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Molecular Determinants of the Cardiometabolic Phenotype

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Abstract

The metabolic syndrome represents a clustering of risk factors that has been shown to predict adverse cardiovascular outcomes. Although the precise mechanisms contributing to the cardiometabolic syndrome (CMS) remain poorly defined, accumulating evidence identifies two intersecting candidate pathways responsible for inflammation and energy homeostasis in the pathophysiology that underlie cardiometabolic traits. Although currently no pharmacologic interventions specifically target CMS, future drug development efforts should attempt to capitalize on molecular nodes at the intersections of these pathways in the CMS.

Keywords

Metabolic syndrome; cardiometabolic syndrome; substrate metabolism; inflammation; obesity; insulin resistance; hypertension; dyslipidemia

1. Introduction

The metabolic syndrome (MetS) represents a clustering of cardiovascular risk factors affecting approximately 22% of the adult population in industrialized countries and over 40% of the those aged 50 years and older [1,2]. Although various diagnostic criteria for MetS exist, consistent features including insulin resistance, type 2 diabetes (T2D), dyslipidemia, and visceral obesity are each reflective of disordered energy metabolism [2-4]. Multiple studies have shown that the individual risk factors adversely affect cardiovascular structure and function. However, the extent to which the diagnosis of MetS, independent of the individual clustering components, predicts subclinical cardiovascular disease remains controversial [5-12]. Nonetheless, there is consistent evidence that a constellation of risk factors acts synergistically, *via* mechanisms that remain poorly defined, to create a cardiometabolic syndrome (CMS) which is characterized by adverse cardiovascular phenotypes and events including left ventricular (LV) diastolic dysfunction, cardiac/vascular hypertrophy, coronary heart disease (CHD), congestive heart failure, stroke, and cardiovascular death [2,5-8,13-24]. In some studies, regression models have identified impaired fasting glucose and/or hyperinsulinemia as the most significant independent predictors of pathologic cardiovascular

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phenotypes and/or events [5,8,20], whereas in other studies excess visceral fat/obesity has been shown as the strongest independent predictor [6,7,25,26]. These seemingly disparate findings are largely due to variations in the definition of MetS [11]. Despite this controversy, abnormal energy metabolism, which can manifest as hyperglycemia, insulin resistance, obesity, and/or dyslipidemia, is likely the driving force behind MetS. Many ongoing efforts to develop novel therapeutic drug targets to address the excess risk associated with MetS attempt to remedy these metabolic abnormalities. This review will highlight two intersecting candidate pathways responsible for inflammation and energy homeostasis in the pathophysiology that underlie cardiometabolic traits.

2. Heritability of Mets Risk Factors

The genetic underpinning of the MetS and its individual risk factors is reflected in the substantial heritability observed by many studies in different ethnic groups for the individual syndrome risk factors. For example, weight, body mass index, and other surrogate measures of adiposity have been found to be highly heritable, with estimates ranging from 0.52 to 0.80 [27-30]. There is greater variability in heritability estimates for measures reflecting insulin resistance and fasting insulin and/or glucose levels, which range from 0.24 to 0.61 [28,31, 32]. Likewise, heritability estimates for fasting triglyceride and high-density lipoprotein cholesterol (HDL) levels also vary, with estimates ranging from 0.20 to 0.47 [27,28,33] and 0.60 to 0.78 [27,33,34], respectively. These relatively wide ranges likely reflect the natural variation in these measures related to diet. Among studies assessing the heritability of blood pressure, ambulatory blood pressure was found to yield higher estimates compared to office measurements. The range of heritability estimates for systolic, diastolic, and pulse pressures by ambulatory measurements are 0.30 to 0.37, 0.24 to 0.37, and 0.21 to 0.63, respectively and were similar in White and Eastern African cohort studies [35,36]. Although studies assessing the heritability of MetS itself, rather than its individual risk factors, are less common, estimates range from 0.13 to 0.42 in published studies [37-39]. Thus, although the heritabilities of the individual and composite indices of MetS vary, there is overwhelming scientific evidence to suggest a heritable component to most, if not all, of the individual risk factor of MetS.

3. Association of Individual Mets Risk Factors With CVD Traits

The individual risk factors that collectively define MetS have been consistently shown to increase cardiovascular disease risk. In considering hypertension, the Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure noted that the “relationship between blood pressure and risk of cardiovascular disease events is continuous, consistent, and independent of other risk factors” [40]. Hypertension is a well-established risk factor for the development of a variety of cardiovascular diseases (CVD), including LV diastolic and/or systolic dysfunction, LV hypertrophy, CHD, heart failure, and death [41-47]. This association is often stronger in African Americans in whom hypertension is also more prevalent [41]. Furthermore, there is increasing evidence that metabolic risk factors are not only potent predictors of future hypertension [48], but may also blunt an optimal control of blood pressure with medications [49], suggesting that drug therapy should be addressed simultaneously to all the aspects of MetS.

