OBESITY AND ASSOCIATED DISORDERS

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Summary

The obesity epidemic has been recognized by the World Health Organization (WHO) as one of the top 10 global health problems. Worldwide, more than one billion adults are overweight and over 300 million are obese. The majority of developed countries, including the United States, Canada and England are experiencing dramatic increases in obesity. Obesity is a condition associated with the accumulation of excessive body fat resulting from chronic imbalance of energy whereby the intake of energy exceeds expenditure. The excess body fat predisposes an obese individual to chronic diseases, such as coronary heart disease, type 2 diabetes and diseases of the gall bladder and cancer. Obesity is associated with an increased risk of morbidity and mortality as well as reduced life expectancy. Health service use and medical costs associated with obesity and related diseases have risen dramatically and are expected to continue to rise. In the preview of the above statement, we will try to put emphasis on the co-morbidities associated with the obesity.

Key words: Obesity, Diabetes, Hypertension, Cancer, Sleep apnea.

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OBESITY

Obesity is multifactorial, chronic disorder that has become a global epidemic [1]. Despite public health education and initiatives, its prevalence continues to increase, with >30% of adults in United States being obese and >60% of adults being overweight or obese [2]. The etiology is multifactorial, with genetic, environmental, socioeconomic, behavioral, and psychological influences and with an increase in related morbidity and mortality [3]. Obesity is a fundamental disorder of energy imbalance in which excessive energy stores accumulate with low energy expenditure [4] and excess fat is accumulated in peripheral tissues, including the white adipose tissue, muscle and liver [5]. Obesity is defined as an increase in body mass index (BMI), which is expressed as weight in kilograms divided by the height in meters squared (kg/m^2) and It is the most widely used measure of obesity [6]. Obesity is generally associated with an increased risk of excessive fat related metabolic diseases (EFRMD) and chronic diseases, including type 2 diabetes mellitus, hypertension and dyslipidemia [7]. In addition, excess weight is generally linked to the onset of several major chronic diseases such as cardiovascular diseases, and cancers. There is also strong evidence that obesity is associated with increased morbidity and mortality. Obesity decreases life expectancy with almost seven years [8] and obese persons have an impaired quality of life [9]. Costs of obesity in various countries have been estimated at 4 to 8% of total health care costs [10, 11].

CLASSIFICATION OF OBESITY

In the classification of obesity, Body Mass Index (BMI) is used to classify obesity. This index is calculated as the body weight (kg) divided by the stature (height (m)) squared (wt/ht^2), or body weight (lb) x 703 divided by the height (stature) squared (Wt (lb) x 703/(Ht (in))2. BMI correlates well with body fat, and is relatively unaffected by height. This is the first step in assessing risk. Current classifications of obesity are based on BMI and waist circumference.

This classification system of obesity by BMI was developed by the World Health Organization "Obesity Task Force" and has been adopted by the Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, a group assembled by the National Heart, Lung, and Blood Institute of the National Institutes of Health [12]. Waist circumference is another important measure of obesity risk. A high-risk waist circumference is accepted to be 80 cm or greater for women and 94 cm or greater for men. Waist circumference is a practical indicator of visceral abdominal fat.

Table: 1 Classification of overweight and obesity as recommended by the NHLBI guidelines.

	BMI (kg/m^2)	Obesity CLASS	Disease risk[a] relative to normal weight and waist circumference Men<102 cm >102 cm Women<88 cm >88 cm	
Underweight	<18.5		-	-
Normal[b]	18.5 – 24.9		-	-
Overweight	25.0-29.9		Increased	High
Obesity	30.0 – 34.9	I	High	Very High
	35.0-39.9	II	Very High	Very High
Extreme obesity	≥40.0	III	Extremely high	Extremely high

[a] Disease risk for type 2 diabetes, hypertension and CVD.

[b] increased waist can also be a marker for increased risk in normal-weight individuals.

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The pathology of obesity produces the myriad of health related problems. These health-related problems can be attributed to either the increased mass of fat or the increased release of peptides from enlarged fat cells. CVD, Cardiovacular disease; GB, gallbladder, NAFLD; non-alcholic fatty liver disease.

