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Research Article

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A Scoping Review of Cardio-Metabolic Syndrome: A Critical Step in Mitigating the Rising Global Burden of Cardiovascular Diseases and Diabetes Mellitus

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Abstract

Background: *Over the years, the relationship between cardiovascular diseases (CVDs) and dysglycemia has been noticed to be positive and continuous. Specifically, for each 1% increase in glycosylated hemoglobin (HbA1c), there is a defined increased risk for CVDs. Also, the risk of developing CVDs for people with overt Type 2 diabetes mellitus (T2DM) increases by 2 to 3 times for men and 3 to 5 times for women compared to people without diabetes mellitus.*

Objectives: *The article briefly discussed the meaning of cardiometabolic syndrome (CMS) as a medical phenomenon and the interconnecting role it plays in the pathogenesis of both CVDs and T2DM. It further highlighted the risk factors that are common in CMS and the evidence-based control measures for the syndrome.*
Methods: A review of related online full articles published from 2000 to 2021 was carried out from different scientific search engines, such as Google Scholar, PubMed, ResearchGate, Mendeley, Medline, and Academia.

Results: *CVDs and T2DM are closely related diseases, both appearing in the same spectrum of chronic diseases. They are closely linked by a similar pathophysiological phenomenon – the CMS. Any attempt to prevent or treat either CVDs or T2DM without due attention and consideration for the CMS, may not result in significant success, especially on a long-term basis.*

Conclusion: *A better understanding and control of CMS and its risk factors are critical in the global efforts to prevent and control the rising global burden of both CVDs and T2DM, especially in developing countries.*

Keywords: Cardio-metabolic syndrome, Cardiovascular diseases, Type 2 Diabetes mellitus, Lifestyle interventions, Public health interventions.

Introduction

For years, cardiovascular diseases (CVDs), such as coronary heart disease and cerebrovascular disease, have been leading causes of death globally [1,2]. Every year, about 17.9 million people die from CVDs, which is approximately 31% of total annual global deaths [2,3]. Diabetes mellitus, particularly Type 2 diabetes mellitus (T2DM), is another noncommunicable disease (NCD) of serious global public health concern. It is the 3rd leading cause of premature death worldwide and a rising global health emergency in the 21st century [4,5]. Approximately 10.5% or 537 million global adults (20-79 years) are presently living with diabetes mellitus, about half of which are yet to be diagnosed, and yet it kills about 6.7 million people annually [6]. These statistics have been projected to increase in the nearest future, with overwhelming costs to the healthcare systems and economic development of most countries.

Frantic efforts have been made by scientists to better understand these complex chronic diseases, and provide evidence-based and sustainable preventive and treatment options. However, despite significant strides over the years, the pathophysiology of T2DM and its relationship with CVDs remains incompletely understood, and to some extent controversial [7]. What is known for now is that the association between T2DM and CVDs appears to be direct and continues, with both appearing in the same spectrum of diverse chronic diseases [8]. For each 1% increase in glycosylated hemoglobin (HbA1c), there is a defined increased risk for CVDs;

while the risk of CVDs for people with overt diabetes mellitus increases by about 2 to 3 times for men and about 3 to 5 times for women compared to people without diabetes mellitus [8].

Further studies have suggested that the vital link between these two chronic diseases, and a possible key to their efficient prevention and control, might not be unrelated to the understanding of a syndrome called the cardio-metabolic syndrome (CMS). The CMS, whose understanding is still evolving, is presently identified as the important pathway that connects several pre-clinical and clinical risk factors and abnormalities that can independently and/or work in synergy to increase the risk of developing CVDs, T2DM, or both [9]. Furthermore, people diagnosed with CMS are often 3 times more likely to suffer from CVDs such as heart attack or stroke, and 2 to 3 times more likely to die from CVD-related deaths compared with people without the syndrome [9,10]. Thus, the presence of CMS in an individual significantly increases his or her risk of developing CVDs, T2DM, and/or their related complications. The purpose of this article is to briefly review CMS as a medical phenomenon and the evidence-based measures for mitigating its rising prevalence – such might be essential in the global efforts to reduce the rising global burdens of both CVDs and T2DM.

