The role of inflammation in metabolic syndrome

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The metabolic consequences of obesity have made this highly prevalent condition one of the most common risk factors for type 2 diabetes, hypertension and atherosclerosis. Simultaneous occurrence of these conditions can be explained through the manifestations of metabolic syndrome [MetS]. Clinical indication of MetS is characterized by a clustering of risk factors for complex chronic diseases which all feature metabolic deterioration as a common component. Diagnosis of MetS can be made if a patient exhibits three of the identified risk factors, some of which include: elevated waist circumference, elevated triglycerides, low high density lipoprotein levels, hypertension and elevated blood glucose. The progression from obesity to MetS involves an alteration in body metabolism mediated by cytokines-signalling molecules that coordinate the inflammatory response. Increased visceral adipose tissue contributes to augmented secretion of pro-inflammatory cytokines which can activate several transcription factors, including NF- κ B, which promote these inflammatory conditions and lead to increased oxidative stress. Exacerbation of the condition then ensues as oxidative stress results in oxidized low density lipoprotein, dyslipidemia, insulin resistance, hypertension and atherogenesis. This review will not only focus on the role of inflammation in the manifestations of MetS, but also outlines some lifestyle and nutritional treatments that can be used to treat the condition and reduce the risk of chronic disease.

Modern North American lifestyles have brought great changes in diet and physical activity that correlate with an increased incidence of cardiovascular disease and insulin resistance. As diets become more caloric and lifestyle more sedentary, excess weight and obesity has reached levels of 23% of the Canadian population. This has been accompanied by a 138% and 60% increase in men and women, respectively, in chronic diseases that can be attributed to the excess weight from 1970-2004.⁵⁰ Metabolic syndrome [MetS] is a clustering of risk factors for such chronic disease as cardiovascular disease and Type 2 diabetes and is associated with abdominal obesity.²⁵ Mechanisms linking the emergence of these chronic conditions to excess weight seem to be related to a state of chronic low-grade inflammation in these individuals.³⁶

Classically, inflammation is described as the response of the body when invoked to deal with injury. It is often of short duration and critical to tissue repair.⁴⁷ Its coordination is mediated by the integration of many chemical signals [cytokines] released from different tissues, which are also chronically expressed during obesity and MetS, although few of the other classic symptoms of inflammation are observed. This distinct type of chronic inflammation is primarily triggered by nutrients and metabolic surplus and initiates similar cytokines and signaling pathways as found in

classical inflammation. The role of these cytokines in these metabolic diseases is still uncertain; however, they may be the result of fundamental biological design.

The abilities to withstand starvation and the effectively respond and defend against pathogens are critical to species survival. The combination of these desired traits is likely to have given rise to the development of biological organization that is very capable of processing and storing energy as well as expression of a powerful immune response.³⁶ The relationship between the immune and metabolic response has been suggested to possibly stem from this idea as well as other evolutionary events. It is important to recognize that functional units that control metabolic and immune functions in higher organisms have evolved from common ancestral structures. For example, the *Drosophila* fat body incorporates mammalian homologues of the liver and haematopoietic and immune systems.^{48, 67} The fly's fat body not only coordinates metabolic responses to nutrients, but also coordinates pathogen response with metabolic status. Although the adipose tissue, liver and haematopoietic system have developed into distinct functional units in humans, they still share a developmental heritage with earlier organisms. It then becomes possible for a situation of overlapping pathways regulating both the immune and metabolic responses with common key regulatory molecules and

signaling systems to exist.³⁶ The mechanisms by which metabolic influences can elicit an immune response involve inflammatory cytokines which can initiate several pathways leading to an increased risk for chronic disease. Of particular interest is the relationship between cytokines and the activation of nuclear transcription factor- κ B [NF- κ B], which seems to have a role in MetS.