More so than body mass in general, visceral or intraperitoneal adiposity has been found to be more closely associated with insulin resistance and/or glucose intolerance [50-53]. Many studies have identified overweight, obesity, and increased waist circumference as associated with increased LV systolic and/or diastolic dysfunction [54-56], LV hypertrophy [57], heart failure [58,59], CHD [60], and CVD death [61,62]. The underlying mechanisms mediating this increased risk are likely due, at least in part, to augmented neurohormonal drive and to increased total blood volumes and cardiac output necessary for supplying the peripheral tissues. This

results in compensatory changes including elevated filling pressures, increased LV wall strain and either concentric or eccentric LV hypertrophy [63,64]. LV hypertrophy is often associated with LV diastolic dysfunction and left atrial dilation, and precedes decompensated heart failure [65]. These relationships are stronger in older adults and in African Americans [41,61].

An estimated 280,000 to 325,000 deaths annually are attributable to obesity in smoker and non/never-smokers, respectively [66]. Furthermore, obese and overweight individuals often have co-morbidities which are independently associated with an increased risk of CVD. Nonetheless, several studies have noted that obesity and/or overweight lose significance in multivariable models that adjust for the presence of cardiovascular risk factors such as dyslipidemia, hypertension, and impaired glucose metabolism [60-62,67,68]. For example, a large (n>240,000) Parisian health registry where adults were followed for 14 years noted that overweight/obesity was not an independent risk factor for cardiovascular mortality after adjusting for traditional risk factors [68]. However, despite the data supporting a negative association between body mass index and CVD burden, some studies have identified an apparent paradox whereby moderate obesity was associated with lower risk of mortality in patients with heart failure, even in the presence of structural heart disease [69,70]. One potential mechanism that has been speculated to mediate this apparent protection is increased metabolic and/or nutritional reserve among moderately obese versus lean patients; however this remains an area of active investigation.

While visceral adiposity is independently associated with cardiovascular traits, it is also clear that an excess of visceral fat is correlated with measures of dyslipidemia. Visceral and subcutaneous adipose tissue was determined by computed tomography in a study of 58 obese and 29 lean control men; obese men were further stratified by visceral adipose tissue (VAT) area. Despite similar body mass index, the high- and low-VAT groups differed in their plasma lipids, with significantly higher triglyceride and lower HDL levels in the obese group in the high- versus low-VAT groups. Furthermore, the triglyceride and HDL levels in the low-VAT group were not significantly different than that of the lean group [71]. Although there remains some variability among studies, the majority have found that triglyceride levels are weakly associated with CVD traits, events, and death [72-74]. Some investigators have proposed that postprandial triglyceride levels may more accurately reflect the overall suitability of the visceral fat depot to store surplus energy [25], thus providing further evidence in support of disordered energy balance in the MetS. Likewise, HDL has also been identified as an inverse multivariate predictor of CHD-risk traits and events [5,20,75].

Insulin resistance, impaired fasting glucose, increased homeostasis model assessment of insulin resistance, T2D, and related traits have also been consistently associated with adverse cardiovascular outcomes [76-79]. Various mechanisms have been proposed that mediate the association between insulin resistance and cardiovascular traits including stimulation of the sympathoadrenal system leading to activation of the renin-angiotensin-aldosterone system and increased inflammation mediating increased oxidative stress and endothelial dysfunction [80-83]. Hyperglycemia has been linked with excess glycated collagen and advance glycosylation products which in turn lead to increased myocardial stiffness and LV diastolic dysfunction in animals [84,85]. Consistent with the hypothesis that energy imbalance underlies many of the adverse phenotypes associated with the CMS, disruption in the trafficking of free fatty acids (FA) has also been implicated (see discussion below) [86,87].

Long-identified as a strong predictor for the development of heart failure, diabetes has been convincingly identified as a significant predictor of incident heart failure, independent of intercurrent myocardial infarction [88,89]. Furthermore, a correlation between glycosylated hemoglobin and risk of heart failure has also been identified among diabetics participating in the landmark United Kingdom Prospective Diabetic Study [90]. Although diabetes frequently

co-exists with other cardiovascular risk factors, the excess occurrence of abnormal LV systolic function and/or heart failure is out of proportion to findings of CHD [11,91,92], supporting the existence of a “diabetic cardiomyopathy,” a consequence of an individual or a combination of factors including deranged cardiac energetics, increased fibrosis, collagen deposition and glycation, microvascular coronary atherosclerosis and endothelial dysfunction, and stimulation of apoptotic cell pathways [46,88,93-100]. The strength of the association between diabetes and adverse cardiovascular outcomes justifies the designation of diabetes as a cardiovascular disease equivalent in the National Cholesterol Education Program Adult Treatment Panel III guidelines [101].

