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Cardiovascular Consequences of Metabolic Syndrome

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Abstract

The metabolic syndrome (MetS) is defined as the concurrence of obesity-associated cardiovascular risk factors including abdominal obesity, impaired glucose tolerance, hypertriglyceridemia, decreased HDL cholesterol, and/or hypertension. Earlier conceptualizations of the MetS focused on insulin resistance as a core feature, and it is clearly coincident with the above list of features. Each component of the MetS is an independent risk factor for cardiovascular disease and the combination of these risk factors elevates rates and severity of cardiovascular disease, related to a spectrum of cardiovascular conditions including microvascular dysfunction, coronary atherosclerosis and calcification, cardiac dysfunction, myocardial infarction, and heart failure. While advances in understanding the etiology and consequences of this complex disorder have been made, the underlying pathophysiologic mechanisms remain incompletely understood, and it is unclear how these concurrent risk factors conspire to produce the variety of obesity-associated adverse cardiovascular diseases. In this review we highlight current knowledge regarding the pathophysiologic consequences of obesity and the MetS on cardiovascular function and disease, including considerations of potential physiologic and molecular mechanisms that may contribute to these adverse outcomes.

Keywords

Metabolic syndrome; obesity; atherosclerosis; cardiovascular disease; adipokines

INTRODUCTION

The association between visceral obesity, hypertension, and atherosclerosis was recognized as early as 1765 by Joannes Baptista Morgagni in his seminal work entitled ‘De sedibus et

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causis morborum per anatomen indagata'.(1) Later studies by Hitzenberger, Richter-Quitner, and Kylin in the early 1920's further documented the co-incident relationships between metabolic abnormalities such as hyperglycemia, hypertension, and other maladies such as hyperuricaemia.(2) These pioneering efforts laid the groundwork for what is now commonly referred to as the "Metabolic Syndrome" (MetS), a clustering of inter-related and co-incident risk factors which include abdominal obesity, impaired glucose tolerance, hypertriglyceridemia, diminished high density lipoprotein (HDL) cholesterol, and/or hypertension.(3) The original conceptualization of this syndrome focused on a central role of insulin resistance,(3) and this is clearly a concurrent and associated feature. More recently the focus has been on the MetS as an epidemiologic tool related to cardiovascular disease risk, and therefore traditional cardiovascular disease risk factors have been adopted as the defining features. Although the precise definition of what clinically constitutes the MetS has generated considerable debate, it is well accepted that these co-morbidities represent a pathological state that substantially augments risk for the development of type 2 diabetes mellitus and atherosclerotic cardiovascular disease.(4)

As of 2014, the Centers for Disease Control and Prevention estimates that ~70% of adults in the United States are overweight or obese, with ~40% of these individuals considered obese (defined as body mass index (BMI) ≥30 kg/m^2). The National Health and Nutritional Examination Survey (NHANES) estimates that ~30% of overweight and ~60% of obese men and women meet the criteria for a diagnosis of MetS;(5) in other words, a majority of obese people carry the concurrent risk features that identify them as carrying augmented risk of cardiovascular disease. Therefore, in parallel with the obesity epidemic, the MetS is a growing epidemic, affecting ~20% of adults in the Western world.(6) Each component of the MetS is an independent risk factor for cardiovascular disease,(4, 6) together producing a wide spectrum of vascular and cardiac diseases.(7-13) While some advances in understanding the etiology and consequences of this complex disorder have been made, the underlying mechanisms that translate these obesity-associated risk factors into the full spectrum of observed cardiovascular pathologies remain insufficiently explained. The purpose of this review is to highlight current knowledge regarding the pathophysiologic consequences of obesity and the MetS and to outline recent advances in potential mechanisms that may contribute to these adverse cardiovascular outcomes. The literature linking type 2 diabetes with cardiovascular outcomes will not be reviewed in detail, because type 2 diabetes exerts effects on cardiovascular disease distinct from those of the underlying obesity and MetS and this would detract from our focus on obesity/MetS. Previous reviews by Abel *et al.*,(14) Poirier *et al.*,(15) Jiamspripong *et al.*,*(16)* Mottillo *et al.*,(17) Bastien *et al.*,(18) and Grundy and colleagues.(4, 11, 19) have summarized current epidemiology or evaluated specific cardiac conditions in the connection between obesity/MetS and cardiovascular disease. Here we focus on physiologic and pathophysiologic aspects of obesity- and MetS-associated changes in hemodynamics, microvascular dysfunction, myocardial metabolism, atherosclerosis and calcification, and infarction and heart failure.

