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TARGETING INFLAMMATION IN METABOLIC SYNDROME

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Abstract

The metabolic syndrome (MetS) is comprised of a cluster of closely related risk factors, including visceral adiposity, insulin resistance, hypertension, high triglyceride and low HDL-C, all of which increase the risk for the development of type 2 diabetes and cardiovascular (CV) disease. A chronic state of inflammation appears to be a central mechanism underlying the pathophysiology of insulin resistance and MetS. In this review, we summarize recent research which has provided insight into the mechanisms by which inflammation underlies the pathophysiology of the individual components of MetS including visceral adiposity, hyperglycemia and insulin resistance, dyslipidemia and hypertension. On the basis of these mechanisms, we summarize therapeutic modalities to target inflammation in the MetS and its individual components. Current therapeutic modalities can modulate the individual components of MetS as well as have a direct anti-inflammatory effect. Lifestyle modifications including exercise, weight loss and diets high in fruits, vegetables, fiber, whole grains and low-fat dairy and low in saturated fat and glucose are recommended as first line therapy. The Mediterranean and DASH diets are especially beneficial and have been shown to prevent development of MetS. Moreover, the Mediterranean diet has been associated with reductions in total and CV mortality. Omega-3 fatty acids and peroxisome proliferator-activated receptor α agonists lower high levels of triglyceride; their role in targeting inflammation is reviewed. Angiotensin converting enzyme inhibitors, angiotensin receptor blockers and aldosterone blockers comprise pharmacologic therapies for hypertension but also target other aspects of MetS including inflammation. Statin drugs target many of the underlying inflammatory pathways involved in MetS.

INTRODUCTION

The metabolic syndrome (MetS) is comprised of a cluster of closely related risk factors, including visceral adiposity, insulin resistance, hypertension and dyslipidemia all of which increase cardiovascular risk.[1] MetS as defined by the Adult Treatment Panel III includes at least three of the following: central obesity (waist circumference ≥ 88 cm (35 inches, 80 cm

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Asian) in women and ≥ 102 cm (40 inches, 90 cm Asian) in men, fasting blood glucose ≥ 5.56 mmol/L (100 mg/dL), triglyceride (TG) levels ≥ 1.7 mmol/L (150 mg/dL), low levels of high density lipoprotein cholesterol (HDL-C) (< 1.04 mmol/L [40 mg/dL] in men and < 1.7 mmol/L [50 mg/dL] in women), and systolic and/or diastolic blood pressure ≥ 130/85 mm Hg.[2] The MetS has a prevalence of 24% in US adults and 43% of adults older than 60 years.[3] MetS is a precursor of type 2 diabetes mellitus and increases the risk of cardiovascular disease (CVD) outcomes 2-fold and all-cause mortality, 1.5-fold.[1] Each of the individual components of MetS is a risk factor for CVD; therefore, recognizing and treating each component is important to lower risk of CVD. Inflammation appears to be a central mechanism underlying the pathophysiology of MetS. In this review, we summarize recent research which has provided insight into the mechanisms by which inflammation contributes to the development of MetS. On the basis of these mechanisms, we summarize therapeutic modalities to target inflammation in the MetS and its individual components.

ROLE OF VISCERAL ADIPOSITY IN METABOLIC SYNDROME

Visceral adiposity is the major risk factor responsible for the development of insulin resistance and the common pathophysiologic link to MetS. The pathophysiology of MetS is related to a diet containing excess calories and/or high saturated fat or glucose content and physical inactivity. Triacylglycerols provide the major source of energy which is used by skeletal muscle. They are comprised of a glycerol backbone in which each of the 3 hydroxyl groups is esterified with a fatty acid.[4] The function of white adipose tissue is to store excess energy as TGs and then lipolyze and release free fatty acids (FFAs) into the circulation for use as energy in muscle. When nutrient intake exceeds the metabolic demand for energy, the excess TG is stored in adipocytes, liver and skeletal muscle. White adipose tissue is a highly active metabolic tissue which releases more than 50 different molecules known as adipocytokines, which regulate inflammation and immune function and the components of MetS including insulin sensitivity and blood pressure homeostasis as well as glucose and lipid metabolism.[5]

There are several ways in which products of adipocytes cause insulin resistance and thus, MetS (illustrated in Figure 1, Panel A). First, adipocytes secrete monocyte chemoattractant protein-1 (MCP-1) and the cytokines, tumor necrosis factor (TNF)-α and interleukin (IL)-6, which cause infiltration of macrophages into adipose tissue.[6] These macrophages in turn release TNF-α and IL-6. TNF-α signaling activates intracellular kinases, c-Jun N-terminal kinase (JNK) and IκB kinase (IKK) which lead to increased serine phosphorylation of insulin receptor substrate-1 (IRS-1), rather than the normal tyrosine phosphorylation (Figure 1, Panel A) [7, 8]. Serine phosphorylation of IRS-1 impairs insulin signaling and causes insulin resistance in muscle, liver and other tissues by leading to decreased activation of phosphoinositide 3-kinase (PI3K) which in turn inhibits protein kinase Akt2 (protein kinase B), a protein which catalyzes the translocation of the insulin-responsive glucose transporter 4 (GLUT-4) to the plasma membrane, thus inhibiting the transport of glucose into cells, (see Figure 1, Panel B).[6, 9] Activation of Akt inhibits Forkhead box protein O1 (FoxO1), a process which inhibits gluconeogenesis, thus lowering plasma glucose levels. In insulin resistance, inhibition of Akt will activate Foxo1 and cause hyperglycemia. Thus, IRS → Akt → FoxO1 signaling cascades are important regulators of glucose metabolism. TNF-α

and IL-6 also activate the pro-inflammatory transcription factor nuclear factor (NF)-κB and activator protein 1 (AP-1), which leads to increased production of pro-inflammatory cytokines, thus exacerbating inflammation. As a central mediator of inflammation, NF-κB regulates over 200 genes involved in inflammation, innate immunity and apoptosis and leads to the production of pro-inflammatory cytokines (e.g., TNF-α, IL-6 and IL-1β), macrophage recruiting factors, vascular cell adhesion molecules (e.g. intercellular adhesion molecule [ICAM] 1, vascular cell adhesion molecule [VCAM] and E- and P-selectins), remodeling proteases (e.g., matrix metalloproteinase [MMP]-2 and MMP9), prothrombotic proteins (plasminogen activator inhibitor 1 [PAI-1] and fibronectin) and enzymes that promote oxidative stress (e.g. $p47^{phox}$) as well as C-reactive protein (CRP) and inducible nitric oxide synthase (iNOS).[10] The cytokines can have a paracrine effect but also be secreted into plasma and affect other organs in an endocrine fashion and cause insulin resistance. Adiponectin is a protein hormone that modulates a number of metabolic processes, including glucose regulation and fatty acid oxidation.[11] Adiponectin is exclusively secreted from adipose tissue with levels inversely correlated with body fat percentage in adults. Low levels of adiponectin lead to increased levels of TNF-α and IL-6 from macrophages and decreased levels of the anti-inflammatory cytokines, IL-10 and IL-1 receptor antagonist, thus causing insulin resistance. Low levels of adiponectin also increase gluconeogenesis by inhibiting AMP-activated protein kinase and causing hyperglycemia (AMPK).[12] Adipocytes can also produce IL-13, a key anti-inflammatory cytokine which phosphorylates the transcription factor signal transducer and activator of transcription 3 which inhibits transcription of hepatic genes for gluconeogenic enzymes such as phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, thus leading to lower levels of glucose.[13] IL-13 deficiency in the mouse leads to post-prandial hyperglycemia, insulin resistance, weight gain and increased levels of TG.[13] These results suggest that IL-13 agonists may be beneficial by ameliorating insulin resistance; however, overproduction of IL-13 is shown to cause hepatic fibrosis.[14] Human studies are yet to be done.

A second mechanism leading to insulin resistance results from actions of the FFAs lipolyzed from the stored TGs in adipocytes. FFAs function in signaling pathways to regulate glucose, fat and lipid metabolism and inflammation. FFAs can adversely affect insulin signaling and cause insulin resistance within adipocytes and in muscle and other tissues.[15] Saturated fatty acids (SFAs) activate the Toll-like receptor (TLR) 4 signaling pathway indirectly through binding to Fetuin A, a circulating glycoprotein secreted from the liver (Figure 1B).[16] Fetuin A then binds to and activates TLR4. This induces activation of JNK and IKK which lead to serine phosphorylation of IRS-1 and inhibition of insulin signaling.[16] JNK and IKK activation also leads to upregulation of NF-κB and AP-1 activation and thus production of inflammatory cytokines and defective insulin signaling.[16, 17] Activation of NF-κB upregulates VCAM1 on the endothelial cell to which monocytes attach and migrate into the subendothelial space where they are converted to macrophages which take up oxidized lipoproteins and form foam cells and the fatty streak. as shown in Figure 2.[18, 19] In support of these signaling events, TLR4-null mice do not develop insulin resistance or adipose inflammation when challenged with FFAs.[20]

Third, saturated fatty acids can be converted to diacylglycerides (DAGs) and ceramides, both of which lead to insulin resistance (Figure 1B). DAGs stimulate protein kinase C (PKC)

which causes serine phosphorylation of IRS-1 and thus, insulin resistance.[21] Ceramides cause insulin resistance by inhibition of Akt activity.[22]

Fourth, FFAs from adipocytes could also lead to the activation of the inflammasome which is a multiprotein oligomer that promotes the production of inflammatory cytokines. FFAs activate the inflammasome by interacting with pattern recognition receptors as Nod-like receptors (NLRs -see Figure 1, Panel B) which also function as sensors for exogenous pathogens.[23] The inflammasome mediates caspase-1-driven cleavage of pro-IL-1β and pro-IL-18 to their active forms, IL-1β and IL-18. SFAs activate NLRs, a process leading to production of the pro-inflammatory cytokines, IL-1β and IL-18, which cause defective insulin signaling in mice.[24] In support of this, mice that are deficient in two inflammasome components, NLR pyrin domain containing 3 and pyrin domain and caspase-recruitment domain, are protected from systemic insulin resistance and hyperglycemia in the setting of obesity.[23]

In adipose tissue, the adrenergic system may play a role in the development of insulin resistance through affecting the levels of G-protein-coupled receptor kinase 2 (GRK2). Elevated levels of GRK2 mediate endothelin-1-induced insulin resistance via inhibition of Galphaq/11 and IRS-1 pathways in 3T3-L1 adipocytes.[25] [reviewed in 26] Moreover, overexpression of GRK2 causes insulin resistance by phosphorylating IRS-1 (Figure 1 Panel B), and inhibition of GRK2 ameliorates insulin resistance in cells and a rat model of insulin resistance.[27] GRK2 inhibits cardiac glucose uptake; inhibition of GRK2 prevents post-ischemic myocardial insulin resistance, normalizes glucose uptake and appears to prevent subsequent heart failure in mice.[28] Development of GRK2 inhibitors could improve insulin sensitivity and potentially prevent heart failure after MI although human trials are yet to be done.

