International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 384-392 www.ijprajournal.com ISSN: 2456-4494

# A Subtitled Analysis of Gene Therapy as a Possible Diabetes Type 1 and Type 2 Treatment

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Submitted: 01-11-2022 Accepted: 12-11-2022

**ABSTRACT:**
Extremely high blood glucose levels brought on by an inability to manufacture insulin or a loss in insulin sensitivity and function are a hallmark of type 1 and type 2 life-threatening diabetes mellitus. Diabetes has increased in prevalence throughout time and is now recognized as one of the leading causes of disease and mortality. Due to its expensive maintenance requirements and expanding complications, diabetes is a substantial financial burden. Patients who take traditional diabetic medications, which focus on insulin secretion and sensitivity, experience unpleasant side effects, which decrease adherence and result in treatment failure. In addition to insulin and oral hypoglycemic drugs, other treatments have been used, such as gene therapy and induced-cell regeneration. Other treatments for diabetes, such as gene therapy and induced-cell regeneration, have not been used as frequently as insulin and oral hypoglycemic medications. This review's goal is to provide an overview of the diabetic medications now on the market as well as information on the advancement of new pharmacological therapies and gene therapy as prospective diabetes interventions in the future.

**Keywords:** Oral hypoglycemic drugs, -cell regeneration, diabetes mellitus, Gene therapy, and Stem cells

## I. INTRODUCTION

Legend has it that one of humanity's first illnesses was diabetic mellitus (DM). Blood glucose levels rise in diabetes mellitus (DM), a metabolic condition that necessitates regular monitoring and effective care. In addition to assisting cells in absorbing glucose for energy, insulin is produced by pancreatic beta cells (-cells). Diabetes mellitus is primarily brought on by poor insulin sensitivity or inadequate insulin production (DM). It is split into numerous kinds, with type 1 and type 2 DM being the most prevalent. Because of T-cell-mediated autoimmunity, which kills pancreatic cells, type 1 diabetes (T1DM) is characterised by an inability to make insulin [1]. Novel therapeutic classes have resulted as a result, including incretin mimics [8], amylin analogues, analogues of the gastric inhibitory peptide (GIP), and inhibitors of the dipeptidyl peptidase-4 (DPP-4) and peroxisome proliferator activated receptor (PPAR). [9]. Trans-differentiation or stem cells that trigger regenerating cells have a direct impact on enhancing form and function [10]. Contrarily, gene therapy has lately been demonstrated to offer tremendous potential for controlling diabetes, with numerous clinical studies confirming its safety and effectiveness for a wide range of complex illnesses. Positive results have been seen with both viral and non-viral forms of gene therapy. Studies have demonstrated that Adeno-associated virus (AAV) vector-based gene therapy, for instance, improves long-term glycemic management and reduces diabetes secondary issues[11].

### Epidemiology

Regardless of income level, the general population is no longer unaware of the term "DM" since it is spreading throughout all nations [12]. By 2049, diabetes would afflict 629 million people, according to recent projections [13]. T1DM affects people of all ages, with a male preponderance in young adults, but it is more prevalent in children, particularly those between the ages of one and fourteen [14]. On the other hand, T2DM is more prevalent in obese adults, albeit it can also affect children, according to current studies [15]. The main contributor to diabetes in the general population is also known as T2DM.

### Risk factors

The majority of cases of type 1 diabetes occur in youngsters, and the underlying genetic predisposition is frequently a major contributing factor. Type 2 adult-onset diabetes is more

