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Cardiometabolic Syndrome: The Convergence of Diabetes, Hypertension, and cardiovascular disease – A Call for Early Intervention and Multidisciplinary Management

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A B S T R A C T

Cardiometabolic Syndrome (CMS) is a complex disease defined by the combined presence of metabolic disturbances like insulin resistance, abdominal obesity, dyslipidemia and hypertension. This clustering substantially elevates the risk of cardiovascular disease, type 2 diabetes, and all-cause mortality. The increasing prevalence of CMS worldwide highlights the pressing need for improved diagnostic approaches and targeted therapeutic measures. Though traditional risk factors, such as poor diet, lack of exercise, etc., are well established, an emerging body of evidence points toward the possible role that environmental toxins, particularly endocrine-disrupting chemicals like bisphenol A (BPA), phthalates, and microplastics from synthetic sources like polyester, appear to have in disrupting hormonal and metabolic homeostasis. This article reviews current diagnostic tools and treatment protocols available, emphasizing that early detection is vital using integrated biomarkers, and advanced technologies involving artificial intelligence (AI) and gut microbiome profiling. It also highlights the use of plant-derived antioxidants for ameliorating toxin-induced metabolic and neurovascular damage. Instead, the paper advocates for a new public health policy that embraces preventative care, environmental regulation, and personalized medicine, to address the complex etiology of CMS and rein in its worldwide impact.

INTRODUCTION

Cardiometabolic syndrome (CMS) refers to a group of interrelated metabolic and cardiovascular disorders that substantially increase the risk for type 2 diabetes mellitus (T2DM), hypertension, and atherosclerotic cardiovascular disease (ASCVD) (1,2). It is defined by central obesity, insulin resistance, dyslipidemia, and hypertension, all of which predispose to adverse cardiovascular events (3–5). Non-communicable diseases (NCDs) have become a leading cause of global health challenge, as cardiovascular disease, diabetes and cancer (collectively termed as chronic metabolic syndrome (CMS)), continue to be a significant contributor to morbidity and mortality which is on rise as a result of lifestyle changes, dietary patterns, and ageing populations (6–9). CMS has a well-documented impact on patient outcome but continues to be underdiagnosed and undertreated which calls for a more holistic and multidisciplinary approach to prevention and treatment (10).

CMS is a multigenic, multifactorial conditioning, caused by the interaction of genetic, environmental, and lifestyle factors (11,12). It is often defined as the presence of 3 or more of the following components: central obesity (increased waist circumference), hypertension (≥130/85 mmHg or current use of antihypertensive medications), hyperglycemia (fasting glucose ≥100 mg/dL or current use of glucose-lowering drugs), and dyslipidemia (high triglycerides ≥150 mg/dL and/or low high-density lipoprotein [HDL] cholesterol) (1,4,13,14). These abnormalities lead to a systemic pro-inflammatory state, endothelial dysfunction, and increased atherosclerotic burden, and can therefore predispose to CV events (12,15–18). This demonstrates that CMS pathophysiology is largely driven by insulin resistance, which sets off a cascade of metabolic derangements characterized by hyperinsulinemia, oxidative stress, and chronic inflammation (5,13,19–23). These alterations over time lead mainly to arterial stiffness combined with left ventricular hypertrophy and accelerated atherosclerosis making the risk of myocardial infarction, stroke, and heart failure significantly higher (1,7,15,16,24,25).

EPIDEMIOLOGICAL BURDEN AND GLOBAL TRENDS

Coupled with widespread obesity, inactivity and dietary disarray, CMS has reached epidemic proportions in every corner of the world (4,13,26). CMS is estimated to afflict between 25–35% of adults worldwide and differs in prevalence based on geographical, ethnic, and socioeconomic factors (26–28). CMS is associated with the increasing obesity burden seen across developed countries (19), with affected individuals representing almost one-third of the adult population in the United States and Western Europe (26,29–31). Likewise, adolescent-driven urbanization, dietary changes, and diminishing physical activity have increased the prevalence of CMS across emerging economies in Asia (the Indian subcontinent), the Middle East, and Latin America (26,32–34).