PRO-INFLAMMATORY AND PRO-RESOLVING LIPID MEDIATORS AND INSULIN RESISTANCE

A fifth mechanism leading to insulin resistance is the recruitment of neutrophils and prolongation of their presence in tissues. Inflammation has two stages: initiation and resolution. In the initiation phase, cytokines (such as TNF-α) or nutrient excess and high fat diets upregulate phospholipase A2 which then releases the omega-6 long chain fatty acid, arachidonic acid (AA), from the second carbonyl group of the glycerol backbone.[29, 30] FFAs upregulate cyclooxygenase (COX) which converts AA to pro-inflammatory eicosanoids (prostaglandin [PG] G2, PGE2, PGF2α, thromboxane [Tx] A2 and TxB2) and 5-lipoxygenase (LOX) which converts AA to the pro-inflammatory leukotrienes (LT) A4 and LTB4, all of which then lead to recruitment of neutrophils into tissue to remove necrotic debris and apoptotic cells (see pro-inflammatory pathway in Figure 2).[31–34] These neutrophils cause insulin resistance in two ways. First, they release TNF-α and IL-6, which cause insulin resistance directly and second, they upregulate COX and LOX enzymes, the latter leading to leukotriene production.[35, 36] Adipose tissue from obese mice has higher levels of LTB4 which can upregulate NF-κB which increases cytokine levels, thus leading to insulin resistance. This also upregulates VCAM on endothelial cells which leads to foam

cell formation and atherosclerosis (Figure 2).[37] Elevated FFAs also promote neutrophil survival in obese diabetic mice during the phase at which they normally undergo apoptosis and are cleared from the inflammatory site.[38] Moreover, FFAs also alter tyrosine phosphorylation of the regulatory p85 subunit of PI3K in macrophages, thus causing defective clearance of apoptotic neutrophils and debris via lymphatics, a process called efferocytosis.[34, 39–44] This prolonged neutrophil survival and defective efferocytosis resulting from elevated FFAs leads to persistence of inflammation and prevention of the resolution phase of acute inflammation and thus prolonged exposure to elevated cytokine levels which cause insulin resistance.

During this neutrophil infiltration, production of PGE2 stimulates synthesis of specialized pro-resolving lipid mediators (SPMs) – lipoxins, resolvins of the E and D series, protectins and maresins (see anti-inflammatory pro-resolving pathway in Figure 2).[45–49] These SPMs are involved in the resolution of inflammation by stopping further neutrophil recruitment to the inflamed tissues and stimulating the non-phlogistic infiltration of monocytes which differentiate into macrophages. These macrophages then phagocytize and clear the apoptotic neutrophils and debris via lymphatics (efferocytosis).[40–44] SPMs also inhibit NF-κB which inhibits cytokine release and thus, prevents insulin resistance. This also inhibits VCAM expression on the endothelial cell, thus preventing foam cell formation and atherosclerosis.[44]

Hyperglycemia also affects the initiation and resolution of the inflammatory cascade. Hyperglycemia induces an increase in long-chain acyl-CoA synthetase 1 (ACSL1) in macrophages from type 1 diabetic mice. The increase in ACSL1 leads to increased arachidonyl-CoA esters and thus the production of pro-inflammatory lipid mediators as PGE2 and leukotrienes. Myeloid deletion of ACSL1 decreases atherosclerosis in the setting of type 1 diabetes in mice.[50] Similar to FFAs, hyperglycemia also promotes leukocyte dysfunction by impairing neutrophil chemotaxis and impairing the phagocytosis of both apoptotic cells and bacteria.[51–53] Hence, in a healthy metabolic state, there is apoptosis and clearance of neutrophils, but in metabolic dysregulation in obesity, MetS and type 2 diabetes, there is increased survival and chronic accumulation of neutrophils at inflammatory sites and defective macrophage phagocytosis in animal models of obesity and diabetes, a process leading to prolonged cytokine release from neutrophils and thus insulin resistance.

ROLE OF DYSLIPIDEMIA IN INFLAMMATION AND METABOLIC SYNDROME

TG-Rich VLDL APOC-III and Pro-inflammatory Signaling

The elevated levels of circulating FFAs in visceral adiposity cause the dyslipidemia of MetS - high levels of TG and low levels of HDL-C. These FFAs are taken up by the liver where microsomal triglyceride transfer protein (MTP) transfers TGs from the cytosol to nascent apolipoprotein (apo) B-100 in the endoplasmic reticulum to form very low density lipoprotein (VLDL) apoB-100 particles, the major TG carrier in plasma.[54] These VLDL particles are then secreted from the liver into plasma where lipoprotein lipase (LPL) and glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1

(GPIHBP1) hydrolyze VLDL TGs to FFAs and glycerol, a process forming smaller particles termed “VLDL remnants” or intermediate density lipoprotein (IDL) (Figure 2).[55, 56]

In addition to apoB-100, VLDL particles contain apoE and apoC-III. The C apolipoproteins of VLDL play an important role in its catabolism and also in inflammation. ApoC-II is an activator of LPL which hydrolyzes the core TGs, thereby, releasing FFAs; this process lowers TG levels in plasma. In contrast, ApoC-III is a 79-amino-acid glycoprotein synthesized by the liver and intestines and an inhibitor of LPL.[57] This inhibition leads to an increase in levels of TG.[58] ApoC-III also increases TG levels by stimulating the synthesis of VLDL and preventing its breakdown by inhibiting the binding of VLDL remnants to the LDL-R mediated by apoE. Thus, TG-rich apoC-III VLDL particles circulate longer and are converted to TG-rich remnants which are then lipolyzed by HL to small, dense LDL particles.[59] All of these particles comprise the dyslipidemia of MetS.

ApoC-III plays an important role in inflammation and the development of insulin resistance and atherosclerosis by acting as a pro-inflammatory mediator by activating the Toll-like receptor 2 (TLR2) signaling pathway in mouse atherosclerosis.[60] This leads to upregulation of NF-κB which upregulates cytokine production, thus causing insulin resistance. Upregulation of VCAM1, which binds peripheral monocytes to endothelial cells, also occurs.[18, 19] Several lines of evidence support the role of apoC-III in human atherosclerosis. ApoC-III containing lipoproteins independently predicted coronary artery disease (CAD) in human epidemiological studies.[61] In a study of the Pennsylvania Amish, subjects lacking one allele for apoC-III had average TG levels of 50 mg/dL, a finding probably due to efficient lipolysis of TGs.[62] Electron beam computed tomography revealed decreased coronary calcium, a marker for CAD risk.[62] Genetic variants in apoC-III are also associated with nonalcoholic fatty liver disease and insulin resistance.[39,40] [63, 64] Thus, TG-rich lipoproteins as VLDL apoC-III exhibit pro-inflammatory properties and may initiate early inflammatory events in MetS and atherosclerosis via signaling mechanisms.

Angiopoietin-like protein (ANGPTL) 3, 4 and 8 inhibit lipoprotein lipase and thus lead to increased levels of TG.[65] In humans homozygous for the S17X loss of function mutation in ANGPTL3, LPL activity was increased and free fatty acid levels were decreased probably due to decreased mobilization of free fatty acids from adipose tissue, leading to decreased production of VLDL.[66] Insulin, glucose and homeostatic model assessment of insulin resistance were also significantly lower, findings suggesting that ANGPTL3 plays a role in lipid and glucose metabolism and that deficiency improves insulin sensitivity. One antibody to human ANGPTL3, which inhibits LPL and thus would be predicted to prevent insulin resistance, is being studied in mice.[67]

Role of Insulin in TG-Rich Lipoprotein Metabolism

Several mechanisms exist by which insulin resistance leads to the elevated levels of TG seen in MetS (illustrated in Figure 2). First, increased lysis of TGs in adipocytes leads to increased plasma levels of FFAs which flux to the liver where they are synthesized into VLDL. Second, insulin inhibits transcription of apoC-III and MTP genes and inhibits apoB degradation; therefore, insulin resistance leads to overproduction of apoC-III and apoB and

increased MTP transfer of TG to VLDL apoB, thus leading to increased production of TG-rich VLDL in the liver and secretion into plasma leading to elevated levels of TG in the plasma.[68–72] FFAs also block apoB degradation. Moreover, insulin resistance causes down regulation of LPL expression and thus leads to decreased catabolism of TG-rich VLDL in the plasma, contributing to further increases in plasma TG levels. Finally, insulin resistance is also associated with increases in intrahepatic expression of genes of TG biosynthesis, i.e. sterol regulatory element-binding protein-1C [73], a process causing increased levels of intrahepatic TGs which cause nonalcoholic fatty liver disease. Therefore, insulin resistance increases production of apoB, FFA, apoC-III and VLDL, all of which lead to increased secretion of TG-rich VLDL which is associated with increased pro-inflammatory mechanisms which can cause MetS, atherosclerosis and thrombosis.

