Palestinian Medical and Pharmaceutical Journal (PMPJ). 2024; 9(2): 193-212

Role of Inflammatory and Growth Factors in Diabetes Mellitus

Sayed Mohammed Firdous[1,*] *& Sourav Pal*[2]

[1]Department of Pharmacology, Calcutta Institute of Pharmaceutical Technology & AHS, Uluberia, Howrah: 711316, West Bengal, India. [2]P.G. Institute of Medical Sciences, Dhurabila, Dhamkuria, Chandrakona Town, Paschim Medinipur: 721201, West Bengal, India

*Correspondance Author: firdous.oncology@gmail.com

Received: (5/7/2023), Accepted: (5/9/2023), Published: (1/6/2024)

ABSTRACT

In diabetes mellitus, both inflammatory and growth factors play significant roles in the development and progression of the disease and its associated complications. Diabetics frequently show signs of chronic, low-grade inflammation. Insulin resistance and beta-cell dysfunction are exacerbated by the high levels of pro-inflammatory cytokines prevalent in diabetes, such as TNF-α and IL-6. High levels of the inflammatory marker C-reactive protein are linked to insulin resistance and an increased risk of cardiovascular disease. An upsurge in in diabetes is caused by NF-κB activation. Complications and pathological processes in diabetes may be exacerbated by a dysregulation of growth factors. The angiogenesis-related growth factor vascular endothelial growth factor (VEGF) can be down-regulated in diabetes, resulting to poor tissue perfusion and diabetic retinopathy. Disputes with insulin sensitivity, dysfunctional beta cells, and diabetic complications have all been linked to disruptions in IGF signalling. An imbalance in PDGF signalling can cause aberrant cell proliferation, fibrosis, and delayed wound healing. When NGF levels and signalling are out of whack, it can lead to nerve injury and diabetic neuropathy. Acquiring an awareness of the dynamic relationship between inflammatory and growth factors is essential to unravelling the causes of diabetes and its consequences. Research into new therapeutic strategies for diabetes is actively focusing on targeting these variables and associated signalling pathways. Controlling blood glucose levels, making healthy lifestyle choices, and using effective medications are all essential components of diabetes management.

Keywords: Diabetes mellitus, Inflammatory cytokines, Growth factors, Inflammation.

INTRODUCTION

Diabetes is a persistent medical ailment that impacts the body's ability to regulate blood sugar or glucose levels. The classification of diabetes has three primary categories: type 1 diabetes, type 2 diabetes, and gestational diabetes [1]. Autoimmune diabetes arises as a consequence of the immune system's inadvertent attack on the pancreatic cells responsible for insulin production, leading to their destruction. Insufficient insulin production leads to a deficiency in glucose uptake by cells, hence impeding its use for energy purposes. Type 1 diabetes is commonly identified throughout childhood and early adulthood, necessitating lifelong treatment with insulin injections. Type 2 diabetes accounts for approximately 90% of all cases of diabetes in the United States [2]. The pancreas can exhibit insufficient insulin production or the body may develop resistance to its effects, resulting in elevated levels of blood glucose. There exists a positive correlation between obesity, insufficient physical activity, and harmful dietary practises, and the likelihood of acquiring type 2 diabetes is heightened as a result. Modifications to one's lifestyle, oral medications, and, in rare cases, insulin injections, can all help control the disease. Pregnancy-onset diabetes is temporary, typically disappearing after delivery. It develops when the body's capacity to properly utilize insulin is disrupted by hormones released during pregnancy. The health of both mother and child depends on the vigilant management of gestational diabetes [3]. Increased thirst and urination are two of the most common signs of diabetes, along with unusual weariness, blurred eyesight, poor wound healing, and persistent infections. Conversely, in the initial phases of type 2 diabetes, some patients may not suffer

obvious symptoms. Heart disease, renal failure, nerve damage, and vision impairment are just some of the long-term effects that have been linked to diabetes [4]. People with diabetes face unique challenges, but they can live normal lives with the help of medical treatment, behavioral changes, and self-management.

The progression and complications of diabetes are influenced by inflammatory and growth factors. Inflammation is the fundamental cause of diabetes. Inflammation of a chronic, low grade is caused by diabetes, especially type 2. Insulin resistance, beta-cell dysfunction, and the complications of diabetes are all caused by inflammation. Inflammatory tumor necrosis factor-alpha (TNF-α) is increased by diabetes. Insulin resistance is caused by preventing insulin from doing its job and preventing glucose from entering cells. Another pro-inflammatory cytokine, interleukin-6 (IL-6), is increased in diabetes [5]. Beta-cell malfunction is associated with insulin resistance. In diabetes, IL-6 may contribute to persistent, subclinical inflammation. The inflammatory marker CRP rises in people with diabetes. High CRP levels are associated with insulin resistance and cardiovascular issues. NF-κβ controls inflammatory responses. When diabetes is present, it becomes active, causing the release of inflammatory molecules [6]. Growth factors are essential for cellular proliferation, tissue repair, and blood vessel formation. Problems in diabetes management may be attributable to growth factor dysregulation. Angiogenesis and new blood vessel development are stimulated by VEGF. Dysregulated VEGF levels restrict angiogenesis and hamper tissue perfusion in diabetic retinopathy and wound healing. The growth, development, and metabolism of cells are all aided by IGFs like IGF-1. Diabetic complications, including insulin resistance and beta-cell dysfunction, can result from disruptions in the IGF signaling pathway. Tissue repair and cell proliferation are aided by PDGF. Abnormal cell growth, fibrosis, and wound healing have all been linked to PDGF signaling dysregulation in diabetes. The production of new nerve cells is kept at a steady rate by NGF. Disruption of NGF signaling can lead to nerve damage and diabetic neuropathy. There is a complex interplay between inflammatory and growth factors and diabetes. Diabetes and its repercussions result from chronic inflammation, which impairs the functioning of growth factors and cellular processes. Approaches to treat diabetes are being made by focusing on these areas and the signals they ought to communicate [7].

Inflammation

The impact of inflammation in the initiation and reoccurrence of diabetes is considerable. There exists a strong association between chronic low-grade inflammation and diabetes, suggesting a potential involvement of this inflammatory state in the pathogenesis and subsequent outcomes of the disease. Individuals diagnosed with type 1 diabetes experience the immune system's deliberate targeting and subsequent destruction of the beta cells located within the pancreas, which are responsible for the production of insulin. Insulin production is halted as a result of this immune reaction. During this phase, the production of pro-inflammatory cytokines, including IL-1 and TNF-α, is initiated by the inflammatory cells that infiltrate the affected area, such as T cells and macrophages. These cytokines sustain the inflammatory response and facilitate the apoptosis of beta cells. Type 2 diabetes is characterized by the presence of chronic, low-grade inflammation. The secretion of inflammatory cytokines, such as TNF-α and interleukin-6 (IL-6), is facilitated by adipose tissue. These cytokines impede cells' normal response to insulin and so lead to insulin resistance [8]. Insulin resistance and inflammation are both made worse by the release of free fatty acids from adipose tissue. Type 2 diabetes is characterized by insulin resistance, which can be exacerbated by inflammation. Reduced glucose absorption by cells and increased glucose synthesis by the liver are the results of pro-inflammatory cytokine interference with insulin signaling pathways. This leads to hyperglycemia and adds fuel to the fire of chronic inflammation. Diabetic problems can also be caused by inflammation. Diseases like diabetes nephropathy, diabetic retinopathy, and diabetic neuropathy can be caused by chronic inflammation in the body. Tissue damage is exacerbated by the inflammatory mechanisms

that cause it. These include the release of reactive oxygen species, the malfunctioning of endothelial cells, and the activation of inflammatory cells. Inflammation in diabetes can be exacerbated by variables such as obesity and lack of physical activity. The release of pro-inflammatory chemicals including adipokines from excess adipose tissue, especially visceral fat, promotes inflammation and insulin resistance. The management of diabetes includes the management of inflammation [9].

Cytokines and the immune system's response to diabetes

The vital part of cytokines in the immune response and inflammation has received considerable interest within the field of diabetes research. The involvement of the pro-inflammatory cytokine IL-1 in the pathogenesis of beta cell demise within the pancreatic islets of individuals afflicted with type 1 diabetes has been established. Findings of triggering in other cytokines, such as IL-6 and TNF-α, may exacerbate insulin shortage and inflammation in persons diagnosed with type 2 diabetes [10]. The cytokine Interleukin-6 (IL-6) is of significant importance in the regulation of immunological and inflammatory processes. There is a correlation between increased levels of interleukin-6 (IL-6) and the development of insulin resistance as well as the onset of cardiovascular problems. Moreover, it has been established that both obesity and type 2 diabetes play a significant role in the etiology of these diseases. Tumor necrosis factor-alpha (TNF-α) is a cytokine characterized by its pro-inflammatory activities, which contribute to the pathogenesis of insulin resistance. The molecule in question is involved in the persistent low-level inflammation commonly observed in individuals with obesity and type 2 diabetes, as well as the interference with the normal functioning of insulin signaling pathways. Immune cells, specifically neutrophils, are drawn towards sites of inflammation as a result of the existence of IL-8, a chemokine. Elevated levels of interleukin-8 (IL-8), a pro-inflammatory cytokine, have been noted in individuals diagnosed with diabetes. The observed increase in IL-8 levels has been demonstrated to exhibit a positive correlation with elevated inflammation and its related consequences. Nevertheless, it is crucial to acknowledge that there is no direct causal relationship between IL-8 levels and the onset or presentation of diabetes [11]. Interleukin-10 (IL-10), which is classified as an anti-inflammatory cytokine, can attenuate both immune system reactivity and inflammatory responses. This intervention holds promise for improving insulin sensitivity in those with type 2 diabetes and mitigating the immunological response in those with type 1 diabetes. There exists a significant association between autoimmune illnesses and interleukin-17 (IL-17), as the latter is recognized as a pro-inflammatory cytokine. It has a significant role in the pathogenesis of inflammation and insulin resistance in individuals with type 2 diabetes, while also being associated with the apoptosis of pancreatic beta cells in type 1 diabetes. The impact of IL-22 on various organs and cell types exhibits significant variability (Figure 1). The impact of diabetes on metabolic health can be influenced by its ability to alter the composition of gut microbiota and its potential to provide protection to pancreatic beta cells in individuals with type 1 diabetes [12].

