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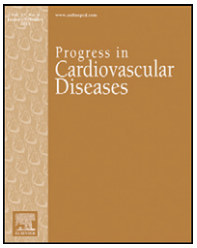

Arterial Function in Cardio-Metabolic Diseases: From the Microcirculation to the Large Conduits

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ABSTRACT

The metabolic syndrome (MetS) is characterized as a constellation of metabolic risk factors such as obesity, hypertension, dyslipidemia, and hyperglycemia that co-occur within a given individual. This consultation of risk factors exposes MetS to a 3-fold increased risk of cardiovascular disease and an even higher risk of developing type 2 diabetes compared to healthy individuals. The pathophysiological mechanisms underlying this increased cardiovascular risk are incompletely understood but likely include alterations to macro- and micro-vasculature. The vasculature plays an important role not only in delivery and adjusting the quantity of blood delivered to the tissues, but the dynamic changes in structure and compliance significantly alter the hemodynamic stress imposed on the heart and end-organs. This review will give an overview of the pathophysiological changes to the vasculature that accompany MetS in both human and animal models, as well as the possible mechanistic pathways.

The metabolic syndrome (MetS), is used to identify patients at an increased risk for cardiovascular disease (CVD), type II diabetes mellitus (T2DM), and all-cause mortality.[1] The MetS is defined by a constellation of cardiovascular (CV) risk factors such as central obesity, elevated glucose, atherogenic dyslipidemia, and elevated blood pressure (BP).[1] This grouping of risk factors exposes the 56 million Americans with MetS to a 3-fold increased risk of CVD and an even higher risk of T2DM compared to healthy individuals.[2]

Part of this increased MetS associated-CVD risk can be attributed to patho-physiological changes to the arterial vasculature, with both micro- and macro-vascular diseases as major complications. The vasculature not only plays an important role in the delivery and adjustment of the quantity of blood delivered to the tissues, but the dynamic changes in structure and compliance significantly alter the hemodynamic stress imposed on the heart and end-organs. This review will give an overview of the patho-physiological changes to the vasculature that accompany MetS in both human and animal models, as well as potential contributing mechanistic pathways. We will also briefly illustrate how physical activity can help to ameliorate, and in some cases reverse, these changes.

Macrovascular adaptations to MetS

The larger conduit arteries (aorta, and carotid) act as a cushioning reservoir or 'Windkessel' that 'stores' blood during cardiac contraction and expels it during diastole to ensure a continuous and steady flow of blood. However, the muscular arteries (brachial, popliteal etc.,) also act primarily as conduit

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Abbreviations and Acronyms

AGEs = advanced glycation end products

BP = blood pressure

cIMT = carotid intima-media wall thickness

CV = cardiovascular

CVD = cardiovascular disease

eNOS = endothelial NO· synthase

HTN = hypertension

MetS = metabolic syndrome

MMP = matrix metalloproteinases

NFκB = nuclear factor κB

NO = nitric oxide

OZR = obese Zucker rats

ROS = reactive oxygen species

T2DM = type II diabetes mellitus

vessels, facilitating the convective delivery of blood to the periphery and organs. Accordingly, the major structural proteins of the aorta and carotid arteries are elastin and collagen is the primary structural component of the peripheral arteries (e.g., brachial artery) to give the vessel its mechanical strength and assist with blood flow delivery by minimizing energy loss. Below is a brief description of the pathophysiological adaptions to the large vessels due to the presence of MetS and or T2DM.

