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REVIEW ARTICLES

Type 2 Diabetes Mechanisms, Role of Cytokines and Their Variations in Disease Development

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SUMMARY

Type 2 diabetes is a chronic and complex disease characterized by impaired pancreatic beta cell function and insulin resistance. Several genetic and environmental factors are playing role in the Type 2 diabetes development. Recent studies pointed out a relationship between the inflammation generation and development of the disease. The inflammation induced-activation of the monocytes enhances the insulin resistance and decreases the insulin secretion due to the impairment of the pancreatic beta cells and also oxidative stress occurring after the disorder of the lipid metabolism affects the disease development. Following the oxidative stress formation, the levels of the reactive oxygen species (ROS) increase and insulin resistance develops consequently.
Cytokines are the keystones in regulation of the homeostatic mechanisms such as inflammation and tissue repair. Thus, variations in their levels and structures are the reasons for the occurrence of various diseases. The single nucleotide polymorphisms (SNP) forming on the cytokine genes affect the cytokine gene expression levels and increase the risk of the disease development. Recent studies showed that there may be possible relationships between some cytokine gene polymorphisms and the development of type 2 diabetes.

Key Words: *Type 2 diabetes, oxidative stress, insulin resistance, inflammation, cytokines, cytokine gene polymorphisms*

Tip 2 Diyabet Mekanizmaları, Hastalık Gelişiminde Sitokin ve Varyasyonlarının Rolleri

ÖZET

Tip 2 diyabet, bozulmuş pankreas beta hücreleri ve insülin direnci ile karakterize kronik ve karmaşık bir hastalıktır. Tip 2 diyabet gelişiminde çeşitli genetik ve çevresel faktörler rol oynamaktadır. Yapılan son çalışmalar hastalık gelişimi ile enflamasyon oluşumu arasında bağlantı olduğunu işaret etmektedir. Enflamasyon aracılı monosit aktivasyonu pankreasın beta hücre fonksiyonlarını bozar ve buna bağlı olarak insülin salınımını azaltır ve insülin direncini arttırır. Ayrıca lipit metabolizmasının bozulmasına bağlı olarak ortaya çıkan oksidatif stres de hastalık gelişimini etkiler. Oksidatif stres oluşumunu takiben reaktif oksijen türevlerinin (ROS) seviyelerinin artışı sonucu insülin direnci gelişir.
Sitokinler enflamasyon ve doku onarımı gibi homeostatik mekanizmaların düzenlenmesinde önemli bir yapıtaşıdırlar. Dolayısıyla seviyelerinde ve yapılarında meydana gelebilecek değişiklikler bazı hastalıkların gelişiminin sebebidir. Sitokinlerin genlerinde meydana gelen tek nükleotid polimorfizmleri (SNP) sitokin gen ekspresyon düzeylerini değiştirerek hastalık gelişimi riskini arttırır. Yapılan son çalışmalar sitokin gen polimorfizmleri ile tip 2 diyabet gelişimi arasında olası bir ilişkinin varlığını göstermektedirler.

Anahtar kelimeler: *Tip 2 diyabet, oksidatif stres, insülin direnci, enflamasyon, Sitokinler, sitokin gen polimorfizmleri*

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INTRODUCTION

Diabetes is a metabolic disorder with an excessive enhancement of blood glucose level developed by the combined effects of genetic and environmental factors (Tierney et al., 2002). The regulation of blood glucose level in body is done by the complex interactions of several chemicals and hormones. The most important hormone responsible from this regulation is insulin secreted from the beta cells of pancreas. Diabetes is the common term identifying some diseases caused by increased blood glucose via either the deficiency in insulin secretion or deficiency in insulin effect (Rother, 2007).

Diabetes is developed either by the decrease in insulin production (Type 1 diabetes) or by progression of insulin resistance to the effects of insulin (Type 2 diabetes) (WHO, 1999). In both situations increase in blood glucose level (hyperglycemia) is the common effect.

