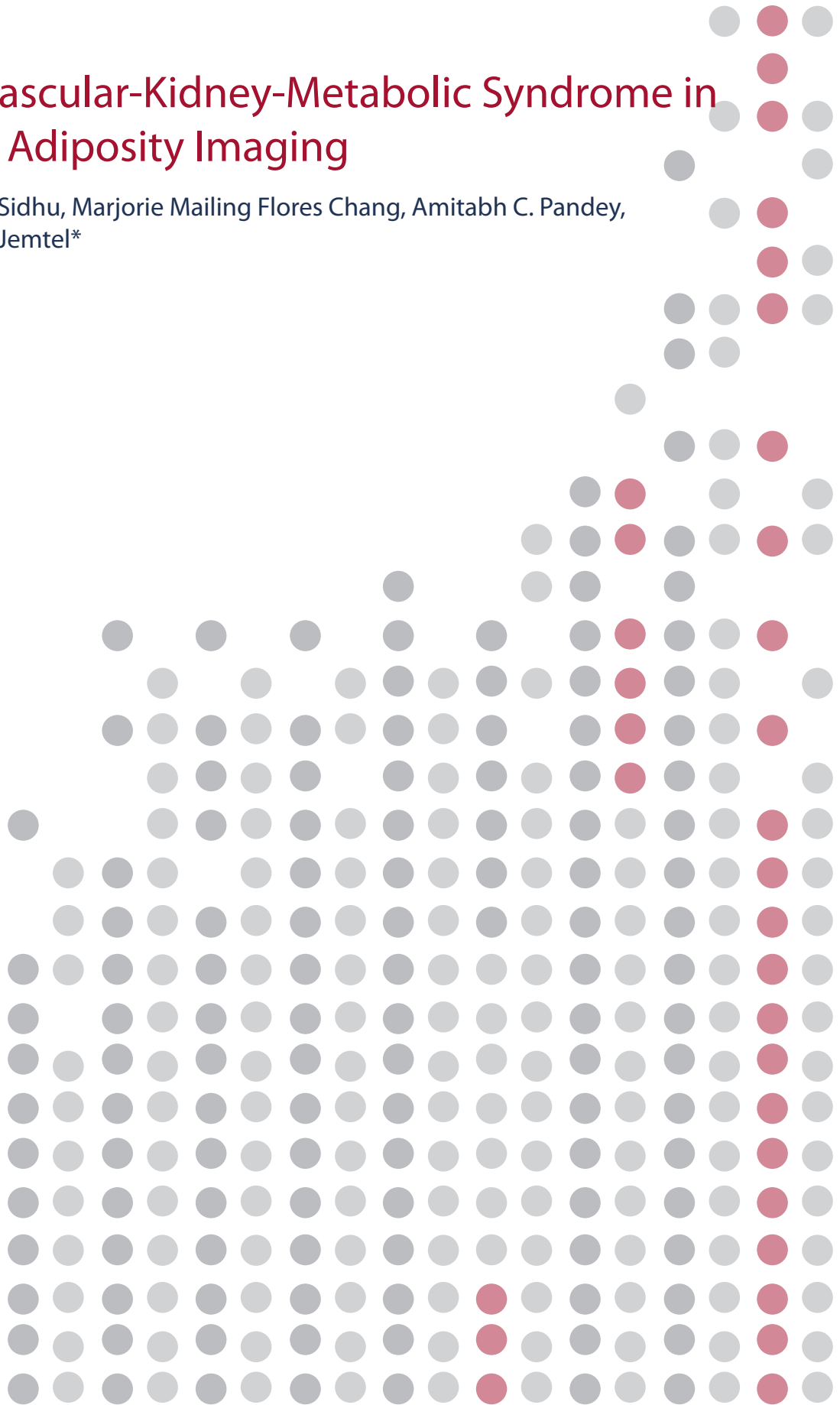


Cardiovascular-Kidney-Metabolic Syndrome in need of Adiposity Imaging

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Review Article

Cardiovascular-Kidney-Metabolic Syndrome in need of Adiposity Imaging

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ABSTRACT

People with obesity have an increased risk of cardiovascular disease. The current guidelines on Cardiovascular-Kidney-Metabolic Syndrome quantitatively assess the 10- and 30-year cardiovascular disease risk with the PREVENT equations. Visceral adipose tissue is an independent marker of cardiovascular morbidity and mortality and can be measured by computed tomography or magnetic resonance imaging. However, it is difficult to do owing to cost and availability. Alternatively, epicardial adipose tissue can be measured on non-contrast CT and correlates well with visceral adipose tissue in patients with obesity or normal body weight. In the current review, we briefly examine the cardiovascular-kidney-metabolic syndrome as well as the mechanisms that promote low-grade chronic inflammation in patients with excess and inflamed visceral adipose tissue. The quantification of epicardial adipose tissue may allow us to directly assess and manage visceral adiposity, the driver of cardiovascular-kidney-metabolic syndrome.

