OBESITY- THE METABOLIC SYNDROME

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Abstracts:.Obesity is the result of excessive intake of calories than energy expenditure. Changes in global food system which is producing more processed, affordable and effectively marketed food is driving people towards obesity. There is a simultaneous increase in obesity in almost all countries, but still there is a wide variation in obesity prevalence between populations. Interactions between environmental and genetic factors including genetic make up explains variability. Obesity leads to other metabolic complications including dyslipidemia, hypertension, insulin resistance and cardio vascular disease collectively called as Metabolic syndrome. So there is urgency for evidence creating policy action with a priority on reduction of supply-side drivers simultaneously creating an awareness to maintain body weight.

Key words: obesity, metabolic syndrome, insulin resistance, dyslipidemia, cardiovascular disease.

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Introduction:obesity can be defined as an excess of body fat. The prevalence of obesity in children and adults in the united states and in many other industrialized countries is rapidly increasing, rising by more than 30% over the past decade. The worldwatch institute has estimated that the number of overweight people in the world is now as great as the number of underfed. Obesity is a problem because of its associated complications leading to metabolic syndrome. The metabolic syndrome is a condition characterized by a special constellation of reversible major risk factors for cardiovascular disease and type 2 diabetes. The main diagnostic components of metabolic syndrome are reduced HDL-cholesterol, raised triglycerides, hypertension ,hyperglycemia and insulin resistance all of which are related to obesity, especially accumulation of abdominal fat and a large waist circumference. Metabolic syndrome now affects 30–40% of people by age 65, driven mainly by adult weight gain, and by a genetic or epigenetic predisposition to intra-abdominal/ectopic fat accumulation related to poor intra-uterine growth. The relationship of obesity to major and emerging risk factors varies, depending on the genetic and acquired characteristics of individuals. In this article we will first discussing the various characteristics of obesity along with thecorelation of obesity to the metabolic syndrome and finally various measures which can be taken to control this global health problem.

Categories of obesity:

A reliable and convenient indicator of body fat is the body mass index(BMI), which is body weight(in kilograms) divided by the square of height (in metres). In clinical terms, a BMI between 25 and 29.9 kg/m^2 is called overweight and a BMI greater than 30kg/$m^2$is called obese. BMI is not a direct measure of adiposity. A better way to define obesity is to actually measure the percentage of total body fat[1] . Obesity is usually defined as 25percent or greater total body fat in men and 35percent or greater in women. Body fat can be estimated with various methods like skin-fold thickness, bioelectrical impedance and underwater weighing, but rarely used because of cost and inconvenience. Clinically obesity is measured by measuring waist circumference.In the United States, abdominal obesity is defined
as a waist circumference in men of 102 cm or more and in women of 88 cm or more[1]. Obesity results from greater energy intake than energy expenditure. Excess of energy intake in the form of food is mainly stored as fat. For each 9.3 calories of excess energy, one gram of fat is stored in the body. Fat is mainly stored in adipocytes in subcutaneous tissue and in the intraperitoneal(visceral) cavity. Obesity can be hypertrophic i.e. increase in size of the adipocytes or it can be hyperplastic i.e. increase in the number of the adipocytes. Some investigators[2]believe that excess of visceral fat (visceral obesity) is more strongly related to metabolic risk factors even

though subcutaneous adipose tissue is a much larger compartment than visceral fat.

Parameters of Metabolic syndrome:

There are six definitions of metabolic syndrome given by world Health Organization (WHO)[3], the European Group for the Study of Insulin Resistance (EGIR) , the National Cholesterol Education Programme Adult Treatment Panel III (NCEPATPIII)[4], the American Association of Clinical Endocrinologists (AACE)[3],the International Diabetes Federation (IDF) and the American Heart Association/National Heart,Lung and Blood Institute (AHA/NHLBI) . The main diagnostic features are summarised in Table 1. The metabolic syndrome is a constellation of metabolic risk factors that consist of the following[4]:

• Atherogenicdyslipidemia [serum elevations of triglycerides, apolipoprotein B (apo B), and small low-density lipoprotein (LDL) particles plus low high-density lipoprotein (HDL) cholesterol]