NUCLEAR TRANSCRIPTION FACTOR – κ B

NF- κ B regulates the transcriptional activity of at least 125 genes, most of which are pro-inflammatory.⁷⁹ Many of the peripheral actions of cytokines released from adipose tissue [adipokines] are mediated through the activation of NF- κ B, and its action is further promoted by the effects of other hormones, metabolites and inflammatory cytokines present in MetS.⁶⁸ Through the example pathway illustrated in **Figure 1**, it can be seen how adipokines can act to induce or suppress the transcription of various factors implicated in MetS.

The activation of NF- κ B can increase oxidative stress, providing a link between inflammation and oxidative stress—both crucial to the development of MetS. Reactive oxygen species [ROS] have been implicated in characteristics of MetS, including, hypertension, atherosclerosis, diabetes and even obesity itself.^{49,77}

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 MetS. Elevated FFAs are thought to increase oxidative stress due to increased β -oxidation and mitochondrial uncoupling which can increase ROS production.²⁸ While hyperglycemia has been shown *in vitro* to increase NF- κ B activation,⁴² insulin acts to decrease its activation.¹⁸ However, due to the insulin resistance that accompanies MetS, 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 MetS. Thus, inflammation may be the underlying factor connecting Type 2 diabetes and cardiovascular disease in MetS.

INFLAMMATION AND TYPE 2 DIABETES

Recent developments in the understanding of insulin's metabolic actions¹⁸ have resulted in the idea that insulin resistance may be the basis of most features of MetS.¹⁷ Increased plasma FFA concentrations are key to the pathology of insulin resistance as they interfere with insulin signalling.¹⁷ Increasing the plasma FFA concentrations in normal subjects, to levels comparable to obese individuals, also results in the induction of oxidative stress, inflammation, impaired vascular reactivity in addition to

insulin resistance.⁷² Insulin has been shown to suppress the pro-inflammatory transcription factor NF- κ B;¹⁹ however, resistance to insulin action would decrease this anti-inflammatory effect. As seen previously, one way by which NF- κ B mediates its inflammatory response is through the action of cytokines. If insulin is unable to suppress this action at tissues, such as adipose, cytokine release can increase.

Visceral adipose tissue is thought to be the origin of this inflammation⁷⁴ as increases in weight causes a gradual infiltration of adipose tissue with macrophages. In fact, data from animal studies have shown that the adipose tissue from obese animals contains a significantly higher number of macrophages compared to lean controls.⁷⁴ Both macrophages and adipocytes are capable of releasing cytokines as eliciting an inflammatory response, and the accumulation of adipose tissue is implicated in the development of MetS via its secreted factors.

Tumour Necrosis Factor- α [TNF- α]

Within adipose tissue, associated macrophages account for nearly all of the TNF- α production⁷⁶ and both TNF- α mRNA and production increase in the adipose tissue of obese individuals.³⁸ 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 resistance⁴⁶ but this may be an indirect result of its paracrine action in adipose tissue. TNF- α causes adipocyte insulin resistance via serine phosphorylation of both the insulin receptor and insulin receptor substrate within adipose tissue. This results in decreased phosphoinositol-3-kinase activity, an essential secondary messenger in insulin signalling.⁴⁰ This impairment in insulin action has also been shown to occur in skeletal muscle via a paracrine action of TNF- α from the macrophages in myocyte associated fat deposits.³⁷ However, this same mechanism has not been found to occur with hepatocytes.³⁹

A second potential mechanism of TNF- α action may be its antagonistic effects on the release of another cytokine, adiponectin. Adiponectin is an anti-inflammatory cytokine whose secretion has been shown to be decreased by TNF- α signalling.⁴⁴ Adiponectin is important in increasing insulin sensitivity which may explain how paracrine effects of TNF- α can affect systemic insulin sensitivity.