HEMODYNAMIC AND CARDIAC EFFECTS OF OBESITY AND THE METABOLIC SYNDROME

The observed association of obesity with hypertension prompted a body of work exploring causes and effects of obesity on the heart. Chronic increases in body weight and adiposity can lead to significant neuro-hormonal changes and adaptations in the cardiovascular system.(18, 20) These alterations include activation of the activation of the renin-angiotensin-aldosterone system,(21, 22) altered levels of adipocytokines,(23-27) and pro-inflammatory cytokines(28, 29), and activation of the sympathetic nervous system.(30-33) Sympathetic nervous system activation can contribute to commonly described increases in heart rate, renal sodium retention, circulating blood volume, ventricular end-diastolic volume (pre-load), cardiac output, and/or blood pressure.(18, 30, 34) More generally, over activation of the sympathetic nervous system can concurrently drive abnormalities of vascular and cardiac function (e.g. vasoconstriction, tachycardia) and abnormalities of metabolic balance (e.g. excess lipolysis driving fatty acid levels, cathechol-induced peripheral and hepatic insulin resistance) (33). The degree to which these changes result directly from adrenergic receptor activation versus secondary alterations in adipokines, cytokines, and renal salt and water retention remains an active area of investigation.

Although insulin resistance has been dropped from the clinical definition of the MetS, the fact remains that underlying insulin resistance contributes to many of the features of the MetS (dysglycemia, elevated fatty acid levels, hyperinsulinemia and potentially a contribution of hyperinsulinemia to sympathetic system activation, among others)(35, 36). The epidemiologic literature consistently demonstrates associations of hyperinsulinemia with obesity-related heart disease (37). Studies of the metabolic physiology of insulin resistance have led to a deeper understanding of the interplay of fuel selection, with excess fatty acids contributing in part to cellular resistance to glucose metabolism but also with impairment in insulin receptor and post-receptor signaling events and abnormalities in mitochondrial number and function all contributing to the overall phenomenon (38-40). The contributions of these factors to abnormalities in myocardial metabolism are reviewed below.

Obesity-associated changes in cardiac function have been described as the ‘cardiomyopathy of obesity’. Data from the Multi-Ethnic Study of Atherosclerosis (MESA) demonstrate a direct association between left ventricular end-diastolic volume and body mass index in men and in women.(41) This large population based study also found that left ventricular mass increased to a greater extent than ventricular volume in obesity.(23, 41) Although early studies into the ‘cardiomyopathy of obesity’ suggested that obesity resulted in volume overload and eccentric cardiac hypertrophy,(42, 43) more recent findings have established that the majority of obese subjects develop concentric left ventricular hypertrophy as well as mild (subclinical) diastolic and/or systolic dysfunction, with normal or elevated left ventricular ejection fraction.(41, 44-48) This can be associated with poor outcomes following cardiac intervention procedures (49). More sensitive measures of contractile function such as left ventricular fractional shortening, systolic velocity, and myocardial strain (circumferential and longitudinal) have been shown to be impaired in the setting of

obesity and/or MetS.(45, 48, 50, 51) Alterations in load-independent measures of myocardial contractility (e.g. end-systolic pressure volume relationship) have also been reported in animal models of obesity/MetS(52-54) and in obese humans with essential hypertension.(55) Importantly, cardiac functional responses to physiologic perturbations (e.g. exercise),(56-58) pathologic conditions (e.g. myocardial ischemia)(59-61), or pharmacologic stimuli (e.g. catecholamines, glucagon-like-peptide-1 mimetics)(52, 62, 63) are also known to be significantly influenced by an obese/MetS phenotype.

