various growth factors and nutrients as well as hormones. Another major pathway in transducing β -cell proliferative signals includes PI3K/Akt/mTOR pathway which can be mediated by insulin, GLP-1, and glucose [77]. The importance of activating Akt is that it connects growth signals to mTOR, then regulates cell growth.

6. Non-pharmacological approach

Since T2DM is essentially a lifestyle problem, prevention by non-pharmacological interventions are very promising. As a sedentary lifestyle paired with excessive food intake is the predominant cause of T2DM, lifestyle interventions are the safe natural

way of prevention. It can be largely presumed that patients will be at a lower risk of experiencing serious side effects by following non-pharmacological approaches, as compared to taking drugs. However, it must be noted that the effects of this non-drug approach may not be everlasting and treatment plan adherence is a big part of ensuring the success of this approach. Lifestyle advice needs to be routinely given and reinforced, along with other tactics to gain compliance.

By following these methods, the development of diabetes, reversible risk factors and complications associated with the disease can be prevented. This can also lower both individual and public health burden by decreasing the cost spent on diabetes care. This, in turn could maintain or even improve one's quality of life.

7. Pharmacological approach

When compared to lifestyle interventions alone, each pharmacological agent used as monotherapy multiplied the number of patients who reached HbA1c target levels below 7% by 2–3 folds. Due to poor diabetes control, most patients would require multiple therapies to achieve good glycaemic control in the long run [78]. Hypoglycaemia is one of the major risk factors that need to be looked out for when combinations of multiple pharmacological agents are used concomitantly. The choice of which pharmacological agents to be chosen for each patient should be a shared decision-making process. The cost, potential side effects, potential benefits, glucose lowering efficacy and dosing regimen are things to be taken into consideration before selecting a medication. Dosage adjustments are necessary for renal impaired patients. Regular monitoring is essential not only for renal impaired patients, but for all those on pharmacological agents.

7.1. Insulin

Insulin injection remains the main treatment for T1DM where insulin deficiency is seen. When oral hypoglycaemic drugs are not successful in regularizing glucose and HbA1c levels in T2DM, insulin can be utilised as monotherapy or together with oral hypoglycaemic agents.

The limiting factor of insulin is that it has to be administered through injections. Despite showing favourable treatment effects, needle phobia causes poor compliance which leads to inadequate glycaemic control. Insulin pumps or can be considered as continuous subcutaneous insulin infusions, are available in the market now. The US Food and Drug Administration (FDA) has classified these pumps as moderate to high risk devices and clinical trials are continuously being done for safety and efficacy purposes [79]. Non-invasive alternative would be via inhaled or oral insulin. However, challenges are in place for use of these routes of administrations. Improved pharmacokinetic and pharmacodynamic parameters may ensure the success of insulin using this administration route. Oral insulin is another appealing possibility. It is presently still in the stage of clinical trials [80], and a lot more research is in store before this formulation hits market shelves.

7.2. Biguanides

Metformin is the most prescribed antidiabetic drug, especially used in obese and overweight individuals. This drug is still the best choice for monotherapy. It functions by increasing insulin sensitivity, boosting the uptake of glucose by phosphorylating GLUT-enhancer factors and suppressing hepatic gluconeogenesis [81]. Metformin can aid in losing weight and shows reasonable triglyceride and serum LDL cholesterol reduction [82]. Metformin also functions by activating one of the enzymes involved in expressing

hepatic gluconeogenic genes, known as AMP-activated protein kinase, in addition to inhibiting mitochondrial complex 1 and enzyme, glycerophosphate dehydrogenase in the mitochondria [83]. All these lead to the lowering of glucose as well as HbA1c levels. However, metformin does not affect β -cells and if there is no weight loss, insulin sensitivity in muscles do not show good progress, with HbA1c levels gradually rising again after the initial drop.

7.3. Sulfonylureas

Sulfonylureas are secretagogues which work by triggering endogenous insulin secretion from pancreatic β -cells. It mainly targets the ATP-sensitive potassium channels on β -cells [84] and is only effective in the presence of residual pancreatic β -cells. Sulfonylureas do not have any longstanding protective effects on β -cell functions and may speed up β -cell failure [85]. After the initial drop in glucose levels, HbA1c concentrations have been shown to increase. There have been a great number of incidences where sulfonylureas cause hypoglycaemia, especially from the older generation drugs. Blood glucose concentrations can be lowered by almost 20%, whereas HbA1c levels can drop by 1%–2%. The unwanted side effect of sulfonylureas is the weight gain [86].

