UNIT NO. 1

CARDIOMETABOLIC RISK UPDATE – A 2011 PERSPECTIVE

A/Prof Goh Lee Gan

ABSTRACT

The rising prevalence of cardiometabolic diseases is a worldwide problem, including Singapore. In 2010, the prevalence of obesity and type 2 diabetes mellitus (T2DM) had risen to 10.8% and 11.6% respectively. In 2009, of the 17,101 deaths (100%), ischaemic heart disease, cerebrovascular disease, and diabetes mellitus contributed respectively 19.2%, 8%, and 1.7% - making a total of 28.9% from cardiometabolic deaths. Cardiometabolic risk may be defined as a continuum of risks ranging from behaviour related factors, on to high risk diseases of the deadly quartet (hypertension, diabetes, hyperlipidemia, and obesity), and cardiovascular and metabolic endpoints. The pathophysicolgical basis of cardiometabolic risk is complex. The mechanisms responsible for the cardiometabolic syndrome are not entirely known, but it is likely that multi-organ insulin resistance, which is a common feature of the cardiometabolic syndrome, is involved. Low grade inflammation and dysfunction of high-density lipoprotein and its apolipoproteins are main drivers of cardiometabolic risk. Population studies in China and India provide insights on the development of cardiometabolic disease. PCOS, erectile dysfunction, antipsychotic medications related weight gain need to be addressed too as cardiometabolic problems. Interventions to reduce cardiometabolic risk include: health behaviour modification, pharmacological and surgical interventions, and avoidance of over-consumption of fructose sweetened beverages.

Keywords: Cardiometabolic risk; Metabolic syndrome; Risk stratification; Global risk assessment; Multi-organ insulin resistance; Health behaviour modification; Surgical intervention; Pharmacological intervention; Fructose; Erectile dysfunction; PCOS

SFP2011; 37(4) (Supp 2): 8-12

INTRODUCTION

The rising prevalence of cardiometabolic diseases is a worldwide problem, including Singapore. In 2010, the prevalence of obesity and type 2 diabetes mellitus (T2DM) had risen to 10.8% and 11.6% respectively. In 2009, of the 17,101 deaths (100%), ischaemic heart disease, cerebrovascular disease, and diabetes mellitus contributed respectively 19.2%, 8%, and 1.7% - making a total of 28.9% from cardiometabolic deaths.

A PUBMED search using the keywords of "cardiometabolic disease" for review papers published in the last 3 years were shortlisted and reviewed for information on concepts, identification, and management of cardiometabolic risk.

GOH LEE GAN, Associate Professor, Division of Family Medicine, University Medicine Cluster, National University Health System, Senior Consultant, Institute of Family Medicine, College of Family Physicians Singapore

CARDIOMETABOLIC RISK, METABOLIC SYNDROME AND RISK STRATIFICATION

Definition

Cardiometabolic risk may be defined as a continuum of risks ranging from behaviour related factors, on to high risk diseases of the deadly quartet (hypertension, diabetes, hyperlipidemia, and obesity), and cardiovascular and metabolic endpoints[2].

Overlapping concepts

The concepts of "cardiometabolic risk" and "metabolic syndrome" and the process of "risk stratification" overlap, and all relate to the atherogenic process and development of type 2 diabetes, an important cardiovascular (CV) risk factor. This situation has led to confusion as to what these terms and concepts really mean and how they can best be used to improve our understanding of cardiovascular disease (CVD) treatment and prevention [1].

The following are proposals offered by a national workgroup on cardiometabolic risks in Canada [1, 2]:

- The term "cardiometabolic risk" or "global cardiometabolic risk" be considered to represent the comprehensive catalogue of factors that contribute to the development of both CVD and type 2 diabetes. Each of these factors increases the risk of CV mortality and mortality to some extent, but the term "global cardiometabolic risk" is mainly intended to encourage consideration of factors that go beyond the set of traditional risk factors and that include new or emerging risk factors. The term is intended to be used to catalogue the sources of risk, but not to quantify risk in either absolute or relative terms.