Effect of TG-Rich Lipoproteins on Level of HDL-C in Humans

The elevated levels of TG-rich lipoproteins in insulin-resistance also impact the concentration, composition and size of HDL particles. Apo A-I is the major apolipoprotein in HDL and comprises 70% of its protein mass. ApoA-II comprises 15–20% and remaining proteins consist of other apolipoproteins (C, E, D, M and A-IV) and the anti-inflammatory and anti-oxidant enzymes such as paraoxonase 1 and platelet-activating factor acetylhydrolase. Apo-AI plays a major role in removal of cholesterol ester (CE) from peripheral cells, including macrophages in the arterial wall, and directing to the liver for recycling or excretion, a process termed reverse cholesterol transport (RCT).[74] HDL has several cardioprotective properties including prevention of oxidation of apoB particles, reduction of inflammation and functioning in reverse cholesterol transport. The cardioprotective effect of HDL has been largely attributed to its role in reverse cholesterol transport. In this pathway, cholesterol ester transfer protein (CETP) catalyzes the transfer of CE from HDL to apoB-containing lipoproteins (VLDL and LDL) in exchange for TG from the apoB-containing lipoproteins (Figure 2).[4, 75] When TG levels are high as in insulin resistance, this exchange results in CE-rich apoB-containing lipoproteins which are depleted of TGs, and TG-rich small, dense HDL particles which are depleted of CEs. The TG-rich and CE-poor HDL particles are catabolized faster than large, CE-rich HDL, a finding resulting in lower levels of HDL-C in the setting of high TG levels.[76–78] Thus, a greater increase in hepatic VLDL-TG synthesis and secretion that characterizes insulin-resistant/hyperinsulinemic individuals results in a lower concentration of HDL-C.

These small, dense HDL also have reduced antioxidant and anti-inflammatory properties; thus, insulin resistance results in a more pro-inflammatory and dysfunctional HDL particle as follows. High levels of the cytokines, TNF-α and IL-6, enhance expression of serum amyloid A (SAA), a pro-inflammatory and pro-oxidant protein.[79, 80] In systemic inflammation, myeloperoxidase oxidizes apoA-I, thus, reducing the level of apoA-I in HDL and replacing with SAA.[81, 82] ApoA-1 plays an important role in cholesterol efflux and its replacement by SAA leads to impairment of reverse cholesterol transport by HDL and thus a dysfunctional HDL. Moreover, McGillicuddy et al.[83] have shown that the endotoxaemia induced SAA expression on HDL compromised the ability of HDL to efflux cholesterol from macrophages (see Figure 1, Panel A). Oxidation of Apo A-I by myeloperoxidase also leads to loss of HDL-mediated, anti-apoptotic and anti-inflammatory

activities. Studies have shown that the activity of anti-inflammatory and anti-oxidant enzymes of HDL, paraoxonase 1 and platelet-activating factor acetylhydrolase, were reduced during acute inflammation.[84, 85]

Anti-inflammatory Effects of HDL on T Cell Function

In addition to participating in reverse cholesterol transport, HDL and apoA-I can exert anti-inflammatory effects by modulating T cell activation. “Lipid rafts” are regions of the plasma membrane which contain free cholesterol, sphingomyelin, and gangliosides.[86] Cholesterol efflux by HDL can reduce the raft-like regions in the membrane, a process which may affect immune cell responses. T cells can participate in insulin resistance and the atherosclerotic process;[87–90] the T regulatory cell (Treg-CD4+CD25+FoxP3+) is anti-inflammatory and reported to suppress atherosclerosis by inhibiting pro-inflammatory T cells.[91–93] Th2 cells are also anti-inflammatory and reduced in obese adipose tissue.[94, 95] Th2 cell frequency in human adipose tissue and the anti-inflammatory cytokine, IL-10, are inversely associated with systemic insulin resistance.[96] Both Th2 and Treg cells inhibit the pro-inflammatory form of macrophages (M1) and prevent their recruitment into tissues. Similar to macrophages, T and B cells can also take up CE, leading to their dysfunction and the development of an autoimmune phenotype.[97, 98] Higher levels of plasma membrane cholesterol enhance the inflammatory T helper response, thus increasing inflammation mediated via T cells. In contrast, reduction of plasma membrane free cholesterol or sphingomyelin via HDL and reverse cholesterol transport has been correlated with the attenuation of inflammatory responses.[99–101] Therefore, HDL and apoA-I can suppress inflammation by modifying the lipid-raft environment by promoting free cholesterol efflux from tissues and inflammatory cells, such as T cells and macrophages, resulting in an increased fraction of Treg cells that attenuate inflammation.

HDL carries the phospholipid, sphingosine-1-phosphate (S1P), a lipid mediator with anti-inflammatory properties when present at low concentration, thus providing another cardioprotective effect of HDL.[102] S1P is thought to promote anti-inflammatory properties of HDL which include a decrease in VCAM1, TNF-α and IL-1. High levels of S1P promote the development of inflammatory T helper 1 cells while suppressing differentiation of Treg cells.

Finally, HDL has an effect on blood pressure by stimulating NO production by upregulating endothelial NO synthase (eNOS); this causes vasodilation and lowers blood pressure.[103–105]

HDL and Glucose Regulation

Emerging evidence suggests that HDL-C may also contribute to the regulation of glucose metabolism. Recent studies have shown that HDL increases non-insulin dependent glucose uptake in endothelial cells, adipose tissue and primary cultured myocytes from patients with type 2 diabetes mellitus by activating AMPK, an insulin independent mediator of glucose uptake and fat oxidation and a target for metformin.[106–110] This relation could account for the rapid reduction in plasma glucose at 30 minutes and improved insulin secretion after 2.5 hours from an intravenous infusion of reconstituted HDL in patients with type 2

diabetes.[108] Recently, Cochran et al.[111] demonstrated a potential mechanism for this beneficial effect of HDL on glucose levels. Using an Ins-1E rat insulinoma cell line and pancreatic islets, they showed that the interaction of ApoA-I with ATP-binding cassette transporter A1 (ABCA1) increases insulin synthesis and secretion by increased transcription of key insulin response and beta cell survival genes by activating a transmembrane adenylyl cyclase via the Gαs subunit of a heterotrimeric G-protein-cAMP-protein kinase A-FoxO1–dependent mechanism. Therefore, this suggests that dysfunctional HDL resulting from insulin resistance leads to less activation of AMPK which in turn prevents glucose uptake by tissues, thus leading to hyperglycemia and uncontrolled inflammation in metabolic tissues.

Evidence has shown that cholesterol accumulation in pancreatic beta cells and impaired excretion via reverse cholesterol transport impairs insulin secretion.[112–115] In dyslipidemic mouse models, the use of either statins or methyl-β-cyclodextrin reduced the cholesterol content in beta cells and thus increased insulin secretion.[112, 116] This suggests that the HDL-mediated cholesterol efflux property might improve beta cell function and improve insulin secretion in the setting of dyslipidemia and diabetes. In support of this, patients with loss-of-function mutations in the ABCA1 transporter gene have low levels of HDL-C and impaired insulin secretion.[117, 118]

THERAPEUTIC MODALITIES FOR METABOLIC SYNDROME VISCERAL ADIPOSITY

Lifestyle Intervention

Visceral adiposity and its resulting insulin resistance are the underlying pathophysiology of MetS with an imbalance between nutrient excess and caloric expenditure being the main contributor. However, rather than being a purely pathological condition, insulin resistance may have evolved to protect the cell from apoptosis in states of nutrient excess.[119] Excessive uptake of glucose and lipids results in intracellular accumulation of glycogen, lipids and other metabolites that can induce apoptosis and cellular death. In response to nutrient excess, all the pathways previously described in this review are activated and lead to insulin resistance which inhibits nutrient uptake, thus, decreasing apoptosis in the heart, liver and skeletal muscle. The net effect of these adaptive responses is enhanced cell survival. It follows then that the most important defense against insulin resistance is avoidance of caloric excess and maintenance of normal weight. Consequently, the current guidelines from the ACC/AHA recommend lifestyle therapy consisting of dietary recommendations, exercise and weight loss as the first line treatment for MetS.[120] Evidence from The Diabetes Prevention Program (DPP) supports this recommendation. The DPP was a randomized trial of 3,234 subjects with prediabetes who were randomized to one of three groups: a lifestyle intervention with exercise, diet and weight loss, metformin 850 twice daily or placebo.[121] Those in the lifestyle group walked on average 6 miles per week and lost 4 kg at the end of 4 year follow-up. Compared to placebo, the new onset of type 2 diabetes was reduced 58% in the lifestyle group compared to 31% in the metformin group. This study demonstrates that moderate exercise and even a small amount of weight loss have a significant benefit and prevent progression to type 2 diabetes.

As outlined earlier in this review, visceral adiposity leads to inflammation and insulin resistance; however, increased intake of saturated fat and glucose in the absence of obesity can be pro-inflammatory and induce oxidative stress.[122] A 75-g glucose challenge increased expression of $p47^{phox}$, which is involved in ROS generation, and increased leukocyte superoxide production by 140% and also increased the pro-inflammatory transcription factors, AP-1 (thereby increasing MMP 2 and MMP 9) and early growth response protein 1 (increasing tissue factor (TF) and PAI-1), leading to increased oxidative stress.[123, 124] Cream (saturated fat) intake also increased oxidative stress to a similar amount as with the glucose load.[125] A 900 kcal meal high in both glucose and fat from a fast food restaurant also induced NF-κB, reduced IκB α, increased IKKα and IKKβ and increased superoxide radical generation by mononuclear cells.[126] In contrast, a 900-kcal AHA step 2 diet meal rich in fruit and fiber did not increase oxidative stress or inflammation.[127] Intake of a low calorie diet (1000 kcal/d for 4 weeks) reduced both oxidative stress and inflammatory mediators in obese subjects.[128] Moreover, a 48-hour fast in non-obese subjects reduced the expression of $p47^{phox}$ and lowered ROS more than 50%.[129]