Interleukin-1β (IL-1β)

It's a cytokine, a signaling molecule produced by the immune system in reaction to inflammation. The genesis and progression of certain diseases, including diabetes, have been linked to their involvement in several physiological processes. Interleukin-1 has been the subject of research into its potential role in the etiology of both type 1 and type 2 diabetes [12, 13]. There is a prevailing belief that IL-1β is implicated in the demise of beta cells responsible for insulin production in the pancreas, which is a distinctive characteristic of type 1 diabetes. The aforementioned process elicits an autoimmune reaction targeting beta cells through the induction of immune cell activation and the synthesis of additional pro-inflammatory cytokines. The inflammatory response plays a crucial role in the reduction of insulin production observed in individuals with type 1 diabetes. Chronic low-grade inflammation is thought to play a role in the development of insulin resistance and the progressive decline of pancreatic beta cell function in individuals with type 2

diabetes. Interleukin-1 beta (IL-1β) plays a significant role in the initiation and progression of the inflammatory response. This study provides evidence that IL-1β triggers the expression of the NF-κB cascades in the presence of elevated glucose levels, resulting in the induction of pericyte death [14]. The muscle and liver are two tissues that can be negatively affected, making them less responsive to insulin. Moreover, IL-1β has been demonstrated to influence beta cell activity and survival, therefore contributing to the gradual drop in insulin production observed in type 2 diabetes. Following these results, scientists have investigated IL-1β inhibitors for possible therapeutic application in the management of diabetes. IL-1β inhibitors, such as anakinra and canakinumab, have shown encouraging results in clinical trials for improving glycemic control and preserving beta cell function in both type 1 and type 2 diabetes [15].

Interleukin-6 (IL-6)

Similar to IL-1, IL-6 has been the subject of an investigation about its potential involvement in diabetes, particularly type 2 diabetes. The development and progression of type 2 diabetes have been attributed to chronic low-grade inflammation and insulin resistance, as indicated by previous research [16]. The association between insulin resistance and the pro-inflammatory cytokine interleukin-6 (IL-6) has been established. Empirical evidence substantiates the hypothesis that IL-6 is implicated in the pathogenesis of insulin resistance. Insulin signaling pathways can be disturbed in various tissues, including skeletal muscle, adipose tissue, and the liver. This disruption can play a role in diminished insulin sensitivity, making it more challenging for the body to respond normally to insulin and ultimately contributing to increased blood sugar levels. IL-6 is known to be secreted by adipose tissue (fat tissue), and this is especially true in obese people. The risk of developing type 2 diabetes is raised when a person has both excess body fat and elevated levels of IL-6 from adipose tissue [16, 17]. The activity of pancreatic beta cells may potentially be affected by IL-6. Low insulin production and dysfunctional beta cells have been linked to elevated IL-6 levels. The inability of beta cells to produce enough insulin to keep blood sugar levels normal is a major contributor to the development of type 2 diabetes. Anti-IL-6 antibodies are being studied for their possible use in treating type 2 diabetes [17]. IL-6 hinders the metabolic process of non-oxidative glucose, resulting in compromised cellular glucose consumption. It exerts inhibitory effects on lipoprotein lipase (LPL), an enzymatic catalyst involved in the hydrolysis of triglycerides inside the circulatory system [18]. As a consequence, there is an elevation in plasma triglyceride concentrations. IL-6 induces the activation of SOCS proteins, hence impeding the signaling cascade mediated by insulin receptors. The aforementioned interference has the potential to diminish the activation of insulin receptors and hence impede the downstream consequences associated with insulin signaling. The protein STAT5B functions as both a signal transducer and a transcription factor for the insulin receptor. IL-6 can induce the activation of STAT5B via phosphorylation, hence facilitating the transcription process of insulin receptor genes. Nevertheless, it has been observed that SOCS proteins possess the ability to engage in competition with STAT5B, inhibiting the activation of the insulin receptor and consequently exerting a detrimental impact on insulin action [19]. Insulin sensitivity and glycemic control can be enhanced in diabetics by inhibiting IL-6 activity, according to some research. More study is required to determine the efficacy and safety of IL-6 inhibitors as a treatment strategy [20].

Interleukin-8 (IL-8)

Through the luring and activating of neutrophils and other immune cells to areas of inflammation or injury, it contributes to the inflammatory response. Although IL-8 isn't directly linked to diabetes, it may have a role in some of the illnesses and consequences that are. Complications of diabetes, such as heart disease, nephropathy (kidney disease), and retinopathy (eye illness), are often accompanied by chronic inflammation. A rise in inflammation and the escalating severity of these ailments have both been linked to the elevated IL-8 levels seen in patients with diabetes. Evidence suggests that IL-8 promotes endothelial dysfunction, leukocyte adhesion, and increased expression of other

inflammatory cytokines, all of which may play a role in the etiology of diabetic complications. [21, 22].

The role of IL-8 in the pathogenesis of insulin resistance has been established by experimental studies conducted in both laboratory settings (in vitro) and living organisms (in vivo). Previous research conducted in laboratory settings has shown that IL-8 has the ability to impede the process of glucose uptake that is typically driven by insulin in adipocytes. The inhibition is facilitated by the stimulation of the mitogen-activated protein kinase (MAPK) pathway, resulting in a reduction in the phosphorylation of the AKT protein. The AKT kinase plays a critical role in insulin signaling, and its phosphorylation is a prerequisite for the facilitation of glucose uptake in response to insulin stimulation. investigations conducted in living organisms, known as in vivo investigations, have also shown that levels of interleukin-8 (IL-8) are increased in patients who have insulin resistance. As an example, a research study discovered that obese women with poor glucose tolerance exhibited significantly elevated levels of IL-8 compared to lean women with normal glucose tolerance. It is believed that the elevated levels of IL-8 in insulin-resistant individuals contribute to insulin resistance through a variety of mechanisms. IL-8 can directly inhibit the glucose uptake stimulated by insulin in adipocytes. Second, IL-8 can stimulate the production of additional pro-inflammatory cytokines, including TNF-α and IL-6. In addition to inhibiting insulin signaling, these cytokines can contribute to insulin resistance. Thirdly, IL-8 is capable of attracting neutrophils to the site of inflammation. Neutrophils release several enzymes and other factors that can cause tissue injury and contribute to the development of insulin resistance [23].

Interleukin-13 (IL-13)

Akin to IL-8, IL-13 is not directly linked to diabetes but may be relevant in the context of complications and diseases connected with the disease. Particularly in asthma and atopic illnesses, IL-13 is well-known for its role in allergic and immunological responses. New evidence, however, reveals that IL-13 also plays a role in the onset and progression of diabetic sequelae such as nephropathy and retinopathy. IL-13 has been linked to increased renal inflammation and fibrosis (tissue scarring) in diabetic nephropathy, two factors that contribute to decreased kidney function. By altering the microvasculature of the retina and fostering inflammation there, it may also play a role in the onset of diabetic retinopathy. More research is needed to completely understand IL-13's function in reducing the risk of diabetes-related complications [24, 25].

In vitro experiments have provided evidence that IL-13 exhibits a suppressive impact on the uptake of glucose induced by insulin in adipocytes and skeletal muscle cells. The process of inhibition discussed is enhanced by the activation of the Janus kinase-signal transducer and activator of the transcription (JAK-STAT) pathway, leading to a decrease in the phosphorylation of the insulin receptor substrate-1 (IRS-1) protein. The kinase IRS-1 is a critical component in the insulin signaling pathway, and its activation is necessary for the facilitation of glucose uptake stimulated by insulin. *In vivo* studies have demonstrated that patients with insulin resistance exhibit elevated levels of IL-13. IL-13 possesses the capacity to augment the transcription of genes linked to the biological processes of lipogenesis and adipogenesis. This event has the potential to lead to a higher occurrence of obesity, hence acting as a risk factor for insulin resistance [26].