- Elevated blood pressure

• Elevated glucose associated with insulin resistance

• Prothrombotic state

• Proinflammatory state

Recently the National Cholesterol Education Program Adult Treatment Panel III report[4]proposed a simple scheme for the routinediagnosis of metabolic syndrome. According to this scheme,a diagnosis of metabolic syndrome can be made if a person has three of the following five features:

• Increased waist circumference (>102 cm in men and 88 cm in women)

• Elevated triglycerides (>150 mg/dl)

• Reduced HDL cholesterol (<40 mg/dl in men and 50mg/dl in women)

• Elevated blood pressure (>130/85 mm Hg or on treatment for hypertension)

• Elevated glucose (>100 mg/dl)

Obesity and Insulin resistance:

Insulin has important physiological effects on the endothelium, increasing NO availability and stimulating vasodilatation, and is proposed to act in anti-atherogenic manner overall [5]. Insulin resistant states are associated with impaired vascular response to insulin and endothelial dysfunction[6]. Obesity is associated with insulin resistance[7]. Insulin resistance is also associated with increased cardiovascular risk, with meta-analyses demonstrating a statistically positive correlation between fasting plasma insulin and the risk of cardiovascular death independent of conventional risk factors (in a non-diabetic study group)[7].

Some studies suggest that there are fewer insulin receptors especially in the skeletal muscle, liver and adipose tissue in obese than in lean subjects. However, most of the insulin resistance appears to be caused by abnormalities of the signaling pathways that link receptor activation with multiple cellular effects. Impaired insulin signaling appears to be closely related to toxic effects of lipid accumulation in tissues such as skeletal muscle and liver due to obesity[8].

Obesity and increased waist circumference:

Few studies suggest that patients of normal weight can also be insulin resistant[9],that is why in the definition of the metabolic syndrome, waist circumference is included. A distinction between a large waist due to increases in subcutaneous adipose tissue versus visceral fat can be made with computed tomography or magnetic resonance imaging[10] . With increases in intra-abdominal or visceral adipose tissue, flux of adipose tissue-derived free fatty acids to the liver through the splanchnic circulation increases, whereas increases in abdominal subcutaneous fat releases products of lipolysis into the systemic circulation and avoid more direct effects on hepatic metabolism (i.e, glucose production, lipid synthesis, and secretion of prothrombotic proteins such as fibrinogen and plasminogen activator inhibitor1[11]. Despite these potential differences in mechanisms related to excessive abdominal adipose tissue distribution, the clinical diagnosis of the metabolic syndrome does not distinguish between increases in subcutaneous and visceral fat.

Inflammatory cytokines:

Chronic increase in the serum level of several pro-inflammatory cytokines can be observed in obese patients, such as tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), together with high-sensitive C reactive protein (hs-CRP), a marker of chronic, low grade inflammation[12]. Based on some recent research data, hsCRP has been proved to be a more sensitive marker associated with obesity compared to IL-6 and TNF-α[13]. IL-6, according to a recent study, has been shown to inhibit subcutaneous adipogenesis. Leptin, responsible for regulation of food intake, is also an immune

modulator; it exhibits pro-inflammatory and pro-aggregating effects. Based on evidence obtained from several studies, leptin stimulates the expression of pro-inflammatory cytokines in immune cells (polymorphonuclear neutrophils - PMN, T lymphocytes, monocytes, macrophages), thus contributing to the low-grade inflammation in the adipose tissue. The effect of leptin on PMN is by induction of TNF-α[14]. Leptin also decreases the NO (nitric oxide) availability and thus contributes to the development of endothelial dysfunction, which plays a major role in the development of atherogenesis. A negative correlation was found by some researchers between leptin and adiponectin in human subjects[15].

Hypertension:

Prevalence of high blood pressure is more in Obese persons as compared to lean persons. Hypertension is a strong risk factor for cardiovascular disease (CVD)[16]. Other known complications of hypertension are coronary heart disease, stroke, left ventricular hypertrophy, heart failure, and chronic renal failure. Yet some studies[17,18] report that the elevated blood pressure accompanying obesity is less likely to produce CVD than when it occurs in lean persons. The implication is that obesity-induced hypertension is not particularly dangerous to the cardiovascular system. This concept generally is not accepted by the hypertension community, nor was it supported by the Framingham Heart Study[19].

