Medical Sciences

Linking Chronic Inflammation with Cardiovascular Disease: From Normal Aging to the Metabolic Syndrome

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The metabolic syndrome (MetS) is a cluster of clinical disorders including an unhealthy body habitus with a large waistline, dyslipidemia, glucose intolerance and hypertension. It is known that these disorders not only increase the chances of developing type 2 diabetes mellitus (T2DM), but also cardiovascular disease (CVD). Furthermore, the co-occurrence of all these risk factors known as the MetS is linked to pathways sharing common underlying mediators and mechanisms. Though insulin resistance has been considered as the root of the problem to explain the conglomerate of metabolic abnormalities within this syndrome; new evidence points to several pro-inflammatory cytokines, reactive oxygen species and free fatty acid intermediates might play an even greater role in regulating a series of intracellular signaling pathways sustain as well as perpetuate the development of the MetS and its CVD complications. Since having a diagnosis of MetS confers not only a 5-fold increase in the risk of T2DM, but also a 2-fold risk of developing CVD over a period of 5 to 10 years; it is vital to better recognize the mechanisms by which the MetS is associated with such adverse outcomes. Therefore, it is the purpose of this review to address (1) how inflammation modifies insulin sensitivity, (2) known factors believed to contribute to this process, and (3) new concepts of inflammatory markers in regulating the development of MetS and its individual components.

Chronic inflammation | Metabolic syndrome | Cardiovascular disease

INTRODUCTION

Despite great efforts to improve public awareness and modify perception and behavior tendencies urging both children and adults to adopt healthier choices and to make lifestyle modifications, most Americans fail and do not follow any of these recommended guidelines to maintain a healthy lifestyle [1]. Specifically, data from the Behavioral Risk Factor Surveillance System including more than 153,000 U.S. adults showed that only 3% of the participants followed a healthy lifestyle. Moreover, only 1 in 10 adults followed no weight, dietary, or smoking recommendations [1]. In addition, overweight and obesity have now reached epidemic proportions in the U.S. and trail only smoking as preventable causes of death [2]. Therefore, weight related issues have not only become increasingly important as an epidemic health concern, but also an essential component of the Metabolic Syndrome (MetS) and a modifiable risk factor for type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD).

Despite all available data regarding the atherogenic damage associated to MetS, there is substantial confusion regarding the conceptual definition of the MetS, particularly clinical screening, cut-off values to define MetS and triggers that initiate and perpetuate MetS. Additionally, preventive management strategies and implementation protocols are scarce and poorly applied by primary care physicians in U.S.

Since the last century, inflammation has been implicated as a potential mediator for the development of T2DM [3]. Although all molecular mechanisms have not been clearly defined, the role of pro-inflammatory cytokines, reactive oxygen species and free fatty acids intermediaries have been suggested as key elements in modulating specific intracellular signaling pathways that appear to regulate insulin sensitivity at least in certain animal models [4]. In order to advance our understanding of the MetS, it is important to link these same pathways to each individual component of the MetS and their potential role in the development of CVD complications.

With this in mind, this review will address: (1) how inflammation modifies insulin sensitivity, (2) known factors believed to contribute to this process, and (3) new concepts of inflammatory markers in regulating the development of MetS and its individual components.

METABOLIC SYNDROME

Even though there has been controversy in defining the MetS and its clinical utility, it is now conclusively apparent that it encompasses a collection of unhealthy body habitus, dyslipidemia, hypertension, glucose intolerance, a proinflammatory state, and a prothrombotic state. The most commonly used criteria at present comes from the World Health Organization (WHO), the European Group for the study of Insulin Resistance (EGIR), the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III), American Association of Clinical Endocrinologists (AACE), and most recently from the International Diabetes Federation (IDF) [5-10]. Clinical recognition of MetS becomes increasingly important, as this syndrome has been shown to confer a 5-fold increase in the risk of T2DM and 2-fold the risk of developing CVD over a period of 5 to 10 years [11]. Furthermore, patients with the MetS are at 2- to 4-fold increased risk of stroke, a 3- to 4-fold increased risk of myocardial infarction (MI), and 2-fold the risk of dying from such an event compared with those without the syndrome regardless of a previous history of cardiovascular events [12,13].

Table 1. A list of these adipocytokines and corresponding proposed biologic contributions [27-36].