The molecular mechanisms underlying this cardiac and hemodynamic phenotype are complex and incompletely characterized. Investigators in this field have identified relevant and important molecular pathways linking obesity to cardiac dysfunction. In particular, alterations in myocardial Ca^{2+} handling via changes in the functional expression of SERCA2A and ryanodine (RyR2) receptors(52, 57, 64) have been of interest, including a recent comprehensive paper demonstrating concurrent effects of RyR2 abnormalities to induced myocellular and β-cell dysfunction (65), affecting subcellular structures in addition to producing abnormalities in intracellular Ca^{2+} handling (66). This shared dependence of the myocardium and β-cell highlights the need for further studies in to the mechanisms underlying the dysfunctional regulation of Ca^{2+} in obesity/MetS. Also of note is a growing interest on modifications in the regulation of myocardial titin (which influences the passive and restoring force of the cardiac sarcomere and can contribute to hypertrophic signaling) as a potential target or mediator of obesity-associated cardiac dysfunction.(52, 67-71) There is of course the added possibility that progressive vascular disease further influences these changes through mechanisms specific to the atherosclerotic process, or relating to microvascular dysfunction, independent of the obese state.(7, 9, 72) These examples highlight the opportunities to better understand the pathophysiologic manifestations of obesity/MetS by exploring key shared cellular mechanisms.

MICROVASCULAR DYSFUNCTION IN OBESITY AND THE METABOLIC SYNDROME

In all vascular beds, the microcirculation is the primary site of blood flow regulation, through regulation of resistance to flow at the level of the microvasculature. Microvascular resistance is simultaneously modulated by a variety of intrinsic (myogenic) and extrinsic (endothelial, neural, hormonal, metabolic) mechanisms which collectively dictate overall tissue perfusion.(73) There is a strong body of evidence demonstrating that control of microvascular tone and microvascular density are significantly impacted by obesity status, and that the MetS is similarly associated with physiologically important alterations in the regulation of arteriolar resistance. For example, changes in microvascular structure and function in obesity/MetS have been shown to result in an overall imbalance between tissue oxygen delivery and metabolism in many vascular beds, including heart,(7, 9, 74, 75) kidney,(76) brain,(77) and skeletal muscle.(78, 79)

In the coronary circulation, microvascular dysfunction has been demonstrated as reductions in coronary vasodilator responsiveness to a variety of pharmacologic agonists.(75, 80-82) Importantly, diminished coronary flow reserve is a powerful predictor of major adverse

cardiovascular events.(72) Furthermore, the MetS significantly impairs the balance between coronary blood flow and myocardial metabolism in response to exercise (local metabolic vasodilation),(83, 84) with alterations in coronary perfusion pressure (pressure-flow autoregulation),(85) and in response to cardiac ischemia (reactive hyperemia).(84) Importantly, these changes occur prior to any evidence of overt atherosclerotic disease and have been associated with diminished diastolic and systolic contractile function in obese/MetS in humans(47, 86, 87) and in animal models.(20, 57, 88) These findings indicate that underlying coronary microvascular dysfunction likely contributes to reductions in cardiac contractile function,(45, 47, 48, 51) to concentric ventricular hypertrophy,(41, 44-48, 89) and to the significant increases in risk of myocardial infarction(17) and cardiovascular mortality(8, 90, 91) observed in obese individuals with the MetS.

Microvascular dysfunction in obesity has also been documented in other vascular beds such as the kidney, brain, and skeletal muscle, as noted above. Obesity and MetS augment renal vasoconstriction in response to angiotensin II,(92, 93) impair renal autoregulation,(94) and blunt myogenic afferent arteriolar constriction.(95) In contrast, diminished vasodilator responsiveness and increased myogenic activation is evident in isolated middle cerebral arteries and gracilis arterioles from obese Zucker rats.(77, 96, 97) This skeletal muscle microvasculopathy is associated with an enhanced rate of fatigue and decreased maximal force development of skeletal muscle,(79, 97, 98) which can be largely corrected through pharmacologic enhancement of perfusion.(98, 99) Renal, cerebral, and skeletal muscle circulations have also been shown to be adversely affected by obesity and the MetS, which produce diminish microvascular-capillary density.(9-13, 100, 101) Significant coronary vascular remodeling and altered vascular wall mechanics have also been documented in obese swine with MetS.(85) Aside from impaired oxygenation and tissue hypoxia, microvascular dysfunction in MetS has also been suggested to play a role in the development of glomerular injury, tubular atrophy, interstitial fibrosis,(76, 95) and exacerbation of injury in the setting of peripheral vascular disease(98) or stroke.(77)