- The term "metabolic syndrome" be considered to represent a specific subset of "cardiometabolic risks" that, when clustered together, impart a relative increase in risk of CVD and development of type 2 diabetes. Metabolic syndrome has been shown to increase overall lifetime CVD risk by about 1.5 – 2-fold [3, 4].

- The term "risk assessment" or "global risk assessment" be

used to describe a process that mathematically weighs the presence or absence of risk factors, as well as their severity, to calculate an absolute CV risk by using validated algorithms derived from long-term observational studies in large patient cohorts.

Cardiometabolic risk screening [1]

The goal of cardiometabolic risk screening is to develop, through identification of the significant traditional and nontraditional risk factors, a comprehensive understanding of a patient's risk for cardiometabolic events, thereby enabling appropriate individual preventive measures to be taken. Information to be collected should include the items listed in Figure 1.

Such an assessment should be taken:

- When any traditional CV risk factor (e.g., hypertension, or dyslipidemia) is first identified, or

- In patients who are overweight or obese (especially if abdominally obese).

Calculation of absolute cardiometabolic risk

The calculation of absolute cardiometabolic risk is done by means of a validated algorithm such as Framingham Risk score, followed by appraisal for the presence or absence of "metabolic syndrome", may help identify patients whose risk might be underestimated through sole consideration of traditional risk factors and who might warrant more comprehensive or intensive intervention, including prompt initiation of health behaviour changes. The Singapore version of the Framingham Risk Score and its use in this context is described in the MOH Clinical Practice Guidelines 1/2011 (March 2011) [5].

PATHOPHYSIOLOGY OF CARDIOMETABOLIC RISK

The pathophysicolgical basis of cardiometabolic risk is complex. The mechanisms responsible for the cardiometabolic syndrome is not entirely known, but it is likely that multi-organ insulin resistance, which is a common feature of the cardiometabolic syndrome, is involved [5, 6].

Alterations in free fatty acid metabolism: These are likely to be a major factor involved in the pathogenesis of hyperglycemia and dyslipidemia associated with the cardiometabolic syndrome. Excessive release of free fatty acids from adipose tissue into plasma and increased plasma free fatty acid concentration can impair the ability of insulin to stimulate muscle glucose uptake and suppress glucose production.

In addition, increased free fatty acid delivery to the liver can increase hepatic very low-density lipoprotein triglyceride production and plasma triglyceride concentration. An increase in plasma triglycerides increases the transfer of triglycerides from very low-density protein to high-density protein lipoprotein clearance and decreased plasma high-density lipoprotein concentration

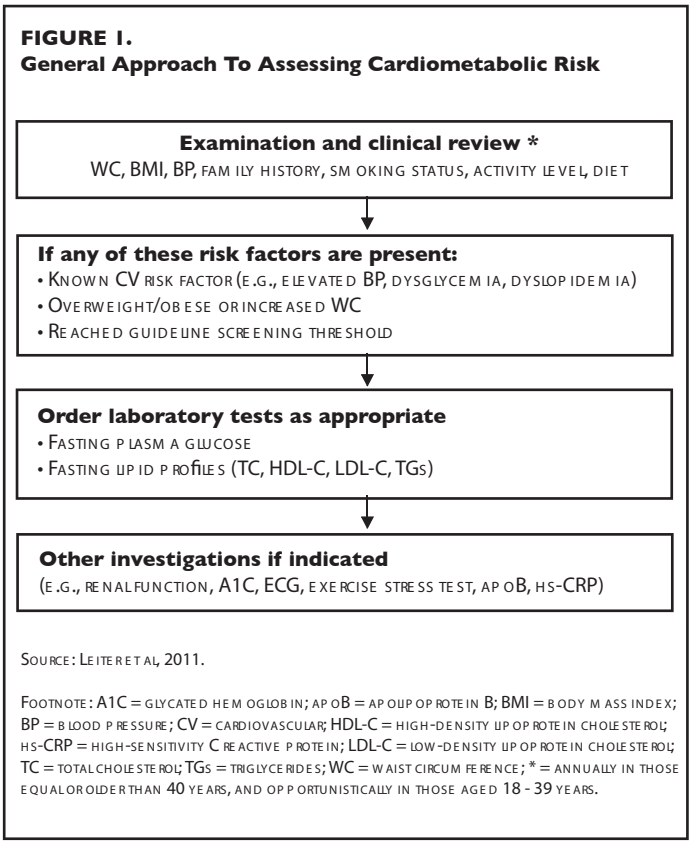
Abdominal adipose tissue: Excess abdominal fat mass, particularly visceral (intraperitoneal) fat, is associated with insulin resistance. It has been hypothesised that fatty acids released during lipolysis of visceral adipose tissue are an important cause of insulin resistance because these fatty acids enter the portal vein and are delivered directly to the liver [5].