Adipocytokine	Biological Action
Free fatty acids (FFA)	• Splanchnic FFA levels may contribute to liver fat accumulation leading to abdominal obesity. • Acute exposure of skeletal muscle to elevated FFA levels induces IR by inhibiting the insulin-mediated glucose uptake. • Chronic exposure of the pancreas to the elevated FFA impairs a pancreatic β-cell function. • FFAs increase both fibrinogen and PAI-1 production.
Tumor necrosis factor alpha (TNF α)	• Paracrine mediator in adipocytes to act locally reducing insulin sensitivity. • TNF-α induces adipocytes apoptosis and promotes IR by the inhibition of the insulin RS 1 signaling pathway. Also, it exacerbates FFA release, inducing atherogenic dyslipidemia. • Plasma TNFα is positively associated with BW, WC, TGs while, negatively associated with plasma TNFα and HDL-C.
C-reactive protein (CRP)	• Elevated CRP level is associated with an increased WC, IR, BMI, and HG and increased number of MetS components. • More likely to be elevated in obese insulin-resistant, but, not in obese insulin-sensitive subjects. • CRP levels independently predict occurrence of future CVD events.
Interleukin 6 (IL-6)	• Released by both adipose tissue and skeletal muscle in humans with inflammatory and anti-inflammatory actions. • IL-6 receptor is also expressed in the hypothalamus controlling appetite and energy intake. IL-6 suppresses lipoprotein lipase activity. • Systemic adipokine that not only impairs insulin sensitivity, but also regulates the hepatic production of CRP. • Positively associated with BMI, fasting insulin, and the development of T2DM and negatively associated HDL-C.
Plasminogen activator inhibitor-1 (PAI-1)	• A serine protease inhibitor is secreted from intra-abdominal adipocytes, platelets, and the vascular endothelium. • It exerts its effects by inhibiting the tissue plasminogen activator (tPA) and thus it is considered as a marker of impaired fibrinolysis and atherothrombosis. • Plasma PAI-1 levels are increased in abdominally obese subjects and inflammatory states, increasing the risk of an intravascular thrombus and adverse cardiovascular outcomes.
Adiponectin	• It regulates the lipid and glucose metabolism, increases insulin sensitivity, regulates food intake and BW, protects against a chronic inflammation, inhibits hepatic gluconeogenic enzymes as well as the rate of endogenous glucose production in the liver. It increases glucose transport in muscles and enhances FFA oxidation. • Multifactorial antiatherogenic action which includes inhibition of endothelial activation, reduced conversion of macrophages to foam cells, and inhibition of the smooth muscle proliferation and arterial remodeling. • Adiponectin is inversely associated with CVD risk factors such as blood pressure, LDL-C, and TGs. • Anti-inflammatory molecule is negatively associated with BW, WC, TGs, fasting insulin, IR, BMI, and BP, whereas a positive association exists between adiponectin and HDL-C. • Its expressions and secretions are reduced by TNFα, possibly through a stimulated production of IL-6, which also inhibits adiponectin secretion; hence, it is seen to be "protective."
Leptin	• Adipokine involved in the regulation of satiety and energy intake. • Plasma leptin levels increase during the development of obesity and decline during the weight loss. Thus, most overweight and obese individuals have elevated leptin levels that do not suppress appetite. This leptin resistance is thought to be a fundamental pathology in obesity. • Leptin receptors are located mostly in the hypothalamus and the brain stem and signals through these receptors controls satiety, energy expenditure, and neuroendocrine function. Increases in the BP through activation of the sympathetic nervous system. Leptin is a NO dependent vasodilator but also increases the PVR and the sympathetic nerve activity. • Concentration of plasma leptin correlates with adiposity and hyperleptinemia is an independent CVD risk factor.

IR = insulin resistance; RS = receptor substrate; BW = body weight; WC = waist circumference; TGs = triglycerides; HDL-C = high-density lipoprotein–cholesterol; BMI = body mass index; HG = hyperglycemia; MetS = Metabolic syndrome; CVD = cardiovascular disease; T2DM = type 2 diabetes mellitus; LDL-C = low-density lipoprotein cholesterol; BP = blood pressure; NO = nitric oxide; and PVR = peripheral vascular resistance.

