MANAGEMENT OF THE METABOLIC SYNDROME AND THE EMERGING ROLE OF NUTRACEUTICAL

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Background
The term Metabolic Syndrome refers to the aggregation of a number of cardiovascular related risk factors; obesity (usually central), hypertension, dyslipidaemia, glucose intolerance, prothrombotic state and inflammation. The Metabolic syndrome is a predictor of type 2 diabetes mellitus and cardiovascular disease. It is associated with a 7-fold increase in the incidence of type 2 diabetes mellitus and a relative risk of 1.54 for cardiovascular events and death after adjustment of traditional risk factors.
Life style modification (increase physical activity and dietary modification) is vital in management. Early diagnosis and strict adherence to life style measures have been demonstrated to retard progression of the syndrome and reduce the incidence of its attendant morbidity and mortality. Recently, nutraceuticals, which are food supplements that have some health benefits, were demonstrated from several studies to have important roles in the management of the metabolic syndrome.

Key words: Metabolic syndrome, management, Nutraceuticals.

INTRODUCTION

The interest and awareness of the global health community was stimulated to the concept of the metabolic syndrome (Mets) when Raeven[1] in his Banting lecture in 1988, observed how dylipidaemia, hypertension and hyperglycaemia cluster in the same individuals. He called this clustering "Syndrome X" and emphasized its role as a risk factor for cardiovascular disease. Raeven do not include abdominal form of obesity which is now been hypothesized as the main underlying factor for Mets.[2] Although the concept of Mets was made more popular by the Raevens lecture, similar concepts to the Mets have been variously described in the past. Kylin in the 1920s described the clustering of hypertension, dyslipidaemia and gout in the same individuals.[3] Two decades later Jean Vague in the late 1940s and early 1950s, in his paper on special sexual differentiation of obesity noted that upper body adiposity (android or male type adiposity) was most often associated with metabolic abnormalities associated with diabetes mellitus and cardiovascular diseases, what he later called "diabetogenic Obesity".[4] His description of obesity fits into what is referred today as central obesity. Haler in 1977 first used the term Mets in associating obesity with diabetes mellitus, hyperlipoproteinaemia, hyperuricaemia and hepatic steatosis when describing additive effects of risk factors for atherosclerosis[5]. Singer in 1977 and Phillip in 1978 also described association of obesity and other risk factors predisposing to cardiovascular disease and diabetes mellitus.[6,7] It is currently define by the International Diabetes Federation (IDF) as the presence of central obesity and any 2 of the following; hypertension $\geq$ 130/85mmHg or on treatment for hypertension, low High Density Lipoprotein Cholesterol (HDL-c) <1.0mmoi/L in men; <1.3mmol/L in women, raised serum triglycerides $\geq$ 1.7mmol/L, fasting plasma glucose >5.6mmol/L or diagnosed diabetes.[8] The Metabolic syndrome is a predictor of type 2 diabetes mellitus and cardiovascular disease. It is associated with a 7-fold increase in the incidence of type 2 diabetes mellitus and a relative risk of 1.54 for cardiovascular events and death after adjustment of traditional risk factors.[9,10] This review highlights the important measures in the management of Mets and the

emerging role of nutraceuticals in its management.

Key words. Management, Metabolic Syndrome, Nutraceuticals.

MANAGEMENT.

The diagnosis of Mets is the first step in its management. Management requires a multi-disciplinary approach, including physicians, health educators skilled in nursing, nutrition and exercise physiology. The goal of treatment is to prevent or slow progression of diabetes, hypertension and cardiovascular diseases.

Weight loss improves all components of the syndrome; a weight loss of 5-10% of body weight can lead to significant reduction in morbidity and mortality.[11] Weight loss has also been shown to reduce oxidative stress,[12] an important factor in the evolution of Mets.

Measures to reduce weight;

Counselling- a six 30 minutes sessions with a clinician, dietician or a nurse in an individual or group setting can produce significant changes in average daily intake of calorie containing nutrients among adult patients at increaserisk for diet related chronic diseases.[13] Such counseling should involve assessing the patients' dietary patterns and activity levels and recommending appropriate change.

Exercise.

