



REVIEW Oxidative Stress, Inflammation and Chronic Disease

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1 Introduction

All chronic diseases are interrelated as they contain an element of increased inflammatory response, often observed long before the disease is documented clinically. The increase in inflammation is mainly the result of lifestyle, stress, lack of physical activity, over-consumption of calorie-condensed foods rich in saturated fat, sugar and starch, making the increase in inflammation uncontrollable. According to the World Health Organization, 46% of global disease burden and 59% of global mortality are due to chronic diseases [1] [2].

Inflammation is the reaction of vascularised tissue to local injury, which results from an immune response to infectious microorganisms. Acute inflammation is the immediate response to vascular changes where the widespread effects of inflammatory mediators produce pain, heat and swelling, usually of short duration. Chronic inflammation is self-perpetuating and may last for weeks, months, or even years. It may develop as the result of a recurrent or progressive acute inflammatory process or from low-grade, smoldering responses that fail to evoke an acute attack. *The influx of macrophages and lymphocytes* are characteristic of chronic inflammation [3].

2 Causes of Inflammation & Oxidative Stress

2.1 Oxidative Stress

Chronic inflammation is seen to be involved in the pathogenesis of insulin resistance and Type 2 Diabetes Mellitus (T2DM). Oxidative stress is the common factor underlying insulin resistance, T2DM and CVD, which helps to explain the presence of inflammation in all these conditions. Inflammation is one of the manifestations of oxidative stress, and the pathways that generate the mediators of inflammation, such as adhesion molecules and interleukins, are all induced by oxidative stress. The sub-clinical pro-inflammatory state observable in conditions including atherosclerosis, cancer, and ageing, is caused through various processes, for example mitochondrial over-generation of free radicals. Free fatty acids (FFA) and glucose induce inflammation through oxidative stress and have a cumulative independent effect [6].

2.1.1 Oxidative Stress and Nutrition Overload, links with Chronic Disease

Over-nutrition and decreased physical activity lead to increased glucose and FFA loads in the cells. Their transformation in energy is accompanied by increased free radical generation (oxidative stress). The muscle cells and adipocytes can protect themselves from this condition, producing a resistance to the action of insulin, aiming to reduce glucose and FFA penetration in the cells. Beta cells and endothelium are insulin independent tissues. Glucose and FFA overload in these cells and cause oxidative stress, which induces a dysfunction of both Beta cells and endothelium. Endothelial dysfunction may lead to the development of cardiovascular disease. Beta cell

dysfunction is characterized by an alteration of insulin secretion, which is worsened by insulin resistance, a condition that requires increased insulin secretion to maintain blood glucose in a normal range. Beta cell dysfunction is particularly characterized by a decreased first-phase insulin secretion to maintain plasma glycemia in a normal range. This in turn produces the clinical picture of impaired glucose tolerance (IGT). This last situation is clinically characterized by increased hyperglycemia. Postprandial hyperglycemia induces oxidative stress in many cells. The persistence of such a condition produces exhaustion of beta cells, leading to overt diabetes. Oxidative stress produced both during IGT and overt diabetes may contribute to the development of CVD, and is associated with many of the complications of diabetes. The cluster of risk factors that accompanies the insulin resistance also contribute towards CVD [6], and other chronic illnesses such as DM, arthritis and certain cancers.

2.2 Postprandial Inflammation

Each meal provokes an inflammatory response, which is transient in duration and low in intensity compared with that of a classical inflammatory disease. Immune cells react to the acute postprandial elevation of several nutrients by mounting a transient oxidative and inflammatory response to this event which is an *exogenous stress* against which it has to mount an *adaptive response*. Constant exposure to meals high in certain nutrients stresses the immune/metabolic homeostatic system. Homeostatic failure of the combined systems leads to both immune and metabolic disorders which result in endothelium dysfunction and CVD. The nutrient-dependent factors influencing postprandial inflammation include [19]:

- **Calorie value of a meal:**
Meals high in calories produce a strong postprandial immune/inflammatory response that cause postprandial fatigue and the tendency to rest or even sleep after the meal.
- **Glycemic index and glycemic load of a meal:**
The amount of carbohydrates in a meal and a fast absorption can cause acute postprandial hyperglycaemic peaks that are classically known to be of crucial importance in the postprandial insulin secretion and tissue sensitivity to its effects.
- **Lipid profile of a meal:**
The most efficient triggers of postprandial inflammatory response appear to be triglycerides and saturated fatty acids. However the most important modulators of postprandial immune response appear to be the polyunsaturated fatty acids (PUFAs) and especially the n-3 and n-6 ratio. N-3 PUFA suppress postprandial inflammation, whereas n-6 PUFA promotes it.

