Cameroon Journal of Experimental Biology (2022) Vol. 16, N°01, 76-80. DOI: https://dx.doi.org/10.4314/cajeb.V16i1.10

CAFOBIOS
Cameroon Forum for Biological Sciences

Cameroon Journal of Experimental Biology

Available Online at http://www.ajol.info/browse-journals.php

CaJEB

A comprehensive cardiometabolic risk score estimation method in rodents

Adeline K. Wuyt [1], Pamela A. Nono Nankam [2], Elvine P. Nguelefack-Mbuyo [1], Télesphore B. Nguelefack *, [1]

[1] Laboratory of Animal Physiology and Phytopharmacology, Faculty of Sciences, University of Dschang, Dschang, Cameroon.
[2] Helmholtz Institute for Metabolic, Obesity and Vascular Research (HI-MAG) of the Helmholtz ZentrumMünchen at the University of Leipzig and University Hospital Leipzig, Germany.

Keywords

Cardiometabolic syndrome;
Cardiometabolic risk;
Rodents;
Risk factors;
Estimation method

Historic

Received : 17 November 2022
Received in revised form : 27 December 2022
Accepted : 29 December 2022

Abstract

Cardiometabolic diseases are among the main leading causes of morbidity and mortality over the world. The coexistence of a bundle of metabolic risk factors in an individual has prompted Reaven to consider it as a syndrome, called "X syndrome". The term has later evolved and the health condition is today called "cardiometabolics syndrome" (CMS). Significant progress in the understanding of the pathophysiology of the CMS has been made during the past years. Being able to adequately assess cardiometabolic risk (CMR) is crucial for proper diagnosis, prevention, and better management of CMS, as this could be helpful to slow down its progression and complications. This could also be useful in the preclinical and clinical evaluation of potential treatment strategies. Several methods have been developed to assess the risk of developing cardiometabolic diseases in chronic and clinical setting. However, these methods show limitations when applying to short and experimental settings involving rodents. Therefore, this commentary aims at redefining and highlighting the main risk factors to be reconsidered in cardiometabolic syndrome definition; and proposing a comprehensive estimation method for the evaluation of the CMR in rodents. This is relevant for an appropriate utilization of the term CMS and a deep evaluation of therapeutic targets in experimental settings.

1. Background

The interaction between metabolic and cardiovascular diseases has been intensively studied both in clinical and basic research settings since 1988. In this course, the term used to describe the cluster of metabolic and cardiovascular diseases occurring simultaneously in a patient has evolved. Indeed, this was first referred to as "syndrome X" by Reaven [1], and was subsequently renamed to "metabolic syndrome", as the association between insulin resistance, dyslipidemia, high blood pressure and obesity became more evident [2-5]. In the last decades, the term "metabolic syndrome" was re-adapted to "cardiometabolic syndrome" (CMS) due to the significant contribution of metabolic dysfunctions to the risk of developing cardiovascular diseases (CVDs) and the similarities in their etiology and pathophysiologic mechanisms [6-7].

Assessing the cardiometabolic risk (CMR) is crucial in determining the risk of developing cardiovascular and other metabolic events and to initiate appropriate treatment [8-9]. Many calculator systems have been developed for this purpose. However, they are mostly relevant in clinical settings while having several limitations in the context of animal experiments, as some of the parameters cannot be measured in short-term experiments. Facing these limitations, it is therefore necessary to develop more comprehensive methods of CMR estimation in experimental animals such as rodents. Beforehand, it is important to agree on the terminology and the key characteristics of the disease. Hence, this commentary aims to discuss the use of the term CMS and propose a calculation method to score the pathology status in rodents. The ultimate objective is to establish disease states in animal models relevant to clinical conditions, with a reconsideration of key parameters to use when grading the pathology in experimental settings.

