

## THE PRESENT AND FUTURE

### JACC STATE-OF-THE-ART REVIEW

# Cardiometabolic-Based Chronic Disease, Adiposity and Dysglycemia Drivers



## JACC State-of-the-Art Review

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### ABSTRACT

A new cardiometabolic-based chronic disease (CMBCD) model is presented that provides a basis for early and sustainable, evidence-based therapeutic targeting to promote cardiometabolic health and mitigate the development and ravages of cardiovascular disease. In the first part of this JACC State-of-the-Art Review, a framework is presented for CMBCD, focusing on 3 primary drivers (genetics, environment, and behavior) and 2 metabolic drivers (adiposity and dysglycemia) with applications to 3 cardiovascular endpoints (coronary heart disease, heart failure, and atrial fibrillation). Specific mechanistic pathways are presented configuring early primary drivers with subsequent adiposity, insulin resistance,  $\beta$ -cell dysfunction, and metabolic syndrome, leading to cardiovascular disease. The context for building this CMBCD model is to expose actionable targets for prevention to achieve optimal cardiovascular outcomes. The tactical implementation of this CMBCD model is the subject of second part of this JACC State-of-the-Art Review. (J Am Coll Cardiol 2020;75:525-38)  
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### WHAT IS CARDIOMETABOLIC-BASED CHRONIC DISEASE?

Cardiovascular disease (CVD) includes a wide spectrum of disorders that affect the heart and blood vessels. In the first part of this JACC State-of-the-Art Review, the focus will be on metabolic events that can be clustered into distinct chronic disease stages, amenable to preventive care, in order to optimize coronary heart disease (CHD), heart failure (HF), and atrial fibrillation (AF) clinical outcomes.

CVD is the leading cause of death in the world (1,2). Decreases in overall CVD mortality rates have been associated with effective primary prevention strategies (3). However, total CVD-related deaths increased due to population growth, aging, and trajectories of obesity and type 2 diabetes (T2D) (2-4). Since 2011, there has been a deceleration in the decline of age-adjusted U.S. CVD mortality rates (5,6). Moreover, there is an increase in CVD (except for CHD) mortality, from 2011 to 2015 (7). What is particularly disturbing is that the increased CVD mortality rate



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## ABBREVIATIONS AND ACRONYMS

<b>ABCD</b>	= adiposity-based chronic disease
<b>AF</b>	= atrial fibrillation
<b>AGE</b>	= advanced glycation end-products
<b>BMI</b>	= body mass index
<b>BP</b>	= blood pressure
<b>CHD</b>	= coronary heart disease
<b>CMBCD</b>	= cardiometabolic-based chronic disease
<b>CV</b>	= cardiovascular
<b>CVD</b>	= cardiovascular disease
<b>DBCD</b>	= dysglycemia-based chronic disease
<b>FFA</b>	= free fatty acid(s)
<b>HDL</b>	= high-density lipoprotein
<b>HF</b>	= heart failure
<b>HTN</b>	= hypertension
<b>IL</b>	= interleukin
<b>LDL</b>	= low-density lipoprotein
<b>LDL-c</b>	= low-density lipoprotein cholesterol
<b>LV</b>	= left ventricular
<b>MetS</b>	= metabolic syndrome
<b>NO</b>	= nitric oxide
<b>T2D</b>	= type 2 diabetes
<b>TNF</b>	= tumor necrosis factor
<b>VLDL</b>	= very low-density lipoprotein
<b>WC</b>	= waist circumference
<b>WHR</b>	= waist-to-height ratio

trends, especially those in low- and middle-income socioeconomic and educational strata, or certain ethnocultural populations with unhealthy lifestyles, are thought to be due to less effective and/or accessible preventive strategies (8-11). Nevertheless, improved survival trends are seen when largescale risk factor modification efforts are delivered within an integrated health care system (12). In a call-to-action paper, multiple failures of the health care system were presented, of which “failure to make risk factor modifications” was the most impactful (13).

In many patients, the treatment of CVD begins with the onset of events such as angina, acute coronary syndrome, stroke, NYHA functional class III/IV congestive HF, or symptomatic peripheral vascular disease. The exceptions include smoking cessation and risk-based lowering of low-density lipoprotein (LDL) cholesterol (LDL-c) as preventive interventions. However, the lowering of LDL-c levels by statin therapy in cardiovascular (CV) outcomes trials resulted in average risk reduction of only ~30%, leaving a preponderant degree of unattended residual risk (14). Given the burden of CVD borne by patients and our societies, more effective prevention strategies are needed. In this regard, the important consideration is that CVD represents a chronic disease process beginning early in life with opportunities for primary, secondary, and tertiary prevention that can mitigate the occurrence of end-stage events.

Furthermore, the chronic disease process integrally involves T2D and obesity, which of course are distinct from end-stage CVD events, but nevertheless are both manifestations and drivers of this chronic disease process. In this review, a medically actionable model is established, consistent with current evidence addressing pathophysiology, which delineates interrelationships among obesity, T2D, and CVD. This new model outlines for the first time comprehensive approaches for primary, secondary, and tertiary prevention focused on CVD (specifically CHD, HF, and AF) as end-stage developments in this chronic disease process. This new entity is reconceptualized as cardiometabolic-based chronic disease (CMBCD), with the central abnormality impelling the progression being insulin resistance. Indeed, the residual risk following statin therapy can largely be attributed to insulin resistance (15-21). The CMBCD model

## HIGHLIGHTS

- The cardiometabolic-based chronic disease model is designed to optimize early and sustainable preventive care.
- Genetics, environment, and behavior are primary drivers, and adiposity and dysglycemia are metabolic drivers of cardiometabolic-based chronic disease.
- Cardiometabolic endpoints include coronary heart disease, heart failure, and atrial fibrillation.
- A detailed prevention plan can be fashioned based on this model.

