ISSN: **3107-6513**

Noval Targets for Diabetes Management Drug Information Services

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Abstract:

Diabetes mellitus (DM) is characterized by an absolute decline in insulin secretion and peripheral resistance and is the most prevalent metabolic and endocrine disorder. However, the pathogenesis of DM also includes adipocyte insulin resistance, increased glucagon secretion, increased renal glomerular glucose absorption, and neurotransmitter dysfunction Current therapeutic interventions against DM focus mostly on glycaemic control without considering the other pathological determinants that eventually lead to treatment failure and the progression of DM.

Diabetes Mellitus (DM) is a multi-factorial chronic health condition that affects a large part of population and according to the World Health Organization (WHO) the number of adults living with diabetes is expected to increase. Since type 2 diabetes mellitus (T2DM) is suffered by the majority of diabetic patients (around 90–95%) and often the mono-target therapy fails in managing blood glucose levels and the other comorbidities, this review focuses on the potential drugs acting on multi-targets involved in the treatment of this type of diabetes.

In particular, the review considers the main systems directly involved in T2DM or involved in diabetes comorbidities. Agonists acting on incretin, glucagon systems, as well as on peroxisome proliferation activated receptors are considered. Inhibitors which target either aldose reductase and tyrosin phosphatase 1B or sodium glucose transporters 1 and 2 are taken into account.

Keywords: Diabetes mellitus; type 2 diabetes mellitus; multi-target compounds; multi-target drugs

Introduction

Diabetes mellitus (DM) is a multi-factorial chronic health condition triggered by several genetic and or environmental factors. Indeed, this pathology is characterized by strong familiarity and the frequency of diabetes varies in different ethnicities, such as black and Hispanic people, and some minorities, like American Indians and Natives of Alaska, are more likely to have diabetes for a specific genetic profile.

The World Health Organization (WHO) Global report on diabetes shows that the number of adults living with diabetes has almost quadrupled since 1980 to 422 million adults and is expected to increase to 693 million by 2045 [1].Pharmacological therapy and/or insulin may be required in order to maintain the blood glucose level as near as possible to normal and to delay or possibly to prevent the development of diabetes-related health problems.

For determining the right therapy, the involved type of diabetes plays a key role and in 2018 American Diabetes Association (ADA) proposed the following classification [2]:

ISSN: 3107-6513

1. Type 1 diabetes mellitus (T1DM): due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency;
2. Type 2 diabetes mellitus (T2DM): due to a progressive loss of β-cell insulin secretion frequently on the background of insulin resistance;
3. Gestational diabetes mellitus (GDM): diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt prior to gestation;
4. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young (MODY)), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis),[3] and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation).

Since T2DM is suffered by the majority of diabetic patients (around 90–95%) this review focuses on the potential drugs acting on multi-targets involved in the treatment of this type of diabetes.

1.1 **Type 2 Diabetes Mellitus (T2DM)**

Type 2 Diabetes Mellitus (T2DM) has been referred for long time as non-insulin dependent diabetes, or adult-onset diabetes characterized by insulin resistance, which could progressively worsen to absolute resistance, but in the past decade reduced β-cell function has been recognized as a key problem in T2DM [4]. This association can be appreciated in **Figure 1.**

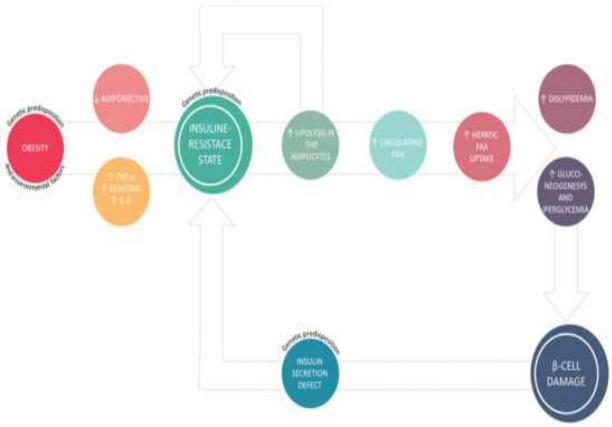

Figure 1. Pathophysiology of type 2 diabetes mellitus (T2DM).

