Article title: The Effect of Low-Grade Chronic Inflammation on the Pathogenesis of Metabolic Syndrome

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The Effect of Low-Grade Chronic Inflammation on the Pathogenesis of Metabolic Syndrome

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Contents

Title	Page
Introduction	1
The Pathogenesis of Low-Grade Chronic Inflammation	2
The Effect of Low-Grade Inflammation on the Pathogenesis of Metabolic Syndrome	5
Prevention of Inflammation	8
Conclusion	9

Introduction

It is well accepted that the metabolic syndrome (MS) increases the risk for the development of cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), stroke and cancer^[1]. Recently, the chronic inflammatory condition that often accompanies the MS has been implicated as a major factor both in the installation of the MS itself and its associated pathophysiological consequences^[2]. However, the inflammatory state that accompanies the MS does not completely fit into the classical definition of acute or chronic inflammation, as it is not accompanied by infection; there is no massive tissue injury and the dimension of the inflammatory activation is also not large. So, it is often called 'low-grade chronic inflammation' or 'meta-inflammation', meaning metabolically-triggered inflammation^[3].

Several studies support to the concept that a proinflammatory state is a component of the MS because of the strong association of elevated C-reactive protein (CRP) with MS-risk factors and high CRP levels impart risk for major coronary events beyond that imparted by the other metabolic risk factors. High-sensitivity CRP (hs-CRP) has been developed and used as a marker to predict coronary vascular diseases in the MS and it was recently used as a predictor for non-alcoholic fatty liver disease (NAFLD) in correlation with serum markers that indicated lipid and glucose metabolism.

However, the reasons for a link between inflammation and MS are not fully understood. One explanation may be that adipose tissue in obese people with the MS releases increased amounts of cytokines into the circulation which in turn accounts for a greater production of CRP by the liver. Another possibility is that insulin resistance (IR)

alone is responsible for a higher production of cytokines. Regardless of the mechanism, the finding that patients with MS exhibit characteristics of a proinflammatory state provides a new and exciting connection between inflammation and metabolic processes [4].

The Pathogenesis of Low-Grade Chronic Inflammation:

Chronic inflammation is also referred to as slow, long-term inflammation lasting for prolonged periods of several months to years. Low grade chronic inflammation can result from the following:

- Failure of eliminating the agent causing an acute inflammation such as infectious organisms.
- Exposure to a low level of a particular irritant or foreign material that cannot be eliminated by enzymatic breakdown or phagocytosis in the body.
- An autoimmune disorder in which the immune system is sensitized to the normal component of the body and attacks healthy tissue giving rise to diseases.
- Recurrent episodes of acute inflammation.
- Inflammatory and biochemical inducers are causing oxidative stress and mitochondrial dysfunction [5].

Inflammation consists of a tightly regulated cascade that is orchestrated by immune signaling molecules called cytokines. The first step of the inflammatory cascade involves identification of infection or damage (Figure 1b) which is achieved by the detection of pathogen-associated molecular patterns (PAMPs) that is directed toward general motifs of molecules expressed by pathogens that are essential for pathogen survival. Damage-associated molecular patterns (DAMPs) are recognized by the innate immune system.

Transmembrane toll-like receptors (TLRs), intracellular nucleotide binding domain and leucine-rich-repeat-containing receptors (NOD-like receptors or NLRs) are germ-line encoded receptors which recognize the damage signals. After recognition of ligands occurs, TLRs activate signaling pathways that culminate in the activation of nuclear factor kappa- B (NF- κ B) and activation of NF- κ B does not require any new protein synthesis (Figure 1c).

The third stage of the cascade is the transcription and translation of genes that induce the expression of pro-inflammatory cytokines such as interleukin-1-beta (IL-1 β), IL-6, tumor necrosis factor-alpha (TNF- α ; Figure 1d). At the site of disturbance, in conjunction with chemokines and various co-stimulatory molecules monocytes and neutrophils are recruited by these soluble proteins (Figure 1e). Noxious chemicals including reactive oxygen species (ROS) and reactive nitrogen species (RNS) from cytoplasmic granules create a cytotoxic environment. To release these chemicals, glucose and oxygen are required; a process known as the respiratory burst. These effector mechanisms are thus major contributors to host collateral damage.

These interactions lead to cardinal signs of heat, swelling, redness, pain and loss of function which are further regulated by the adaptive immune system (Figure 1f). The fourth and last critical phase is its resolution (Figure 1g). Pro-inflammatory prostaglandins and leukotrienes recruit macrophages during acute inflammation. Further neutrophil recruitment is blocked by lipoxins and instead favor enhanced infiltration of monocytes which is important for wound healing ^[6].