Consumption of the Mediterranean diet has been associated with a lower prevalence of MetS.[130, 131] It consists of monounsaturated fatty acids from olives and olive oil, whole grain cereals, fruits, vegetables, low-fat dairy, fish, nuts and legumes and has been associated with decreased all-cause and cardiovascular mortality. In the Lyon Diet Heart Study, subjects with a first MI randomized to a Mediterranean diet (< 35% total fat, < 10% saturated, < 4% linoleic acid, > 0.6% alpha-linolenic acid) had a 72% reduction in cardiac death and nonfatal MI (RR: 0.28;95% CI, 0.15–0.53) with a 56% reduction in total mortality after 4-years of follow-up (RR: 0.44; 95% CI, 0.21–0.94, p=0.03).[132] These reductions are greater than those with statin therapy. In the primary prevention Prevencion-con-Dieta-Mediterranea (PREDIMED) trial, those randomized to a Mediterranean diet with either extra-virgin olive oil or nuts had multivariable-adjusted hazard ratios of 0.70 (95% CI, 0.54–0.92) and 0.72 (95% CI, 0.54–0.96), respectively, for the primary endpoint of myocardial infarction, stroke or death from cardiovascular causes. These reductions are comparable to those of statin drugs. In a meta-analysis of 17 intervention trials with 2,300 subjects, a Mediterranean diet was associated with a significant increase in flow-mediated dilation of the brachial artery and higher levels of adiponectin and significant decreases in CRP, IL-6 and ICAM.[133] Additional potential mechanisms for the beneficial effects include a decrease in ROS activation of NF-kB, MMP and COX 2 from the polyphenols of the Mediterranean diet.[134] Therefore, a Mediterranean diet may improve cardiovascular outcomes and mortality by decreasing inflammation and improving endothelial function. In a recent review of dietary patterns in prospective and randomized controlled trials of MetS, both the Mediterranean diet and Dietary Approaches to Stop Hypertension (DASH) diet (characterized by high intake of fruits, vegetables, whole grains and low-fat dairy) were found to improve several components of MetS.[135] Two of the studies - one with the Mediterranean Diet and one with the DASH diet - were found to improve all five components of MetS.[136, 137]

Taken together, the above studies suggest that macronutrient intake of high fat and/or high glucose foods are pro-inflammatory conditions and lead to insulin resistance (Figure 2) and

that Mediterranean and DASH-type diets high in fruit, vegetables, fiber, low-fat dairy and fish have the opposite effect. Therefore, high fruit, vegetable and fiber content in the absence of weight loss can reduce oxidative stress and inflammation and therefore, improve insulin sensitivity.

Exercise

Many clinical studies have examined the effect of exercise on insulin resistance and inflammation.[138] Exercise of adequate intensity has been associated with protection against TNF-α induced insulin resistance and an increase in epinephrine which also blunts the TNF-α response. Muscle-derived IL-6 is increased with exercise; the increase correlates with muscle mass and exercise intensity. IL-6 has both pro- and anti-inflammatory properties. Elevation of IL-6 from muscle improves insulin secretion and insulin signaling. Exercise also increases adiponectin levels mainly in overweight individuals. Higher levels of adiponectin decrease inflammation, decrease hepatic glucose production and increase glucose uptake and fatty acid oxidation in skeletal muscle and thus improve insulin sensitivity.

Exercise also has a beneficial effect on fatty acid metabolism and lipolytic activity via upregulation of peroxisome proliferator-activated receptor (PPAR)-δ.[139] PPARs are a constellation of three distinct nuclear receptors: PPAR-α, PPAR-δ, PPAR-γ. PPAR-δ plays an important role in lipid metabolism, making it an attractive therapeutic target for MetS.[140] In animal models, administration of a PPAR-δ agonist led to a 79% increase in HDL-C.[141] This increase is mediated by the enhancement of ABCA1 activity.[142] As a result, PPAR-δ improves cholesterol efflux. In humans, PPAR-δ activation also lowers LDL-C and TG levels.[143] It attenuates weight gain and TG accumulation in the liver and adipose tissue through increasing lipid catabolism.[140, 144] The activation of PPAR-δ has an anti-inflammatory effect by enhancing the expression of various anti-oxidant enzymes. PPAR-δ agonists suppress pro-inflammatory cytokines such as TNF-α in macrophages.[145] There are no current pharmacologic agonists for PPAR-δ; therefore, achieving its beneficial effects through upregulation via exercise is important. Scavenger receptor B1 (SRB1) and ABCA1 mechanisms are also involved and could be responsible for the increase in HDL-C and reduction in TG with physical activity.[146]

DYSLIPIDEMIA OF METABOLIC SYNDROME: HIGH TG and LOW HDL-C

Lifestyle recommendations remain first line therapy for high TG and low levels of HDL-C.[120] Weight loss itself will improve insulin sensitivity by lowering levels of TGs. TG levels can be lowered 20–30% with weight reduction.[147] Physical activity can also lower TG levels via activation of LPL which hydrolyzes VLDL and thus lowers TG levels. In contrast, inactivity leads to loss of skeletal muscle LPL, thus, shifting from fatty acid to glucose oxidation and leading to a redistribution of TG to heart and liver and thus increasing TG in these tissues and leading to insulin resistance.

Omega-3 Fatty Acids

When TGs are 200–499, omega-3 fatty acid (omega-3 FA) intake through increasing intake of fatty fish or fish oil capsules is recommended.[148, 149] Omega-3 FAs are long chain fatty acids which include eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). EPA and DHA are derived from linolenic acid. Humans lack the enzyme for this conversion; therefore, EPA and DHA are essential fatty acids and must be derived from dietary sources.[150] Three grams per day of EPA and DHA can lower TG level by 50% or more by reducing VLDL production.[151–154] In a mouse model, through the activation of PPAR-α and inhibition of the sterol regulatory element binding protein-1, omega-3 FAs reduced the expression of proteins involved in the synthesis of VLDL, thus reducing its release into plasma and lowering TG levels.[155, 156]

Omega-3 FAs also confer favorable effects through reducing inflammation. Omega-3 FAs act by reducing the reactive oxygen species (ROS), especially H2O2, thus leading to a decrease in inhibitor IκB and reduction in the activation of NF-κB. This in turn leads to a decrease in the expression of pro-inflammatory cytokines and adhesion molecules.[157, 158] In a mouse model, adding omega-3 FAs to a high fat diet led to a reduction in macrophage number and lowered the levels of the adhesion molecules ICAM and VCAM.[159] Furthermore, EPA and DHA supplementation for 45 days reduced lipid peroxidation and increased adiponectin levels.[160] Similarly, the favorable effects of omega-3 FAs on inflammation have been demonstrated in human studies. The supplementation of omega-3 FAs leads to reduced production of TNF-α and IL-8 from human monocytes.[161] Omega-3 FAs also inhibit the production of pro-inflammatory cytokines such as IL-1 β and TNF-α.[162, 163] Moreover, in hypertriglyceridemic men, the supplementation of DHA for 91 days reduced neutrophil count as well as CRP and IL-6 levels.[164]

In mice, the supplementation of omega-3 FAs increases adiponectin production from white adipose tissue which improves insulin sensitivity in the skeletal muscle by increasing AMPK.[165] Omega-3 FAs also improve insulin sensitivity by binding to the G-protein coupled receptor (GPR) 120 located on macrophages. This in turn activates β-arrestin2 which inhibits the Tak1 signaling pathway, inhibiting transcription by NF-κB and thus blocking pro-inflammatory pathways and preserving insulin sensitivity.[166, 167] Moreover, omega-3 FAs improve insulin sensitivity by inhibiting Tak1 and JNK/AP-1, thus leading to normal tyrosine phosphorylation of IRS-1.[168, 169] A loss-of-function polymorphism in the human GPR120 gene is associated with obesity, a finding suggesting a role for this anti-inflammatory lipid pathway in man.[166]

As shown in Figure 2, EPA and DHA are the precursors of the E-series resolvins (RvE) and D series resolvins (RvD), respectively. The resolvins inhibit the upregulation of NF-κB, thus preventing cytokine release and insulin resistance. Inhibition of NF-κB also inhibits expression of VCAM and infiltration of monocytes into the subendothelial space. Based on studies using a mouse model, a higher ratio of omega-6 to omega-3 polyunsaturated fatty acids was thought to be a key factor in defective phagocytosis induced by FFAs.[39] In support of this, addition of EPA and DHA restored efferocytosis that was impaired by incubation of macrophages with FFAs.[39, 170] Resolvins promote the anti-inflammatory form of macrophages (M2) which promote efferocytosis by clearing apoptotic cells via

efflux to the lymphatics in adipose tissue in mice.[171] Resolvin (Rv) D1 has been shown to reverse defects in diabetic macrophage phagocytosis and delayed resolution in an acute peritonitis model in obese diabetic mice.[172] Resolvins also promote reverse cholesterol transport.[173] Therefore, omega-3 FAs may be a dietary source, which through their conversion to resolvins, can be used to inhibit the initiation of inflammatory signaling, promote the resolution of inflammation and also promote reverse cholesterol transport.

The benefits of omega-3 FA supplementation also include improvements in endothelial function and blood pressure.[86, 174, 175] In humans, the administration of omega-3 FAs was associated with an increase in flow-mediated vasodilation of the brachial artery.[175] In a meta-analysis, > 2 g/day of EPA and DHA lowered both systolic and diastolic blood pressure.[176] Potential mechanisms have been examined in vitro. In rat aorta, DHA was shown to decrease intracellular smooth muscle calcium resulting in vasorelaxation.[177] EPA increased the production of NO through the reduction of ROS.[178] Furthermore, omega-3 FAs enhanced the expression of eNOS which caused more production of nitric oxide (NO) from endothelial cells.[179] The plasma membrane of endothelial cells has caveolae which are important in the cellular signaling pathways of pro-inflammatory cytokines such as TNF-α, as well as the NO-cGMP and NF-κB induced COX2. Through modifying the composition of the caveolae in the plasma membrane, omega-3 FAs suppressed the pro-inflammatory cytokine pathways and promoted NO production in bovine endothelial cells.[180] In human aortic endothelial cells, the administration of DHA reduced the expression of ICAM and VCAM after exposure to pro-inflammatory cytokines. Furthermore, it reduced the production of IL-6 and IL-8 from endothelial cells.[181, 182]

Emerging evidence from clinical trials in humans has shed light on the effect of omega-3 FA on inflammatory pathways, lipid levels and insulin sensitivity. In a 4 month randomized, placebo-controlled, double-blind trial of 138 sedentary and overweight healthy adults, low and high dose omega-3 FA supplementation (1.25 g and 2.5 g/d) reduced the production of serum IL-6 by 10% and 12%, respectively, compared to a 36% increase in the placebo group.[183] Moreover, low and high omega-3 FA doses reduced TNF-α by 0.2 and 2.3%, respectively, compared to a 12% increase in the placebo (a combination of palm, olive, soy, canola, and coco butter oils that approximated the saturated:monounsaturated:polyunsaturated ratio consumed by US adults).[183] In a 28-week, randomized, double-blind trial of 111 healthy men and women aged 66–80 years, randomization to 1.8 g EPA+DHA per day (n=36) significantly reduced the peripheral blood mononuclear cells' expression of genes involved in inflammatory and atherogenic pathways compared to 0.4 g EPA+DHA per day (n=37) or 4.0 g high–oleic acid sunflower oil (HOSF) per day (n=38).[184] These pathways included NF-κB signaling, eicosanoid biosynthesis, scavenger receptor activity, adipogenesis and hypoxia signaling.[184] In an 8-week, randomized, single-blind, parallel trial of 59 subjects with early-stage type 2 diabetes mellitus or MetS, those randomized to 6.02 grams per day of omega-3 FA (3.58 g EPA + 2.44 g DHA) had significantly increased HDL-C and insulin levels and significantly decreased HbA1c and TG levels at 8 weeks compared to baseline.[185]