Dyslipidemia:

The hallmark of dyslipidemia in obesity is hypertriglyceridemia in part due to increased free fatty acid (FFA) fluxes to the liver, which leads to hepatic accumulation of triglycerides (TG). This leads to an increased hepatic synthesis of large very low density lipoproteins (VLDL) 1, which hampers the lipolysis of chylomicrons due to competition mainly at the level of lipoprotein lipase (LPL) with increased remnant TG being transported to the liver. Lipolysis is further impaired in obesity by reduced mRNA expression levels of LPL in adipose tissue and reduced LPL activity in skeletal muscle. Hypertriglyceridemia further induces an increased exchange of cholesterolesters (CE) and TG between VLDL and HDL and low density lipoproteins (LDL) by cholesterylester-transfer-protein (CETP). This leads to decreased HDL-C concentrations and a reduction in TG content in LDL. In addition, hepatic lipase (HL) removes TG and phospholipids from LDL for the final formation of TG-depleted small dense LDL[20].

Glucose intolerance:

The defects in insulin action in glucose metabolism include deficiencies in the ability of the hormone to suppress glucose production by the liver and kidney, and to mediate glucose uptake and metabolism in insulin sensitive tissues (i.e, muscle and adipose tissue). The relation between impaired fasting glucose or impaired glucose tolerance and insulin resistance is well supported by human, non-human primate, and rodent studies. To compensate for defects in insulin action, insulin secretion and/or clearance must be modified to sustain euglycaemia. If this compensation fails, defects in insulin secretion predominate. Insulin resistance in pancreatic islet cells implies that signals that generate glucose-dependent insulin secretion have been adversely modified, and fatty acids are prime candidates. Although free fatty acids can stimulate insulin secretion, increasing and prolonged exposure to excessive concentrations results in falls in insulin secretion[21]. The mechanism for this alteration has been attributed to lipotoxicity through several potential different mechanisms[22,23].

Abdominal obesity and cardiovascular disease:

Circulating concentrations of plasminogen activator inhibitor-1, angiotensin II, C-reactive protein (CRP), fibrinogen, and TNF-α are all related to BMI[24]. It has been estimated that in vivo, ≈30% of the total circulating concentrations of IL-6 originate from adipose tissue[25].This is of importance because IL-6 modulates CRP production in the liver, and CRP may be a marker of a chronic inflammatory state that can trigger acute coronary syndrome[26].Obesity results in a pro-inflammatory state with increased visceral fat deposits and alteration of adipokine secretion, with concomitant insulin resistance. In the vasculature, the cumulative effects of these changes result in alterations of NO/superoxide balance, resulting in endothelial dysfunction and increased cardiovascular risk through atheroma formation.

Excess body weight causes increased metabolic demand which causes increase in blood volume leading to increased cardiac output[27].Thus, at any given level of activity, the cardiac workload is greater for obese subjects. Obese subjects have higher cardiac output and a lower total peripheral resistance than do lean individuals. The increased cardiac output is due to increased stroke volume mainly because heart rate increases little if at all[28]. Also, in obesity, the Frank-Starling curve is shifted to the left because of incremental increases in left ventricular filling pressure and volume, which over time may produce chamber dilation. Ventricular chamber dilation may then lead to increased wall stress, which leads to left ventricular hypertrophy.

Management of obesity

The first step in the management of obesity is that energy expenditure should be more than the energy intake**.** Reduction of fatty tissue through exercise is well characterised to reduce the incidence of type 2 diabetes[29]. The risk of CVD associated with obesity can be reduced with the increase in physical activity[30]. Weight loss has been shown to improve endothelial dysfunction[31], with a loss of 5-10% of body weight conveying benefit .Drugs like orlistat and sibutramine have been shown to reduce visceral obesity and improve metabolic parameters in obesity. Liposuction,Jejunoileal bypass and Gastric Bypass Surgery/ Gastric Banding Surgery has been shown to significantly reduce abdominal adiposity and improve metabolic profile, providing another therapeutic option in morbidly obese patients[32].

The metabolic syndrome shows genetic susceptibility, but acquired underlying risk factors like being overweight or obese, physical inactivity, and an atherogenic diet—commonly elicit clinical manifestations. So management should focus on the prevention of risk factors along with Clinical management of the signs and symptoms.