Interleukin-17 (IL-17)

Empirical evidence suggests the involvement of IL-17 in the initiation, continuation, and worsening of diabetes and its related consequences, however, a definitive causal relationship has not been established. The distinctive hallmark of type 1 diabetes is the death of beta cells in the pancreas responsible for generating insulin. Existing research indicates a potential involvement of IL-17 in this pathogenic process. The extant body of research has yielded empirical evidence indicating that IL-17 assumes a prominent function in the recruitment and activation of immune cells that selectively target and inflict damage onto beta cells, hence leading to a subsequent decline in

insulin synthesis. The induction of IL-17 can lead to inflammation in pancreatic islets, which in turn can enhance the immune response targeting beta cells. The association between insulin resistance and IL-17, as well as chronic low-grade inflammation, has been shown in individuals with type 2 diabetes [27]. Type 2 diabetes is distinguished by the presence of insulin resistance, a physiological state wherein cells exhibit diminished responsiveness to insulin, resulting in the aberrant accumulation of glucose inside cells rather than its release into the bloodstream for energy utilization. Insulin resistance and pancreatic dysfunction can be exacerbated by IL-17's ability to stimulate the production of additional pro-inflammatory cytokines including TNF-α and IL-6. The potential therapeutic benefits of inhibiting IL-17 activity in diabetes are supported by its role in the disease. Diabetes and its complications have been studied, and drugs that block IL-17 or its receptors have been investigated as a potential treatment. However, further study is needed to completely understand the complicated role of IL-17 in diabetes and to determine the efficacy and safety of such therapies [28,29].

Based on the study's findings, it is postulated that IL-17 may potentially contribute to the pathogenesis of insulin resistance. The inhibitory effect of the cytokine IL-17 on insulin-stimulated glucose absorption has been found in adipocytes and skeletal muscle cells. Moreover, it possesses the capacity to induce the production of several pro-inflammatory cytokines, such as TNF-α and IL-6. Moreover, it has been observed that these cytokines have the capacity to hinder the signaling pathways of insulin, hence contributing to the progression of insulin resistance. In addition to the aforementioned processes, it is noteworthy that IL-17 has the capacity to stimulate the synthesis of chemokines, which serve to attract inflammatory cells to the specific location of inflammation. The release of substances by these inflammatory cells has the potential to cause tissue damage and exacerbate insulin resistance [30]. The findings of a research study conducted on the IDDM rat model, which is used to simulate type 1 diabetes, revealed that the implementation of combination therapy using anti-TCR, anti-IL-17A, and/or anti-IL-6 agents can effectively initiate a state of remission in autoimmune diabetes. This indicates that targeting IL-17A and IL-6 may be a potential treatment strategy for type 1 diabetes [31].

Interleukin-22 (IL-22)

Despite speculation of an unambiguous association between IL-22 and diabetes, recent studies have shown promise in illuminating its potential involvement in both the development and management of the disease and its consequences. Researchers have discovered that IL-22 protects the insulin-producing pancreatic beta cells in type 1 diabetes. Studies in animals have demonstrated that IL-22 helps beta cells live longer and function better, which protects their ability to secrete insulin. As a result, IL-22 may be useful as a therapeutic agent for preventing beta cell dysfunction and treating type 1 diabetes. The significance of IL-22 in type 2 diabetes is more nuanced [32]. Some research suggests that IL-22 may improve insulin sensitivity and glucose metabolism, while other research suggests that it may contribute to the development of insulin resistance and chronic inflammation. Possible determinants of IL-22's role in type 2 diabetes include disease progression and the nature of the cells and tissues at play. In addition, IL-22 has been linked to the regulation of gut microbiota, which is coming to be seen as a key role in diabetes pathogenesis and progression. When it comes to metabolic health and insulin sensitivity, IL-22 may have an effect by altering the composition of the gut flora. More studies are needed to completely understand the processes and consequences of IL-22 in various forms of diabetes, although there is current research into the potential therapeutic use of IL-22 or IL-22-based therapeutics for diabetes. While IL-22 has shown promise in preclinical and experimental trials, further clinical research is needed before these results can be translated into viable treatments for human diabetes [32,33].

The role of NLRP3 regulation in the aetiology of diabetes has been investigated in relation to the cytokine IL-22. According to a

study, the activation of the NLRP3 inflammasome can be inhibited by IL-22, leading to the improvement of renal damage and fibrosis in diabetic nephropathy [34]. This implies that IL-22 might exert a favourable impact on diabetic nephropathy through the modulation of NLRP3. In a separate investigation, the involvement of the NLRP3 inflammasome in the long-term problems associated with diabetes was examined. The text suggests that there may be a connection between the regulation of NLRP3 and issues related to diabetes, as chronic hyperglycemia has been found to increase the expression of the NLRP3 modulator TXNIP [35]. Additionally, a study revealed that IL-22 has the ability to regulate islet endoplasmic reticulum (ER) stress and insulin secretion [36]. This observation implies that IL-22 might have potential involvement in the regulation of beta cell stress in diabetes. According to the article, researchers discovered that a fusion protein including an anti-ANGPTL3 antibody and IL-22 exhibited therapeutic effects in mice, leading to the improvement of their condition. This finding suggests that the administration of IL-22, in conjunction with other therapeutic medications, may yield beneficial outcomes in the treatment of diabetes complications. Based on the aforementioned data, it may be inferred that IL-22 potentially plays a role in the modulation of NLRP3 in the pathogenesis of diabetes, specifically in the context of diabetic nephropathy. Nevertheless, additional investigation is required in order to comprehensively comprehend the mechanisms and potential therapeutic implications of IL-22 in the context of diabetes [34, 37].

Interleukin-10 (IL-10)

The immunomodulatory effects of IL-10 in type 1 diabetes have been studied. IL-10 has been proven in experiments to prevent the loss of insulin-secreting beta cells in the pancreas, therefore reversing type 1 diabetes. In the pathophysiology of T1D, it can inhibit immune cell activation and the production of inflammatory cytokines. Still under study, however, is IL-10's potential as a therapeutic intervention for type 1 diabetes. Improvements in insulin sensitivity and glucose metabolism have been shown with IL-10 treatment of type 2 diabetes. Peripheral tissues, including adipose tissue and skeletal muscle, can benefit from IL-10's anti-inflammatory and insulin-enhancing properties. It has been demonstrated in studies that IL-10 can generate an anti-inflammatory milieu and reduce insulin resistance by preventing the generation of pro-inflammatory cytokines. The specific role and therapeutic potential of IL-10 in diabetes are still being investigated, despite its documented positive benefits in animal models and some clinical research [38].

In the context of insulin resistance, IL-10 has been found to have both beneficial and detrimental effects. It can inhibit the production and activity of pro-inflammatory cytokines, such as IL-6 and TNF-α. By suppressing these inflammatory mediators, IL-10 helps maintain a balanced immune response and prevent excessive inflammation, which can contribute to insulin resistance. Some studies suggest that IL-10 may improve insulin sensitivity in certain conditions. Increased levels of IL-10 have been associated with enhanced insulin sensitivity, which means cells are more responsive to insulin's actions, leading to better glucose uptake and utilization. IL-10 can influence the polarization of macrophages, which are immune cells involved in inflammation. Macrophages can be polarized into two main phenotypes: M1 (pro-inflammatory) and M2 (anti-inflammatory). IL-10 promotes the M2 phenotype, which can help dampen inflammation and improve insulin sensitivity [39].

TNF-α

Inflammatory and immunological responses rely heavily on TNF-α, a pro-inflammatory cytokine. Multiple physiological and pathological processes, including diabetes, have been linked to the presence of TNF-α. Extensive study has been conducted to investigate the involvement of TNF-α in the advancement of diabetes, particularly type 2 diabetes. The association between TNF-α and insulin resistance has been established, wherein insulin resistance is defined as a state characterized by diminished cellular responsiveness to the physiological actions of insulin. Elevated levels of TNF-α can lead to a decrease in glucose uptake and

an increase in blood sugar levels due to its impact on insulin signaling pathways in various tissues, such as the liver, muscle, and adipose tissue. Adipocytes are a type of endocrine cell that has the ability to secrete a diverse range of cytokines, one of which is TNF-α [40]. In individuals who are afflicted with obesity, adipose tissue experiences a condition of inflammation, which is distinguished by the release of TNF-α by adipocytes. Upon the stimulation of TNF-α, NF-κ β is expressed, leading to a notable increase in the expression of various pro-inflammatory mediators such as IL-6, IL-1β, and COX-2. These mediators play a role in the worsening of insulin resistance and inflammation. TNF-α has a diverse range of impacts on the insulin signalling system. The obstruction of insulin signalling is distinguished by the hindrance of phosphorylation events that involve insulin receptor substrate-1 (IRS-1). The interference of insulin results in a decrease in the uptake of glucose in muscle and adipose tissues, which are two specialised tissues that are selectively affected by insulin. Moreover, there is evidence indicating that the cytokine TNF-α elicits an upregulation in the expression of suppressor of cytokine signalling 3 (SOCS3), which functions as a suppressor of insulin signalling. Elevated concentrations of SOCS3 have been observed to impede the functionality of IRS-1 and play a role in the progression of insulin resistance [41]. Adipose tissue shows elevated TNF-α production in obesity-associated diabetes. Disruption of adipocyte function and dysregulated adipokine release result from elevated TNF-α production. Insulin sensitivity is influenced by adipokines like adiponectin and leptin, and an imbalance of these adipokines can lead to insulin resistance [42].