Studies in mice support a benefit of omega-3 FAs, the precursors of SPMs, in alleviating atherosclerosis. In mice, dietary omega-3 FA supplementation lessened atherosclerosis and

high doses of EPA actually caused regression of lesions.[186–189] When levels of the omega–3/omega–6 ratio were increased in mice through genetic means, less atherosclerosis occurred.[189] Consumption of EPA and DHA in obese atherosclerotic mice led to increased efferocytosis.[39] A potential mechanism for the beneficial effect is that omega-3 FAs lead to the production of SPMs which, due to their anti-inflammatory and pro-resolving properties, lead to resolution of inflammation in the arterial wall and thus preservation of insulin sensitivity and less progression of atherosclerotic plaque in the coronary arteries.

Observational studies in humans have shown a relation between omega-3 FA levels and cardiovascular outcomes. In the Cardiovascular Health Study, a prospective cohort study of 2,692 US adults free of CAD at baseline, higher plasma levels of omega-3 FAs were associated with a 27% reduction in total mortality (HR=0.73; 95% CI, 0.61–0.86, p-trend ≤ 0.008), a finding largely attributable to fewer cardiovascular deaths with a reduction in arrhythmic cardiac deaths (HR=0.52 95% CI, 0.31–0.86, p-trend = 0.008).[190] High plasma levels of omega-3-FAs have been associated with slower progression of coronary artery atherosclerosis as assessed by intravascular ultrasound.[191] Moreover, a meta-analysis of patients with CAD who took greater than 1 g of EPA/DHA daily for more than one year showed significantly fewer major cardiovascular events.[192] In the observational Multi-Ethnic Study of Atherosclerosis (MESA) trial, higher plasma levels of EPA and DHA were associated with significantly fewer cardiovascular events compared to those with lower levels of EPA and DHA and higher levels of omega-6 fatty acids.[193]

Randomized trials have demonstrated a beneficial effect of omega-3 FA administration in reducing morbidity and mortality. The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI) trial involved the randomization of 11,324 patients with a recent myocardial infarction (MI) to one of four arms: 1 g/day of Lovaza, a synthetic compound containing both EPA and DHA, vitamin E, both, or neither.[194] After a follow up of 3.5 years, those on Lovaza alone had a 15% reduction in total death, non-fatal MI and non-fatal stroke compared to controls (p=0.023) due to a 45% reduction in sudden death occurring within the first 3 months. There was a 20% reduction in CVD death, nonfatal MI and nonfatal stroke in the Lovaza group (p=0.008). Another trial, the Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS), assessed the long term addition of EPA to statin therapy in 18,645 patients with total cholesterol ≥ 252 mg/dL. After 4.5 years, the addition of EPA was associated with a reduction in the primary endpoint which included sudden cardiac death, fatal or non-fatal MI, unstable angina, percutaneous coronary intervention or coronary artery bypass grafting (2.8% vs 3.5%; p=0.01).[195]

Peroxisome proliferator-activated receptor family

When TGs are greater than 400–500 mg/dL, PPAR-α agonists are recommended.[148, 149] A major regulator of fatty acid homeostasis, PPAR-α acts as a sensor of circulating TG in the liver. Higher levels of circulating TG result in transcriptional activation of PPAR-α which prevents lipid accumulation in the liver by leading to expression of genes involved in β- and ω-fatty acid oxidation.[196] PPAR-α activation also affects genes leading to decreased production of VLDL and increased production of ApoA-I and ApoA-II, both of which are associated with higher levels of HDL-C.[197]

The activation of PPAR-α has an anti-inflammatory effect in endothelial cells of blood vessels through suppressing MCP-1 and the adhesion molecules, ICAM and VCAM.[198] Furthermore, PPAR-α activation inhibits NF-κB mediated inflammation and reduces the secretion of endothelin-1, a potent vasoconstrictor.[199] The activation of PPAR-α is also associated with reducing the expression of TNF-α and INF-γ in T lymphocytes.[200] In addition to its effects on TG, PPAR-α activation enhances the expression of the ABCA1 transporter and SRB1, thus contributing to the stimulation of reverse cholesterol transport.[201]

The effect of PPAR-α activators on CVD events has been examined. In the Helsinki Heart Study, men with MetS but no CVD who were randomized to gemfibrozil 600 mg twice daily had an absolute risk reduction of 27.2% (71% relative risk reduction) in nonfatal MI and CAD death ($p<0.0005$).[202] Among the different fibrates, fenofibrate is the most widely prescribed. Fenofibrate is shown to decrease TG by 41–53%, decrease LDL-C by 30–65% and increase HDL-C by 20–45%. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial, of 8,183 patients with MetS, those randomized to fenofibrate 200 mg daily had an 11% relative risk reduction in total CVD events ($p=0.052$).[203] Of the 314 with MetS and TG > 204 mg/dL and HDL-C < 40 mg/dL in men and < 50 mg/dL in women, the risk of developing CVD in 5 years was 17.8% in those receiving placebo. Fenofibrate provided the greatest benefit in this group in whom a 27% relative risk reduction in total CVD events occurred (HR=0.73; $p=0.005$) (number needed to treat=23).[203] The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial randomized 5,518 type 2 diabetic patients to either simvastatin alone or in combination with fenofibrate. The addition of fenofibrate did not significantly reduce the primary endpoint, fatal CVD, non-fatal MI or non-fatal stroke (absolute risk reduction=0.2, $p=0.32$). However, in a subset of patients with TG > 204 mg/dl and HDL ≤ 34 mg/dl, the reduction in the primary endpoint was of borderline statistical significance (absolute risk reduction=4.9%) ($p=0.057$) [204].

ApoC-III mRNA Inhibitor

A promising agent in ongoing human clinical trials is an inhibitor of apoC-III messenger RNA (ISIS 304801). Administration to patients with familial hypercholesterolemia reduced ApoC-III by 71–90% after 13 weeks and TG by 56–86%.[205]. In preclinical rodent models, inhibition of ApoC-III with an antisense oligonucleotide was associated with a reduction in TG levels. Administration of an ApoC III antisense drug to healthy human subjects in phase I randomized controlled trials led to a dose dependent reduction in TG with no increase in hepatic steatosis or major safety issues.[206] The human studies cited earlier showed an association with lower coronary artery calcium and CV events; therefore, this may be a promising modality to lower TG levels and CV events. It would be predicted that apoC-III should also have an anti-inflammatory effect.

In terms of HDL, it should be noted that large randomized trials of niacin and the CETP inhibitor, Torcetrapib, to raise HDL-C have not shown a benefit and in fact, adverse side effects have been noted.[207–209] As noted earlier, the function of HDL appears more important than its level; however, we have no current therapy to improve the function of HDL.

HYPERTENSION

Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB)

The renin angiotensin aldosterone system (RAAS) is linked to the development of hypertension, insulin resistance, and weight gain, all of which are components of MetS. Therefore, it is not surprising that the inhibition of this pathway has a beneficial effect on patients with MetS.[210] There is a significant intracellular cross talk between the pathways involved in angiotensin and insulin signaling. Angiotensin II stimulation enhances the expression of iNOS and COX-2.[211, 212] It also results in the production of ROS and activation of redox sensitive pathways such as NF-κB, which leads to the production of pro-inflammatory cytokines (Figure 1, Panel B).[213, 214] Through these mechanisms, IL-6, IL-8, and TNF-α and adhesion molecules (VCAM and ICAM) are up-regulated.[213] These pro-inflammatory cytokines enhance the abnormal serine phosphorylation of IRS-1, thus causing insulin resistance.[215, 216] Moreover, angiotensin II activates tyrosine-protein kinase CSK (c-Src) and results in tyrosine phosphorylation of phosphoinositide-dependent kinase-1 (PDK-1), both of which reduce IRS-1 levels.[216] The abnormal phosphorylation of IRS-1 and the subsequent reduction in Akt activity lead to decreased expression of GLUT-4 on the plasma membrane and insulin resistance.[216, 217]

Insulin resistance can cause hypertension through several mechanisms. First, the generation of ROS increases levels of endothelin 1, a potent vasoconstrictor (Figure 1, Panel A). Second, increased oxidative stress leads to reduced bioavailability of NO, a natural, endogenous vasodilator, which in turn increases vascular tone and causes vasoconstriction and elevated blood pressure. Third, increased oxidative stress also increases levels of asymmetric dimethylarginine (ADMA), an inhibitor of NO. Fourth, hyperinsulinemia alone could activate RAAS resulting in sodium retention and subsequent blood pressure elevation leading to a vicious cycle.[218] Additionally, RAAS can play an important role in insulin resistance through its effect on adipocytes as well. The stimulation of angiotensin II inhibits the formation of insulin sensitive adipocytes from periadipocytes and causes more fat storage to occur in muscles instead which makes them insulin resistant as well.[219] Blockade of the RAAS system exerts its beneficial effect by allowing periadipocytes to normally differentiate into insulin sensitive adipocytes.[220]

