A SELECTION OF TEN CURRENT READINGS ON TOPICS RELATED TO CARDIOMETABOLIC RISK UPDATE – available as free full-text

Selection of readings made by A/Prof Goh Lee Gan

READING 1 – Molecular determinants of the cardiometabolic phenotype

de las Fuentes L, de Simone G, Arnett DK, Dávila-Román VG. Molecular determinants of the cardiometabolic phenotype. Endocr Metab Immune Disord Drug Targets. 2010 Jun;10(2):109-23. Review. PubMed PMID: 20384572; PubMed Central PMCID: PMC2887744.

URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2887744/pdf/nihms207662.pdf (free full-text)

Cardiovascular Imaging and Clinical Research Core Laboratory, Cardiovascular Division, Washington University School of Medicine, St. Louis, MO 63110, USA. lfuentes@wustl.edu

ABSTRACT

The metabolic syndrome represents a clustering of risk factors that has been shown to predict adverse cardiovascular outcomes. Although the precise mechanisms contributing to the cardiometabolic syndrome (CMS) remain poorly defined, accumulating evidence identifies two intersecting candidate pathways responsible for inflammation and energy homeostasis in the pathophysiology that underlie cardiometabolic traits. Although currently no pharmacologic interventions specifically target CMS, future drug development efforts should attempt to capitalise on molecular nodes at the intersections of these pathways in the CMS.PMCID: PMC2887744 PMID: 20384572 [PubMed - indexed for MEDLINE]

READING 2 – Prevention of atherosclerosis in overweight/obese patients

Lim S, Despres JP, Koh KK. Prevention of atherosclerosis in overweight/obese patients. - In need of novel multi-targeted approaches-. Circ J. 2011 Apr 25;75(5):1019-27. Epub 2011 Mar 25. Review. PubMed PMID: 21441697.

URL: http://www.jstage.jst.go.jp.libproxy1.nus.edu.sg/article/circj/75/5/1019/_pdf (free full-text)

Division of Endocrinology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea.

ABSTRACT

Obesity has reached epidemic proportions and complications related to obesity contribute substantially to both healthcare costs and mortality. Obesity, particularly when accompanied by an excess of visceral/ectopic fat, is a major risk factor for diseases ranging from insulin resistance, type 2 diabetes, nonalcoholic fatty liver disease, and cardiovascular disease. The epidemic proportions reached by obesity has made these conditions a global problem in human health. Accordingly, preventive and/or therapeutic interventions should be considered in obese patients. Regular physical activity/exercise has numerous beneficial effects on the cardiometabolic risk profile and on the cardiovascular system. However, our current clinical environment is not designed to provide the regular support needed by patients to help them maintain over the long term their improved physical activity/nutritional habits. Because hypertension, dyslipidemia, hyperinsulinemia, and excess visceral adipose tissue are linked by complex reciprocal molecular interactions, it is logical to expect that targeting an interconnected pathway may provide multiple benefits. At this stage, combined therapy of statins or PPAR agonists and

renin-angiotensin-aldosterone system blockers to target multiple therapeutic pathways may optimally improve the cardiometabolic risk profile through both distinct and interrelated mechanisms. In the present article, we will discuss updated novel approaches, including potential multi-targeted intervention strategies, based on underlying pathophysiological processes. PMID: 21441697 [PubMed - indexed for MEDLINE]

READING 3 – Is high fructose consumption harmful?

Wiernsperger N, Geloen A, Rapin JR. Fructose and cardiometabolic disorders: the controversy will, and must, continue. Clinics (Sao Paulo). 2010 Jul;65(7):729-38. Review. PubMed PMID: 20668632; PubMed Central PMCID:PMC2910863.

URL: http://www.scielo.br/pdf/clin/v65n7/a13v65n7.pdf (free full-text)

INSERM U, INSA Lyon, Villeurbanne, France. nicolas.wiernsperger@free.fr

ABSTRACT

The present review updates the current knowledge on the question of whether high fructose consumption is harmful or not and details new findings which further pushes this old debate. Due to large differences in its metabolic handling when compared to glucose, fructose was indeed suggested to be beneficial for the diet of diabetic patients. However its growing industrial use as a sweetener, especially in soft drinks, has focused attention on its potential harmfulness, possibly leading to dyslipidemia, obesity, insulin resistance/metabolic syndrome and even diabetes. Many new data have been generated over the last years, confirming the lipogenic effect of fructose as well as risks of vascular dysfunction and hypertension. Fructose exerts various direct effects in the liver, affecting both hepatocytes and Kupffer cells and resulting in non-alcoholic steatotic hepatitis, a well known precursor of the metabolic syndrome. Hepatic metabolic abnormalities underlie indirect peripheral metabolic and vascular disturbances, for which uric acid is possibly the culprit. Nevertheless major caveats exist (species, gender, source of fructose, study protocols) which are detailed in this review and presently prevent any firm conclusion. New studies taking into account these confounding factors should be undertaken in order to ascertain whether or not high fructose diet is harmful. PMCID: PMC2910863 PMID: 20668632 [PubMed - indexed for MEDLINE]

READING 4 – Polycystic ovary syndrome impacts on health across the lifespan

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. Review. PubMed PMID: 20591140; PubMed Central PMCID: PMC2909929.

URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2909929/pdf/1741-7015-8-41.pdf (free full-text)

Monash University, Clayton, Australia.

ABSTRACT

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. The phenotype varies widely depending on life stage, genotype, ethnicity and environmental factors including

lifestyle and bodyweight. Importantly, PCOS has unique interactions with the ever increasing obesity prevalence worldwide as obesity-induced insulin resistance significantly exacerbates all the features of PCOS. Furthermore, it has clinical implications across the lifespan and is relevant to related family members with an increased risk for metabolic conditions reported in first-degree relatives. Therapy should focus on both the short and long-term reproductive, metabolic and psychological features. Given the aetiological role of insulin resistance and the impact of obesity on both hyperinsulinaemia and hyperandrogenism, multidisciplinary lifestyle improvement aimed at normalising insulin resistance, improving androgen status and aiding weight management is recognised as a crucial initial treatment strategy. 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. Comprehensive evidence-based guidelines are needed to aid early diagnosis, appropriate investigation, regular screening and treatment of this common condition. Whilst reproductive features of PCOS are well recognised and are covered here, this review focuses primarily on the less appreciated cardiometabolic and psychological features of PCOS. PMCID: PMC2909929 PMID: 20591140 [PubMed - indexed for MEDLINE]

READING 5 – Maternal incronutrient deficiency and chronic disease

Christian P, Stewart CP. Maternal micronutrient deficiency, fetal development, and the risk of chronic disease. J Nutr. 2010 Mar;140(3):437-45. Epub 2010 Jan 13. Review. PubMed PMID: 20071652.

URL: http://jn.nutrition.org/content/140/3/437.full.pdf+html (free full-text)

Center for Human Nutrition, Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21200, USA. pchristi@jhsph.edu

ABSTRACT

Early life nutritional exposures, combined with changes in lifestyle in adult life, can result in increased risk of chronic diseases. Although much of the focus on the developmental origins of disease has been on birth size and growth in postnatal life and the availability of energy and protein during these critical developmental periods, micronutrient deficiencies may also play an important role in fetal growth and development. Micronutrient status in fetal and early life may alter metabolism, vasculature, and organ growth and function, leading to increased risk of cardiometabolic disorders, adiposity, altered kidney function, and, ultimately, to type 2 diabetes and cardiovascular diseases. This review elucidates pathways through which micronutrient deficiencies lead to developmental impairment and describes the research to date on the evidence that micronutrient deficiencies in utero influence the development of chronic disease risk. Animal studies, observational human studies examining maternal diet or micronutrient status, and limited data from intervention studies are reviewed. Where data are lacking, plausible mechanisms and pathways of action have been derived from the existing animal and in vitro models. This review fills a critical gap in the literature related to the seminal role of micronutrients in early life and extends the discussion on the developmental origins of health and disease beyond birth size and energy and protein deficiency. PMID: 20071652 [PubMed - indexed for MEDLINE]

READING 6 – Maternal obesity on offspring obesity and cardiometabolic disease risk

Drake AJ, Reynolds RM. Impact of maternal obesity on offspring obesity and cardiometabolic disease risk. Reproduction. 2010 Sep;140(3):387-98. Epub 2010 Jun 18. Review. PubMed PMID: 20562299.

URL: http://www.reproduction-online.org/content/140/3/387.full.pdf+html (free full-text)

Endocrinology Unit, Queen's Medical Research Institute, Centre for Cardiovascular Sciences, University of Edinburgh, 47 Little France Crescent, Edinburgh, EH16 6TJ, UK.

ABSTRACT

The prevalence of obesity among pregnant women is increasing. In addition to the short-term complications of obesity during pregnancy in both mother and child, it is now recognised that maternal obesity has long-term adverse outcomes for the health of her offspring in later life. Evidence from both animal and human studies indicates that maternal obesity increases the risk for the offspring in developing obesity and altering body composition in child- and adulthood and, additionally, it also has an impact on the offspring's cardiometabolic health with dysregulation of metabolism including glucose/insulin homoeostasis, and development of hypertension and vascular dysfunction. Potential mechanisms include effects on the development and function of adipose tissue, pancreas, muscle, liver, the vasculature and the brain. Further studies are required to elucidate the mechanisms underpinning the programming of disease risk in the offspring as a consequence of maternal obesity. The ultimate aim is to identify potential targets, which may be amenable to prevention or early intervention in order to improve the health of this and future generations. PMID: 20562299 [PubMed - indexed for MEDLINE]

READING 7 – Managing mixed dyslipidemia in special populations

Miller M. Managing mixed dyslipidemia in special populations. Prev Cardiol. 2010 Spring;13(2):78-83. Review. PubMed PMID: 20377810; PubMed Central PMCID: PMC2923824.

URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2923824/pdf/nihms-224667.pdf (free full-text)

Department of Medicine, University of Maryland Hospital, Baltimore, MD, USA.
mmiller@medicine.umaryland.edu

ABSTRACT

Controlling low-density lipoprotein cholesterol is one of the major focuses of cardiovascular care. However, the twin global pandemics of obesity and diabetes are promoting an increased prevalence of associated cardiometabolic risk factors. These factors include mixed dyslipidemia, which is prevalent among several important subgroups of the overall population. Cardiovascular risk increases as women reach and extend beyond menopause, partly reflective of dyslipidemia. In addition, women with polycystic ovary syndrome display a cluster of risk factors reminiscent of the metabolic syndrome. Certain ethnic groups are also at increased risk for type 2 diabetes or the metabolic syndrome. Dyslipidemia contributes significantly to overall cardiovascular risk in the elderly, and the frequency of children and adolescents presenting with type 2 diabetes or metabolic syndrome is increasing worldwide. Physicians should be aware of the possibility of mixed dyslipidemia in patients at elevated cardiometabolic risk. However, while combination therapy may successfully correct the associated dyslipidemia, it remains to be established whether the addition of a second agent improves coronary risk beyond statin monotherapy. PMCID: PMC2923824 PMID: 20377810 [PubMed - indexed for MEDLINE]

READING 8 – Recent advances in the management of chronic stable angina (I)

Kones R. Recent advances in the management of chronic stable angina I: approach to the patient, diagnosis, pathophysiology, risk stratification, and gender disparities. Vasc Health Risk Manag. 2010 Aug 9;6:635-56. Review. PubMed PMID: 20730020; PubMed Central PMCID: PMC2922325.

URL: http://www.dovepress.com/articles.php?article_id=4852 (free full-text)

The Cardiometabolic Research Institute, Houston, Texas 77054, USA. drrkones@comcast.net

ABSTRACT

The potential importance of both prevention and personal responsibility in controlling heart disease, the leading cause of death in the USA and elsewhere, has attracted renewed attention. Coronary artery disease is preventable, using relatively simple and inexpensive lifestyle changes. The inexorable rise in the prevalence of obesity, diabetes, dyslipidemia, and hypertension, often in the risk cluster known as the metabolic syndrome, drives the ever-increasing incidence of heart disease. Population-wide improvements in personal health habits appear to be a fundamental, evidence based public health measure, yet numerous barriers prevent implementation. A common symptom in patients with coronary artery disease, classical angina refers to the typical chest pressure or discomfort that results when myocardial oxygen demand rises and coronary blood flow is reduced by fixed, atherosclerotic, obstructive lesions. Different forms of angina and diagnosis, with a short description of the significance of pain and silent ischemia, are discussed in this review. The well accepted concept of myocardial oxygen imbalance in the genesis of angina is presented with new data about clinical pathology of stable angina and acute coronary syndromes. The roles of stress electrocardiography and stress myocardial perfusion scintigraphic imaging are reviewed, along with the information these tests provide about risk and prognosis. Finally, the current status of gender disparities in heart disease is summarised. Enhanced risk stratification and identification of patients in whom procedures will meaningfully change management is an ongoing quest. Current guidelines emphasise efficient triage of patients with suspected coronary artery disease. Many experts believe the predictive value of current decision protocols for coronary artery disease still needs improvement in order to optimise outcomes, yet avoid unnecessary coronary angiograms and radiation exposure. Coronary angiography remains the gold standard in the diagnosis of coronary artery obstructive disease. Part II of this two part series will address anti-ischemic therapies, new agents, cardiovascular risk reduction, options to treat refractory angina, and revascularisation. PMCID: PMC2922325 PMID: 20730020 [PubMed - indexed for MEDLINE]

READING 9 – Recent advances in the management of chronic stable angina (II)

Kones R. Recent advances in the management of chronic stable angina II. Anti-ischemic therapy, options for refractory angina, risk factor reduction, and revascularisation. Vasc Health Risk Manag. 2010 Sep 7;6:749-74. Review. PubMed PMID: 20859545; PubMed Central PMCID: PMC2941787.

URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2941787/pdf/vhrm-6-749.pdf (free full-text)

Cardiometabolic Research Institute, Houston, Texas 77055, USA. drrkones@comcast.net

ABSTRACT

The objectives in treating angina are relief of pain and prevention of disease progression through risk reduction. Mechanisms, indications, clinical forms, doses, and side effects of the traditional antianginal agents - nitrates, ß-blockers, and calcium channel blockers - are reviewed. A number of patients have contraindications or remain unrelieved from anginal discomfort with these drugs. Among newer alternatives, ranolazine, recently approved in the United States, indirectly prevents the intracellular calcium overload involved in cardiac ischemia and is a welcome addition to available treatments. None, however, are disease-modifying agents. Two options for refractory angina, enhanced external counterpulsation and spinal cord stimulation (SCS), are presented in detail. They are both well-studied and are effective means of treating at least some patients with this perplexing form of angina. Traditional modifiable risk factors for coronary artery disease (CAD) - smoking, hypertension, dyslipidemia, diabetes, and obesity - account for most of the population-attributable risk. Individual therapy of

high-risk patients differs from population-wide efforts to prevent risk factors from appearing or reducing their severity, in order to lower the national burden of disease. Current American College of Cardiology/American Heart Association guidelines to lower risk in patients with chronic angina are reviewed. The Clinical Outcomes Utilising Revascularisation and Aggressive Drug Evaluation (COURAGE) trial showed that in patients with stable angina, optimal medical therapy alone and percutaneous coronary intervention (PCI) with medical therapy were equal in preventing myocardial infarction and death. The integration of COURAGE results into current practice is discussed. For patients who are unstable, with very high risk, with left main coronary artery lesions, in whom medical therapy fails, and in those with acute coronary syndromes, PCI is indicated. Asymptomatic patients with CAD and those with stable angina may defer intervention without additional risk to see if they will improve on optimum medical therapy. For many patients, coronary artery bypass surgery offers the best opportunity for relieving angina, reducing the need for additional revascularisation procedures and improving survival. Optimal medical therapy, percutaneous coronary intervention, and surgery are not competing therapies, but are complementary and form a continuum, each filling an important evidence-based need in modern comprehensive management. PMCID: PMC2941787 PMID: 20859545 [PubMed - indexed for MEDLINE]

READING 10
- Effectiveness of medications used to attenuate antipsychotic-related weight gain

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. Epub 2010 Mar 24. Review. PubMed PMID: 20336059; PubMed Central PMCID: PMC3055458.

URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3055458/pdf/npp201021a.pdf (free full-text)

Child Study Center, New York University School of Medicine, New York, NY, USA.

ABSTRACT

Antipsychotic-related weight gain and metabolic effects are a critical outcome for patients requiring these medications. A literature search using MEDLINE, Web of Science, PsycNET, and EMBASE for randomised, open and double-blind, placebo-controlled trials of medications targeting antipsychotic-induced weight gain was performed. Primary outcome measures were change and endpoint values in body weight and body mass index (BMI). Secondary outcomes included >or=7% weight gain, all-cause discontinuation, change in waist circumference, glucose and lipid metabolism parameters, and psychiatric symptoms. Sensitivity analyses were conducted to explain heterogeneity of the results. Across 32 studies including 1482 subjects, 15 different medications were tested: amantadine, dextroamphetamine, d-fenfluramine, famotidine, fluoxetine, fluvoxamine, metformin, nizatidine, orlistat, phenylpropanolamine, reboxetine, rosiglitazone, sibutramine, topiramate, and metformin+sibutramine. Compared with placebo, metformin had the greatest weight loss (N=7, n=334, -2.94 kg (confidence interval (CI:-4.89,-0.99)), followed by d-fenfluramine (N=1, n=16, -2.60 kg (CI:-5.14,-0.06)), sibutramine (N=2, n=55, -2.56 kg (CI:-3.91,-1.22)), topiramate (N=2, n=133, -2.52 kg (CI:-4.87,-0.16)), and reboxetine (N=2, n=79, -1.90 kg (CI:-3.07,-0.72)). Weight loss remained significant with metformin initiation after weight gain had occurred, but not when started concomitantly with antipsychotics. Nausea rates were not higher with any treatment compared with placebo. In all, 5 of 15 psychopharmacologic interventions aimed at ameliorating antipsychotic-induced weight gain outperformed placebo. Results were most robust for metformin, although these were modest and heterogeneous. Only one (negative) combination treatment study was available and head-to-head studies are absent. None of the agents were able to entirely reverse weight gain because of antipsychotics. At present, no treatment has sufficient evidence to recommend broad clinical usage. Antipsychotics with no or minimal cardiometabolic liability, as well as interventions that prevent or normalise adverse antipsychotic cardiometabolic effects are needed. PMCID: PMC3055458 PMID: 20336059 [PubMed - indexed for MEDLINE]