TNF- α is one of the cytokines produced chiefly by activated macrophages. Natural killer cells, neutrophils, mast cells, eosinophils, neurons and CD4+ lymphocytes. It is primarily responsible for the regulation of the functions of immune cells. Studies reveal that in obese subjects its level increases in adipose tissue (visceral rather than subcutaneous) and reduces as weight decreases ^[6].

C-Reactive Protein (CRP) is an acute- phase protein which increase by macrophages and T cells in response to inflammation following IL-6 secretion. Studies showed that the risk of hypertension, T2DM and CVD increased as its level increasing in human. Recent research suggests that patients with elevated basal levels of CRP are at an increased risk of T2DM, hypertension and CVD [6].

Adiponectin (ApN) is produced by adipose tissue. Studies showed that circulating ApN is negatively correlated with the body mass index (BMI) and decreased in obesity, in patients with T2DM or CVD. Abnormal hormonal milieu together with the enhanced oxidative stress and pro inflammatory state may be the mechanisms involve in the down regulation of ApN during obesity and the metabolic syndrome [6].

Figure 1: Primers of the inflammatory cascade ^[6].

The Effect of Low-Grade Inflammation on the Pathogenesis of Metabolic Syndrome:

Although a pivotal response to infection and tissue injury, inflammation has also been associated with many pathological processes. Overt acute inflammation leads to tissue damage and non-resolving inflammation causes chronic tissue malfunction, suggesting an evolutionary trade-off between the rapid and effective response to perturbations in tissue homeostasis and the collateral damage on tissue function. Obesity, raised fasting plasma glucose, high cholesterol and hypertension a cluster, is considered as a most dangerous risk factors are so-called metabolic syndrome ^[7].

NF- κ B regulates the transcriptional activity of at least 125 genes, most of which are pro-inflammatory. Many of the peripheral actions of cytokines released from adipose tissue [adipokines] are mediated through the activation NF- κ B, and its action is further promoted by the effects of other hormones, metabolites and inflammatory cytokines present in MS. The activation of NF- κ B can increase oxidative stress, providing a link between inflammation and oxidative stress, both crucial to the development of MS. Reactive oxygen species [ROS] have been implicated in characteristics of MS, including, hypertension, atherosclerosis, diabetes and even obesity itself ^[8].

Aside from cytokines, the action of NF- κ B can also be affected by insulin, free fatty acid [FFA] and glucose levels in circulation, all of which are elevated in MS. Elevated FFAs are thought to increase oxidative stress due to increased β -oxidation and mitochondrial uncoupling which can increase ROS production. While hyperglycemia has been shown to increase NF- κ B activation, insulin acts to decrease its activation. However, due to the insulin resistance that accompanies MS, the insulin is unable to have its anti-inflammatory effects, resulting in NF- κ B activation. Insulin resistance results in both hyperglycemia and increased circulating FFAs and seems to be one of the

promoting agents for low grade chronic inflammation in MS. Thus, inflammation may be the underlying factor connecting Type 2 diabetes and cardiovascular disease in MS.

Within adipose tissue, associated macrophages account for nearly all of the TNF- α production and both TNF- α and mRNA production increase in the adipose tissue of obese individuals. TNF- α is a pro-inflammatory cytokine as it activates NF- κ B, leading to increased oxidative stress and further cytokine production in peripheral tissues. It has also been associated with an increase in liver and muscle insulin resistance but this may be an indirect result of its paracrine action in adipose tissue. Many adipokines such as MCP-1, also known as C-C motif chemokine ligand 2 (CCL2), TNF- α and resistin secreted by adipocytes from obese subjects can promote macrophage infiltration and accumulation in adipose tissue and subendothelial space. It has been confirmed by recent studies that showed the association of abdominal obesity with an increased amount of macrophages in adipose tissue. These macrophages are also implicated in the secretion of a panel of inflammatory cytokines (TNF- α , IL-6, MCP-1, PAI-1) acting in a paracrine and endocrine manner, finally causing a state of permanent low-grade inflammation in obese subjects. The primary mechanisms of action of adipose tissue-produced inflammatory adipokines can be referred to according to the anatomic location of fat depot in which the adipokines are produced. Thus, adipokines released by the visceral depot would exert a greater effect on hepatic

carbohydrate and lipid metabolism, stimulating hepatic release of acute phase response proteins in the liver as CRP [8].

