Evidence-Based Cardiometabolic Disease Models as a Foundation for Preventive Care and Gene Therapy Approaches

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Abstract

The cardiometabolic-based chronic disease model lays the foundations for accurate, evidence-based preventive targeting in order to develop a gene therapeutic plan that promotes cardiometabolic health thereby lowering the risk of CVD onset and complications. This approach is useful for clinical trial design, knowledge translation, and patient education because of its methodological formalism, which can be refined over time. A step-by-step structure for cardiometabolic-based chronic disease is explored in the first part of this Review, concentrating on two main drivers, adiposity and dysglycemia, as they contribute to three major CVD problems: CHD, HF, and AF. The relevant molecular, biochemical, and physiological pathways are discussed before being broken down into clinical targets. The aim of the cardiometabolic-based chronic disease model is to produce long-term, optimum CV outcomes as well as benefit from gene therapy by avoiding disease as soon as possible.

Cardiovascular disease (CVD) is a broad term that refers to a variety of conditions that affect the heart and blood vessels. The first section of this Review will concentrate on metabolic events that can be grouped into distinct chronic disease periods that can be treated with proactive treatment to improve coronary heart disease (CHD), heart failure (HF), and atrial fibrillation (AF) clinical results.

CVD is the world's leading cause of death (1,2). Efficient primary preventive methods have been linked to lower average CVD mortality rates (3). However, due to population rise, ageing, and obesity and type 2 diabetes (T2D) trajectories, cumulative CVD-related deaths increased (2, 3, 4). The decrease in age-adjusted CVD mortality rates in the United States has slowed since 2011. (5,6). Furthermore, between 2011 and 2015, there was a rise in CVD (except for CHD) mortality (7). What's more alarming is that rising CVD mortality rates are thought to be attributable to less successful and/or affordable preventive measures, especially among low- and middle-income socioeconomic and educational strata, as well as some ethnocultural communities with unhealthy lifestyles (8, 9, 10, 11). Nonetheless, as large-scale risk factor adjustment measures are delivered through an interconnected health care environment, mortality trends change (12). Many shortcomings in the health-care system were presented in a call-to-action report, the most impactful of which was "failure to make risk factor changes" (13).

The treatment of CVD also starts with the onset of symptoms like angina, acute coronary syndrome, stroke, NYHA functional class III/IV congestive HF, or symptomatic peripheral vascular dysfunction in many patients. As prevention measures, smoking abstinence and risk-based reduction of low-density lipoprotein cholesterol (LDL-c) are cases. However, in cardiovascular (CV) outcomes experiments, reducing LDL-c levels with statin treatment resulted in an overall risk reduction of just 30%, leaving a significant amount of unattended residual risk (14). More successful CVD preventive measures are needed, given the burden of CVD borne by patients and our communities. In this respect, it's important to remember that CVD is a chronic illness that starts early in life and can be prevented by major, secondary, and tertiary prevention, reducing the risk of end-stage incidents. Furthermore, T2D and obesity are central to the chronic disease mechanism, which, although distinct from end-stage CVD cases, are both symptoms and drivers of this chronic disease process. This analysis establishes a medically actionable model that delineates inter-relationships among obesity, T2D, and CVD, based on existing evidence addressing pathophysiology. For the first time, this new model lays out systematic primary, secondary, and tertiary preventive strategies focusing on CVD (specifically, CHD, HF, and AF) as end-stage innovations in the chronic disease phase. Insulin tolerance is the fundamental abnormality behind the development of this new entity, which is renamed cardiometabolic-based chronic disease (CMBCD). Insulin tolerance is to blame for the majority of the risk that remains after statin therapy (15, 16, 17, 18, 19, 20, 21). Rather than relying on costly and intrusive technological treatments after disease morbidities are completely articulated, the CMBCD paradigm focuses on modifiable risk factors that can reduce patient pain and social costs associated with CVD.