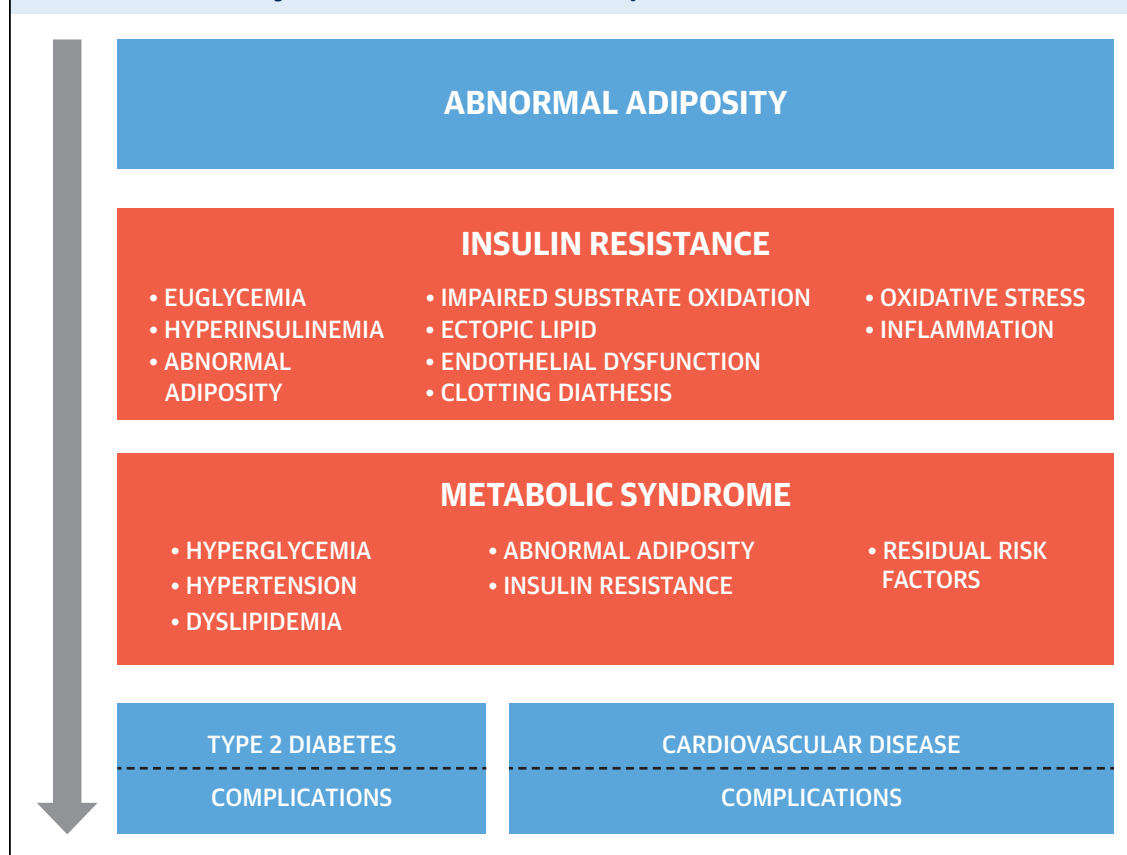
addresses modifiable risk factors that can mitigate the patient suffering and social costs of CVD rather than over-reliance on expensive and invasive technological interventions once disease morbidities are fully expressed.

Insulin resistance is at the intersection of abnormal adiposity and dysglycemia (Figures 1 and 2, Central Illustration). These metabolic drivers derive from primary drivers of genetics, environment, and behavior, and lead to progression of CMBCD. Specifically, abnormal adiposity is embodied in the newly proposed diagnostic term for obesity, adiposity-based chronic disease (ABCD) (22), and dysglycemia progresses according to the model defined by dysglycemia-based chronic disease (DBCD) (23). ABCD and DBCD intersect at the level of insulin resistance to worsen CMBCD within the context of chronic disease care templates (24-26). Taken together, this formulation is intended to clarify existing confusion in the published reports related to pathophysiological relationships among insulin resistance, metabolic syndrome (MetS), obesity, T2D, and CVD.

## PRIMARY DRIVERS OF CMBCD

**GENETICS.** There are many molecular factors associated with cardiometabolic effects (Table 1). However, the majority of chronic disease heritability is unexplained by identified genome wide association studies findings. Rather, familial inheritance is more dependent on modifiable risks (27). These interactions also vary with different ethnicities and behaviors, which provide additional context for the expression of phenotypic traits (27). The use of system genetics to identify molecular drivers is useful, but it is this complex interaction of genes,

**FIGURE 1** The Intermediating Roles of Insulin Resistance and Metabolic Syndrome in Cardiometabolic-Based Chronic Disease



