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Review Article

Evaluation of Cardiovascular Kidney Metabolic Syndrome and Cardiovascular Hepato-renal Metabolic Syndrome (CHARM): From Encryption to Decryption

Balaji Pishey Ashwathnarayan Roa[1,*], Smitha Ranoji Rao Varne[2]

[1]Associate Professor of Physiology and ESH Hypertension Specialist, Diabetologist, Preksha Wellness and Yoga Center, Bangalore, Karnataka, INDIA.
[2]Consultant Naturopathy and Yoga, Integrative Medicine and Nutritionist, Preksha Wellness and Yoga Center, Bangalore, Karnataka, INDIA.

ABSTRACT

Due to derangement of normal homeostasis in the human body, we have an orchestra of syndromes like Metabolic Syndrome (MeTS), Cardiometabolic Syndrome (CMS), Cardiorenal Syndrome (CRS), Hepato-Renal Syndrome (HRS) and recently in 2023, American Heart Association (AHA) introduced Cardiovascular Kidney Metabolic syndrome (CKM), all have serious impact on an individual's health and healthcare costs. It is necessary to recognize the basic pathophysiology and the rising prevalence of these syndromes worldwide, as timely diagnostic and therapeutic interventions having strong physiological basis, can halt their progression and potentially be reversed. This review article has been planned by searching MEDLINE database to bring out a brief and lucid pathophysiology regarding the above mentioned syndromes and with the exponential rise in prevalence of Non-Alcoholic Fatty Liver Disease (NAFLD) or the newer term Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD), the possibility of the origin of another new syndrome called as Cardiovascular Hepato-Renal Metabolic syndrome (CHARM) has occurred, because the role of liver pathophysiology has been underestimated and masked under metabolic aspect of CKM syndrome by American heart association.

Keywords: Homeostasis, Metabolic syndrome, Cardiometabolic syndrome, Cardiorenal syndrome, Hepatorenal syndrome.

***Correspondence:**
Dr. Balaji P Pishey Ashwathnarayan Roa
Associate Professor of Physiology and ESH Hypertension Specialist, Diabetologist, Preksha Wellness and Yoga Center, Bangalore, Karnataka, INDIA.
Email: drpaba@rediffmail.com, drpaba2@gmail.com
ORCID ID: 0009-0003-3230-8990

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INTRODUCTION

Homeostasis (milieu intérieur), coined by an American physiologist, Walter Bradford Cannon, in 1929, is the phenomenon of the constancy of internal environment, depends upon normal harmonious physiological functions of various organs and metabolism in the human body.[1] Health is affected by multiple factors like unhealthy lifestyle (food, smoking, alcohol, physical inactivity), environmental factors, genetic and metabolic abnormalities. Metabolism refers to the total sum of reactions that occur throughout the body within each cell and that provide energy to the body. This energy gets used for vital processes and the synthesis of numerous new organic materials. Derangement of normal Physiological functions and metabolism results in various disorders and syndromes. There has been reasonable scientific evidence regarding pathophysiology of metabolic syndrome, cardiometabolic syndrome, cardiorenal syndrome, hepato-renal syndrome and recently in 2023, American Heart Association (AHA) termed cardiovascular kidney metabolic syndrome.[2] Further, there has been growing evidence regarding the role of Non-Alcoholic Fatty Liver Disease (NAFLD), or the newer term Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD), resulting in Cardiovascular Disease (CVD), which in turn can lead to multi organ disorder and failure.[3] Thus, possibly generating another complex syndrome called as cardiovascular hepato-renal metabolic syndrome. Now let us recapitulate all these above-mentioned syndromes from a complex encrypted form to a simple decrypted form in a sequential pattern.