Adiponectin

Adiponectin consists of both a collagenous tail and globular head which can circulate as high molecular weight complexes, trimer-dimers or just globular heads.⁷⁴ With increasing obesity, adiponectin expression in visceral adipose decreases,⁷⁴ which may lead to the decreased serum concentrations observed and may be due to the increase in TNF- α released from adipose. Administration of either full

Figure 1: Role of adipokines in increasing NF-κB activation and clinical manifestations of Metabolic Syndrome (Adapted from Sonnenberg et al., 2004).

length or globular head adiponectin has been shown to decrease plasma glucose and increase insulin sensitivity in mice models of obesity and insulin resistance.⁵

The insulin sensitizing effects of globular adiponectin appears to be mediated by an increase in FFA oxidation via activation of AMP-activated protein kinase [AMPK] in skeletal muscles.⁸² In addition, full length adiponectin also activates AMPK in the liver, reducing hepatic glucose production and increasing glucose uptake.⁸⁰ Adiponectin elicits its response by binding to AdipoR1 or AdipoR2 receptors, which are found either in the muscle or liver.⁸¹ Signalling mechanisms from these receptors have not yet been conclusively deciphered.

Leptin

Leptin acts similarly to adiponectin in that it increases insulin sensitivity via AMPK activation; however, leptin also has beneficial effects on the central nervous system and food intake regulation. Mature adipocytes secrete leptin proportionally to the amount of adipose mass as well as nutritional status.⁷⁴ The leptin released acts in an endocrine fashion, binding to its receptor in the hypothalamus, muscle and pancreatic β-cells.⁷⁴ Leptin's primary role is to signal nutrient sufficiency and it has been shown to reduce food intake, body weight and adipose tissue in *ob/ob* mice.⁷⁴ However, in obese individuals, leptin concentrations are

elevated and it is hypothesized that there may be some defect in leptin signalling or transport across that blood-brain barrier.⁷⁴

As a result of leptin's conflicting abundance in obese individuals and the coexistence of insulin resistance and obesity, a correlation between insulin and leptin signalling has been suggested.^{15,45,70} In isolated rodent islet cells, leptin induces β-cell proliferation and protects against FFA-induced β-cell apoptosis.^{41,57} However, chronic exposure of human islets to leptin results in β-cell apoptosis by reducing levels of interleukin IL-1 receptor antagonist and IL-1β synthesis and secretion.⁵² In addition, rats that have been overfed exhibit both insulin and leptin resistance.⁷⁵ It appears as though leptin is anti-inflammatory when expressed at normal levels, but chronic high levels of leptin seem to lead to resistance or even detrimental effects.

The progression of insulin resistance has also been associated with an increased risk for cardiovascular disease via cytokine activities which may be caused by the actions of the NF-κB system. The insulin resistance that results from increased FFA concentrations decreases insulin's ability to decrease NF-κB activity leading to increased oxidative stress and further cytokine production in immune cells and peripheral tissues. The ROS and cytokines that result also have detrimental effects to cardiovascular function in addition to their effects on energy metabolism.

INFLAMMATION AND CARDIOVASCULAR DISEASE

Evidence has accumulated over the past decade that suggests the atherosclerotic process is regulated by inflammatory mechanisms.⁴⁹ Insulin resistance plays a key role in the development of MetS²⁰ as it promotes an inflammation which can negatively affect arterial and arteriolar function.² 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.¹ Promotion of the NF-κB 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.

ENDOTHELIAL DYSFUNCTION

Endothelial dysfunction is the earliest event in atherogenesis.⁸³ Key events include the adhesion of leucocytes to the vascular endothelium and subsequent migration into the intima. Rolling and adhesion of leucocytes on the endothelium are triggered by the expression of cell adhesion molecules (CAMs) on the endothelial cells.^{49,64} CAMs expressed in early atherogenesis and also associated with MetS are vascular cell adhesion

molecule 1 [VCAM-1], intercellular adhesion molecule 1 [ICAM-1] and E-selectin. Prospective surveys of individuals with MetS have found that the levels of soluble endothelial adhesion molecules are higher in patients with MetS when compared to controls.⁶ CAM levels can also be affected by the cytokine adiponectin,⁶⁵ accounting for some of its anti-inflammatory actions.