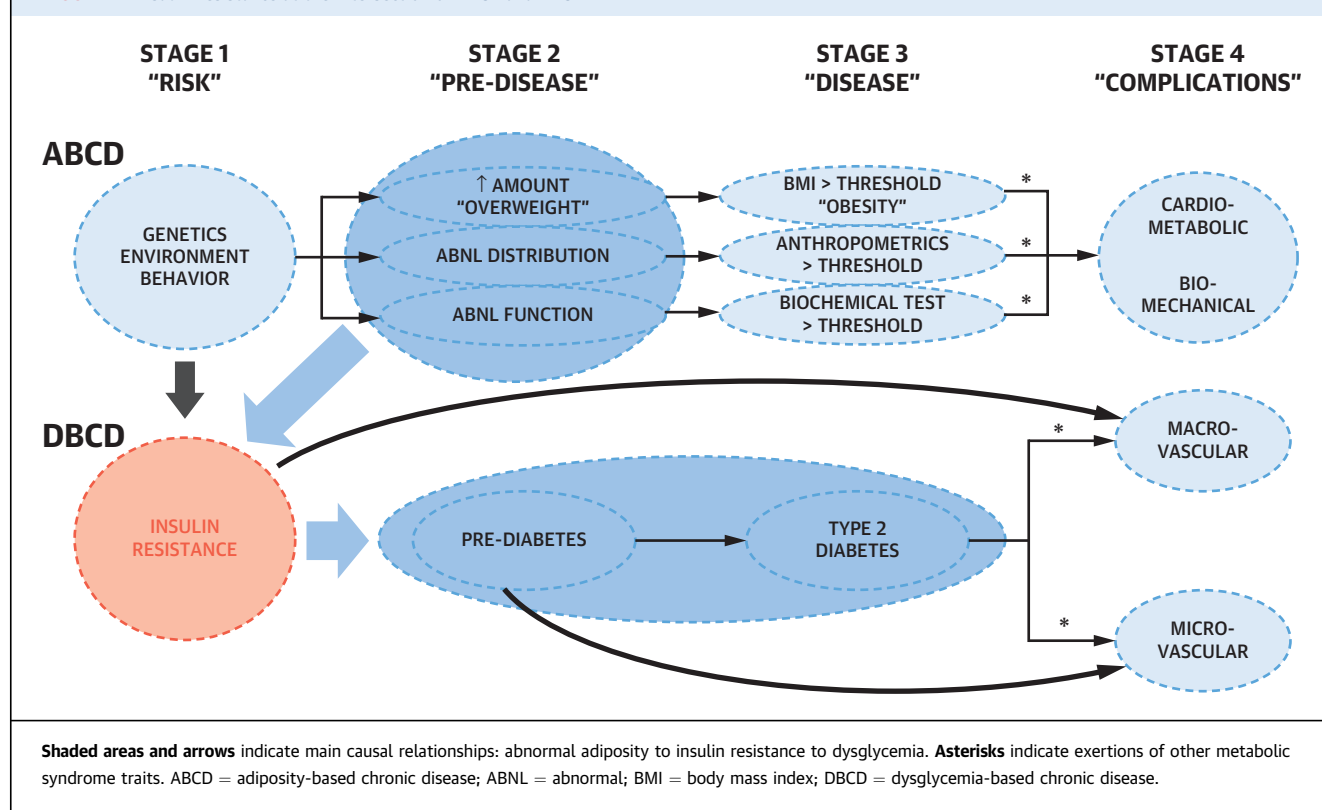
environment, and behavior that ultimately determines risk and disease phenotype. As an example, ethnicity-specific susceptibility genes and their biological processes participate in the complex pathogenesis of T2D and CVD (28). In light of only a minority of gene variants explaining CHD, disease drivers corresponding to hub genes at the top of a regulatory network, represent a stronger mechanism of heritability (29). Specifically, gene regulatory networks in the atherosclerotic arterial wall and abdominal adipose tissue are 2 main disease drivers for CHD (29). Although currently below the routine detection threshold in clinical medicine, and lacking genetic risk scores with ample validation for routine clinical prediction, identification and correlation of molecular factors with clinical events characterize the first stage in a chronic disease model.

Epigenetic regulation provides a biological explanation of how genes and environment interact to create a specific phenotype. For instance, epigenetic modifications arising in utero with maternal gestational diabetes may confer an insulin resistance

phenotype in offspring, which persists into adulthood potentially leading to T2D, obesity, and CVD (30-33). It has been proposed that a systems approach to the complex interactions among genetic, epigenetic, environmental, and MetS factors can yield useful explanatory models (34-39).

By examining 25 single-nucleotide polymorphisms, Geng et al. (40) found evidence supporting a causal effect of a genetic predisposition for higher childhood body mass index (BMI) with increased T2D and CHD risk. In a meta-analysis, childhood obesity was found to be a risk factor for CVD based on associations with certain adult risk factors (systolic blood pressure [BP], diastolic BP, total cholesterol, high-density lipoprotein [HDL], LDL, non-HDL, and triglycerides) (41). In fact, newborns of women who were obese had thicker intraventricular septa and reduced cardiac function (42). In the Cardiovascular Risk in YFS (Young Finns Study) (43), a weighted genetic risk score of 97 single-nucleotide polymorphisms in children improved prediction of adulthood obesity. In addition to adiposity amount, reflected by BMI, android

**FIGURE 2** Insulin Resistance at the Intersection of ABCD and DBCD



distribution of adiposity was preferentially associated with greater insulin resistance, leading to higher fasting insulin, triglyceride, HDL, interleukin (IL)-6, monocyte chemoattractant protein (MCP), and C-reactive protein levels, and also correlated with differences in gene expression (44).

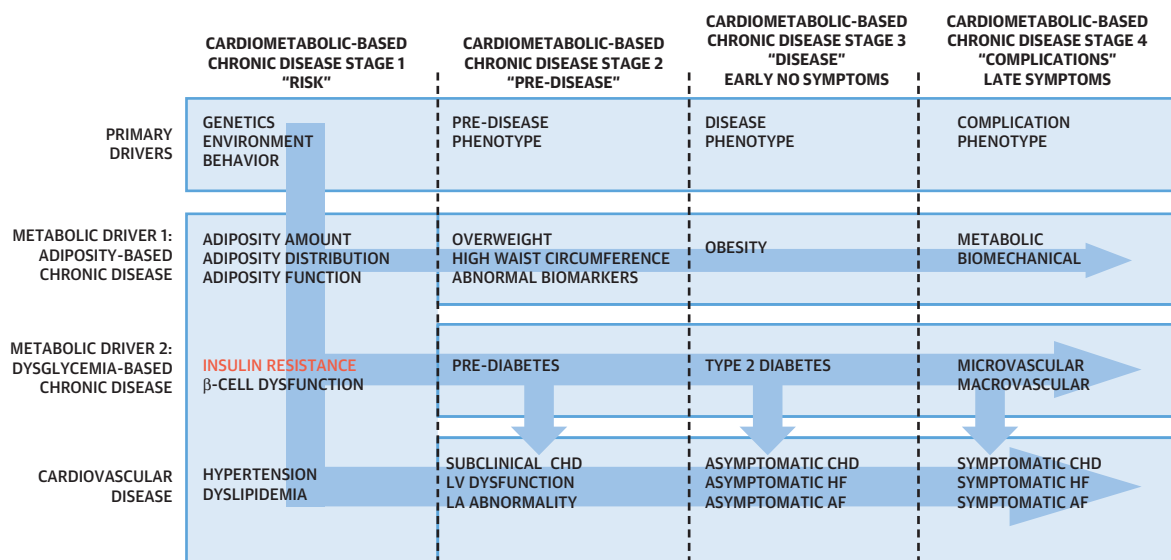
**ENVIRONMENT.** The built (or man-made) and nonphysical (cultural) environment provide context for the expression of genetic cardiometabolic risk factors (10). Local cluster detection and spatial regression techniques with a global footprint provide statistical information about relevant and actionable environmental variables (45). Specifically, the following variables are associated with CVD: lower socioeconomic strata and decreased access to quality health care, low education and literacy levels, regions of high alcohol intake, both urban (for children) and rural (with heat- or cold-waves affecting health care access) habitats, air and noise pollution, and poor quality of drinking water (45).