Metabolic Syndrome (MeTS) also called as syndrome X, is a group of interrelated abnormalities (namely obesity, dyslipidaemia, hyperglycaemia and hypertension) that increase the risk for cardiovascular disease and type 2 diabetes mellitus. The most accepted and described pathophysiology of the metabolic syndrome is insulin resistance occurring due to overloads of circulating fatty acids, released from an expanded adipose tissue mass.[4-6] If the patient has any three of the following criteria mentioned below, he/she has metabolic syndrome:

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- Waist circumference more than 40 inches in male and 35 inches among females.
- Elevated Triglycerides (TG) 150 mg per deciliter of blood (mg/dL) or greater.
- Reduced High-Density Lipoprotein cholesterol (HDL) less than 40 mg/dL in male or less than 50 mg/dL in females.
- Elevated fasting blood sugar of l00 mg/dL or greater.
- Blood Pressure (BP) values of systolic 130 mmHg or higher and/or diastolic 85 mmHg or higher.

Cardiometabolic Syndrome (CMS) almost has overlapping pathophysiological basis as in case of syndrome X and includes constellation of a group of conditions including central abdominal obesity, insulin-resistant glucose metabolism, dyslipidemia and increased blood pressure. Alterations in fatty acid metabolism (example: excessive fatty acid release into plasma) is the most likely pathophysiological basis of these metabolic abnormalities. CMS is now recognized as an important disease entity by the World Health Organization (WHO) and the American Society of Endocrinology.[7,8]

Cardiorenal Syndrome (CRS) is defined as any acute or chronic problem in the heart or kidneys that could result in an acute or chronic problem of the other. There are five subtypes of cardiorenal syndrome based on the etiopathology:

- Type 1: Sudden decline in cardiac function that results in an acute decrease in renal function.
- Type 2: Chronic heart dysfunction that results in a sustained reduction in renal function.
- Type 3: Sudden decline in renal function that results in an acute reduction in cardiac function.
- Type 4: Chronic decrease in kidney function that results in chronic cardiac dysfunction.
- Type 5: Systemic diseases that result in both cardiac and kidney dysfunction.

Cardiorenal syndrome Type 1 is the most common form and most studied type. The basic pathophysiology is inadequate renal blood flow or perfusion pressure stimulating renin release by the juxtaglomerular cells of the afferent arterioles because of a low flow state in the ascending limb of the loop of Henle and the pressure-sensing baroreceptors, leading to a) the retention of sodium, b) increased vascular congestion and c) further worsening of renal function due to renal afferent arteriolar vasoconstriction. Each type of CRS has its unique pathophysiology, management strategies and accordingly prognosis is also variable.[9,10]

Hepatorenal Syndrome (HRS) is a condition affecting the kidneys and the liver, where in there is progressive renal failure that occurs in a patient with acute or chronic liver disease. The most common causes are viral hepatitis, drugs/medications; most commonly acetaminophen, chronic alcoholism or any drugs that induce cytochrome p450; and Non-Alcoholic Steatohepatitis (NASH)/Non-Alcoholic Fatty Liver Disease (NAFLD). The pathophysiological hallmark of HRS is severe renal vasoconstriction, resulting from complex changes in splanchnic and general circulations as well as systemic and renal vasoconstrictors and vasodilators.[11,12]

Recently, there is increasing scientific data regarding association between NAFLD and the development and progression of Chronic Kidney Disease (CKD). A large meta-analysis by Mantovani and his team, showed a significantly increased long-term risk of developing CKD in patients with NAFLD.[13] NAFLD has been shown to be associated with the development of CKD in Korean individuals.[14] Concordantly, another study found that there was significantly increased risk of developing CKD in a large, real-world cohort of adult NAFLD patients in Germany.[15]

