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Recent Emerging Molecular Target for Diabetes: A Comprehensive Review

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ABSTRACT

Type 2 diabetes, a chronic metabolic disorder that includes consistent high blood sugar levels, presents an extensive health problem around the globe. Traditional therapeutic approaches, including insulin therapy and oral hypoglycaemic agents, have been the cornerstone of diabetes management for decades. However, these conventional treatments often fall short in addressing the multifaceted nature of the disease and its complications. Recent advancements in molecular biology have unveiled novel targets that offer promising avenues for more effective and personalized diabetes management. This paper provides emerging molecular targets, MTOR, comparing these approaches, we aim to highlight the potential and integrating these targets to enhance treatment outcomes, reduce complications, and improve the quality of life for individuals with diabetes. Previous research studies confirm the effects of various diets on glycaemic management, growth rates, and quality of life, focusing on type 1 diabetes mellitus and celiac disease. There is limited research on the impact of a gluten-free, carbohydrate-counting diet on glycaemic management, growth, and quality of life in individuals with both celiac disease and type 1 diabetes mellitus. Mammalian Target of Rapamycin conventionally well-known target for the cancerous study, although MTOR have have the continuous impact the diabetic study moreover extensively focuses for the utilization and management of the glucose, lipid profile, and weight in patients, but few studies substantiate these benefits the included genetic patterns.

Keywords: Diabetes mellitus, DPP-4 inhibitors, SGLT2 inhibitors, AMPK, and TGF-β signalling.

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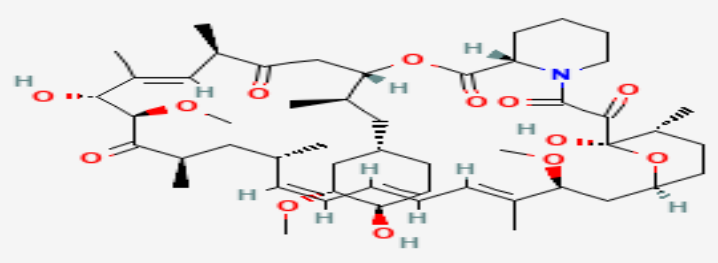
INTRODUCTION

Foot disease is one of the most severe complications of diabetes, that manifested with the clinical symptoms include ulceration, infections, and tissue necrosis in foot, which significantly impaired the quality of life and execute a substantial socioeconomic problem. However, these treatments often fail to address the underlying pathophysiological mechanisms and long-term complications associated with the disease. Recent advancements in molecular biology have led to the identification of novel molecular targets that offer promising new avenues for diabetes management. These modern therapeutic approaches aim to provide more effective and personalized treatment options by targeting specific pathways involved in glucose metabolism, insulin signalling, and beta-cell function (Hughes & Merrins, 2026). For instance, newer drugs Dipeptidyl peptidase-4 (DPP4), inhibitor have shown significant benefits in improving glycaemic control and reducing cardiovascular risks. Similarly, Sodium-glucose cotransporter 2 (SGLT2) inhibitors have emerged as a valuable addition to the therapeutic arsenal, offering benefits beyond glycaemic control, including weight loss and renal protection. The study has been focused on both conventional and modern molecular targets in diabetes therapy by comparing the mechanisms of action, efficacy, and limitations of these approaches, our aim is to highlight Combining established treatments with emerging biological targets, has the ability to improve diabetics' treatment results and overall quality of life. As per our literature review, Dipeptidyl peptidase-4 (DPP4) inhibitor and, Sodium-glucose cotransporter 2 (SGLT2) inhibitors have shown the renal benefits, however diabetes is root cause of the multi organ dysfunction with different pathological pathway, Activation of the TGF-β, ECM protein Production Smad Pathway, and oxidative stress are participated to restore and attenuate the abolish effect. hyperexpression of human leukocyte antigen (HLA) class I on the islet cells, we examined its expression in subjects with recent-onset type 1 diabetes (Skog et al 2015). Two HLA class I alleles (*B*08*, *B*58*) and three class II alleles (DQB1*02, DRB1*03 and DRB1*04) were associated with T1D susceptibility, while one class I (B*51) and three class II (DQB1*05, DQB1*06 and DRB1*16) alleles were associated with Type 1 diabetes (T1D) protection (Al-Balushi, et al., 2023).