Conclusion:

The association between abdominal obesity, metabolic syndrome and CVD is well characterised. Our understanding of the connection between obesity and vascular disease is complicated by a plethora of possibilities. Obesity acts on so many metabolic pathways, producing so many potential risk factors, that it is virtually impossible to differentiate between the more important and less important. This complexity provides a great challenge for basic and clinical research. It also raises the possibility for new goals of therapy for the metabolic syndrome. With this said, the basic challenge is how to intervene at the public health level to reduce the high prevalence of obesity in the general population. This approach offers the greatest possibility for reducing the cardiovascular risk that accompanies obesity.

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CRITERIA	WHO (1999)	EGIR (1999)	NCEP ATP III (2001)	IDF (2005)
REQUIREMENT	Diabetes, impaired fasting plasma glucose, glucose intolerance or insulin resistance plus two or more of the following:	Hyperinsulinaemia (fasting insulin values above quartile for the non-diabetic population) plus with two or more of the following:	Three or more of the following:	Central obesity (ethic specific values, or BMI ≥ 30 kg/m^2) plus two or more of the following:
CENTRAL OBESITY	BMI > 30 kg/m^2 or waist-to-hip ratio > 0.90 in male or > 0.85 in female	Waist circumference ≥ 94 cm in male or ≥ 80 cm in female	Waist circumference ≥ 102 cm in male or ≥ 88 cm in female	
BLOOD PRESSURE	≥ 140/90 mmHg	≥ 140/90 mmHg) or treatment for hypertension	≥ 135/85 mmHg	≥ 135/85 mmHg or treatment for hypertension
TRIGLYCERIDE	≥ 1.7 mmol/L (150 mg/dL)	≥ 2.0 mmol/L (180 mg/dL) or treatment for dyslipidemia	≥ 1.7 mmol/L (150 mg/dL)	≥ 1.7 mmol/L (150 mg/dL) or treatment for dyslipidemia
HDL-C	< 0.9 mmol/L (35 mg/dL) in male or < 1.0 mmol/L (39 mg/dL) in female	< 1.0 mmol/L (40 mg/dL) or treatment for dyslipidemia	< 1.0 mmol/L (40 mg/dL) in male or < 1.3 mmol/L (50 mg/dL) in female	< 1.0 mmol/L (40 mg/dL) in male or < 1.3 mmol/L (50 mg/dL) in female or treatment for dyslipidemia
FASTING PLASMA GLUCOSE		≥ 6.1 mmol/L (110 mg/dL)	≥ 6.1 mmol/L (110 mg/dL)	≥ 5.6 mmol/L (100 mg/dL) or previously diagnosed Type 2 diabetes
MICROALBUMINURIA	Urinary albumin excretion rate ≥ 50 μg/min or albumin: creatinine ratio ≥ 30 mg/g	-	-	-

BMI: body mass index, EGIR: European Group for the Study of Insulin Resistance, HDL-C: High-density lipoprotein cholesterol, IDF: International Diabetes Federation, NCEP ATPIII: National Cholesterol Education Program Adult Treatment Panel III, WHO: World Health Organization

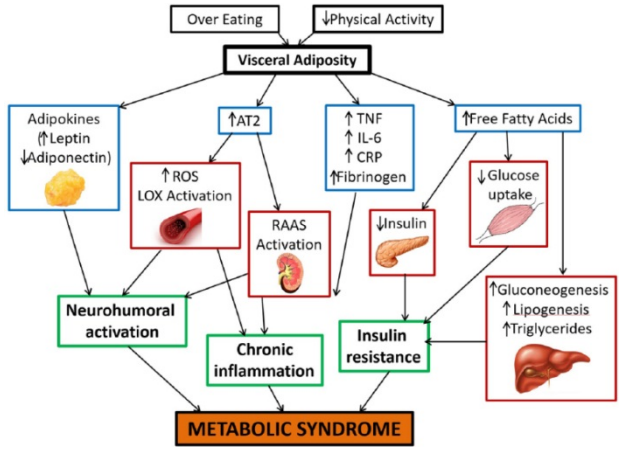

figure 1: Pathophysiology of The Metabolic Syndrome

Table1: criteria for metabolic syndrome