4. Mets as an Independent Predictor of CVD Outcomes

Just as the individual risk factors are associated with cardiovascular disease risk, the diagnosis of MetS also carries significant risk of adverse events and outcomes. Several studies have explored this relationship. For example, in the biracial HyperGEN (n=1969) and Atherosclerosis Risk in Communities studies, LV mass indexed to height increased in association with increasing number of MetS risk factors [7,24]. In a Framingham Heart Study, data from the offspring cohort (n=5135) followed prospectively for 16 years was analyzed. In men, an increasing number of MetS risk factors was responsible for age-adjusted relative risk (95% confidence intervals [CI]) of 2.88 (1.99-4.16) for CVD, 2.54 (1.62-3.98) for CHD, and 6.92 (4.47-10.81) for T2D. Similar analyses in women showed that the relative risks were somewhat lower for CVD and CHD (2.25 [1.31-3.88] and 1.54 [0.68-3.53], respectively), although similar for T2D (6.90 [4.34-10.94]) [102]. Post-hoc analyses of cholesterol treatment clinical trials have identified similar risks. In the West of Scotland Coronary Prevention Study, the risk for CHD was higher as the number of MetS risk factor accumulated (hazard ratio [95% CI] = 1.76 [1.44-2.15]); a similar risk was identified for diabetes (hazard ratio [95% CI] = 3.50 [2.51-4.90]). This risk was somewhat diminished (1.30 [1.00-1.67]) when other conventional risk factors (i.e., age, smoking status, total cholesterol-to-HDL cholesterol ratio, and systolic blood pressure) were included in the regression model [17]. Similarly, the Scandinavian Simvastatin Survival Study found that patients with both elevated low-density lipoprotein cholesterol (LDL) and MetS had the highest risk of major coronary events and derived the greatest benefit from statin therapy [103]. MetS has also been shown to increase the risk of heart failure, often independently of the presence of CHD [18,19]. In a unique community-based study of 50-year old men without known CHD (n=2314), the presence of MetS at baseline was associated with a 20-year hazards ratio of 1.66 (1.02-2.70), even after controlling for interim CVD events such as myocardial infarction and hypertension [18]. Another analysis of data from the National Health and Nutrition Examination Survey study confirmed these association by showing that CHD morality was twice as prevalent in those with MetS [12].

In addition to the five major components of MetS, a panel of non-traditional risk factors have also been studied as not only predictors of cardiovascular traits but as a means of gaining further insight into potential underlying, unifying mechanisms of MetS. For example, markers reflective of prothrombotic and antifibrinolytic states and inflammation, including increased fibrinogen and plasminogen activator inhibitor-1, C-reactive protein (CRP), and interleukin (IL)-6, have also been identified as moderate predictors of future CHD events and death [104-106]. More recently, non-alcoholic fatty liver disease and its corollary in the heart, myocardial steatosis, have emerged as novel risk indicators of MetS and associated CVD traits including LV diastolic dysfunction [97,107,108]. Thus, the overwhelming volume of clinical studies and epidemiologic data support that MetS is associated with excess cardiovascular morbidity and mortality, thus justifying the term CMS.

5. Inflammation-Metabolism Intersections in the CMS

Although the underlying pathophysiologic mechanisms responsible for MetS and related cardiometabolic traits are not yet clearly defined, gene networks constructed from literature references highlight the potential for complex networks of pleiotropic pathways that simultaneously modulate multiple MetS risk traits [109]. In CMS, two intersecting candidate pathways responsible for inflammation and energy homeostasis have been consistently implicated. Insulin resistance clearly plays a critical role in mediating the increased cardiovascular risk associated with the MetS. Traditionally, insulin resistance has been viewed as a consequence of glucotoxicity. However in recent years, overwhelming evidence has led to a paradigm shift such that disordered FA metabolism and storage are now recognized as the major driving force behind the low-grade inflammatory state that is characteristic of the CMS [110-112].

Although increased visceral adiposity is not requisite for the diagnosis, the majority of individuals with MetS have increased waist circumference [5,113]. Long thought to represent a simple repository for excess calories, adipose tissue is now recognized as a complex, highly innervated and vascular organ populated with macrophages and stromal cells and capable of elaborating numerous soluble proteins that maintain energy balance and appropriate substrate environment. However, excess fat mass is not the only threat to normal energy hemostasis. Innate and acquired forms of lipodystrophy, which manifest as peripheral fat wasting and visceral adiposity, are characterized by ectopic deposition of free FA in multiple organs leading to profound insulin resistance and dyslipidemia [114,115]. While inherited forms of lipodystrophy are rare and typically confined in pedigrees, acquired forms are more common, typically a consequence of protease inhibitor use in patients with human immunodeficiency virus [115]. Thus, volume is not the only determinant of a “healthy” fat organ; rather, consideration must be made of the location of the fat and the adipokines it elaborates.

A major function of adipocytes is to provide appropriate storage of excess energy in the form of triglycerides. When circulating energy stores are not sufficient to maintain energy demands, triglycerides in adipocytes are hydrolyzed and released in the form of free FA and glycerol [116]. Whether adipocytes function to uptake FA, perform lipogenesis, or perform lipolysis is determined by multiple external inputs such as circulating substrate levels, insulin, catecholamines, cytokines, and natriuretic peptides, among other substances. Notably, blood from intraabdominal fat stores drains directly into the liver *via* the portal vein, thus highlighting the critical communication that takes place between adipocytes which store and elaborate substrates and the liver which processes free FA and glycerol into fuel for use by peripheral tissues. Increased delivery of free FA to hepatocytes may lead to ectopic storage (steatohepatitis or non-alcoholic fatty liver disease), which results in greater peripheral hyperinsulemia compared to free FAs delivered peripherally [117]. Moreover, increased circulating free FAs may lead to ectopic accumulation in other tissues such as heart, skeletal muscle, and pancreatic islet cells, further promoting insulin resistance [117-119].