Describing Cardio-Metabolic Syndrome as A Medical Phenomenon

The CMS, which is also called the Lifestyle syndrome or the New World syndrome [9,11], is a disease condition that describes the constellation of a series of maladaptive cardiovascular, metabolic, renal, prothrombotic, and inflammatory abnormalities in a single patient [12,13]. CMS is said to be present when there is a clustering of central obesity, hypertension, dyslipidemia, insulin resistance, and glucose intolerance in a single patient; that together may increase the risk of developing and/or worsen the prognosis of either CVDs, T2DM, or both [11,14]. CMS is also said to be present if an individual has the clinical evidence of diabetes mellitus and insulin resistance together with any two other risk factors – either hypertension, obesity, triglycerides, reduced High-Density Lipoprotein cholesterol (HDL-C) level, or microalbuminuria [15].

Anytime there is a co-existence of two or more of the three major chronic diseases in CMS (i.e., hypertension, diabetes mellitus, and cardiovascular disease) in one patient, it is called cardio-metabolic multimorbidity [16]. While the other diseases of public health and clinical concerns that may be associated with or may complicate CMS include nephropathy, nonalcoholic fatty liver disease (NAFLD), schizophrenia, depression, sleep apnea, psoriasis, erectile dysfunction, gallstone diseases, and some cancers – such as cancers of the lung, colorectum, liver, gallbladder, thyroid, pancreas, urinary bladder, uterus, cervix, and multiple myeloma [15,17].

Although some scientists view cardiometabolic syndrome (CMS) and metabolic syndrome (MS) as different nomenclature describing the same disease [17,18], others believe that the formal should be seen as a broader disease condition that should replace the latter. This is so because the pathogenesis of CMS may expand far to some pre-clinical and clinical risk factors that are not described in MS, such as consumption of unhealthy diet; physical inactivity; tobacco use; and high blood glucose in the diabetic range, and not just pre-diabetic range as seen in MS. Therefore, the population at risk of CMS is seen to be larger than that of MS, and its interventions extend far into the public health domain of healthcare, compared to MS [19].

The nomenclature – CMS was believed to have been introduced as a medical term to conveniently identify and treat people in the general population, who are at risk of developing either CVDs and/or T2DM; who may likely benefit from appropriate preventive lifestyle or public health and/or pharmacological interventions, but may have been denied the opportunity by the diagnostic criteria for MS [10]. Consequently, most recent articles now prefer the term cardiometabolic syndrome/disease/disorder (and not MS) when describing the constellation of overlapping cardiovascular and metabolic risk factors and abnormalities, since it can be extended to describe the ever-narrowing interface between preventive cardiology and preventive diabetes specialties [8].

In addition, the study of CMS as a medical condition also provides the opportunity to further describe and explore the various pharmacological and nonpharmacological interventions that could reduce disease complications that are both cardiovascular and metabolic in nature, a feat which MS as a medical phenomenon could not achieve [7]. Thus, the science of CMS provides the much-needed opportunity for preventive public healthcare professionals, lifestyle medicine specialist, diabetologists, cardiologists, and other related healthcare specialists to join forces together and provide the required comprehensive and evidence-based preventive and control efforts in the modern management of CVDs and T2DM, especially in the early diagnosis and treatment of millions of patients who are at-risk of developing either one or both of these chronic diseases, or who have co-existing cardiovascular and metabolic diseases [8].