Insulin resistance occurs as abnormal adiposity and dysglycemia collide (Figures 1 and 2, Central Illustration). These metabolic drivers are derived from key genetic, environmental, and behavioral drivers, and they contribute to the development of CMBCD. Dysglycemia develops according to the model described by dysglycemia-based chronic disease (DBCD) (22), and abnormal adiposity is reflected in the recently suggested diagnostic concept for obesity, adiposity-based chronic disease (ABCD) (22). (23). In the form of chronic disease treatment templates, ABCD and DBCD intersect at the stage of insulin resistance to exacerbate CMBCD (24, 25, 26). Taken together, this formulation aims to clear up the ambiguity in recent literature about the pathophysiological associations between insulin resistance, metabolic syndrome (MetS), obesity, T2D, and cardiovascular disease (CVD).

CMBCD Genetics' Primary Drivers

Many molecular factors have been linked to cardiometabolic symptoms (Table 1). The bulk of chronic disease heritability, though, remains unclear by results from genome wide interaction studies. Familial inheritance, on the other hand, is more reliant on modifiable threats (27). Different ethnicities and attitudes affect these relationships, providing greater explanation for the presentation of phenotypic traits (27). The use of machine genetics to classify molecular drivers is beneficial, but risk and disease phenotype are largely determined by the dynamic combination of genes, environment, and behaviour. Ethnicity-specific risk genes and biological pathways, for example, play a role in the complex pathogenesis of T2D and CVD (28). In light of the fact that only a small number of gene variants are responsible for CHD, disease drivers, which correspond to hub genes at the top of a regulatory network, constitute a more powerful heritability mechanism (29). Two major disease drivers for CHD are gene regulation networks in the atherosclerotic arterial wall and abdominal adipose tissue (29). The first step in a chronic disease model is the recognition and association of molecular variables with clinical cases, despite the fact that it is actually below the routine detection level in clinical medicine and lacks genetic risk scores with sufficient validity for routine clinical prediction.

Epigenetic control is a biological theory that explains how genes and the environment interact to produce a particular phenotype. For example, epigenetic changes caused by maternal gestational diabetes in the womb may confer an insulin resistance phenotype in offspring, which can continue through adulthood and contribute to T2D, obesity, and cardiovascular disease (30, 31, 32, 33). A systems approach to the complex interactions among genetic, epigenetic, environmental, and MetS factors has been proposed as a way to generate useful explanatory models (34, 35, 36, 37, 38, 39).

Geng et al. (40) found evidence for a causal influence of a genetic predisposition for higher childhood body mass index (BMI) with elevated T2D and CHD incidence by analyzing 25 single-nucleotide polymorphisms. Based on correlations with some adult risk factors (systolic blood pressure [BP], diastolic blood pressure [BP], total cholesterol, high-density lipoprotein [HDL], LDL, non-HDL, and triglycerides), childhood obesity was shown to be a risk factor for CVD in a meta-analysis (41). In reality, obese mothers' newborns had thicker intraventricular septa and poor cardiac output (42). A weighted genetic risk score of 97 single-nucleotide polymorphisms in children increased adulthood obesity estimation in the Cardiovascular Risk

in YFS (Young Finns Study) (43). In addition to the sum of adiposity, as measured by BMI, the distribution of adiposity in androids was associated with higher insulin resistance, as measured by fasting insulin, triglyceride, HDL, interleukin (IL)-6, monocyte chemoattractant protein (MCP), and C-reactive protein levels, as well as variations in gene expression (44).

The natural world

The constructed (or man-made) world, as well as the nonphysical (cultural) environment, play a role in the transmission of genetic cardiometabolic risk factors (10). Statistical knowledge about specific and actionable environmental variables is provided by local cluster identification and spatial regression techniques with a global footprint (45). CVD is linked to the following variables in particular: Lower socioeconomic strata and less access to affordable health services, low schooling and literacy rate, high alcohol consumption areas, both urban (for children) and rural (with heat or cold waves impacting health care access) habitats, air and noise emissions, and inadequate drinking water quality are all factors (45).