It has been estimated that the worldwide prevalence of MetS ranges from <10% to as much as 84%, depending on the region, urban or rural environment, sex, age, race, and ethnicity studied, as well as definition used to classify patients [14,15]; hence it is estimated that one-quarter of the world's adult population has MetS [9]. These staggering statistics become even more significant when considering the association between MetS and the elevated CVD risk involving subclinical target organ damage [16]; particularly when most physicians cannot measure indices of insulin sensitivity in the context of their clinical practice. This difficulty persists despite efforts by some organizations such as the WHO, NCEP-ATP III, EGIR, AACE, and IDF in proposing the use of simple clinical parameters with cut-off values to identify individuals who would probably be insulin resistant and who would also show the atherogenic and diabetogenic abnormalities associated with MetS. In this setting, glucose tolerance testing, the homeostatic model assessment (HOMA) and more recently the quantitative insulin sensitivity check index (QUICKI) have demonstrated to be useful tools for determining insulin resistance. However, no direct marker of insulin resistance to diagnose the MetS is currently recommended in medical guidelines.

Inclusion of abdominal obesity as a clinically measurable variable to identify MetS was a key conceptual step in the right direction. Waist circumference, though imperfect, correlates fairly well with total abdominal fat and is also the most prevalent manifestation of the MetS [17-20]. Nonetheless, it cannot distinguish visceral adiposity from the amount of subcutaneous

abdominal fat [5,21,22]. This is crucially important since increased visceral adiposity, along with increased macrophage type 1 infiltration into omental adipose tissue, are critical to the development of insulin resistance in obese patients independent of body mass index and total body fat mass [23-26].

Even though the role of fat cells in metabolic dysfunction has long been considered, their potential role in an inflammatory process is a relatively new concept as data has now shown that adipocytes and immune cells share certain properties such as complement activation and pro-inflammatory cytokine production [27,28]. In addition, fat cell precursors also share features with macrophages, such as the capacity for phagocytosis in response to several stimuli, as well as numerous genes that code for transcription factors, cytokines, inflammatory signaling molecules, and fatty acid transporters [29-33].

Furthermore, adipose tissue has been characterized as a heterogeneous mix of adipocytes, stromal preadipocytes, immune cells, and endothelium that respond rapidly and dynamically to alterations in nutrient excess through adipocyte hypertrophy and hyperplasia [34]. It has been suggested that progressive adipocyte enlargement results in visceral obesity, causing a state of hypoxia that has been considered the main trigger of necrosis and macrophage infiltration into adipose tissue leading to an overproduction of biologically active metabolites known as adipocytokines [35,36]. See a list of these adipocytokines and corresponding proposed biologic contributions in Table 1.

In three recent studies, the association between MetS and inflammation has been highlighted. First, data from Ebron et al, showed that a larger body mass index was associated not only with an increased atherogenic dyslipidemia and insulin resistance in individuals with MetS, but also with a low-grade level of inflammation; particularly shown by the positive association between BMI and the proinflammatory C-reactive protein and interleukin-6 [37]. Second, data from Slagter and associates demonstrated the impact obesity has on quality of life and found that quality of life is enhanced by grade of obesity, T2D, MetS and inflammation, and that these are mainly related to reduced physical health [38]. Third, data from Marques-Rocha et al, showed that the use of a Mediterranean-based nutritional diet induced changes in the expression of let-7b and miR-155-3p in white blood cells from patients with MetS after an 8-week intervention [39]. Moreover, the quality of this Mediterranean-based diet had an important effect on the expression of inflammation-related micro RNAs (miRNAs). The latter is critically important since expression of these miRNAs not only has been associated with regulation of inflammatory genes, but also important in the development of human diseases.