Keywords: Cardiovascular disease; Hypertension; Macrophages; Coronary artery disease; Heart failure

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Introduction

Between the ages of 35-70 years the risk of developing cardiovascular disease (CVD) is 58% greater in individuals with >30 body mass index [BMI, kg/m²] than in those within normal BMI ranges [1]. From 1999 to 2020 age adjusted cardiovascular deaths related to obesity increased by 3-fold, with ischemic heart disease as the most common primary cause of death [2]. More than two-thirds of obesity related deaths are caused by CVDs. [3]. Obesity indirectly mediates the development of coronary artery disease (CAD) through associated conditions like hypertension (HTN), type 2 diabetes (T2D), and dyslipidemia. Obesity directly amplifies the atherosclerotic vascular burden by increasing the prevalence of inflammatory cells including macrophages in atherosclerotic plaques owing to low-grade systemic inflammation and local inflammation in the perivascular adipose tissue (PVAT) [4,5]. Besides directly amplifying vascular inflammation, obesity atherogenic dyslipidemia plays a key role in atherosclerosis-related clinical events [6].

Perturbed by the prevalence and impact of multiorgan dysfunction on life expectancy, the American Heart Association (AHA) Presidential Advisory devised a new paradigm where excess and dysfunctional adiposity leads to the cardiovascular-kidney-metabolic (CKM) syndrome that underlies the increasing risk of CVD and premature mortality [7]. Three years later the American College of Cardiology/AHA Joint Committee on Clinical

Practice Guidelines reported on prevention, detection, evaluation and management of CKM syndrome [8]. We succinctly examine management differences between the CKM syndrome and clinical entities that link obesity to a poor prognosis like heart failure with preserved ejection fraction (HFpEF).

Cardiovascular Kidney Metabolic Syndrome

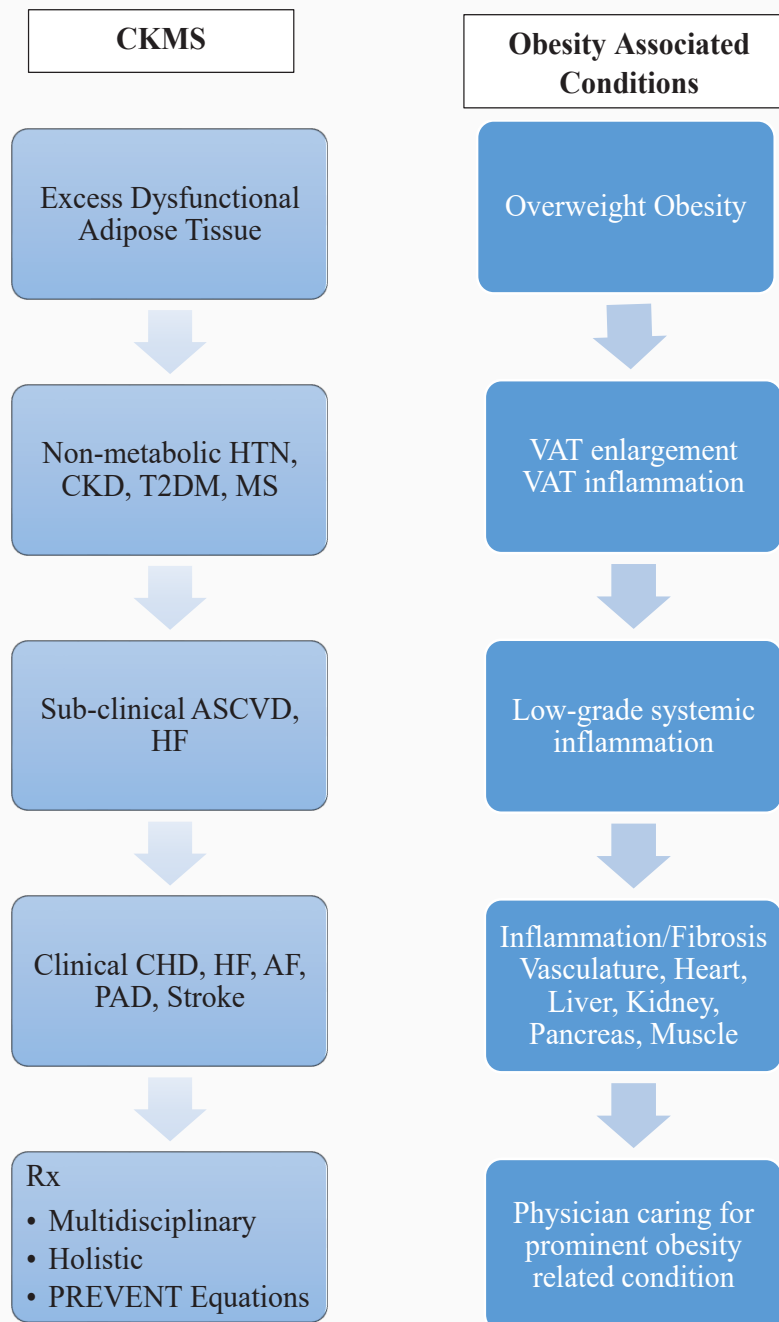
The CKM syndrome is an assemblage of vascular, renal, and metabolic diseases that provide a blueprint for a multimodal approach to holistic treatment of common cardiovascular conditions [8]. An excess of “dysfunctional” adiposity sets off the CKM syndrome that progresses in 3 stages. The first stage consists of metabolic and other conditions like hypertriglyceridemic lipidemia, hyperglycemia, and low estimated glomerular filtration rate or albuminuria. The second stage comprises subclinical atherosclerotic cardiovascular disease (ASCVD) and fluid retention as evidence of chronic kidney disease (CKD). The third stage is made of full-blown coronary heart disease (CHD), heart failure (HF), peripheral arterial disease (PAD), atrial fibrillation (AF), CKD and stroke. Quantitative assessment of 10-year and 30-year CVD risk are made with the predicting risk of CVD EVENTS (PREVENT) equations. PREVENT CVD and its ASCVD component (PREVENT-ASCVD) and HF (PREVENT-HF) are an integral part of the CKM syndrome framework [8]. PREVENT equations help predict CKM syndrome progression and characterize CKM syndrome stages. Of key therapeutic importance, PREVENT equations help predict CKM, allow early identification of the progressive nature of the CKM syndrome, thereby maximizing therapeutic modalities that for the most part slow down the functional decline of obesity-related conditions. Therapeutic modalities consist of lifestyle interventions, nutrition, sodium-glucose cotransporter 2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP-1RAs), and metabolic bariatric surgery (MBS). These modalities help patients regain functional capacity, enhance life expectancy and remedy T2D, HTN, metabolic associated liver disease (MASLVD), HFpEF, and obesity-related atherogenic dyslipidemias. MBS, the most effective intervention for weight loss, decreases the 10-year risks of total CVD and its subtypes by 21.7% at 1 year after surgery according to PREVENT equations [9].