Ectopic fat: Ectopic accumulation of fat in liver and muscle cells is associated with insulin resistance in those tissues.

Increased blood pressure: The relationship between insulin resistance and hypertension is well established [7, 5]. Fatty acids themselves can cause vasoconstriction. Additionally, insulin resistance can increase blood pressure because insulin is a vasodilator, and hyperinsulinemia increases renal sodium reabsorption. Persons who are insulin-resistant tend to lose the vasodilatory effect of insulin but preserve the renal effect on sodium reabsorption, and sodium reabsorption is increased in persons with cardiometabolic syndrome.

Low grade inflammation and dysfunction of high-density lipoprotein and its apolipoproteins are major drivers of cardiometabolic risk: Dysfunction of high density lipoprotein (HDL) particles that even become proinflammatory or lose atheroprotective properties is closely linked to obesity. The great impact in public health of the dysfunction of protective serum proteins requires individual clinical recognition, appropriate preventive measures, and delineation of management, including with anti-inflammatory drugs [8].

FIGURE 1.
General Approach To Assessing Cardiometabolic Risk



Source: Leiter et al, 2011.

Footnote: A1C = glycated hemoglobin; apoB = apolipoprotein B; BMI = body mass index; BP = blood pressure; CV = cardiovascular; HDL-C = high-density lipoprotein cholesterol; hs-CRP = high-sensitivity C reactive protein; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TGs = triglycerides; WC = waist circumference; * = annually in those equal or older than 40 years, and opportunistically in those aged 18 - 39 years.

Exposure to suboptimal nutrition during critical periods of development: Evidence from both epidemiological and experimental animal studies now demonstrates that metabolic syndrome onset is increasingly likely following exposure to suboptimal nutrition during critical periods of development, as observed in maternal obesity. Thus, the developmental priming of the metabolic syndrome provides a common origin for this multifactorial disorder [9, 10].

Moving beyond weight loss in nonalcholic fatty liver disease (NAFLD): Epidemiologic data now show an independent relationship between liver fat, physical activity, and fitness, and a growing body of longitudinal research demonstrates that increased physical activity participation per se significantly reduces hepatic steatosis and serum aminotransferases in individuals with NAFLD, independent of weight loss [11].

EPIDEMIOLOGY OF CARDIOMETABOLIC RISK IN POPULATIONS & POPULATION SUBGROUPS

Insights from population studies

Several population studies have highlighted the rising prevalence of cardiometabolic risks and a study of the developments in these countries will be useful in a better understanding of the population control measures necessary.

China: A study from China highlights the rising incidence of cardiovascular diseae fueled by an epidemic of cardiometabolic risk factors. While hypertension and smoking have received considerable spotlight, little attention has been given to obesity, diabetes, and metabolic syndrome [14].

India: The prevalence of obesity and the metabolic syndrome is rapidly increasing in India and other south Asian countries, leading to increased morbidity and mortality due to type 2 diabetes and cardiovascular disease. The main drivers are rapid nutrition, lifestyle, and socioeconomic transitions, consequent to increasing affluence, urbanisation, mechanisation, and rural to urban migration. Less investigated determinants of the metabolic syndrome include psychological stress in urban setting, genetic predisposition, adverse perinatal environment, and childhood "catch up" obesity [15].