Initial clinical studies have shown that ACE-I can improve insulin sensitivity.[221] In fact, ACE-I were reported to induce hypoglycemia in diabetics in some clinical trials.[222, 223] The beneficial effects of ACE-I and ARB in patients with MetS are derived from their ability to inhibit the conversion of angiotensin I to the more potent angiotensin II and the blockage of the angiotensin I receptor, respectively. This results in inhibition of the formation of ROS and inflammatory cytokines (Figure 3). Ohshima et al.[224] showed that the administration of azilsartan, an ACE-I, inhibits the formation of MCP-1, TNF-α, and IL-1β in a mouse model. ACE-I also has an anti-inflammatory effect through modulating T cells. ACE-I inhibits Th17 and Th1-mediated autoimmunity and promotes the production of T regulatory cells which favorably modulate inflammation.[225] Activation of TLR4 cellular signaling pathways by angiotensin-II leads to a synergistic inflammatory reaction.[226] Both in vitro and in vivo, candesartan, an ARB, has an anti-inflammatory effect by reducing TLR2, TLR4

and NF-κB activation in monocytes.[227] Finally, higher RAAS activity is associated with higher weights.[228] This increase in activity is reversed with weight loss.[229] In rodent models, the administration of ACE-I or ARB prevents weight gain as well.[230, 231]

Aldosterone receptor antagonists

Patients with MetS have higher levels of aldosterone which has a pro-inflammatory effect on the vasculature and adipose tissue (Figure 1, Panel A).[232, 233] In obese rodent models, aldosterone enhances the expression of inflammatory cytokines in preadipocytes and reduces the levels of adiponectin and PPAR-γ.[234] Moreover, the expression of mineralocorticoid receptors in preadipocytes is important for their differentiation into adipocytes.[233] Higher levels of aldosterone could contribute to inflammation through enhancing the expression of adhesion molecules such as ICAM.[235]

Mineralocorticoids promote a state of insulin resistance. The insulin receptor gene has a glucocorticoid response element located in its promoter region which interacts with the activated mineralocorticoid receptor. Such interaction leads to the down regulation of insulin receptor gene expression.[236] Furthermore, glucocorticoid receptor activation results in oxidative damage and suppression of adiponectin and PPAR-γ, all of which are related to obesity and lead to insulin resistance. These effects are reversed with mineralocorticoid receptor blockade using spironolactone.[234, 237]

Studies in obese mice demonstrate the beneficial effects of eplerenone, another mineralocorticoid receptor antagonist. Eplerenone resulted in reduction of inflammation and expression of pro-inflammatory cytokines including the production of TNF-α, MCP-1 and PAI type1 in retroperitoneal adipose tissue in obese mice.[234, 237] Aldosterone worsened insulin sensitivity through alteration of intra-cellular IRS-1. Furthermore, in the vasculature, aldosterone increased the degradation of IRS-1 in the proteasome through the production of ROS and c-Src.[238] In mouse models of obesity and insulin resistance, the blockade of mineralocorticoid receptors led to a decrease in TG levels and a reduction in hepatic steatosis.[234, 237, 239] Similarly in humans, eplerenone was found to reduce TG levels in hypertensive patients with MetS by almost 80 mg/dl.[240] In subjects with NYHA class II heart failure and an EF ≤ 35%. Eplerenone was also found to reduce death from CVD causes or hospitalization for heart failure by 37% (HR, 0.63; 95% CI, 0.54 to 0.74; $p<0.001$).[241]

ELEVATED CARDIOVASCULAR RISK IN METABOLIC SYNDROME

Statins

Statins are recommended in patients with MetS when LDL-C ≥ 190 or 10-year risk of ≥ 7.5% in primary prevention and for all subjects with established CVD. Statins are potent cholesterol lowering drugs with an established benefit in reducing cardiovascular morbidity and mortality and total mortality.[242] Their cholesterol lowering effect is mediated through the inhibition of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, the rate limiting step in the mevalonate pathway and cholesterol synthesis. It is also well known that statins have a pleiotropic effect that is independent of their lipid lowering action. In the mevalonate pathway, the production of isoprenoid intermediates modifies several proteins

including small guanosine triphosphate binding proteins. These include Ras, Rho and Rac proteins which upregulate cytokines, adhesion molecules and ROS, therefore, resulting in a pro-inflammatory response and oxidative stress.

Statins inhibit the formation of isoprenoid intermediates resulting in an anti-inflammatory effect mediated by the suppression of pro-inflammatory genes and shifting the redox state to anti-oxidant production rather than ROS formation.[243] This shift in oxidative state is important since it down regulates the redox sensitive NF-κB and AP-1 pathways, both of which are major regulators of genes involved in inflammation. The administration of statins is associated with a reduction in pro-inflammatory cytokines including IL-1, IL-6, IL-8, TNF-α and MCP-1.[243] Furthermore, statins block T cells from differentiating into the pro-inflammatory Th17 phenotype and promote anti-inflammatory T regulatory cell formation. In addition, statins reduce the activation of TLR2 and TLR4.[244–246]

Statins also have a favorable effect on endothelial cells. Through reducing ROS and inducing eNOS, statins increase NO bioavailability, thus causing vasodilation and lowering of blood pressure. Furthermore, statins are shown to reduce the production of ADMA, an L-arginine like molecule which interferes with NO production. In vitro, statins reduce endothelial cell apoptosis and reduce the levels of endothelin-1 and pro-endothelin mRNA by inhibition of Rho protein activation.[247]

Through their anti-inflammatory effect, statins may help reverse the hypercoagulability associated with MetS. The production of pro-inflammatory cytokines in MetS leads to the inhibition of the fibrinolytic/antithrombotic pathways.[248] Through inhibition of IL-1 and TNF-α production and improvement of endothelial function, statins help reverse the prothrombotic state.

Risk of Diabetes with Statin Drugs

In the West of Scotland Coronary Prevention Study, pravastatin treatment decreased the risk of type 2 diabetes by 30%;[249] however, in a meta-analysis of 13 major statin trials, statin therapy was associated with a 9% increase in new onset diabetes over a 4 year period compared to placebo.[250] This increase in risk was related to the dose of both simvastatin and atorvastatin.[251] One proposed mechanism is impairment of adipocyte maturation, therefore, reducing the amount of adiponectin produced..[252–254] Pravastatin increases the level of adiponectin from adipocytes through upregulating the expression of adiponectin mRNA as well as increasing insulin sensitivity, possibly accounting for its reduction in diabetes risk.[249, 255] A second potential mechanism is a reduction in levels of CoQ10 by inhibition of its precursor, mevalonate. CoQ10 is an energy transporter in the mitochondria and also has an antioxidant effect. CoQ10 deficiency is observed in diabetics.[256] This deficiency can also lead to mitochondrial dysfunction in muscle cells and beta cells leading to insulin resistance in muscles and a reduction in insulin production from beta cells, respectively.[257–259]

CONCLUDING REMARKS

Insulin resistance related to central obesity and/or intake of high saturated fat and glucose diets appears to underlie the pathophysiology of all components of metabolic syndrome - central adiposity, hypertension, high TG, low HDL-C and hyperglycemia. Chronic inflammation leads to insulin resistance and is a common mechanism linking all these components. If untreated, MetS can progress to type 2 diabetes which increases risk for cardiovascular disease; therefore, early recognition of MetS and treatment is critical to prevent these adverse sequelae. Lifestyle recommendations including exercise, weight loss and diets high in fruits, vegetables, fiber, whole grains and low-fat dairy and low in saturated fat and glucose are first line therapy. The Mediterranean and DASH diets are especially beneficial and have been shown to prevent development of MetS. Moreover, the Mediterranean diet has been associated with reductions in total and CV mortality. Omega-3 fatty acids and PPAR-a agonists reduce elevated TG levels. Omega-3 fatty acids have also shown a significant reduction in CV events. ACE inhibitors and ARBs reduce blood pressure and statin drugs lower elevated cardiovascular risk. All of these drugs target inflammation in various ways. Ongoing studies are uncovering inflammatory pathways which can be a target for novel treatments and preventive strategies to combat metabolic tissue inflammation and insulin resistance. Clearly, preventing obesity and insulin resistance is most important in terms of reducing overall inflammation and preventing the adverse sequelae from MetS. Further studies are required to develop additional therapeutic approaches aimed at preventing and treating adipose tissue-induced inflammation and insulin resistance in metabolic syndrome.

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Abbreviations

AA	arachidonic acid
ABCA1	ATP-binding cassette transporter A1
ACE-I	angiotensin converting enzyme inhibitor
ACSL1	acyl-CoA synthase 1
ADMA	asymmetric dimethylarginine
Akt	protein kinase B
Aldo	aldosterone
AMPK	AMP-activated protein kinase
ANGPTL	Angiopoietin-like protein
Ang	angiotensin
AngII	angiotensin II

AP-1	activator protein 1
Apo	apolipoprotein
ARB	angiotensin receptor blocker
Aspirin-COX-2	aspirin acetylated cyclooxygenase 2
AT-LX	aspirin triggered lipoxins
AT-PD1	aspirin triggered protectins
AT-RvD	aspirin triggered resolvins
C	cholesterol
CAD	coronary artery disease
CE	cholesterol ester
CETP	cholesterol ester transfer protein
CoQ10	Coenzyme Q10
COX	cyclooxygenase
COX-2	cyclooxygenase-2
CRP	c-reactive protein
c-Src	tyrosine protein kinase CSK
CVD	cardiovascular disease
DAG	diacylglycerides
DHA	docosahexaenoic acid
EF	ejection fraction
eNOS	endothelial nitric oxide synthase
EPA	eicosapentaenoic acid
ET	endothelin
FetA	Fetuin A
FFA	free fatty acids
FoxO1	forkhead box protein O1
Glu	glucose
GLUT4	glucose transporter type 4
GPR	G-protein coupled receptor

GRK2	G-protein-coupled receptor kinase 2
HDL	high density lipoprotein
HMG-CoA	hydroxymethylglutaryl-coenzyme A
ICAM-1	intracellular adhesion molecule-1
IDL	intermediate density lipoprotein
IKK	inhibitor of nuclear factor kappa-B kinase
IL	interleukin
ILR	interleukin receptor
iNOS	inducible nitric oxide synthase
LT	leukotriene
IRS	insulin receptor substrate
IκB	inhibitor of nuclear factor kappa-B
JAK	janus kinase
JNK	c-Jun N-terminal kinase
LOX	lipoxygenase
LPL	lipoprotein lipase
LX	lipoxin
MAPK	Mitogen-activated protein kinases
MCP-1	monocyte chemoattractant protein-1
MetS	metabolic syndrome
MI	myocardial infarction
MMP	matrix metalloproteinase
MTP	microsomal triglyceride transfer protein
NF-κB	nuclear factor kappa B
NLR	nod-like receptor
NO	nitric oxide
Omega-3 FAs	omega-3 fatty acids
oxLDL	oxidized low density lipoprotein
PAI-1	plasminogen activator inhibitor-1