Toxins in the environment or endocrine disruptors may alter CV outcomes by modulating gene expression and interfering with molecular trafficking and other pathophysiological pathways. Polymorphisms in the genes IL8RA, TXN, NR3C2, COX5A, and GCLC, for example, may interfere with higher levels of seafood arsenicals to raise T2D rates (46). In normal-weight Korean subjects, exposure to chronic organic contaminants is linked to MetS characteristics, likely due to toxic effects on-cell function, independent of adiposity or insulin tolerance (47,48). Fine particulate matter (air pollutant), sunshine, and maximum heat index were correlated with CVD risk in a study by Al-Hamdan et al. (49) in the United States, with odds ratios for mortality mitigated by T2D, obesity, and some lifestyle, behavioral, and socioeconomic influences, particularly among Blacks and older adults (65 years of age). Telomere shortening has been linked to CHD and can be caused by environmental contaminants, chronic stress, or inflammation (50). While definitive interventional trials that reduce CMBCD steps are incomplete, the combination of genetics and dietary factors can modulate the gut microbiome in ways that influence inflammatory and metabolic networks, eventually leading to abnormal adiposity, insulin resistance, dysglycemia, and CVD (51).

Specific activities can not only modulate but also offer resources for action until phenotypic expression of genetic and environmental factors initiates a disease phase. Pickens et al. (52) summarized findings from a 2015 U.S. study on health-risk habits in adults 18 years of age in a 2018 Morbidity and Mortality Weekly Report surveillance review, which offered background for genetic and environmental drivers of chronic disease, including those dependent on cardiometabolic pathways. The median self-reported prevalence of good and bad health by state ranged from 11.2 percent to 34.1 percent, with 13.2 percent without health care, just 58.1 percent to 79.8% having a regular annual checkup, and just 73.3 percent to 86.7 percent having a blood cholesterol check (52). Tobacco smoking was 9.0 percent to 27.2 percent, binge alcohol drinking was 11.2 percent to 26.0 percent, lack of leisure time physical exercise was 17.6 percent to 47.1 percent, and poor fruit or vegetable intake was 33.3 percent to 55.5 percent or 16.6 percent to 31.3 percent, respectively, in terms of prevalence rates of particular modifiable CVD risks by state (52). Lower BMI, waist-to-height ratio (WHtR), and waist circumference

(WC) were correlated with higher diet-quality scores, suggesting increased healthier eating habits (53). These health-risk habits combined with genetic and environmental factors to create the prevalence incidence ranges shown below by state: Obesity ranges from 19.9% to 36.0 percent; diabetes ranges from 11.2 percent to 26.8%; hypertension (HTN) ranges from 24.2 percent to 39.9 percent; high cholesterol ranges from 27.1 percent to 37.3 percent; coronary heart disease (CHD) ranges from 7.2 percent to 16.8 percent; and stroke ranges from 2.5 percent to 7.5 percent (52).

Drivers of Metabolism

Chronic disorder caused by adiposity

Adiposity that is out of the ordinary

Obesity is a less stigmatized medical concept that is more statistically reliable, actionable, and less stigmatized than ABCD. ABCD is a chronic, systemic condition characterized by defects in the volume, production, and function of adipose tissue, as well as cardiometabolic, biomechanical, and psychological complications, all of which contribute to morbidity and mortality (22). The American Association of Clinical Endocrinologists and the European Association for the Study of Obesity have both adopted the ABCD designation (22,54). ABCD is divided into two categories: adiposity-based, which represents anomalies in adipose tissue density, function, and distribution; and chronic disease, which reflects the risk, presence, and severity of complications (22).

