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Inflammation, diet, and type 2 diabetes: a mini-review

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ABSTRACT

Inflammation is a common feature of type 2 diabetes (T2D). Inflammatory cytokines increase in patients with type 2 diabetes, metabolic syndrome, and heart disease. Various types of cells can produce inflammatory cytokines and then release them into the bloodstream, where their complex interactions with target tissues raise a tissue-specific immune response. This review focused on C-reactive protein (CRP), tumor necrosis factor (TNF)-α as an inflammatory cytokine, and adiponectin produced by adipose tissues. Despite the major role of cytokines in the development of T2D, further studies are required to investigate the possible effects of the macronutrient composition of diet on these cytokines.

KEYWORDS

Type 2 diabetes; C-reactive protein; adiponectin; diet

Introduction

Inflammatory cytokines increase in patients with various types of diseases including type 2 diabetes, metabolic syndrome, and heart disease, and cancer.[1,12] These cytokines which increase in metabolic syndrome include tumor necrosis factor (TNF)-α, and interleukin (IL)-6. C-reactive protein (CRP), and adiponectin are also increased in T2D.[3] Various types of cells can produce inflammatory cytokines and then release them into the bloodstream, where their complex interactions with target tissues lead to a tissue-specific immune response.[4] Systematic inflammation increases the level of TNF-α, CRP, adiponectin, and interleukin-6 in the blood by about 2–3 times. Cytokines are small protein molecules released in response to a given stimulus. They are able to activate signaling pathways and induce an immune response through binding to specific receptors. Cytokines secreted by adipocytes can modulate both the secretion and function of insulin and body weight. Moreover, they probably play an important role in the development of insulin resistance and atherosclerosis and its likely consequences.[5] Adiponectin is the only cytokine that is...
mainly produced by adipose tissues, while TNF-α is produced by a variety of cells such as macrophages in addition to adipocytes. TNF-α is an inflammatory cytokine involved in metabolic disorders such as obesity and insulin resistance (IR).\cite{6} In addition to well-known stimuli, it has also been demonstrated that defects in certain genes such as caveolin-1 (CAV-1) can promote inflammatory status and production of IL-6 and TNF-α.\cite{7}

Adiponectin, a plasma protein produced by adipose tissues, has been demonstrated to have anti-inflammatory effects and is sensitive to insulin. In fact, it inhibits the ability of macrophages to activate.\cite{8} Adiponectin exerts these effects through inducing prexisome proliferator-activate receptor gamma (PPAR-γ), that is a type II nuclear receptor.\cite{9,10,11} An increase in the production of TNF-α is likely to lead to the synthesis of interleukins such as interleukin-8 (IL-8) that, in turn, contributes to inflammation and, thus, atherogenesis through the process of leukocyte adhesion.\cite{12} In fact, during inflammation, IL-8 is produced by a wide variety of cells. This chemokine is able to recruit and activate some types of immune cells, i.e. neutrophils.\cite{13}

CRP is another protein produced by the liver, and its high concentrations have been shown to be associated with cardiovascular disease (CVD), obesity, diabetes, smoking, and a sedentary lifestyle.\cite{14} Production of CRP by the liver can be stimulated by both TNF-α and IL-6. In addition, CRP can be produced and released by mature fat cells upon their stimulation by TNF-α, lipopolysaccharides (LPS), and resistin (adipose tissue-specific secretory factor).\cite{15,16} It has been reported that high concentrations of adiponectin are related to insulin sensitivity and a lower risk of CVD. While, low concentrations of this protein may play a prominent role in metabolic syndrome.\cite{17} Adiponectin causes an increase in the expression levels of 5′ adenosine monophosphate-activated protein kinase (AMPK) in both liver and skeletal muscle. AMPK is an enzyme which plays a central role in energy homeostasis. This enzyme acts as a sensor to detect energy. Activation and phosphorylation of AMPK inhibit the function of acetyl-CoA carboxylase (ACC), the enzyme responsible for the synthesis of malonyl-CoA which is the first step in the production of fatty acids.\cite{18} Therefore, inhibition of ACC decreases malonyl-CoA concentrations. Malonyl-CoA itself is an inhibitor of carnitine palmitoyltransferase-1 (CPT-1) that, in turn, functions as a rate-limiting enzyme in the oxidation of fatty acids. Also, a reduction in malonyl-CoA levels leads to an increase in fatty acid oxidation. This process in the skeletal muscle cells results in a reduction in the delivery of free fatty acids to the liver, synthesis of triglycerides, and secretion of VLDL by the liver.\cite{19} As mentioned earlier, MAPK induces the PPAR receptor, increases the oxidation of fatty acids, and finally reduces insulin resistance.\cite{20}
Obesity, diabetes, and inflammatory cytokines

Excess weight gain causes adipose tissue dysfunction, chronic activation of the immune system, macrophage infiltration, and increased secretion of TNF-α and interleukin-6. The native immune system is the first line of defense against invasive pathogens. The molecular prototype of pathogen recognition by innate immune cells is achieved through their binding to the cell surface receptors, referred to as pathogen recognition receptors (PRRs). This binding allows the receptors to activate the nuclear factor-κβ (NF-κβ) signaling pathway, resulting in inflammatory responses.