Women and polycystic ovary syndrome (PCOS)

Polycystic ovary syndrome (PCOS) is of clinical and public health importance as it is very common, affecting up to one in five women of reproductive age. It has significant and diverse clinical implications including reproductive (infertility, hyperandrogenism, hirsutism), metabolic (insulin resistance, impaired glucose tolerance, type 2 diabetes mellitus, adverse cardiovascular risk profiles) and psychological features (increased anxiety, depression and worsened quality of life). Polycystic ovary syndrome is a heterogeneous condition and, as such, clinical and research agendas are broad and involve many disciplines [16].

Metformin has been introduced as a therapeutic option in PCOS, targeting of cardiometabolic and reproductive abnormalities on the basis of its action on the reduction of glucose levels and the attenuation of insulin resistance. The use of metformin in pregnant women with PCOS is another of its positive features. Overall, available data supports the therapeutic usefulness of metformin on cardiometabolic risk and reproduction assistance in PCOS women [17].

Modest weight loss of 5% to 10% of initial body weight has been demonstrated to improve many of the features of PCOS. Management should focus on support, education, addressing psychological factors and strongly emphasising healthy lifestyle with targeted medical therapy as required. Monitoring and management of long-term metabolic complications is also an important part of routine clinical care [16].

Men and Erectile dysfunction

Erectile dysfunction (ED) is a marker of increased cardiovascular (CVS) risk. In younger men with ED, the Framingham risk assessment has inadequate sensitivity. There is a need to develop a more sensitive risk-stratification protocol for this population. The presence of ED should prompt assessment of cardiac risk and aggressive risk factor treatment. Available risk assessment factors should initially be used to stratify each patient. ED patients younger than 60 years of age and with no clinical CVD are at risk of CAD events (>10%) and should undergo further risk assessment. Additional tests of arterial damage and biomarkers may aid in refinement of risk for future cardiac events [18].

Mental health patients and related weight gain from antipsychotic medications

Antipsychotic-related weight gain and metabolic effects are a critical outcome for patients requiring these medications. Across 32 studies including 1482 subjects, 15 different medications were tested and compared with placebo. Metformin was found to have the greatest weight loss {N=7, n=334, -2.94 kg [confidence interval (CI: -4.89, -0.99)]} [19].

INTERVENTIONS TO REDUCE CARDIOMETABOLIC RISK

Health behaviour modification

Health behaviour modification is recommended as the primary treatment strategy for the management of cardiometabolic risk and should include simultaneous counselling regarding physical activity, smoking cessation, caloric intake, and diet composition, as these are associated with improvements on all cardiometabolic risk factors [3].

The magnitude of improvement in these variables appears to

be dependent on baseline values, with greater improvements reported among those with the greatest disturbances. Improvements in cardiometabolic risk factors tend to be more pronounced when a modest reduction in body weight is achieved, significant improvements are also observed even in the absence of significant weight change. Moderate-intensity exercise for 30 to 60 minutes on most days of the week, together with a moderate reduction in caloric intake (500 kcal/day), can result in significant reductions in cardiometabolic risk. The long-term benefit of health behaviour interventions requires sustained efforts in compliance and adherence.

Pharmacologic and surgical interventions

While health behaviour interventions are the primary strategy to reduce cardiometabolic risk, adjunctive pharmacologic therapy or surgery may be required. The majority of pharmacologic interventions to reduce cardiometabolic risk also apply to the patient with diabetes, since most patients with diabetes have increased cardiometabolic risk.

Weight loss: For patients with a BMI ≥ 30 kg/m^2, or those with a BMI ≥ 27 kg/m^2 plus CV risk factors and/or impaired glucose tolerance (IGT), guidelines recommend that weight-loss medications can be considered if weight loss is <0.5 kg (1 lb) per week after health behaviour changes have been attempted for 3 to 6 months. There are currently no data to show that weight reduction induced by medications results in improved clinical outcomes.