Due to WHO, 422 million people on earth are diabetes patients and high percent of these are middle aged persons (45-64 years old) living in low or moderate-income countries. In recent years approximately 1,5 million persons were died due to diabetes in 2015 and this disease is 1 of the leading causes of death in the world. Worse, this numbers is predicted to be two folded in next 10 years (WHO, 2016).

The main cause of diabetes seems to be the improper diet. The starches, sugars, and saturated fats in mass-produced foods are the chief culprit. But there are many things that provoke the development of diabetes. Nowadays type 2 diabetes is considered, at least in part, to be an environmental illness because the environmental chemicals have a major effect in development of the illness. Recent researches have shown that diabetes can be caused by exposure to persistent organic pollutants (POPs) (including dioxins, furans, polychlorinated biphenyls, polybrominated biphenyls, polybrominated diphenyl ethers, or organochlorine pesticides), exudates from common plastics (phthalate esters and bisphenol A), air pollution, primary and secondary tobacco smoke (smoke components including aliphatic, aromatic, or polyaromatic hydrocarbons), and some pharmaceuticals (some statins and second-generation antipsychotic drugs.) (Zeliger, 2013; Meo et al., 2015; Metz, 2016; Chen and Wu, 2017; Green et al., 2017; Rosenbaum et al., 2017;). These chemicals vary widely in structure, chemical properties, and composition and are not currently believed to induce a similar effect. Especially the lipophilic substances are responsible from the development of diabetes. This hypothesis suggests that the type 2 diabetes pandemic as well as the rapid increase of other environmental disease prevalence is, at least in part, due to sequential exposure to levels of lipophilic and hydrophilic environmental pollutants that are much lower than those currently believed to be toxic. As a consequence of this hypothesis, the allowable levels of exposure to these pollutants should be dramatically lowered.

Classification of Diabetes

Type 1 diabetes

Type 1 diabetes (insulin-dependent, juvenile or childhood onset) is a disease characterized by deficient insulin production via the demolishment of insulin producing beta cells in pancreatic islets of Langerhans. It can be classified as "immune-mediated" or "idiopathic". Immune mediated form is more common form. In this type, T-cells mediated immune response is the originated basically from the loss in the beta cells of pancreas. The cause of Type 1 is unknown and it is not preventable with current knowledge (Rother, 2007, WHO 2017).

Type 2 diabetes

Type 2 diabetes is a multifactorial disease (non insulin-dependent or adult onset) results from the body's ineffective use of insulin resulted in chronic hyperglycemia. Type 2 diabetes comprises the majority of people with diabetes around the world, and is largely the result of excess body weight and physical inactivity (WHO, 2017).

These failures affect the free lipid acids usage of liver, muscles and fatty tissues. Genetic abnormalities, environmental factors, excess diet, decrease in activities, increased glucose production in liver, lipid enhancements in organs, muscles and liver, destruction of beta cells and imbalance between oxidation and inflammation are several factors leading to hyperglycemia.

Chronic hyperglycemia leads to microvascular diseases such as retinopathy, nephropathy, neuropathy and macrovascular disease including fatal and non-fatal myocardial infarction, stroke (Lamb and Goldstein, 2008).

Gestational diabetes

Gestational diabetes (diabetes developed during pregnancy) is similar to the Type 2 in many respects. The diseases' frequency is low and it develops due to the decrease of insulin secretion and its effects. Its incidence rate is about 2-5 % in whole pregnancies and it disappears after birth.

Women with gestational diabetes are at an increased risk of complications during pregnancy and at delivery. They and their children are also at increased risk of type 2 diabetes in the future (WHO, 2017).

Inflammation

Inflammation is a pervasive form of defense that is broadly defined as a nonspecific response to tissue malfunction and is employed by both innate and adaptive immune systems to combat pathogenic

intruders. In inflammation site blood stream is increased resulting in increase of body heat, rash, pain and swelling generation.