Environment toxins or endocrine disruptors can affect the risk for T2D by modulating gene expression, as well as interacting with molecular trafficking and other pathophysiological pathways to influence CV outcomes. For example, polymorphisms in *IL8RA*,

*TXN*, *NR3C2*, *COX5A*, and *GCLC* can interact with higher levels of seafood arsenicals to increase T2D prevalence rates (46). Exposure to persistent organic pollutants is associated with MetS traits in normal-weight Korean subjects, possibly due to toxic effects on  $\beta$ -cell function, independent of adiposity or insulin resistance (47,48). In a study by Al-Hamdan et al. (49) in the United States, fine particulate matter (air pollutant), sunlight, and maximum heat index were associated with CVD risk, more so among Blacks and older adults ( $\geq 65$  years of age), with odds ratios for mortality mitigated by T2D, obesity, and certain lifestyle, behavioral, and socioeconomic factors. Telomere shortening, which can result from environmental toxins, as well as chronic stress or inflammation, has been associated with CHD (50). The interaction between genetics and dietary factors can also modulate the gut microbiome in ways that affect inflammatory and metabolic networks, and eventually lead to abnormal adiposity, insulin resistance, dysglycemia, and CVD, though conclusive interventional studies that mitigate CMBCD steps are lacking (51).

**BEHAVIOR.** Once phenotypic expression of genetic and environmental factors initiates a disease process,

## CENTRAL ILLUSTRATION Cardiometabolic-Based Chronic Disease: Adiposity and Dysglycemia Drivers



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The 4 stages of CMBCD are depicted at the **top**. In CMBCD Stage I (**first column**), adiposity, dysglycemia, and other metabolic drivers act concurrently and independently to produce cardiovascular disease. For cardiovascular disease pre-disease (**bottom row, second column**), subclinical coronary heart disease is suspected by interrogating 3 vascular beds: increased coronary calcium score, 3-dimensional carotid ultrasound, and ankle-brachial index; left ventricular dysfunction by echocardiography; and left atrial abnormality by electrocardiogram and echocardiogram. Stages are currently defined by artificial boundaries, determined by thresholds of detectability, and positioned along a continuum. **Arrows** indicate complex causal relationships among drivers and stages. Insulin resistance (**red**) occupies a critical integrating pathophysiological role. AF = atrial fibrillation; CHD = coronary heart disease; LA = left atrial; LV = left ventricular; CMBCD = cardiometabolic-based chronic disease.

individual behaviors, not only can modulate that expression, but also can provide opportunities for intervention. In a 2018 *Morbidity and Mortality Weekly Report* surveillance summary, Pickens et al. (52) presented results from a 2015 U.S. survey on health-risk behaviors in adults  $\geq 18$  years of age that provided context for genetic and environmental drivers of chronic disease, especially those based on cardiometabolic pathways. The estimated self-reported prevalence by state of fair to poor health was 11.2% to 34.1%, with 13.2% without health insurance coverage, only 58.1% to 79.8% having a routine annual checkup, and only 73.3% to 86.7% having a blood cholesterol check (52). With respect to prevalence rates of specific modifiable CVD risks by state, tobacco smoking was 9.0% to 27.2%, binge alcohol drinking was 11.2% to 26.0%, absence of leisure time physical activity 17.6% to 47.1%, and low fruit or vegetable consumption 33.3% to 55.5% or 16.6% to 31.3%, respectively (52). Higher diet-quality scores reflecting increased healthy eating patterns were associated with lower BMI, waist-to-height ratio (WHtR), and waist circumference (WC) (53). These

health-risk behaviors interacted with genetic and environmental drivers to produce the following prevalence rate ranges by state: obesity 19.9% to 36.0%; diabetes 11.2% to 26.8%; hypertension (HTN) 24.2% to 39.9%; high cholesterol 27.1% to 37.3%; CHD 7.2% to 16.8%; and stroke 2.5% to 7.5% (52).

### METABOLIC DRIVERS

**ADIPOSITY-BASED CHRONIC DISEASE. Abnormal adiposity.** ABCD is a more scientifically accurate, actionable, and less stigmatized diagnostic term than obesity. ABCD is a complex chronic progressive disease that involves abnormalities in the amount, distribution, and function of adipose tissue characterized by cardiometabolic, biomechanical, or psychological complications that confer morbidity and mortality (22). The ABCD designation has been adopted by the American Association of Clinical Endocrinologists and the European Association for the Study of Obesity (22,54). The diagnosis of ABCD has 2 parts: adiposity-based, which reflects abnormalities in the mass, function, and distribution of adipose

