Clinical Update

Metabolic syndrome

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Introduction

Metabolic syndrome is a multiplex risk factor that arises from insulin resistance accompanying abnormal adipose deposition and function. Other names given to this syndrome includes Syndrome X, Insulin resistance syndrome, deadly quartet, and Reaven's syndrome[1]. Varieties of cardiovascular risk factors areassociated with this syndrome.Overweight and central obesity are the key features. It is said to be a syndrome associated with sedentary life style. It is a very good predictor of cardiovascular events and associated mortality. The prevalence increases with age. Approximately 75% of type 2 diabetes mellitus(DM) or Impaired glucose tolerance (IGT) suffer from metabolic syndrome; 50% of coronary artery disease(CAD) patients have metabolic syndrome; about 1/3rd of metabolic syndrome patients have premature CAD[2].

Evaluation of metabolic syndrome

Evaluation of metabolic syndrome includes detailed history, physical examination and relevant investigations. Increased hunger, thirst, or urination may accompany hyperglycemia. Chest pain or shortness of breath should be enquired to rule out cardiovascular disease.Patient's dietary habits and exercise routines should be recorded. Social history is important for identifying additional risks, such as tobacco use,ethanol abuse etc.A family history should be obtained because genetics may play an important role in metabolic syndrome.Menstrual irregularities may be associated with polycystic ovarian syndrome and should be elucidated in the history.

Physical examination is important as 2 out of 5 criteria to define metabolic syndrome are physical parameters i.e. waist circumference and blood pressure. In addition signs for insulin resistance like acanthosis nigricans, and skin tags should be examined. Signs of endocrinopathy like hirsutism,acne, striaeetc to be looked for.Complications of undiagnosed long standing diabetes like peripheral neuropathy and retinopathy also may be found. Signs of severe dyslipidemia include xanthomas or xanthelasmas also can be found in certain patients. Arterial bruits may portend a higher risk of cardiovascular complications.

Waist circumference is measured by locating the top of right iliac crest and placing a tape horizontal to the floor.Ensure tape is snug and not to compress the skin and record the measurement in expiration. The cut off values of waist circumference for different ethnic groups is given in table 1.

Diagnostic criteria is defined for metabolic syndrome by various associations and organizations. Definition given by International Diabetic Federation (IDF) and NCEP ATP III is more practical quite similar to each other. (Table 2)

Table 1

Country / ethnic group	Waist circumference value	
	Male	Female
Europids*	≥94cm	≥80cm
South Asians**	≥90cm	≥80cm
Chinese	≥90cm	≥80cm
Japanese	≥85cm	≥90cm
Ethnic south and Central Americans	Use south asian recommendations until more specific data are available	
Sub – Saharan Africans	Use European data until more specific data are available	
Eastern Meditterranean and Middle East (Arab) populations	Use European data until more specific data are available	

*In the USA, the ATP 111 values are likely to continue to be used for clinical purposes, **Based on Chinese Malay and Asian Indians populations

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Table 2

Criterion	NCEP ATP 111(3 or more criteria)	IDF (abdominal obesity plus 2 or more other criteria)
Abdominal obesity Men Women	 >40inches >35 inches	 >37inches >31.5inches
Hypertriglyceridemia	≥150mg/dl	≥150mg/dl
Low HDL Men Women	 <40mg/dl <50mg/dl	 <40mg/dl <50mg/dl
Hypertension	≥130/85 mmHg or on antihyper-tensive medication	≥130/85 mmHg
Impaired fasting glucose or diabetes	≥110 mg/dl* OR taking insulin or hypoglycaemic medication	≥100 mg/dl

NCEP ATP 111: National Cholesterol Education Program Adult Treatment Panel 111, IDF : International diabetes federation * recently lowered to 100mg/dl

Pathophysiology

Pathophysiology of metabolic syndrome is complex. Visceral adipose tissue is particularly incriminated in the genesis of insulin resistance by production of adipocytokines. Adipocytes produce an excess of inflammatory factors, Cytokines: IL-6, IL-10 and TNF-α and Chemokines: M1P1a, MCP1. These mediators block the intracellular insulinsignaling pathways at different steps[1]. Obesity is associated with an inhibition of adiponectin production. Increase of adipose tissue in obese individuals leads to an imbalance in the production and secretion of anti-inflammatory and pro-inflammatory factors, and shifts the balance in favour of pro-inflammatory factors. These effects lead to insulin resistance and as a consequence, an anarchic discharge of free fatty acids (FFA) by adipocytes occurs. These FFA exerts a "toxic" effect at different levels, in particular hepatic and muscular, leading to a certain number of clinical and metabolic abnormalities, characteristic of the metabolic syndrome[3].