CMS is not limited to older individuals; it is becoming more common in younger people, due in part to increasing rates of childhood obesity and metabolic disease (26,35,36). This trend will have important long-term implications, as early-onset CMS is associated with an increased lifetime risk for cardiovascular events and premature mortality (23,30,35,37). Moreover, CMS tends to have a higher impact on people from low-income groups because of less access to healthcare, unhealthy nutrition, and increased stress conditions worsening the illness progression in these individuals (23,26,38). In view of these trends, CMS has emerged as a critical public health threat that calls for rapid action on both the individual and system levels (26).

IMPORTANCE OF ADDRESSING CMS FOR FUTURE HEALTHCARE SUSTAINABILITY

CMS is a major contributor to the global burden of disease and ranks highest as a root cause of both cardiovascular morbidity and mortality (4,28,39). The economic burden of CMS-related diseases — including heart failure, stroke and chronic kidney disease — is great, with annual healthcare costs greater than hundreds of billions of dollars(8,40). By continuing on this trajectory, CMS is likely to further burden already limited health care resources in the face of increased prevalence of metabolic diseases of global ageing populations (26,41,42).

Such a paradigm change needs to become more educated from disease management to disease prevention (13,23,43). Thus, early identification of those at risk, lifestyle changes, and introduction of new pharmacologic therapies are crucial to counteract the burden of CMS (2,25,26). In addition, a multidisciplinary approach integrating cardiologists with endocrinologists, nephrologists, and primary care physicians remains essential in providing optimal care for patients(44–46). Any new-data-generated precision treatment strategies can be successfully developed in the near future to revolutionize CMS management through advances in, for instance, precision medicine, digital health technology, and artificial intelligent (AI) risk stratification (23,47–49).

The treatment of CMS takes on both the form of a clinical need as well as a public health challenge (45). Screening for CMEs early can help policymakers design healthier food environments, activities and policies that can drastically reduce the burden of CMS complications (7,49). With no interventions in place, the continuing rise of CMS will only aggravate the global epidemic of cardiovascular disease, which could lead to greater healthcare expenditure and unnecessary loss of life (26,42). Thus, a timely and integrated response to CMS is necessary through early detection, lifestyle changes, and innovative therapeutic strategies (26).

PATHOPHYSIOLOGY OF CARDIOMETABOLIC SYNDROME

Cardiometabolic syndrome (CMS) is defined as a complex of metabolic and cardiovascular pathophysiology, with overlapping mechanisms that include insulin resistance, endothelial dysfunction, dyslipidemia, and chronic low-grade inflammation (1,2). As these interwoven pathways progress, they exacerbate type 2 diabetes mellitus (T2DM), hypertension, and cardiovascular disease (CVD), leading to increased morbidity and mortality (2,43,50). A deeper understanding of these mechanisms is important for the design of targeted approaches to prevent the long-term impact of CMS.

COMMON PATHOPHYSIOLOGICAL PATHWAYS LINKING DIABETES, HYPERTENSION, AND CARDIOVASCULAR DISEASE

Insulin resistance is a pivotal pathogenic process in CMS, disturbing glucose homeostasis and profoundly affecting vascular function (12). Normal physiological insulin action is vasodilator by stimulating endothelial nitric oxide synthase (eNOS) and increasing nitric oxide (NO) bioavailability. However, in the setting of insulin-resistant states, vasoprotective effects are blunted by the three factors. **Endothelial dysfunction,** with lower NO production it produces defective vasodilating operation, vascular rigidity, and high blood pressure, increasing risk of hypertension (11,51–53). **Prothrombotic State insulin resistance** promotes platelet

aggregation and hinders fibrinolysis there by rendering predisposition to thrombotic events (eg, myocardial infarction and stroke)(29). **Uncontrolled lipid metabolism**, with insulin resistance it enhances hepatic triglyceride overproduction and leads to higher VLDL and lower HDL, which is aggravating atherogenesis (47,54).

Endothelial dysfunction is a common feature of CMS and represents a pivotal bridge between metabolic and cardiovascular pathophysiology (22,23). Hyperglycemia, dyslipidemia, and insulin resistance all contribute to a state of oxidative stress and inflammation which exacerbates both processes impeding endothelial integrity (10,13,47). Key mechanisms include oxidative stress, pro-inflammatory cytokines, and leukocyte-endothelial interactions (55,56). Oxidative stress, pervasive ROS overproduction causes NO inactivation, driving vascular stiffness and atherogenesis (53). While pro-inflammatory cytokines happen when tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) impair insulin signaling and stimulate vascular inflammation that promotes endothelial dysfunction (12,57). Leukocyte-Endothelial interactions is up regulation of adhesion molecules (VCAM-1, ICAM-1) on endothelial cells results in enhanced monocyte migration into the vascular intima which contributes to acceleration of plaque formation in the arterial wall (58).