Crystal structure of a complex of the ribosome large subunit with rapamycin



1*R*,9*S*,12*S*,15*R*,16*E*,18*R*,19*R*,21*R*,23*S*,24*E*,26*E*,28*E*,30*S*,32*S*,35*R*)-1,18-dihydroxy-12-[(2*R*)-1-[(1*S*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]propan-2-yl]-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-azatricyclo[30.3.1.$0^{4,9}$]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentone

Methodology

Numerous scientifically databases such as PubMed SciFinder, Science Direct, Scopus and Google Scholar, used to gather relevant information about diabetes, using keywords such as DPP-4 inhibitors, and" AND "SGLT2 inhibitors" AND "AMPK" OR "TGF-β signalling". All articles dealing with keywords cover, regardless of the date of publication. If two studies contained the same information, the more recent study was selected.

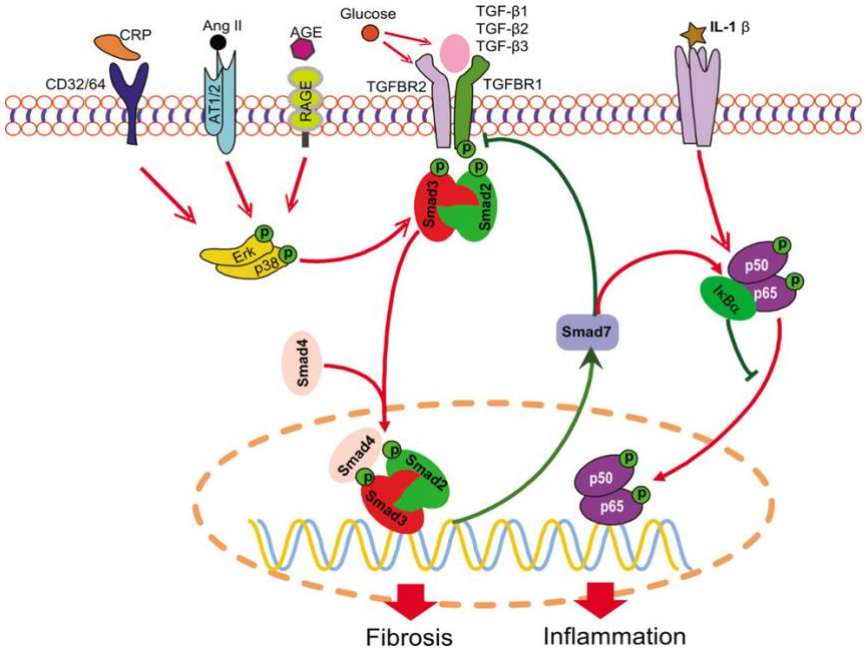


Figure 1: Signalling mechanism for fibrosis at which glucose bind with the extra cellular subunit of TGF phosphorylate the Smad, Erk, p38, Smad subunit directly participated in the protein synthesis

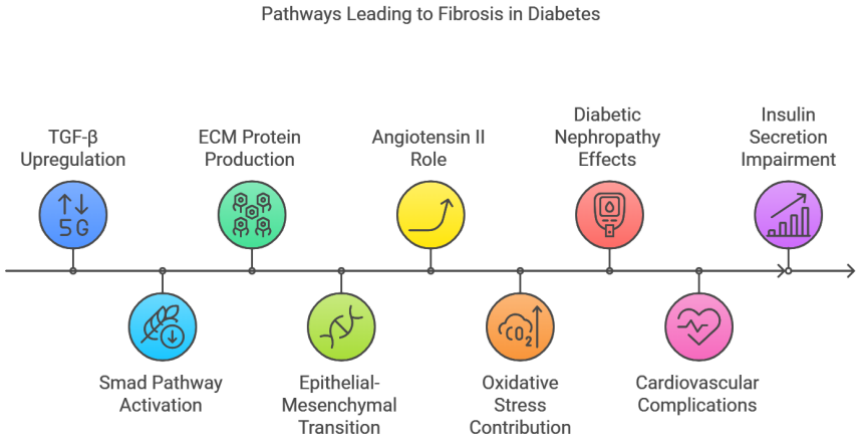


Figure 2: Modern molecular Approaches

Identification of Protein Involved in Biological Process

answer key Gene ontology analysis was used to monitor the mechanism involved in biological process such as blood coagulation and remodelling of the lipoprotein and establish the finding of protein involve in these It has been reported that several proteins connected with type 2 diabetes vascular complications in which 14 uniquely associated with microvascular complications, 13 with macrovascular and 23 common for both. Pathway analysis revealed seven main pathways underlying type 2 diabetes vascular complications including platelet degranulation and extracellular matrix interactions. Gene ontology analysis showed that these proteins functioned predominantly in the extracellular matrix and were involved in biological processes related to blood coagulation and lipoproteins remodelling.