More recently, echocardiographically determined epicardial fat thickness has been shown to better reflect magnetic resonance imaging-derived visceral fat mass than traditional waist circumference or waist-to-hip circumference ratios [109]. Epicardial fat thickness has been correlated with multiple measures of insulin resistance and glucose intolerance, and has been shown to be greater in individuals with MetS than without MetS. Much like the visceral adipose tissue drains directly into the liver *via* the portal vein, epicardial fat elaborates adipokines into the local microcirculation and thus modulates the metabolic and inflammatory environment shared by the myocardium. The buffer capacity for inert lipids is limited in both the liver and heart. Initially, excess FAs are stored in the form of triglycerides; however, excess lipids are

forced into alternative non-oxidative pathways that yield toxic reactive lipid species that result in cellular dysfunction and/or apoptosis (also known as “lipotoxicity”) [120].

6. Abnormal Fatty Acid Uptake and Oxidation in CMS

Long-chain FAs are the primary source of energy for the myocardium in the fasting state. Since most organs (including the heart) are not capable of *de novo* synthesis of FA and possess limited amounts of FA stored in cytoplasmic compartments, they rely heavily on exogenous FAs [121]. Altered myocardial substrate metabolism has been shown in several animal and human studies to be associated with abnormal cardiovascular phenotypes, including heart failure, hypertrophy, and diastolic dysfunction [94,122-127]. Patients with idiopathic dilated cardiomyopathy and/or hypertension heart disease have been found to have decreased myocardial efficiency [123,124]. Furthermore, a high serum triglyceride level is associated with diastolic dysfunction, further supporting a role for altered substrate metabolism in cardiovascular function [128]. In myocytes, 60-80% of FA uptake is *via* the sarcolemmal protein-facilitated FA transporter, CD36 [129]. The expression of CD36 is tissue-specific and entrained to the metabolic environment (ie, serum lipid, glucose, and insulin levels) by promoter elements responsive to peroxisome proliferator-activated receptors (PPARs: namely PPAR α , - β/δ and - γ). Interestingly, much like the myocardial glucose transporters GLUT1 and GLUT4, CD36 exists not only on the plasma membrane but also in intracellular pools that translocate to the cellular surface enabling acute regulation in appropriate substrate environments. Surface translocation of CD36 occurs with elevated serum insulin levels, obesity, and muscle contraction [130,131]. In animals, CD36 expression has been shown to track with rates of FA metabolism and to be upregulated in dysmetabolic states, including diabetes and high-fat feeding, and during heart development [132,133]. Studies of animal models have shown that CD36 plays a critical role in cardiovascular pathology. The spontaneously hypertensive rat (SHR) is characterized not only by hypertension, but also with other MetS traits, including insulin resistance and dyslipidemia. In SHR rats, modest decreases in myocardial FA transport rates and marked increases in myocardial glucose uptake are accompanied by ventricular hypertrophy, traits ameliorated by a diet mixture of short- and medium-chain FAs where transport is not dependent upon CD36 [134]. In mapping and microarray screening for blood pressure, insulin resistance, and dyslipidemic loci in congenic SHR strains, a defective CD36 gene has been identified as a likely candidate for all three traits [135]. Re-expression of CD36 in SHR recovered the phenotype.

The PPARs are nuclear receptor transcription factors with pleiotropic effects on intra- and extracellular lipid metabolism, glucose homeostasis, cell proliferation, inflammation, and atherosclerosis. Under normal conditions, PPAR α provides a link between physiologic and dietary-related stimuli and the expression of genes involved in myocardial FA utilization and LV hypertrophy in the mammalian heart, including CD36 [136]. In adipose tissue, PPAR γ is the primary regulator of CD36 expression and mediates adipocyte differentiation which is essential for preventing the ectopic deposition of FAs in non-adipose tissue [137]. CD36, under the regulation of endothelial cell PPAR γ expression, is also the scavenger receptor for oxidized-LDL; expression on macrophages promotes atherosclerotic plaque formation [138,139]. The peroxisome proliferator-activated receptor- γ coactivator-1 (PGC-1), a coactivator of the PPARs, is a critical transcriptional regulator of energy metabolism at multiple levels of cellular glucose and FA import and the entire program of mitochondrial metabolic pathways (FA oxidation, glucose oxidation, the tricarboxylic acid cycle, and oxidative phosphorylation) [140,141]. PGC-1 family members are also known to act through nuclear respiratory factor family members and transcription factor of activated mitochondria to enhance expression of oxidative phosphorylation enzymes and myocyte enhancer factor 2 proteins to stimulate the expression of glucose transporters [138,142,143].

