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RESEARCH ARTICLE

The Role of Cytokines in the Progression of Diabetes

Ali A. Abu Siyam*

Department of Medical Laboratory Sciences, Faculty of Allied Medical Sciences, Jadara University, Irbid, Jordan

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***Corresponding Author:**

aabusiyam@jadara.edu.jo

ABSTRACT

The main objective of the present study was to review the updates of literature regarding the role of cytokines in the progression of diabetes. Inflammatory aspects are associated with the progression of diabetes and may be considered as etiological agents. Main research engines were used to collect the resources for this study including PubMed, Google Scholar, Science Direct, and others. The results of this review put more emphasis on widespread diabetes worldwide. Cytokines are considered as a part of the inflammatory processes that participate in the development of diabetes. Cytokines are a group of proteins, glycoproteins, or peptides that are used to signal between cells, and they are possibly predicting the development of diabetic complications such as microalbuminuria, macrovascular disease, and neuropathy, and in the compositional makeup of these complications. In this review a comprehensive discussion of cytokines and their roles in the development of diabetes was introduced.

INTRODUCTION

Several diseases that manifest with the development of diabetes are associated with multiple and diverse etiological mechanisms (Lovic et al., 2020). Diabetes is a chronic and complex disease that has always been considered an important public health problem around the globe (Tomic et al., 2022). It is considered one of the leading causes of global morbidity and mortality due to its close association with complications affecting various body organs and systems (Liu et al., 2020). The peak of diabetes among different age groups and in both genders has been the main concern for many researchers to minimize or eradicate this high prevalence of diabetes or the risk of developing it in the community (Hill-Briggs et al., 2021). Many risk factors have been associated with the development of diabetes, such as smoking, a sedentary lifestyle, obesity, a family history of diabetes, diet low in olive oil, breast milk, plain water, and genotyping (Pop-Busui et al., 2022).

Among all these etiological factors, chronic inflammation plays a large role in the pathogenesis of diabetes (Poznyak et al., 2020). Diabetes develops due to progressive beta-cell dysfunction in the presence of insulin resistance (Forrester et al., 202). Individuals with pre-diabetic status show abnormal glucose metabolism and insulin resistance, which increases the chances of developing the full-blown disease (Rayego-Mateos et al., 2020). Those patients with chronic, severe cellular stress along with cytokine overproduction within the pancreatic islet are at risk of developing clinically evident disease compared to those with mild and less severe derangement (Tang et al., 2023). The progression of prediabetes to diabetic status leads to the development of diabetic nephropathy, retinopathy, neuropathy, macrovascular complications, dyslipidemia, and hypertension (Lee and Olefsky, 2021).

Cytokines can play an important role in the progression and development of diabetes (Stenvinkel et al., 2021).

1.1. Types of Diabetes

In 2021, there were an estimated 151.7 million people diagnosed with diabetes, and it is the seventh leading cause of death worldwide (Bastan et al., 2023). In broad terms, diabetes can be categorized into three types: Type 1 (T1D), Type 2 (T2D), and gestational diabetes (GDM) (Albai et al., 2024). Each type has inherent differences in terms of their predominance, pathology, symptoms, and long-term complications, and affects individuals in unique circumstances (Barati et al.2021). T1D is an autoimmune-mediated disease characterized by the destruction of the insulin-producing beta cells of the pancreas (Kamrath et al., 2023). The signs, symptoms, and complications of diabetes, in general, can often develop suddenly and lead to established long-term diabetes, possible sequelae, and micro- or macrovascular complications (Guler et al.2023). T2D is a heterogeneous metabolic disorder that presents a variety of symptoms and associated conditions, such as metabolic syndrome, insulin resistance, and obesity, among others, and a wide array of potential long-term microvascular and macrovascular impairments (Guo et al.2023). Gestational diabetes occurs during pregnancy and can have serious implications for both the mother and baby, such as preeclampsia and large-for-gestational-age babies (Nicolau et al.2022). If GDM is controlled, the aforementioned complications can be avoided, and often, by the time their baby is delivered, the mother's blood glucose levels return to normal. However, women who develop GDM also have an increased risk of developing T2D (Gandaglia et al., 2021).