Figure 1 represents the current model that will integrate the maladaptive immune and inflammatory responses leading to insulin resistance and CVD.
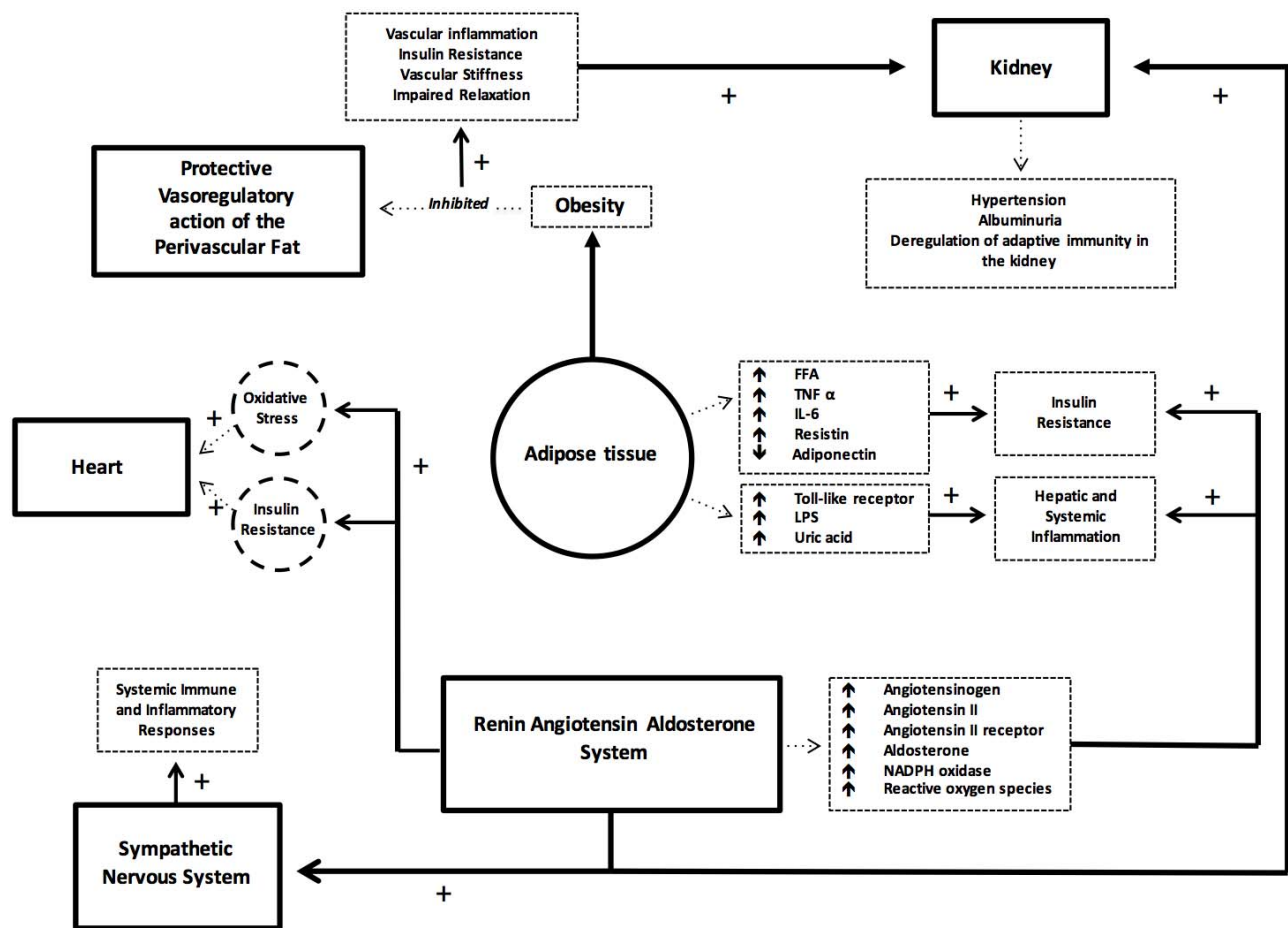

Figure 1: Current model integrating maladaptive immune and inflammatory responses leading to insulin resistance and CVD.

DIABETES MELLITUS

The combination of T2DM and obesity is rapidly growing and has become a major public health issue associated with inordinate morbidity and mortality. In fact, the incidence of this metabolic combination rises steeply as HbA1c increases from the 5.0% to 6.5% [40]. It has been estimated that approximately 79 million adults in the U.S. 20 years or older have prediabetes [41]. This staggering number of patients clearly indicates the presence of CVD related complications of epidemic proportions [42-46].

A low-level chronic inflammation state not only has been shown to be clearly associated with the development on insulin resistance and T2DM [47-49]; but also current data seems to suggest that elevation of certain cytokines vary according to ethnicity [50-56]. In the Multi-Ethnic Study of Atherosclerosis (MESA), inflammation markers differed significantly by race/ethnicity. IL-6, CRP, and fibrinogen were lower among Chinese patients while Hispanic and black subjects had higher levels when compared with white subjects [50].