There are three basic purposes of inflammation in organism:

- Extinguishing the cause of the disease
- If it is not possible to extinguish the factors, to create a boundary around them (demarcation)
- Clearing away the damaged tissues

The factors affecting the inflammation process are as follows:

1. Living factors: Microorganisms including bacteria, virus, fungi and helminths are important factor affecting inflammation. These factors lead to neutrophilic chemotaxis by their receptors and antigens resulting the generation of inflammation.

2. Physical factors: Mechanic traumas, heat and cold, electricity, UV light ionization radiation, mineral dusts and unknown objects are some physical factors leading to inflammation. Inflammation process occurs in classic form.

3. Chemical factors: Acids, bases, disinfectants, heavy metal compounds, endogen and exogenous toxins, some drugs and metabolic products such as urea retention are some of the chemical factors. The tissue destruction and degeneration they caused lead to inflammation shaped as immune response so it is possible to limit the tissue damage.

4. Subjects causing immunological reactions: Unfamiliar proteins, endogen and exogenous materials causing hypersensitivity and immune complexes can cause immune reactions resulting in inflammation

5. Anoxemia and necrosis: The decrease in blood coming to tissues provokes inflammation reactions in this site and demarcation.

6. Idiopathic reactions: The causes of some inflammation-induced diseases (SLE, sarcoidosis) are not introduced yet.

7. Tissue damage and recovery: All recoveries accompanying with tissue damage are accepted as inflammation processes.

8. Contact inflammation: An inflammation in a part of the body can spread to closer tissues. It can be most seen in urinary tract infection and upper respiratory infection (Riede and Werner, 2004).

Genetic factors

Several diseases including Diabetes mellitus are recognized as complex traits, the developments of which are influenced by interactions between environmental factors and multiple genes (Zondervan et al., 2001). Sensitivity relies on both the factors of individual and environmental factors' impact. Genetic factors are playing a major role in development and/or severity of the diseases. Type 2 diabetes is also associated with a strong genetic predisposition as the other diseases (Turki et al., 2017). Compared to mutations, common allelic variants are present in high frequencies (>1%) in the general population. Among these variants, the most represented type of variations is single nucleotide substitutions, referred to as single nucleotide polymorphisms (SNPs). Although genetic association studies help to uncover the contribution of genetic background in disease susceptibility and severity, complex interplay between genetic and environmental factors creates a challenge in understanding the aetiology of complex diseases. Genetic modifiers are known for a number of common complex diseases where immune/inflammatory mediators and environmental factors play a role (Pruett et al., 2006). Cytokines, chemokines, and growth factors play a crucial role in the onset, progression and termination of important biological reactions so that the SNPs occurred in these will affect the initiation and progression of the diseases (Ollier, 2004).

The roles of cytokines in inflammation pathophysiology

Cytokines are small polypeptide mediators produced in several tissues affecting their biological functions by their intercellular signalling cell receptors. They are signal proteins having molecular weights less than 30 kDa. They start signal communication and secondary message carrier routes in their target cells by connecting their receptor ligands to these cells so that they provide the communications between cells. As a result gene activation, growth and differentiation, migration and apoptosis occurs which lead to mitotic division. Cytokines play also important role in inflammatory processes as in tissue homeostasis (Elias and Zitnik, 1992; Zhang and An, 2007).

Cytokines are important components in several crucial biological processes such as inflammation, cell growth and differentiation, morphogenesis and homeostasis (Elias and Zitnik, 1992). In a way, cytokines can be considered as the hormones of immune and inflammatory responses (Dinarello, 2007)

Cytokine is a general name, as cytokines are produced in several tissues so they get their names related to the tissues where they are secreted. For example cytokines produced in lymphocytes are called lymphokines, the ones produced in monocytes/macrophages are titled as monokines and the ones secreted from leucocytes are titled as interleukines. Apart from these cells, cytokines can be also produced in alveolar epithelium cells, mast cells, NK cells, beta cells and fibroblasts (Zhang and An, 2007).