7.4. Thiazolidinediones

Thiazolidinediones (TZDs) are peroxisome proliferator-activated receptor γ activators which works by improving the insulin sensitivity in adipocytes, cardiac muscles and the liver [87]. They work on β -cells to preserve the secretion of insulin. As a result, it is used as a treatment plan for insulin resistant in T2DM patients, showing lasting effects for up to 5 years [88]. The common side effect of TZD is increased body weight. However, the greater the weight gain, the better in HbA1c lowering as well as recovery in β -cell functions and insulin sensitivity [89]. In patients with T2DM, TZD can decrease the thickness of their carotid arteries. Rosiglitazone was previously banned by the FDA due to the great number of cardiovascular related events, but the ban has currently been lifted. Pioglitazone is contraindicated in class III to IV cardiac failure patients. Although it is well-tolerated even in older renal impaired people, it is best not to be indicated in elderly congestive heart failure patients due to the increased likelihood associated with fractures in women [90].

7.5. Dipeptidyl peptidase-4 (DPP4) inhibitors

DPP4 inhibitors, also called as gliptins, are a group of relatively newer treatment agent which works by inhibiting the enzyme, dipeptidyl peptidase 4. Inhibition of this enzyme is responsible for delaying the inactivation of incretin hormones such as glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP), which involved in regulating glucose homeostasis physiologically [91]. GLP-1 and GIP stimulate insulin synthesis from pancreatic β -cells [92]. GLP-1 also diminishes glucagon secretion from pancreatic α -cells. These effects collectively result in improved glycaemic control in individuals having T2DM. These drugs have fewer reported adverse effects, low hypoglycaemia risk and show weight neutrality [93].

7.6. Glucagon-like peptide 1 (GLP-1) analogues

The use of GLP-1 analogues are basically as incretin-based therapies that increase the secretion of insulin via a glucose-dependent fashion, decrease the secretion of glucagon and ultimately repress the production of hepatic glucose [94]. A lasting lowering in HbA1c of up to three years has been observed. Although

these drugs are not as tolerable as DPP4 inhibitors, they bring about better lowering in HbA1c levels and stimulate weight loss [95]. They rectify endothelial dysfunctions, prolong gastric emptying time, improve lipid profiles and lower blood pressure [96]. There is some data put forward that states the positive influences of incretin-based therapies on sleep, inflammation (by reducing reactive protein levels), the central nervous system, hepatic and cardiovascular health [97].

7.7. Sodium–glucose co-transporter-2 (SGLT2) inhibitors

SGLT2 inhibitors, also known as gliflozins, suppress sodium transport and boost glucose elimination via the kidneys by inhibiting glucose absorption in proximal renal tubules, thus lowering the plasma blood glucose concentration [98]. Pharmacological agents in this class include canagliflozin, dapagliflozin and empagliflozin. They can be used in patients at any stage of diabetes because they work independently on insulin [97]. These drugs can improve β -cell functions, enhance insulin sensitivity and ameliorate glucotoxicity as a result of glucosuria. They have the ability to decrease HbA1c levels by 0.5%–1%, reduce weight and lower blood pressure [99]. Side effects that have been observed are urinary tract infections, genital mycotic infections particularly in females and volume depletion-related symptoms [100]. Extra caution needs to be taken when prescribing this drug to elderly patients and those who are on diuretics.

7.8. Combination therapy

Combination therapy is started for faster, more effective control on blood glucose and dose reductions in individual medications. It is normally initiated when monotherapy is inadequate in keeping blood glucose levels under control. Exogenous insulin can be combined with various oral antidiabetic drugs to allow insulin dosage lowering. Combining insulin with metformin or TZD improve glycaemic control. When basal insulin is combined with GLP-1 receptor agonists, HbA1c levels are decreased accompanied by the reduction in weight. SGLT2 inhibitors are mainly applied together with either metformin or other agents [101]. It can also be used in combination with DPP4 inhibitors to improve glycaemic control and reduce weight, without raising the risk of hypoglycaemia [102].

A combination of low dose metformin, and drugs belong to TZD class (pioglitazone, and rosiglitazone), have shown effectiveness in preventing prediabetic individuals from becoming diabetics [103].

8. Conclusion

Diabetes mellitus is a huge burden not only on the patients, but also for their family, community and the country. All types of diabetes should be detected as early as possible and managed appropriately to prevent its progression and complications. While it may be harder to prevent T1DM, T2DM is preventable via lifestyle modifications, namely by diet and exercise in conjunction with maintaining a healthy weight. The main reason for diabetic treatment failure is noncompliance and this is mainly due to the unwanted side effects of conventional medicines. Therefore, new innovative pharmacological agents are in the process of development for a better management of this disease. Current discovery also shows that there are possibilities in using gene therapy and stem cells as therapeutic targets for personalised interventions with potentially better clinical outcomes and lesser adverse effect.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.dsx.2018.10.008>.

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