Nutrient-independent factors influencing postprandial inflammation include obesity, diabetes mellitus and a sedentary lifestyle. These factors also influence the degree of the chronic low-level metabolic inflammation that is assessed over the fasting state as opposed to the postprandial metabolic inflammation, which is assessed 4-8 hours postprandially. The obese have accentuated postprandial inflammatory responses as well as elevated inflammatory indices in the fasting state. The severity of the postprandial inflammation of the obese is reversible upon reduction of body weight. Patients with type 2 DM have high postprandial inflammatory response irrespective of the nutritional content of a meal. The magnitude of the postprandial inflammatory response in diabetes correlates with the degree of insulin resistance [19].

2.3 Obesity

Poor diet and physical inactivity are the most important factors contributing to the increase in overweight and obesity [16]. Overweight and obesity are associated with multiple coexisting conditions, including hypertension, glucose intolerance, dyslipidemia, and obstructive sleep apnea.

Additionally, obesity is associated with an increased risk of death from cardiovascular disease, diabetes, kidney disease, and obesity-related cancers (colon, oesophageal, uterine, ovarian, kidney, and pancreatic) [14].

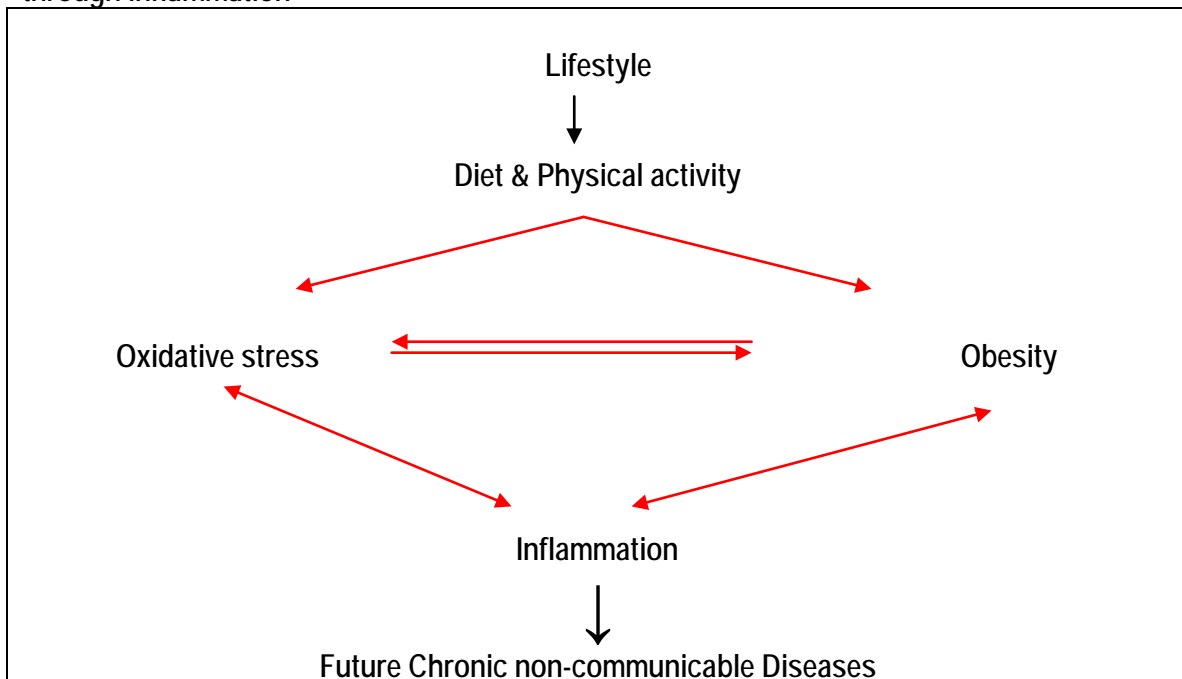
2.3.1 Obesity and Inflammation

Obesity is typified by excessive calorie consumption and insulin resistance, which are closely related to the excessive pro-inflammatory cytokine production seen in chronic inflammation. Nutrient excess produces reactive oxygen species, resulting in oxidative stress that damages cells and triggers an inflammatory response. The increased inflammation blocks the protective action of insulin, which normally stimulates target cells to absorb nutrients. Unfortunately, as excessive nutrients are consumed, neighbouring cells and tissues that remain insulin sensitive are placed at risk. As insulin resistance progresses, inflammation is exacerbated, initiating a cycle of excessive nutrient intake, insulin resistance and inflammation. In some cells, nutrient excess impairs endoplasmic reticulum function and accelerates the accumulation of fatty acid derivatives that also promote inflammation. The inflammatory response seems to be triggered and to reside predominantly in adipose tissue, which secretes various hormones known as adipokines. Deregulation of these proteins is associated with excessive weight gain, an inflammatory state, and various chronic diseases, including osteoarthritis [12].

2.4 Lifestyle Factors

The association between diet, physical activity and obesity is well established, and between obesity and inflammation. Evidence suggests that low-grade chronic inflammation predicts an increased risk of chronic disease and promotes its progression. Both the underlying causes and preventative measures are related to lifestyle factors [19].