Exercise is the primary determinant of fitness and is also effective in reducing fatness (obesity).[14] Cardiorespiratory fitness even without weight loss is associated with improve cardiovascular risk parameters and increase insulin sensitivity,[15] decrease incidence of metabolic syndrome[16] and cardiovascular mortality independent of measures of reducing obesity.[17,18]

The importance of regular physical activity and its attendant physical fitness without weight loss in reducing the risk of cardiovascular diseases and type 2 DM was also demonstrated in a study by Katzmarz et al.[19] They followed up 15,446 healthy men and 3757 with Mets for 10 years to determine the relationship between cardiorespiratory fitness and mortality. Compared to healthy participants, men with metabolic syndrome without cardiorespiratory fitness were twice likely to die of cardiovascular disease and 1.3 times as likely to die of other causes. However, if they were fit without weight loss, there risk will be similar to those of the healthy men.

Physical activity appears to have even greater effect on patients with cluster of abnormalities associated with insulin resistance. This was demonstrated by the Health Risk factors, Exercise Training and Genetics (HERITAGE) family study, which showed increase levels of HDL-C with exercise only in patients with abdominal obesity and lipid component of the Mets.[20]

Different forms of exercise have been found to be healthy and beneficial. Simple daily, vigorous (brisk) walking can significantly reduce cardiac risk factors and improve glucose metabolism[21]. A Meta –analysis involving the use of pedometers, noticed increase motivation to indulge in physical activity if daily goals are set in their use.[22] A specific set goal of 10,000 steps/day is associated with significant increase in physical activity, decrease BMI and decrease systolic blood pressure.[22]

Despite changing guidelines, the optimal dose of exercise to be recommended is unknown. However a study on Dose Response to exercise in women (DREW) aged 45-75 years demonstrated a graded dose response improvement across different levels of exercise training.[23] With respect to the Mets, Lee in his study on dose response relationship to physical activity and fitness demonstrated that a little exercise is good and more is even better.[24] Hence our patients with Mets should be encouraged to engage in exercise activity no matter how little and be encouraged to increase the exercise intensity gradually. Patients should generally be advised to plan to exercise/be active at least 3 days and up to 5 days a week. They should slowly add days as they become comfortable. They can start with 10-15minutes of activity and build up to 30 minutes daily over months. Exercise should involve activity they enjoy, it should not be viewed as a burden or chore as exercise should be lifelong and done consistently.

DIET.

Portion control- which involves adjusting the size (portion) of our meal in relation to our BMI has been demonstrated to be a key weight loss measure. Hamumet al[25] showed that portion control was associated with greater weight loss during a 24 month period than reduce dietary fat consumption or increase physical activity. Their study found that 38% of obese patient who constantly practice portion control lost 5% or more of their baseline weight, while 33% obese patient who do not, gain 5% or more of their baseline weight.

The **Mediterranean** diet, based on the macronutrients profile of the Mediterranean cultures

composing of fresh fruits, vegetables, complex carbohydrate (e.g. whole grain), olive oil, and omega-3 polyunsaturated fat and nuts like almond have been demonstrated by the following studies[26, 27, 28] to reduce the incidence of myocardial infarction, cardiovascular mortality and a decrease in the incidence of metabolic syndrome. Esposito et al [29] also found a reduction of insulin resistance and pro-inflammatory cytokines in patient on the Mediterranean diet group compared to those on the traditional heart-healthy low fat diet.

DIABETES PREVENTION.

Clinical data supports the use of aggressive life style in the treatment of abnormal glucose metabolism to prevent or delay frank diabetes compared to the use of pharmacotherapy. For impaired fasting glycaemia the threshold for treatment is Fasting plasma Glucose (FPG) >110mg/dl (6.1mmol/L) and the treatment goal is FPG <100mg/dl (<5.6mmol/L).[30] Treatment involves use of life style measures as discussed earlier. The Diabetes Prevention Programs(DPP) found a lower incidence of developing diabetes in patients with impair glucose tolerance on life style modification compared to patients who are on pharmacotherapy with Metformin.[31]

BLOOD PRESSURE TREATMENT.

Life style measures are also strongly advocated as mentioned above. Threshold for treatment is based on the presence of risk factors for cardiovascular disease, and since subjects with metabolic syndrome are at increased risk of developing hypertension and other cardiovascular diseases; threshold for treatment are usually lower. When BP <140/90mmhg and no organ damage is present, non-pharmacologic measures are needed to be introduced first.[32] If diabetes is present antihypertensive drugs are introduced at even lower BP $\geq$130/80mmHg and the goal is to maintain BP a<130/80mmHg.[33]Favoured drugs for BP control are those that induce reduction in insulin resistance and subsequent changes in blood glucose and Lipid levels.