**TABLE 1** Some Important Molecular Factors Associated With CMBCD

Factor*	Phenotypic Trait	Cardiometabolic Effect
<i>BCL2</i>	Regulates apoptosis	Insulin resistance
eNOS	Hypermethylation and nitric oxide	Adult MetS
<i>FAM19A2</i>	Brain chemokine	Insulin resistance
<i>HLA-B, HLA-DRB1, HLA-C</i>	Major histocompatibility complex	Adiposity
<i>IGF1</i>	Insulin-like growth factor 1	Insulin resistance
<i>IRS1</i>	Insulin receptor substrate 1	Insulin resistance
<i>KCNQ1</i>	K voltage-gated channel subfamily Q member 1	$\beta$ -Cell function
<i>NAT2</i>	N-acetyltransferase 2	Lipids, insulin resistance
Netrin	Angiogenesis pathway	Vascular
p66 <sup>Shc</sup>	Hypomethylation and free radicals	Adult MetS
<i>PON1 Q192R/L55M</i>	Paraoxonase 1 gene variants	Insulin resistance
<i>PPARG</i>	Peroxisome proliferator activated receptor $\gamma$	Insulin resistance
<i>RXR2</i>	Ryanodine receptor 2	$\beta$ -Cell function
SLIT-ROBO	Angiogenesis pathway	Vascular
<i>TCF7L2</i>	Transcription factor 7 like 2	$\beta$ -Cell function

\*Specific genes are in italics.  
CMBCD = cardiometabolic-based chronic disease; eNOS = endothelial nitric oxide synthase; MetS = metabolic syndrome.

tissue; and chronic disease, which reflects the risk, presence, and severity of complications (22).

Abnormal adiposity amount reflected by weight gain and BMI is related to CVD, but this is not straightforward because excessive fat mass is neither a necessary nor a sufficient factor. Not all patients with obesity are insulin resistant, and lean individuals can also exhibit an insulin-resistant state with increased risk of T2D and CVD. The relationship between generalized increase in adiposity and insulin sensitivity indicates that only about 11% of individual variability in insulin sensitivity can be explained by BMI (55). However, if weight gain occurs on an insulin-resistant background, there is an asymmetrical accumulation of fat favoring the intra-abdominal depot, and adipose tissue inflammation with influx of macrophages and abnormalities in circulating adipokines (55). Further weight gain can worsen insulin resistance and intensify inflammation, oxidative stress, and glucose intolerance (55). Thus, in many, but not all, individuals, there is an interaction between excess adiposity and insulin resistance that increases CVD risk.

Abnormal adiposity distribution reflects an imbalance of caloric intake and energy expenditure with extensive individual variability based on primary drivers. Increased gluteofemoral subcutaneous adipose tissue is associated with entrapment of free fatty acids (FFA), which decreases ectopic FFA uptake, markers of insulin resistance, inflammation, and CVD risk (44,56-58). In fact, leg (59) and thigh (60), and

not arm (59), subcutaneous fat exert significant protective cardiometabolic effects. Subcutaneous adipose tissue accounts for approximately 80% of total adipose tissue and contributes the most FFA to the liver (61). Because dysfunctional adipose tissue cannot adequately accommodate fuel storage in the setting of excessive caloric intake, FFA levels rise, and ectopic lipid accumulates in tissues that normally have no or little fat storage. These ectopic sites include skeletal muscle, liver, epicardium (between the outer wall of myocardium and visceral layer of pericardium), pericardium (between the visceral and parietal layers of pericardium), intestines, kidney, and pancreas (55).

Abnormal adiposity function produces changes in adipokine signatures, circulating satiety hormones, and consequent interactions with satiety centers in the hypothalamus and other central nervous system loci affecting eating behavior. These changes can promote caloric intake and the maintenance of an excess adipose tissue mass. Adipokines participate in networked interactions with CV pathways (62). In the face of weight loss after lifestyle intervention, multiple maladaptive responses in satiety hormones, energy expenditure, and psychological factors can drive weight regain back to previously high BMI levels (63,64).

**Effects of adiposity on insulin resistance.** Ectopic fat contributes to insulin resistance. Intrahepatic fat, a form of ectopic fat, is associated with increased cardiometabolic risk factors and CVD (58,65). However, there is much to learn about the predictive value of ectopic fat and more specifically of nonalcoholic fatty liver disease in ABCD and CMBCD.

Patients with BMI in the overweight or obesity range may be insulin sensitive and not at increased risk of T2D and/or CVD. These patients are sometimes referred to as the “metabolically healthy obese” (66,67). Some diagnostic uncertainty exists, but when defined as the absence of all MetS traits, about 15% to 20% of U.S. adults with overweight or obesity in the NHANES (National Health and Nutrition Examination Survey) cohort are classified as metabolically healthy (68). The pathophysiological and epidemiological association of modestly increased BMI with lower risks and improved prognosis for certain chronic diseases including CVD is referred to as “the obesity paradox” and may result from reverse causality (69,70).

**Effects of adiposity on  $\beta$ -cell dysfunction.** In a murine model, the obese pathophysiological state is associated with local expansion of intraislet macrophages, which impair  $\beta$ -cell function (71). However, short of an abnormal inflammatory milieu mediating this relationship, strong evidence about direct



signaling from adipose tissue to  $\beta$ -cells or intraislet macrophages is lacking. Another explanation implicates abnormal autophagy, which disrupts  $\beta$ -cell function, and hence, in the setting of ABCD-related insulin resistance, sets the stage for hyperglycemia and progression to pre-diabetes and T2D (72). These and other mechanisms connect obesity, overconsumption of calories, and insulin resistance with  $\beta$ -cell exhaustion (Table 2). Each of these pathways is a candidate target to abrogate ABCD to insulin resistance progression (73).