Although, the above discussed syndromes are well recognized, there is growing awareness that metabolic abnormalities play a vital pathophysiological role in bidirectional cardiovascular-kidney interactions. In addition, renal dysfunction is increasingly recognized as a key mediator of the relationship between metabolic risk factors and CVD, particularly cardiac failure. Therefore, rather than simply considering cardiorenal syndrome and cardiometabolic disease as separate entities, American heart association has termed it as CKM syndrome.[2,16-18] The possible pathophysiological consequences of CKM syndrome replicate relationships among metabolic risk factors, CKD and the cardiovascular system. CKM syndrome mostly originates from excess or dysfunctional adipose tissue or both. Abnormal adipose tissue, particularly visceral adipose tissue, secretes proinflammatory and prooxidative products that damage arterial, cardiac and kidney tissues.[19] Inflammatory processes lead to insulin resistance, resulting in impaired glucose tolerance. The progress of metabolic dysfunction-associated steatotic liver disease (previously called nonalcoholic fatty liver disease) further magnifies systemic inflammation and insulin resistance. When released into the systemic circulation, pro-oxidative and proinflammatory mediators exacerbate pathophysiological processes involved in atherosclerosis and myocardial damage; in glomerulosclerosis, kidney tubular inflammation and kidney fibrosis; and in the development of metabolic risk factors. Along with the systemic effects of adipose tissue, the ectopic fat also could be local source of mediators and can produce compressive organ damage, especially when deposited in the epicardium and pericardium, ratifying arrhythmogenesis, cardiac dysfunction and coronary atherosclerosis and within and around the kidney, contributing to hypertension and abnormal blood pressure variability.[20-25]

Thus, Cardiovascular-Kidney-Metabolic (CKM) syndrome can be defined as a health disorder attributable to interrelationship

among obesity, diabetes, Chronic Kidney Disease (CKD) and Cardiovascular Disease (CVD), including cardiac failure, atrial fibrillation, coronary heart disease, stroke and peripheral artery disease. CKM syndrome includes those at risk for CVD and those with existing CVD. CKM syndrome is categorized into 5 stages: Stage 0 (no risk), stage 1 (overweight/ prediabetes), stage 2 (kidney disease, diabetes, high blood pressure and triglycerides), stage 3 (early asymptomatic cardiac disease, metabolic risk factors and kidney disease) and stage 4 (symptomatic cardiac disease, excess body fat percentage, metabolic risk factors, or kidney disease).[2,17, 20-25]

Moving further, MASLD is now increasingly being recognized as a cause of end-stage liver disease. Presently, the most common cause of death in MASLD or NAFLD patients remains to be CVD. Several pathophysiological mechanisms have been suggested to be responsible for associating NAFLD with CVD, including low-grade systemic inflammation, oxidative stress, adipokines, insulin resistance, pro-coagulation and hypofibrinolysis, plasmic reticulum stress, lipotoxicity and gut microbiome dysbiosis which could also be influenced by other factors such as genetic and epigenetic abnormalities. NAFLD has also been shown to be associated with the development of Chronic Kidney Disease (CKD) and hence, the potential to indirectly modulate the risk of CVD through CKD.[26-29] Thus, overlapping of cardiometabolic and cardiorenal syndromes along with involving the underestimated key role of liver pathophysiology (MASLD), need to be considered in broader term and consensus is mandated to coin the new term cardiovascular hepato-renal metabolic syndrome.

Thus, Cardiovascular Hepato-Renal Metabolic Syndrome (CHARM) can be described as a complex interrelated chain of multi organ disorders involving hypertension, diabetes, obesity, hyperlipidemia, MASLD, CKD and CVD.

Screening for CKM and CHARM risk factors are suggested across the life time to enhance approaches to prevention and management in both youth and adults.

Screening tests for CKM and CHARM syndrome.[2,17]

For Age below 21 years

- Screening for overweight and obesity using sex- and age-specific Centre for Disease Control (CDC) growth charts: annually.
- Blood Pressure (BP) assessment (stronger evidence/ recommendation for those with CKM factors): starting at age 3 year, annually for children with no risk factors; at every health encounter for children with obesity, diabetes, kidney disease, or structural cardiac disease.
- Mental and behavioral health, Social Determinants of Health (SDOH) screening for all children.
- Fasting lipid profile recommended: once between 9 and 11 years of age and then again between 17 and 21 years of age.

Screening is advised beginning at 2 years of age, if a family history is suggestive of either early CVD or significant primary hypercholesterolemia.

Additionally check Fasting Plasma Glucose (FPG)/Oral Glucose Tolerance Test (OGTT)/HbA1c, ALT: starting at 9-11 years of age.

If normal, may repeat every 2-3 years for all children with obesity.

If normal, may repeat every 2-3 years for children with overweight if additional risk factors present (family history of obesity-related diseases, elevated blood pressure or lipid levels, tobacco use).