The amount of abnormal adiposity, as measured by weight gain and BMI, is linked to CVD, but the relationship is complicated since excessive fat mass is neither a necessary nor adequate consideration. Not all patients with obesity are insulin resistant, and even lean people may develop insulin resistance, increasing their risk of T2D and CVD. Just about 11% of human variations in insulin sensitivity can be clarified by BMI, according to the association between generalized rise in adiposity and insulin sensitivity (55). If weight gain happens in the context of insulin resistance, there is asymmetrical fat deposition favoring the intra-abdominal depot, as well as adipose tissue inflammation with macrophage influx and anomalies in circulating adipokines (55). Inflammation, oxidative stress, and glucose intolerance can all be exacerbated by additional weight gain (55). Thus, there is an association between excess adiposity and insulin resistance that raises CVD risk in many, though not all, people.

Individual heterogeneity in adiposity distribution is dependent on key drivers and represents an excess in dietary consumption and energy expenditure. Entrapment of free fatty acids (FFA) is linked to increased gluteofemoral subcutaneous adipose tissue, which reduces ectopic FFA uptake, insulin resistance markers, inflammation, and CVD danger (44,56, 57, 58). In reality, subcutaneous fat in the legs (59) and thighs (60), rather than the arm (59), has major cardiometabolic benefits. The liver receives the most FFA from subcutaneous adipose tissue, which accounts for around 80% of overall adipose tissue (61). FFA levels increase, and ectopic lipid accumulates in tissues that usually have little or no fat storage because unstable adipose tissue can not properly accommodate fuel storage in the face of excessive caloric intake.

Skeletal tissue, stomach, epicardium (the layer between the exterior wall of the myocardium and the visceral layer of the pericardium), pericardium (the layer between the visceral and parietal layers of the pericardium), intestines, kidney, and pancreas are among the ectopic locations (55).

Adipokine signatures, endogenous satiety receptors, and subsequent associations with satiety centers in the hypothalamus and other central nervous system loci influencing eating activity are both affected by abnormal adiposity feature. These improvements can encourage calorie intake and the preservation of adipose tissue mass. Adipokines interact with CV pathways in a networked fashion (62). In the face of weight loss following lifestyle intervention, multiple maladaptive responses in satiety hormones, energy consumption, and psychological factors can push weight regain back to historically high BMI levels (63,64).

Insulin tolerance and the effects of obesity

Insulin tolerance is exacerbated by ectopic fat. Intrahepatic fat, a form of ectopic fat, has been linked to increased cardiometabolic risk factors and cardiovascular disease (CVD) (58,65). However, there is still a lot to learn about the predictive potential of ectopic fat, especially nonalcoholic fatty liver disease, in ABCD and CMBCD.

Patients with a BMI in the overweight or obese range may be insulin sensitive and not at risk for T2D or CVD. The "metabolically stable obese" is a term used to describe these patients (66,67). While there is some diagnostic confusion, about 15% to 20% of U.S. individuals overweight or obese in the NHANES (National Health and Nutrition Examination Survey) cohort are categorized as metabolically stable when all MetS traits are absent (68). The obesity paradox is a pathophysiological and epidemiological correlation with modestly elevated BMI with lower risks and better prognosis for some chronic disorders, like CVD. It can be due to reverse causality (69,70).

Adiposity's effect on-cell dysfunction

The obese pathophysiological condition is linked to a local expansion of intraislet macrophages, which impairs-cell function in a murine model (71). Good evidence of direct signalling from adipose tissue to-cells or intraislet macrophages is absent in the absence of an irregular inflammatory milieu mediating this interaction. Another theory involves pathological autophagy, which disrupts-cell activity and, as a result, sets the stage for hyperglycemia and progression to pre-diabetes and T2D in the context of ABCD-related insulin resistance (72). Obesity, excessive calorie intake, and insulin tolerance are all linked to-cell fatigue by these and other pathways (Table 2). Each of these pathways is a potential priority for reversing the progression of ABCD to insulin resistance (73).