**Effects of adiposity on CVD.** In addition to pathways where adiposity amount induces insulin resistance, there are also pathways where abnormal adiposity distribution, particularly among different ethnicities, are associated with increased CVD risk and mortality (74). In a cross-sectional study in the Jilin Province, China, increases in abdominal adiposity characterized by increased WC, WHtR, or body roundness index are associated with dyslipidemia (75). Also, in Chinese patients HTN was associated with WHtR, BMI, WC, and WHtR in a meta-analysis (76), and Framingham Risk Scores with sagittal abdominal diameter in those with nondialysis chronic kidney disease (77). In yet another Chinese study, abnormal adiposity increased the likelihood of ischemic stroke through hypertensive effects (78). In the KoGES study (Korean Genome and Epidemiology Study), visceral adipose tissue was associated with increased left ventricular (LV) mass index and decreased LV diastolic function (79). In the Iranian CASPIAN-V (Fifth Survey of Childhood and Adolescence Surveillance and Prevention of Adult Non-communicable Disease) study (80), various anthropometrics in normal-weight children and adolescents were predictive for cardiometabolic risk.

The association of epicardial adipose tissue with CVD (81) was more pronounced in women (82), and incidental to increased cardiometabolic risk associated with underlying adiposity changes (83), or from direct effects of epicardial fat on neighboring structures (84). Interestingly, epicardial and visceral adipose tissue were positively associated with atherosclerotic burden, whereas subcutaneous adipose tissue had a negative association (85). Epicardial adipose tissue was also associated with vascular inflammation and arterial stiffness (86), aortic valve sclerosis score (87), LV hypertrophy and cardiomyocyte fibrosis/apoptosis, (88), and obstructive sleep apnea (89). Epicardial adipose tissue secretes more phospholipase A2 II with ischemia, resulting in more phospholipid hydrolysis and generation of local FFA (90). Increased FFA production by epicardial adipose tissue affects nerve impulse propagation and

**TABLE 2 Mechanisms Linking Abnormal Adiposity With  $\beta$ -Cell Dysfunction**

Abnormal autophagy
Amyloid protein islet associated polypeptide—IL-1 $\beta$ pathway
Apoptosis via IL-1 $\beta$ —FasL pathways
Diacylglycerols/ceramide effects on serine/threonine kinases, insulin receptor substrate-1, and the insulin receptor
Glucotoxicity via NF- $\kappa$ B/TNF- $\alpha$ /IL-6 pathways and ROS production
Leucine-rich repeat containing protein 8A effects on $\beta$ -cell swelling and calcium channels
Lipotoxicity
Local expansion of intra-islet macrophages
mTOR/S6K1 pathway
Pancreatic incretins (e.g., gastric inhibitor polypeptide; glucagon-like peptide 1)

IL = interleukin; mTOR = mechanistic target of rapamycin; NF = nuclear factor; ROS = reactive oxygen species; TNF = tumor necrosis factor.

development of arrhythmias (90). In addition, perivascular adipose tissue, oftentimes difficult to separate from epicardial adipose tissue, has properties of white, beige, or brown adipose tissue (91).

Adipose tissue macrophages normally accumulate, become activated (developing crown-like structures and CD9<sup>+</sup> expression) to clear dead adipocytes, and contribute to the obesity phenotype (92). Patients with insulin resistance preferentially accumulate fat in the intra-abdominal compartment containing increased resident macrophages, predominantly classically activated, proinflammatory M1 (producing tumor necrosis factor [TNF]- $\alpha$ , IL-6, and MCP-1), and a lesser proportion of alternatively activated M2 macrophages (93-97). M1 polarization can increase insulin resistance and CVD risk (98,99).

Complex interactions among adiposity and MetS traits can lead to obesity cardiomyopathy. This can occur through effects on hypoventilation, pulmonary HTN, and right ventricular failure, as well as decreased systemic vascular resistance leading to increased blood volume and cardiac output, right ventricular and then LV failure (100). The entanglement among adiposity, dysglycemia, and other MetS traits also centers on dyslipidemia and HTN. Although increased circulating lipids are cardiometabolic risk factors, it is fat accumulation reflected by anthropometrics that is better correlated with pre-HTN (101).

**DYSGLYCEMIA-BASED CHRONIC DISEASE. From abnormal adiposity to insulin resistance.** DBCD (23) provides a framework for early intervention for CMBCD. Similar to ABCD, the DBCD model may be a more accurate and actionable diagnostic term than *diabetes* for the spectrum of pathophysiological events stemming from insulin resistance, pre-diabetes, T2D, and CVD. *Dysglycemia* is a general term that includes all forms of diabetes (but only T2D

**TABLE 3 Key Adiposity and Dysglycemia Effects on CVD**

Effect	Coronary Heart Disease	Heart Failure	Atrial Fibrillation
ABCD	↑ Prevalence ↑ CAC progression	↑ HFpEF > HFrEF	↑ Prevalence ↑ Peri/epicardial AT ↓ UCP1 expression
DBCD	↑ Platelet reactivity ↑ Risk first MI ↓ Myocardial perfusion	↑ ECV ↑ HFpEF ↑ Impaired relaxation ↑ Microvascular disease ↑ NT-proBNP/cytokines ↑ Cardiac lipotoxicity ↑ AGE-dependent remodeling ↓ Myocardial performance	↑ Prevalence Hypoglycemia/↑ QT <sub>c</sub>
MetS	↑ Prevalence ↑ Coronary plaques ↓ Prognosis after first ACS	↑ Prevalence	↑ Prevalence

See text for references.

ABCD = adiposity-based chronic disease; ACS = acute coronary syndrome; AGE = advanced glycation end-products; AT = adipose tissue; CAC = coronary artery calcium; CVD = cardiovascular disease; DBCD = dysglycemia-based chronic disease; ECV = extracellular volume; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; MI = myocardial infarction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

in the context of this paper) and pre-diabetes, including states of increased molecular risk for T2D, such as insulin resistance. The cardinal manifestations of insulin resistance are normoglycemia or hyperglycemia with hyperinsulinemia. The DBCD designation has been adopted by the American Association of Clinical Endocrinologists (23).