2. Cardiometabolic Syndrome and Cardiometabolic Risk Scoring

Cardiometabolic syndrome (CMS) is defined as a cluster of several metabolic abnormalities such as insulin resistance, impaired glucose metabolism, atherogenic dyslipidemia, high blood pressure, and visceral obesity concurrently occurring in an individual [10]. Recent advancements in the understanding of CMS development have led to the consideration of additional bio-clinical parameters such as inflammation and microalbuminuria [11-12], thereby, progressively integrating renal diseases into the concept of CMS. Clinically, CMS and metabolic syndrome are synonyms, and they are diagnosed upon simultaneous appearance of three or more of the following traits: high waist circumference, high triglyceridemia, reduced HDL-cholesterol, increased blood pressure, and elevated fasting blood sugar. Although we agree that this definition is relevant for the metabolic syndrome, we however, have some reserve as far as CMS is concerned. We strongly suggest increased blood pressure and insulin resistance to be compulsory for the definition of CMS because they could be considered as "the

*Corresponding author : F Laboratory of Animal Physiology and Phytopharmacology, Faculty of Sciences, University of Dschang, Dschang, Cameroon. nguelefack@yahoo.fr, Tel.: +237 677564362.

locomotive" of the CMS onset and "the driver" of its complications. Indeed, insulin resistance plays a pivotal role in the pathophysiologic mechanisms of the metabolic dysregulations occurring during the development of the CMS [13], and is highly associated to it either as a cause or a consequence [14]. In addition, hypertension *per se* is a high-risk factor for the incidence of insulin resistance and type 2 diabetes [15], as well as a primary risk factor for all other cardiovascular diseases [16-17]. In all cases, these two metabolic dysfunctions might therefore create and sustain a vicious cycle that can lead to the development of the CMS in human or in animal models [18]. Thus, considering arterial hypertension and insulin resistance as mandatory risk factors makes the difference between metabolic syndrome and CMS. Nevertheless, it should be acknowledged that other disorders associated with CMS are susceptible to occur independently of insulin resistance and hypertension, and should therefore be included in the CMR estimation.

Cardiometabolic risk (CMR) is another piece of the puzzle that leads to the onset of CMS [6]. As such, CMR should be considered as a process and CMS as a state of the disease. In this line, CMS would be defined using the obvious incidence and potential manifestation while CMR should be estimated or calculated. Besides, the CMR estimation may also be useful to grade the CMS. Therefore, in accordance with Reaven's statement (referring to Syndrome X), we suggest that CMS should not be defined by the presence of a specific number of related abnormalities, because focusing only on the occurrence of limited number of risk factors could lead to a misuse of the term, even if insulin resistance and high blood pressure are considered. This suggestion is supported by the fact that: i) the impact of a given parameter on the development of CMS becomes more important as a single risk factor is obviously present, thus, letting borderline value more harmful. Secondly, ii) the overlaps of a cluster of "almost normal" risk factors in the same patient can be a favorable ground for the development of the complications of cardiometabolic diseases, increasing the risk of morbidity and mortality. Therefore, an adequate estimation of the CMR should integrate as many CMS risk factors as possible. The accurate assessment of the CMR will be necessary for the early diagnosis, prevention, and better management of CMS in order to prevent its progression and complications; and would be useful for the development and discovery of new potential targets inexperimental settings.

3. Existing cardiometabolic risk scoring systems

In the last decade, many calculator systems have been developed to assess the CMR, among which:

- The Framingham risk score (FRS), a gender-specific algorithm estimating the 10-year cardiovascular risk of an individual [19].
- The Metabolic Syndrome Severity Score (MetSSS) automatically quantifies and compares the cumulative amount of risk derived from the presence of risk factors responsible for metabolic syndrome [20].
- The Continuous Metabolic Syndrome Score calculated using individual measures corrected to the accepted international standards (siMSS) that allow the estimation of individual CMR, even when the reference data for a population is not available [21].
- The Psychosis Metabolic Risk Calculator (PsyMetRiC), an age-appropriate algorithm used to predict the risk of incident metabolic syndrome in young people with psychosis [22].

These existing calculator systems demonstrate that CMR estimation has been thoroughly examined and improved over time, aiming as much as possible to integrate various key parameters or to target the worrying aspects of CMS. However, as mentioned above, they are only applied clinically. Moreover, some of the parameters included in these calculator systems cannot be measured in animal models or during short-term experiments.