CVD effects of adiposity

There are pathways where abnormal adiposity distribution, especially among different ethnicities, is associated with increased CVD risk and mortality, in addition to pathways where adiposity amount induces insulin resistance (74). Increases in abdominal adiposity, as measured by WC, WHtR, or body roundness index, were linked to dyslipidemia in a cross-sectional analysis in Jilin Province, China (75). In a meta-analysis (76), HTN was linked to WHtR, BMI, WC, and WHtR in Chinese patients, and Framingham Risk Scores were linked to sagittal abdominal diameter in nondialysis chronic kidney disease patients (77). Another Chinese research found that abnormal adiposity raised the risk of ischemic stroke by causing hypertensive symptoms (78). Visceral adipose tissue was linked to a higher left ventricular mass index and lower LV diastolic role in the KoGES study (Korean Genome and Epidemiology Study) (79). Various anthropometrics in normal-weight children and teenagers are predictive of cardiometabolic vulnerability in the Iranian CASPIAN-V (Fifth Survey of Childhood and Adolescence Surveillance and Prevention of Adult Noncommunicable Disease) study (80).

The connection between epicardial adipose tissue and CVD (81) was stronger in women (82), and was caused by increased cardiometabolic risk due to underlying adiposity changes (83), or direct effects of epicardial fat on neighboring structures (84). Surprisingly, atherosclerotic pressure was positively correlated with epicardial and visceral adipose tissue, but not with subcutaneous adipose tissue (85). Vascular inflammation and arterial stiffness (86), aortic valve sclerosis score (87), LV hypertrophy and cardiomyocyte fibrosis/apoptosis (88), and obstructive sleep apnea (89) were both linked to epicardial adipose tissue (89). With ischemia, epicardial adipose tissue secretes more phospholipase A2 II, resulting in increased phospholipid hydrolysis and local FFA production (90). Increased FFA output by epicardial adipose tissue has an effect on nerve impulse propagation and arrhythmia growth (90). Furthermore, perivascular adipose tissue, which is also difficult to distinguish from epicardial adipose tissue, has white, beige, or brown adipose tissue properties (91).

Adipose tissue macrophages accumulate, become activated (developing crown-like structures and CD9+ expression), and contribute to the obesity phenotype by clearing dead adipocytes (92). Patients with insulin resistance preferentially accumulate fat in the intra-abdominal compartment, which contains a higher proportion of classically active proinflammatory M1 macrophages (producing TNF-, IL-6, and MCP-1) and a lower proportion of alternatively activated M2 macrophages (93, 94, 95, 96, 97). Insulin resistance and the risk of cardiovascular disease can also be exacerbated by M1 polarization (98,99).

Obesity cardiomyopathy can be caused by complex relationships between adiposity and MetS traits. Hypoventilation, pulmonary hypertension, and right ventricular failure, as well as reduced systemic vascular resistance contributing to elevated blood flow and cardiac production, right ventricular, and then LV failure, may all contribute to this (100). Dyslipidemia and HTN are also intertwined with adiposity, dysglycemia, and other MetS characteristics. While increased circulating lipids are cardiometabolic risk factors, anthropometric fat accumulation is more closely linked to pre-HTN (101).

Chronic disorder caused by hypoglycemia

From abnormal adiposity to insulin resistance, there's a lot to consider.

The DBCD (23) architecture offers a framework for CMBCD early intervention. The DBCD model, like ABCD, could be a more precise and actionable diagnostic concept for the continuum of pathophysiological events resulting from insulin resistance, pre-diabetes, T2D, and CVD than diabetes. Dysglycemia is a broad concept that encompasses all types of diabetes (but only T2D in this paper) and pre-diabetes, as well as states that raise the molecular risk of T2D, such as insulin resistance. Normoglycemia or hyperglycemia with hyperinsulinemia are the two most common signs of insulin resistance. The American Association of Clinical Endocrinologists has introduced the DBCD designation (23).

Insulin resistance has an impact on-cell dysfunction.