It is now apparent that a series of intracellular signaling pathways activated by a state of chronic, low-grade inflammation, particularly within the white adipose tissue, participate in the regulation of insulin signaling that in turn regulates a series of downstream signaling events [57,58]. Moreover, inhibition of these signaling steps is known to be a primary mechanism through which inflammatory signaling leads to insulin resistance [59-61]. Specific to these pathways are several serine/threonine kinases activated by inflammatory or stressful stimuli that contribute to inhibition of insulin signaling, including JNK, inhibitor of NF-κB kinase (IKK), and PKC-θ [62]. Furthermore, activation of these kinases, at least in obesity, not only has been shown to highlight the overlap that exists between metabolic and immune pathways; but also these same kinases, particularly IKK and JNK, are activated in the innate immune response by Toll-like receptor (TLR) signaling in response to LPS, peptidoglycan, double-stranded RNA, and other microbial products [63].

The inflammatory activation mediated by inflammasomes through IL-1β activation may contribute to insulin resistance and T2DM [64]. In obesity, levels of palmitate and ceramide have been found to be elevated and these lipids are known to activate inflammasomes [65]. In the mice mode, insulin sensitivity improves when mice deficient in central inflammasome molecules are fed high-fat diets and this improvement is accompanied by suppression of immune and inflammatory responses [66, 67].

Data from both genetic and pharmacological manipulations on different effectors of the inflammatory response have shown modulation of insulin sensitivity in different animal models [68]. Tissue-specific over-expression of IK kinase in liver and adipose tissue, but not in skeletal muscle, leads to systemic insulin resistance. In contrast, selective inhibition of the nuclear factor-KB function in liver and adipose tissue protects against insulin resistance in nutritional and genetic animal models of obesity [69].

HYPERTENSION

Hypertension is one of the most frequently encountered conditions in clinical practice [70]. The most recent JNC-8 addressed the need for treatment in order to lower systemic blood pressure readings to 150/90 mmHg in those aged 60 and older, and to 140/90 for adults less than 60 years of age [71]. In the population age 18 and older with diabetes, the guidelines recommend initiating drug treatment to a goal of systolic BP < 140mmHg, and diastolic blood pressure goals of < 90mmHg.

These guidelines also apply to patients with chronic kidney disease. Establishment of hypertension as a primary component of MetS not only has allowed for earlier detection and proper management [72]; but has also allowed for better understanding of the multifactorial etiology of this condition.

As previously mentioned, the metabolically active visceral fat linked to insulin sensitivity through the production of adipocytokines including leptin, tumor necrosis factor-α (TNF-α), angiotensinogen, interleukin-6 (Il-6), and non-esterified fatty acids (NEFA), interact in a diversity of metabolic pathways culminating in the activation of the renin-angiotensin-aldosterone system (RAAS) pathway and the development of insulin resistance [73].

Studies in experimental animals have provided mechanistic insights into CVD, as well as renal changes associated with obesity. Specifically, reproducible increases in systemic blood pressure have been identified in both dogs and rabbits fed fat diets that result in excess weight gain [74-77]. In fact, the metabolic, endocrine, cardiovascular, and renal changes caused by dietary-induced obesity in these experimental animals have closely mimicked changes observed in obese humans.

Nowadays, there is overwhelming evidence that excess weight gain and visceral obesity are major causes of hypertension, perhaps accounting for as much as 65–75% of the risk for human essential hypertension [73]. Although the mechanisms of obesity-induced hypertension are still being intensively studied, research in experimental animals and humans suggest important roles for impaired renal-pressure natriuresis due to physical compression of the kidneys and activation of RAAS and sympathetic nervous system [78]. As obesity and its metabolic and hemodynamic consequences are sustained over many years, renal injury gradually makes the hypertension more severe and more resistance to therapy.

In addition to the potential mechanical compression caused by obesity that may mediate the development of hypertension, several other mediators of sympathetic nervous system activation have been proposed. These include the presence of impaired baroreceptor reflexes; activation of chemoreceptor-mediated reflexes secondary to the development of sleep apnea with intermittent hypoxia; hyperinsulinemia; Angiotensin II (Ang II); and cytokines released from adipocytes such as leptin, tumor necrosis factor-α and interleukin-6 [79-82].

Surely adipose tissue is known to widely express angiotensinogen, angiotensin converting enzyme (ACE), and type 1 angiotensin receptor (AT1) gene, with the potential of increasing the overall production of Ang II and thus activate RAAS [83]. While RAAS plays a key role in the modulation of many key cardiovascular functions, it is known that patients with Mets have an altered up regulation of RAAS resulting in chronic activation of inflammatory responses [84].