A Brief Epidemiology of Cardiometabolic Syndrome

The prevalence of CMS and its resulting multi-morbidities are increasing globally, spearing no region or race. CMS is now categorized as a pandemic that presently affects more than 25% of the world's adult population [9,11]. In the United States alone, more than 50 million people were diagnosed with CMS in 1999, these rose to 64 million just within one year, and its prevalence has been increasing steadily in the United States and all countries of the world [15]. Rather more worrisome is the fact that CMS as a disease entity is not limited to the adult population alone. In many countries, the risk of developing CMS in childhood is increasing, with a negative impact on the disease profile and quality of life in adulthood [20-22]. This is partly due to the rising global prevalence of physical inactivity, consumption of unhealthy diets, and obesity among the general population, especially the younger age groups [15,22].

Also, the direct and indirect healthcare costs of managing CMS are increasing, and about to get to an unsustainable limit. For instance, the result of a meta-analysis involving 383,420 CMS patients informed that the adjusted total annual healthcare cost of managing at least one disease component of CMS in a patient is around $5,564, which rises significantly to around $12,287 when a patient has at least 4 components of CMS [10]. A cohort study of 6 years also revealed that the annual cost of managing CVDs in a patient with 4 or more components of CMS is $10,367 more compared to a CVD patient who is without the syndrome [10]. Thus, without proper and compressive preventive and control strategies, the progressive rise in the global prevalence of CMS might continue to increase the healthcare and economic burdens of CVDs, T2DM, and other related chronic diseases far beyond the control of any community and government, be it developed or developing.

However, there exists enough piece of evidence to suggest that CMS is not only preventable but also reversible. Successful prevention or reversal of CMS will most likely result in a significant reduction in the risk of developing CVDs, T2DM, and other related complications and diseases. A situation if well optimized might save the interconnected global healthcare systems and economy from the pending heavy disease-burden induced global meltdown. Consequently, the issues around CMS have been receiving increasing global attention among researchers, public health physicians, clinicians, and policymakers, especially as it involves the full understanding of the pathophysiology of CMS, and the evidence-based preventive and control measures for the syndrome [11].

A Glimpse into the Lifestyle Induced-Pathogenesis of Cardio-Metabolic Syndrome

In the recent past, significant strides have been made to understand the multifaceted mechanisms that are associated with the development of CMS and its associated diseases, yet much is still unknown [16]. The complex series of behavioral and biological processes that cumulate into the development of CMS can best be explained as a vicious cycle involving the interplay of environmental, ageing, behavioural/lifestyle, genetic, and epigenetic factors, with lifestyle factors having the most dominant and most important contribution [9,15,17]. Genetics, ageing, environment, sociocultural believes, and socioeconomic factors are the foundational or root determinants of CMS [23]. However, just like a loaded gun in a safety pouch, the effects of these factors remain insignificant in most cases, until the underlying behavioral or lifestyle risk factors pull the trigger. Hence, frequent unhealthy lifestyle practices, like the consumption of unhealthy diets, physical inactivity, substance abuse, poor sleep, and poor stress management, are the primary underlying behavioural/lifestyle risk factors that usually kick-start the cascade of events that culminate into CMS [10,12,23].

In the pre-clinical phase of the disease, frequent consumption of unhealthy diets (usually in the presence of other unhealthy lifestyles factors – such as physical inactivity, poor sleep, etc.) will often lead to the increased production of adipose tissues (subcutaneous and/or visceral) by the body, which can then progress to overweight/obesity and excess secretion of free fatty acid into the bloodstream [10,21,22]. This pre-clinical situation is usually surpassed by the body before it causes significant multi-cellular damage by increasing the blood insulin level. Insulin helps to prevent further adipose tissue lipolysis and the release of additional fatty acids into the bloodstream [24]. However, if the exposure to the underlying lifestyle risk factors persisted for a relatively long period, the process can lead to excessive secretion of insulin into the bloodstream (i.e., hyperinsulinemia), which is usually accompanied by increased blood levels of LDL-cholesterol and triglycerides and decreased blood level of HDL-cholesterol [10,24]. Hyperinsulinemia also increases hunger and crave for high-caloric foods, which setup a vicious cycle of events.