7. Adipokines as Modulators of Substrate Metabolism and Inflammation

Adipocytes, and in particular visceral adipocytes, elaborate a class of substances known as adipokines that function as autocrine, paracrine, and endocrine signals critical in maintaining energy homeostasis. Leptin, which is secreted in direct proportion to subcutaneous fat, is a neurohormonal signal that triggers satiety in the hypothalamus. Animal models such as the leptin-deficient ob/ob mice or the leptin receptor-mutant Zucker Diabetic Fatty rat have helped clarify the role played by this signaling pathway in mediating obesity and insulin resistance [144]. While several studies have shown benefit in recombinant leptin therapy for lipodystrophy, replacement as an anti-obesity therapy is still under evaluation in clinical trials although early results are promising when leptin is combined with a strict hypocaloric diet [145-147]. Unlike leptin, the adipokine adiponectin is suppressed as fat mass increases. Adiponectin maintains insulin sensitivity by activating the AMP-activated kinase in metabolically active organs, stimulating FA oxidation and glucose catabolism (extensively reviewed in [148,149]).

Cytokines are well represented among the adipokines, the products of not only adipocytes but also infiltrating macrophages and stromal cells. Among the cytokines elaborated are tumor necrosis factor alpha (TNF- α), interleukins IL-1, IL-6, IL-8, monocyte chemoattractant protein-1. TNF- α , released from infiltrating macrophages upon exposure to free FA, favors insulin resistance and lipolysis with resultant increase in serum free FA levels; while decreased expression restores insulin sensitivity and lowers circulating free FAs [112]. TNF- α is also an inhibitor of adipogenesis *via* suppression of PPAR γ expression [150]. Likewise, IL-6 is abundantly produced by visceral adipocytes with expression levels correlated with fat mass. IL-6 is associated with glucose intolerance and insulin resistance, and increased levels are a risk factor for the development of T2D [53,151,152]. In the liver, adipose-derived IL-6 mediates insulin resistance *via* a nuclear factor-kappa B (NF κ B)-dependent pathway that is reversed by salicylate, an inhibitor of NF κ B signaling [153,154]. NF κ B is the pre-eminent transcriptional regulatory factor controlling the expression of and cellular response to inflammatory cytokines [155,156]. Not only is NF κ B activity increased in LV hypertrophy and the failing heart, but anti-inflammatory drugs that inhibit NF κ B have been proposed as cardioprotective agents [157,158]. The mitogen-activated protein kinase (MAPK) signal transduction cascade is a critical mediator of the NF κ B pathway and has been shown to respond to a variety of cytokines and receptors, as well as cardiac insults including experimental pressure overload hypertrophy, myocardial infarction, and oxidative stress [158-163]. Inhibitors of MAPKs are under active investigation as anti-inflammatory drugs and may be useful in the treatment of cardiac disease [161,164]. Cytokines have also been recognized to reciprocally impact nuclear receptor control of intermediary metabolism by altering the expression and activity of PPAR α , - β/δ , and - γ , as well as PGC-1 [150,165]. Consequently, modulation of the inflammatory cascade has emerged as a potential therapeutic avenue for treatment of CVD.

8. Acute and Chronic Inflammation in CVD

It is well established that inflammatory events such as septic shock or viral myocarditis are often accompanied by cardiac dysfunction [166,167]. The myocardium itself secretes inflammatory protein messengers in response to acute myocardial damage or heart failure [168-170]. Myocardial inflammation impacts cardiac structure and function by several mechanisms, including negative inotropic effects, cardiac myocyte apoptosis, and extracellular matrix degradation, all of which are associated with cardiac fibrosis, remodeling, and/or systolic/diastolic dysfunction [157,158,169,171,172]. Chronic low level inflammation, such as that evident by elevated CRP, is also linked to the development of CHD and heart failure, and represents a common finding among individuals with MetS and its component risk factors

[173-178]. Studies in humans have found that inflammatory mediators are increased in chronic systolic heart failure and are predictive of 6-year incidence of symptomatic heart failure [174-179]. In normal subjects and in patients with essential hypertension, markers of systemic inflammation (i.e., IL-6, TNF- α , and CRP) were found to independently predict blood pressure, arterial stiffness, and LV diastolic dysfunction [180-182]. Likewise, osteopontin, a paracrine regulator involved in both upstream and downstream activation of inflammatory pathways has been implicated in atherosclerotic plaque formation and carotid intima-media thickening [183-185].