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 384-392 www.ijprajournal.com ISSN: 2456-4494

frequently linked to sedentary behaviour, mindless eating (consuming high-carbohydrate, high-fat foods), and inheritance. A few weak genes have been identified as risk factors for T1DM because this kind of diabetes is primarily brought on by inherited genes that are passed down via families. This group includes some HLA-types (human leukocyte antigens). Studies have shown that identical twins are significantly more likely than fraternal twins to develop T1DM, suggesting a strong hereditary susceptibility within the family. Environmental factors such viral infections, poor vitamin D levels, and insufficient UV exposure can also contribute to T1DM. This was demonstrated by a study examining the link between UVB exposure and the incidence of T1DM, which found an inverse relationship [16]. Childhood obesity, rapid newborn growth, older maternal age, and short nursing length are among the nutritional and lifestyle variables that contribute to the development of T1DM [17]. Although T1DM is primarily caused by an individual's genetic predisposition, it is actually caused by a complex interaction of genetic, immunological, and environmental variables that destroy pancreatic-cell function. Although genetics play a role in T2DM, diet and lifestyle are the most important factors. Foods heavy in carbohydrates but low in fiber, sugary beverages, and a sedentary lifestyle all increase a person's risk of T2DM. Because of the low level of physical activity, the body absorbs less glucose in the blood to be used for energy production. The body absorbs less glucose in the blood for use as energy since there is less physical activity. As a result, obesity and growing diabetes rates are commonly linked. Women who have undergone gestational diabetes are more likely than women who have not to acquire T2DM [18].

**Etiology diabetes mellitus type 1**

T1DM, commonly known as insulin-dependent diabetes, is characterised by insulin deficiency brought on by an autoimmune response that gradually kills pancreatic cells. A patient with T1DM had extensive immune cell infiltration in their pancreas, including T and B lymphocytes, macrophages, dendritic cells, natural killer cells, islet-reactive autoantibodies, and islet reactive T-cells [19]. The probability of developing T1DM is linked to -cell turnover or injury, which causes autoantigens to be released. The T-helper cells are subsequently given auto-antigens from -cells by the antigen-presenting cell (APC). APC and the major histocompatibility complex will then migrate to the pancreatic lymph node (MHC). Autoantibodies and autoreactive T lymphocytes are activated and directed against -cell autoantigens when APC is present [20]. These activated T-cells reactivate when they come into contact with cognate -cell antigens, destroying the -cells. T1DM is brought on by macrophages and T-cells producing cytokines like interleukin-22 (IL-22), interferon (IFN), and tumour necrosis factor (TNF) [21]. They can cause inflammation by generating nitric oxide synthase (NOS), which causes reactive oxygen species to develop (ROS). ROS can cause tissue damage by disrupting -cells [22,23]. Furthermore, cytokines can activate the production of apoptosis-inducing receptors (AIF), such as Fas, which leads to Fas-mediated death of -cells. When Fas surface ligands come into touch with effector T-cells, they kill them. Effector T-cells secrete chemicals called perforin that help protease granzymes pass through [19]. By enabling perforin molecules to pass through and activating the cells' nucleases, these granzymes result in cell death. Hydrogen peroxide and superoxide anion have been linked to macrophage toxicity. Macrophages create soluble mediators including reactive oxygen species (ROS) and cytokines like interleukin-1 beta (IL-1) and interferon gamma (IFN-) in response to tumour necrosis factor-alpha (TNF-) and lipopolysaccharide, which ultimately lead to cell apoptosis [22,23]. -cells have the ability to self-destruct when subjected to a particular environment. -cells produce more MHC II when there is inflammation, which allows them to transport antigen to CD4 T-cells that can produce diabetes [22]. The islets of Langerhans are also colonised by many chemokines produced by -cells, which then draw immune cells to the pancreas via the chemokine receptor [24]. Combining innate and adaptive immunity results in T1DM. According to current study, the gut microbiota has become a key player in the emergence of autoimmune illnesses, including T1DM. In conjunction with innate immunity, the gut microbiota modulates pattern-recognition receptors (PRR) and orchestrates the innate inflammatory response. In response to the recognition of PAMPs by PRR, pro-inflammatory cytokines are activated, increasing phagocytosis, autophagy, and interferon activity, all of which encourage cell death. Examples of toll-like receptors (TLR) that contribute to the propensity for T1DM disease include TLR7, TLR8, MyD88, and NLPR3. [25] The main cause of type 2 diabetes mellitus T2DM is insulin resistance. Obesity, which is characterised by poor dietary and lifestyle choices, is one of its key causes. Insulin sensitivity is influenced by consuming carbs, exercising, and