The adipose tissue is an endocrine organ that can secrete several hormones and cytokines , namely TNF-α, IL-6, resist in which are able to induce a chronic inflammation state and insulin resistance. Furthermore, in obese patients with metabolic syndrome is more common to observe low adiponectin levels and a leptin-resistance state [5]. In this situation, insulin has no anti-lipolytic effect, consequently there is an increased production and secretion, in the systemic circulation, of fatty free acid (FFA) that also are responsible for the insulin-resistance state.

Usually, the early stage of this pathology could be asymptomatic, or symptoms could be so mild that they go unnoticed.

- **Genetic influences**

Genetics play a very strong role in the development of T2DM [6]. The most common forms of T2DM are polygenetic, so there are changes in multiple genes, but there are also some rare forms of diabetes that are caused by single gene mutation, known as monogenic diabetes.

- **Environmental influences**

New understandings of the progression of T2DM are related both to the lifestyle and to the gut microbiota and the dynamics that leads to microbiome dysbiosis .

- **Age**

ISSN: 3107-6513

Until two decades ago, T2DM was usually found in adults and seniors. This was consequential to the increase of insulin resistance due to body composition modification.

- **Obesity**

A person with a body mass index (BMI) equal to or greater than 30 kg/m^2 is generally considered obese .

- **Poor physical fitness**

Sedentary lifestyle may increase risk of T2DM [7]. Physical activities help to control body weight and lower blood glucose in addition to many other benefits.

- **Hypertension and high triglycerides levels**

These are conditions usually associated with insulin resistance, so they increase diabetes risk.

- **Smoking**

Smoking is associated with diabetes and other health conditions such as cancer and heart diseases.

- **Gestational Diabetes**

Women, that develop diabetes during the pregnancy, have higher risk of suffering for T2DM later in life.

- **Polycystic Ovary Syndrome**

Polycystic Ovary Syndrome (PCOS) is a common hormonal disorder that causes irregular menstrual cycles, hirsutism, acne, and, frequently, obesity.

There are many anti-diabetic drugs that exert clinical effects via different mechanisms. The four major groups of anti-diabetic agents are:

a) biguanides, like metformin, which reduce gluconeogenesis in the liver;

b) insulin secretagogues which stimulate the pancreas to secrete insulin and include drugs such as sulfonylureas;

c)insulin sensitizers which improve sensitivity of peripheral tissues to insulin and include thiazolidinediones and[8];

d)insulin or its analogues which provide insulin exogenously in the form of recombinant insulin.

Metformin is the first-line pharmacotherapy for T2DM. Besides reducing the glucose level, this has an insulin-sensitizing effect with multiple[9] actions on tissues such as the liver, skeletal muscle, endothelium, adipose tissue, and the ovary.

Although the existence of plenty of diabetic drugs, other drug monotherapy proved unsuccessful in providing satisfactory managing blood glucose levels and the other comorbidities and therefore therapeutic management is often achieved by combinations therapy with drugs that act with different mechanism of actions as illustrated in Figure 2 .

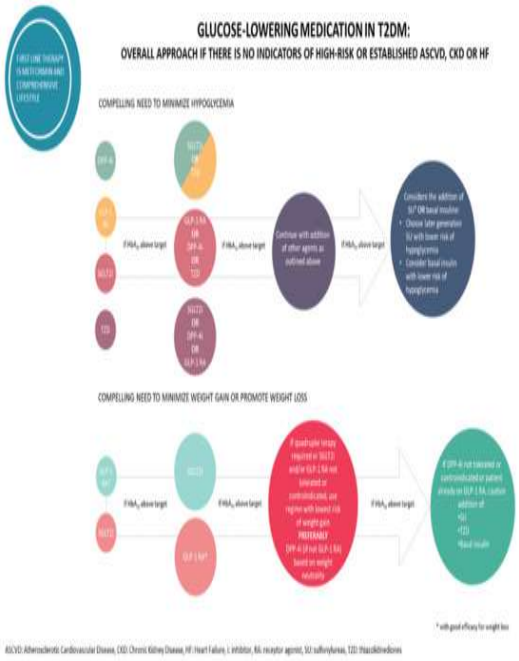

Figure 2. Glucose-lowering medication in T2DM.

1.2. Multi-Target Compounds

Traditionally drug design had the aim of targeting selectively a single biological entity in order to avoid other interactions that could potentially lead to unwanted side effects.[10] However, this

ISSN: 3107-6513

approach is now considered outdated and over the past years most efforts in drug design were made to develop compounds that are able to exert numerous physiological actions especially for diseases of complex ethicology, such as cancer, inflammation, central nervous system (CNS) disorders, and diabetes.