On a worldwide scale, T2D is far more prevalent than T1D (Chetty, 2022). As of 2021, T2D reportedly had an estimated 422 million cases, thereby accounting for around 90% of all diagnosed diabetes (Viraj, 2023). Incidences of T1D, however, are less frequently identified and account for only approximately 6% of all diagnosed cases in adults (Sappy, 2024). In comparison with T2D and T1D, gestational diabetes has the lowest prevalence, affecting an estimated 16–20% of the pregnancies worldwide (Durrani et al., 2021). Even so, GDM is still thought to have an approximate global prevalence of 6–12% regardless of variable earlier detection and diagnostic criteria (Le Pard, 2022). Given the differences in aetiology, symptoms, and associated complications, it is apparent that diabetes is a multifaceted, complex condition that requires extensive research to fully understand, manage, and treat (Younes, 2024).

1.2. Pathophysiology of Diabetes

Diabetes is a chronic metabolic disorder characterized by the inability to maintain normal glucose levels in the bloodstream due to failure of the pancreatic insulin-producing beta cells to secrete enough insulin (Type 2) or an autoimmune-mediated attack resulting in specific loss of beta cells (Type 1) (Choudhury and Rajeswari, 2021). The pancreas may actually synthesize a normal amount of insulin, but the failing beta cells are unable to do so in the correct manner (insulin secretion defect) (Banday et al., 2020). Even if the insulin levels or the amount of insulin produced by the pancreas may be higher, the response of many target cells to insulin is not appropriate, producing the condition of insulin resistance (Dilworth et al., 2021). All type 1 diabetic patients and many type 2 diabetic patients, over the years, require insulin therapy (Daryabor et al., 2020). The term 'over the years,' however, does not mean the exact same thing for each Type 2 diabetic patient (Zorena et al., 2020). While some of them require insulin early on, a typical Type 1 patient starts requiring insulin soon after the first diabetes-specific symptom develops: because of the total lack of insulin, Type 1 patients are typically insulinopenic, while Type 2 ones are typically insulin resistant (Zhao et al., 2023).

When islet beta cells sense a glucose concentration reaching 100-125 mg/dl (normal glycemia is less than 100 mg/dl), they release insulin with a promptness proportional to glycemia (Bolli et al., 2021). On a lower glycemic range, glycoregulation occurs primarily through an increasing production of Hormone Sensitive Lipase made by adipocytes, which in response to the glycemic drop increases the needed energy via lipolysis of triglycerides (Zhu et al., 2021). The rise in circulating glycerol induces in the liver

an increasing production and release of glucose, which normalizes glycemia (Sobrevia, 2022). On a higher glycemic range, the initial step of glycoregulation passes to the beta cells, and hence the first possible mechanism of failure to return to normoglycemia is the inability of the beta cell to sense glucose rise (De et al., 2023). Hyperglycemia leads to a wide variety of alterations in lipid metabolism, including subtle changes in lipoprotein metabolism that can be found in normolipidemic patients (Dimitriadis et al., 2021). Although strong evidence supports potential perturbations at the cellular and molecular levels in diabetes, the mechanisms of diabetic lipid derangements remain largely unknown (Di et al., 2024).

The cellular defects responsible for diabetes must likely be initiated by the perspective to resist, in the short and long term, the harmful effects of hyperglycemia (Ying et al., 2020). The recent observation that oral antidiabetic agents may hold lipid-lowering effects on diabetes per se has been attributed, at least in part, to the improvement of impaired beta cell metabolism (Al-Mansoori et al., 2022). There is strong evidence for a significant genetic component in the pathogenesis of T1DM, and there is a growing number of genetic loci identified by genome-wide association studies implicated in the development of T2DM (Ahmed et al., 2021). Nevertheless, genetic predisposition alone cannot produce diabetes (Kawai et al.,2021). In addition to a combination of genetic predisposition, one or several environmental factors are required (Zatterale et al., 2020). As will be described later, cytokines secreted by the adipose tissue can represent some of the environmental factors causing beta cell failure (Murakami et al., 2022).