Hence, Angiotesin Converting Enzyme Inhibitors (ACEI) and Angiotesin Receptor Blockers (ARB) or Calcium Channel Blockers is preferable over diuretics and β-Blockers as monotherapy if there are no compelling indications for its use. If combination of drugs is required, low range doses of diuretics can be used. Reduction in new onset diabetes rates has been observed during treatment with ACEI, ARBs and even calcium channel blockers.[34,35]

TREATMENT OF DYSLIPIDAEMIA.

The treatment of dyslipidaemia in patients with Mets should be very aggressive because studies of the combine thickness of the intima and media of the carotid artery as a surrogate for atherosclerosis-have shown clearly that atherosclerosis is more prevalent and severe in patients with Mets.[36]Therefore patients with Mets should be treated with the same intensity as patient diagnosed as having coronary artery disease. Life style measures as discussed earlier remain an integral component in the management of dyslipidaemia in patients with Mets.

Low Density Lipoprotein Cholesterol (LDL-C).

Although not used in the definition of Mets, LDL-C has an integral role in the pathogenesis of atherosclerosis. Targeting LDL is a component of any measure to reduce cardiovascular risk. Several clinical trials support the effectiveness of statins in reducing cardiovascular risk in patients with the Mets.[37,38] Similar to the National Cholesterol Educational Program Adult Treatment Panel (NCEP ATP) III guidelines, statin therapy should be considered in all patients with the Mets and an augmented intermediate 10 year cardiovascular risk (10 year risk $\geq$ 6%) if the LDL-C remains above goal after life style intervention. Patient at intermediate risk should have a goal of less than 130mg/dl with an optional goal of less than 100mg, and patient at high risk should have LDL-C lowered to <100mg/dl.

AtherogenicDyslipidaemia.

Although LDL-C has been considered the principal lipoprotein determinant of atherosclerosis and a potent risk factor for cardiovascular disease, more than half of all events occur in patients with "normal" LDL-C levels.[39]Atherogenicdyslipidaemia, which includes fasting and post prandial hypertriglyceridaemia, elevated levels of very low density lipoprotein cholesterol (VLDL-C), low high density lipoprotein cholesterol (HDL-C) and atherogenic small dense LDL-C lowering. Small, dense LDL-C particles contribute to atherosclerosis because it transport cholesterol more efficiently into the vessel wall and have greater susceptibility for oxidation.[39]

Non-High-Density Lipoprotein Cholesterol (Non-HDL).

Epidemiologic studies showed that non HDL-C (measured by Total Cholesterol - HDL-C) predicts cardiovascular disease better than LDL-C especially when Triglycerides are high.[40] Non-HDL-C

estimates offers benefit of being an aggregate of all apoprotein B containing particles. These includes; lipoprotein a, VLDL-C, intermediate density lipoprotein cholesterol (IDL-C) and chylomicron remnants which are thought to contribute to atherosclerosis.

Triglycerides and the Non-HDL-C can be lowered with Fibrates drugs which are agonist of Peroxisome Proliferator Activator Receptor (PPAR) α transcriptional factor. Fibrates also modestly raise HDL-C and increase the size of LDL-C particles via pathways downstream of PPAR-α.[41]

When used in combination with statin therapy, fibrates provide incremental improvements in Triglycerides, LDL-C, apolipoprotein B, and HDL-C levels.[42]The benefits of the combination therapy must be however weighed against the elevated risk of myalgias, myosities and rhabdomyolysis. This risk is reduced by combining statins with fenofibrates which does not affect statins pharmacokinetics, unlike when statins are combined with Gemfibozil.[43]

Omega-3 fatty acids are useful in the treatment of hypertriglyceridaemia in large doses. They have also been shown to provide additional triglycerides reduction in statin treated individuals.[44]

THE EMERGING ROLE OF NUTRACEUTICALS IN THE MANAGEMENT OF METABOLIC SYNDROME.