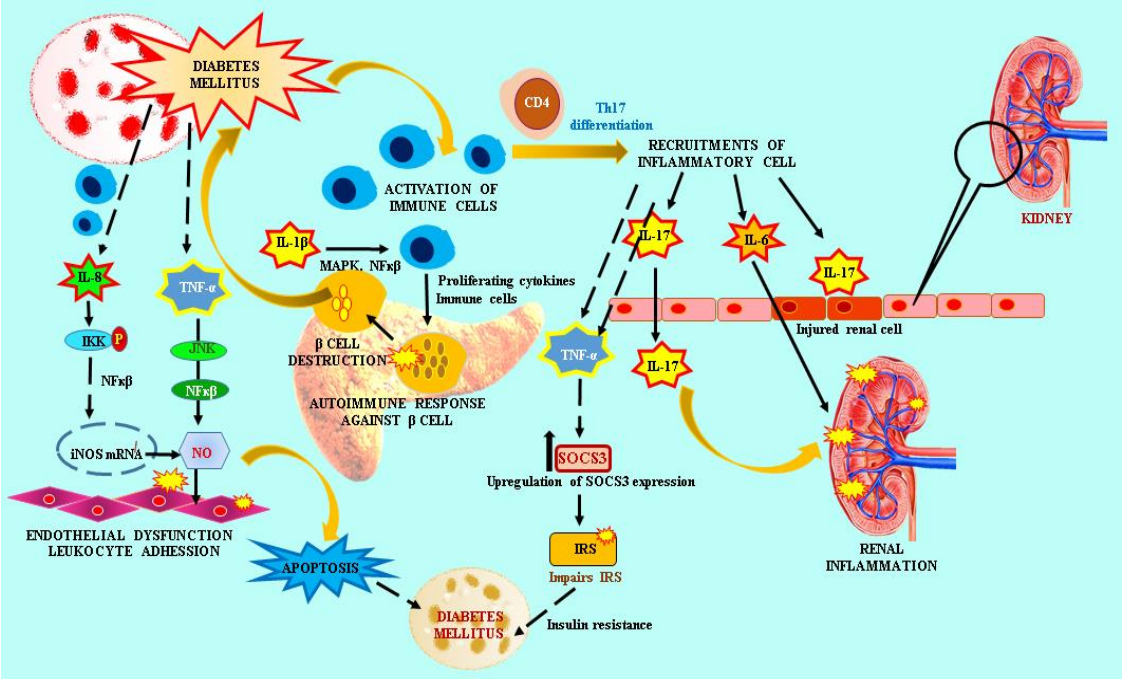

Figure (1): Cytokines mediated immune response and incident of diabetes mellitus.

Growth factors and their role in diabetes mellitus

Immune cell activation in diabetes mellitus induces Th17 differentiation and the recruitment of inflammatory cells. The cytokines IL-17 and IL-16 contribute to cell damage and renal inflammation. TNF-α induces SOCS3 expression, thereby compromising IRS and insulin resistance. Elevated levels of IL-8 and TNF-α induce endothelial dysfunction by enhancing NO production via IKK/NF-κβ-mediated iNOS expression and JNK- NF-κβ pathways. Autoimmune response induced by proliferating cytokines and immune cells targets B cells through IL-8, thereby contributing to diabetic pathology.

Different growth factors have been investigated to see if they play a part in the onset, progression, and consequences of diabetes. Similar to insulin in structure, Insulin-like Growth Factors (IGFs) are peptide hormones. There would be no cell development, proliferation, or differentiation without them. Growth hormone controls IGF-1 production, which occurs predominantly in the liver. It's been linked to controlling blood sugar levels, improving insulin sensitivity, and preventing diabetes complications. The protein called epidermal growth factor (EGF) plays a crucial role in various biological processes, including but not limited to cell proliferation, wound healing, and tissue regeneration. The investigation of EGF has primarily been around chronic ulceration and delayed wound healing associated with diabetes. Platelet-derived growth factor (PDGF) is a growth factor that facilitates cellular proliferation and contributes to the process of wound healing. Following tissue damage, platelets and other cellular components release it. The association between PDGF and both mesangial cell proliferation and extracellular matrix protein deposition in diabetic nephropathy has been established [43]. Furthermore, TGF-β has a significant function in the immune system, in addition to its involvement in cell formation and differentiation. There exists a correlation between the occurrence of both autoimmune and non-autoimmune diabetes and this particular phenomenon. Transforming growth factor-beta (TGF-β) plays a significant role in the advancement of complications associated with diabetes, such as diabetic nephropathy and diabetic retinopathy. This is achieved through its involvement in immunological regulation, fibrosis, and tissue remodeling. Fibroblast growth factors (FGFs) encompass a collection of growth factors that assume pivotal roles in several biological processes, including but not limited to cell proliferation, angiogenesis, and tissue healing. Studies on fibroblast growth factors 1 and 2 have focused on their role in diabetic wound healing and tissue regeneration. Neurotrophic growth factor (NGF) promotes the health and longevity of neurons. Diabetic neuropathy, which is characterized by nerve degeneration and dysfunction, may have its origins in NGF (Figure 2) [44].

IGF-1

The major member of the IGF family, IGF-1, has intimate ties to insulin. The liver is the primary site of its production after being stimulated by growth hormones. IGF-1 has been linked to improvements in insulin sensitivity. It can increase the cells' ability to take up glucose and boost glycogen production. Insulin resistance, a hallmark of type 2 diabetes, may be exacerbated by low IGF-1 levels or faulty IGF-1 signaling [45]. Insulin-producing pancreatic beta cells are affected by IGF-1, both in their ability to function and their likelihood of survival. Some research suggests that a lack of IGF-1 can hinder beta cell function. IGF-1 has been shown to increase beta cell proliferation and insulin release. Changes in IGF-1 signaling have been linked to the onset of diabetes complications. There exists data suggesting that the development of diabetes sequelae, such as nephropathy, retinopathy, and neuropathy, may be influenced by reduced levels of IGF-1 or modifications in IGF-1 signaling [46]. The study conducted at a population-based level reveals a correlation between a variation in the promoter region of the IGF-I gene and its influence on gene expression. The prevalence of the 192-base pair allele deficiency in the population is estimated to be around 12%. This specific polymorphism has been linked to reduced height, lower levels of IGF-1, and an increased vulnerability to type 2 diabetes and myocardial infarction. The etiology of these disorders is postulated to be associated with a genetic predisposition, leading to prolonged exposure to low concentrations of IGF-I in persons lacking the 192-bp allele [47].

Insulin-like Growth Factor Binding Proteins (IGFBPs)

The regulation of the amount and activity of IGFs in the human body is governed by a group of proteins known as insulin-like growth factor binding proteins (IGFBPs). The IGFBPs play a crucial role in the transportation and modulation of the effects of insulin-like growth factors (IGFs) on their respective target organs [48]. Changes in the expression and function of IGFBPs can have an impact on the bioavailability and activity of IGFs, a phenomenon that has been observed in

individuals with diabetes. The concentrations of IGFBP-1 exhibit an inverse relationship with insulin levels. The levels of IGFBP-1 increase in conditions characterized by insulin deficiency, such as fasting or uncontrolled diabetes. Elevated concentrations of IGFBP-1 have been associated with decreased expression of IGF-1 and the onset of insulin resistance. The majority of the circulating IGF-1 is bound and regulated by insulin-like growth factor binding protein 3 (IGFBP-3). A robust correlation has been demonstrated between insulin resistance and metabolic diseases, notably type 2 diabetes. Individuals with insulin resistance and type 2 diabetes have been found to exhibit decreased levels of IGFBP-3. There is a significant amount of knowledge yet to be acquired regarding the intricate relationship between IGFs, insulin, and the condition of diabetes [48, 49]. The potential linkage between circulating IGFBP-2 and the risk of type 2 diabetes could be elucidated through insulin-regulated pathways. Adenovirus-mediated IGFBP-2 overexpression normalized insulin and glucose levels in diabetes-prone animals and prevented the metabolic effects of defective insulin signaling. IGFBP-2 operates downstream of insulin since streptozocin-induced type 1 diabetic rats showed these benefits. Glucose homeostasis improved regardless of diet and weight. IGFBP-2 increases GLUT4-mediated glucose uptake in adipocytes in vitro, suggesting direct insulin-signaling mechanisms [50].

EGF

The growth factor in question is of significant importance in a range of cellular activities, encompassing cell development, proliferation, and tissue repair [51]. Diabetes is frequently linked to compromised wound healing, particularly in the context of chronic wounds like diabetic foot ulcers. EGF plays a crucial role in the modulation of the wound healing mechanism, encompassing the facilitation of cellular migration, proliferation, and angiogenesis. In the context of diabetes, the compromised synthesis and reactivity to EGF can play a role in the hindered process of wound healing and the development of persistent ulcers. Diabetes can lead to various skin disorders, including dry skin, infections, and poor skin integrity. EGF has been investigated for its potential therapeutic role in managing diabetic skin conditions. Topical application of EGF or EGF-containing products has shown promising results in improving skin health and wound healing in individuals with diabetes. The EGF binds to the receptor tyrosine kinase EGF receptor (EGFR or ErbB1) and activates it. Activation of EGFR's intrinsic kinase activity requires ligand interaction, which triggers dimerization and autophosphorylation of the receptor. The Ras/Raf/MEK/ERK pathway, the PI3K/AKT pathway, and the PLCγ pathway are just a few of the intracellular signaling cascades that are activated when EGFR is expressed. Cellular functions like proliferation, differentiation, migration, and survival are all regulated by these pathways [51,52].