Figure 1. Consequences of an obesogenic lifestyle on the development of chronic diseases through inflammation



2.4.1 High Risk Dietary and Lifestyle Practices

Eating patterns associated with increased calorie intake and poorer nutrient quality [15]:

- Increased frequency and caloric density of daily eating occasions, with low nutrient quality of these food choices.
- Increased portion size
- Eating away from home more often, particularly in fast-food restaurants
- Changing to a different pattern on weekends
- Increased intake of calorically sweetened beverages
- Increased dietary intake of saturated and trans fats
- Increased intake of sugar and refined starches
- Reduced fruit and vegetable intake
- Physical inactivity

3. Conditions associated with Oxidative Stress and Inflammation

Many diseases, including cardiovascular disease, Alzheimer's disease, Parkinsons' disease, diabetes, cancer, arthritis and other inflammatory conditions as well as aging are associated with oxidative stress. Further, inflammatory processes are involved in the pathogenesis of the most common chronic non-communicable diseases and may also play an important initiating role in their development. Some of these conditions are discussed below.

3.1 Insulin Resistance

Insulin resistance (IR) is defined as an inadequate response by insulin target tissues, such as skeletal muscle, liver and adipose tissue, to the physiologic effects of circulating insulin. Impaired insulin sensitivity results in decreased insulin-stimulated glucose uptake into skeletal muscle, impaired insulin-mediated inhibition of hepatic glucose production in the liver, and a reduced ability of insulin to inhibit lipolysis in adipose tissue. Insulin resistance is a major predictor for the development of various metabolic outcomes, including type 2 DM, and is a defining feature of metabolic syndrome (MS). MS encompasses a group of conditions, including IR, dyslipidemia, hypertension, and obesity, and is often accompanied by hyperinsulinemia, sleep apnea and other disorders. The most common acquired factors causing insulin resistance are obesity, sedentary lifestyle, and ageing, all of which are interrelated. Certain nutrients such as fatty acids have been found to induce insulin resistance through proinflammatory pathways [21]. As mentioned above, *oxidative stress and inflammation is the common persistent pathogenic factor mediating the appearance of IR* as well as the passage from IR to overt DM, via IGT, while producing the increased risk condition typical of prediabetic and diabetic subjects by favouring atherosclerotic complications [6]. It can thus be said that oxidative stress and inflammation can lead to subsequent IR, which places an increased risk for chronic disease.