**Effect of insulin resistance on  $\beta$ -cell dysfunction.** Insulin resistance in muscle and liver increases the demand for insulin secretion from pancreatic  $\beta$ -cells to maintain glucose homeostasis. As long as robust insulin secretory responses are sustained, patients remain normoglycemic. However, eventually postprandial glucose levels rise when early-phase insulin secretion becomes insufficient for normal post-prandial glycemic excursions. With progressive  $\beta$ -cell enfeeblement over time, insulin secretory capacity declines further, fasting glucose levels rise, and eventually, patients reach diagnostic thresholds for pre-diabetes and then T2D (102).

**Effect of insulin resistance on CVD.** Insulin resistance with normoglycemia can lead to accelerated atherosclerosis, myocardial dysfunction, and risk of CVD events (15-17,103-109). The constellation of abnormalities, including inflammation, atrial enlargement, and ventricular diastolic and systolic dysfunction have been associated with an increased risk of atrial fibrillation. The effects of insulin resistance on vascular biology include: 1) defects in glucose homeostasis, substrate oxidation, and mitochondrial function; 2) increased inflammation and oxidative stress; 3) alterations in lipids and lipoproteins; 4) impaired lipid storage in adipocytes via defects in

both lipolysis and triacylglycerol synthesis; and 5) vasoregulation due to a reduction in endothelial nitric oxide synthase (eNOS) activity and nitric oxide (NO) production (110,93-97,111-116). Insulin resistance is also positively associated with acetylcholine-induced coronary artery spasm in patients without frank T2D (117).

The IRAS (Insulin Resistance Atherosclerosis Study) (15,16,18) and the BIP (Bezafibrate Infarction Prevention Trial) (19-21) both demonstrated that insulin resistance was associated with the development of CVD events. Gast et al. (17) conducted a meta-analysis of 65 studies and found that insulin resistance determined by the homeostasis model assessment of insulin resistance was significantly associated with relative risk for CVD events.

**Effect of insulin resistance on dyslipidemia.** The dyslipidemia associated with insulin resistance is characterized by: 1) excessive postprandial chylomicronemia; 2) elevated plasma triglycerides; 3) low HDL-c; and 4) increased LDL particle concentration without necessarily a change in LDL-c levels due to the presence of small dense LDL (104,116,118). There is also increased circulating large triglyceride-containing very low-density lipoprotein (VLDL) molecules due to greater hepatic production (from increased FFA flux to the liver) and reduced clearance due to decreases in lipoprotein lipase (119). The high levels of VLDL, together with the actions of cholesteryl ester transfer protein (CETP) and hepatic lipase, participate in the generation of small dense LDL (119). CETP facilitates the exchange of cholesteryl esters and triglycerides among lipoproteins, resulting in a net loss of cholesterol esters and gain of triacylglycerols by HDL and LDL, and a reciprocal net gain of cholesterol esters and loss of triacylglycerols by chylomicrons and VLDL (119). The resulting triglyceride-rich LDL becomes a substrate for the lipolytic action of hepatic lipase resulting in the formation of small dense LDL (120). Hepatic lipase also acts on triglyceride-rich HDL to produce small dense HDL, resulting in a decrease in HDL-c, which are susceptible to increased catabolism (120).

Increased small dense LDL particle concentration is a risk factor for CVD, independent of overall LDL-c levels (121-123). The ARIC (Atherosclerosis Risk In Communities) study prospectively demonstrated that plasma levels of small dense LDL were independently predictive of CHD (121). Upon entering the vascular wall, macrophages preferentially take up modified LDL particles, leading to cholesterol accumulation, foam cell formation, and induction of inflammation, via Toll-like receptor 4 (TLR-4) and the necrosis



factor kappa-B (NFκB) pathway (124-126). Thus, changes in lipids and lipoproteins that occur solely as a function of insulin resistance are atherogenic, accelerate atherosclerosis independent of overall LDL-c, and begin early in the course of CMBCD.

**Effect of insulin resistance on endothelial dysfunction.**

Insulin resistance correlates with endothelial dysfunction even in patients without diabetes (127). Insulin signaling through PI3K/Akt in endothelium regulates eNOS activity and production of the vasodilator NO (128,129). With insulin resistance, this pathway is inhibited, whereas the insulin mitogenic Ras/Raf mitogen-activated protein kinase (MAPK) signaling pathway is unimpeded and hyperactive due to hyperinsulinemia (128,129). MAPK signaling increases production of the vasoconstrictor endothelin-1, such that the net effect of imbalance between metabolic and mitogenic insulin signaling pathways is vasoconstriction (128,129). The mitogenic pathway also promotes vascular smooth muscle cell proliferation and expression of vascular cell adhesion protein (VCAM)-1 and E-selectin (130). In addition, insulin resistance is associated with increased activity of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) (131). Augmentation in signaling through the mineralocorticoid receptor further increases production of reactive oxygen species (ROS), impairs vascular relaxation, and induces cell adhesion molecules (132,133).

The combinations of these processes affecting the vascular wall enhance vasoreactivity and explain the relationship among insulin resistance, elevated blood pressure, development of HTN, and progression over time to CVD. In addition, the insulin-resistant state is characterized by a clotting diathesis (134-137) due to endothelial dysfunction, insulin resistance, and decreased NO production, which increases platelet adhesiveness, along with increased circulating fibrinogen and plasminogen activator inhibitor 1 (PAI-1) production by adipose tissue.

**Effect of insulin resistance on inflammation.** A sine qua non of insulin resistance is inflamed adipose tissue that increases release of proinflammatory cytokines. These cytokines and other circulating factors, such as oxidized and triglyceride-rich lipoproteins, add to the local effects of lipotoxicity, glucotoxicity, and oxidative stress to augment vascular wall inflammation. These factors increase cell adhesion molecule expression that promotes monocyte margination, uptake, conversion into macrophages, and avid accumulation of cholesterol particularly in the form of modified LDL (138). Moreover, insulin resistance generates small dense LDL particles that

are prone to modification by oxidation, acetylation, and glycation. These modifications render the lipoprotein particles proinflammatory and induce an immune response forming LDL-containing immune complexes that compound their atherogenicity (139). Resident macrophages in the vascular wall readily take up modified LDL particles and convert to foam cells, leading to formation of fatty streaks and plaque development.