A related aspect of microvascular dysfunction is impaired dilator/constrictor tone. It is apparent that underlying activation of the renin-angiotensin-aldosterone system, the sympathetic nervous system, and inflammatory pathways contributes to a diminished vasodilator and augmented vasoconstrictor phenotype of the MetS.(7) A hallmark of MetS-induced vascular disease is impaired endothelial function, which is associated not only with diminished bioavailability of nitric oxide but also increased production and/or vascular sensitivity to endothelial-dependent vasoconstrictors such as endothelin-1, prostaglandin H_2, and thromboxane A_2.(7, 20, 31) Endothelial dysfunction is pathologically important not only for the modulation of vascular resistance and tissue perfusion but also as a critical step in the initiation and progression of vascular atherogenesis.(102) MetS is also associated with alterations in the functional expression of, and electromechanical coupling between, voltage-dependent K^+ and Ca^{2+} channels.(7, 83, 84, 88, 103, 104) Continued research to elucidate the precise mechanisms responsible for the deleterious impact of the MetS on microvascular function is needed, and stands to provide novel targets for directed therapies needed to treat the pathologic consequences of this multifactorial syndrome.

MYOCARDIAL METABOLISM IN OBESITY AND THE METABOLIC SYNDROME

As noted in the introduction, insulin resistance is a key underlying component of the pathophysiology of the MetS. This applies to the heart, which is subject to systemic alterations in fuel delivery as well as to the effects of systemically and locally produced regulatory factors such as hormones and adipokines. Here we review what is known about the dysregulation of myocardial metabolism in obesity/MetS and how this contributes to functional abnormalities that characterize this syndrome.

The myocardium is a metabolic omnivore. In other words, myocardium is capable of sustained function using fuels including, but not limited to, acetate, glucose or long-chain fatty acids. In health the heart preferentially consumes fatty acids, which provides the most energy per unit of fuel (i.e. moles of ATP per mole of fatty acid), but conversely requires more oxygen for each ATP unit generated (requiring 0.24 mole O_2 per mole ATP generated) compared to glucose (0.16 mole O_2 per mole ATP generated).(105) Like other tissues, the myocardium responds to insulin by shifting toward glucose uptake and glucose oxidation,(106) and interestingly the myocardium also responds to glucagon-like peptide 1 (GLP-1) to shift toward glucose uptake and oxidation.(52, 107, 108) Although the capacity of myocardial tissues to respond in this way is established, it is not clear how these actions contribute to the regulation of myocardial fuel selection in the course of normal physiology.

Abnormalities in myocardial fuel substrate selection in obesity have been described, as well as abnormalities in the responses to shifts in substrate availability, and abnormalities in the responses to hormonal controls. In obesity, the myocardium exhibits abnormally increased rates of fatty acid uptake and oxidation, and an impaired ability to shift away from this increased fatty acid utilization.(109, 110) Such abnormalities have been shown in animal models of insulin resistance,(111-113) in humans with obesity/insulin resistance,(46, 114, 115) and in obese humans with Type 2 diabetes.(116) This lipotoxicity effect is in addition to the previously described adverse effects of hyperglycemia on myocardial fuel selection (which combined exert ‘glucolipotoxicity’) (117), although the hyperglycemia is modest in MetS in the absence of concurrent diabetes. Notably, emerging data suggests a sexual dimorphism, with increased rates of fatty acid uptake and utilization in female animal models(110, 118) and in women.(115, 119, 120) The implications of this sexual difference in fuel selection on obesity-related myocardial disease are not yet known, but this phenomenon may help explain the relatively greater adverse effect of the development of diabetes on myocardial outcomes in women.(114)

Increased fatty acid uptake is not due simply to increased rates of fatty acid delivery in the setting of obesity. Rather, there is evidence for increased transport capacity and increased rates of fatty acid transport. The major sarcolemmal fatty acid transport proteins, CD36 and FATP, are over-expressed in animal models of obesity.(112, 121, 122) Lipoprotein lipase, functioning in adipocytes or in vasculature more proximal to the myocardium to liberate fatty acids from the circulating storage form of triacyglyerols, may also contribute to the detrimental phenotype of elevated fatty acid uptake.(123) Augmented fatty acid uptake in obesity is also not simply a neutral shift in fuel preference. Experimental studies limiting or

augmenting fatty acid uptake have demonstrated that increased fatty acid uptake can lead to impairments in myocardial function, and that limiting fatty acid uptake can rescue the heart from this lipotoxic circumstance.(46, 124-128)