Answer key

In type 1 diabetes, the immune system targets the pancreatic beta cells that produce insulin. (Florez, et al., 2006) state that heredity plays a significant role in the risk of developing type 1 diabetes.

HLA Genes:

Several genes critical for the immune system's proper function are situated in the answer key) region on chromosome 6. Type 1 diabetes has a significant association with certain HLA class II alleles, notably HLA-DR3 and HLA-DR4 suggest that individuals carrying these alleles have a greater chance of developing the disease. Other Genetic Factors: Variants in other genes that contribute to an increased risk of type 1 diabetes include those involved with insulin (INS), PTPN22, and IL2RA (Artasensi, Pedretti, Vistoli, & Fumagalli, 2020) . demonstrated that these genes are implicated in beta-cell function and immune regulation (Skog, et al., 2015).

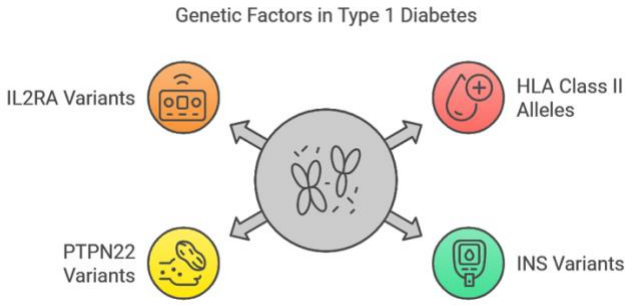


Figure 3: Targeted Genes for the type 1 diabetes

Type 2 Diabetes Mellitus (T2DM)

In type 2 diabetes, is characterized by insulin resistance and beta-cell malfunction in the pancreas develop over time. Type 2 diabetes mellitus risk factors are largely genetic. Complexity of Genes: Type 2 diabetes is a polygenic disease, which means that it is influenced by more than one gene. Research has linked more than 400 genetic variations to type 2 diabetes. Insulin signaling, glucose biotransformation, and β-cell activity are just a few

of the processes in that these genes are engaged (Mccarthy, 2010). A higher chance of getting type 2 diabetes is associated with a positive family history of the disease. (Meigs, Cupples, & Wilson, 2000), found that the lifetime risk of type 2 diabetes in children with one afflicted parent is around 40%, and that risk rises to 70% in children with both affected parents. Particular Variants in Genes: Type 2 diabetes is linked to many genetic junctions. Insulin secretion and action are mediated by TCF7L2, while adipocyte differentiation and energy molecule metabolism are regulated by PPARG, two prominent examples (Florez, et al., 2006).

Genetic Testing and Risk Prediction

Genetic testing for DM risk is still in its infancy. While it can identify individuals at high risk, the complex interplay between genetics and environment means that genetic testing alone is not sufficient for predicting DM. However, as our understanding of the genetic basis of DM improves, genetic testing may become a more valuable tool for early diagnosis and personalized treatment strategies (Lyssenko, et al., 2008). Genetic history is a decisive aspect in the development and progression of Diabetes Mellitus. Both T1DM and T2DM have strong genetic components, with multiple genes influencing susceptibility. Understanding these genetic factors can aid in risk prediction, early diagnosis, and the development of targeted therapies (Obrosova, 2005).

Mechanisms of organ damage in diabetes

Diabetes leads to organ damage through several interrelated mechanisms, which primarily revolve around hyperglycaemia, insulin resistance, and subsequent metabolic imbalances (Donath & Shoelson, Towards an anti-inflammatory treatment for type 2 diabetes?, 2011).

Non-enzymatic condensation

Chronic hyperglycaemia results in the glycation of proteins and lipids without the involvement of enzyme). These substances accumulate in many tissues, where they modify protein assembly and function, disrupt cellular processes, and exacerbate inflammation and oxidative stress. AGEs attach to particular receptors (RAGEs), initiating signaling pathways that intensify tissue damage in organs such as the kidneys, eyes, and cardiovascular system (Geraldes & King, 2010). Oxidative Stress. Diabetes is marked by elevated level of reactive oxygen species (ROS) and a concurrent reduction in antioxidant defenses. Increased ROS levels induce direct cellular harm via lipid peroxidation, DNA damage, and protein alteration. Oxidative stress significantly contributes to endothelial dysfunction, which is fundamental to several diabetes sequelae, including nephropathy, retinopathy, and cardiovascular disease (IMURA, 2024).