Insulin tolerance in the muscle and liver raises the need for pancreatic ß-cell insulin secretion to sustain glucose homeostasis. Patients remain normoglycemic as long as robust insulin secretory responses are maintained. However, as early-phase insulin secretion is inadequate for typical post-prandial glycemic excursions, post-prandial glucose levels increase. Insulin secretory ability decreases further as ß-cell enfeeblement progresses, fasting glucose levels increase, and patients gradually meet diagnostic thresholds for pre-diabetes and then T2D. (102).

The effect of insulin resistance on cardiovascular disease

Insulin tolerance combined with normoglycemia can result in elevated atherosclerosis, myocardial instability, and an increased risk of cardiovascular disease (CVD) (15, 16, 17,103, 104, 105, 106, 107, 108, 109). An elevated risk of atrial fibrillation has been linked to a constellation of anomalies involving inflammation, atrial enlargement, and ventricular diastolic and systolic dysfunction. Insulin resistance has many effects on vascular biology, including: 1) glucose homeostasis, substrate oxidation, and mitochondrial function; 2) increased inflammation and oxidative stress; 3) lipid and lipoprotein changes; 4) impaired lipid storage in adipocytes due to defects in both lipolysis and triacylglycerol synthesis; and 5) vasoregulation due to a decrease in endothelial nitrilase (110,93, 94, 95, 96, 97,111, 112, 113, 114, 115, 116). In patients without frank T2D, insulin resistance is also linked to acetylcholine-induced coronary artery spasm (117).

Insulin resistance was linked to the occurrence of CVD events in the IRAS (Insulin Resistance Atherosclerosis Study) (15,16,18) and the BIP (Bezafibrate Infarction Prevention Trial) (19, 20, 21). Gast et al. (17) performed a meta-analysis of 65 studies and discovered that insulin tolerance as measured by the homeostasis model was strongly correlated with the risk of CVD events.

Insulin resistance's effect on dyslipidemia

Excessive postprandial chylomicronemia, elevated plasma triglycerides, low HDL-c, and enhanced LDL particle concentration without specifically a difference in LDL-c levels owing to the existence of tiny compact LDL particles define the dyslipidemia associated with insulin resistance (104,116,118). There are also more massive triglyceride-containing very low-density lipoprotein (VLDL) molecules in circulation as a result of increased hepatic output (from increased FFA flux to the liver) and decreased clearance due to lipoprotein lipase reductions (119). The formation of small compact LDL is aided by elevated levels of VLDL, as well as the activities of cholesteryl ester transfer protein (CETP) and hepatic lipase (119). CETP promotes the transfer of cholesteryl esters and triglycerides between lipoproteins, resulting in a net loss of cholesterol esters and a 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 triglyceride-rich LDL that results becomes a substrate for hepatic lipase's lipolytic action, resulting in the development of small dense LDL (120). Hepatic lipase also converts triglyceride-rich HDL into small dense HDL, lowering HDL-c levels and making them more vulnerable to catabolism (120).

Increased small dense LDL particle concentration, regardless of total LDL-c levels, is a risk factor for CVD (121, 122, 123). The ARIC (Atherosclerosis Risk In Communities) study found that plasma levels of small dense LDL were an independent predictor of coronary heart disease (121). Macrophages preferentially pick up modified LDL particles as they reach the vascular wall, leading to cholesterol aggregation, foam cell development, and inflammation induction through the Toll-like receptor 4 (TLR-4) and necrosis factor kappa-B (NFB) pathway (124, 125, 126). As a result, improvements in lipids and lipoproteins that arise exclusively as a result of insulin resistance are atherogenic, exacerbate atherosclerosis regardless of total LDL-c, and start early in the CMBCD process.