Dyslipidemia, which is characteristic of CMS, promotes atherosclerosis by several mechanisms like **atherogenic lipoproteins**, where elevated small, dense low-density lipoprotein (LDL) levels increase lipid trapping within arterial walls (11,15). **Formation of foam cells**, where macrophages take in oxidized LDL (oxLDL), forming foam cells that contribute to plaque formation (58–60). **Plaque instability**, here chronic inflammation erodes the fibrous caps of atherosclerotic plaques, leading to higher risk of rupture and acute coronary events (13,23,61).

THE ROLE OF ADIPOSITY AND CHRONIC INFLAMMATION

It is now recognized that adipose tissue, especially visceral fat, acts as an endocrine organ and secretes bioactive molecules (i.e., adipokines) that regulate metabolism and vascular homeostasis (56,62,63). Adipokine imbalance induces metabolic dysfunction and prone to cardiovascular pathology in obesity and CMS (56,63). Leptin resistance which lead to hyperleptinemia induces sympathetic over activity and hypertension in addition to deranging normal appetite control. Adiponectin deficiency leads to low levels of adiponectin are correlated with insulin-resistant and proinflammatory states, as well as endothelial dysfunction (64). Pro-inflammatory adipokines causes rise in resistin and visfatin release potentiates inflammation and insulin resistance (64).

Chronic low-grade inflammation as a hallmark of CMS is mediated by adipose tissue-derived cytokines. Tumor necrosis factor-alpha (TNF-α) promotes insulin resistance via disturbances in insulin receptor signaling, alongside elevations within endothelial activation (10,55,56). IL-6 drives hepatic CRP synthesis, the classical acute phase reactant and major biomarker of systemic inflammation and cardiovascular risk (14,56,57). C-Reactive protein (CRP) plays the dual role of a marker and mediator of Atherosclerosis by promoting Endothelial dysfunction and plaque instability (23,32,57).

Ember Researchers have recently identified the critical involvement of gut microbiota in the regulation of metabolic and cardiometabolic parameters (47). Dysbiosis (i.e., alteration of gut microbial profiles) has been associated with CMS via various mechanisms (47). Agitation of Metabolism causes short-chain fatty acids (SCFAs) generated by intestinal flora to affect insulin markers and inflammatory responses. Elevate Trimethylamine-N-Oxide (TMAO) Pathway, high

TMAO levels, a by-product of gut microbial pathway, correlate with raised atherosclerosis and CVD occurrences (65,66). Intestinal permeability and endotoxemia, damages to gut barrier function enables enhanced absorption of bacterial endotoxins into circulation, causing low-grade inflammation and, ultimately, insulin resistance (66).

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

The pathophysiology of CMS highlights the complex interlinking crossroad between metabolic and cardiovascular pathways (23,55). Understanding more about these mechanisms may open up therapeutic avenues. On the pharmacological side, both GLP-1 receptor agonists and SGLT2 inhibitors offer promise in improving metabolic and cardiovascular outcomes (24,45,51). IL-6 inhibitors and CRP-targeted therapies are among the potential anti-inflammatory agents that may represent new approaches to CMS management (57,60). Other than conventional dietary approaches, probiotics, prebiotics, and fecal albumin transplantation are on the verge of being validated as treatments for re-restoring gut microbial homeostasis, and subsequently improving cardiometabolic health (50,66).

CLINICAL PRESENTATION AND DIAGNOSIS

These abnormalities underlie a condition referred to as Cardiometabolic Syndrome (CMS), which is recognized as a well-established predisposition for type 2 diabetes mellitus (T2DM), hypertension, and cardiovascular disease (CVD) (25,26,49,67). Due to its insidious nature and the worldwide burden of complications related to it, early diagnosis and risk stratification is necessary to start the therapy on time (7,26,35). This section describes the clinical presentation, diagnostic criteria, and screening tools used to identify individuals at risk for CMS (39,68).