The knowledge-based approach also known as "framework combination" relies upon structure–activity relationship (SAR) knowledge of every single target involved, in which the pharmacophores are combined in different ways (as represented in Figure 3), where they can be connected by a linker, or they can be overlapping in the same compound or highly integrated in a multi-target drug[11].

Throughput screening (HTS), which allows large, diverse compound sets to be screened against several targets of interest, in parallel.

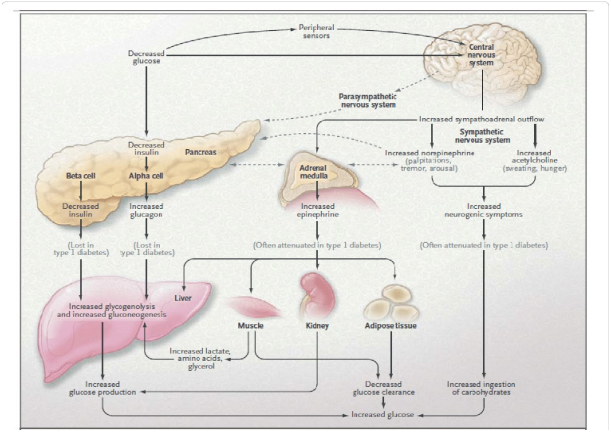

Figure 3. Different strategies to design multi-target ligands.

Finally, in silico methods gained an increasingly popularity as multi-target drug design tools. A promising tool is the fragment-based drug design (FBDD) approach where fragments, even when binding weakly to the biological target, are identified.

Though the multi-target approach has only been purposely applied in the last decades, many of the previously known therapeutic agents are in fact multi-target ligands [12], which is especially true for those drugs that were discovered by serendipity, phenotypic screening, or traditional medicine.

Pathophysiology There is direct association between hyperglycaemias and the physiological responses. The brain recognizes the hyperglycaemia and sends a message via nerve impulses to pancreas to decrease its effect. Figure (4)

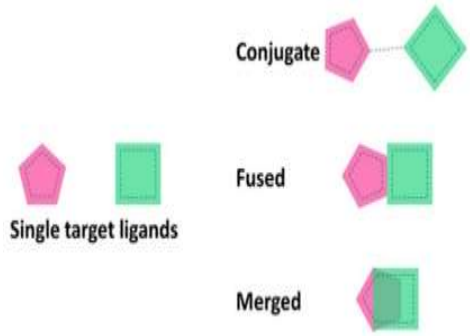

Figure 4 the physiological response to hyperglycemia

Type 1 diabetes mellitus

Type 1 diabetes mellitus is known by autoimmune reduction of insulin producing cells in the pancreas by CD4+ and CD8+ T cells and macrophages[13] which infiltrates the islets. Various features classify type 1 diabetes mellitus as an autoimmune disease:

- Immune-competent and accessory cells present and infiltrates in pancreatic islets.
- The associated susceptibility for the disease with class II genes of major histocompatibility complex and human leucocyte antigen. [14]
- Islet specific autoantibodies are present.
- The response of the disease to immunotherapy.
- Usual occurrence of other organ specific auto-immune disease in the affected person.

The majority of islet antibodies are move against glutamic acid decarboxylase (GAD) inside the

ISSN: 3107-6513

pancreatic B cells. As a result of the autoimmune destruction of the pancreatic beta cells; a deficiency in insulin secretion, which leads to metabolic[15] derangement linked with type 1 diabetes mellitus. However, insulin deficiency considers as the primary defect in type 1 diabetes mellitus, also it was found that there is a defect in administration of insulin. In addition, it results in poor expression of GLUT 4 class of glucose transporters which present in the adipose tissue. (Figure 5). (Baynest, 2015)

Figure 5 A it shows the normal physiological effect of reduction in insulin linked with a low glucose concentration which leads to stimulation of alpha cell glucagon secretion. In Figure 3B presents the pathophysiological failure of beta cell, which leads to no decrease in insulin and no increase in alpha-cell glucagon secretion, in spite of the low glucose concentration.