4. Estimation of the risk of cardiometabolic disease development in rodents

We have now developed a comprehensive calculation method for the assessment of CMR experimentally in rodents. This method relies on the fundamental pillars of the CMS that can be evaluated using the following parameters in animal models: dyslipidemia (triglycerides (TG) and high-density lipoprotein-cholesterol (HDL-C)), hypertension (systolic blood pressure (SBP) and diastolic blood pressure (DBP)), glucose metabolism disorder (fasting plasma glucose (FPG) and insulin resistance (IR)), obesity (adiposity index (AI)), and age (in months). The selection of these parameters is based on criteria set by international organizations such as the International Diabetes Federation (IDF) [23], National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III) [24], National Institutes of Health National Heart, Lung, and Blood Institute (NHLBI)/ American Heart Association (AHA) [25] and the World Health Organization (WHO) [26], as well as the state of the art in the pathophysiology of the CMS.

Insulin sensitivity/resistance can be evaluated either by direct testing *in vivo* (using methods like the hyperinsulinemic-euglycemic glucose clamp, the insulin tolerance test (ITT), insulin suppression test) or by using surrogate indexes (such as the Homeostasis Model Assessment (HOMA) or the Quantitative Insulin Sensitivity Check Index (QUICKI)) [27-28]. The two main methods of assessing insulin resistance chosen for this CMR score formula are the HOMA-IR index and the ITT. The ITT has the advantage of being feasible in an environment where the assessment of insulin is challenging.

Taken together, we propose the following formula as calculator equation for the estimation of the CMR score in rodents:

R-CMRS = (TG×SBP×DBP×FPG×AI×IR×Age) /(HDL-C x 1000)

R-CMRS*: Rodents-CardioMetabolic Risk Score (Arbitrary Unit),* ***TG****: Triacylglycerol (g/l),* ***SBP****: Systolic Blood Pressure (mHg),* ***DBP****: Diastolic Blood Pressure (mHg),* ***FPG****: Fasting Plasma Glucose (g/l),* ***AI****: Adiposity Index (Arbitrary Unit),* ***IR:*** *Insulin Resistance (estimated by the measurement of* ***HOMA-IR****: Homeostasis Model Assessment of Insulin Resistance (Arbitrary Unit) or* ***ITT****: Insulin Tolerance Test, expressed as* $1/K_{ITT}$ value*),* ***HDL-C****: High-Density Lipoprotein-Cholesterol (g/l),* ***Age*** *(Months).*

Considering CMS criteria established by the above-mentioned international organizations, CMS risk factors can be summarized with their respective ranges as follow:

- Dyslipidemia: TG: ≥ 150 mg/dl, HDL-C: ≤ 35-40 mg/dl,
- Hypertension: SBP: ≥ 130 mmHg, DBP: ≥ 85mmHg,
- Obesity or Adiposity Index (AI) in rodents: 4.36 (4.17-4.55) for lean, 5.96 (5.69-6.23) for overweight and 8.78 (7.53-10.02) for obese animals [29].
- Dysglycemia (or high fasting glucose level): FPG: ≥100 mg/dl.

Insulin Resistance: HOMA-IR (ranging between 0.7 and 2.0 with values between 0.5-1.4 considered as healthy (optimal), 1.5-1.9 as early insulin resistance and values ≥ 2 as significant insulin resistance; adapted from Matthew et al., 1985 [30]) or ITT (with a K_{ITT} values > 2.0% per minute considered as normo-sensitive and values <1.5% per minute considered as abnormal) [27, 31-32].

From the proposed Rodents-CardioMetabolic Risk Score (R-CMRS), we further suggest a scale range estimated from the previous CMS established risk factors values, which could be used as a R-CMRS severity classification (Table I).