Distinct from questions of fatty acid availability and uptake, there is a question of whether insulin resistance contributes separately to abnormal myocardial metabolism in obesity. Many prior reports have linked obesity and insulin resistance with increased myocardial fatty acid uptake and utilization, as detailed above. Resistance to insulin action in the heart to drive glucose uptake is not consistently seen, particularly in human studies.(46, 129-132) Experimental evidence from animal models demonstrates impairment in insulin-stimulated myocardial glucose uptake, impairment in insulin's effects to modulate blood flow, and impairment in insulin's role as a regulator of cell growth and cell cycle in the setting of obesity or isolated myocardial fat loading.(127, 131, 133-135) Nevertheless, from the systemic viewpoint it appears that the actions of insulin in tissues outside the heart, acting to regulate fuel supply and other regulatory factors, exert larger effects on myocardial metabolism than its direct actions on the heart.(106, 129) It is therefore unclear whether myocardium-specific insulin resistance is a therapeutic target. Nevertheless, treatments that improve systemic insulin resistance can exert beneficial effects on myocardial metabolism, so systemic insulin resistance remains a valid overall target.(136-138)

Other features of obesity, such as abnormalities in adipokines (e.g. adiponectin and leptin) and increased systemic inflammation, may impact myocardial fuel selection or myocardial responses to injury.(139-141) Effects of adiponectin to directly modulate myocardial metabolism have been shown in experimental models,(142) and the importance of leptin for normal cardiac function and development is demonstrated by the abnormal cardiac phenotype of leptin-deficient animals.(143) The actions of these and other adipose-derived factors on the heart may reflect concurrent effects on systemic hemodynamics, vascular function, endothelial response to injury in addition any direct effects on myocardial metabolism.(27, 142, 144)

The implications of these metabolic abnormalities along with microvascular dysfunction and atherosclerotic vascular lesions on cardiovascular outcomes in obesity and the MetS are discussed separately below.

ATHEROSCLEROTIC DISEASE AND VASCULAR CALCIFICATION

Thirty years of focused research have shown that increasing degrees of obesity and the MetS are associated with accelerated atherosclerosis and a greater incidence of coronary heart disease.(145-150) These higher rates of atherosclerotic disease have been shown to result in an ~2-fold increase in risk of myocardial infarction(17) and a significantly elevated risk of cardiovascular mortality.(8, 90, 91) Further, this increase in cardiovascular risk is proportionally greater in women compared to men.(10, 17, 90) Recent findings from the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study indicate compositional differences in coronary plaques underlie these increased event rates, with evidence for increased prevalence of adverse features (total plaque burden, necrotic core and calcium content, among others) in untreated, non-culprit

lesions from patients with MetS or diabetes.(151) Increased prevalence and absolute progression of coronary artery calcification has also been demonstrated in the setting of the MetS and augmented cardiometabolic risk.(152-154)

The molecular mechanisms underlying the augmented initiation and progression of MetS-induced vascular disease remain an area of active research. Recent work has focused on the idea of adipose-derived hormones and cytokines ('adipokines') as molecular links between adiposity and vascular disease(155). Roles of adipokines in the regulation of many relevant features of obesity-associated cardiovascular disease have been described, including effects of adipokines on insulin sensitivity (leptin, adiponectin and resistin), inflammation (IL-8, monocyte chemotactic protein 1, leptin, chemerin), coagulation (plasminogen activator inhibitor-1), and vascular function and atherosclerosis (leptin, resistin, tumor necrosis factor-alpha, adiponectin,visfatin, omentin).(24, 156-163) Relevant fat depots also include the fat on the heart itself. Cardiac adipose tissue volume expands with obesity, but accumulates preferentially around coronary arteries, and atherosclerotic plaques occur predominantly in arteries encased by perivascular adipose tissue (PVAT).(164, 165) Recent work is evaluating an "outside-to-inside" signaling paradigm by which adipokines released from coronary perivascular adipose tissue (PVAT) are capable of influencing the development of vascular dysfunction and atherosclerosis in immediately adjacent vessels.(156, 166-170) Future studies are needed to better delineate the relative importance of systemically derived versus locally produced adipokines, to better understand the molecular mechanisms linking adipokines to vascular pathophysiology, and to assess whether these signaling pathways constitute therapeutic targets that may be of specific benefit in combating cardiovascular disease in obesity and MetS.