For age above 21 years

- Screening for social determinants of health.
- Measurement of Body Mass Index (BMI) and waist circumference: annually.
- Screening for MetS components (elevated BP, elevated triglycerides, low HDL cholesterol and hyperglycemia).

Annually for patients with stage 2 CKM

Every 2-3 years for those with stage 1 CKM or history of gestational diabetes.

Every 3-5 years for those with stage 0 CKM.

- Screening for advanced liver fibrosis related to MASLD every 1-2 years for individuals with diabetes mellitus, prediabetes, or ≥2 metabolic risk factors using the Fibrosis-4 (FIB-4 index), or a 3-step approach as described under screening for NAFLD.
- Assessment of Urine Albumin-Creatinine Ratio (UACR) along with serum creatinine/cystatin C for accurate KDIGO staging

Annually for patients with stage 2 CKM or higher

More frequently for those with higher Kidney Disease Improving Global Outcomes (KDIGO) risk

- Coronary artery calcium screening reasonable in those with intermediate 10-years Atherosclerotic Cardiovascular Disease (ASCVD) risk to guide intensification of preventive therapies.
- Subclinical Heart Failure (HF) screening with echocardiogram and/or cardiac biomarkers likely based on age/comorbidities/risk score but not yet defined.
- The Apnea-Hypopnea Index score (AHI), yet to be defined.
- Estimation of T3, T4, TSH, yet to be defined.

Screening tests for NAFLD[30,31]

3-step approach is suggested to screen for NAFLD in high-risk patients (those with diabetes mellitus or metabolic syndrome above the age of 50 years).

First step, patients should be screened for NAFLD with abdominal ultrasound scanning and Alanine Transaminase (ALT), with healthy ALT levels defined as 19 to 25 U/L for females and 29 to 33 U/L for males. Second step, if fatty liver is determined to be present, patients should be assessed for the severity of liver fibrosis using clinical prediction rule(s). Treating physicians are recommended to use both the NAFLD Fibrosis Score (NFS) and the Fibrosis-4 (FIB-4 score), as they have good diagnostic accuracy in detecting advanced fibrosis and are simple to calculate in the clinic. Third step, If the both NFS and the FIB-4 score are indeterminate or discordant, patients should be subjected for transient elastography and gastroenterologist opinion.

Social Determinants of Health

There is excess burden of CKM and CHARM syndrome among patients with adverse Social Determinants of Health (SDOH) and considering the impact of SDOH on CKM and CHARM syndrome management and outcomes, systematic SDOH screening is also vital, as well as incorporating SDOH into risk prediction and addressing SDOH as part of clinical care model for patients with these syndromes.[1,17]

SDOH screening can include essential and optional domains[32]

Essential domains are food insecurity, housing instability, utility needs, financial resource strain, transportation difficulties, exposure to violence, sociodemographic data.

Optional domains include childcare, education, health literacy, employment, health behavior pattern, social isolation and supports, behavioral/mental health.

CONCLUSION

The development of CKM and CHARM syndromes are multifactorial, including metabolic, genetic, environmental and social factors. The management of these syndromes should strongly focus on correcting the pathophysiological and biological under pinning and follow an interdisciplinary approach including a clinical physiologist and the emphasis on lifestyle - diet, exercise, yoga/pranayama, quitting alcohol and smoking and socio-economic support is paramount. Most importantly, considering the patient as a whole and not as an individual disease, can reduce morbidity and premature mortality among patients. However, further research and innovative management strategies are recommended in this regard.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

CKM: Cardiovascular Kidney Metabolic Syndrome; **CHARM:** Cardiovascular Hepato-Renal Metabolic Syndrome; **MeTS:** Metabolic Syndrome; **CMS:** Cardiometabolic Syndrome; **CRS:** Cardiorenal Syndrome; **HRS:** Hepatorenal Syndrome; **NAFLD:** Non-Alcoholic Fatty Liver Disease; **MASLD:** Metabolic Dysfunction-Associated Steatotic Liver Disease; **CKD:** Chronic Kidney Disease; **SDOH:** Social Determinants of Health.

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