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 384-392 www.ijprajournal.com ISSN: 2456-4494

being under stress. Because they have more adipose tissue, obese people create more hormones and other chemicals, which may alter their insulin sensitivity.In obese individuals, non-esterified fatty acids (NEFA) in the blood have been associated to insulin resistance. The presence of both a high fatty acid environment and hyperglycemic conditions can result in decreased insulin gene expression [26]. The accumulation of sterol and islet inflammation caused by dysfunctional cholesterol transporters kills -cells [27]. The main cause of T2DM is insulin resistance. Obesity, which is characterised by poor dietary and lifestyle choices, is one of its key causes. Consuming carbohydrates, engaging in physical activity, and receiving stress signals all affect insulin sensitivity. Obese persons produce more hormones and other substances because they have more adipose tissue, which could lead to changes in insulin sensitivity. In obese individuals, non-esterified fatty acids (NEFA) in the blood have been associated to insulin resistance. The presence of both a high fatty acid environment and hyperglycemic conditions can result in decreased insulin gene expression [26]. The accumulation of sterol and islet inflammation caused by dysfunctional cholesterol transporters kills -cells [27]. Fatty acids can also exacerbate inflammatory damage by directly activating inflammatory pathways because adipose tissues play a crucial role in the synthesis of inflammatory mediators like TNF-, MCP-1, IL-6, IL-1, and PAI-1. For instance, the pro-inflammatory cytokine TNF- spreads insulin receptor substrate (IRS) proteins and increases serine phosphorylation on IRS-1, hence promoting insulin resistance. Nuclear factor-B (NF-B) and c-Jun NH2-terminal kinase (JNK) signaling pathways are also activated by TNF-. Insulin resistance will occur from the phosphorylation of IRS-1 at Ser 307 caused by either method [30]. Patients with T2DM experience in vivo islet inflammation in the pancreas due to an increase in inflammatory cytokines and immune cells. In the meantime, high fat feeding in vitro boosted the production of macrophage migration inhibitory factor (MIF), which caused lipotoxic cell death in -cells [31]. By increasing intracellular diacylglycerol accumulation, a triacylglycerol substance that inhibits insulin signaling, lipids also have an impact on insulin sensitivity. Lipids also boost the activity of protein kinase C proteins, which are crucial for suppressing insulin signaling [32[Saturated fatty acids (SFAs) activate Toll-like receptor 4 (TLR4), which increases the production of IKK, NF-B transcription factors, and pro-inflammatory mediators in adipose tissue macrophages, leading to inflammation linked to insulin resistance [30]. Overall, it appears that both T1DM and T2DM have an inflammatory component to their etiologies.

**Therapeutic methods**

**Gene treatment**

Viral methods like lentivirus, adenovirus, and AAV, as well as non-viral methods such liposomes and bare DNA, have been utilised to deliver the insulin gene into many tissues, including the pancreas, liver, adipocytes, and muscle [33]. In that they produce glucose-dependent insulinotropic polypeptide (GIP) and have prohormone convertases, which are crucial for digesting proinsulin, enteroendocrine K-cells, for instance, are comparable to pancreatic -cells [34]. Therefore, several researchers changed K-cells in vitro to produce and release insulin; nevertheless, after implantation, these cells failed to effectively treat diabetes. Surprisingly, despite receiving the diabetes-causing medication streptozotocin, transgenic mice created to express insulin under the GIP promoter maintained normal glucose levels (STZ). This demonstrated that K-cell production of insulin was sufficient to regulate blood glucose levels [35]. Adeno-associated viral (AAV) vectors have recently been employed as a gene therapy technique for the treatment of DM to co-express the genes for insulin and glucokinasein skeletal muscles. Normoglycemia can be achieved utilising diabetes gene therapy over the long term without the requirement for exogenous insulin [11]. AAV vectors can infect both active and dormant cells without integrating the host cell's DNA, leading to a minimal immunological reaction. These characteristics make AAV vectors the ideal option for gene therapy. In this study, AAV vectors expressing the genes for insulin and glucokinase were delivered into the skeletal muscles of mice and dogs with STZ-induced diabetes. The translocation of the GLUT4 and glucokinase enzymes is facilitated by the co-expression of two genes, which promotes glucose absorption in altered muscle cells. In modified skeletal muscle, expression of the glucokinase enzyme results in a reduction of glucose phosphorylation to glucose-6-phosphate. It can test blood sugar levels and demonstrate how much insulin is required to achieve normoglycemia as a glucose sensor [36]. On the other hand, gene therapy for the treatment of diabetes uses a humanised liver mouse model. Pancreatic and duodenal homeobox 1 (pdx-1), also known as insulin promoter factor 1, was transfected