Method:

Inflammatory biochemicals

Hyperglycaemia and insulin resistance promote a chronic inflammatory state by activating proinflammatory pathways, elevated inflammatory mediator in diabetes, contributing to endothelial dysfunction, atherosclerosis, and fibrosis in organs like the kidneys, liver, and heart. Diabetes induces hemodynamic changes, including hypertension and hyperfiltration in the kidneys (Cooper M. , 2001). These changes increase shear stress on blood vessels, leading to endothelial damage. In the kidneys, this results in glomerular damage and the expansion of hyperglycemic nephropathy (Dai & Liu, 2004). The combination of hypertension and hyperglycaemia exacerbates the risk of cardiovascular events (Navar, 1997).

Activation of Pathway

The polyol system is triggered when blood glucose levels are high, and this enzyme converts glucose to sorbitol. Nephropathy, diabetic neuropathy, and nephropathy are complications that can develop when sorbitol builds up in cells and causes oxidative stress and damage, especially in organs such as the kidneys, nerves, and retina (Zatz, Meyer, Rennke, & Brenner, 1985). The activation of PKC isoforms take place in response to diabetes, which play a role in vascular dysfunction. PKC activation results in increased permeability of blood vessels, altered blood flow, and boosted progression of components of the extracellular matrix, leading to fibrosis and vascular complications in diabetes, including retinopathy and nephropathy (Fioretto & Mauer, 2007). Dysregulation is often accompanied by dyslipidaemia, considered by raised levels of lipid profile parameters (Giugliano, Ceriello, & Paolisso, 1996). This dysregulation in lipid metabolism contributes to atherosclerosis, fatty liver disease, and cardiovascular complications by promoting endothelial dysfunction, oxidative stress, and inflammation (Lewis, Hunsicker, Bain, & Rohde, 1993).

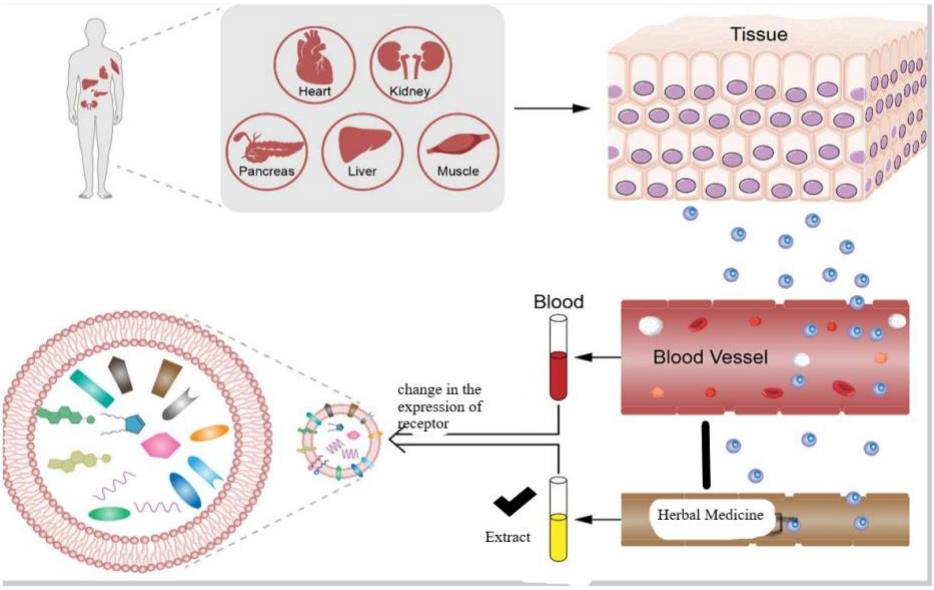


Figure 5: Answer Key by Herbal Medicine

Diabetic peripheral neuropathy (DPN)

Type 1 or type 2 diabetes, up to 50% develop diabetic peripheral neuropathy (DPN). DPN is a condition where peripheral nerve function is lost from the distal to the proximal region. It lowers quality of life by causing physical impairment and occasionally discomfort (Zatz, Meyer, Rennke, & Brenner, 1985). The etiology of diabetic peripheral neuropathy (DPN) is diverse, but the processes all point to a common theme: the peripheral nerves' distinctive structure causes bioenergetic failure. The results of current clinical trials are insufficient to enhance early diagnosis and prognosis, inpoint biological pathways that may lead to therapeutic targets, and explore lifestyle strategies for bettering clinical outcomes.