Over the past 10 years, several studies have presented evidence for the existence of a new arm of the RAAS, namely the ACE (angiotensin-converting enzyme) 2/Ang-(1-7) [angiotensin-(1-7)]/Mas axis [85]. Angiotensin-(1-7) can be produced from Ang I or Ang II via endo- or carboxy-peptidases; therefore, ACE2 appears to play a central role in Ang-(1-7) formation. Recent studies have shown that the Ang-(1-7)/Mas axis not only modulate both lipid and glucose metabolism, but also counter regulate the effects of Ang II [86].

Furthermore, for over two decades, different subsets of Th1 interferon-γ-producing and Th2 interleukin-4 producing lymphocytes, as well as Th17 producing interleukin-17 and T-suppressor lymphocytes that participate as pro- and anti-inflammatory cells have been shown to participate in the process of vascular remodeling that occurs with hypertension [87]. In

addition, the role of pro-inflammatory T-lymphocytes has also been shown to mediate the effects of Ang II and mineralocorticoids in both Dahl-salt sensitive and spontaneously hypertensive rats [87,88].

Though the specific mechanism mediating this activation of immunity remains largely unknown, it has been proposed that formation of neo-antigens could be generated by elevated blood pressure through damage-associated molecular pathways. Moreover, Th1 cells once activated may contribute to increases in systemic blood pressure through the interaction of cytokines produced or through their effects on perivascular fat [88].

Obviously, confirmation of these mechanisms in humans might provide new therapeutic venues not only to change our current approach to managing hypertension, but also how we can improve CVD outcomes.

DYSLIPIDEMIA

Overproduction of very-low-density lipoprotein remnants with apolipoproteins B-100, small low-density lipoprotein particles, and reduced levels of high-density lipoprotein cholesterol are the primary dyslipidemic abnormalities of most MetS patients [89]. The triglyceride portion in very-low-density lipoprotein remnants is initially hydrolyzed by lipoprotein lipase to intermediate density lipoproteins, and these in turn are further hydrolyzed into low-density lipoprotein particles [90]. The cholesterol esters in these low-density lipoproteins are then exchanged for triglycerides in very-low density lipoproteins by cholesterol ester transfer proteins, followed by hydrolysis of triglycerides in low-density lipoproteins by hepatic lipase, which produces small, dense low-density lipoproteins.

In adipocytes, reduced fatty acid trapping and retention by adipose tissue may result from a primary defect in the incorporation of free fatty acids into triglycerides. Alternatively, insulin resistance may promote reduced retention of free fatty acids by adipocytes. Both of these abnormalities lead to increased levels of free fatty acids in plasma, increased flux of free fatty acids back to the liver, enhanced production of triglycerides, decreased proteolysis of Apo B-100, and increased VLDL production [90].

Regardless of their fundamental causes, small, dense low-density lipoproteins particles remain in circulation for longer periods of time; hence, are more susceptible to oxidation. Consequently, these oxidized particles are more prone to enter more easily the arterial wall and thus retained more readily. These trapped small and dense low-density lipoproteins not only promote endothelial dysfunction and enhanced production of procoagulants by endothelial cells, but also appear more atherogenic than normal low-dense lipoproteins.

In addition to the abnormalities described with regards to low-density lipoproteins, we also need to be reminded of the long-standing association existing between elevated triglycerides and CVD [91,92]. This elevated level of triglycerides is known to occur as a result of several clinical conditions [93]; however, for the purpose of this review, isolated elevation of triglycerides should prompt physicians to exclude T2DM or the MetS [94-101]. In addition, high triglycerides are also regularly found in obese individuals [102-105].

In diabetic patients, high triglyceride levels and low HDL concentrations are not only proinflammatory [106], but also elevated levels of triglycerides rather than hyperglycemia results in large release of pro-inflammatory proteins by adipose tissue contributing to CVD [107]. While dyslipidemia has been studied as a component of the Mets, further studies regarding the chronic inflammatory state derived from this pathologic process are still lacking. Specifically, dyslipidemic abnormalities have been mostly studied in conjunction to T2DM and obesity, but their sole contributory effect has not yet been thoroughly elucidated.

NORMAL AGING

Though normal aging is not part of the MetS is an inevitable universal truth for every living organism associated with the ultimate exposure to various chronic ailments and diseases; hence somewhat related to changes in inflammation and the body response to these changes.