PDGF

One of the many diabetic complications, diabetic nephropathy, damages the kidneys. Renal fibrosis and glomerulosclerosis (scarring of the kidney's filtration units, the glomeruli) both worsen as this condition advances, and PDGF has been implicated in both processes. PDGF stimulates the proliferation of mesangial cells, which produce extracellular matrix proteins and are essential for glomerular shape and function. Abnormal cell proliferation, fibrosis, and compromised kidney function have all been linked to elevated PDGF signaling. Multiple intracellular signaling cascades are activated when PDGFRs (Platelet-Derived Growth Factor Receptors) are expressed [53]. These include the PI3K/AKT pathway, the PLCγ pathway, and the Ras/Raf/MEK/ERK pathway. Cell proliferation, survival, and migration are only some of the cellular activities that are controlled by these pathways. The aberrant proliferation and migration of VSMCs is a common cause of vascular problems in people with diabetes. The triggering of vascular smooth muscle cell (VSMC) proliferation and migration is observed in response to PDGF, indicating the potential involvement of this growth factor in the pathogenesis of diabetic vascular complications, including atherosclerosis and restenosis. Collagen, fibronectin, and proteoglycans are only some of the ECM components that PDGF can stimulate

production of. Tissue fibrosis is a feature of several diabetic diseases, including diabetic nephropathy and diabetic retinopathy, and is linked to increased ECM formation and buildup. Recent studies have provided evidence linking PDGF to the development of insulin resistance. The findings of genetic investigations and cell modeling have provided evidence that heightened levels of insulin induce hypomethylation of the CpG region in the PDGF-A gene. This hypomethylation event subsequently results in the overexpression of PDGF-A and augmented production of PDGF-AA in the liver [54]. The expression of PDGF-AA is additionally enhanced by the action of protein kinase C (PKC), hence contributing to the development of insulin resistance. This is achieved by the reduction of IRS1 and insulin receptor (INSR) abundance, as well as the activation of PKC. The potential treatment strategies for enhancing insulin sensitivity in hepatocytes include the utilization of antibodies, PDGFR inhibitors, or metformin to block the activity of PDGF-AA [54, 55]. Furthermore, the absence of PDGF-B in mice with obesity resulted in a decrease in fasting insulin levels and an improvement in hepatic vascular endothelial transport. This led to greater regulation of glucose levels in the body and improved clearance of insulin. The presence of elevated PDGF signaling in the hepatic tissue of individuals afflicted with obesity and type 2 diabetes plays a role in the development of insulin resistance [55]. Complications of diabetes can form and worsen due to PDGF's ability to interact with inflammatory processes and angiogenesis. It has been established that PDGF promotes angiogenesis, and the development of new blood vessels, and is implicated in the recruitment and expression of inflammatory cells like macrophages [56].

FGFs

Wound healing is hindered in people with diabetes, while this is especially true for long-standing ulcers like diabetic foot ulcers. Scientific inquiry on the effects of FGFs on wound healing has focused primarily on Fibroblast Growth Factor 2 (FGF-2 or basic FGF). Cell migration, proliferation, and the development of new blood vessels are all aided by fibroblast growth factor-2 (FGF-2). FGF-based therapeutics, such as recombinant FGF or FGF-containing wound dressings, have demonstrated positive results in accelerating wound healing in diabetic patients. Impaired angiogenesis, or the development of new blood vessels, is crucial for tissue repair and organ function, but diabetes can prevent it. Angiogenesis is triggered by FGFs like FGF-2 and others in the FGF family. They encourage the growth of new blood arteries by increasing the proliferation and migration of endothelial cells. Inadequate angiogenesis and damaged tissue repair may be caused, in part, by diabetes-related impairments in FGF signaling or FGF levels [57]. Diabetic retinopathy appears as an ailment that damages the retina's blood vessels and is a common complication of diabetes. Research on FGFs has been conducted about diabetic retinopathy, with a focus on FGF-2. FGFRs plunge signals throughout the cell, activating downstream cascades like Ras/Raf/MEK/ERK, PI3K/AKT, and PLCγ when expressed. A cell's ability to divide, survive, and specialize is controlled by these pathways. The function of pancreatic beta cells may be regulated by FGF signaling. It has been found that fibroblast growth factors 1 and 21 (FGF1 and FGF21) improve beta cell survival, proliferation, and insulin secretion. The anti-inflammatory capabilities of FGF21 may help shield beta cells from damage caused by cytokines. Insulin sensitivity in peripheral tissues may be affected by FGF signaling. Insulin sensitivity in adipose tissue, liver, and skeletal muscle is improved by FGF21. It improves insulin signaling pathways, increases glucose absorption and utilization, and decreases lipolysis (fat breakdown). The metabolism and function of adipose tissue may be affected by FGF signaling. For example, FGF21 encourages the browning of white adipose tissue, which in turn raises the basal metabolic rate and improves other metabolic indices. The insulin-related adipokine adiponectin is secreted under the control of FGF21 [58, 59].

NGF

Sensory neurons, in particular, rely on NGF, a neurotrophic factor, for their development, survival, and maintenance. Nerve damage and dysfunction, known as

diabetic neuropathy, is a common consequence of diabetes. Diminished NGF levels have been linked to apoptosis (the death of nerve cells) and poor neuron regeneration. As a potential treatment for diabetic neuropathy, restoring NGF levels or increasing NGF signaling pathways has been studied. Second, neuropathic pain, characterized by anomalous sensations like burning, tingling, or shooting pain, might be a symptom of diabetic neuropathy [60]. The NGF may play a role in controlling pain. Increased pain sensitivity in diabetic neuropathy may be caused by elevated levels of NGF in the peripheral tissues and nerve terminals. When NGF engages with the receptor tyrosine kinases TrkA and p75NTR, it triggers the corresponding cellular responses. p75NTR can have pro-survival or pro-apoptotic effects, depending on the cellular environment and the presence of additional co-receptors, whereas TrkA is the high-affinity receptor responsible for the pro-survival and trophic effects of NGF. Nerve injury and decreased NGF availability in peripheral tissues have been linked to diabetes and other metabolic disorders. Sensory and autonomic neurons in the periphery rely heavily on NGF for their survival and maintenance. Diminished NGF levels may negatively impact these neurons, aggravating the condition known as diabetic neuropathy. Nerve damage is exacerbated by diabetes's comorbid condition, chronic inflammation [61]. NGF can stimulate the production of inflammatory cytokines such as TNF-α and interleukins, worsening nerve damage and inflammation. Under pathological situations, activation of p75NTR in the presence of NGF can cause apoptosis of sensory neurons. This may be one cause of diabetic neuropathy's characteristic gradual sensory function decline [62]. Numerous studies have demonstrated the expression of NGF and its receptor TrkA in various tissues, including the pancreatic β cells. Elevated levels of glucose have the potential to significantly increase the release of NGF, which in turn activates TrkA receptors in β-cells to effectively improve insulin production in response to glucose stimulation [63]. There is evidence suggesting that levels of NGF exhibit an inverse correlation with insulin resistance. The ability of NGF to mitigate insulin resistance has been observed in both in vitro and in vivo studies, mostly through the expression of IRS1 [64]. Nevertheless, a study revealed a positive correlation between levels of NGF and insulin resistance, suggesting that this relationship could be attributed to a compensatory mechanism. The data presented indicate that NGF functions as a safeguarding element in the regulation of glucose metabolism and insulin sensitivity, and also holds substantial importance in the process of insulin release triggered by glucose.

Transforming growth factor-beta (TGF- β)

When discussing diabetes, TGF-β has been linked to complications in both type 1 and type 2 cases. Regulatory T cells (Tregs) are essential for immunological tolerance maintenance and protection against autoimmunity, and TGF-β may enhance their development. Smad proteins must be activated for the TGF-signaling pathway to function. Smad2 and Smad3 join Smad4 in complexes after being phosphorylated by the type I receptor, allowing them to enter the nucleus [65]. Target genes that regulate many cellular processes are controlled by these complexes' transcriptional modification. However, in the context of type 1 diabetes, TGF-β can also contribute to the suppression of Tregs, impairing their function and activating autoreactive T cells that target beta cells. TGF-β has been implicated in the development of insulin resistance, a key feature of type 2 diabetes. TGF-β stimulates the production of extracellular ECM proteins, such as collagen, fibronectin, and proteoglycans, leading to tissue fibrosis. This fibrotic process can lead to the dysfunction of these tissues, impairing their ability to respond to insulin properly [65, 66].

Vascular endothelial growth factor (VEGF)

Despite VEGF's more common association with vascular growth and function, it is also relevant to discuss the effects of diabetes and its consequences. Retinal blood vessel disease known as diabetic retinopathy is a common consequence of diabetes. VEGF is critically important in this disease. When blood vessel injury causes an ischemia environment in the retina, the body responds by increasing VEGF synthesis to promote new vessel formation. The growth factor VEGF