MYOCARDIAL INFARCTION AND HEART FAILURE IN OBESITY AND THE METABOLIC SYNDROME

Obesity and the MetS are associated with increased risk of heart disease, with two distinct diseases represented. First, obesity predisposes to congestive heart failure. Second, obesity is a contributor to risk of atherosclerotic heart disease, distinct from the effects of concurrent diabetes. The other components of the MetS are themselves epidemiologic risk factors for these conditions, working concurrent with the obesity effect to augment risk for each of these conditions.

The association of obesity with congestive heart failure is well recognized but remains unexplained. This condition was historically called 'obesity cardiomyopathy', and felt to arise due to effects of systemic and pulmonary hypertension, with contributory effects of obstructive sleep apnea.(20, 171) Unlike heart failure associated with atherosclerotic disease, diastolic dysfunction is a dominant aspect of the obesity-associated impairment in myocardial function.(172) Experimental and clinical trial evidence suggests that some of this dysfunction is associated with the aberrant fatty acid uptake phenotype of the obese heart, and amenable to improvement by reducing myocardial fatty acid uptake.(173-176) Epidemiologic evidence links hyperinsulinemia with heart failure,(177-179) and there is a body of experimental study evidence suggesting that insulin resistance in the heart is a

contributor to the pathogenesis of heart failure.(129, 131) Unfortunately this literature is confusing in that insulin resistance is also described as a consequence of heart failure of various etiologies, with opposite systemic metabolic phenotypes to what is seen in obesity. (180-182) Emerging evidence suggests that impaired myocardial metabolic responses to GLP-1 may exist in obesity.(62, 183) GLP-1 derived treatments may represent a novel approach to metabolic modulation for heart failure,(184, 185) although the myocardial effects in populations with obesity will need to be carefully evaluated.

The association of obesity with atherosclerotic heart disease has been recognized for more than 50 years.(147) The ongoing obesity epidemic has made this component of population cardiovascular disease risk increasingly apparent, and urgent. The approach to cardiovascular disease prevention and management is not different in those with obesity, and is focused on prevention through management of risk factors such as blood pressure, smoking, and cholesterol (primarily with ‘statin’ class medications) and on revascularization when necessary. Weight loss interventions, including diet/exercise (‘lifestyle’) paradigms, pharmacologic treatment and surgically induced weight loss, can reverse the magnitude of cardiovascular risk that is represented in the MetS components (186-189). However, lifestyle change to induce weight loss failed to improve cardiovascular risk among a population with type 2 diabetes in the LookAHEAD study.(186) Similarly, medications that induce weight loss have not been shown to prevent future cardiovascular disease, and in some instances these medications also exert separate adverse cardiac effects.(187, 188) In contrast, surgically-induced weight loss studies suggest long-term survival benefits including diabetes remission and reduced rates of atherosclerotic coronary vascular disease, (186, 190, 191), along with improvements in obesity-associated derangements in cardiac microcirculation, structure, and function (192, 193). These discordant results suggest that either the degree of weight loss with non-surgical approaches was insufficient to achieve benefit, or that surgically induced weight loss confers weight-independent cardioprotection. Therapies targeting metabolic abnormalities for atherosclerotic heart disease in obesity are under investigation. Prior studies were focused on potential benefits of PPAR-gamma agonists (modulating fatty acid delivery and peripheral insulin resistance),(194) but this class of agents has since fallen out of favor with subsequent revelations of increased fluid retention rates, increased rates of bone loss, and uncertainty regarding net cardiovascular disease benefits. More recently the glucagon-like peptide 1 (GLP-1) mimetics have begun to be evaluated. These treatments, originally developed for management of glycemia in Type 2 diabetes, may have distinct beneficial effects to reduce rates of atherosclerotic disease and it is likely that studies of cardioprotection in obesity will be soon to follow.(183, 195-197)

INSIGHTS FROM PROTEOMIC AND GENOMIC STUDIES

As with the physiologic changes seen in obesity/MetS, the genetic and molecular factors underlying the cardiovascular perturbations in MetS are complex and inter-related. A considerable body of evidence has been produced identifying molecular changes associated with obesity and the individual components of the MetS. Modern high-throughput, comprehensive molecular methodologies (the so-called ‘omics’ methods) assessing genetics, nucleic acids, proteins, or metabolites hold the promise of providing insights into biologic processes with an opportunity to assess all concurrent molecular changes. These methods

can provide powerful integrative insights into whole-body, tissue, and/or cellular physiology, but at the cost of producing a large number of inter-related results that can be challenging to interpret. Associations between select miR species and specific cardiovascular disease, along with associations with putative mechanistic mediators, have been observed for atrial fibrillation (198), and cerebrovascular disease (199), along with associations with pathophysiologic mediators of vascular disease including lipid metabolism (200)and endothelial dysfunction (201). A comprehensive review of the current state of knowledge linking miR and cardiovascular disease has recently been published (202). The literature specifically evaluating miR associations with cardiovascular disease in obesity/MetS is relatively sparse, and in the current context worthy of a detailed presentation.