3.2 Beta Cell Dysfunction

The decline of insulin secretory function is paralleled by progressive reduction of Beta-cell mass. Beta-cell apoptosis can occur in response to several insults acting through at least three pathways leading to destruction of cell chromosomes:

1. cytokine-induced (inflammation) cell death, mediated by cell surface receptors
2. mitochondrial disruption, secondary to oxygen free radicals (oxidative stress)
3. endoplasmic reticulum stress pathway.

Beta-cells are vulnerable to all three forms of apoptosis and in type 2 diabetes they can be triggered by metabolic alterations, such as glucotoxicity or lipotoxicity. The progressive loss of functional beta-cell mass accounts for progression toward overt diabetes and subsequent progressive worsening of glycaemic control [25].

3.3 Diabetes Mellitus

Type-2 diabetes mellitus is a progressive and complex disorder, which is linked to the development of macrovascular and microvascular (namely neuropathy, renal failure and vision loss) complications. Macrovascular complications are the major cause of death in patients with DM. Insulin resistance results in the progressive loss of islet beta-cell function. This results in dysregulation of blood glucose levels, especially in the postprandial state. Hyperglycemia in diabetes is associated with a higher risk of retinopathy, macrovascular disease, increased carotid-media thickness, oxidative stress, inflammation, endothelial dysfunction, some cancers and impaired cognitive function [7].

3.4 Endothelial Dysfunction

The endothelium is a single layer of thin flat cells that lines the heart, blood vessels and lymphatic vessels. Endothelial cells are involved in many aspects of vascular biology, including the regulation of blood pressure, blood clotting, the formation of new blood vessels, inflammation and swelling and the formation or inhibition of plaque formation on blood vessel walls. Endothelial cells also control the passage of materials and white blood cells into and out of the blood stream. Endothelial dysfunction refers to the loss of proper function of the endothelial cells, it is the hallmark of vascular disease and can lead to atherosclerosis and coronary heart disease. People who have insulin resistance and problems with endothelial function have increased levels of thrombotic factors in the blood that are likely to adhere to the walls of blood vessels and endothelium. They also have a reduced ability to regulate blood pressure through the endothelial cells that line the blood vessels [18].

3.5 Osteoarthritis

Osteoarthritis is (OA) a chronic joint disease that involves the loss of habitually weight-bearing joint cartilage. OA may occur in any synovial joint in the body, although the condition is most common in hands, knees, hips and spine [13]. The loss can result in pain, swelling, loss of motion, changes in joint shape and abnormal bone growth [8]. Inflammatory processes are involved, leading to stiffness and pain [10]. Inflammatory cytokines seen in OA include IL-1, Interferon gamma, TNF-alpha, IL-6, transforming growth factor beta and insulin-like growth factor 1 [9]. OA occurs through hereditary factors and trauma. Mechanical insult may lead to the appearance of the disease at a particular site. Obesity plays a role in the occurrence and progression of the disease [11]. Since obese individuals have higher concentrations of inflammatory markers, inflammation may contribute to functional limitation and disease progression in those who have OA [12].

4. Markers of Inflammation

Cytokines are low-molecular-weight regulatory proteins that are produced during all phases of an immune response. **Interleukin-1 (IL-1), IL-6 and tumor necrosis factor (TNF)** are the major mediators of the early inflammatory response. They can stimulate the production of acute-phase proteins by the liver, mobilize neutrophils to the site of insult, direct the hypothalamus for a fever response, and increase the adhesion molecules on the vascular epithelium. TNF is a potent cytokine with multiple immunologic and inflammatory effects, associated with rheumatoid arthritis, osteoarthritis and inflammatory bowel disease [4]. Other cytokines seen in inflammation include interleukin-1 receptor antagonist (**IL-1ra**), **IL-8, IL-1, IL-18 and interferon- γ** [19] [22].

Fibrinogen is an acute-phase inflammatory marker and is seen as an independent predictor of coronary heart disease (CHD). Factors associated with elevated fibrinogen include smoking, diabetes, hypertension, obesity, sedentary lifestyle, elevated triglycerides, and genetic factors [5].