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 384-392 www.ijprajournal.com ISSN: 2456-4494

using AAV sero-type 2 (AAV2) as a medium by Li et al. for the development and maturation of pancreatic -cells [37]. Green fluorescent protein expression in the liver is evidence that the PDX1 gene secretes insulin ectopically to maintain glycemic control. The results show that STZ-induced diabetic mice with AAV-pdx-1 gene injections had decreased high glucose content. Another gene that controlled the pancreas' endocrine destiny during development was neurogenin 3 (Ngn3) [38]. Insulin is produced and oval cells undergo transdifferentiation when liver cells are transfected with an adenovirus carrying Ngn3 [39]. After NeuroD1 was injected into the livers of STZ-induced diabetic mice, upregulation of downstream and upstream pancreatic transcription factors, including Pax4, Pax6, Ngn3, Nkx6.1, and Nkx2.2, was seen without inducing hepatitis or hepatotoxicity [40,41]. In addition, NeuroD1 promoted insulin expression in primary duct cells the most effectively when compared to Ngn3, pdx-1, and Pax4 [42]. It may be best to target promoters in other cells, such as those for insulin-like growth factor binding protein-1, glucose 6-phosphatase (G6Pase), phosphoenolpyruvate carboxykinase (PEPCK), S-14, and liver-type pyruvate kinase (L-PK) (IGFBP-1). Although insulin was secreted as a result of these genes being stimulated in the liver as part of a hepatic insulin gene therapy, the secretion was weak in comparison to powerful constitutive promoters like CMV [43]. For instance, L-PK was used to boost the liver's production of insulin, which improved glucose responsiveness and the ability to maintain normoglycemia for up to a month. The inhibition of this promoter by insulin is the only obstacle. On the other hand, this feedback could be avoided by using S14 and albumin [44]. Plasmid DNA-containing insulin fragments are administered intravenously in a nonviral manner. The liver and muscles of STZ-induced diabetic rats received injections of this plasmid, causing normoglycemia for one week and thirty weeks, respectively. The DNA transposon approach, which carried the gene into the host chromosome, was used to resolve the liver's short-lived expression. A large amount of active insulin was found in muscle after co-injecting insulin-carrying plasmid DNA with furin[45]. Insulin secretion, hyperglycemia, and diabetic sequelae all dramatically improved for more than 47 weeks in pigs after ex vivo transfection of human insulin gene into pancreatic or liver cells and autologous transplant [46]. As gene silencing occurred, this progress came to a halt; however, the mechanism of this silencing is yet unknown. Another effective technique involves injecting a lentivirus vector—carrying a human-modified insulin gene—into the liver portal system of diabetic rats. Surprisingly, this method enables liver cells to recognise glucose and react by producing, releasing, and storing human insulin. [47].

**Non-pharmacological approach**

T2DM is mostly a lifestyle issue, hence non-pharmacological methods of prevention show great promise. Lifestyle modifications are a natural method of disease prevention because a sedentary lifestyle coupled with a high-calorie diet is the main cause of T2DM. It is frequently believed that patients who choose for non-pharmacological therapy are less likely than those who take drugs to experience severe adverse effects. The effectiveness of this non-drug therapy depends critically on patients adhering to their treatment plans, thus it is important to keep in mind that its effects could not last eternally. Lifestyle advice and other compliance techniques must to be provided and reemphasized frequently. By using these methods, diabetes, reversible risk factors, and associated complications can all be avoided. Both individual costs and the strain on the public health system can be decreased by lowering the cost of diabetic care. One's quality of life may afterwards be preserved or even elevated as a result.