Although acute and chronic inflammation is mechanistically linked to CVD, it remains unclear whether modulating inflammatory pathways improves CMS traits. Studies in hypertensive animals suggest that anti-inflammatory agents improve LV diastolic dysfunction, although regression of hypertension and LV hypertrophy are not consistent findings [186-188]. In a small clinical trial, short term therapy with high-dose aspirin, an inhibitor of NF κ B signaling, has been shown to improve fasting glucose, improve dyslipidemia, and reduce CRP [189]. Statins have also been found to exert direct anti-inflammatory effects in patients with MetS, possibly accounting for some of the cardiovascular benefit associated with this drug [190]. The TNF- α inhibitor infliximab has also been shown to improve vascular reactivity in patients with metabolic syndrome during hyperinsulinemia [191]. However, despite the data linking the inflammatory cascade with phenotypes of myocardial structure and function, there remains considerable controversy regarding the specific role played by the inflammatory cascade in cardiovascular disease traits. For example, pharmacologic inhibition of MAPK, a pivotal node in the inflammatory signaling cascade, prevented cardiac inflammation and attenuated LV systolic dysfunction in a mouse model of diabetes, although cardiac fibrosis and diastolic function were not affected. However, other studies in hypertensive and transgenic animal models suggest that interfering with the inflammatory cascade prevents myocardial fibrosis and subsequent development of LV diastolic dysfunction, without attenuating the hypertrophic response [186,187,192]. More importantly, clinical trials treating symptomatic systolic heart failure patients with the TNF- α blockers etanercept and infliximab have yielded disappointing results with either no benefit or trends towards increased mortality in the treatment arms, despite improvement in inflammatory biomarkers [193,194]. Lacking, however, are similar trials in patients with normal LV function. Thus, it remains uncertain whether antiinflammatory drugs represent a viable therapeutic target for the prevention of cardiovascular events in patients with the CMS.

Thus, overwhelming evidence has emerged suggesting that metabolic and inflammatory pathways to cardiovascular disease are functionally interconnected. Ligand-mediated activation of the PPARs reduces the expression of inflammatory cytokines and inhibits inflammation [111,195,196]. At least a portion of these effects are *via* physical interaction with, and deactivation of, NF κ B to reduce expression of genes involved in the inflammatory response [111,197-200]. On the other hand, inflammation reciprocally impacts nuclear receptor control of intermediary metabolism. In heart, acute inflammation causes diminished expression of PPARs and PGC-1 coincident with a down-regulation of enzymes involved in FA oxidation likely *via* NF κ B deactivation of PPARs [165,201]. In addition to their effects on inflammatory pathways, MAPKs also alter the activity of the PGC-1 and PPAR proteins *via* direct phosphorylation events [126]. While the exact mechanisms by which MAPK activity affects cardiac pathology is still unclear, studies suggest that the MAPK cascades are poised at the interface between the inflammatory and metabolic pathways and serve as critical integrators of these two biological systems.

9. Regression of CMS Phenotypes with Life Style Changes and Weight Reduction

Lifestyle interventions including increased physical activity and weight loss are universal recommendations for risk factor modification in individuals with MetS [101]. Most studies show that CHD risk factors and events decrease with weight reduction [56,58,202-205]. Improvement in blood pressure is often one of the earlier responses to weight loss; despite partial weight regain, blood pressures tend to remain lower than baseline in patient undergoing moderate weight loss [203,206]. More dramatic loss of weight following gastric banding has been associated with reduced glucose and insulin levels, lower serum free FAs, and an improved lipid profile following 25% loss of body weight [207]. More modest degrees of weight loss yield equivocal findings. For example, no improvement in lipids, glucose, insulin, or body fat distribution was noted in obese older women who lost on average 6 kg after a 24-week diet and exercise intervention [204].

Many non-traditional risk factors have been shown to regress with improved control of diabetes, hypertension, and with weight loss and/or exercise [208,209]. The response of cytokines to weight loss has been variable, with most studies showing at least trends towards improvement in adiponectin, leptin, TNF- α , IL-6, and CRP [151,210-213]. In one study, TNF- α expression and protein levels from subcutaneous fat were correlated with percent body fat, although paradoxically, lower levels were noted in individuals with body mass index (BMI) > 45 kg/m² [151]. TNF- α expression and protein levels were decreased, and lipoprotein lipase levels increased following weight loss by low calorie diet and exercise in obese subjects achieving 26% weight reduction [151]. Weight loss has also been shown to reduce steatohepatitis [214]. Unfortunately, while molecular analyses on visceral fat would likely be more informative, this tissue is more difficult to acquire in otherwise healthy humans.

In work recently published by our group, hypocaloric weight loss intervention over 24 months resulting in moderate weight loss (9.2%) was associated with beneficial changes in a number of indices of cardiovascular function including LV systolic and diastolic function, LV mass, and carotid artery intima media thickness [203]. The maximum benefit lagged behind maximal weight loss by 6-12 months. Although the maximum benefits of weight loss were somewhat diminished by subsequent weight regain, a net improvement persisted in all four measures after two years except for LV mass [203]. Given that the bulk of the evidence suggests that weight loss leads to an improvement of cardiovascular risk traits, lifestyle modification resulting in weight reduction remains the cornerstone intervention for patients with MetS. However, as recently shown by us and others, initial success in weight loss is most often followed by subsequent weight regain [203]; thus, effective pharmacologic interventions are desirable.