Properties of cytokines

1. The target cells they affect show diversity. For example, IL-4 released from activated T cell can affect the activation, proliferation and differentiation

of B-lymphocytes but only affect the proliferation of mast cells.

2. Their life span is short.

3. They can affect in very small concentrations (10^{-12} M).

4. Their interactions are progressing in a very sensitive balance (Elias and Zitnik, 1992)

Inflammation reactions are essential defence mechanism of immune system in normal conditions but when the stimuli become permanent and unlimited; these reactions culminate in the development of several diseases via chronic and excess production of inflammatory mediators such as cytokines. Chronic inflammation is characterized by slowly progressing attack via penetration of many lymphocytes and monocytes morphologically. Following this, fibroblast proliferation, fibrosis and microvascular proliferation generate. Asthma, diabetes mellitus, Alzheimer's disease and autoimmune disease can be developed after chronic inflammation process (Yucesoy et al., 2003).

The cytokine production of immune system cells occur due to stimulants specific or not specific to antigens. B and T cells play role in antigen specific response on the other hand only T cells are responsible from non antigen specific response.

The cytokines playing role in inflammation can be classified as Type I, II and III due to their release from helper T cells. Cytokines are made by many cell populations but the predominant producers are helper T cells and macrophages Precursor T cells are located in thymus and they start to reproduce and activate when they meet antigens. Th1 cells necessary for control of intracellular proteins play role in cellular immunity. Their antibody responses are weak and temporary. Th 2 cells give strong responses but have weak cellular activities. They help B lymphocytes so they are important in humoral immunity and control of extracellular pathogens. Th 3 cells are regulatory cells responsible from immune mechanisms related with oral tolerance against the antigens. These cells have suppressor effects on Th 1 and Th 2 cells (Zhang and An, 2007).

Cytokines released from Th1 cells:

These are Type 1 cytokines activating the production of macrophage neutrophils and IgG_2 antibodies and they play a major role in inflammatory response and immunity. Type 1 cytokines are;

- TNF-α, β (Tumor necrosis factor-α,β)
- IFN-γ (Interferon- γ)
- IL-2 (Interleukin-2)
- IL-12 (Interleukin-12) (Opal and De Palo, 2000)

Cytokines released from Th2 cells:

These are Type 1 cytokines activating B cells. They enhance the production of eozinophils, mast cells, IgG and IgE antibodies. They play a role in humoral response and allergy. Type 2 cytokines are;

- IL-4 (Interleukin-4)
- IL-5 (Interleukin-5)
- IL-6 (Interleukin-6)
- IL-10(Interleukin-10)
- IL-13(Interleukin-13)

Th 1 and Th 2 cells control the inflammatory reactions against to pathogens by regulation of each other via the secretion of cytokines. For example; IFN-γ released from Th 1 cells inhibits the proliferation of Th 2 cells. IL-10 released from Th 2 cells suppresses Th 1 function by inhibition of cytokine production. Th 2 sourced IL-4, inhibits the differentiation and augmentation of Th 1 cell. The major role of cytokines in inflammation is controlling the management and continuity of immune responses. The common feature of them is being specific communication signals inter immune system cells and between immune system and the other organs. On account of strong and multi-directional biological effects their activities and release levels are arranged tightly. This regulation mechanism is also provided by the existence of specific antibodies, cytokine-binding factors and specific inhibitor proteins in biological fluids apart from the interactions between different cytokines. The imbalance in the functions leads to undesirable reactions. It is thought that some autoimmune diseases are related with excessive active Th 1 and allergy with Th 2 cells (Opal and De Palo, 2000; Cemiloglu and Yucesoy, 2005).