Answer Key

Glomerular hemodynamic disturbances refer to fluctuations in the blood stream and compression within the glomeruli, the tiny filtering units in the kidneys (Taskinen, 2002). These disturbances are a key feature of various kidney diseases, including diabetic nephropathy, hypertension-induced nephropathy, and additional arrangements of kidney failure (Obrosova, 2005). The primary disturbances include glomerular hyperfiltration, increased glomerular capillary pressure, and altered renal blood flow (Yusuf, et al., 2000).

Answer Key

Glomerular hyperfiltration is characterized by an abnormally high filtration rate through the glomeruli. It often occurs in the initial phases of diabetes and hypertension as a compensatory mechanism in response to systemic vasodilation or increased blood volume (& Rich, 2008). While initially adaptive, chronic hyperfiltration can lead to glomerular damage over time. The increased filtration pressure stretches the glomerular capillaries, leading to structural damage such as glomerulosclerosis (scarring of the glomeruli) and eventual decline in kidney function. In conditions like diabetes and hypertension, systemic blood pressure is often elevated, which translates into increased pressure within the glomerular capillaries. This heightened pressure can damage the delicate filtration barrier of the nephron, consisting of the endothelial cells, vault sheath, and podocytes (Dai & Liu, 2004). As a result, proteinuria (the occurrence of excess proteins in the urine) often develops, which is a symbol of kidney damage. Persistent high glomerular pressure accelerates the progression of kidney disease by promoting fibrosis and further loss of glomerular function (Hostetter, Olson, Rennke, Venkatachalam, & Brenner, 1981).

Changes in renal blood flow contribute to glomerular hemodynamic disturbances. In diabetes, the afferent arterioles (which bring blood into the glomerulus) often dilate, while the efferent arterioles (which take blood away) constrict (Agita & Alsagaff, 2017). This imbalance increases the pressure within the glomerulus, exacerbating hyperfiltration and contributing to

glomerular damage (Biochemistry and molecular cell biology of diabetic complications, 2001). The dysregulation of renal blood flow is partly mediated by influences such as angiotensin II, nitric oxide, and endothelin, which are dysregulated in diabetes and hypertension. In conditions like diabetes and hypertension, the RAAS is often overactivated, foremost to amplified production of protein angiotensin II, which constricts the efferent arterioles more as compared to afferent (Venditti, et al., 2024). This discriminatory constriction rises glomerular capillary pressure, exacerbating hyperfiltration and promoting glomerular injury. Ramipril or losartan, are often used in clinical practice to mitigate these effects and protect the kidneys although specialized cells in the glomerulus that play a crucial role in maintaining the integrity of the filtration barrier that is the podocytes Hemodynamic and hyperfiltration, leads to podocyte injury and loss (Taskinen, 2002). Podocyte impartiality from the glomerular crypt sheath is a key incident in answer key. Once lost, podocytes cannot be replaced, making their preservation critical in preventing kidney disease progression. sodium-glucose co-transporter-2 (SGLT-2) a major role in glucose reabsorption in renal proximal tubules, accounting for approximately 80–90% of filtered glucose absorption [60,61]. Pharmacological inhibition of SGLT-2 reduces renal glucose reabsorption and consequently enhances urinary glucose excretion, thereby lowering blood glucose levels. This mechanism makes SGLT-2 inhibitors an important therapeutic option for the management of type 2 diabetes mellitus (T2DM). These combined inhibitors improve glycaemia control independent of insulin secretion with a low risk of hypoglycaemia by decreasing renal glucose reabsorption and increasing urinary glucose excretion

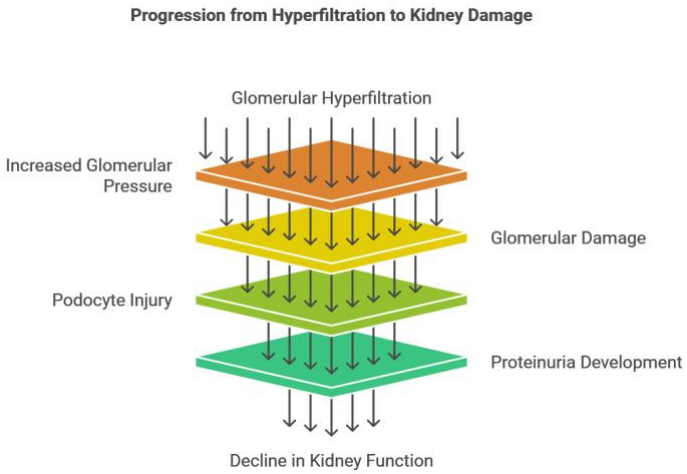


Figure 4: Mechanism of Diabetes associated kidney dysfunction

Inflammation and fibrosis.