10. Drug Targets for CMS

PPAR γ is a ligand-activated nuclear receptor responsive to FA derivatives and eicosanoids (primarily prostaglandin J2) [111]. In addition to the key role played by PPAR γ as coordinator of adipocyte differentiation, it is also the major regulator of lipid storage in adipose tissue [215]. PPAR γ regulates the expression of a number of genes involved in FA uptake, transport, and esterification, including lipoprotein lipase which frees FA from circulating lipoproteins, CD36, which translocates FA across the plasma membrane, and FA transport and binding proteins which shuttle FAs in the cytoplasm [163,216,217].

A number of preclinical studies have elucidated the role played by PPAR γ in energy homeostasis, inflammation, and cardiovascular diseases. Global PPAR γ knock-out models are lethal due to abnormal placental development [218]. PPAR γ +/- mice are viable with normal insulin sensitivity on standard chow diets, but on a high-fat diet they appear protected against

obesity and insulin resistance compared to wild-type littermates [219,220]. Similarly, animals with a selective deletion of PPAR γ in adipocytes are also resistant to weight gain in response to a high-fat diet; normal insulin sensitivity is maintained although the expression of both leptin and adiponectin is decreased [221]. Conditional knockouts of PPAR γ expression in endothelial cells result in elevated blood pressure and heart rate only in those animals fed high-fat diets. [222]. Thus, animal models suggest that diet may participate in meaningful gene-environment interactions in modulating CMS traits.

PPAR γ is the target for synthetic class of agonists, the thiazolidinediones (TZDs), used to treat T2D. PPAR γ agonists enhance adipocyte insulin sensitivity, inhibit lipolysis, reduce myocardial triglyceride accumulation and plasma free FAs, and decrease the expression of leptin and TNF- α ; adiponectin expression is increased [144,195,223,224]. Although PPAR γ agonists decrease visceral and hepatic fat, thus improving insulin sensitivity, TZD therapy results in a redistribution of visceral to subcutaneous fat, contributing to weight gain [225]. Furthermore, PPAR γ -mediated stimulation of a sodium channel in the renal collecting duct contributes to peripheral edema which may increase the risk of heart failure [226].

T2D patients experience a 2-3 times greater all-cause mortality compared to a non-diabetic/non-MetS group; much of the excess mortality is attributable to CVD [77-79]. As such, therapies for T2D must be evaluated in the context of their impact on cardiovascular risk factors and events. In clinical studies, the pleiotropic effects of TZDs have been demonstrated in studies showing improved glycemic control, reduced dyslipidemia, slowing of progression of carotid intima-media thickness, decreased target vessel revascularization, and improved indices of vascular function in T2D patients [227-231]. The mechanism for these beneficial changes is due, at least in part, to improved energy homeostasis. Cultured skeletal muscle cells from normal subjects and T2D patients have been shown to have normalize palmitate accumulation in response to the TZD troglitazone [232]. Individuals heterozygous for dominant-negative PPAR γ mutations resulting in partial lipodystrophy are characterized by severe peripheral and hepatic insulin resistance, metabolic syndrome, and steatohepatitis; in these patients, treatment with the TZD rosiglitazone restored some subcutaneous fat mass, reduced insulin resistance, and improved leptin and adiponectin levels [233]. However, the advantages of TZD therapy must be weighted in the context of potential adverse effects [225].

Most clinical studies have noted improvement in cardiovascular outcomes with TZD therapy despite lingering concerns regarding increased risk in some populations. Famously, the first TZD marketed, troglitazone, was removed from the market after increased risk of liver failure was identified [234]. For the other TZDs, only smaller clinical studies are available that directly assess cardiovascular structure and function. One such small study identified no significant differences in echocardiography-derived indices of LV structure and mass in patients with T2D treated with rosiglitazone versus a sulfonylurea [235]. Another small study (n=30) of T2D patients noted improved LV diastolic function with pioglitazone despite no change to LV mass [236].

Larger randomized clinical trials provide outcome data. The prospective, randomized PROactive Study (n=5238) found that pioglitazone reduced the risk of the secondary endpoint, a composite endpoint of all-cause mortality, nonfatal myocardial infarction, and stroke; however, the primary endpoint including a broad composite of cardiovascular and procedural events did not achieve statistical significance [230]. Glycemic control (despite a reduction in the rate of transition to insulin), dyslipidemia, and blood pressure were improved with the study drug [230]. However, heart failure and peripheral edema were more common with pioglitazone [229,230]. Recently, the RECORD study identified increased heart failure risk associated with rosiglitazone in an open-label, prospective, randomized study. Although the risk of

cardiovascular events and death was similar to the control group, hospital admissions for heart failure were increased (hazards ratio 2.0 [95% CI 1.35-3.27]) [237]. However, some hospitalized patients with isolated peripheral edema may have been misclassified as having heart failure. A Kaiser Permanente Medical Care Program cohort study, however, failed to identify similar finding with pioglitazone [238]. The RECORD study also identified an increased risk of lower leg fractures in women in the treatment arm, prompting renewed concerns about the long-term safety of TZDs. Finally, a meta-analysis of randomized rosiglitazone trials including 15,565 individuals found the odds ratio for myocardial infarction was 1.43 (95% CI 1.03-1.98, $p=0.03$) and for cardiovascular death 1.64 (95% CI 0.98-2.74, $p=0.06$), a finding of borderline significance [239]. Hoping to further clarify risks associated with TZD therapy, the Italian National Agency of Pharmacological Surveillance (AIFA) has recently endorsed a multicenter prospective trial on incident heart failure in 5,000 T2D patients taking pioglitazone. Thus, although the weight of the evidence supports that TZDs benefit many T2D patients, lingering safety concerns have led to interest in developing alternative drugs with partial PPAR γ -agonist properties. Due to variability in risk assessments, patients with New York Heart Association functional class III or IV heart failure are generally excluded from TZD therapy.