Dietary supplements that provides nutritional value and have additional health benefits are termed nutraceuticals. Various natural components derived from plants extracts, spices herbs and essential oils have demonstrated benefits in the managements of patients with Mets. Because the benefits of these nutraceuticals are still being evaluated, these therapies are not recommended as replacements for pharmacotherapy currently used in Mets. They can however be use to supplement the other management measures. Some of these nutraceutical include;

CURCUMIN (TUMERIC).

Curcumin is a derivative of turmeric (*curcoma longa*), a spice commonly used in South-East Asia and is increasingly being used in our environment. The active ingredient, diferuloylmethane, has anti-inflammatory and anti-oxidant properties. Curcumin has been shown to inhibit nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κβ) activation which leads to reduction in the expression of pro-inflammatory cytokines, downregulate Tumour necrosis factor Alpha (TNF-α) expression, and suppress expression of plasminogen activator inhibitor type 1.[45-47] Curcumin also inhibits the Wnt/β-catenin, which is involve in the pathway for development of obesity and activate peroxisome activator receptor gamma in hepatic stellate cells[48] which improves insulin resistance. Curcumin is also known to interrupt leptin signaling, thus increasing adiponectin expressions. Adequate adiponectin levels improve insulin resistance, thus improving glucose intolerance. They also have anti-inflammatory and antithrombogenic properties. The anti-inflammatory, anti-thrombogenic, insulin sensitizing and the negative effect on obesity will impact positively on all components of Mets.

GARLIC.

Garlic (*Allium Sativum*), a commonly used condiment, is found to have anti-oxidant and anti-thrombotic properties. It was reported by Padiya and colleagues to improve insulin sensitivity in fructose fed rats and may have similar effect in humans.[49] While it was reported to lower total cholesterol and triglycerides by Reinhart and colleagues in a meta-analysis of 29 randomised placebo-controlled trials comparing effect of garlic on lipid profiles[50] Gomez-Arbaleaz and colleagues demonstrated improvement in adiponectin levels with the use of garlic in people with Mets.[51] The anti-inflammatory effect comes from the organo-sulfur component of garlic derivatives. They compound have an anti-oxidant action due to its thiol group that fights ROS-mediated inflammation. The improve insulin sensitivity property, increasing adiponectin levels, which also improves insulin sensitivity and glucose tolerance as well as its anti-inflammatory properties makes its used very important in treating and preventing the features of Mets.

CINNAMON.

Cinnamon (*cinamomumVerum*) derived from tree bark and used as spice and flavouring agent, is used frequently in Chinese and Indian traditional medicines. Cinnamon extracts and polyphenol have anti-thrombotic, insulin sensitizing, lipid lowering, anti-inflammatory and anti-oxidants properties which are beneficial in the management of Mets. Cinnamon polyphenols have insulin-like activity and several studies have reported improvement in glycaemic control and lipid levels. In a randomized placebo controlled trial, Ziegen Fuss and Colleagues demonstrated that the use of an aqueous extract of

cinnamon was associated with improvement in fasting plasma glucose, blood pressure and body fat composition in people with Mets.[52] All the mechanistic pathways for this benefit in Mets is yet to be elucidated, however, some studies in mouse models indicate that cinnamon extracts can regulate adipocyte gene expression to improve glucose transporter(GLUT 4) and insulin signaling.[53]

BERBERINE.

Is an alkaloid from the plant *Rhizomacoptidis* and is used in China for its anti-microbial properties. It is also known to have anti-diabetic properties. Berberine acts through up-regulation of genes involve in energy utilization and down regulation of genes involve in lipogenesis.[54] It has insulin sensitivity action similar to metformin and thiazolidinediones, mediated by adenosine monophosphate associated protein kinase activation in adipocytes.[55] Studies in human with Mets have reported a reduction in waist circumference, triglycerides levels and systolic blood pressure especially in women.[56]

NEEM.

AzadirachtaIndica, also known as Neem or Nim tree, is known to have medicinal value. Neem extract is associated with an increase glucose tolerance by reducing intestinal and pancreatic glucosidase activity, which helps improve post prandial hyperglycaemia. Increase glucose 6 phosphate-dehydrogenase activities which increase glucose utilization has also been previously observed.[57] Furthermore, neem extracts can also help with regeneration of pancreatic β-cells, improving insulin secretion.