Laboratory investigations

Further investigations in a patient with family history of CAD include HDL-C and LDL-C, lipoprotein (a),apolipoprotein-B100 ,high-sensitivity C-reactive protein (hsCRP), 5homocysteine ,fractionated LDL-C. Increased thyroid stimulating hormone (TSH) has been linked to a higher prevalence of metabolic syndrome. Hyperuricemia appears to be much more common in patients with metabolic syndrome than in the general population, and this is attributed to the inflammatory effects of metabolic syndrome[4].

Imaging is not routinely indicated in the diagnosis of metabolic syndrome. However to evaluate many complications of the syndrome, in particular cardiovascular diseases, certain imaging modalities may be warranted. Electrocardiography (rest/stress ECG), ultrasonography (rest/stress echocardiography), stress single-photon emission computed tomography (SPECT) and cardiac positron emission tomography (PET) etc[5].

Exacerbating factors of metabolic syndrome also should be evaluated. Sleep-related breathing disorders, such as obstructive sleep apnea, are becoming increasingly relevant and novel risk factors for metabolic syndrome. The difficulty in clarifying the associations between obstructive sleep apnea and metabolic syndrome lie in part with the confounding effect of obesity.Nevertheless, patients reporting significant sleep disturbances, snoring, possible pauses, and/or daytime drowsiness may benefit by a polysomnography[6].

Treatment principles

Metabolic syndrome is closely linked to overweight, obesity and inactivity. So the principles of treatment include dietary modifications, exercise program and pharmacologicalinterventions. These interventions can delay the progression of metabolic syndrome to diabetes mellitus[7].

Lifestyle change and weight loss are considered to be the most important initial steps in treating metabolic syndrome. Studies comparing ethnically similar populations exposed to different dietary environments suggested that Westernized diets are strongly associated with a higher risk of developing metabolic syndrome. Diets rich in dairy, fish, and cereal grains may be associated with a lower risk of developing metabolic syndrome[8].

Approximately 500 kcal of restriction daily, equates to weight reduction of 1 lb per week.Diets restricted in carbohydrate typically provide a rapid initial weight loss. Adherence to the diet is more important than which diet is chosen. A high-quality diet i.e., enriched in fruits, vegetables, whole grains, lean poultry, and fish should be encouraged to provide the maximum overall health benefit[9].

Gradual increases in physical activity should be encouraged to enhance adherence and avoid injury. Some high-risk patients should undergo formal cardiovascular evaluation before initiating an exercise program. Physical activity could be formal exercise such as jogging, swimming, tennis or routine activities, such as gardening, walking, cycling and housecleaning. Usually 60–90 min of daily activity (minimum of 30 min) is recommended.

Medications

Metformin is the drug of choice, typically used at the beginning of hyperglycemia treatment in patients with metabolic syndrome(HbA1C 5.6-6.5). Metformin may help to reverse the patho-physiologic changes of metabolic syndrome. Other insulin sensitizers include peroxisome proliferator-activated receptor agonists such as fibrates eg: fenofibrate(available in strengths 200mg,67mg), and thiazolidinedioneseg: pioglitazone(15-45 mg). Each of which may produce favorable metabolic alterations as single agents in patients with metabolic syndrome[10].

Management of elevated LDL-C includes consideration of all statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) Eg simvastatin, atorvastatin, rosuvastatin[11]. Niacin may aid in the management of reduced HDL-C and in the treatment of elevated triglycerides. Angiotensin converting enzyme inhibitors(ACEI) prevent the conversion of angiotensin I to angiotensin II- a potent vasoconstrictor and lowers aldosterone secretion. ACEI are effective and well-tolerated drugs with no adverse effects on plasma lipid levels or glucose tolerance. They prevent the progression of diabetic nephropathy and other forms of glomerulopathies . But ACEI appear to be less effective in black patients than in white patients. ACEI are contraindicated in pregnancy. Cough and angioedema are less common with newer members of this class than with captopril[12]. Serum potassium and serum creatinine concentrations should be monitored for the development of hyperkalemia and azotemia. Examples of agents from this class include captopril, lisinopril, and enalapril. In patients not tolerant to ACEI, Angiotensin receptor blockers (ARB) are the drug of choice. Examples of this group include losartan, candersartan, valsartan, telmisartan etc[13].

In summary metabolic syndrome is a disease due to adaptation of unhealthy eating pattern and sedentary life style. Intense lifestyle changes in eating pattern and active non sedentary life style are the keys of prevention and treatment.

List of Abbreviations

Impaired glucose tolerance (IGT) coronary artery disease(CAD)diabetes mellitus(DM), International Diabetic Federation (IDF), NCEP ATP 111: National Cholesterol Education Program Adult Treatment Panel 111, free fatty acids (FFA),high-sensitivity C-reactive protein (hsCRP),thyroid stimulating hormone (TSH)Angiotensin converting enzyme inhibitors(ACEI),Angiotensin receptor blockers(ARB)

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