plays a significant part in the development of diabetic retinopathy. In the retina, elevated levels of VEGF are produced in response to both chronic hyperglycemia and hypoxia. When present in abundance, VEGF interacts with VEGFR-2, leading to the formation of receptor dimers and subsequent autophosphorylation. This event triggers the activation of multiple signaling pathways, including the Ras/Raf/MEK/ERK system, the PI3K/AKT network, and the PLCγ cascades. These pathways all contribute to the development of pathological angiogenesis. The growth of aberrant blood vessels in the retina is another result that might cause blindness [67]. In diabetic nephropathy, there is often a dysregulation of VEGF signaling, leading to alterations in glomerular function and increased permeability of blood vessels. This can contribute to the development of proteinuria and progressive kidney damage. Several studies have indicated that VEGFR1 exerts a negative regulatory effect on the VEGF-A signaling pathway. This regulatory mechanism involves the inhibition of VEGF-A binding to VEGFR2, hence impeding the generation of mitogenic signals. In contrast, it has been demonstrated that VEGFR1 can generate mitogenic signals through its interaction with signal-transducing proteins under specific circumstances. Under typical circumstances, VEGFR1 has a negative regulatory effect on the signaling pathways of VEGF-A and VEGFR2. This regulatory mechanism serves to maintain a delicate equilibrium between blood vessel creation and cellular migration. Nevertheless, in the context of diabetic kidneys, there is a notable reduction of around 40% in the expression of VEGFR1, which subsequently results in an augmented signaling pathway involving VEGF-A and VEGFR2. In contrast, it has been determined that VEGFR1 has a constructive role in facilitating the signalling of VEGF-A and VEGFR2 in certain primary tumour models and cases of wet age-related macular degeneration. The observed favourable impact could potentially be attributed to the regulatory role of VEGFR1 in modulating the level of VEGF-A signalling perceived by endothelial cells, hence leading to a compensatory upregulation of VEGF-A production. Recent research studies utilising a VEGFR2 inhibitor in animal models of diabetes have revealed notable enhancements in several aspects of diabetic nephropathy, such as enlargement of the mesangial matrix, thickening of the basement membrane, inflammation in the tubulointerstitium, and reduction in albuminuria [68]. Anti-VEGF drugs, namely intravitreal injections, have been formulated to suppress the overexpression of VEGF and mitigate the proliferation of anomalous blood vessels and subsequent leakage [69]. According to recent findings, the application of a VEGFR2 kinase inhibitor known as SU5416 to block VEGFR2 in diabetic mice during experiments resulted in the emergence of histological features resembling those observed in advanced cases of Diabetic Nephropathy in humans [70, 71].

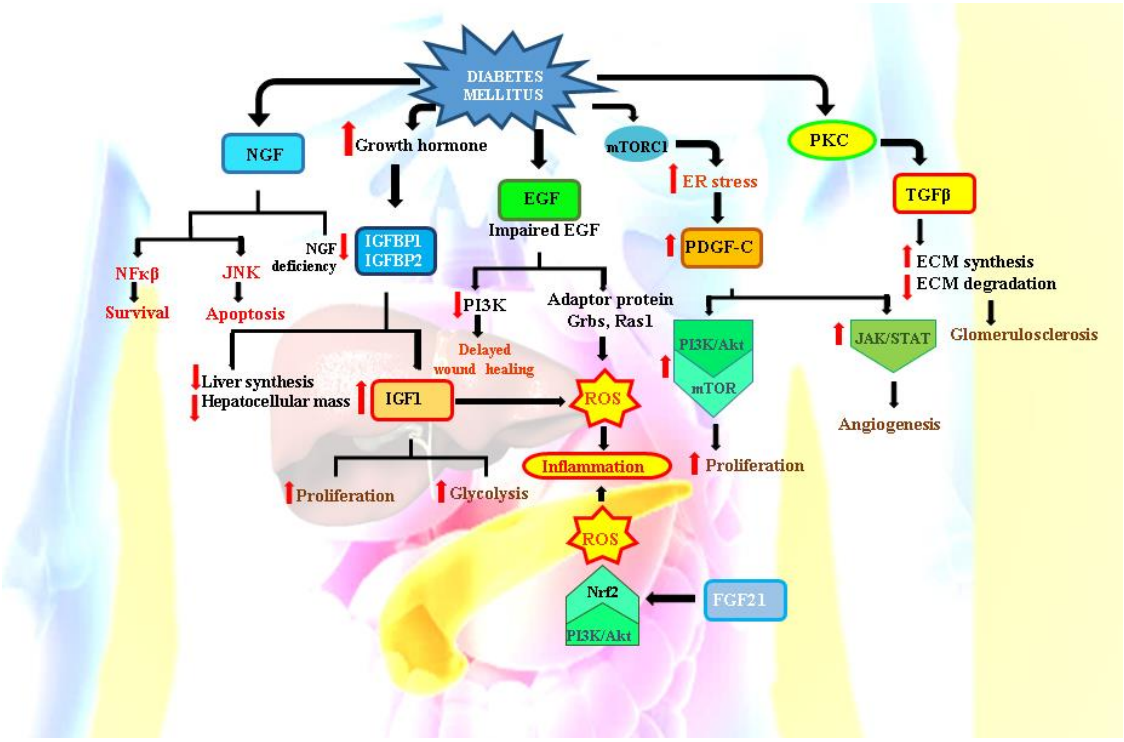

Figure (2): Diabetes mellitus and signaling cascades of growth factor.

In diabetes mellitus, elevated growth hormone levels (IGFBP1, IGFBP2) decrease liver synthesis, resulting in a decrease in hepatocellular mass, whereas elevated IGF1 levels stimulate ROS production and subsequent inflammation. Impaired EGF expression in diabetes mellitus delays wound healing via PI3K downregulation and induces neuroinflammation via ROS production. Through the PI3K-mTOR and JAK/STAT pathways, ER stress increases PDGFC expression, which in turn increases proliferation and angiogenesis. TGF-β expression is increased by the diabetic upregulation of PKC. In contrast, FGF21 increases PI3K/Akt and Nrf2, both of which promote inflammation via ROS.

Prospective therapeutic approach

Inflammatory and growth factors, in particular, have been shown to play crucial roles in the onset and progression of diabetes mellitus and its consequences. In diabetes, pro-inflammatory cytokines such as TNF-α and IL-6 cause persistent low-grade inflammation. Diabetes problems, including insulin resistance and pancreatic beta-cell malfunction, are aided by this inflammation. IL-6 has the potential to improve the condition of diabetic nephropathy by impeding the activation of NLRP3 inflammasome, which is partially achieved by reducing the activity of IL-17A. This observation implies that the inhibition of the IL-6 receptor could serve as a viable therapeutic approach for managing diabetic nephropathy. The induction of remission in autoimmune diabetes can be achieved with the use of combination therapy involving anti-TCR, anti-IL-17A, and/or anti-IL-6 agents. These findings suggest that the therapeutic targeting of IL-17A and IL-6 could potentially serve as a viable treatment approach for type 1 diabetes. The activation of the NLRP3 inflammasome can be inhibited by IL-22, leading to the improvement of kidney damage and fibrosis in diabetic nephropathy. This observation implies that using IL-22 therapy could serve as a promising therapeutic approach for managing diabetic nephropathy. The protective impact of IL-10 is achieved by the downregulation of pro-inflammatory cytokine expression. Inflammatory macrophages are polarised by IL-10. IL-10 enhances M2, thereby minimizing inflammation and improving insulin sensitivity. Growth factors help with new cell development, wound healing, and blood vessel formation. Recent

findings using a VEGFR2 inhibitor in experimental diabetic models demonstrated improvements in diabetic nephropathy features, including mesangial matrix expansion, basement membrane thickening, tubulointerstitial inflammation, and albuminuria reduction [68]. Anti-VEGF medications, such as intravitreal injections for diabetic retinopathy, have been developed to inhibit excessive VEGF activity and reduce abnormal blood vessel growth and leakage. The potential treatment strategies for enhancing insulin sensitivity in hepatocytes include the utilization of antibodies, PDGFR inhibitors, or metformin to block the activity of PDGF-AA. Inflammation frequently interferes with the normal functioning of growth factors, adding complexity to the interplay between inflammatory and growth factors. There is hope for the creation of novel treatment strategies for diabetes by focusing on these variables and associated signaling pathways. In conclusion, the inflammatory cytokines and growth factors played a crucial role in insulin resistance.

CONCLUSION

In conclusion, extensive research has confirmed that inflammatory cytokines and growth factors exert a substantial influence on the onset and progression of diabetes mellitus and its related complications. The development of insulin resistance and malfunction of pancreatic beta-cells in diabetes can be related to the presence of chronic, moderate inflammation. This inflammatory response is predominantly initiated by pro-inflammatory cytokines, including TNF-α and IL-6. The prospective management of diabetic nephropathy and type 1 diabetes lies in the targeting of IL-6 receptor and IL-17A, respectively. Additionally, the use of IL-22 treatment exhibits promises in alleviating kidney damage and fibrosis associated with diabetic nephropathy. The protective effects of IL-10 can be attributed to its ability to downregulate pro-inflammatory cytokines and promote M2 macrophage polarisation, potentially leading to an improvement in insulin sensitivity. Growth factors, such as VEGFR2, present potential therapeutic avenues for the management of diabetic nephropathy and diabetic retinopathy. The improvement of insulin sensitivity could potentially be achieved by inhibiting the activity of PDGF-AA in hepatocytes. The intricate interaction between inflammatory and growth factors introduces a level of intricacy, although the strategic focus on these factors and their corresponding signaling pathways presents new opportunities for innovative approaches to diabetic therapeutics. In general, comprehending and modulating the functions of inflammatory and growth factors offer potential approaches to address insulin resistance and its associated outcomes in the context of diabetes.

REFERENCES

1] Sweeting A, Wong J, Murphy HR, Ross GP. (2022). A clinical update on gestational diabetes mellitus. *Endocrine reviews*. 43(5):763-93.

2] Safiri S, Karamzad N, Kaufman JS, Bell AW, Nejadghaderi SA, Sullman MJ, Moradi-Lakeh M, Collins G, Kolahi AA. (2022). Prevalence, deaths and disability-adjusted life-years (days) due to type 2 diabetes and its attributable risk factors in 204 countries and territories, 1990-2019: results from the global burden of disease study 2019. *Frontiers in endocrinology*. 13:838027.

3] Su MC, Chang MY, Sun JC. (2023). Self-management experience of first-time diagnosed gestational diabetes mellitus: A focus group interview. *Nursing Open*. 10(3):1744-54.