Dyslipidemia and Unstable Atherosclerotic Plaques

An increased expression of CAMs leads to enhanced recruitment of monocytes within the arterial wall.⁸³ An unstable plaque is prone to rupture leading to thrombus formation and vessel wall occlusion. An abundance of macrophages and other inflammatory cells are hallmarks of unstable atherosclerotic plaques.⁸³

Abnormalities in lipoprotein distribution also contribute to the instability of a plaque. Triglyceride rich lipoproteins, their remnants, and smaller, denser, low-density lipoprotein [LDL] particles all have potentially inflammatory actions when they interact with the arterial wall.^{16,22} In contrast, high-density lipoproteins [HDL] appear to have anti-inflammatory actions.⁸³ The lipoprotein profile of MetS is characterized by an increase in pro-inflammatory lipoproteins and low concentration of anti-inflammatory HDL particles.⁸³ The elevated atherogenic potential of LDL particles is mostly accounted for by their increased susceptibility to oxidation.¹² A study of healthy men found that MetS was accompanied by high plasma concentrations of oxidized LDL [oxLDL] compared to those without.⁶⁶ The oxLDL levels were associated with most of the MetS risk factors and also related to small LDL particle size. Levels of oxLDL are interrelated with the NF- κ B pathway as cytokine levels and other markers of inflammation modulate oxLDL levels and oxLDL also acts to further stimulate NF- κ B and produce more ROS.⁵³

C-Reactive Protein [CRP]

CRP levels are strongly correlated with inflammation and atherosclerosis and are also elevated in MetS. This has been demonstrated in various studies, including a survey of free-living individuals without diabetes or clinical coronary artery disease. The results showed that CRP positively correlated with body mass index [BMI], waist circumference, blood pressure, triglycerides, fasting insulin and blood glucose levels; it also inversely correlated with HDL levels.³¹ CRP is an inflammatory marker produced by the liver under stimulation by cytokines IL-6 and TNF- α .^{78,83} It attaches to the plasma membrane of damaged cells and causes cell death through activation of the complement cascade.⁶³ CRP also enhances the uptake of LDL at the endothelium and stimulates macrophages to express cytokines,⁸⁶ while plasma levels have been correlated with levels of CAMs.⁶¹ In addition, CRP may also participate directly in the cell wall mechanisms leading to atherosclerotic lesions and cardiac events.⁹

Tumour Necrosis Factor- α [TNF- α]

TNF- α has been implicated in endothelial dysfunction as it has been shown to increase leukocyte adhesion to the endothelium,⁸⁴ activate NF- κ B dependent inflammatory pathways,³ induce endothelial cell expression of VCAM-1,⁶² induce smooth muscle expression of metalloproteinases contributing to plaque destabilization⁷³ and suppress the expression of nitric oxide synthase²⁹ leading to decreased capacity to vasodilate vessels. TNF- α also stimulates the production of IL-6 stimulates hepatic CRP production.^{8,34} Antagonistic to TNF- α action is adiponectin which is present in decreased levels in MetS.

Adiponectin

In addition to its role in decreasing insulin resistance, adiponectin also appears to be antiatherogenic. It stimulates the production of nitric oxide,¹⁴ reduces the expression of CAM in endothelial cells and decreases cytokine production from macrophages by inhibiting NF- κ B signalling. It further counteracts the pro-inflammatory actions of TNF- α on arterial walls and suppresses the transformation of macrophages into foam cells.^{4,60} Adiponectin expression and secretion from adipose tissue is reduced by TNF- α ,^{43,51} possibly through stimulated production of IL-6,³⁵ which inhibits adiponectin secretion.³⁰ **Figure 2** provides an overview of the role of inflammation in MetS.

OTHER FACTORS IN THE METABOLIC SYNDROME

Figure 2: Whole body effects of selected cytokines in the inflammation of Metabolic Syndrome (Adapted from Eckel et al., 2005).

There are many other components of MetS that can be accounted for by chronic low grade inflammation and the characteristics presented were only briefly reviewed. There are also other cytokines and biomarkers present in MetS that have not been mentioned. Certainly factors associated with blood coagulation and other cytokines are also significant though some are less characterized than ones mentioned.