At a point, the process will overwhelm the body, and it will not be able to continue to increase blood insulin levels to match the increasing free fatty acids in the blood. Consequently, the excess serum free fatty acids saturate the bloodstream and get deposited in different blood vessels in the body (such as the coronary, cerebral, carotid, etc.) and other components of the cardiovascular system. Progressive free fatty acid deposits, usually in collaboration with other proinflammatory biomarkers and substances will often damage the blood vessels resulting in atherosclerosis and poor ability to sustain vascular functions, such as blood pressure control. This will ultimately result in elevated blood pressure and further compromise the integrity of the cardiovascular system [25]. The inefficiency in the functionality of the blood vessels also tends to increase the risks of stroke, heart diseases, kidney failure, and other cardiovascular diseases, not only in people with hypertension but also in those with suboptimal blood pressure [25].

The free fatty acids in the bloodstream also infiltrate others organs and cells, such as the liver, muscle, and pancreatic cells. With time, the infiltration of the liver tends to alter the functions of the organ leading to its failure to suppress gluconeogenesis. This will result in increased hepatic glucose production and consequently increased blood glucose levels (hyperglycemia) [26]. Hence, elevated blood pressure or glucose is sometimes the first clinical sign of CMS. The excess free fatty acids that infiltrated the muscles cells usually disrupt the glucose handling capacity of the muscle, and increase the production of non-infectious proinflammatory biomarkers (like adipokines and cytokines); these suppress cellular insulin-stimulated glucose uptake thereby resulting in peripheral insulin resistance, which will further lead to or worsen hyperglycemia [25]. Also, the intramyocellular fat accumulation tends to disrupt insulin receptors via the production of lipotoxic mediators, which further worsen insulin resistance and hyperinsulinemia. The insulin resistance and hyperinsulinemia worsen over time due to the persistent high serum level of the pro-inflammatory biomarkers, which causes further damage to the liver and beta cells of the pancreas, especially as muscle and adipocyte cells begin resisting further fat storage [25-27]. Aside resulting poor glycemic control, hyperinsulinemia usually increases sympathetic nervous system activity as well, which may further contribute to the development

or worsen the control of hypertension. These cascades of events will also lead to increased vasoconstriction, elevated fluid retention, and a further increase in blood pressure and damage to the cardiovascular system [7,10,15]. The beta cells in the pancreas are also further damaged by the infiltrated free fatty acids, thereby suppressing insulin secretion in response to elevated glucose in the bloodstream, resulting in further hyperglycemia up to the diabetes range [25-27].

A Closer Dissection of the Cardio-Metabolic Risk Factors

In parallel to the rising global prevalence of CMS is the increasing prevalence of the various interplaying and overlapping implicated risk factors – called cardio-metabolic risk factors; a phenomenon that is aggressively driving the increasing global burden of CVDs and T2DM [9]. The complex relationship that exists between global rapid economic growth, aging population, globalization, rapid unplanned urbanization, obesity, and unhealthy lifestyle changes, is an important factor that has been associated with an increase in the global prevalence of CMS, and by extension CVDs and T2DM [28,29]. The association among these often clustered and interlinked cardio-metabolic risk factors have been known for a long time, and their interplay and co-existence most often leads to the development of CMS, T2DM, CVDs, and other related chronic diseases [30-33].

The cardio-metabolic risk factors can be broadly divided into primary and intermediate-risk factors. The primary risk factors are the root or underlying attributes, characteristics, behaviours, lifestyles, or exposures of an individual that increases the likelihood of developing CMS and other chronic NCDs. These include age, race, gender, genetics, epigenetics, environment (physical and social), and unhealthy lifestyles practices – such as unhealthy/atherogenic diets, physical inactivity, tobacco use, alcohol abuse, poor sleep, and poor stress control (see figure 1) [34]. In facts, studies have demonstrated a positive correlation between physical inactivity and increased prevalence of cardio-metabolic morbidity and mortality in a dose-dependent manner [35]. While the intermediate-risk factors are those biophysical or biochemical factors that result from the consistent and often prolong exposure and interactions between the various primary risk factors [34]. The presence of any, or the combination of the intermediate-risk factors confers a higher likelihood of developing CMS and the other chronic NCDs. These intermediate-risk factors include overweight/obesity (especially central obesity), hyperglycemia, high blood pressure/hypertension, hyperinsulinemia, and dyslipidemia (see figure 1) [23,34].