DIAGNOSTIC CRITERIA AND SCREENING TOOLS

Diagnosis of CMS can be established where approached by standardized criteria defined by international health organizations including the National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III), the World Health Organization (WHO), and the International Diabetes Federation (IDF). Whilst these definitions have commonalities, they differ with respect to exact cut off points and whether they prioritize central obesity and/or insulin resistance (32,45,69,70).

According to NCEP ATP III (2001; updated 2005), the definition of metabolic syndrome is the presence of three or more of the following five criterions (21,69,70). Abdominal obesity (waist circumference >102 cm in men and >88 cm in women), hypertriglyceridemia (Serum triglycerides ≥150 mg/dL), Low HDL cholesterol (30 kg/m² or waist-to-hip ratio >0.9 in men and >0.85 in women), Fasting plasma glucose (FPG) (100 mg/dL or use of antidiabetic medication) Although this definition does not specifically require that insulin resistance be present, it offers a practical framework to identify at-risk persons in the clinical setting (24,26,28,32,53,71).

The WHO criteria (1999) focus on insulin resistance as the central feature of metabolic syndrome (53). To make a diagnosis, there must be documented insulin resistance (impaired glucose tolerance, diabetes, or hyperinsulinemia), plus two of the following, Obesity (body mass index (BMI) >30 kg/m² or waist-to-hip ratio (WHR) >0.9 in men and >0.85 in women), Dyslipidemia (Triglycerides ≥150 mg/dL and/or HDL 90 cm in South Asian men; >80 cm in South Asian women), hypertension (Blood pressure ≥140/90 mmHg), and Microalbuminuria: urine albumin excretion rate ≥20 μg/min or albumin-to-creatinine ratio ≥30 mg/g

(26,28,54,55,72). While this definition emphasizes the metabolic foundation of CMS, the scope of the evaluation of insulin resistance is still a hindrance for the wide adoption of CMS in day-to-day clinical practice.

Visceral fat accumulation has been increasingly recognized as a critical element of CMS pathogenesis, and the 2005 IDF criteria emphasize abdominal obesity as one important aspect of the metabolic syndrome (26,54,57). A diagnosis requires, waist circumference ethnic-specific cutoffs (e.g. >90 cm in South Asian men, >80 cm in South Asian women), and two or more of the following triglycerides (≥ 150 mg/dL), HDL cholesterol (<40 mg/dL in men and <50 mg/dL in women), blood pressure (≥130/85 mmHg), and fasting glucose (≥100 mg/dL)(23,28,53) (25,67,73,74). These criteria stress the ethnic differences in presentation of CMS and provide for earlier recognition of individuals at increased risk; especially in groups with a predisposition to central obesity (71,74).

Laboratory and imaging biomarkers offer insights into disease progression and cardiovascular risk beyond clinical diagnostic criteria (62). Following diagnostic modalities contribute to improved risk stratification and promote individualized preventive measures. Glycemic markers (fasting glucose, glycosylated hemoglobin (HbA1c), and insulin resistance indices (HOMA-IR, QUICKI)), Lipid profile (triglycerides, HDL, LDL subfractions, apolipoproteins), Inflammatory markers (hs-CRP, IL-6 and TNF-α), Cardiac biomarkers (Lipoprotein(a), troponins, NT-proBNP for evaluating subclinical cardiac dysfunction), Imaging modalities (evaluation of cardiovascular involvement, including carotid intima-media thickness (CIMT), coronary artery calcium (CAC) scoring, and echocardiography) (19,23,24,28,51,53,57,72,75).

EARLY DETECTION STRATEGIES

Timely recognition of CMS elements allows for prompt scaling-up of interventions aimed at preventing the evolution to established diabetes, hypertension, and cardiovascular disease (35).

ROLE OF HBA1C, FASTING GLUCOSE, AND INSULIN RESISTANCE MARKERS

HbA1c has proved to be an established marker of long-term glycemic control and an independent predictor of CVD risk (19,72). It reflects average blood glucose levels over 2–3 months, in contrast to fasting glucose, and hence is a valuable tool for screening individuals at risk for diabetes and CMS (45). HbA1c ≥5.7% (39 mmol/mol) diagnoses prediabetes while HbA1c ≥6.5% (48 mmol/mol) diagnose threshold for diabetes (19,32,55,72,76). Measurements of fasting glucose and insulin resistance indicators e.g. HOMA-IR [Homeostatic Model Assessment of Insulin Resistance] and QUICKI [Quantitative Insulin Sensitivity Check Index] can improve risk stratification by measuring insulin sensitivity (53,65). Higher fast blood glucose, still in the prediabete range, correlates with the increased risk of letal CMS (76).