BERGAMOT OIL

Bergamot essential oil is a citrus essential oil, derived from citrus bergamia and has anti-cancer, anti-inflammatory, antimicrobial and anti-anxiety properties. In the setting of Mets, the anti-oxidant effect of bergamot oil is also significant. Mollace and colleague studied the effect of the anti-oxidant component of bergamot oil on LOX-1 expression and free radical generation on carotid injury in rat.[58] It was reported in their study to be associated with smooth muscle cell proliferation, neointima formation, ROS generation and increase LOX 1 expression and free radical generation. Pre-treatment of these rats with bergamot essential oil decreased neointima formation, LOX-1 formation and free radical formation reducing the degree of stenosis.[58]Other neutral compounds such as procyanins, 6-shogoal procyanins, and flavanoids have also been associated anti-oxidants properties and may be beneficial for the management of Mets.

RESVERATROL.

Resveratrol (3,5,4-trihydoxystilbene) is a polyphenol present in plants such as grapes, nuts, and derivatives such as wine. It is a regulator of the Sirtuin pathway, which regulates several cellular functions related to metabolism, oxidation and aging. It has favourable effects on cellular energy homeostasis, such as decreasing adipogenesis and increasing lipolysis through multiple mechanisms. It also inhibits cyclo-oxygenase with resultant anti-oxidant effects[59]. The use of Resveratrol in Mets has been studied in animal models as well as humans. Clinical studies in patients with insulin resistance and non-alcoholic fatty liver disease has shown promising results.[60] Its use has been shown to improve insulin sensitivity, glucose tolerance and overall weight and body mass index in patients with Mets.[61]

QUERCETIN.

Quercetin, a plant derived from flavanoid found in vegetable and fruits such as onions, berries, and teas have been reported to have anti-oxidant and anti-inflammatory metabolic effects. Quercetin acts via the mitochondrian pathways and involve in adipokinesis and lipolysis that affect the development of obesity.[62] Rivera and colleague studied the effect of quercetin in obese zucker rats. The study found that rats that received quercetin had lower blood pressure, cholesterol and lower insulin resistance compared to rats not on quercetin. Higher doses of quercetin produced anti-inflammatory effect in visceral adipose tissue.[63]Pfeufer and colleague studied the metabolic implications of quercetin in humans specifically men with apolipoprotein- E genotype, and discovered that quercetin improves metabolic parameters such as waist circumference, post-prandial glucose, lipids, but also increase inflammatory markers such as TNF-α[64].

OMEGA-3-FATTY ACIDS.

Omega-3-long chain polyunsaturated fatty acids (PUFA) have been extensively studied in multiple epidemiologic studies, specifically in relation to their protective role in Mets related diseases.[65] Two specific PUFAs, eicosapentaenoic acid and

docosahexaenoic acid, found abundantly in fish oil have received wide attention, leading to major societal preventive recommendations.[66] Omega-3-polyunsaturated fatty acids (PUFAs) have been shown to inhibit lipogenesis and induce fatty acid oxidation in liver and adipose tissue via regulation of key transcriptional factors such as peroxisome activated receptors and sterol regulatory element binding protein.[67-70] Despite favourable impact on various components of Mets, long term data on prevention of cardiovascular end points with the use of PUFAs have not been confirmed. However strong pathophysiological correlate of underlying mechanism are encouraging and need further studies.

SULFORAPHANE.

Sulforaphane, a phytochemical is extracted from vegetables of the brassica family such as broccoli. It has been recently shown to have potential beneficial effects in Mets, due to its anti-oxidants and anti-inflammatory properties. Sulforaphane activates nuclear factor erythroid 2 related factors 2, an anti-oxidant transcription factor. Several animal studies have demonstrated a protective role of sulforaphane against various disorders such as hypertension, hyperlipidaemia and diabetes, all key components of the Mets.[71-72]

CONCLUSION.

Diagnosis of metabolic syndrome should be routinely carried out by clinicians when evaluating patients for any of its component. Early diagnosis and prompt initiation of preventive measures (counseling, dietary measures and graded increase in physical activity) will go a long way in retarding progression and/or treatment of clustered components. The role of Nutraceuticals is increasingly becoming vital in management as they target specific key pathophysiologic mechanisms involve in the development of the syndrome. We advocate for further research in our environment on their effectiveness in the management of Mets.

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