Table 1: Classification of the R-CMRS according to the severity

Risk level	R-CMRS range
Low (Normal)	≤0.1
Intermediated (Moderate)	0.1-0.35
High (Severe)	0.35-1
Very High (Highly Severe)	≥1

Conclusion

Cardiometabolic syndrome (CMS) is a damaging health threat, and its main leading risk factors include insulin resistance and high blood pressure among others. The proposed R-CMRS and the associated severity classification range are therefore, not only useful for a suitable evaluation of the severity of experimentally induced CMS model in rodents but also to investigate the therapeutic activity of potential drugs or molecules to mitigate the development and progression of this condition.

Competing Interest: The authors declare there are no competing interests.

Authors Contribution: TBN and AKW conceived the work and drafted the paper. PANN and EPNM substantially revised this work and were involved in manuscript writing. All authors have revised and agreed on the final version.

Funding: None.

References

1. Reaven G. 2001. Syndrome X. Curr. Treat. Options Cardiovasc. Med. *3:* 323–332.
2. Cheng T. O. 2006. Cardiac syndrome X versus metabolic syndrome X. Int. J. Cardiol 119(2):137–138.
3. Alberti K. G. M. M., Eckel R. H., Grundy S. M., Zimmet P. Z., Cleeman J. I., Donato K. A., Fruchart J.-C., James W. P. T., Loria C. M., Smith Jr. S. C. 2009. Harmonizing the metabolic syndrome : A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 120(16):1640-1645.
4. Parish R.M., Mohan V. 2012. Changing definitions of metabolic syndrome. Indian. J. Endocrinol. Metab. 16(1): 7-12.
5. Nilsson P. M., Tuomilehto J., Ryde L. *2*019. The metabolic syndrome – What is it and how should it be managed? Eur. J. Prev. Cardiol, 26(2): 33–46.
6. Després J.-P. 2020. From syndrome X to cardiometabolic risk: clinical and public health implications. Proc. Nutr. Soc.79(1): 4 – 10.
7. Wittwer J., Bradle D. 2021. Clusterin and Its Role in Insulin Resistance and the Cardiometabolic Syndrome. Front. Immunol.,12:450.
8. Vasudevan A. R., Ballantyne C. M. 2005. Cardiometabolic Risk Assessment: An Approach to the Prevention of Cardiovascular Disease and Diabetes Mellitus. Clin. Cornerstone. 7(2-3):7-16.
9. Dragana S., Milica O. 2013. Cardiometabolic Risk Calculation in the Assessment of Cardiometabolic Risk Profiles. *TEM J.* 2(3):224-228.
10. Woldu M., Minzi O., Shibeshi W., Shewaamare A., Engidawork E. 2022. Biomarkers and Prevalence of Cardiometabolic Syndrome Among People Living With HIV/AIDS, Addis Ababa, Ethiopia: A Hospital-Based Study. Clin. Med. Insights: Endocrinol. 15: 1–15.
11. Huang P. L. 2009. A comprehensive definition for metabolic syndrome. DMM. 2(5-6): 231-237.
12. Sasya M., Devi K. S. S., Babu J. K., BalaguruRayappan J. B., Krishnan U. M. 2020. Metabolic syndrome-An emerging constellation of risk factors: electrochemical detection strategies. Sensors. 20(1):103.
13. Kim J-a. 2021. Insulin Resistance and Cardiometabolic Syndrome. Cardiometab. Syndr. J. 1(1):24-45
14. Guo S. 2014. Insulin signaling, resistance, and the metabolic syndrome: insights from mouse models to disease mechanisms. *J. Endocrinol.* 220(2): T1-T23.
15. Mancusi C., Izzo R., di Gioia G., Losi M. A. , Barbato E., Morisco C. 2020. Insulin Resistance the Hinge between Hypertension and Type 2 Diabetes. High Blood Press Cardiovasc Prev, 27:515–526.
16. Salvetti A., Brogi G., Di Legge V., Bernini G. P. 1993. The Inter-Relationship between Insulin Resistance and Hypertension. *Drugs*. 46: 149-159.
17. Fuchs F. D., Whelton P. K. 2020. High Blood Pressure and Cardiovascular Disease. *Hypertension*. 75:285-292.
18. da Silva A. A., do Carmo J. M., Li X., Wang Z., Mouton A. J., Hall J. E. 2020. Role of hyperinsulinemia and insulin resistance in hypertension: metabolic syndrome revisited. Can. J. Cardiol. 36(5): 671-682.
19. D'Agostino R. B., Sr. Vasan R. S., Pencina M. J., Wolf P. A., Cobain M., Massaro J. M., Kannel W. B. 2008. General cardiovascular risk profile for use in primary care: the Framingham Heart study. Circulation. 117(6):743–53.
20. Wiley J. F., Carrington M. J. 2016. A metabolic syndrome severity score: A tool to quantify cardio-metabolic risk factors. *Prev. Med.* 88: 189-195.