AMBULATORY BLOOD PRESSURE MONITORING (ABPM) IN EARLY HYPERTENSION DETECTION

Masked hypertension or nocturnal hypertension, are strong predictors of cardiovascular events, are often undetected by the traditional office BP measurement (1). 24-hour BP recordings with Ambulatory Blood Pressure monitoring (ABPM) enable identification of nocturnal hypertension (non-dipping of the BP by >10% during sleep), white-coat hypertension (high BP at office but normal outside office), masked hypertension (elevated ambulatory BP but normal office BP) (1,7). The importance of ABPM in risk stratification, and as a guide in antihypertensive therapy

for individual patients with metabolic syndrome (9,77).

BIOMARKERS FOR PREDICTING CARDIOVASCULAR RISK

New biomarkers demonstrate the ability to provide information regarding cardiovascular risk other than above standard lipid profile parameters (6,43,47,55,68). Lipoprotein(a) [Lp(a)] is a known independent cardiovascular risk factor, especially in states of insulin resistance (23). High-sensitivity cardiac troponins (hs-cTnI, hs-cTnT) identify subclinical myocardial damage and estimate subsequent cardiovascular events in metabolic syndrome (78,79). NT-proBNP (N-terminal pro B-type natriuretic peptide) evaluates the risk of subclinical cardiac constitution and heart failure among obesity, and diabetes (78,79).

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

CMS presents heterogeneously and requires a multimodal approach to diagnosis, with utilization of clinical criteria, laboratory biomarkers, and imaging modalities (29,43,80,81). Developments in the fields of personalized medicine, artificial intelligence (AI)-based risk prediction models, and genomics-based screening have the potential to enhance early detection methods and facilitate improved preventive healthcare (23,47,67,76,78). Emerging imaging technologies such as Augmented and Virtual Reality (AR/VR) have shown promise in enhancing visualization and diagnostic accuracy in radiological workflows, potentially improving early identification of cardiometabolic abnormalities through immersive 3D imaging and procedural simulations(82). Future research will need to validating ethnicity-specific diagnostic thresholds to improve early detection of CMS, integration of new biomarkers into standard screening regimes, designing algorithms using AI to integrate metabolic and cardiovascular risk predictors (23,47,67).

CURRENT TREATMENT APPROACHES

Multidisciplinary strategies integrating diet adaptation and medications despite the increased burden of diabetes, hypertension, and cardiovascular disease (CVD) must be undertaken for the management of Cardiometabolic Syndrome (CMS) (7,25,55,70). Considering the bidirectional links of metabolic and cardiovascular malfunction, broad-based approaches addressing diabetes, lipid abnormalities, hypertension, and chronic inflammation are important for best results (10,13,47).

LIFESTYLE INTERVENTIONS

CMS management still relies on lifestyle changes as the first-line therapeutic strategy, as they modulate directly metabolic homeostasis and cardiovascular health (9,25,47). Randomized double-blind trials (RCTs) provide evidence for the impact of structured lifestyle interventions on reductions in the incidence of diabetes and CVD among high-risk individuals (23,80,83).

Dietary interventions are major regulators of insulin sensitivity, lipid metabolism, and vascular function. Some dietary patterns found to be effective in managing CMS (6,47,51). Like Mediterranean Diet (MedDiet) which is high in monounsaturated fats (e.g., olive oil, nuts), fiber, and polyphenols, MedDiet is associated with greater improvements in glycemic control, inflammation, and cardiovascular risk. Studies like PREDIMED (Prevención con Dieta Mediterránea) showed 30% fewer major cardiovascular events in such dietary patterns (5,26,35,65). DASH Diet (Dietary Approaches to Stop Hypertension) is an eating pattern emphasizing high levels of potassium, magnesium, and fiber that has been shown to lower blood pressure, LDL cholesterol, insulin resistance with overall lessening of the gravitas of CMS

(41,65,70). Low-Carbohydrate and Ketogenic Diets are the diets low in carbohydrates — especially those low in refined carbohydrates — have been associated with improvement in insulin sensitivity, loss of body weight, and reduction in triglycerides, and are viable dietary approaches for the management of metabolic syndrome, but sticking with it over the long run is a problem (14,26).