4] Vijayasimha M, Jayarajan D, Srikanth M. (2022). 18 ACUTE KIDNEY INJURY AND THE PRESENT BIOCHEMICAL TESTS TO DIAGNOSE. *Recent Trends and Latest Innovations in Life Sciences*. 2022:164.

5] Shi GJ, Shi GR, Zhou JY, Zhang WJ, Gao CY, Jiang YP, Zi ZG, Zhao HH, Yang Y, Yu JQ. (2018). Involvement of growth factors in diabetes mellitus and its complications: a general review. *Biomedicine & Pharmacotherapy*. 101:510-27.

6] Matsumori A. (2022). Novel biomarkers of inflammation for the management of diabetes: immunoglobulin-free light chains. *Biomedicines*. 10(3):666.

7] Fico E, Rosso P, Triaca V, Segatto M, Lambiase A, Tirassa P. (2022). NGF prevents loss of TrkA/VEGFR2 cells, and VEGF isoform dysregulation in the retina of adult diabetic rats. *Cells*. 11(20):3246.

8] Nwadiugwu MC. (2021). Inflammatory activities in type 2 diabetes patients with co-morbid angiopathies and exploring beneficial interventions: a systematic review. *Frontiers in Public Health*. 8:600427.

9] Lu Q, Chen J, Li R, Wang Y, Tu Z, Geng T, Liu L, Pan A, Liu G. (2023). Healthy lifestyle, plasma metabolites, and risk of cardiovascular disease among individuals with diabetes. *Atherosclerosis*. 367:48-55.

10] Alfadul H, Sabico S, Al-Daghri NM. (2022). The role of interleukin-1β in type 2 diabetes mellitus: A systematic review and meta-analysis. *Frontiers in Endocrinology*. 13:901616.

11] Sorkhabi R, hossein Ahoor M, Haghjo AG, Tabei E, Taheri N. (2022). Assessment of tear inflammatory cytokines concentration in patients with diabetes with varying severity of involvement. *Experimental Eye Research*. 224:109233.

12] Rampanelli E, Nieuwdorp M. (2023). Gut microbiome in type 1 diabetes: the immunological perspective. *Expert Review of Clinical Immunology*. 19(1):93-109.

13] Onikanni AS, Lawal B, Oyinloye BE, Mostafa-Hedeab G, Alorabi M, Cavalu S, Olusola AO, Wang CH, Batiha GE. (2022). Therapeutic efficacy of Clompanus pubescens leaves fractions via downregulation of neuronal cholinesterases/Na+-K+ ATPase/IL-1 β, and improving the neurocognitive and antioxidants status of streptozotocin-induced diabetic rats. *Biomedicine & Pharmacotherapy*. 148:112730.

14] Yun JH. (2021). Interleukin-1β induces pericyte apoptosis via the NF-κB pathway in diabetic retinopathy. *Biochemical and Biophysical Research Communications*. 546:46-53.

15] Everett BM, Donath MY, Pradhan AD, Thuren T, Pais P, Nicolau JC, Glynn RJ, Libby P, Ridker PM. (2018). Anti-inflammatory therapy with canakinumab for the prevention and management of diabetes. *Journal of the American College of Cardiology*. 71(21):2392-401.

16] Rehman K, Akash MS, Liaqat A, Kamal S, Qadir MI, Rasul A. (2017). Role of interleukin-6 in development of insulin resistance and type 2 diabetes mellitus. *Critical Reviews™ in Eukaryotic Gene Expression*. 27(3).

17] Hussein NM, Mahmood AR. (2022). Association of interleukin-6 level and DNA polymorphism in type 2 diabetic patients in Kirkuk city. *Periodicals of Engineering and Natural Sciences*. 10(1):411-20.

18] Ekta, Gupta M, Kaur A, Singh TG, Bedi O. (2020). Pathobiological and molecular connections involved in the high fructose and high fat diet-induced diabetes associated nonalcoholic fatty liver disease. *Inflammation Research*. 69:851-67.

19] Rehman K, Akash MS. (2016). Mechanisms of inflammatory responses and development of insulin resistance: how are they interlinked? *Journal of biomedical science*. 23(1):1-8.

20] Akbari M, Hassan-Zadeh V. (2018). IL-6 signaling pathways and the development of type 2 diabetes. *Inflammopharmacology*. 26:685-98.

21] Yue T, Shi Y, Luo S, Weng J, Wu Y, Zheng X. (2022). The role of inflammation in immune system of diabetic retinopathy: Molecular mechanisms, pathogenetic role and therapeutic implications. *Frontiers in Immunology*. 13:1055087

22] Liu SY, Chen J, Li YF. (2018). Clinical significance of serum interleukin-8 and soluble tumor necrosis factor-like weak inducer of apoptosis levels in patients with diabetic nephropathy. *Journal of diabetes investigation*. 9(5):1182-8.

23] Stoica RA, Drăgana N, Ancuceanu R, Geicu OI, Guja C, Pantea-Stoian A,

Gheorghe DC, Stefan-van Staden RI, Serafinceanu C, Costache A, Ionescu-Tîrgoviște C. (2022). Interleukin-8, CXCL10, CXCL11 and their role in insulin resistance in adult females with subclinical hypothyroidism and prediabetes. *Journal of Clinical & Translational Endocrinology*. 28:100299.

24] Kong L, Andrikopoulos S, MacIsaac RJ, Mackay LK, Nikolic-Paterson DJ, Torkamani N, Zafari N, Marin EC, Ekinci EI. (2022). Role of the adaptive immune system in diabetic kidney disease. *Journal of diabetes investigation*. 13(2):213-26.

25] Yoshida S, Kobayashi Y, Nakama T, Zhou Y, Ishikawa K, Arita R, Nakao S, Miyazaki M, Sassa Y, Oshima Y, Izuhara K. (2015). Increased expression of M-CSF and IL-13 in vitreous of patients with proliferative diabetic retinopathy: implications for M2 macrophage-involving fibrovascular membrane formation. *British Journal of Ophthalmology*. 99(5):629-34.

26] Martínez-Reyes CP, Gómez-Arauz AY, Torres-Castro I, Manjarrez-Reyna AN, Palomera LF, Olivos-García A, Mendoza-Tenorio E, Sánchez-Medina GA, Islas-Andrade S, Melendez-Mier G, Escobedo G. (2018). Serum levels of interleukin-13 increase in subjects with insulin resistance but do not correlate with markers of low-grade systemic inflammation. *Journal of diabetes research*. 2018.

27] Abdel-Moneim A, Bakery HH, Allam G. (2018). The potential pathogenic role of IL-17/Th17 cells in both type 1 and type 2 diabetes mellitus. *Biomedicine & Pharmacotherapy*. 101:287-92.

28] Qiu AW, Cao X, Zhang WW, Liu QH. (2021). IL-17A is involved in diabetic inflammatory pathogenesis by its receptor IL-17RA. *Experimental Biology and Medicine*. 246(1):57-65.

29] Parhi A, Das S, Mahapatra S, Pradhan N, Behera M, Patnaik B, Rattan R. (2019). The level and role of Interleukin-17 in patients of type 2 diabetes mellitus with and without complications. *Journal of diabetes mellitus*. 9(04):176-85.

30] Abdel-Moneim A, Bakery HH, Allam G. (2018). The potential pathogenic role of IL-17/Th17 cells in both type 1 and type 2 diabetes mellitus. *Biomedicine & Pharmacotherapy*. 101:287-92.

31] Jörns A, Ishikawa D, Teraoku H, Yoshimoto T, Wedekind D, Lenzen S. (2022). Remission of autoimmune diabetes by anti-TCR combination therapies with anti-IL-17A or/and anti-IL-6 in the IDDM rat model of type 1 diabetes. *BMC medicine*. 18(1):1-4.

32] Gong F, Wu J, Zhou P, Zhang M, Liu J, Liu Y, Lu X, Liu Z. (2016). Interleukin-22 might act as a double-edged sword in type 2 diabetes and coronary artery disease. *Mediators of inflammation*. 2016.

33] Ma Q, Hu X, Liu F, Cao Z, Han L, Zhou K, Bai Y, Zhang Y, Nan Y, Lv Q, Rao J. (2022). A novel fusion protein consisting of anti-ANGPTL3 antibody and interleukin-22 ameliorates diabetic nephropathy in mice. *Frontiers in Immunology*. 13:1011442.

34] Wang S, Li Y, Fan J, Zhang X, Luan J, Bian Q, Ding T, Wang Y, Wang Z, Song P, Cui D. (2017). Interleukin-22 ameliorated renal injury and fibrosis in diabetic nephropathy through inhibition of NLRP3 inflammasome activation. *Cell death & disease*. 8(7): e2937-.

35] Menini S, Iacobini C, Vitale M, Pugliese G. (2020). The inflammasome in chronic complications of diabetes and related metabolic disorders. *Cells*. 9(8):1812.

36] Moon S, Jung HS. (2022). Endoplasmic reticulum stress and dysregulated autophagy in human pancreatic beta cells. *Diabetes & Metabolism Journal*. 46(4):533-42.

37] Shen J, Fang Y, Zhu H, Ge W. (2018). Plasma interleukin-22 levels are associated with prediabetes and type 2 diabetes in the Han Chinese population. *Journal of diabetes investigation*. 9(1):33-8.