Cytokines are classified as pro-inflammatory and anti-inflammatory due to their roles in inflammation reactions. IL-1 and TNF-α are the major pro-inflammatory cytokines playing role in inflammatory responses. They serve as "endogenous pyrogens" with IL-6. The most important function of TNF-α is the cytolytic activity on tumor cells (Luster et al., 2000). Furthermore it is responsible from several alterations in endothelium with IL-1. They inhibit the thrombotic processes by inhibiting the anticoagulant mechanisms so that they play role in pathological processes such as venous thrombosis, atherosclerosis and vasculitis. The excessive secretion of TNF-α causes severe pathological results. IL-1 has anti-proliferative and cytotoxic activity similar to TNF-α. Also it is responsible from stimulation of Th cells (Yucesoy et al., 2011).

IL-1 directly affects the synthesis of immunoglobulins and the proliferation of B-cells also stimulates NK-cells and fibroblasts' proliferation and activation. It plays role in up regulation of inflammatory response with IL-11 and IFN-γ. IFN-γ has antiviral and antiparasitic activities; it acts in unison with TNF-α and they inhibit lots of normal and metamorphic cells' proliferations. IFN-γ also affects as immunomodulator.

On the other side, anti-inflammatory cytokines (IL-4, IL-10, IL-13) are responsible from the down-regulation of inflammatory response. They suppress the existence of pro-inflammatory cytokines. They are used in treatment of several inflammatory diseases due to their strong anti-inflammatory effects.

The activities of some cytokines such as IL-1, IL-6 and TNF-α are inhibited by TGF-β. TGF-β is an important cytokine playing role in cell activation, adhesion, reproduction, migration, differentiation and maturation (Schins and Borm, 1999). If the level of TGF-β is high, it induces the inflammatory response. It inhibits the improvement of NK cells and proliferation of T lymphocytes. Similarly to IL-4, Il-10 and IL-13, it controls the inflammatory response by regulation of tissue damaging cells and inhibiting macrophage activation.

It has been shown that, the clinical results of several infectious, malignant and autoimmune diseases are affected by the balance between the productions of pro- and anti-inflammatory cytokines.

The genetic variation of cytokines in development of diabetes and the other inflammatory diseases

As cytokines are key regulators of homeostatic mechanisms, possible variations in their levels or their structures may be associated with the disease process (Ollier, 2004). Polymorphisms in cytokine genes have been reported to contribute to the recognized stable inter-individual variation in the level of cytokine production rates (Pociot et al., 1992; Danis et al., 1995; Perrey et al., 1998). Inter-individual differences in spontaneous and stimulated production of IL-1 and TNF-α support the possibility of inflammatory diseases including Type 2 diabetes are related to the genetic propensity of the host to produce these proteins. At the IL-1 and TNF loci, some allelic variants have been found to be significantly over-represented in inflammatory diseases. These variations affect the level of TNF-α expression in response to various stimuli. Epidemiological studies have pointed out that cytokine SNPs occurring in both pro- and anti-inflammatory cytokine genes are associated with chronic inflammatory or immune-mediated diseases (Mc Dowell et al., 1995; Sullivan et al., 1997; Fishman et al., 1998; Zhai et al., 1998; Francis et al., 1999; Tountas et al., 1999; Franceschi et al., 2001; Yucesoy et al., 2001; Kim et al., 2002; Ohtsuka et al., 2002; Yucesoy et al., 2005; Jonth et al., 2007: Ates et al., 2008; Ates et al., 2011).

Recent studies showed the relationship between some cytokine and chemokine gene polymorphisms and the development of type 2 diabetes (Navarro-Gonzales and Mora-Fernandez, 2008; Song et al., 2013; Chang et al., 2016; Luna et al., 2016; Neelofar et al., 2016; Rodrigues et al., 2017; Saxena et al., 2017).

In our recent researches, we aimed to search and evaluate the possible relations between the TNF-α (-308), IL-1β (+3953) and IL-6 (-174) gene polymorphisms and the development of the diabetes in a group of Turkish patient population. In regards to our genotyping results, TNF-α, IL-1β gene polymorphisms are significantly related with the development of Type 2 diabetes 3,11 fold and 2,01 fold respectively. On the other hand, there is a little but not significant effect of IL-6 gene polymorphisms on the disease development (Ates et al., 2008; Ates et al., 2011).