Regular physical activity is a pillar of CMS treatment and is well founded in evidence overall showing improvement in insulin sensitivity, endothelial function, and cardiovascular outcomes. What the American College of Sports Medicine (ACSM) and the American Heart Association (AHA) recommend, the aerobic exercise which is 150 minutes/week of moderate-intensity exercise (e.g., brisk walking, cycling) or 75 min/wk of vigorous-intensity exercise to reduce CMS risk factors. Resistance Training which is two days a week of strength training helps with insulin sensitivity, muscle glucose uptake, and metabolic flexibility (13,67,76). High-Intensity Interval Training (HIIT), new data indicates that short bursts of a high-intensity workout seem to have greater cardiometabolic benefit, especially with respect to VO_2 max, endothelial function, and mitochondrial efficiency (84).

Chronic deprivation of sleep and dysregulation of stress further aggravate metabolic and cardiovascular dysfunction (6). Studies indicate that sleep duration < 6 hours night correlates to up regulated insulin-resistance, obesity, hypertension Sleep apnea is prevalent in CMS and induces sympathetic over activity and vascular dysfunction (6,85). Strategies for stress management include mindfulness, cognitive behavioral therapy (CBT), and relaxation exercises have been shown effective in reducing cortisol levels, enhancing glucose metabolism, and lowering blood pressure (62,84). The cornerstone for long-term CMS management and prevention is a holistic lifestyle approach that combines diet, exercise, sleep hygiene, and reduction of stress.

PHARMACOLOGICAL INTERVENTIONS

Pharmacological therapy is necessary to augment lifestyle changes for patients with moderately increased and severely increased metabolic disruption (2,47,58). Management is focused on specific components of CMS including hypertension, insulin resistance, and dyslipidemia (19).

Blood pressure control is considered an important CMS target as it has been associated with the prevention of cardiovascular events in hypertensive patients (28,39,51). First-line agents include, Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs) which Lower vascular inflammation and endothelial dysfunction and are also preferred in patients with diabetes, given their renal protective effects(73,86,87). Beta-Blockers are also first line agents that are utilized in presence of concomitant heart failure or arrhythmias (23,88,89). Newer agents like nebivolol also enhance endothelial function without adversely affecting glucose metabolism. Calcium Channel Blockers (CCBs) are useful for isolated systolic hypertension and in older adults (70,83,86,90). Diuretic agents (Thiazides, Aldosterone antagonists) enhances regulation of fluid and blood pressure but need to be monitored for metabolic side effects (e.g., hyperglycemia, hypokalemia) (13,55,90).

Because an underlying pathophysiology of CMS is insulin resistance, it follows that pharmacological agents may be needed that improve glycemic control and simultaneously reduce cardiovascular risk (47,53). Metformin, first-line treatment for insulin resistance and prediabetes decreases hepatic glucogenesis and increases insulin susceptibility (14,35,44,91). Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors (Example: Empagliflozin, Dapagliflozin) are glucose

excretion promoters via urine, decrease cardiovascular mortality and heart failure risk (i.e., EMPAREG-OUTCOME trial) (9,46,55). Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists (e.g., Liraglutide, Semaglutide) are gut–brain signalling to improve insulin secretion and satiety, also cardiac protective effects have been seen in LEADER & SUSTAIN-6 (45,72).

Control of dyslipidemia is needed to reduce risk of atherosclerotic cardiovascular disease (46).

First-line agents include, Statins (Atorvastatin, Rosuvastatin) which lower LDL cholesterol and vascular inflammation also causes 25–30% decrease in CVD risk in primary prevention trials (39). PCSK9 Inhibitors (Alirocumab, Evolocumab) which are monoclonal antibodies that reduce LDL by 50–60% in high-risk individuals (2). Omega-3 Fatty Acids (EPA, DHA) causes reduction in triglycerides and CV events (REDUCE-IT trial) (2).

For advanced cases of CMS-associated organ failure, emerging artificial organ technologies such as ventricular assist devices, wearable artificial kidneys, and biohybrid systems offer potential life-extending options, particularly in bridging patients to transplantation or supplementing failing organ function(92).