Obesity can activate the immune system through two mechanisms: 1) dysfunction of organelles, and 2) hypoxia in the adipose tissue. Regarding the first mechanism, mitochondria and endoplasmic reticulum (ER) are two key organelles that are affected by changes in the nutritional homeostasis in obese persons. Mitochondria are a double-membrane organelle responsible for cellular respiration. They also play a significant role in the regulation of metabolism and signal transduction pathways in the cell, including calcium signaling and signaling through reactive oxygen species. Mitochondria are also important to synthetic reactions in the cell, e.g. steroid and heme molecule synthesis. Endoplasmic reticulum has various cellular functions; however, the main function of ER is synthesis, proper folding, modifications, and finally transportation of protein molecules. This organelle also plays a role in the synthesis of both cholesterol and triglycerides and in calcium homeostasis.

Adipocyte hypertrophy increases lipolysis that subsequently leads to hyperlipidemia. In the later stages of disease development, along with the elevation of glucose levels in the blood, hyperlipidemia results in the subsequent formation of reactive oxygen species (ROS). Too much ROS might result in oxidative stress. Multiple studies have found that oxidative stress is linked to the dysfunction of the immune system. Indeed, oxidative stress can activate the immune system through the induction of NF-κβ as well. In sum, high food consumption increases the workload of ER. Heavy workloads of ER and ER stress can elicit an unfolded protein response (UPR) and probably result in the production of proteins which fold improperly. The UPR mechanism functions through three master signaling molecules in the cell, including protein kinase RNA-like endoplasmic reticulum kinase (PERK), serine/threonine-protein kinase/endoribonuclease inositol-requiring enzyme 1 α (IRE1α), and activating transcription factor 6 (ATF-6). These proteins increase inflammatory responses through the activation of NF-κβ.

Regarding the second mechanism, the theory of hypoxia in adipose tissue supports that hypoxia can be considered as the trigger for the dysregulation of adiponectin during obesity. Along with adipose tissue growth, the angiogenesis process is also increased. Hypoxia signals the activation of some transcription factors known as hypoxia-inducible factors (HIF). Activated
HIFs consequently activate the transcription of target genes which are involved in various molecular processes, including angiogenesis, glucose metabolism, and inflammation. Hypoxia elicits inflammatory responses in macrophages and inhibits adipocyte differentiation. Chronically elevated levels of TNF-α and IL-6 increase IR in skeletal muscles lead to the dysfunction of endothelial cells and release CRP from the liver. In general, the elevation of free fatty acids in the bloodstream activates Toll-like receptors (TLR). TLRs are a family of 12 members which can be activated by lipids. For instance, TLR2 is able to recognize both lipoproteins and glycolipids, while TLR4 recognizes lipopolysaccharide molecules. There is a body of evidence implicating that both TLR2 and TLR4 molecules can also respond to fatty acids and, subsequently, they induce inflammatory cytokines in macrophages.

Furthermore, elevated blood cytokines levels are able to activate the c-Jun N-terminal kinase (JNK) signal transduction pathway. This pathway is involved in inflammatory responses and IR. Activation of the JNK signaling pathway induces insulin receptor substrate-1 (IRS-1) protein phosphorylation on serine residues instead of tyrosine. The phosphorylation of human IRS-1 protein on serine 312 residue negatively affects interactions which normally occur between the IRS-1 phosphotyrosine-binding (PTB) domain and insulin receptor, thereby inhibiting insulin signaling and leading to IR. Consequently, activation of these signaling pathways and IR creates an impaired loop. Hyperglycemia induces endothelium and macrophages to produce more IL-6 and increases the production of suppressors of cytokine signaling (SOCS) proteins. The SOCS proteins’ function is to regulate immune responses through inhibition of the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway. Their pathologic elevation impairs signaling cascades and insulin release. The active role of CRP in inflammation has been demonstrated through the function of CRP to induce the production of intracellular adhesion molecule 1 (ICAM-1) and monocyte chemoattractant protein 1 (MCP-1) by endothelial cells. ICAM-1 causes the binding of mononuclear cells to the endothelium layer and then the infiltration of those cells into the sub-endothelial space.