The normal process of aging is known to be associated with increased total body fat, particularly central obesity, that unfortunately contributes to a number of important health problems such as insulin resistance, cardiovascular disease, sarcopenia and disability [108-112]. With regards to the particular kind of adipose tissue that contributes to such problems, white adipose tissue has been proposed to be a key regulator of lifespan. In several model organisms, genetic manipulations that modify fat mass also impact on life expectancy, in part through sirtuin 1 (SIRT1) and suppression of the nuclear receptor protein peroxisome proliferator-activated receptors gamma (PPARγ) [113-115].

While the complete underlying mechanism for the association between age-related obesity and disease is not completely understood, adipose tissue inflammation has been identified as a critical regulator of the overall low-level systemic inflammatory milieu in diet-induced and genetic obesity models [116,117].

Adipose tissue is composed of a heterogeneous cell population that becomes evident after fat is further purified through collagenase digestion. This process culminates with the dissociation of adipocytes and stromal vascular fraction. In the latter, the dominant cell components are the leukocytes, mainly macrophages and lymphocytes, and adipose tissue stromal cells, including preadipocytes and fibroblasts [118].

The normal process of aging is associated with profound alterations in the innate immune system. First, there are significant alterations in the T and B cell compartments, involution of the thymus gland, functional decline in the monocytes and macrophages, low expression of Toll-like receptors from activated splenic and peritoneal macrophages, and an altered secretion of several chemokines and cytokines [119]. Second, aging decreases both humoral and cellular immune responses [120,121]. Third, residential macrophages impair the proliferative response of activated peripheral T-lymphocytes, and paired to neutrophils they can sometimes exhibit inappropriate respiratory bursts with concomitant release of reactive nitrogen and oxygen intermediates which may decrease the ability to destroy pathogens [122]. Furthermore, aged dendritic cells have been reportedly found to be less efficient in activating T and B cell populations and aged natural killer cells exhibit a reduced ability and efficiency in killing tumor cells. Fourth, mitogen activated peripheral blood mononuclear cells isolated from elderly population not only show a higher production of pro-inflammatory cytokines, such as IL-1, IL-6 and TNF-α *ex-vivo*, compared to young people; but also there is an up-regulation of COX-2 expression leading to an increase in the production of prostaglandin E2, a critical regulator, of age-related inflammatory changes [123]. Fifth, reduced efficacy of vaccine-induced protection against infections/diseases and poor response to new pathogens, mainly due to defective T, suggest that naive CD4 cells are defective in generating efficient memory and are found to produce less IL-2 and exhibit poor proliferation and

differentiation upon antigen stimulation in older mice [124-126]. Finally, alterations in B cells have also been recognized in age-related changes in immune system. Specifically, available antibody repertoires to specific antigens and pathogens are markedly different in old vs. young splenic or peripheral blood B cells [121,127]. In addition, peripheral B cell lymphocyte percentages and numbers significantly decrease with age. Antibodies generated in old mice (20 months or older) and in humans (65 years or older) are less protective compared with the antibodies generated in the young individuals [128,129].

It has been widely conceptualized that chronic antigenic stress throughout life causes the accumulation of molecular and cellular scars, which act as potential triggers in mounting the inflammatory response associated with the pathogenesis of all age related diseases [130]. Thus, an underlying low grade inflammatory activity seen in the elderly, coupled with a decreased overall concentration of sex steroids; changes in life style patterns including smoking history and obesity; as well as a low grade of cytokine production caused by sub-clinical disorders due to asymptomatic infection with bacterium; leads to increased levels of circulating TNF-α, IL-6, soluble IL-2 receptors, C reactive protein and cholesterol, which act as inflammatory mediators [130-133]. Similarly, previous exposure to past infections is an additional risk factor that leads to a rise in the levels of chronic inflammatory markers and subsequent development of an increased susceptibility to risk of heart attack, stroke, and cancer [134]. Current evidence seems to point out that this chronic, low-grade inflammatory process, characterized by increased levels of cytokines, might develop in otherwise healthy individuals possibly as early as the age of 55 years old [135].

For example, in the heart muscle, this chronic inflammatory process leading to mitochondrial damage results in an increased free radical production that further activates the chronic inflammatory vicious cycle. Without a proper defense mechanism, this positive feedback loop exacerbates oxidative damage, reduction in ATP production, loss of cardiomyocytes, and formation of fibrotic tissue [135-138]. Furthermore, while aging and inflammation had differential effects on the expression levels of AT_1R, recent experimental data using the mice model suggest an increase in $AT_1R:AT_2R$ under these conditions and supports the notion that it may contribute to the pathogenesis of cardiomyopathies [139].