The occurrence of CKD is construed as a major amplifier of the risk of atherosclerotic vascular and HF events. However, the role of CKD in the progression of CVD after decades of low-grade systemic inflammation may be rooted in lower functional reserve of heart and vasculature compared with that of kidney or liver. Noteworthy, assessment and treatment of overweight and obesity rank 6 among 10 take-home messages of CKM syndrome clinical practice guidelines [8]. Quantitative risk assessment guides clinician-patient

discussions regarding compliance with lifestyle and dietary modifications and therapeutic strategies. In the presence of multiple conditions, the CKM syndrome framework favors interdisciplinary care approaches with a point-person to manage the care of patients with ≥ 2 CKM syndrome conditions. While interdisciplinary care aims at reducing care fragmentation, it may make it difficult due to competing recommendations. Customizing beneficial therapies to a patient's profile and close follow-up are critical steps for successful CKM syndrome management.

Obesity-associated Major Cardiovascular Disease.

When the subcutaneous adipose tissue can no longer store lipids and overnutrition persists, the storage of lipids takes place through hyperplasia in the visceral adipose tissue (VAT) or in other ectopic adipose tissue depots like epicardial (EAT), hepatic, pancreatic, renal or skeletal muscle [10]. Hypertrophy of visceral adipocytes leads to VAT inflammation with endoplasmic reticulum (ER) stress, mitochondrial fragmentation, and M1 macrophages infiltration with systemic release of free fatty acids (FFAs), tumor necrosis factor (TNF)- α , interleukin (IL)-6 and adipocytes-derived extracellular vesicles (EVs) containing micro ribonucleic acids (miRNAs) and misfolded proteins that target distal cells. In turn, sustained VAT inflammation promotes low-grade systemic inflammation that drives obesity-related cardiac, renal, hepatic, and vascular inflammation and fibrosis. Local inflammation and intra-cellular accumulation of lipids, lipotoxicity, and inflammation coexist and feed each other resulting in fibrosis in the liver, pancreas, heart, kidney, or skeletal muscle. Lipotoxicity bolsters inflammation that reduces adiponectin and spreads through release of EVs. Obesity-induced chronic inflammation is a key driver of vascular pathology [4]. Through activation of AMP-activated protein kinase (AMPK) TNF- α upregulates adhesion molecules that promote leukocytes adhesion to vascular wall and inflammation. Over production of reactive oxygen species (ROS), i.e. oxidative stress plays a key role in vascular endothelial dysfunction and vascular smooth muscle cells (VSMCs) proliferation in obesity [11]. VAT is strongly linked to dyslipidemia and an atherogenic metabolic profile encompassing high triglycerides and low high-density lipoprotein in the fasting state and high triglyceride-rich-lipoprotein in the postprandial state following a fat reach meal independent of total adiposity [12]. Alterations in lipoprotein lipase activity, insulin and postprandial lipid handling contribute to lipid profile with abundant triglyceride-rich lipoprotein, small dense low-density lipoproteins, remnant particles and lipoprotein a (lpa) [6] Last, PVAT and liver switch from a protective (anti-inflammatory) to a pathogenic (pro-inflammatory) state in obesity (Figure 1).