Using microarrays, Phillip-Couderc *et al.* identified 63 genes that were differentially expressed in dog ventricles following 24 weeks of diet-induced obesity and hypertension.(203) Using hierarchical clustering analyses, they were able to identify groups of co-regulated genes and ascribe predicted functions to the products of the differentially expressed genes. The identified gene groupings were associated with many diverse cellular functions in the myocardium including regulation of cell proliferation and cell structure, key functional pathways such as calcium handling, response to cellular stress, and regulation of energy metabolism and mitochondrial function.(203) Of note, this study demonstrated that changes to the transcriptome took place continuously over the 24 week experimental timeline.

Nucleic acids are now well recognized to fill roles beyond information storage and transmission. Multiple functional RNA moieties have been discovered, including subsets with particular topological structures (e.g. shRNA), and others with sequence-specific actions to modulate transcription (siRNA) or post-transcriptional events (lncRNA, miRNA). One important group of post-transcriptional modulators, the microRNAs (miR), have been reported to contribute to the regulation of metabolic disease(204-206) and of cardiovascular disease.(207-209) Initial studies of the effects of miRs were associative and often focused on single miR species, but studies of the regulation of miRs, direct actions of miRs, and concurrent changes in multiple miR species are beginning to appear. For example, recent work by our lab(52) and others(204, 210) suggests that a complex system of factors (obesity/MetS, myocardial ischemia, pharmacologic therapy) alters the expression of miRs which in turn are linked with the regulation of cellular functions and/or pathophysiologic responses. The emerging paradigm is one in which miR expression changes are not necessarily inextricably related to a particular pathology (though some may be(210)), but instead are determined by multiple concurrent factors including underlying metabolic disease, cardiovascular pathology (e.g. atherosclerotic disease, ischemic heart disease, heart failure) and exposure to pharmacotherapy. For example a randomized, placebo-controlled, double-blinded study with 18 placebo and 17 metformin treated patients with type 2 diabetes mellitus found that metformin-specific changes in insulin resistance were associated with differential changes in circulating levels of miR-140-5p, miR-222, miR-142, and miR-192.(204) Work from our laboratory in Ossabaw swine assessed left ventricular miR expression changes in response to combinations of stimuli including diet-induced obesity, myocardial ischemia, and exendin-4, a GLP-1 mimetic.(52) We found that miR expression was regulated in complex ways, where some miR changes were related to the obese condition

(e.g. miR133a-5p), while others were specific to the exendin treatment (e.g. miR15, miR let7).(52) These observations are associative; how these miRs are related to the physiologic effects or treatment responses is unknown at present. These observations highlight both the strengths and the challenges of exploring physiology using high-throughput measures.

As with other high-throughput integrative testing approaches, proteomic approaches promise to advance our understanding of physiology and pathophysiology. Many forms of protein mass-spectrometry allow for antibody-independent, label-free quantification and analysis of protein components within a tissue. Whole proteome analyses have previously been utilized to demonstrate obesity-specific changes in abundance and phosphorylation of proteins related to ion transport, mitochondrial metabolism, antioxidant function and cardiac contractile function.(211-215) Some work has been done exploring the proteomic responses to ischemia in non-obese models,(216-219) but very little work has been done to date exploring obesity-specific proteomic changes associated with myocardial ischemia or in relation to obesity-specific cardiac dysfunction. Our own work presents an initial foray into these questions.(52) In our studies in Ossabaw swine, the proteomic changes associated with obesity, ischemia and exendin-4 treatment provided intriguing novel observations of obesity-related changes in the structural protein titin and in multiple components of the myocelluar calcium-regulating machinery.(52) These results need confirmation and further exploration, but along with the miR observations underscore the value of these ‘omic’ approaches as tools for discovery.