EMERGING AND NOVEL THERAPIES

The Future of CMS Treatment Personalized medicine and targeted interventions are paving the way for the future of CMS treatment. Precision medicine and genetic markers are emerging novel therapies as Genetic profiling enables the identification of high-risk individuals from polygenic risk scores and also enables targeted pharmacotherapy (e.g., statin response; antihypertensive choice based on genpol) (10,23,68,74). If we use gut micro-biome as targeted interventions, gut micro-biome is important for metabolic health (47,66). Emerging therapies include probiotics and prebiotics for insulin sensitivity, and fecal microbiota transplantation (FMT) to modulate metabolic inflammation (93,94). Anti-Inflammatory therapies could also be a new way of treatment as chronic inflammation induces CMS pathology, thus anti-inflammatory agents could be potential adjuvants. Such as colchicine which Lowers cardiovascular events in higher-risk patients (CANTOS trial)and other is Interleukin-1 (IL-1) Inhibitors (Canakinumab) aims at inflammation-mediated CVD risk (95).

FUTURE DIRECTIONS AND RESEARCH GAPS

However, considerable knowledge gaps remain in several areas, including risk prediction, personalized treatments, and public health initiatives. Hence, rapid technological advances including AI, big data analytics, and precision medicine may represent opportunities to improve outcomes, while policy-led systems interventions are required to combat the global burden of CMS (89,96). This section discusses avenues for future directions and fields in need of further investigación.

THE ROLE OF ARTIFICIAL INTELLIGENCE AND BIG DATA IN CMS RISK PREDICTION

For CMS, AI and machine learning (ML) have transformed risk stratification, early identification, and treatment optimization (97). The multifactorial etiology of CMS enables analysis of large-scale, multidimensional data within the framework of artificial intelligence (AI) driven models, generated from electronic health record (EHR), wearable devices, and genomic databases (98,99).

The AI algorithms can enhance the diagnosis and risk stratification of CMS machine learning-based models using EHRs and imaging data can identify subclinical metabolic

dysfunction prior to manifest disease thus enhancing early detection (96,97,100). AI-based platforms, such as polygenic risk scores (PRS) and deep-learning models, amalgamate genetic, biochemical, and lifestyle data to customize prevention approaches leading to individualized risk assessment (101–103). AI-based solutions can evaluate carotid intima-media thickness (CIMT), coronary artery calcification (CAC), and liver fat percentage for assessment of CMS risk in a non-invasive manner leading to automated imaging assessment (23,102).

Smart watches as continuous glucose monitors (CGMs), and ambulatory blood pressure monitors (ABPMs) are now widely available, which enables metabolic and cardiovascular parameters to be assessed in real-time (32,104). Further research should be directed towards, AI-powered consolidation of wearable data to develop dynamic, personalized CMS risk profiles. Digital biomarkers had been used for early intervention and treatment response monitoring (104). Clinical validation of AI-assisted interventions to demonstrate effectiveness and improve patient adherence (102). Given these, its underlying issues (data privacy, algorithm bias, lack of regulatory approval, etc.) need to be thoroughly explored in order to leverage the AI technology better in the management of the CMS (101,102).

INTEGRATING PRECISION MEDICINE FOR PERSONALIZED TREATMENT PLANS

Then, standard treatment of CMS does not take into consideration genetic variability, metabolic phenotypes or environmental influences (105). Precision medicines are intended to maximize the efficacy of an intervention by identifying a subgroup of patients with certain characteristics which will extract maximum benefit from the therapy thus aligning mechanisms to improve health outcomes (106).

Discoveries in genomics, transcriptomics and proteomics have uncovered new biomarkers and therapeutic targets for CMS (23,55). Some of the areas currently being researched include, Pharmacogenomics, Genetic Variations Impacting Drug Metabolism and Efficacy (ex: SLCO1B1 Gene Polymorphism and Statin Response) (107). Epigenetic modifications, which explore the role of DNA methylation and histone modifications in CMS heterogeneity and therapy resistance (43,99). Lipidomics and metabolomics which works for finding metabolic signatures that identify risk for CVD and diabetes, leading to better-targeted interventions (99).