38] Rodrigues KF, Pietrani NT, Bosco AA, Campos FM, Sandrim VC, Gomes KB. (2017). IL-6, TNF-α, and IL-10 levels/polymorphisms and their association with type 2 diabetes mellitus and obesity in Brazilian individuals. *Archives of endocrinology and metabolism*. 61:438-46.

39] Liu Q, Yang C, Wang S, Shi D, Wei C, Song J, Lin X, Dou R, Bai J, Xiang Z, Huang S. (2022). Wnt5a-induced M2 polarization of tumor-associated macrophages via IL-10 promotes colorectal cancer progression. *Cell Communication and Signaling*. 18:1-9.

40] Xue J, Gao J, Gu Y, Wang A, Yu S, Li B, Yin Y, Wang J, Su W, Zhang H, Ren W. (2022). Human umbilical cord-derived mesenchymal stem cells alleviate insulin resistance in diet-induced obese mice via an interaction with splenocytes. *Stem Cell Research & Therapy*. 13(1):1-8.

41] Ruscica M, Ricci C, Macchi C, Magni P, Cristofani R, Liu J, Corsini A, Ferri N. (2016). Suppressor of cytokine signaling-3 (SOCS-3) induces proprotein convertase subtilisin kexin type 9 (PCSK9) expression in hepatic HepG2 cell line. *Journal of Biological Chemistry*. 291(7):3508-19.

42] Zatterale F, Longo M, Naderi J, Raciti GA, Desiderio A, Miele C, Beguinot F. (2022). Chronic adipose tissue inflammation linking obesity to insulin resistance and type 2 diabetes. *Frontiers in physiology*. 10:1607.

43] Li M, Chi X, Wang Y, Setrerrahmane S, Xie W, Xu H. (2022). Trends in insulin resistance: Insights into mechanisms and therapeutic strategy. *Signal Transduction and Targeted Therapy*. 7(1):216.

44] Al-Mansoori L, Al-Jaber H, Prince MS, Elrayess MA. (2022). Role of inflammatory cytokines, growth factors and adipokines in adipogenesis and insulin resistance. *Inflammation*. 1:1-4.

45] Samario-Román J, Larqué C, Pánico P, Ortiz-Huidobro RI, Velasco M, Escalona R, Hiriart M. (2023). NGF and its role in immunoendocrine communication during metabolic syndrome. *International Journal of Molecular Sciences*. 24(3):1957.

46] Gardner EJ, Kentistou KA, Stankovic S, Lockhart S, Wheeler E, Day FR, Kerrison ND, Wareham NJ, Langenberg C, O'Rahilly S, Ong KK. (2022). Damaging missense variants in IGF1R implicate a role for IGF-1 resistance in the etiology of type 2 diabetes. *Cell genomics*. 2(12).

47] Biadgo B, Tamir W, Ambachew S. (2020). Insulin-like Growth Factor and its Therapeutic Potential for Diabetes Complications Mechanisms and Metabolic Links: A Review. *Review of Diabetic Studies*. 16(1):24-34.

48] Vaessen N, Heutink P, Janssen JA, Witteman JC, Testers L, Hofman A, Lamberts SW, Oostra BA, Pols HA, van Duijn CM. (2001). A polymorphism in the gene for IGF-I: functional properties and risk for type 2 diabetes and myocardial infarction. *Diabetes*. 50(3):637-42.

49] Aguirre GA, De Ita JR, De La Garza RG, Castilla-Cortazar I. (2016). Insulin-like growth factor-1 deficiency and metabolic syndrome. *Journal of translational medicine*. 14:1-23.

50] Kim MS, Lee DY. (2015). Insulin-like growth factor (IGF)-I and IGF binding proteins axis in diabetes mellitus. *Annals of pediatric endocrinology & metabolism*. 20(2):69.

51] Wittenbecher C, Ouni M, Kuxhaus O, Jähnert M, Gottmann P, Teichmann A, Meidtner K, Kriebel J, Grallert H, Pischon T, Boeing H. (2019). Insulin-like growth factor binding protein 2 (IGFBP-2) and the risk of developing type 2 diabetes. *Diabetes*. 68(1):188-97.

52] Zhang J, Hu W, Diao Q, Wang Z, Miao J, Chen X, Xue Z. (2019). Therapeutic effect of the epidermal growth factor on diabetic foot ulcer and the underlying mechanisms. *Experimental and therapeutic medicine*. 17(3):1643-8.

53] Rahim F, Yan X, Shah JA, Bibi N, Khan ZU, Nawaz S, Ming Y. (2023). Epidermal growth factor outperforms placebo in the

treatment of diabetic foot ulcer: a meta-analysis. *F1000Research*. 11:773.

54] Mercier C, Brazeau T, Lamoureux J, Boisvert E, Robillard S, Breton V, Paré M, Guay A, Lizotte F, Despatis MA, Geraldes P. (2021). Diabetes impaired ischemia-induced PDGF (Platelet-Derived Growth Factor) signaling actions and vessel formation through the activation of scr homology 2-containing phosphatase-1. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 41(9):2469-82.

55] Abderrahmani A, Yengo L, Caiazzo R, Canouil M, Cauchi S, Raverdy V, Plaisance V, Pawlowski V, Lobbens S, Maillet J, Rolland L. (2018). Increased hepatic PDGF-AA signaling mediates liver insulin resistance in obesity-associated type 2 diabetes. *Diabetes*. 67(7):1310-21.

56] Cao Z, Liu Y, Wang Y, Leng P. (2023). Research progress on the role of PDGF/PDGFR in type 2 diabetes. *Biomedicine & Pharmacotherapy*. 164:114983.

57] Liu X, Zhang F, Chai Y, Wang L, Yu B. (2020). The role of bone-derived PDGF-AA in age-related pancreatic β cell proliferation and function. *Biochemical and Biophysical Research Communications*. 524(1):22-7.

58] Dai Q, Fan X, Meng X, Sun S, Su Y, Ling X, Chen X, Wang K, Dai X, Zhang C, Da S. (2021). FGF21 promotes ischaemic angiogenesis and endothelial progenitor cells function under diabetic conditions in an AMPK/NAD+-dependent manner. *Journal of Cellular and Molecular Medicine*. 25(6):3091-102.

59] Hanneken A, de Juan E, Lutty GA, Fox GM, Schiffer S, Hjelmeland LM. (1991). Altered distribution of basic fibroblast growth factor in diabetic retinopathy. *Archives of ophthalmology*. 109(7):1005-11.

60] Jin S, Xia N, Han L. (2021). Association between serum fibroblast growth factor 21 level and sight-threatening diabetic retinopathy in Chinese patients with type 2 diabetes. *BMJ Open Diabetes Research and Care*. 9(1): e002126.

61] Kim HC, Cho YJ, Ahn CW, Park KS, Kim JC, Nam JS, Im YS, Lee JE, Lee SC, Lee HK. (2009). Nerve growth factor and expression of its receptors in patients with diabetic neuropathy. *Diabetic Medicine*. 26(12):1228-34.

62] Barker PA, Mantyh P, Arendt-Nielsen L, Viktrup L, Tive L. (2020). Nerve growth factor signaling and its contribution to pain. *Journal of pain research*. 26:1223-41.

63] Anand P, Terenghi G, Warner G, Kopelman P, Williams-Chestnut RE, Sinicropi DV. (1996). The role of endogenous nerve growth factor in human diabetic neuropathy. *Nature medicine*. 2(6):703-7.

64] Houtz J, Borden P, Ceasrine A, Minichiello L, Kuruvilla R. Neurotrophin signaling is required for glucose-induced insulin secretion. (2016). *Developmental cell*. 39(3):329-45.

65] Tang M, Luo M, Lu W, Zhang R, Liang W, Gu J, Yu X, Zhang X, Hu C. (2020). Nerve growth factor is closely related to glucose metabolism, insulin sensitivity, and insulin secretion in the second trimester: a case–control study in Chinese. *Nutrition & Metabolism*. 17(1):1-8.

66] Behl T, Gupta A, Sehgal A, Singh S, Sharma N, Garg M, Bhatia S, Al-Harrasi A, Aleya L, Bungau S. (2022). Exploring the multifaceted role of TGF-β signaling in diabetic complications. *Environmental Science and Pollution Research*. 29(24):35643-56.

67] Ma X, Cui Z, Du Z, Lin H. (2020). Transforming growth factor-β signaling, a potential mechanism associated with diabetes mellitus and pancreatic cancer? *Journal of cellular physiology*. 235(9):5882-92.

68] Cabral T, Mello LG, Lima LH, Polido J, Regatieri CV, Belfort R, Mahajan VB. (2017). Retinal and choroidal angiogenesis: a review of new targets.

International journal of retina and vitreous. 3:1-3.

69] Zhang A, Fang H, Chen J, He L, Chen Y. (2020). Role of VEGF-A and LRG1 in abnormal angiogenesis associated with diabetic nephropathy. *Frontiers in Physiology*. 11:1064.

70] White MJ, Briquez PS, White DA, Hubbell JA. (2021). VEGF-A, PDGF-BB and HB-EGF engineered for promiscuous super affinity to the extracellular matrix improve wound healing in a model of type 1 diabetes. *NPJ Regenerative Medicine*. 6(1):76.

71] Lavoz C, Rodrigues-Diez RR, Plaza A, Carpio D, Egido J, Ruiz-Ortega M, Mezzano S. (2020). VEGFR2 blockade improves renal damage in an experimental model of type 2 diabetic nephropathy. *Journal of Clinical Medicine*. 9(2):302.