21. Soldatovic I., Vukovic R., Culafic D., Gajic M., Dimitrijevic S. V. 2016. siMS score: simple method for quantifying metabolic syndrome. *PLoSOne*.11(1):e0146143.
22. Perry B. I., Osimo E. F., Upthegrove R., Mallikarjun P. K., Yorke J., Stochl J., Perez J., Zammit S., Howes O., Jones P. B., Khandaker G. M. 2021. Development and external validation of the Psychosis Metabolic Risk Calculator (PsyMetRiC): a cardiometabolic risk prediction algorithm for young people with psychosis. *Lancet Psychiatry*. 8(7):589-598.
23. Saif-Ali R., Kamaruddin N. A., AL-Habori M., Al-Dubai S. A., Ngah W. Z. W. 2020. Relationship of metabolic syndrome defined by IDF or revised NCEP ATP III with glycemic control among Malaysians with Type 2 Diabetes. *Diabetol. Metab. Syndr*. 12:67.
24. Excecutive National Cholesterol Education Program (NCEP) Expert Panel on Detection A. 2002. Treatment of high blood cholesterol in, third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. *Circulation*. 106(25):3143–3421.
25. Grundy S. M., Cleeman J. I., Daniels S. R., Donato K. A., Eckel R. H., Franklin B.A., Gordon D. J., Krauss R. M., Savage P. J., Smith Jr. S. C., Spertus J. A., Costa F. 2005. Diagnosis and management of the metabolic syndrome: an American Heart Association/national heart, lung, and blood Institute Scientific Statement. *Circulation*. 112 (17):2735–2752.
26. Alberti K. G., Zimmet P. Z. 1998. Definition, diagnosis and classification of diabetes mellitus and its complications. partI: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diab. Med.* 15(7):539–53.
27. Patarrãoa R. S. Lautt W. W., Macedo M. P. 2014. Assessment of Methods and indexes of insulin sensitivity. Rev. port. endocrinol. diabetes metabol. 9(1):65–73.
28. Antunes L. C., Elkfury J. L., Jornada M. N., Foletto K. C., Bertoluci M. C. 2016. Validation of HOMA-IR in a model of insulin-resistance induced by a high-fat diet in Wistar rats. *Arch. Endocrinol. Metab.* 60 (2). 138-142.
29. Leopoldo A. S., Lima-Leopoldo A. P., Nascimento A. F., Luvizotto R. A. M., Sugizaki M. M., Campos D. H. S., da Silva D. C. T., Padovani C. R., Cicogna A. C. 2016. Classification of different degrees of adiposity in sedentary rats. Braz. J. Med. Biol. Res. 49(4): e5028.
30. Matthews D. R., Hosker J. P., Rudenski A. S., Naylor B. A., Treacher D. F., Turner R. C. 1985. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 28(7):412-419.
31. Bonora E., Moghetti P., Zancanaro C., Cigolini M., Querena M., Cacciatori V., Corgnati A., Muggeo M. 1989. Estimates of in vivo insulin action in man: Comparison of insulin tolerance tests with euglycemic and hyperglycemic glucose clamp studies. *J. Clin. Endocrinol. Metab*. 68(2):374–378.
32. Young R. P., Critchley J. A., Anderson P. J., Lau M. S., Lee K. K., Chan J. C. 1996. The short insulin tolerance test: feasibility study using venous sampling. *Diabet Med*. 13(5):429–433.