**Pharmacological drug approach**

When compared to lifestyle treatments alone, each pharmaceutical drug administered as monotherapy raised the proportion of patients who achieved HbA1c target values below 7% by two to three times. Due to inadequate diabetes management, the majority of patients will need a variety of drugs to attain appropriate glycaemic control throughout time [48]. Hypoglycemia is one of the main risks to be on the lookout for when numerous pharmacological medications are given at the same time. It is best to decide together which pharmacological treatments to administer to each patient. Before selecting a medication, one should take into account the cost, likely side effects, potential advantages, efficacy in decreasing blood sugar, and dose schedule. Dosage adjustments are necessary for patients with impaired renal function. Not just individuals with renal impairment, but all patients using pharmacological drugs require regular monitoring.

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**Insulin**

The most popular form of treatment for T1DM patients with insulin insufficiency is currently insulin injections. When oral hypoglycemic treatments fail to regulate glucose and HbA1c levels in T2DM, insulin may be used alone or in conjunction with other medications to lower blood sugar levels. The restriction of insulin is that it can only be administered intravenously. Even though needle phobia has successful treatment outcomes, it results in low compliance, which compromises glycemic control. Nowadays, it's very common to find insulin pumps, also referred to as continuous subcutaneous insulin infusions. The US Food and Drug Administration (FDA) has classified these pumps as moderate to high risk devices, and clinical trials to determine their safety and effectiveness are still ongoing [49]. A non-invasive choice for insulin would be inhaled or taken orally. Utilizing these administration ways is not without challenges, though. This method of administration of insulin may assist ensure its success due to improved pharmacokinetic and pharmacodynamic variables. Oral insulin is an additional intriguing choice. There is still much research to be done before this formulation is available on store shelves [50], and it is currently in clinical tests.

**Biguanides**

The most popular diabetic treatment is metformin, particularly for obese and overweight patients. This medication is still the best choice for monotherapy. It promotes glucose uptake by phosphorylating GLUT enhancer factors, boosts insulin sensitivity, and inhibits hepatic gluconeogenesis [51]. Metformin can aid in weight loss by reducing triglyceride and LDL cholesterol levels [52]. Additionally, metformin operates by blocking mitochondrial complex 1 and the enzyme glycerophosphate dehydrogenase in the mitochondria, as well as stimulating AMP-activated protein kinase, an enzyme associated with the production of hepatic gluconeogenic genes [53]. Readings for glucose and HbA1c are decreased as a result of all of these causes. Contrarily, metformin has no impact on -cells and, in the absence of weight reduction, does not enhance insulin sensitivity in muscles, resulting in HbA1c levels that continue to rise after the initial decline.

**Sulfonylureas**

Secretagogues known as sulfonylureas work by encouraging pancreatic cells to release natural insulin. It works best when there are still some residual pancreatic cells and particularly targets the ATP-sensitive potassium channels on -cells [54]. Sulfonylureas may expedite -cell death and have no long-term protective advantages for -cell activities [55]. It has been noted that HbA1c levels increase following the initial drop in glucose levels. Sulfonylureas have been implicated in numerous reports of hypoglycemia, especially when used alongside drugs from older generations. While HbA1c levels can be decreased by 1% to 2%, blood glucose concentrations can be decreased by about 20%. Sulfonylureas have the adverse effect of causing weight gain [56].

**Thiazolidinediones**

Thiazolidinediones (TZDs) increase insulin sensitivity in adipocytes, cardiac muscles, and the liver by activating the peroxisome proliferator-activated receptor (PPAR) [57]. To control insulin secretion, they focus on -cells. It is therefore used as a component of an insulin resistance therapy programme for people with type 2 diabetes, with outcomes lasting up to five years [58]. An undesirable consequence of TZD is frequently increased body weight. However, the HbA1c reduction and recovery of -cell function and insulin sensitivity improved with more weight gain [59]. Patients with T2DM who take TZD can lessen the thickness of their carotid arteries. The FDA has already made rosiglitazone illegal due to a large rise in cardiovascular events. Patients with class III to IV heart failure are not advised to take pioglitazone. It is well tolerated even in elderly people with renal impairment, however because of the increased risk of fractures in women, it is not recommended for elderly people with congestive heart failure [60].