2. Immune System and Cytokines

The immune system, existing in a myriad of types and varieties, is responsible for tissue repair and pathogen resistance in the defense systems of the human and animal body (Woodell-May and Sommerfeld, 2020). Over recent decades, it has become increasingly apparent that the immune system is also deeply involved in the progression of various diseases (Tan et al., 2020). In its function as the host's defense system, the immune system responds to various types of stimuli by releasing cytokines (Roy et al., 2022). These mediators not only inform their environment of the presence of the stimuli but also control and coordinate the immune response (Zhao et al., 2021). This includes the beginning, perpetuation, and stopping of immunity (Paces et al., 2020). Therefore, it is not surprising that a state of uncontrolled or excessive inflammation and repair has ensued and is referred to as the basis of many diseases of the inflammatory, degenerative, and some neoplastic diseases (Garner and de Visser, 2020).

The primary components of the immune system are broadly divided into those that work in the blood and those that work in the tissues (Uciechowski and Dempke, 2020). The immune response involves cells such as granulocytes, mast cells, natural killer cells, and lymphocytes that work in the blood and a collateral network of cells that reside in the tissues, lymph nodes, spleen, and Peyer's patches (Dong, 2021). Cellular communication within the immune system that produces cytokines is mainly of polypeptide origin and is synthesized on ribosomes, like many humoral factors (Yang et al., 2021). Cytokines are a group of proteins, glycoproteins, or peptides that are used to signal between cells (Zhang et al., 2020). The immune cytokines are used to control their own numbers and functions, those of the supporting cellular structure of the tissues, and their ameliorative or pathogenic effects on the host tissues themselves (Propper and Balkwill, 2022).

2.1. Overview of Immune System

Cytokines are proteins that serve as communication signals to help the immune system react and eliminate threats like infections (Bhol et al., 2024). They serve as the messengers of the immune system and relay information among different cell types (Rabaan et al., 2021). Cytokines contribute to the induction of inflammation and play important roles in modulating both beneficial and detrimental immune functions (Li et al.2020). Immune cells are generally categorized into two types: the innate immune system, which serves as a rapid and general first line of defense against infectious agents, and the adaptive immune response, which takes longer to engage but acts with much more precision to eliminate pathogens (Salvador et al., 2021). Macrophages, neutrophils, dendritic cells, and natural killer cells are some of the cells participating in the innate immune response (Salvador et al., 2021). These cells

collectively coordinate and regulate the adaptive immune response, largely through their secreted cytokines (Megha et al., 2021). The adaptive immune system includes cells like B cells and T cells (Dong, 2021). When an infection is present, the dendritic cells pick up and present foreign invaders, such as viruses or dead bacteria, to T and B cells for their investigation (Hanna and Frangogiannis, 2020). Each T cell and each B cell has a unique receptor protein that can recognize different pathogens, and when a B cell or T cell binds to its target, it is stimulated to divide and secrete factors to enhance the function of fellow immune cells (Zasłona and O'Neill, 2020). After the pathogen is eliminated, some of these cells remain in the body as a pool of long-lived cells to help the body recognize the invader quickly if it is encountered again (Zasłona and O'Neill, 2020). Cytokines are involved in regulating the development and maintenance of immune cells as well as directing the immune response (Zasłona and O'Neill, 2020). These proteins function collectively to maintain an appropriate balance between immune activation and regulation essential for overall health (Sobah et al., 2021). Dysregulated cytokines can contribute to the development of several diseases (Sobah et al., 2021).