Inflammation and fibrosis are key pathological processes in the progression of diabetic difficulties, particularly in organs such as the kidneys, liver, heart, and pancreas. Both inflammation and fibrosis are closely interlinked, with chronic inflammation driving the

fibrotic response, which in turn contributes to further tissue damage and organ dysfunction. Here's a detailed overview of how these processes occur in diabetes. answer key , particularly category 2 diabetes, where it contributes to insulin resistance and the progression of diabetic complications. In diabetes, raised stages cause inflammatory (Hulsmans & Holvoet, 2010). These cytokines are produced by various cells, including macrophages, adipocytes, and endothelial cells, in response to hyperglycaemia, free fatty acids, and oxidative stress (Donath & Shoelson, Towards an anti-inflammatory treatment for type 2 diabetes?, 2011). These cytokines exacerbate insulin resistance by interfering with insulin signalling pathways and promoting a pro-inflammatory state within tissues. Activation of Inflammatory Pathways: Key inflammatory pathways are activated in diabetes, including the NF-κB pathway, which is a central regulator of inflammation. NF-κB activation leads to the transcription of genes that encode for pro-inflammatory cytokines, adhesion molecules, and other mediators that promote inflammation (King, 2008). This process contributes to endothelial dysfunction, which is a precursor to vascular complications in diabetes, such as atherosclerosis and diabetic nephropathy. Macrophage Infiltration: In diabetic tissues, particularly in adipose tissue, there is an increased infiltration of macrophages (King, 2008). These macrophages shift from an answer key further amplifying the inflammatory response. The chronic presence of these pro-inflammatory macrophages in tissues like the kidney, liver, and pancreas drives ongoing tissue damage and fibrosis. Fibrosis is the excessive accumulation of extracellular matrix (ECM) components, such as collagen, in tissues. In diabetes, fibrosis is a common consequence of chronic inflammation and occurs in various organs, leading to impaired function (Hostetter, Olson, Rennke, Venkatachalam, & Brenner, 1981).

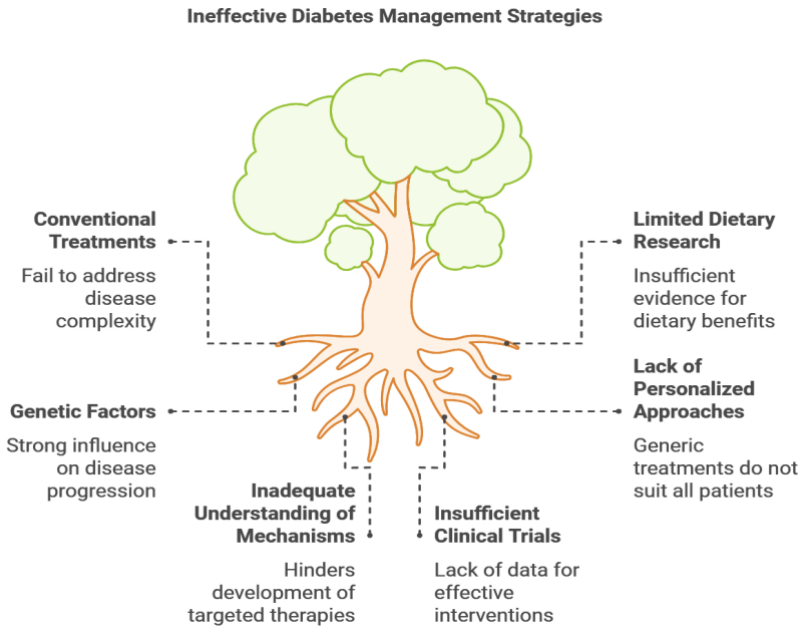


Figure 5: Answer Key

TGF-β and Smad Signalling:

answer key that mediates fibrosis in diabetes. TGF-β is upregulated in response to chronic hyperglycaemia and inflammation. It signals through the Smad pathway to stimulate the production of ECM proteins such as collagen, fibronectin, and laminin. This excessive ECM deposition leads to tissue fibrosis, which is particularly evident in diabetic nephropathy, where it causes glomerulosclerosis and tubulointerstitial fibrosis. answer key fibrosis is partly driven by EMT, a process where tubular epithelial cells lose their epithelial characteristics and acquire a mesenchymal phenotype, becoming myofibroblasts. These myofibroblasts are major producers of ECM components, contributing to fibrosis. EMT is stimulated by factors such as TGF-β, high glucose levels, and inflammatory cytokines. Role of Angiotensin II: Angiotensin II, a key component of the renin-angiotensin-aldosterone system (RAAS), is also implicated in the fibrosis observed in diabetes. Angiotensin II promotes the expression of TGF-β and other pro-fibrotic factors, leading to increased ECM production and fibrosis. This is why answer key , are commonly used to slow the progression of diabetic nephropathy and other fibrotic complications. Oxidative stress, which is elevated in diabetes due to hyperglycemia and other metabolic abnormalities, also contributes to fibrosis. ROS (reactive oxygen species) can activate TGF-β signaling and other fibrotic pathways, exacerbating ECM deposition and tissue scarring. Kidneys: In diabetic nephropathy, chronic inflammation and fibrosis lead to glomerulosclerosis, tubulointerstitial fibrosis, and progressive kidney function decline. This results in end-stage renal disease if left untreated. Patients are at increased risk of non-alcoholic fatty liver disease (NAFLD), which can progress to non-alcoholic steatohepatitis (NASH) characterized by inflammation and fibrosis, potentially leading to cirrhosis whereas diabetic cardiomyopathy involves myocardial fibrosis, driven by inflammation, oxidative stress, and RAAS activation. This leads to heart failure and other cardiovascular complications. chronic inflammation and fibrosis can impair insulin secretion, exacerbate hyperglycaemia and perpetuating the cycle of diabetes

Answer Key

It is a gut hormone that, similarly to GLP-1, is secreted in response to feeding. Its biological effects are attributed to a dual activation of GLP-1R and GcgR. However, OXM is rapidly inactivated (around 12 minutes) in plasma by DPP-4 which cleavages the first two N-terminal amino acids of the peptide. Therefore, OXM mimetics should inevitably involve a modified N-terminus in order to protect the compound against DPP-4 inactivation and possibly to avoid decreasing of the efficacy. On these bases, investigation of OXM-analogues has been performed [54] to improve half-life. For example, the strategy proposed by Pocai [52] was to introduce a D-Ser2 (S) substitution, while an enhanced metabolic stability was achieved

through a cholesterol moiety (chol) at the C-terminus of these peptides. Furthermore, the polyethylene glycol spacer minimizes the loss in agonist potency because of plasma protein/lipid binding (Figure 6). Finally, the treatment with these compounds induced similar improvements in glycemic control compared to selective GLP-1R agonists and additionally it has been shown to decrease bodyweight and food intake (IMURA, 2024).

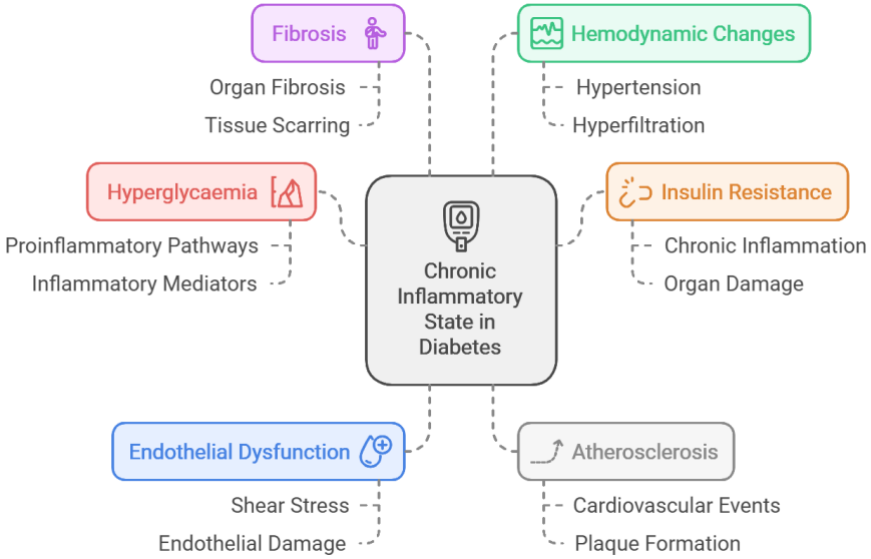


Figure 6: Answer Key

Hexosamine pathway of glucose oxidation.