TREATMENT OPTIONS

Initial treatment of MetS characteristics should include lifestyle and dietary factors as well as nutritional interventions. Both have been shown to be beneficial and can potentially decrease medical dependence. Teaching individuals with MetS how to promote their own health is important to making good lifestyle choices.

Lifestyle Factors

Body weight reduction through diet, exercise or surgery has been proven to be beneficial in lowering inflammation and improving MetS characteristics.¹³ In addition, physical activity can influence insulin sensitivity and MetS independent of weight loss.⁷ Several studies have shown that an increase in physical activity can improve, at least in the relatively short term, insulin sensitivity,²¹ with a subsequent decrease in plasma triglyceride levels and increase in HDL cholesterol levels.²³ Exercise beneficially influences the production of cytokines and adipokines, such as CRP, IL-6 and TNF- α , irrespective of changes in total body weight.⁵⁶ Moreover, physical activity reduces plasma concentrations of other inflammatory markers, such as intercellular adhesion molecule-1, VCAM and P-selectin, which are associated with endothelial dysfunction.⁸⁵ Physical activity interventions reduce the prevalence of MetS,⁵⁸ and physical activity is inversely associated with a number of components of the MetS in apparently healthy men.¹⁰

Dietary Intake

Macronutrient intake may produce oxidative stress and inflammatory responses. Glucose ingestion in normal subjects is associated with increased superoxide generation in leukocytes and mononuclear cells, as well as with raised amount and activity of NF- κ B.¹⁷ A mixed meal from a fast-food chain has also been shown to induce activation of NF- κ B associated with the generation of reactive oxygen species by mononuclear cells. Interestingly enough, superoxide is an activator of at least two major pro-inflammatory transcription factors, including NF- κ B. These findings are in line with previous studies demonstrating that after oral or intravenous glucose challenges, in both normal subjects and patients with Type 2 diabetes mellitus, there is an increased generation of ROS and raised circulating levels of inflammatory cytokines, TNF- α and IL-6.^{11,27}

A single high-fat meal in normal subjects produces endothelial activation, as evidenced by increased concentrations of the adhesion molecules VCAM-1 and ICAM-1, in association with raised plasma concentrations of IL-6 and TNF- α .⁵⁴ Moreover, the same high-fat meal may increase the circulating levels of IL-18,²⁶ a pro-inflammatory cytokine supposed to be involved in plaque destabilization, associated with the simultaneous decrease of circulating adiponectin.⁷¹

Antioxidants

An impaired serum redox balance with decreased antioxidant capacity and increased lipid peroxidation has been observed in patients with visceral obesity and MetS.⁶⁹ Increasing the antioxidant content of the diet, either with a Mediterranean diet³² or with increased fruit and vegetable consumption,⁵⁵ may be of use in the treatment of MetS. The Mediterranean diet contains high levels of olive oil and vegetables, providing a wide antioxidant capacity.³³ In a recent controlled crossover trial with an olive oil intervention, lowered plasma oxLDL and lipid peroxide were found,³² suggesting that the antioxidants in olive oil may provide some protection against cardiovascular disease risk factors. Most epidemiological studies of fruit and vegetable consumption have found a reduced risk for stroke,⁵⁵ however, experimental and human studies of antioxidant addition to the diets of individuals with MetS have yielded controversial results.³³

CONCLUSIONS AND FUTURE RESEARCH

The proinflammatory state of obesity and MetS probably originates from excessive caloric intake due to overnutrition in most individuals. Inflammation can induce insulin resistance and lead to the manifestations of MetS. Adipokines produced by the excess visceral adipose tissue in obesity also play a central role in manifesting these characteristics of MetS. Future research should aim to further clarify the role of these adipokines in MetS so as to control the actions of these factors and prevent progression of the syndrome. Emphasis should be placed on the roles of proper nutrition and lifestyle to prevent and treat the condition in addition to prescribed medications. This provides the opportunity for individuals to prevent or treat MetS themselves and learn how to better care for their health.

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