Type 2 diabetes mellitus These mechanisms are break down in type 2 diabetes, the main consequences in the pathology of type 2 diabetes are impaired insulin secretion via a dysfunction of the pancreatic beta cells, in addition, impairment of insulin action through insulin resistance.[16,17] In other words, the plasma insulin concentration been elevated in both fasting and feeding state. (Figure 6)

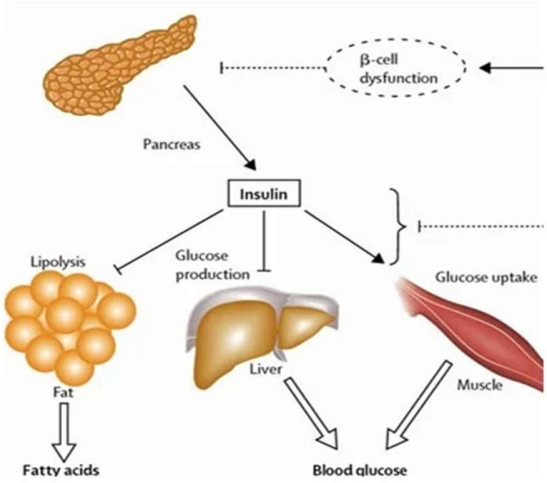

Figure 6 pathophysiology of hyperglycaemias and increased fatty acids in type 2 diabetes Insulin resistance

It is believed through the primary events, that there is initial deficit in insulin secretion and mainly this relative insulin deficiency associated with peripheral insulin resistance. The significant resistance to the insulin leads to impaired insulin mediated glucose uptake in the peripheral, in addition, incomplete suppressed hepatic glucose output and impaired triglyceride uptake by fat Patients with type 2 diabetes has elevated and accelerated endogenous glucose production or impairment in fasting glucose[18].

Novel target for diabetes management

Current understanding of the pathophysiology of DM from the triumvirate of β cell failure to "ominous octet" has identified multiple pathogenic hotspots in the pathogenesis of DM . Likewise, recognition of the "ominous octet" in the pathogenesis of DM has provided insight into the development of novel therapeutic agents against DM [19]. In a subsequent section of this manuscript, we have discussed the novel therapeutic agents against DM that can be used in the future for effective management of DM, some of these therapeutic agents are in phase 3 of clinical trials and some are in the preclinical phase of development.

- **FGF21 Analogues**

ISSN: 3107-6513

The main factor limiting the use of native FGF21 is its short circulating half-life (30 min to 2 hours). This is partly due to renal clearance because of its moderate molecular size, but largely due to inactivation. FGF21 is susceptible to cleavage of the C-terminal domain by an endopeptidase, FAP (fibroblast activating protein), which removes the last 10 amino acids, drastically reducing binding to the coreceptor β-klotho.[20] Notably, FAP is highly expressed in the livers of patients with MASH. As such, engineering of FGF21 analogues to increase plasma half-life has been a prerequisite to study the potential benefits of FGF21 in various metabolic conditions such as dyslipidaemia, obesity, type 2 diabetes, and MASLD.

- **GDF-15 Modulators**

The development of T2DM occurs as a result of the combination of IR and a defective insulin secretion by β cells. Obese subjects at risk of developing T2DM may display an initial state of IR. Under these conditions,[21] β cells increase insulin secretion to compensate for the reduced action of insulin, maintaining glucose tolerance. However, over time, β cell insulin secretion declines, leading to insufficient insulin levels that, in a context of IR, results in glucolipotoxicity and obesity-induced...

- **Glucokinase receptor antagonists**

Given that glucokinase sets the rate of metabolic flux in the beta-cell, it was initially predicted that glucokinase activation would enhance beta-cell metabolism and promote insulin secretion. However, this turned out not to be quite so straightforward.
Instead, overexpression of gck in ins1 cells suppressed glucose utilisation at high glucose, without affecting it at low glucose . Levels of glycolytic metabolites upstream of glyceraldehyde 3-phosphate dehydrogenase (gapdh) were markedly elevated, consistent with limited flux through this enzyme [22]. This was found to result from a failure to regenerate sufficient nad^+, an essential cofactor for gapdh.