PD1	protectins
PG	prostaglandins
PI3K	phosphatidylinositol 3-kinase
PKC	protein kinase C
PPAR	peroxisome proliferator-activated receptor
RAAS	renin angiotensin aldosterone system
RCT	reverse cholesterol transport
ROS	reactive oxygen species
ROS	reactive oxygen species
RvD	DHA derived resolvins
RvE	EPA derived resolvins
S1P	sphingosine 1-phosphate
SAA	serum amyloid A
SFA	saturated fatty acids
SOCS-3	suppressor of cytokine signaling 3
SPMs	specialized pro-resolving mediators
TF	tissue factor
TG	triglycerides
Th	T-helper cells
TLR	toll-like receptor
TNF-α	tumor necrosis factor α
Treg	T regulatory cells
TX	thromboxane
VCAM-1	vascular cell adhesion molecule 1
VLDL	very low density lipoprotein

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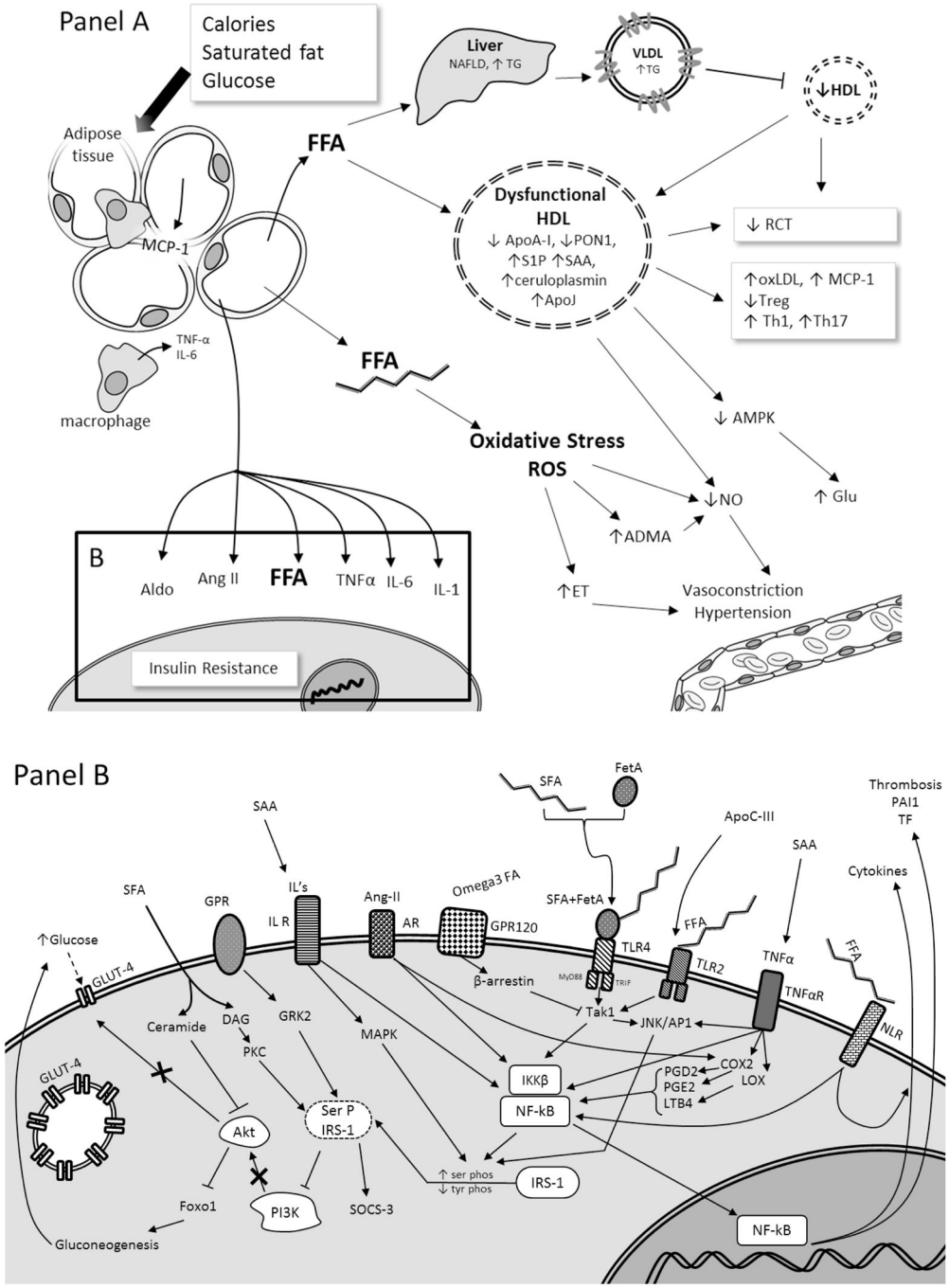

Figure 1. Extracellular and intracellular pathways involving inflammation in metabolic syndrome

Panel A: Overview of the interaction between inflammation and the components of metabolic syndrome. When caloric intake exceeds metabolic energy demand, the level of saturated fat and glucose rise in blood. This excess caloric intake is converted into TG's which are stored in the adipose tissue of visceral fat. Adipocytes release free fatty acids and inflammatory mediators such as IL-1, IL-6, and TNF-α which can cause insulin resistance. Adipocytes release MCP-1 which attracts macrophages and causes local inflammation and

release of further cytokines. Adipocytes can contribute to insulin resistance and hypertension through the production of angiotensin and aldosterone. FFAs in the plasma are taken up by the liver and packed into TG rich VLDL, which leads to lower levels of HDL-C and a dysfunctional HDL which reduces reverse cholesterol transport and increases oxLDL and MCP-1. Dysfunctional HDL also can modulate T cells through inhibiting Treg and promoting pro-inflammatory Th1 and Th17 cell production. Dysfunctional HDL can increase blood glucose levels through reducing AMPK levels and can lead to vasoconstriction of blood vessels through reducing NO levels. FFAs have a similar effect on blood vessels through the production of oxidative stress and reactive oxygen species which reduce NO, increase ADMA and increase endothelin, thus causing vasoconstriction and hypertension.

Panel B: The intracellular pathways involved in insulin resistance. In insulin sensitive tissue, the activation of the insulin receptor leads to tyrosine phosphorylation of the insulin receptor substrate (IRS). This leads to an increase in PI3K and subsequent activation of Akt. Akt activation leads to the expression of GLUT-4 on the plasma membrane and the transport of glucose into the cell. Akt activation also inhibits Foxo1 and therefore inhibits gluconeogenesis and prevents hyperglycemia. FFA, saturated fatty acids, nod-like receptors and cytokines can impair the intracellular insulin signaling pathway leading to insulin resistance. This occurs through different kinases which increase serine phosphorylation and decrease tyrosine phosphorylation of IRS-1. Binding of interleukins, TNF-α or angiotensin, to their respective receptors activates IKK-β/NF-κB and leads to abnormal phosphorylation of IRS. In addition, IL R activation can lead to abnormal phosphorylation of IRS directly through MAPK. Overexpression of GRK2 causes insulin resistance by phosphorylating IRS-1. TNF-α can also activate IKK-β/NF-κB through activation of COX-2 and subsequent production of PGE2, PGD2 or LTB4. FFA can bind directly to the NLR or TLR2 or bind to TLR4 after combining with FetA in the plasma. Activation of these receptors leads to activation of NF-κB and IKK-β leading to abnormal phosphorylation of IRS and upregulation of genes of pro-inflammatory cytokines or proteins involved in thrombosis such as PAI-1 or tissue factor. Omega-3 fatty acids can inhibit the downstream signaling pathway of TLR2/4 through binding to the GPR120 receptor. This produces β-arrestin which inhibits Tak1, a key protein in the signaling pathway of TLR2/4.

Akt, protein kinase B; Aldo, aldosterone; AMPK, AMP-activated protein kinase; AngII, angiotensin II; ApoA, apolipoprotein A; ApoJ, apolipoprotein J; ASDMA, asymmetric dimethylarginine; COX2, cyclooxigenase-2; DAG, diacylglycerides; EF, endothelin; FetA, Fetuin A; FFA, free fatty acids; FoxO1, Forkhead box protein O1; Glu, Glucose; GLUT4, glucose transpoter type 4; GPR, G-protein coupled receptor; GRK2, G-protein-coupled receptor kinase 2; HDL, high density lipoprotein; IKK-β, inhibitor of nuclear factor kappa-B kinase subunit β; ILR, interleukin receptor; IRS, insulin receptor substrate; LTB4, Leukotriene B4; MAPK, Mitogen-activated protein kinases; MCP-1, monocyte chemotactic protein-1; NAFLD, non-alcoholic fatty liver disease; NF-κB, Nuclear factor kappa B; NLR, nod-like receptor; NO, nitric oxide; Omega-3 FA, omega 3 fatty acids; oxLDL, oxidized low density lipoprotein; PAI-1, Plasminogen activator inhibitor-1; PGD2, prostaglandin D2; PGE2, prostaglandin E2; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; PON1, paraoxonase1; RCT, reverse cholesterol transport; ROS, reactive oxygen species; S1P, sphingosine 1-phosphate; SAA, serum amyloid A; SFA, saturated fatty acids; SOCS-3,

Suppressor of cytokine signaling 3; TF, tissue factor; TG, triglycerides; Th, T helper cells; TLR, toll-like receptor; TNF-α, tumor necrosis factor α, IL, interleukin; Treg, T regulatory cells; VLDL, very low density lipoprotein;