Bariatric surgery has been shown to lower all-cause mortality by 24% to 40% because of a reduction in deaths from myocardial infarction (MI), diabetes, and cancer, as well as prevention of the development of diabetes in patients with severe obesity. Currently, bariatric surgery can be considered in Caucasians with BMI ≥ 40 kg/m^2 or BMI ≥ 35 kg/m^2 plus comorbid conditions, in whom efforts at medical therapy have failed and who have an acceptable operative risk. The corresponding BMI cut-offs for Asians will be 37.5 and 32.5 to 37.4 respectively [3].

Obesity in DM: Obesity is a well known risk factor for type 2 diabetes mellitus. Individuals with type 2 diabetes mellitus are at risk for weight gain as a result of multiple influences, including sedentary lifestyle, high-calorie diet, diabetes medications, sociocultural factors, chronic medical and psychiatric illnesses, and a dysregulated enteroendocrine axis. Because both diabetes mellitus and obesity predispose patients to abnormal cardiometabolic profiles and increased cardiovascular disease, management of diabetes mellitus should focus on weight management and optimising cardiometabolic parameters, concomitant with glycemic control. Lifestyle modification incorporating healthy, calorie-appropriate diets and increased physical activity, in addition to metformin, are central components to diabetes management and weight management. These interventions have been shown to improve body weight, glycemic control, and overall cardiometabolic profile. The weight-neutral and weight-losing diabetes medications include metformin, alpha-glucosidase inhibitors, glucagon-like peptide-1 analogs, dipeptidyl peptidase-4 inhibitors, and amylin analogs. It is essential that providers understand the metabolic and weight effects of diabetes medications in order to develop strategies for managing diabetes mellitus while helping patients maintain or lose weight in order to improve their overall health outcomes [20].

Optimise BP: Clinical trials have not specifically evaluated BP lowering in individuals solely with cardiometabolic risk. However, in patients with cardiometabolic risk associated with dysglycemia, it may be advisable to use agents that may be associated with improvement of glucose metabolism [ie, renin-angiotensin-aldosterone system (RAAS) inhibitors] or antihypertensive drugs that are metabolically neutral [ie, calcium channel blockers (CCBs)] [3].

Optimise lipid levels: In patients with cardiometabolic risk with a moderate or high Framingham Risk Score, treatment should be initiated with a statin to reduce low-density lipoprotein cholesterol (LDL-C) by at least 50% and to <2.0 mmol/L. Apo B levels are a better measurement of lipid-related risk in these patients, and the target level for treatment is <0.8 g/L in high-risk and moderate-risk individuals. There is a large residual risk for patients at high risk for CVD and these should be treated [3].

Optimise blood glucose levels, prevent progression to diabetes, and manage hyperglycemia: While health behaviour modification, with weight loss and increased physical activity, is the most effective, pharmacotherapy can also be considered to prevent progression to type 2 diabetes [3].

Consumption of fructose sweetened beverages: Such has increased steadily over the past century and with this increase has come more and more reports associating their use with the risk of overweight, diabetes and cardiometabolic disease. In a meta-analysis of the relationship between soft drink consumption and cardiometabolic risk, there was a 24% overall increased risk comparing the top and bottom quantiles of consumption. Several factors might account for this increased risk, including increased carbohydrate load and increased amounts of dietary fructose. Fructose acutely increases thermogenesis, triglycerides and lipogenesis as well as blood pressure [21].

CONCLUSIONS

- "Global cardiometabolic risk" is an umbrella term for a comprehensive list of existing and emerging factors that predict CVD and/ or type 2 diabetes.
- A risk stratification approach ensures that a best approach is taken to reduce cardiometabolic disease.

- Interventions to reduce cardiometabolic risk can take place simultaneously at the levels of health behaviour modification, interventions directed at weight control, blood pressure control, blood sugar control, as well as management of CVD and metabolic endpoints.