In total, patients with type 2 diabetes with elevated levels of CRP are at high risk for the development of CVD. In terms of clinical investigations, CRP has been used as a biomarker as it has a relatively long serum half-life; CRP concentrations do not undergo rapid changes and remain constant in individuals without a severe infectious or inflammatory disease. Accordingly, CRP as an independent biomarker is capable of predicting the risk of diabetes and hypertension. Furthermore, CRP levels are associated with obesity, and it has been demonstrated that its levels can be reduced by physical activity in patients who suffer from T2D. Also, evidence suggests that CRP can induce leptin resistance or impair its signaling pathways. Leptin is a peptide hormone.
produced by adipose tissues. Leptin levels are indirectly correlated with certain inflammatory molecules such as IL-8, IL-1b in patients with metabolic syndrome without atherosclerotic cardiovascular disease (ASCVD) or diabetes. [41] The human leptin gene, LEP, locates on chromosome 7 and encodes a protein weight 16 KDa. Leptin binds to the leptin receptor, LepRb, belonging to the cytokine family receptors, [42,43] and activates a number of downstream signaling pathways. These pathways in turn play prominent roles in regulating numerous physiological processes, including glucose metabolism, storage of fat in adipocytes, and immune functions. [44,45] Indeed, many immune cells express LepRb; also, leptin can directly activate relevant signal transduction pathways in these cells. [46,47] Multiple studies on adipocytes have demonstrated that glycemic control increases the level of leptin and downregulates adiponectin expression at both mRNA and protein levels. [48] Furthermore, a recent study has reported that both adiponectin levels and adiponectin/leptin ratio are negatively associated with CRP levels. And, adiponectin concentration is much more lower in patients with metabolic syndrome (MS) in comparison to healthy controls. [49]

Normally, lipolysis in the adipose tissue can be inhibited by insulin. By definition, lipolysis is the biochemical process of hydrolytic cleavage of triacylglycerol (TAG) molecules stored in lipid droplets in all types of cells. [50] The lipolysis process produces non-stratified fatty acids and glycerol. These molecules are then released into the bloodstream in order to be consumed by body organs as energy sources. [51] Therefore, in the state of IR, lack of insulin function can lead to greater mobilization of FFAs. After eating a meal, lower lipoprotein lipase activity creates a hepatic TG-rich chylomicron, and IR increases FFAs and TG-rich VLDL particles. [52] TG-rich HDL particles are produced by cholesteryl-ester transfer protein. Then, hepatic lipase hydrolyzes TG, and HDL particles can be easily removed by the kidneys. [53] It has been shown that an abnormally high triglyceride and a low level of HDL-cholesterol in serum particularly confer a high risk for the development of atherosclerosis. IR can also contribute to the development of metabolic syndrome, a complex condition comprised of not only insulin resistance but also dyslipidemia. Furthermore, insulin is capable of inducing vascular endothelium to produce nitric oxide (NO). Alongside other biological functions, NO also has the potential to act as a vasodilator and promote the relaxation of vascular smooth muscle cells. Therefore, the state of IR is likely to cause vascular endothelial cell dysfunction. It is well established that endothelial dysfunction is the first step in developing a wide range of disorders, including atherosclerosis. [54]

**Diet, inflammatory cytokines, and crp in patients with type 2 diabetes**

Numerous studies have reported a relationship between a low-fiber diet on the one hand, and an increase in inflammatory cytokines and higher T2D
risk on the other.\textsuperscript{[55–58]} The study found that Western diet was associated with plasma CRP and sICAM-1 after adjusting for confounders such as body mass index (BMI). However, diets rich in fruits and vegetables were inversely associated with plasma CRP.\textsuperscript{[55]} Heidemann et al.\textsuperscript{[56]} found that diets with a high fiber content and low alcohol, red and processed meats, and beer bread was associated with higher plasma adiponectin and lower CRP levels. Similarly, a cross-sectional study on Iranian women demonstrated that a healthy dietary pattern was inversely associated with plasma CRP and soluble vascular cell adhesion molecule-1 (SiCAM-1).\textsuperscript{[57]} In 2009, a follow-up study was conducted on 3428 healthy adult men aged 60 to 79 years which extended over a seven-year period and investigated whether the participants developed type 2 diabetes. At the end of the study, 162 participants developed type 2 diabetes. The results demonstrated that a low-fiber diet (< 20 g) was associated with a higher risk of type 2 diabetes.\textsuperscript{[59]} Another study on insulin resistance conducted by Masters et al.\textsuperscript{[60]} on 941 healthy participants found that CRP levels were inversely associated with wholegrain. Data from a comprehensive study on atherosclerosis showed that a diet rich in fruit and cereal was negatively associated with serum levels of CRP, IL-6, and SiCAM-1, in addition, diets high in fat and processed meat were associated with high serum levels of CRP, IL-6.\textsuperscript{[61]}

**Conclusion**

Currently, there is a plethora of information about TNF-α, CRP, and adiponectin and their role in either the regulation of inflammation or the development of type 2 diabetes. Low levels of CRP have been also proposed to have a significant role in conditions like metabolic syndrome and obesity. Population studies have proved a significant association between concentrations of TNF-alpha and CRP in the blood and an increased risk of diabetes and CVD. Interestingly, animal studies have recently shown that production of some of inflammatory factors e.g. TNF-α can be affected by inactivation of genes such as CAV-1. High concentrations of plasma adiponectin are related to insulin sensitivity and a lower risk of CVD. In contrast, low concentrations of adiponectin have been observed in patients with metabolic syndrome. Furthermore, weight loss is associated with a decrease in CRP and TNF-α, and with an increase in adiponectin. Further studies are required to investigate the effects of the macronutrient composition of diet on these factors.

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