Similarly, neuro-inflammation and cytokine production have been acknowledged as potential triggers of the functional changes occurring in the brain during "normal" and "pathological" aging. In particular, the aged brain seems to be characterized by increased levels of pro-inflammatory cytokines [140]. A growing number of reports have now shown that cytokines may specifically interact with neuronal channels regulating neuronal excitability, synaptic plasticity and responses to injury.

Based on currently available data, a common pathway linking normal aging with known associated abnormalities is associated with a general decline in mitochondrial function [141-142]; which in turn not only reduces ATP production [143], but also affects the overall oxidative stress as the mitochondria regulates reactive oxygen species [140]. Even though the specific role of reactive oxygen species as the sole cause of aging remains controversial, it is known that accumulation of reactive oxygen species as a result of a dysfunctional mitochondria due to normal aging results in activation of protein 3 inflammasome in macrophages, which produce proinflammatory cytokines [144]. Accumulation of this protein impairs cellular housekeeping and expose the cell to higher risk in many age-related diseases such as atherosclerosis and T2DM.

Obviously, a change in the endogenous concentration of reactive oxygen species would then alter the activity of antioxidants. Since an increased antioxidant activity can decrease the potential for CVD development by regulating reactive oxygen species and nitric oxide production [145-146]; subsequent attenuation of shear stress can then reduce the activation of endothelial nitric oxide synthase activity. This would result in the reduction of nitric oxide that will ultimately affect vasodilatory responses, leading to consequential endothelial dysfunction and vascular injury [147].

Therefore, better recognition of the physiologic and pathologic changes that occur with normal aging would definitively improve our understanding of the complexities involving the well-recognized process of chronic inflammation that occurs with normal aging, placing patients at an inordinate risk of CVD.

ARE BIOMARKERS READY FOR PRIME TIME?

It is quite evident that significant advances have occurred in our understanding of CVD. Nonetheless, additional breakthroughs will undoubtedly occur as we gather more data regarding alterations in inflammatory markers and how these changes cause vascular injury and accelerated atherosclerosis. Though considerable controversy still exists in how to diagnose individuals at a higher risk of developing cardiovascular disease, it is important to acknowledge the utility of C-reactive protein (CRP). Results from multiple large-scale prospective studies have demonstrated the utility of CRP in predicting adverse cardiovascular events such as myocardial infarction, ischemic stroke, and sudden cardiac death [148,149]. In fact, the addition of high sensitive CRP (hsCRP) information has shown to add prognostic information beyond that available from the well-known Framingham Risk Score [150].

Furthermore, the initial result from the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial showing that 20 mg of rosuvastatin significantly reduced the primary composite endpoint by 44% when compared to placebo, clearly suggests that patients with elevated CRP stand to benefit from statin therapy, regardless of their LDL-C level [151]. Though this study was mainly focused on secondary outcomes and not on primary prevention.

On the last publication by the American College of Cardiology/American Heart Association task force on practice guidelines, it was recommended that hs-CRP might be used to inform treatment decision making if after quantitative risk assessment a treatment decision remains uncertain [152].

In addition, the new venues of inflammatory markers open new opportunities. For example, we wait with great enthusiasm for the results of ongoing trials such as CANTOS in which Interleukin-1β inhibition using cankinumab is used; CIRT that uses low-dose methotrexate; and COLCOT evaluating if long-term use of colchicine reduces CVD events in patients post myocardial infarction. Each of these trials is driven by protocols that utilizes anti-inflammatory measures in an attempt to reduce CVD events among stable coronary disease patients who remain at risk of another events due to a persistent pro-inflammatory response [153,154]. Moreover, some other targets such as the IL-6 pathway appear also promising.

Therefore, continued vigilance of the results of ongoing trials is required, not only to determine which markers would be indeed critical in identifying individuals at a higher risk of cardiovascular disease, but also to identify which therapies might be useful on improving cardiovascular health.

CONCLUSION

While several therapeutic modalities have been identified to target inflammation in the basis of MetS, ongoing studies continue to surface new molecular and cellular pathways that could be potential links to the pathogenesis of cardiovascular comorbidities in MetS. These findings could aid in the premature identification of high-risk individuals and in the development of goal-targeted treatment. Also, additional studies are warranted to determine whether anti-inflammatory medications such as NSAIDs and colchicine can be effective in preventing the complications of obesity.

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