2.2. Functions of Cytokines

Cytokines act as intercellular signaling molecules in immune responses (Kamali et al., 2021). They mediate cell-to-cell communication, whether these cells are nearby or located in distal sites of the body (Liu et al., 2022). Cytokines are structurally diverse and functionally versatile (Bhol et al., 2024). They mediate both stimulatory and suppressive effects on the immune system, and a single cytokine can modulate more than one target cell (Rabaan et al., 2021). Based on their functions, cytokines are divided into two groups: pro-inflammatory cytokines, which are responsible for inducing or amplifying an immune response, and anti-inflammatory cytokines, which are responsible for inhibiting or downregulating the immune response (Passos et al., 2022).

Interleukin-10 (IL-10), for example, is an important regulator of the immune response (Bhol et al., 2024). It can inhibit the production of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α, as well as MHC class II expression and antigen presentation (Zhang et al., 2021). The cytokines mainly function through the regulation of lymphocytes and macrophages, the major producers of cytokines (Chen et al., 2021). Cytokines contribute to the inflammatory response that destroys internal and external environmental toxins, such as pathogens and viral infectious microorganisms (Sierawska et al., 2022). On the other hand, if uncontrolled, the cytokine response can also promote autoimmune diseases against the host body, heavy inflammation, anaphylaxis, and even cancer (Ragu et al., 2020). The human body must maintain a balanced immune response through the regulation of both types of cytokines so that the body can function well in its immune regulation (Summer et al., 2024).

3. Cytokines in Diabetes

Diabetes has a strong inflammatory component, characterized by the production of inflammatory cytokines and mediators (Khanna et al., 2022). Adipose tissue is the source of numerous regulatory and pro-inflammatory cytokines, which are believed to be the main contributors to the development of insulin resistance and metabolic syndrome in obesity (van de Vyver, 2023). Independent of the target organ, the serum concentrations of some of these mediators are higher in patients with T2DM than in the control population (Bakkar et al., 2020). The adipose tissue from patients with T2DM can synthesize and release more pro-inflammatory cytokines (Sharif et al., 2021). These factors produced locally in the adipose tissue have local and systemic effects (Okdahl et al., 2022). Accumulated evidence during the last years indicates that diabetes is associated with a state of persistent, low-grade inflammation (Pesaro et al., 2021). This inflammatory process is thought to be the cause of insulin resistance, which classically precedes the development of the major type of the disease, type 2 diabetes (Cecoro et al., 2020). Several studies have implicated cytokines in the pathogenesis and progression of diabetes (Rizvi et al., 2022).

Cytokine expression is observed in various diabetic states (Aly et al., 2020). In adipose tissue, the levels of inflammatory cytokines such as tumor necrosis factor-α, interleukin (IL)-1, IL-6, monocyte chemoattractant protein 1, the anti-inflammatory cytokines IL-10 and transforming growth factor-β, and

cytokine-binding proteins do not correlate with glycemia (Zheng et al., 2021). In pancreatic tissue from individuals with clinical T1D, the expression of mRNA for inducible and endothelial nitric oxide synthase, as well as IL-1, IL-6, IL-8, IL-10, IL-12, and tumor necrosis factor-α, is increased, whereas the expression of the anti-inflammatory cytokine IL-4 is normal (Dos et al., 2023). The synthesis of chemoattractive and pro-inflammatory cytokines in the pancreas of new-onset T1, T2, and secondary diabetic patients is the primary response to cytokines (Araújo et al., 2020). In vitro studies on fibroblasts of T1D animals demonstrated that the upregulation of inflammatory markers is accompanied by selective impairment of insulin signaling (Papachristoforou et al., 2020). Studies on clonal β-cells have demonstrated that they are a source of pro-inflammatory cytokines (Iglesias et al., 2020). Serum concentrations of cytokines have been measured in association with the development of diabetes to check whether they could be used as reliable predictors of the disease (Bashir et al., 2020). Function given the standard established for other autoimmune diseases; these or other pro-inflammatory molecules might be good candidates for the management of diabetic individuals (Darwish et al., 2021). Anti-inflammatory cytokines with indirect or direct cytoprotective effects have been measured in serum and wound exudate of diabetes patients (Kartika et al., 2020). One final observation is that the acute phase response is characteristic of the complications of diabetes surfacing as one or multiple risk factors (Kartika et al., 2020). Different cytokine profiles are needed to discriminate insulin resistance, excess cardiovascular risk, and advancing vascular disease in patients with type 2 diabetes (Bashir et al., 2020).