C-Reactive Protein (CRP) is a protein synthesized in the liver as the acute-phase response to inflammation. Since atherogenesis is an inflammatory process, CRP has been shown to be elevated in people with angina, myocardial infarction, stroke and peripheral vascular disease. Elevated CRP levels are also an independent risk factor and a causal agent for atherothrombosis [5]. Other acute phase protein inflammatory markers include **serum amyloid A (SAA)** and **plasminogen activator inhibitor-1 (PAI-1)** [19].

Adhesion molecules **intercellular adhesion molecule-1 (ICAM-1)** and **vascular cell adhesion molecule-1 (VCAM-1)**, together with chemokines **monocyte chemoattractant protein-1 (MCP-1 or CCL2)** and **CCL-1 to CCL-28**, are inflammatory markers and are seen in vascular endothelial dysfunction, and subsequently in type 2 DM. MCP-1 is commonly seen in metabolic inflammation [19] [22].

Markers of the oxidant/antioxidant balance, when assessing metabolic inflammation, include; **vitamin C** and **erythrocyte reduced glutathione (GSH)** among others [19].

Ferritin can act as a positive acute-phase reactant protein and may be elevated in conditions that do not reflect iron stores such as acute inflammation, infections, type 2 DM [22], metastatic cancer and lymphoma. Cytokines and other inflammatory mediators can increase ferritin synthesis, ferritin leakage from cells, or both [18].

5 Intervention

Intervention on modifiable risk factors is a critically important public health goal to reduce the risk of obesity and chronic diseases, such as diabetes, hypertension, osteoarthritis, coronary heart disease and some cancers. *Habitual diet is the major modifiable risk factor.* Successful weight loss and maintenance programs involve attention to several factors, including behavioral change strategies, adherence to a rigorous diet and exercise. Diet and lifestyle interventions are recommended for all chronic diseases mentioned above. These recommendations include [15]:

- Balance calorie intake and physical activity to achieve a healthy body weight
- Choose whole-grain, high-fibre foods

A study done by Herder, et al. in 2008, it was found that an increase in physical activity as well as an increased dietary consumption of natural fibre (both water soluble and insoluble fibres) was associated with reductions in inflammatory markers, namely CRP and IL-6. Since sub-clinical inflammation is associated with an increased risk of chronic diseases, the importance of physical activity and dietary fibre intake is recommended as a lifestyle intervention recommendation [17].
- Consume a diet rich in fruit and vegetables
- Consume fish, especially oily fish, at least twice a week
- Limit your intake of saturated fat to <7% of energy, trans fat to <1% of energy and cholesterol to <300mg/day by:
 - Choosing lean meats and legumes
 - Selecting fat free and low fat dairy products
 - Minimizing intake of partially hydrogenated fats
- Minimize intake of beverages and foods with added sugars
- If you consume alcohol, do so in moderation (equivalent to no more than 1 drink in women or 2 drinks in men per day)

- Avoid or stop smoking [1]
- Control physical and mental stress [1]
- Supplementation may be considered in specific circumstances.

6 Conclusion

Clinical evidence suggests that oxidative stress and inflammatory processes linked to free radical over generation may be the key in the generation of insulin resistance, diabetes, cardiovascular disease and other chronic diseases. To optimize the treatment of these patients, it is necessary to understand the root cause of oxidative stress. Excess nourishment, stress in combination with sedentary lifestyle, can independently or collectively result in overabundance of glucose and fatty acid accumulation within muscle, adipose tissue and pancreatic cells. This leads to the generation of excess reactive oxygen species through the mitochondrial electron-transport chain, and inflammation. Other mechanism are also implicated

The importance of a healthy lifestyle remains the core component of preventing and managing chronic disease. Abstaining from smoking, regular physical activity and modest (if any) intake of alcohol, a diet low in inflammation-inducing molecules, saturated and trans fatty acids, dairy products, sugar and refined carbohydrates; and high in anti-inflammatory molecules, n-3 fatty acids, plant fibres, vitamins and antioxidants found in fruit and vegetables, is effective in supporting optimal ageing and reducing the incidence of chronic diseases [1]. Certain supplements may be useful in reducing the inflammatory process and may be considered as an adjunct to healthy diet and lifestyle. However, further studies are required to prove clinical effectiveness for certain supplements.

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