Novel approaches for diabetes treatment:

A promising cell resource for diabetes treatment is human pluripotent stem cell-derived islets (hPSC-islets), which contain nearly pure populations of endocrine cells [23]. Unlike conventional iPSCs, which are created by overexpressing transcription factors in somatic cells, CiPSCs (Chemical-induced Pluripotent Stem Cells) are produced using small-molecule chemicals as reprogramming factors. These chemicals are easy to manufacture, non-genomic, scalable, and tumble, providing a more standardized approach. This method offers an alternative means to generate human pluripotent stem cells (hPSCs) that may be more suitable for therapeutic applications [24] After differentiation into β cells, corrected SC-β cells should exhibit robust dynamic insulin secretion in vitro in response to glucose, similar to WFS1 in iPSCs derived from a patient with Wolfram syndrome (WS) .

CRISPR/Cas9 systems (clustered regularly interspaced short palindromic repeats-associated Cas protein system) evolved as part of prokaryotes' adaptive immune response to defend against bacteriophages, invading plasmids, and viruses. In the bacterial genome, A–T-rich leader sequences are adjacent to 27–42 base pair palindromic repeats, which are separated by proto-spacers. These spacers are segments of DNA derived from previously encountered bacteriophages, serving as a molecular record of past infections. The CRISPR system utilizes these protospacers as templates to recognize and defend against subsequent viral invaders. [25]. CRISPR/Cas9 technology is increasingly used to manipulate human pluripotent stem cells (hPSCs) to model monogenic diseases (MDs) and study pancreatic development.

These technologies enable the creation of gene-edited hPSCs to explore mutations associated with MDs, particularly those impacting pancreatic development and beta-cell function . For instance, Wang et al. investigates how mutations in PDX1[26] and related factors influence pancreatic cell commitment, demonstrating how low PDX1 levels

ISSN: 3107-6513

affect beta-cell function and development [.Similarly, Cardenas-Diaz et al. utilized CRISPR to ablate HNF1A in ESCs, discovering that it interrupted beta-cell development .

Most clinical studies conducted thus far involve small, homogeneous cohorts, making it difficult to assess how these therapies will perform across genetically and environmentally diverse populations. Importantly, the irreversible nature of genome editing amplifies the importance of long-term surveillance, as adverse outcomes may emerge years after treatment.[27]

Limitations and Challenges

Describing resistance, and dysregulated glucose metabolism. While existing drugs (metformin, sulfonylureas, SGLT2 inhibitors, GLP-1 agonists) are effective, they[28] do not fully prevent disease progression. Therefore, novel molecular targets are being investigated.

Conclusions

Nowadays, diabetes mellitus is gaining vast and immense attention owing to its catastrophic consequences on the human population globally. There has been a persistent search going on all over the world from all ages to combat the disease due to its huge devastating effects on the lives of human beings. For this reason, the disease needs to be continuously monitored and managed for leading and maintaining a healthy and sound life. The drugs (insulin, metformin, tolbutamide, glipizide, etc.), which were being used conventionally for a long span for the management of DM are now being substituted by better drugs owing to their potency, enhanced pharmacological action, long-lasting effects, lesser or reduced after-effects along with remarkable results on maintaining the blood glucose levels within the desired range. Moreover, the significance and importance of exercise, dynamic lifestyle, and diet for the management of the disease should not be overlooked especially in the case of T2DM.

Presently, various pharmacological agents tested for the amelioration of the disease showed more promising results but have been associated with various side effects. For that reason, the disease is being evaluated on a large scales globally and phytomedicines are gaining immense attention owing to their promising effects on DM. Also, the rationale for testing phytomedicines on a large scale is due to its low cost, lesser side effects, long-lasting beneficial effects, and better patient observance in contrast to the synthetic drugs/allopathic drugs used for the management of DM.

Diabetes mellitus is accounted for extensive health and economic burden annually, however, the development in the field of drug delivery and disease management is stagnant. Simultaneously, the limitations associated with the current marketed formulations demand for easy and non-invasive systems with long lasting hypoglycaemics effect and patient compliance. Cognizance of NDDS pertaining to diabetes treatment has risen gradually that is evidenced from nanoparticulate systems in which noteworthy results were found. Moreover, the pharmacoeconomic analysis indicates lower cost of treatment by means of NDDSs.

But the commercial, societal and regulatory aspects related with these systems are still ambiguous even when massive research has been done. Therefore, to make these systems available in the global market, their safety profile, safety pharmacology, environmental effects during formulation and their potential effects on the health are to be addressed properly. Furthermore, the developed formulations need to be extensively optimized in different animal species to minimize the incidences of failure at clinical level in different human subject.

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