3.1. Pro-inflammatory Cytokines

Diabetes is characterized by dysregulated glucose homeostasis due to insulin resistance and pancreatic beta-cell dysfunction, leading to elevated blood glucose levels (Milas et al., 2020). Substantial evidence suggests that pro-inflammatory cytokines play an important role in the development of diabetes (Al-Mansoori et al., 2022). The pro-inflammatory cytokines include tumor necrosis factor, interleukin-6, and interleukin-1 (Donate-Correa et al., 2021). Tumor necrosis factor and interleukin-6 are frequently elevated in type 2 diabetic patients as well as in obesity (Bashir et al., 2020). A 63 kDa soluble receptor known as the soluble tumor necrosis factor receptor 1 has been recently discovered to be a significant predictor for the development of type 2 diabetes (Kong et al. 2021).

There are two possible ways through which chronic elevation of pro-inflammatory cytokines might lead to disease (Tesi et al., 2021). First, a cytokine imbalance leads to insulin resistance due to the abrogation of the insulin signaling pathway at multiple levels. Secondly, pro-inflammatory cytokines promote beta-cell apoptosis, resulting in diminished insulin production (Demine et al., 2020). Beta-cells are highly susceptible to this attack, as they do not express the anti-inflammatory counter-regulators to the pro-inflammatory cytokines (Cerf, 2020). Obesity, and especially upper body fat distribution, is associated with a chronic low-grade inflammation that is characterized by elevated levels of plasma acute-phase proteins, such as CRP and interleukin-6, and acute-phase reactants, such as fibrinogen (You et al., 2022).

This implies that pro-inflammatory cytokines contribute to the development of these insulin-resistant states, modulating the production and action of endocrine hormones and tissue substrates (Al-Mansoori et al., 2022). Therefore, a reduction above all of circulating levels of tumor necrosis factor and interleukin-6 molecules can limit metabolic disturbances (Ahmed et al., 2021). By counteracting these two aspects, it might be possible to prevent and counteract the complications of diabetes, especially those in which inflammation plays a role (Greco et al., 2023). Although these findings have considerable pathophysiological and therapeutic interest, the situation appears to be more complex in inflammation that requires a balance between pro- and anti-inflammatory responses (Mirabelli et al., 2024).

3.2. Anti-inflammatory Cytokines

The progression of recent years to view diabetes as an inflammatory disease has shed interest on anti-inflammatory cytokines as possible adaptive responses to the constantly elevated levels of pro-inflammatory cytokines in the progression of insulin resistance (Li et al.2020). Anti-inflammatory cytokines, mainly IL-10 and TGF-beta, have properties related to modulating inflammatory responses,