REFERENCES

1. Volpe M, Camm J, Coca A, Unger T. The cardiovascular continnum refined: a hypeothesis. Blood Press 2010 Oct;19(5):273-7.
2. Dahlof B. Cardiovascular disease risk factors: epidemiology and risk assessment. Am J Cardiol, 2010 Jan 4;105(11 Suppl):3A-9A.
3. Cardiometabolic Risk Working Group: Executive Committee, Leiter LA, Fitchett DH, Gilbert RE, et al. Identification and management of cardiometabolic risk in Canada: a position paper by the cardiometabolic risk working group (executive summary). Can J Cardiol. 2011 Mar-Apr;27(2):124-31.
4. Galassi A, Reynolds K, He J. Metabolic syndrome and risk of cardiovascular disease; a meta-analysis. Am J Med 2006;119:812-9.
5. Gami AS, Witt BJ, Howard DE, et al. Metabiolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol 2007;49:403-14.
6. MOH. Screening for Cardiovasculr Disease and Risk Factors. MOH Clinical Practice Guidelines 1/2011.
7. Kirk E, Klein S. Pathogenesis and pathophysiology of the cardiometabolic syndrome. The Journal of Clinical Hypertensin 2009; 11:12:761-765.
8.Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988;37:1595-1607.
9. Ferrannini E, Buzzigoli G, Bonadonna R, t al. Insulin resistance in essential hypertension. N Engl J Med 1987;317:350-357.
10. Onat A, Herpgeng G. Low-grade inflammation, and dysfunction of high-density lipoprotein and its apolipoproteins as a major driver of cardiometabolic riks. Metabolism 2011 Apr; 60(4):499-512.
11. Drake AJ. Reynolds RM. Impact of maternal obesity on offspring obesity and cardiometabolic disease risk. Reproduction 2010 Sep;140(3):387-98.
12. Bruce KD, Cagampang FR. Epigenetic priming of the metabolic syndrome. Toxicol Mech Methods, 2011 May;21(40:353-61.
13. Johnson NA, George J. Fitness versus fatness: moving beyond weight loss in nonalcoholic fatty liver disease. Hepatology 2010 Jul;52(1):370-81.
14. Shen J, Goyal A, and Sperling L. The emerging epidemic of obesity, diabetes, and the metabolic syndrome in China. Cardiol Res Pract 2012;2012:178675. Epub 2011 Sep 22.
15. Misra A, Khurana L. The metabolic syndrome in South Asians: determinants, epidemiology, determinants, and prevention.
16. Teede H, Deeks A, Moran L. Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. BMC Med. 2010 Jun 30;8:41.
17. Diamanti-Kandarakis E, Economou F, Palimeri S, Christakou C. Metformin in polycystic ovary syndrome. Ann N Y Acad Sci. 2010 Sep;1205:192-8.
18. Miner MM. Erectile dysfunction: a harbinger or consequence: does its detection lead to a window of curability? J Androl. 2011 Mar-Apr;32(2):125-34.
19. Maayan L, Vakhrusheva J, Correll CU. Effectiveness of medications used to attenuate antipsychotic-related weight gain and metabolic abnormalities: a systematic review and meta-analysis. Neuropsychopharmacology. 2010 Jun;35(7):1520-30.
20. Siram AT, Yanagisawa R, Skamagas M. Weight management in type 2 diabetes mellitus. Mt Sinai J Med. 2010 Sep-Oct;77(5):533-48.
21. Bray GA. Soft drink consumption and obesity: it is all about fructose. Curr Opin Lipidol. 2010 Feb;21(1):51-7.

LEARNING POINTS

- **Cardiometabolic risk may be defined as a continuum of risks ranging from behaviour related factors, on to high risk diseases of the deadly quartet (hypertension, diabetes, hyperlipidemia and obesity) and cardiovascular and metabolic endpoints.**
- **The mechanisms responsible for the cardiometabolic syndrome is not entirely known, but it is likely that multi-organ insulin resistance, which is a common feature of the cardiometabolic syndrome, is involved.**
- **Low grade inflammation and dysfunction of high-density lipoprotein and its apolipoproteins are main drivers of cardiometabolic risk.**
- **PCOS, erectile dysfunction, antipsychotic medications related weight gain need to addressed too as cardiometabolic problems.**
- **Interventions to reduce cardiometabolic risk includes: health behaviour modification, pharmacological and surgical interventions and avoidance of over-consumption of fructose sweetened beverages.**