TNF- α has been implicated in endothelial dysfunction as it has been shown to increase leukocyte adhesion to the endothelium, activate NF- κ B dependent inflammatory pathways, induce endothelial cell expression of VCAM-1, induce smooth muscle expression of metalloproteinases contributing to plaque destabilization and suppress the expression of nitric oxide synthase leading to decreased capacity to vasodilate vessels. TNF- α also stimulates the production of IL-6 stimulates hepatic CRP production. Antagonistic to TNF- α action is adiponectin which is present in decreased levels in MS.

The underlying mechanism of vascular dysfunction, at endothelium and smooth muscle levels, appears to be secondary to the excessive ROS generated which seems to be increased by adipokines. Promotion of the NF- κ B inflammatory pathway plays an important role in the development of chronic subclinical vascular inflammation, resulting in endothelial dysfunction and later the formation of an unstable atherosclerotic plaque, rich in inflammatory cells. An increased expression of CAMs leads to enhanced recruitment of monocytes within the arterial wall. An unstable plaque is prone to rupture leading to thrombus formation and vessel wall occlusion [8].

CRP levels are strongly correlated with inflammation and atherosclerosis and are also elevated in MetS. CRP is an inflammatory marker produced by the liver under stimulation by cytokines IL-6 and TNF- α . It attaches to the plasma membrane of damaged cells and causes cell death through activation of the complement cascade and stimulates macrophages to express cytokines. CRP may also participate directly in the cell wall mechanisms leading to atherosclerotic lesions and cardiac events ^[8].

The pathogenesis of atherosclerosis is a process that requires a complex and orchestrated interaction between endothelial cells, smooth muscle cells and macrophages. The initial stages of atherosclerosis are characterized by sub-endothelial retention of circulating LDL particles, which leads to their oxidative modification by ROS and enzymatic attacks. Subsequently mmLDLs can activate TLRs, resulting in the rapid transcription of inflammasome processed cytokines (e.g., IL-1 β) as well as that of multiple other pro-inflammatory soluble factors such as chemokines and cytokines. The recruitment of myeloid cells and T-cells into the intima is generated by the pro-inflammatory environment where monocytes differentiate into macrophages and then into foam cells due to cholesterol accumulation. Foam cells are a pathognomonic feature of atherosclerotic plaques which play a critical role in progression of disease. Severity of atherosclerosis is elevated as plasma concentrations of IL-1 β and IL-18 are elevated ^[9].

Gout is a disease associated with high concentrations of uric acid. The prevalence of gout increases in the population. Moreover, the prevalence has also increased affecting 21% of the adult population. The pathogenesis of gout is piloted by the accumulation and deposition of crystals of uric acid in the joints and as such these crystals are

activating inflammasome. Clinical studies on gout shows that blockage of IL-1 β significantly reduce severity of disease ^[10].

Prevention of Inflammation:

Chronic inflammation can have a deleterious effect on the body and is a key factor causing almost all chronic degenerative diseases. Some of the most effective ways to prevent chronic inflammation are:

- Increased uptake of anti-inflammatory foods as; whole grains, natural foods, vegetables and fruits which are helpful in defeating inflammation.
- Avoiding use of antibiotics, antacids, and non-steroidal anti-inflammatory drugs (NSAIDs) as the cause inflammation in intestinal walls which in turn release toxins and trigger chronic, body-wide inflammation.
- Regular exercise is helpful in controlling weight as well as decreasing the risk of CVD and strengthening the heart, muscles, and bones.
- Avoiding stress as chronic psychological stress is linked to greater risk for depression, heart disease and body losing its ability to regulate the inflammatory response and normal defense as it is associated with an increase in cortisol levels which in turns leads to the suppression of the immune system ^[5].

Conclusion:

Inflammation is a tissue-destroying process that involves the recruitment of blood-derived products. Rapidly destroy or isolate the underlying source of the

disturbance, removes damaged tissue and restore tissue homeostasis is the primary function of inflammation. Inflammatory and chronic metabolic alterations that together are termed metabolic syndrome. The risk of developing serious pathological conditions such as (CVD) and T2DM is significantly associated with inflammation and its concurrent multi-organ abnormalities which represent a great burden upon societies, as they require significant resources from health care systems. Thus, understanding the tissue-specific pathogenic processes that lead to disease progression is required for the development of more effective therapeutic approaches.

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