Macrophages play an essential role at all stages of atherosclerotic lesion progression (140,141). Proinflammatory M1 macrophages differentiate in response to TLR and interferon-γ signaling and are activated by lipopolysaccharides and lipoproteins. These cells secrete proinflammatory factors, such as TNFα, IL-1β, and various chemokines (C-X-C motif chemokine ligand [CXCL]-9, CXCL-10, and CXCL-11), as well as produce high levels of ROS (142). By contrast, M2 macrophages secrete anti-inflammatory factors, such as IL-1 receptor agonist and IL-10. With insulin resistance, resident M1 macrophages are increased in the vascular wall and adipose tissue. Although both macrophage phenotypes are detected in atherosclerotic lesions, proinflammatory M1 macrophages are enriched in progressing plaques, where they play a critical role in atherogenesis, and M2 macrophages are present in regressing plaques (142).

**Effect of insulin resistance on cardiac metabolism.**

With the insulin resistance state, the same processes that impair insulin action in skeletal muscle also occur in the myocardium. There is increased accumulation of ectopic lipid in the cardiomyocyte, resulting in myocardial lipotoxicity, in the face of greater serum FFA levels (143). Intracellular diacylglycerol, inflammatory factors, mitochondrial dysfunction, and oxidative stress activate serine kinases that phosphorylate and impair insulin signaling through the insulin receptor and IRS-1, and also activate NFκB pathways that can amplify myocyte inflammation (143). These coordinated events reduce the ability of insulin to stimulate glucose uptake and oxidation in the heart. The myocardium uses fatty acids as its preferred fuel choice, except in the presence of pacing or ischemia when the heart relies on glucose for fuel. Due to defects in insulin action and mitochondrial function, this flexibility to convert to glucose metabolism is impaired. The metabolic alterations in substrate utilization, combined with inappropriate activation of the RAAS, endothelial dysfunction, sympathetic nervous system activation, oxidative stress, and inflammation, produce structural abnormalities in the heart (144,145). Cellular injury and abnormalities in contractile proteins promote cardiac tissue interstitial fibrosis, and cardiac

stiffness impairs diastole relaxation and filling of the ventricle before systole (144). The result is HF with preserved ejection fraction accompanied by increased left atrial size, LV mass, and development of diastolic dysfunction (144). Over time, diastolic dysfunction can progress to systolic dysfunction and HF with reduced ejection fraction.

**Pre-diabetes to CVD.** Cardiovascular risk is conclusively associated with pre-diabetes (146-148), MetS (149), and T2D (148-150). Multifactorial risk factor control leads to durable reduction in the number of CVD events and mortality (151), even in patients with T2D (152). The UKPDS (United Kingdom Prospective Diabetes Study) established an epidemiological link between hyperglycemia and CHD by showing there was a linear relationship between  $A_{1C}$  and CVD events, including myocardial infarction (153). A diagnosis of pre-diabetes may be associated with subsequent restenosis after elective percutaneous coronary intervention (154). However, the excess risk of CVD observed in patients with pre-diabetes may be explained by comorbid cardiometabolic risk factors (155).

Hyperglycemia impairs insulin-stimulated glucose transport due to direct effects on target cells (156-160). Hyperglycemia also directly augments oxidative stress and inflammatory pathways (161-163). Advanced glycation end-products (AGE) are increased with T2D, due to prolonged exposure of proteins and lipids to hyperglycemia, and contribute to oxidative injury and CV complications (164). There is more fibrosis and myocardial stiffness due to AGE formation and collagen cross-linking (165). The dyslipidemia of insulin resistance and modification of lipoproteins by oxidation (166) or AGE (167) are aggravated by hyperglycemia.

**T2D to CVD.** The association of increased CVD risk in patients with T2D is well established (168-171). In patients with T2D in Denmark, CVD risks were greater than those with type 1 diabetes or latent autoimmune diabetes in adults (172). Among those with T2D, glycemic variability and hypoglycemia (173) correlated with atherosclerosis and macrovascular

complications, possibly due to effects on inflammation. In the Rio de Janeiro Type 2 Diabetes Cohort Study, patients with T2D and ankle-brachial index  $\leq 0.90$  had increased risk for all-cause mortality, CV mortality, and major adverse cardiac events (174).

The risk for hospitalization for HF is also higher with T2D, though decreased with advanced age ( $>75$  years) and target  $A_{1C}$  ( $<7\%$ ), or without albuminuria (175). In patients with T2D, myocardial dysfunction and HF develop at an earlier age, occur more frequently, and exert greater morbidity due to interactions among insulin signaling, impaired glucose utilization, inflammation, oxidative stress, and endothelial dysfunction (103,135,176-179).

## CONCLUSIONS

The CMBCD model provides a basis for specific, evidence-based therapeutic targeting in order to build a care plan that promotes cardiometabolic health and mitigates the development and ravages of CVD (Table 3). This approach has the advantage of scientific formalism that can be enriched over time, amenable to clinical trial design, knowledge translation, and medical education. In the first part of this JACC State-of-the-Art Review, a step-by-step framework is presented for CMBCD, focusing on 2 main drivers, adiposity and dysglycemia, as applied to 3 main CVD problems: CHD, HF, and AF. Specific molecular, biochemical, and physiological pathways are presented and these are parsed out into specific therapeutic targets. The context for building this CMBCD model is prevention as early as possible to achieve sustainable and optimal CV outcomes and value. The tactical implementation of this CMBCD model is the subject of second part of this JACC State-of-the-Art Review.

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**KEY WORDS** adipokines, adiposity, atherosclerosis, atrial fibrillation, cardiomyopathy, cardiovascular, chronic disease, dysglycemia, insulin resistance, obesity, type 2 diabetes