Under glycemia conditions, the F6P level increases and the molecule is metabolized by glucosamine-fructose aminotransferase to glucosamine-6-phosphate, which subsequently turns into answer key ? Accumulation of UDP-GlcNAc triggers activation of O-glucosamine-N-acetyltransferase, which is associated with the prooxidant role of the hexosamine pathway in DM. Activity of this enzyme and hexosamine pathway is associated with changes in gene expression and increased expression of transcription factors TGF-α and TGF-β that inhibit mitogenesis of mesangial cells, activate the proliferation of the collagen matrix and thickening of the basement membrane [36]. PKC activation pathway. PARP1 that is activated as a result of DNA damage caused by OS, inhibits GA3PDG activity, which leads to GA3P and its isomer, dihydroxyacetone-3-phosphate (DHA3P) accumulation. DHA3P, which in the presence of free fatty acids, is oxidized to glycerol-3-phosphate by the glycerol-3-phosphate dehydrogenase, forms diacylglycerol, which interacts with the AGE receptor, stimulating OS reactions through PKC activation (Pickup & Crook, 1998).Polyol pathway of glucose oxidation. In hyperglycemia, aldose reductase is activated that leads to an increase in the level of sorbitol that is converted by sorbitol dehydrogenase to fructose. High levels of fructose cause accumulation of GA3P and DHAP that leads to OS due to methylglyoxal formation and PKC activation [45]. In addition, increased activity of aldose reductase causes

a decrease in NADPH levels, which subsequently leads to GPx activity and glutathione levels decrease. This situation causes the AOD suppression, which leads to OS (Pagtalunan, et al., 1997).

CONCLUSION

As per our literature review, Dipeptidyl peptidase-4 (DPP4) inhibitor and, Sodium-glucose cotransporter 2 (SGLT2) inhibitors have shown the renal benefits, however diabetes is root cause of the multi organ dysfunction with different pathological pathway, Activation of the TGF-β, ECM protein Production Smad Pathway, and oxidative stress are participated to restore and attenuate the abolish effect. hyperexpression of human leukocyte antigen (HLA) class I on the islet cells, we examined its expression in subjects with recent-onset type 1 diabetes (Skog et al 2015). Two HLA class I alleles (*B*08*, *B*58*) and three class II alleles (*DQB1*02*, *DRB1*03* and *DRB1*04*) were associated with T1D susceptibility, while one class I (*B*51*) and three class II (*DQB1*05*, *DQB1*06* and *DRB1*16*) alleles were associated with Type 1 diabetes (T1D) protection (albushi et al., 2023). The management of diabetes has evolved significantly over the years, shifting from conventional approaches to more targeted molecular strategies. Conventional treatments, such as insulin therapy and oral hypoglycaemic agents like sulfonylureas and metformin, focus primarily on controlling blood glucose levels. These therapies have been successful in reducing complications and improving the quality of life for many patients. However, they often do not address the underlying pathophysiological mechanisms of diabetes, and their effectiveness can diminish over time, necessitating additional treatments. In contrast, modern molecular targets have opened new avenues in diabetes management by directly influencing specific pathways involved in the disease's progression. These include GLP-1 receptor agonists, which enhance insulin secretion and promote weight loss; SGLT2 inhibitors, which reduce blood glucose by increasing urinary glucose excretion; and DPP-4 inhibitors, which prolong the action of incretin hormones. These therapies not only provide better glycaemic control but also offer cardiovascular and renal benefits, addressing the broader complications of diabetes as shown in table 2. Furthermore, emerging therapies targeting the molecular mechanisms of insulin resistance, β-cell dysfunction, and inflammation show promise in altering the disease course rather than just managing symptoms. The integration of these targeted therapies into clinical practice represents a significant advancement in personalized medicine for diabetes, potentially leading to more effective and sustainable disease management, while conventional therapies remain essential, the advent of modern molecular targets has revolutionized diabetes management, offering more comprehensive and effective strategies to address both glycaemic control and the multifaceted complications of the disease. Continued research and

development in this area hold the promise of even more refined and individualized treatment options in the future.

AUTHOR CONTRIBUTIONS

Conceptualization and writing Original Draft: Dr. Jagpal Singh Literature collection and image Dr. Ankita Singh and Ashok Kumar drafting the content of this review.

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