The gut microbiome is an important modulator of metabolic health, regulating insulin sensitivity, lipid metabolism, and systemic inflammation (108). Further studies should investigate the microbiome-based interventions, including probiotics, prebiotics, and fecal microbiota transplantation (FMT), for metabolic pathway modulation (93–95). It should also explore personalized dietary interventions according to gut microbiome composition to enhance CMS prevention (6,47). Longitudinal studies examining the effects of microbiota-targeted therapies on metabolic and cardiovascular outcomes are also the unexplored areas (66).

The synergistic potential of AI and metabolomics-based dietary interventions is a front-runner for targeted nutrition recommendations (109). Research is needed to design precision dietary protocols by real-time metabolic response (e.g., decay of postprandial glucose and lipids). To tailor exercise prescriptions based on genetic predispositions for endurance or resistance training advantages also to validate AI-driven interventions in clinical trials to assess their feasibility and long-term efficacy long term studies are required (109).

PUBLIC HEALTH POLICIES FOR REDUCING CMS PREVALENCE

CMS is spreading globally, and while clinical interventions are important, there is a need for population-level interventions (89). Urban planning, food regulations, and health education as public health policies are probably going to have more impact than pharmacology or adjuvant therapies on metabolic and cardiovascular health (110).

Urban designs that favour car travel and limited access to recreational spaces increase the likelihood of Sedentary lifestyles which could lead to CMS risk (110,111). An initiative driven by policy should consist of more pedestrian/cycling infrastructure to promote physical activity (39). More accessible public parks and green areas that have been linked to lower obesity and diabetes rates could be a helpful initiative. Also the incorporation of workplace wellness initiatives that encourage physical activity and healthier diets could also be a useful policy (110).

Thus, the contemporary food system (i.e. hyper-processed foods, sugar excess, trans fats) is perhaps the foremost reality underlying the CMS pandemic (25,29). Policy directions for the future should be as follows. A tax on sugar-sweetened beverages (SSBs) and unhealthy processed foods, like in Mexico and the UK. Legislation requiring mandatory front-of-pack labeling (FOPL) to increase consumer awareness of nutritional quality (112). Provisions on trans fats and sodium in processed foods to reduce CMS risk factors (113).

In this case, it is necessary to promote the change among the people through a cross-agenda approach. Strategies should include, making metabolic health a core element of school education the critical aspects of everyday life are developed into school programs to ensure lifelong healthy habits (112). Focused awareness campaign building on CMS risk factors among vulnerable populations should be an effective strategy. Digital health platforms and telemedicine can be introduced to enhance access for lifestyle counseling and chronic disease management (48).

RESEARCH GAPS AND FUTURE INVESTIGATIONS

While some progress has been made in CMS research, many questions remain unanswered. Future investigations should include priority to longitudinal investigations of AI, gut microbiome and CMS at different stages (101,108). Also the clinical validation of AI algorithms for CMS prediction models and their incorporation into routine care should be kept in mind (96,103). Cost-effectiveness analyses of precision medicine strategies in CMS management and RCTs assessing policy-oriented strategies for reducing CMS should be the focus of future studies.

CONCLUSION

Cardiometabolic syndrome (CMS) is a complex/multifactorial disease that poses important problems for global health. CMS continues to be a global driver of morbidity and mortality, with its close association with type 2 diabetes, hypertension, dyslipidemia and cardiovascular disease. Understanding the nuanced interaction between genetic predisposition, lifestyle factors, and environmental influences is key to preventing and managing the disease effectively. CMS should be treated not just reactively, but proactively with multidisciplinary approaches that encompass primary care providers, specialists, and public health efforts. Lifestyle changes including diet, exercise, and stress management are the cornerstones in both prevention and treatment. While lifestyle changes are important, they are often inadequate, leading pharmacologic and other novel therapeutic strategies to feature prominently in CMS management. However, critical gaps

remain in early diagnosis, individualized treatment, and large-scale prevention strategies in CMS. Further research is needed on more modern and innovative biomarkers, genetic risk factors, and artificial intelligence in predicting and managing CMS. Public health policies also need to change to promote preventive measures like better urban planning, food regulations and broad-based health education campaigns. To combat this growing burden of civilization medical diseases (CMS), there is now an urgent need for collaborative efforts across the worlds of clinicians, researchers, policymakers and technology experts. They can help transform the future of CMS management through precision medicine, digital health innovations, and evidence-based public health strategies that optimize patient outcomes and healthcare costs worldwide.

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