Inflammation modulators

Chronic inflammation related with metabolism and immune system is formed of cellular and systemic response network. This network is capable of connecting lots of complex signal route (Wellen and Hotamisligil 2005). Adrenaline and noradrenaline, stress hormones, angiotensin II, some cytokines such as TNF-α, IL-6, IL-1β, are some of the mediators of these routes (Black, 2006). Each one has several regulatory duties in vital processes like metabolism and immune system (American Diabetes Association, 2005).

Genetic factors as similar to environmental factors can increase the fat deposition. This fat deposition is related with chronic, systemic or local inflammation characterized by infiltration of inflammatory cells, abnormal production of pro-inflammatory cytokines and the increase of acute phase reactants such as CRP. This phenomenon called meta-inflammation (metabolic inflammation) (Hotamisligil, 2006), connects the immune system to haemostatic systems. It also causes imbalance in haemostatic mechanisms.

Oxidative stress modulators

The instability between reactive oxygen species (ROS) and antioxidant production is named as oxidative stress. Via shifting the signalling pathways, oxidative stress provokes serious tissue damage (Wold et al., 2005). ROS are molecular oxygen ($.O_2^-$) products which are the by-products of usual aerobic metabolism. ROS contain unstable oxygen radicals such as superoxide radical ($.O_2^-$), nitric oxide radical (.NO), hydroxyl radical ($.OH^-$) and non-radicals like hydrogen peroxide (H_2O_2), peroxynitrite ($ONOO^-$) (Lamb and Goldstein, 2008).

Oxidative stress and meta-inflammation are functioning as mediators between pro-inflammatory cytokines and ROS. ROS are known as the toxic by-products of metabolism but they can function as signal transmitter in physiological process (Bloch-Damti and Bashan, 2005). For instance, in short exposure to ROS with low doses, specific routes become active and insulin like effects can be observed (Goldstein et al., 2005). On the other side, chronic exposure to ROS causes increase of mediator production functioning in stress signal routes leading to tissue damage in important target organs such as pancreas (Hotamisligil, 2006). Some symptoms like systolic-diastolic blood pressure and blood glucose level increase can be evident with these effects.

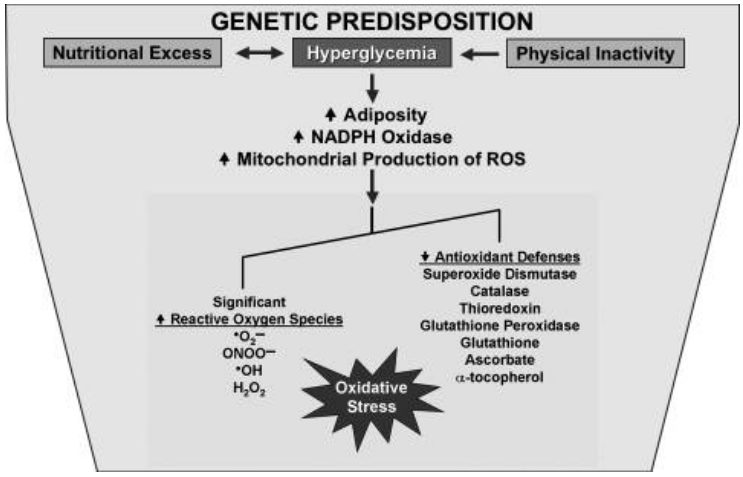

Figure 1. The factors playing role in hyperglycemia and the relationship between hyperglycemia and oxidative stress generation (Lamb and Goldstein, 2008).