Endothelial failure as a result of insulin resistance

Even in people who do not have diabetes, insulin resistance is linked to endothelial dysfunction (127). Insulin signaling in the endothelium via PI3K/Akt controls eNOS activity and the output of the vasodilator NO (128,129). This pathway is disrupted by insulin resistance, while the insulin mitogenic Ras/Raf mitogen-activated protein kinase (MAPK) signaling pathway is unaffected and hyperactive as a result of hyperinsulinemia (128,129). MAPK signaling increases the synthesis of the vasoconstrictor endothelin-1, resulting in vasoconstriction as a result of an imbalance between metabolic and mitogenic insulin signaling pathways (128,129). The mitogenic pathway also facilitates the proliferation of vascular smooth muscle cells and the expression of VCAM-1 and E-selectin (130). Furthermore, insulin resistance is linked to increased sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) function (131). Increased mineralocorticoid receptor signaling increases the synthesis of reactive oxygen species (ROS), reduces vascular relaxation, and induces cell adhesion molecules (132,133).

The interaction of these processes on the vascular wall increases vasoreactivity and explains the connection between insulin tolerance, high blood pressure, the production of HTN, and the progression of CVD over time. Furthermore, the insulin-resistant condition is characterized by a clotting diathesis (134, 135, 136, 137) caused by endothelial dysfunction, insulin tolerance, and reduced NO production, which improves platelet adhesiveness, as well as increased circulating fibrinogen and plasminogen activator inhibitor 1 (PAI-1) production by adipose tissue.

Insulin resistance has an effect on inflammation.

Inflamed adipose tissue, which enhances the production of proinflammatory cytokines, is a requirement for insulin tolerance. These cytokines, as well as other circulating factors including oxidized and triglyceride-rich lipoproteins, amplify the local effects of lipotoxicity, glucotoxicity, and oxidative stress, resulting in increased vascular wall inflammation. These factors promote monocyte margination, absorption, conversion into macrophages, and avid cholesterol accumulation, especially in the form of modified LDL, through increasing cell adhesion molecule expression (138). Insulin tolerance also results in thin, compact LDL particles that are vulnerable to oxidation, acetylation, and glycation. These changes make the lipoprotein particles proinflammatory and cause an immune reaction, resulting in the formation of LDL-containing immune complexes, which increase their atherogenicity (139). The vascular wall's resident macrophages readily absorb transformed LDL particles and transform them into foam cells, resulting in the formation of fatty streaks and plaque formation.

Macrophages play an important part in the development of atherosclerotic lesions at all stages (140,141). TLR and interferon signalling distinguish proinflammatory M1 macrophages, which are activated by lipopolysaccharides and lipoproteins. These cells contain high levels of ROS and secrete proinflammatory factors such as TNF, IL-1, and various chemokines (C-X-C motif chemokine ligand [CXCL]-9, CXCL-10, and CXCL-11) (142). M2 macrophages, on the other hand, secrete anti-inflammatory factors including IL-1 receptor agonist and IL-10. Insulin tolerance causes an increase in resident M1 macrophages in the vascular wall and adipose tissue. While both macrophage phenotypes are found in atherosclerotic lesions, proinflammatory M1 macrophages are more abundant in developing plaques, where they play a key role in atherogenesis, whereas M2 macrophages are more prevalent in regressing plaques (142).

Insulin resistance has an effect on cardiac metabolism.

The same mechanisms that inhibit insulin activity in skeletal muscle also impair insulin action in the myocardium in the insulin resistance state. In the face of higher serum FFA levels, there is a rise in ectopic lipid aggregation in the cardiomyocyte, resulting in myocardial lipotoxicity (143). Intracellular diacylglycerol, inflammatory factors, mitochondrial dysfunction, and oxidative stress both stimulate serine kinases, which phosphorylate and inhibit insulin signaling through the insulin receptor and IRS-1, as well as NFB pathways, which can amplify myocyte inflammation (143). Insulin's capacity to induce glucose uptake and oxidation in the heart is reduced as a result of these organized activities. Except in the presence of pacing or ischemia,