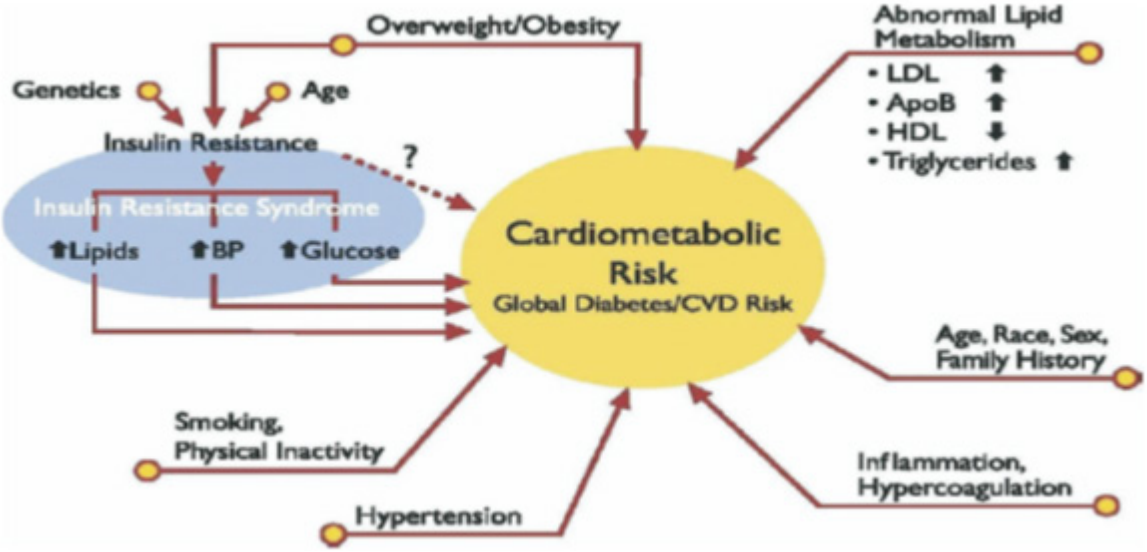

Figure 1: The Interactions between the major Cardio-Metabolic Risk Factors in the Pathogenesis of CVDs and Diabetes mellitus [30].

Needed Actions to Reverse the Global Rising Burden of Cardio-metabolic Syndrome

Although the burden of CMS is increasing globally, available piece of evidence strongly suggests that the syndrome is highly preventable and amenable to effective and integrated multi-disciplinary public health and clinical interventions [11,36]. The process of CMS development primarily starts pre-clinically in the community when people engage in unhealthy lifestyle practices over a relatively long period, usually in the presence of a favorable environment (such as unplanned urban settlement, poor social connectedness, etc.). Hence, the basis of intervention in the management of CMS and by extension CVDs and T2DM should be for healthcare professionals to firstly increase the awareness and education about CMS among the general population. Secondly, they are to assess the prevalence of the major primary and intermediate-risk factors in the community and during visits to healthcare facilities, and then design appropriate intervention policies and programs that can mitigate the identified risk factors early before they lead to the development of the chronic diseases [37].

The community-based intervention may include mass awareness and education campaign (through social and conventional media), workplace health promotion programs, provision of recreational and social centers in strategic places, walkway consideration in road constructions, provision and enforcement of policies on public tobacco use, increase taxation on alcohol and calorie-dense foods, tax reduction incentives for vegetables and fruits farming, health-friendly restaurants, etc. Such interventions should be evidence-based, multidisciplinary, innovative, comprehensive, and culturally sensitive, reflecting the interplay that exists between CVDs, T2DM, and their various risk factors [23].