**Dipeptidyl peptidase-4 (DPP4) inhibitors**

Gliptins, also referred to as DPP4 inhibitors, are a brand-new class of medicinal drugs that work by obstructing the dipeptidyl peptidase 4 enzyme. Incretin hormones that play a role in physiologically maintaining glucose homeostasis, such as glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), are deactivated more slowly when this enzyme is inhibited [61]. GLP-1 and GIP enhance pancreatic -cells' ability to produce insulin [92]. The release of glucagon by pancreatic cells is inhibited by GLP-1. These effects work synergistically to improve glycemic control in T2DM patients. These drugs are weight-neutral, have fewer adverse effects than previously documented, and pose less of a risk for hypoglycemia [62].

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**GLP-1 (glucagon-like peptide-1) analogues**

In essence, GLP-1 analogues are incretin-based drugs that increase insulin secretion in a glucose-dependent manner, lower glucagon secretion, and ultimately suppress hepatic glucose production [63]. For up to three years, HbA1c levels have been shown to decrease. Although these drugs are not as well tolerated as DPP4 inhibitors, they produce greater weight loss and HbA1c reduction [64]. Blood pressure is lowered, lipid profiles are improved, endothelial dysfunctions are fixed, and stomach emptying time is lengthened [65]. There is some proof that incretin-based drugs are beneficial for cardiovascular health, the liver, sleep, inflammation (by reducing reactive protein levels), and the central nervous system [66].

**Sodium–glucose co-transporter-2 (SGLT2) inhibitors**

SGLT2 inhibitors, also known as gliflozins, diminish salt transport and enhance glucose excretion via the kidneys, decreasing plasma blood glucose concentrations by limiting glucose absorption in proximal renal tubules [67]. They can be used in people with diabetes at any stage because they do not depend on insulin to function [66]. These drugs can aid in improving insulin sensitivity, -cell function, and glucotoxicity brought on by glucosuria. They can lower blood pressure, lose weight, and reduce HbA1c levels by 0.5 to 1% [68]. Volume depletion-related symptoms, such as urinary tract infections and vaginal mycotic infections, have all been documented [69]. Extra care must be taken when providing this drug to individuals who are old or using diuretics.

**Combination therapy**

Combination therapy is started for quicker, more efficient blood glucose management and dose reductions in individual medications. It is typically started when monotherapy fails to maintain blood glucose levels under control. To minimise insulin dosage, exogenous insulin can be used in conjunction with a number of oral diabetic medicines. Metformin or TZD coupled with insulin improves glycemic control. Basal insulin combined with GLP-1 receptor agonists results in decreased HbA1c levels and weight loss. Metformin and other medications are frequently taken in conjunction with SGLT2 inhibitors [70]. Additionally, it can be used with DPP4 inhibitors to enhance weight reduction and glycaemic control while reducing the risk of hypoglycemia [71]. It has been discovered that low-dose metformin coupled with the TZD drugs pioglitazone and rosiglitazone is helpful in preventing prediabetic persons from developing diabetes. [72].

## II. CONCLUSION

For patients, their families, communities, and the nation as a whole, diabetes mellitus is a significant financial burden. All forms of diabetes should be identified as soon as is practical and kept under control to stop its progression and effects. While T1DM is more difficult to prevent, T2DM can be stopped with dietary and activity adjustments, maintaining a healthy weight, and other lifestyle changes. The main reason why diabetes therapy fails is noncompliance, which is mostly due to the unfavorable side effects of conventional drugs. In order to better control illnesses, new cutting-edge pharmacological drugs are currently being created. Additionally, current research indicates that gene therapy and stem cells may serve as therapeutic targets for customized interventions that result in better clinical outcomes and fewer side effects.

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International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 384-392 www.ijprajournal.com ISSN: 2456-4494

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