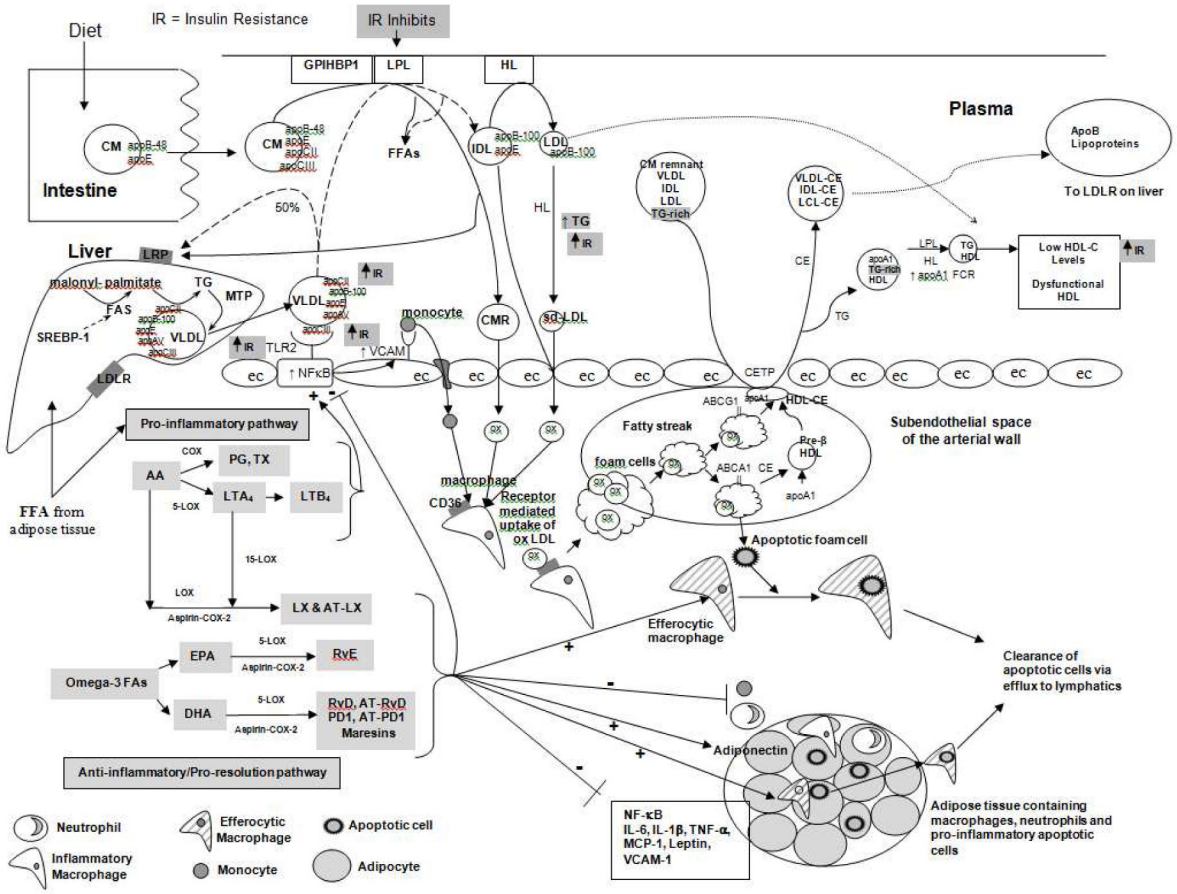

Figure 2. Relationships Among Inflammation, Insulin Resistance and Pro-Inflammatory and Anti-Inflammatory/Pro-Resolving Pathways in TG-rich lipoprotein and HDL metabolism

In adipose and muscle capillaries, TG in VLDL (from liver) are hydrolyzed into FFA by endothelial-bound LPL and GP1HBP1. ApoC-II activates LPL, thus lowering levels of TG whereas apoC-III inhibits LPL, thus raising TG levels. The apoC-III in TG-rich VLDL can bind to the TLR2 receptor, thus activating NF-κB, a pro-inflammatory transcription factor, which upregulates VCAM1 on the endothelial cell to which monocytes attach and migrate into the subendothelial space where they are converted to macrophages which take up oxidized lipoproteins and form foam cells and the fatty streak. When TG levels are high, HL converts TG-rich LDL to small, dense LDL which have a longer half-life and are more readily oxidized. HDL particles pick up the cholesterol ester from foam cells and transfer it via CETP to apoB-containing particles in exchange for TG. These TG-enriched HDL particles are catabolized faster than large, CE-rich HDL, a finding resulting in lower levels of HDL-C, and a dysfunctional HDL particle, in the setting of high TG levels and insulin resistance. Insulin resistance (IR) affects the pathway as shown.

In the acute phase of inflammation induced by nutrient excess, FFAs from adipose tissue or nutrient intake lead to activation of the pro-inflammatory pathway in which AA is converted via COX and LOX enzymes to pro-inflammatory eicosanoids (PGs, TX and LTs) that stimulate the expression of NF-κB and adhesion molecules (VCAM-1), release of cytokines and chemokines and recruitment of monocytes and neutrophils to the tissues. Following this

acute phase, AA, EPA and DHA are actively converted via LOX and aspirin acetylated COX-2 into specialized pro-resolving mediators (SPMs) that promote the resolution phase of inflammation (anti-inflammatory/pro-resolution pathway) by several mechanisms: 1) decrease NF-κB expression in immune cells and endothelial and adipose cells, 2) decrease the production of IL-1β, IL-6 and TNF-α from adipocytes and macrophages, monocyte chemoattractant protein-1 (MCP-1) from macrophages and leptin from adipocytes, 3) decrease expression of adhesion molecule receptors (e.g. VCAM-1) on the endothelium, 4) decrease monocyte infiltration in the inflamed tissue preventing foam cell formation in the arterial wall and crown-like foamy macrophages in the adipose tissue, 5) increase the production of adiponectin from adipocytes, 6) inhibit neutrophil migration to the adipose tissue and 7) stimulate the formation of efferocytic, anti-inflammatory macrophages which promote efferocytosis and clearance of the pro-inflammatory apoptotic cells from the inflamed adipose tissue and arterial wall.

AA, arachidonic acid; Aspirin-COX-2, aspirin acetylated cyclooxygenase 2; AT-RvD, aspirin triggered resolvins; CE, cholesterol ester; COX, cyclooxygenase; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; IL, interleukin; LOX, lipoxygenase; LT, leukotrienes; LX, lipoxin; AT-LX, aspirin triggered lipoxins; MCP-1, monocyte chemoattractant protein-1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; Omega-3 FAs, omega-3 polyunsaturated fatty acids; PD1, protectins, AT-PD1, aspirin triggered protectins; PG, prostaglandins; RvD; DHA derived resolvins; RvE, EPA derived resolvins; TNF-α, tumor necrosis factor α; TX, thromboxane; VCAM-1, vascular cell adhesion molecule 1.

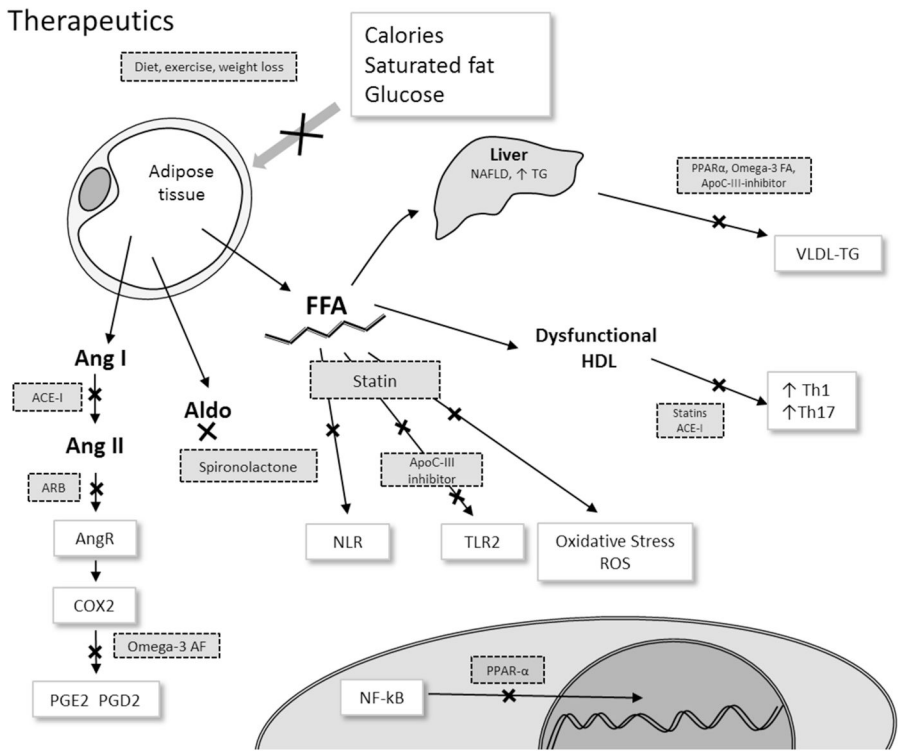

Figure 3. Therapeutic modalities in the treatment of metabolic syndrome

Different therapeutic modalities can target the components of metabolic syndrome and inflammation at different levels. Diet modification and exercise can reduce the caloric intake and increase energy expenditure and prevent the development of adiposity. Omega-3 FAs, PPAR-α and apoC-III inhibitors can reduce the production of VLDL from the liver and lower TG levels. Statins reduce oxidative stress and prevent the activation of NLR and TLR2 receptors. ApoC-III inhibitors can prevent the activation of TLR2 as well. Statins as well as ACE-I can modulate inflammation through inhibiting the production of pro-inflammatory Th1 and Th17 cells. ACE-I and ARB can block the production of angiotensin II or block its binding to the angiotensin receptor, respectively. In addition to lowering TG levels, omega-3 FAs can prevent the production of PGE2 or PGD2 by inhibiting the COX-2 enzyme. Omega-3 FAs can also be converted to resolvins which promote resolution of inflammation and thus improve insulin sensitivity and promote reverse cholesterol transport. Finally, PPAR-α can modulate inflammation through inhibiting NF-κB.

ACE-I, angiotensin converting enzyme inhibitor; Aldo, aldosterone; Ang, angiotensin; ApoC-III-inh, Apolipoprotein C-III inhibitor; ARB, angiotensin receptor blocker; COX2, cyclooxigenase-2; FFA, free fatty acids; HDL, high density lipoprotein; NLR, nod-like receptor; Omega-3 FA, omega-3 fatty acids; PGD2, prostaglandin D2; PGE2, prostaglandin E2; PPAR-α, Peroxisome proliferator-activated receptor alpha; ROS, reactive oxygen species; Th, T helper cells; TLR, toll-like receptor.