healing and repair of tissue, immuno-regulation, induction of negative immuno-modulation, regulation of humoral immunity, usefulness in transfusion immunosuppression, promotion of B-lymphocyte terminal function, and are responsible for apoptosis of immune cells (Markovics et al., 2021). A recent defense of IL-10 in the progression of insulin resistance has established it as the principal anti-inflammatory cytokine opposed to pro-inflammatory IL-6 (Bhol et al., 2024). The activation of IL-10 in patients with type 2 diabetes has been employed as an indicator of the progression of this disease and its chronic complications (Peña-Romero and Orenes-Piñero, 2022). A broader perspective reveals that the role of IL-10 is not solely anti-inflammatory, but also includes pro-inflammatory actions, which can lead to the activation of IL-6, the inhibition of β-cells, and the worsening of insulin resistance (Rabaan et al., 2021). Anti-inflammatory cytokines have different effects depending on the immunological environment. They have not only a synergistic action but also an antagonistic effect with pro-inflammatory cytokines (Megha et al., 2021). Indeed, IL-10 has been reported to promote or worsen insulin resistance (Megha et al., 2021). A particularly attractive area of research with anti-inflammatory cytokines includes their possible protective role in the stimulation of insulin resistance and atherosclerosis when given exogenously in animal and human trials (Cristofori et al., 2021). Further understanding of the production of these anti-cytokines includes production from macrophages, β-cells including islet cells, pancreatic polypeptide cells, tumor somatostatin cells, placental type 1 and type 2 cells, fibroblasts, resting B cells, T (CD4 and CD8) suppressor and helper cells, vascular endothelial cells, and activated T cells (Suzuki et al., 2020). In addition to its IL-10 stimulating effects in vitro, biological therapy using selective administration of TGF-beta serves immunotherapy features in systemic autoimmunity (Kline et al., 2021). In addition to the activation and production of IL-10, T-helper 1 (IL-2, TNF-alpha, and IFN-gamma), but not T-helper 2, stimulated with anti-CD3, also produces TGF-beta (Kline et al., 2021). In fact, regulatory T cells have been reported to release TGF-beta in the tight link between autoimmunity development and loss of pancreatic islet cell subpopulations, including β-cells of the pancreas in both human and animal models with diabetes, types 1 and 2 (Suzuki et al., 2020). From a therapeutic point of view, dissection of the beneficial effects derived from growth factors and anti-inflammatory cytokines from β-cell stimulating agents may have implications for the development of efficient and safe therapeutic strategies in insulin resistance (Cristofori et al., 2021). A further understanding of the immunological and biochemical actions of cytokines in insulin resistance has the potential to provide leads to an understanding of the genetic, environmental, and immunological factors that contribute to a chronic diabetes condition, giving clues to finding possibly preventive and curative therapies (Cristofori et al., 2021). Importantly, a careful understanding of cytokine prevention may provide us with the potential to develop increasingly sophisticated treatment strategies to manage diabetes and its comorbidities in individuals (Alkhatib, 2024).

4. Clinical Implications

The role of cytokines in disease progression has been known for some time, but may be only now starting to find a place in the clinician's toolbox (Nirenjen et al., 2023). It has been long established that the pro-inflammatory environment is a driver of diabetes development, and the specific cytokine profile of an individual can be used to predict their risk of type 1 diabetes progression (Diedisheim et al., 2020). It is currently being debated whether cytokines are an important aspect of the progression of type 2 diabetes mellitus, with the cytokine profile possibly being predictive of the development of diabetic complications such as microalbuminuria, macrovascular disease, and neuropathy, and in the compositional makeup of these complications (Nedosugova et al., 2022). Cytokines have known involvement in insulin action; thereby, aiming to improve the adipokine/cytokine profile could be a therapeutic target for the diabetic patient (Kinuthia et al., 2020). These adverse health effects exist above the effect of obesity; decomplicating this background will require further understanding of the underlying biology (Girard and Vandiedonck, 2022).

The cytokine and adipokine profile may also have a diagnostic role in the diabetes field, and adipokine measurements may be used to help discriminate between obese or metabolically unhealthy individuals

(Zyśk et al., 2021). As basic researchers and clinicians appreciate the importance of adipokines and cytokines in adipose tissue biology, it is likely that the use of adipokine measurements will become increasingly important in day-to-day patient management (Araújo et al.2020). Specific therapeutic targets at different cytokines are now available, but none are specific to diabetes, so the potential benefits or harms of these drugs on the adverse effects of obesity require more study (Zorena et al.2020). The utility of cytokine pathways as therapeutic targets in both research and clinical patients will depend on our growing understanding of the pathophysiology of these agents acting in concert rather than as single elements (Clemente-Suárez et al., 2023).