SUMMARY AND FUTURE DIRECTIONS

The MetS is defined as the concurrence of mutually associated cardiovascular risk factors including abdominal obesity, impaired glucose tolerance, hypertriglyceridemia, decreased HDL cholesterol, and/or hypertension. In association with these factors, many investigators have described the activation of the sympathetic nervous system, renin-angiotensin system, and increased levels of pro-inflammatory adipokines and cytokines which subsequently contribute to increases in heart rate, circulating blood volume, ventricular end-diastolic volume, cardiac output, and vascular resistance. This hemodynamic phenotype is associated with cardiovascular disease risk. The associated pathophysiologic changes include alterations in myocardial substrate metabolism, microvascular dysfunction, impaired oxygen supply/demand balance, cardiac (diastolic) contractile dysfunction, and concentric cardiac hypertrophy (summarized in the **Figure**). These changes are distinct from the pathophysiology in conduit vessels through the processes of traditional atherosclerosis and arterial calcification, which are also augmented and contribute to adverse cardiovascular outcomes. (17) Despite significant advances made to date, the physiological and molecular mechanisms of metabolic, functional and vascular disease in obesity/MetS remain poorly understood. The most obvious hurdle is the complicated, inter-dependent multi-factorial nature of the syndrome itself, making it difficult to disentangle relevant factors or specific combinations of factors. It is also possible that the most relevant features are separate from the defining cardiovascular disease risk factors and have yet to be identified. Adipokines have been suggested as one possible example of such integrative underlying factors, but the potential also exists for ‘omic’ approaches to provide insight into molecules and mechanisms of which we are not yet even aware. There is a clear need for ongoing

exploration of these issues, to better understand and better treat obesity and MetS-associated cardiovascular disease, in order to better address the considerable public health implications of these conditions.

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Abbreviations

BMI	Body Mass Index
MetS	Metabolic Syndrome
NHANES	National Health and Nutritional Examination Survey
miR	microRNA
HDL	high-density lipoprotein

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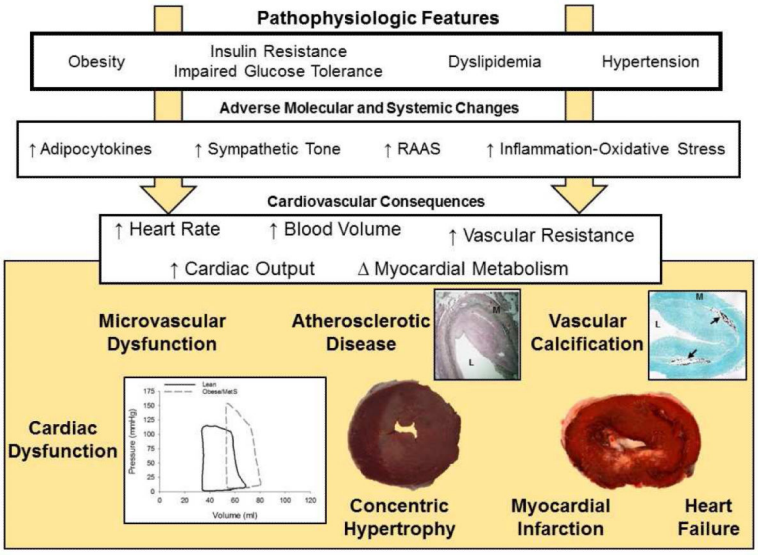

Figure.

Schematic diagram of the pathologic features, adverse molecular and systemic changes, and cardiovascular consequences of the metabolic syndrome. Clustering of causally inter-related risk factors including abdominal obesity, impaired glucose tolerance, hypertriglyceridemia, decreased HDL cholesterol, and/or hypertension is associated activation of the sympathetic nervous system, renin-angiotensin-aldosterone system (RAAS), and increased levels of pro-inflammatory adipokines and cytokines. These phenotypic changes subsequently contribute to increases in heart rate, circulating blood volume, cardiac output, vascular resistance, and changes in myocardial metabolism. The consequences of these changes include microvascular dysfunction, cardiac contractile dysfunction (augmented end-diastolic volume and systemic pressure development observed in left ventricular pressure-volume relationship (data from Sassoon *et al.*(52)), atherosclerotic disease (L = lumen; M = media; image of human coronary artery from Noblet *et al.(170)*), vascular calcification (arrow points to calcification; image provided by Dr. Michael Sturek with permission), concentric cardiac hypertrophy, myocardial infarction, and heart failure.