The clinical intervention efforts, in particular, should be aggressive and targeted primarily at mitigating the identified intermediate-risk factors – such as the reduction of obesity and abdominal adiposity, reduce LDL cholesterol and triglycerides, increase HDL cholesterol, reduce blood pressure, reduce hyperinsulinemia and insulin resistance, improvement of glucose tolerance, and reduce total chronic disease risk scores [38]. These should be done even if there are no overt CVDs or T2DM in the individual. However, the intermediate cardio-metabolic risk factors can only be effectively controlled through public health and clinical interventions that emphasize healthy lifestyles and lifestyle modification, to reduce modifiable primary risk factors [7,39]. For instance, studies have demonstrated that a significant number of middle- and older-aged persons who engage in regular physical activity, experiences reduction in most components of CMS, namely in the level of hypertension, body mass index, truncal obesity, glucose intolerance, insulin resistance, dyslipidemia, and some inflammatory markers [40].

Moreover, the benefits of lifestyle intervention on the cardio-metabolic risk factors are usually both acute (lasting hours to days) and chronic (lasting for weeks to years), with a concomitant overall increased possibility of CMS reversal in the affected individuals [40]. However, to be successful, the public health and clinical intervention measures should be systematic and comprehensive, executed through appropriate health policies and programs beginning with mass and targeted health education to the general public and at-risk population. In addition, in some cases, pharmacological interventions (such as the use of anti-lipids, anti-coagulants, etc.) and/or other forms of therapy (such as psychotherapy, bariatric surgery, etc.) may be needed as adjunct therapies. The non-lifestyle interventions are usually indicated either when lifestyle modification only is not effective, sustainable, or when the values or scores of the total or individual risk factors are significantly high and clinically unsafe and need to be reduced over a shorter period [41].

Conclusion

The health and socio-economic impacts of the rising global burden of CMS are devastating, causing tens of millions of avoidable deaths and significant economic loss every year. If left unmitigated, its negative impacts on the cardiovascular, metabolic, renal, and immune systems will likely continue unabated; a situation that might lead to an unprecedented global economic disaster and unimaginable human suffering and death. To halt the trend, all stakeholders must work as a unit, with the international public healthcare bodies and lifestyle medicine organizations taking the lead. Scientific research and public and clinical interventions must focus on identifying and addressing the diverse constellation of different major preclinical and clinical risk factors that are implicated in CMS. We should also design and implement a new care model or health-promotion centered model that focuses on an integrated approach to preventing and treating CMS and its related diseases through the prevention, assessment, and treatment of the modifiable cardiometabolic risk factors primarily through evidence-based lifestyle (and when necessary pharmacological) interventions; especially across diverse general and at-risk populations, and in patients in an early stage of chronic disease evolution [10,23].

Since unhealthy lifestyle practices are regarded as the most important risk factors in the rising global burden of CMS, developing in-depth knowledge and skill on how to prevent and treat these risk factors is most needed by 21st-century public health and primary healthcare physicians. Deliberate strategies must be implemented to train medical professionals on lifestyle interventions at both undergraduate and postgraduate levels. Furthermore, to be effective, lifestyle interventions must be evidence-based, practicable, sustainable, and should provide opportunities to motivate the affected individuals toward appropriate attitudinal and behavioral changes. Such lifestyle interventions need to be delivered to the patients by well-trained and motivated (especially financial) healthcare professionals [42]. Finally, more deliberate investments must be committed to the evolving science of CMS to have a deeper understating of the syndrome and how such knowledge may be utilized to effectively mitigate the rising global burden of CVDs, T2DM, and other related chronic diseases.

Conflict of Interest

The author declares no conflict of interest.

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