Conduit remodeling

The arterial wall is an active, flexible, and integrated tissue made up of fibroblasts, endothelial, smooth muscle, and adventitia cells and extracellular matrix components. In the presence of physiological and pathological stimuli, these components reorganize to maintain the integrity of the vessel wall. Several changes occur to conduit artery structure in the MetS that could serve to increase the potential for vascular dysfunction (Fig 1). Carotid wall thickness (cIMT) increases between 0.08 and 0.11 mm in MetS vs. healthy controls,[3,4] with cIMT increasing as the prevalence of the MetS components increases.[5] Further, women with MetS may also be more prone to arterial thickening than their male counterparts.[6] Of note, there is a similar increase in cIMT (≈0.13 mm) in T2DM[7] as in MetS without T2DM.[5,8] A recent longitudinal study confirmed that the transition from being healthy to having MetS coincides with an increase in cIMT (0.011 vs. 0.005 mm/year), and lumen diameter (0.055 vs. 0.023 mm/year).[9] The remodeling of the large arteries in response to disease is largely due to an increase in circumferential wall stress and flow-mediated shear stress.[10] Thus, the arteries undergo either changes in lumen size and/or arterial wall thickness to maintain tensile wall stress within ideal limits (i.e., described by the Law of Laplace). However, in both MetS and T2DM, carotid arterial adaptations do not fully restore circumferential wall stress to levels comparable with those of healthy age-matched individuals.[8] Animal models of MetS also demonstrate that the conduit vessels undergo remodeling similar to that noted in human MetS.[11]

Along with an increase in cIMT, conduit vessels become stiffer (23–34%), as measured by pulse wave velocity, in the MetS.[3,12] Although arterial stiffness increases with the number of components of MetS,[13] arterial stiffness seems to be greater (≈17%) with the co-occurrence of T2DM and MetS.[14] The hypertensive component of MetS helps to explain, in part, the increase in arterial stiffness because at higher mean pressures the less compliant collagen fibers predominate in the maintenance of arterial-wall stresses. However, evidence suggests that increased arterial stiffness precedes the development of hypertension (HTN),[15] and arterial stiffness is increased in MetS without HTN.[16] These data suggest that arterial stiffness is an important part of the pathological changes associated with MetS that are not entirely due to the elevated pressures. Similarly, although arterial stiffness is elevated in T2DM, even in the absence of HTN,[14] arterial stiffness develops in the impaired glucose metabolism state[3] suggesting that macrovascular disease associated with T2DM begins in the pre-diabetic state.

Conduit arterial remodeling with MetS is clinically significant given that a 0.1 mm increase in cIMT is associated with a 15–18% increased risk for a CV event.[17] Similarly, a 1 m/second increase in arterial stiffness corresponds to an age-, sex-, and risk factor-adjusted risk increase of 15% in CV mortality.[18]

Large artery endothelial function

Endothelial cells play a pivotal role in regulating several arterial properties, including vascular tone, vascular permeability, angiogenesis, and the response to inflammation. Endothelial cells modulate arterial stiffness via endothelial-derived substances.[19] It is therefore not surprising that endothelial dysfunction is strongly and independently associated with CVD events.[20] All of the components of MetS have adverse effects on the endothelium,[21–24] and endothelium-dependent vasodilation of the brachial artery is impaired with MetS.[25,26] Further, circulating markers of endothelial dysfunction (soluble intercellular adhesion molecule, tissue plasminogen, plasminogen activator inhibitor-1 levels and activity) are elevated in MetS.[27,28]

Microvascular adaptations to MetS

The small vessels of the microvasculature have several key functions, which rely on position, dimension, and mechanisms of individual segments. The small arteries regulate vascular resistance by changing their caliber, and microvascular reactivity which is an important mechanism that regulates local blood flow and tissue perfusion. Below is a brief description of the patho-physiological adaptions to the small vessels due to the presence of MetS and or T2DM.

Microvascular remodeling

Much of our knowledge regarding the structure changes to the microcirculation with MetS comes from animal models. However, small resistance arteries dissected from the abdominal subcutaneous tissue of MetS individuals had increased in wall thickness and media-to-lumen ratio compared to healthy controls, indicating hypertrophic remodeling.[29] In T2DM with MetS, the small arteries taken from a subcutaneous gluteal fat biopsy demonstrated eutrophic inward remodeling (constant wall thickness with a smaller diameter).[30] A decrease (≈37%) in