Abbreviations: CKMS: Cardiovascular-Kidney-Metabolic Syndrome; VAT: Visceral Adipose Tissue; HTN: (Hypertension; CKD: Chronic Kidney Disease; T2D: Type 2 Diabetes); MS: Metabolic Syndrome; ASCVD: Atherosclerotic Cardiovascular Disease; HF: Heart Failure; CHD: Coronary Heart Disease; AF: Atrial Fibrillation; PAD: Peripheral Arterial Disease

Correlation Between Visceral and Epicardial Adipose Tissue

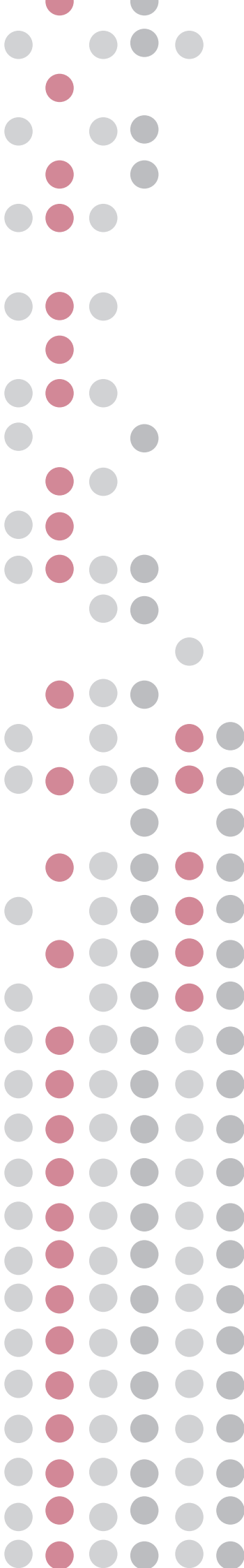
VAT is an independent marker of cardiovascular and metabolic morbidity and mortality that can be measured by computed tomography (CT) or magnetic resonance imaging (MRI) [13]. However, VAT is not routinely measured in clinical practice owing to cost and CT/MRI availability. As VAT accumulation precedes VAT inflammation, enlarging VAT signals the accumulation of inflamed (dysfunctional) adipose tissue that drives low-grade systemic inflammation and CKM syndrome emergence. Fortunately, EAT volume that can be conveniently measured on non-contrast CT, highly correlates with VAT volume in subjects with obesity and normal body weight [14,15]. Non-contrast CT provides CT measurements that can be obtained on routine scans and tracked over time [16]. EAT is the adipose tissue located between the visceral pericardium and the surface of the heart. The pulmonary artery bifurcation defines the superior limit of the heart, and the posterior descending artery defines its inferior limit [17]. EAT volume and attenuation can be quantified by fully automated Deep Learning software incorporated into QFAT software (version 2.0 Cedars Sinai Medical Center, Los Angeles, CA) on non-contrast cardiac CTs [17]. The validity of Deep Learning assessment of EAT on coronary computed tomography angiograms (CCTA) was corroborated in challenging patients (recent cardiac surgery, BMI ≥ 40 , coronary calcium score ≥ 400 and metallic artifact in the pericardium [18]. Deep Learning allows routine EAT measurement as automated quantification time is considerably shorter (12 seconds versus 18 minutes) than manual quantification time. Hence, EAT volume may be used for cardiovascular diagnosis and risk prediction like coronary artery calcium (CAC) score is used for assessment of coronary artery disease risk [19].

Summary

In summary, PREVENT-ASCVD, -HF and -CVD equations are extremely helpful in staging and management of the cardiovascular-kidney-metabolic syndrome. PREVENT equations allow us to initiate therapies at early stages of the syndrome, thereby maximizing the likelihood of stage regression. In addition to PREVENT equations, visualization and measurement of epicardial adipose tissue on non-contrast cardiac computed tomography may facilitate diagnosis, staging, and follow-up of the cardiovascular-kidney-metabolic syndrome. Moreover, by shifting the focus from loss of body weight to epicardial adipose tissue and cardiovascular health it may help patients to better understand and adhere to therapeutic modalities.

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