Oxidative stress origins

Enhancement in levels of free fatty acids and hyperglycemia can reveal O_2^- by activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase after mitochondrial respiration (Nisoli et al., 2007). NADPH oxidase is a major origin for generation of O_2^- and can be found in adiposities, vascular smooth muscle cells, endothelium cells, fibroblasts and monocyte/macrophages (Griendling et al., 2000). Furthermore, immune system is also a strong source for formation of ROS (Lamb and Goldstein, 2008).

Oxidative-inflammation and its effect on generation of insulin resistance

In normal circumstances, the processes related with oxidation and inflammation functions as regulators of physiological balance but when a mechanism suppresses the other in chronic conditions instability occurs and it becomes harmful (Tuncman et al., 2006). Inflammation and oxidative stress interaction (oxidative-inflammation) causes Oxidative-Inflammatory Cascade (OIC) disease. OIC is an important stability factor constituted by metabolic and immune system modulators and its continuity is provided by positive feed-back (Kunsch and Medford, 1999). Generated ROS in adipose tissue, mitochondria and immune system during this process activates stress-sensitive kinases such as c-Jun N-terminal kinases (JNK), protein kinase C (PKC) isoforms, P38 mitogen-active protein kinase (p38-MAPK) and kappa B kinase inhibitor (IKK-β). These activates pro-inflammatory modulators like TNF-α, IL-6 and monocyte chemo attractant protein-1 (MCP-1). The activation of TNF-α, IL-6 and MCP-1 decrease the local/systemic production of ROS leading to increase of positive feed-back (Lamb and Goldstein, 2008) (Figure 2).

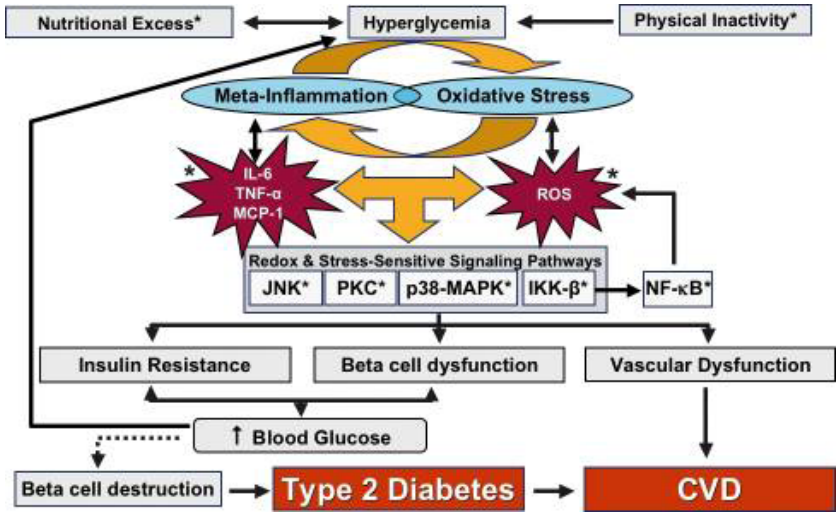

Figure 2. Oxidative inflammation and its effect on development of Type 2 diabetes complications (Lamb and Goldstein, 2008).

Insulin resistance (IR) is playing a major role in development and progression of Type 2 diabetes (Furukawa et al., 2017; Matsumoto et al., 2017). Insulin physiologically connects to the receptors located on insulin-sensitive tissues such as muscle, liver and adipose tissues and activates some insulin-sensitive routes leading to tyrosine phosphorylation of insulin receptor substrate (IRS) proteins. The enhancement of serum insulin levels is an important clinical sign of IR (Lamb and Goldstein, 2008).

ROS can give harm to cellular DNA, membranes, lipids and proteins or causing inflammatory gene expression blocking the metabolic routes induced by insulin. Even though there are numerous stress-sensitive kinases/routes related with ROS production JNK route (especially JNK-1) is seen the regulator of IR (Nisoli et al., 2007). JNK route increases the serine phosphorylation of IRS-1 and related to this the insulin-sensitive tyrosine phosphorylation of IRS-1 decreases (Nishikawa et al., 2007).