Selective PPAR γ -modulators (SPPAR γ Ms) are a new class of drugs designed to selectively activate PPAR γ pathways in specific tissues. For example, current efforts attempt to design a SPPAR γ M that avoids stimulating sodium channels in the kidney, thus minimizing the risk of peripheral edema and/or heart failure. The selectivity of these compounds rests in the manner in which the drug conformed to the PPAR γ ligand-binding domain [240,241]. Angiotensin is a critical regulator of blood pressure, vascular remodeling, and insulin resistance. In animal models, TZDs attenuate angiotensin-induced hypertension and the hypertrophic response to myocardial strain in mice [231,242]. Some angiotensin-receptor blockers, telmisartan in particular, have been shown to function as SPPAR γ Ms at clinically relevant serum concentrations. Recently, smaller clinical trials have suggested that telmisartan may improve glucose tolerance and decrease the risk of new-onset T2D in hypertensive patients, possibly by inducing adipocyte differentiation and/or the expression of adiponectin [241,243-245]. Although telmisartan is a partial PPAR γ agonist capable of enhancing the expression of target genes including PGC-1, lipoprotein lipase, and adiponectin, it has not been associated with peripheral edema or fluid retention as have the TZDs [244].

PPAR α agonists including fibric acid derivatives such as fenofibrate and gemfibrozil are commonly prescribed in patients with hypertriglyceridemia. More recently, clinical trials have addressed the cardiometabolic benefits of PPAR α agonists. Worthy of mention, is a novel dual PPAR α/γ agonist which has shown early promise in phase II clinical trials. The SYNCHRONY study is a dose-ranging, double-blinded study of 332 patients with T2D treated with the dual agonist aleglitazar [246]. After 16 weeks of treatment, aleglitazar, particularly at higher dosages, was noted to effectively decrease HgbA_{1C} and improve fasting lipid levels to a greater extent than both the placebo and pioglitazone groups. Side effect profiles were similar and weight gain was less compared to the pioglitazone group [246]. Thus, the PPARs represent targets for ongoing drug development as efforts to maximize the metabolic modulating effects of these transcription regulators while minimizing adverse events. Consistent with animal models of reduced PPAR γ activation (ie, PPAR γ ^{-/-} and adipocyte-restricted knock-outs), early data suggests that partial PPAR γ agonists designed to maximize benefit while minimizing adverse effects hold promise for future drug development.

In recent years, the endocannabinoid system represented a promising drug target in the treatment of CMS due to its role in maintaining energy balance (reviewed in [247]). In addition to its well-known effect of stimulating appetite, receptor agonists activate the MAPK/NF κ B signaling cascade at the center of the inflammation-metabolism pathways. Rimonabant, a

potent endocannabinoid receptor agonist, was tested in clinical trials including overweight and obese (BMI >27 kg/m²) individuals. The group receiving the higher dose (20 mg) of rimonabant experienced a 6.3 kg weight reduction at 1 year compared to 1.6 kg loss in the diet-only control group with a concomitant improvement in CMS risk factors [248]. However, the study was limited by an excessive dropout rate, largely a consequence of adverse psychiatric, nervous system, and gastrointestinal effects. Concerns related to the neuropsychiatric effects of rimonabant lead the US Food and Drug Administration Advisory Committee to not approve the drug based on an overall odds ratio for suicidality of 1.9 (95% CI 1.1-3.1) on the 20 mg dose versus placebo [249]. Subsequent efforts to develop endocannabinoid receptor agonists without neuropsychiatric adverse effects have thus far been unsuccessful [250].

11. Conclusions

The clustering of cardiovascular risk factors in MetS and in the CMS reflects the intersection of pathways responsible for energy homeostasis and inflammation. Lifestyle changes, including caloric restriction and increased energy expenditure, represent the foundation upon which all therapeutic efforts should build. The pleiotropic effects of the molecular mechanisms underlying obesity, insulin resistance, dyslipidemia, atherosclerosis and myocardial dysfunction suggest that drug development efforts will necessarily impact multiple organ systems. Currently, no pharmacologic interventions specifically target CMS; rather, treatment is directed at the individual component risk factors. In this review, the molecular pathways responsible for substrate metabolism and for controlling inflammation were noted to intersect at the level of MAPK and NFκB signaling. Importantly, the endocannabinoid receptors also activate these kinases. Thus, future drug development efforts should attempt to capitalize on molecular nodes at the intersections of these pathways in the CMS.

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