when the heart depends on glucose for oxygen, the myocardium prefers fatty acids as a fuel source. This flexibility to translate to glucose metabolism is hampered by deficiencies in insulin action and mitochondrial function. Endothelial dysfunction, sympathetic nervous system activation, oxidative stress, and inflammation, in combination with metabolic changes in substrate use, result in structural defects in the heart (144,145). Cardiac stiffness impairs diastole relaxing and loading of the ventricle before systole, and cellular damage and defects of contractile proteins facilitate cardiac tissue interstitial fibrosis (144). As a result, the patient develops HF with retained ejection fraction, as well as increased left atrial scale, LV mass, and diastolic dysfunction (144). Diastolic dysfunction can lead to systolic dysfunction and HF with a low ejection fraction over time.

Via pre-diabetes to cardiovascular disease

Pre-diabetes (146, 147, 148), MetS (149), and T2D are all linked to an increased risk of cardiovascular disease (148, 149, 150). Even in patients with T2D, multifactorial risk factor management leads to a long-term drop in the number of CVD accidents and mortality (151). (152). The UKPDS (United Kingdom Prospective Diabetes Study) identified an epidemiological correlation between hyperglycemia and coronary heart disease (CHD) by demonstrating a linear association between A1C and CVD cases, such as myocardial infarction (153). After elective percutaneous coronary surgery, a diagnosis of pre-diabetes can be linked to subsequent restenosis (154). However, comorbid cardiometabolic risk factors can explain the increased risk of CVD seen in patients with pre-diabetes (155).

Due to immediate effects on target cells, hyperglycemia impairs insulin-stimulated glucose transport (156, 157, 158, 159, 160). Hyperglycemia also boosts oxidative stress and inflammatory processes explicitly (161, 162, 163). Due to extended exposure to proteins and lipids to hyperglycemia, advanced glycation end-products (AGE) are elevated in T2D, contributing to oxidative injury and CV complications (164). Because of AGE aggregation and collagen cross-linking, there is further fibrosis and myocardial stiffness (165). Hyperglycemia aggravates insulin resistance dyslipidemia and lipoprotein modulation by oxidation (166) or AGE (167).

From T2D to CVD

The link between T2D and an increased risk of cardiovascular disease is well known (168, 169, 170, 171). CVD complications were higher in T2D patients in Denmark than in people with type 1 diabetes or latent autoimmune diabetes in adults (172). Glycemic variability and hypoglycemia (173) are linked to atherosclerosis and macrovascular complications in people with T2D, likely because of their effects on inflammation. Patients with T2D and an ankle-brachial index of less than 0.90 have an elevated risk of all-cause death, CV mortality, and significant adverse heart injuries in the Rio de Janeiro Type 2 Diabetes Cohort Study (174).

T2D raises the risk of HF hospitalization, but this risk decreases with advanced age (> 75 years) and aim A1C (7%), or without albuminuria (175).Due to interactions among insulin signalling, impaired glucose utilization, inflammation, oxidative stress, and endothelial dysfunction,

myocardial dysfunction and HF evolve at a younger age, arise more often, and cause greater morbidity in T2D patients (103,135,176, 177, 178, 179, 165-191).

Final Thoughts

The CMBCD model lays the groundwork for precise, evidence-based preventive targeting in order to create a treatment strategy that supports cardiometabolic wellbeing while reducing the risk of CVD's onset and consequences. This method benefits from methodological formalism that can be improved over time, making it suitable for clinical trial design, information translation, and medical education. In the first section of this Review, a step-by-step structure for CMBCD is discussed, focusing on two major drivers, adiposity and dysglycemia, as they relate to three major CVD problems: CHD, HF, and AF. Relevant genetic, metabolic, and physiological mechanisms are presented, and they are then broken down into therapeutic goals. The aim of this CMBCD paradigm is to achieve sustainable and optimal CV results and benefit for gene therapy by preventing disease as early as possible.

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