JNK1, causes fat deposition by decreasing energy consumption so chronic JNK activation and obesity sourced-glucose intolerance occurs. Then, a cycle progressing to vascular and β-cell destruction generates (Nishikawa et al., 2007). This leads to chronic hyperglycemia. ROS production increases the oxidative stress in far tissues leading to dysregulation of adiposities. It increases the productions of TNF-α, plasminogen activating inhibitor-1 (PAI-1), MCP-1, resistin, leptin and decreases the production of adiponectin causing the break-down of IR (Trayhurn and Wood, 2005).

Adiponectin is a circulation adipokine produced by adipose tissues. Adiponectin functions in insulin transmission and vascular processes also suppress systemic and cellular ROS production (Goldstein and Scalia, 2007). Leptin and resistin regulate lipolysis and the flow of free lipid acids from adiposities (Gorogawa et al., 2002). Hyperglycemia alters the trombocyte functions due to the increase of PAI-1 and release of TNF-α from macrophages. PAI-1, increases the trombocyte activation and aggregation. This fact is playing an important role in the pathophysiology lying under vascular dysfunction and myocardial infarcts (Lamb and Goldstein, 2008).

The effect of OIC on β-cell destruction

The recent studies related with the thought about whether the lipids are influential on the development of Type 2 diabetes or not, lipid-centred remark takes the lead from the conventional glucose-centred sight (McGarry 2002). Due to lipid-centred sight; the abnormalities of free lipid acids leads to the accumulation of lipids in muscles, liver and β-cells (Unger and Orci, 2000).

Glucotoxicity and lipotoxicity induce oxidative stress as well as increase the production of IL-6 and TNF-α (Lamb and Goldstein, 2008).

β-cells are sensitive to the cell destruction effect of oxidative stress because antioxidant enzyme production decreases related with the increase of NADPH activity due to the ROS production enhancement in mitochondria (Goldstein et al., 2005; Goligorsky 2005).

Serine-phosphorylation of JNK sensitive IRS-1 decreases the insulin production in β-cells. It was clearly seen that JNK route activation is the primary route of the devastation of pancreatic β-cells in diabetes (Kaneto et al., 2002).

Augmentation of glucose metabolism and initializing of OIC to inhibit IR

The alteration of OIC mechanisms taking part in metabolic and immune processes may ameliorate glucose metabolism, insulin resistance and vascular functions. Therefore the progression of Type 2 diabetes decelerates (Lamb and Goldstein, 2008).

Tissue necrosis factor-α, affects the motions of endothelium, brain, β-cells, bones, muscles and adipose and causes the production of ROS by binding the mitochondria and macrophages to each other. Tissue necrosis factor-α can be thought as a key target in order to initialize the OIC balance although IL-6 and MCP-1 have similar effects (Pedersen, 2007).

Cytokines released from muscles (myokines) have low preventive effect against to inflammation based chronic diseases. They also mediate the occurrence of the beneficial effects of exercise to health (Pedersen, 2007).

All these pro-inflammatory cytokines or enzymes stimulate ROS production and they take part in positive feed-back cycle.

Cytokines and ROS, activate JNK, IKK-β, PKC and the other stress and inflammation activator kinases. Due to the lack of JNK-1, adiposities deficiency and insulin resistance generates. JNK-1 plays an important role in regulation of OIC. For this reason, all these kinases are seen as pharmacological targets for enhancement of insulin and the initializing of OIC (Evans et al, 2005).

Type 2 diabetes is a complex inflammatory disease that causes a world-wide problem due it is morbidity and mortality. Understanding the underlying mechanisms and processes triggering the development and severity of this disease provides opportunities for designing new therapies to target mediators of these processes. Early detection can improve glucose utilisation, lower the risks of hyperglycaemic effects, delay or prevent the onset oxidative stress-induced insulin resistance and provide long-term benefits.

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