4.1. Role of Cytokines in Diabetes Complications

There is growing evidence that cytokines are present in injured tissue and are involved in the promotion and possibly resolution of the conditions in diabetic patients (Lu et al., 2020). The mechanism and signaling pathways involved are unknown, but isolated cytokines have been shown to promote and ameliorate these conditions (Al-Mansoori et al., 2022). This and the continuing reports of successful treatments directed at single cytokines support their involvement in the advanced-stage complications in diabetes (Al-Mansoori et al., 2022). Obesity-associated diabetes results in complications that include atherosclerosis, retinopathy, neuropathy, proteinuria, and end-stage renal disease (Sharifiaghdam et al., 2022). There are now data that support a role of inflammation, the family of cytokines, and transcription factors in insulin resistance as well as the molecular and cellular steps involved in atheroma growth (Duan et al.2022). Endothelin production is driven by glycemia and promotes oxidative stress, amplifying a cycle that promotes diabetic nephropathy (Zorena et al., 2020).

Cytokines have been shown to be angiogenic, and atherosclerosis is considered to be an inflammatory disease (Ucgun et al., 2020). In the vasculature, chronic TNF-α infusion in mice promotes the development of a condition resembling diabetic retinopathy (Gong et al., 2022). Increased vascular permeability is associated with decreased endothelial voltage-gated K+ channel activity as well as increased ROS production (Kuo et al., 2022). The correlation between increased vitreal TNF-α levels and increasing vascular endothelial growth factor and severity of diabetic retinopathy is consistent with regression analysis showing the ratio of vascular endothelial growth factor to TNF-α to be predictive of retinopathy severity (Fickweiler et al., 2022). There is also an elevation of TNF-α in the animal models of diabetes and in humans with diabetic nephropathy (Zhang et al., 2020). Moreover, systemic elevation of TNF-α seems to be a recent report of the elevation of the cytokine in the kidney of humans with diabetic nephropathy (Wu et al., 2021). Thus, changes in cytokine levels, such as elevation of vitreal TNF-α, may contribute to the pathology and, in fact, be as important or possibly even more important than hyperglycemia (Morales-Lopez et al., 2024). There is growing evidence that end-organ failure is produced by complex cellular interactions (Iyer et al., 2021).

5. CONCLUSION AND FUTURE PERSPECTIVES

Cytokines have a pivotal role in the development of obesity and inflammation-induced insulin resistance (Al-Mansoori et al., 2022). The abnormally high production rate of these small proteins capable of influencing gene expression leads to the induction of a series of signals contributing to the phenotype of type 2 diabetes (Wu and Ballantyne, 2020). Several molecular inhibitory mechanisms mediating the effects of these cytokines on signal transduction have been shown to contribute to adipose inflammation, defective lipid metabolism, and abnormal angiogenesis, and hence to the progression of the phenotype of type 2 diabetes (Lee et al., 2022). Future studies are required to fully integrate the molecular details of these pathways operating at different tissues in the body (Zhao et al., 2023). Moreover, the initiation steps of the abnormal production of these cytokines and the mechanism of their release into the circulation are not fully known (Lee et al., 2022). Last but not least, the differential patterns of expression of these cytokines in obese insulin-sensitive people versus obese insulin-resistant people are rather surprising and require further investigation (Püschel et al., 2022). Several small clinical trials exploring the effects of interference with the expression or release of these cytokines have been initiated, and they

hold the promise of new type 2 diabetes therapies in the near future (Klimczak and Śliwińska, 2024). All that is needed are observational studies to corroborate the impact of these pathways, and translational trials are required in the next step to translate the biomolecular discoveries into clinical applications for the well-being of the diabetic patient (Kojta et al., 2020). In summary, intervention in the dialogue between adipocytes and macrophages may serve as a strategy for the management of type 2 diabetes.

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