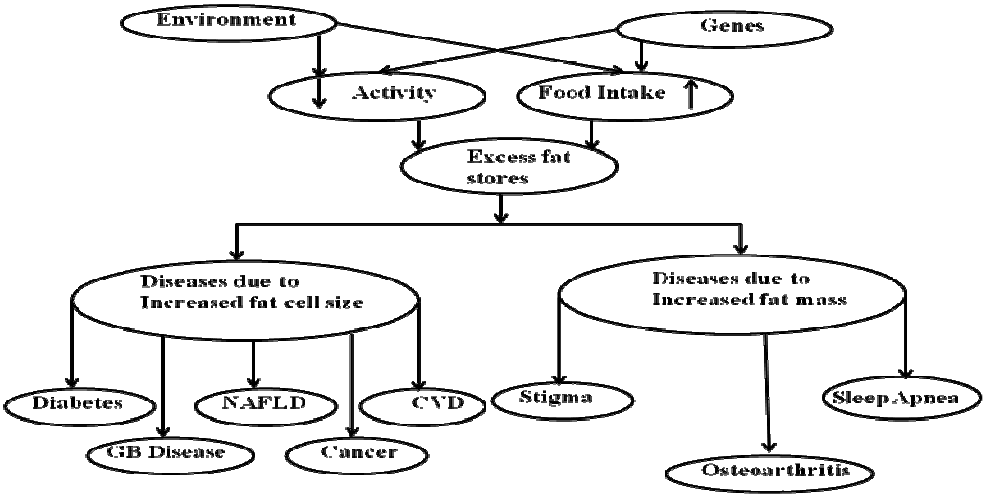

Figure: 1 Obesity and associated disorderes

OBESITY AND DIABETES MELLITUS

Obesity leads to insulin resistance via various inter-related mechanisms. Firstly, insulin signalling and glucose homeostasis is blunted by obesity-induced intracellular fat deposition [13]. Infiltration of fat into the pancreatic islet cells amplifies the age-related decline in the islets' capacity to maintain the increased insulin output and glucose intolerance and the premature Type 2 DM readily develops [14]. Obesity-related modifications in adipocytes function induce a paracrine suppressive effect on adiponectin expression, a powerful insulin sensitizer, down regulated in obesity [13, 15]. In addition, up-regulation of proinflammatory adipokines in obesity like interleukin (IL-1 and 6) and tumor necrosis factor-alpha (TNF-α), also contributes to blunted insulin-signaling in peripheral tissues.

Obese individuals have decreased number of insulin receptor expression and decreased tyrosine kinase activity in skeletal muscle cells [16] and adipocytes [17]. Both insulin receptor expression and its tyrosine kinase activities are restored by weight loss, which also improves insulin sensitivity [18]. Moreover, it is well established that there are sex related differences in the manifestation of CVD in patients with diabetes, with women having a greater risk than men [19].

Recent data suggest that adipose tissue is not simply an inert depot for excess calories but is metabolically active. It generates and exports inflammatory markers, hormones and FAs that interact with other tissues. In particular, adipocytes appear to have a stress response to excess lipid, which causes the endoplasmic reticulum (the locus of protein production and folding) to undergo what has been termed the 'unfolded protein response.' This response impairs insulin signaling, and hence contributes to insulin resistance and if prolonged, may result in apoptosis [20]. This process has also been implicated in the death of the insulin-producing pancreatic β- cells, which may also contribute to the development of type 2 diabetes.

NONALCOHOLIC FATTY LIVER DISEASE (NAFLD) AND NONALCOHOLIC STEATOHEPATITIS.

NAFLD is the term that describes a constellation of liver abnormalities associated with obesity, including hepatomegaly, elevated liver enzymes, and abnormal liver histology, such as steatosis, steatohepatitis, fibrosis, and cirrhosis [21]. A retrospective analysis of liver biopsy specimens obtained from overweight and obese patients with abnormal liver biochemistries, but without evidence of acquired, autoimmune, or genetic liver disease, demonstrated a 30% prevalence of septal fibrosis and a 10% prevalence of cirrhosis [22]. Another study using a cross-sectional analysis of liver biopsies, suggests that in obese patients, the prevalences of steatosis, steatohepatitis, and cirrhosis are approximately 75%, 20%, and 2%, respectively [23].

GALLBLADDER DISEASE.

Cholelithiasis is the primary hepatobiliary pathology associated with overweight [24]. The old clinical adage "fat, female, fertile, and forty" describes the epidemiological factors often associated with the development of gallbladder disease. This is admirably demonstrated in the Nurses' Health Study [25]. Approximately 20 mg of additional cholesterol are synthesized for each kilogram of extra body fat. Thus, a 10-kg increase in body fat leads to the daily synthesis of as much cholesterol as is contained in the yolk of one egg. The increased cholesterol is, in turn,, excreted in the bile. High cholesterol concentrations relative to bile acids and phospholipids in bile increase the likelihood of precipitation of cholesterol gallstones in the gallbladder. Other factors, such as nidation conditions, also determine whether gallstones form [26]. The second gastrointestinal feature altered in obesity is the quantity of fat in the liver [26]. Increased steatosis is characteristic of the livers of overweight individuals and may reflect increased VLDL production associated with hyperinsulinemia. The accumulation of lipid in the liver suggests that the secretion of VLDL in response to hyperinsulinemia is inadequate to keep up with the high rate of triglyceride turnover.

OBESITY AND CANCER

A number of epidemiological and clinical studies provide clear evidence that obesity is associated with a higher incidence and a higher mortality for many site-specific cancers (including liver, biliary tract, pancreas, oesophagus, stomach, colon and rectum, kidney, breast, prostate, uterus, gonads and the lymphopoietic system). The International Agency for Research on Cancer (IARC) recently stated that the risk of cancer of the endometrium, breast, colon, oesophagus and kidney increases with increasing body weight excess [27]. After adjusting their data for other factors that could influence cancer death risk (age, smoking, diet, alcohol and education), the Department of Epidemiology of the American Cancer Society calculated that 14% of cancer deaths in men and 20% of cancer deaths in women may be attributable to overweight and obesity[28]. All the metabolic and hormonal abnormalities of the obese patient, therefore, contribute to environmental conditions favouring malignant transformation and tumour progression. Altogether, these factors significantly increase the risk of cancer and the risk of cancer mortality in obese patients.

OBESITY AND DYSLIPIDEMIAS

Dyslipidemia is another classical risk factor for CVD that often tracks with obesity, especially in obese patients who also have the metabolic syndrome. High triglycerides and low levels of HDL levels are commonly seen with obesity. Low HDL is a risk factor for CVD in addition to the more commonly known lipid risk factor-increased low-density lipoprotein (LDL). The increase in triglycerides appears to be at least in part due to an increase in fatty acid (FA) turnover and delivery to the liver resulting in an increase in very low-density lipoprotein (VLDL) production [29].

Insulin resistance (often accompanying obesity) lowers HDL levels partly due to increased apolipoprotein A-1 (a component of HDL) catabolism and HDL remodeling from increased hepatic lipase action [30]. HDL production from remnant particles of triglyceride-rich lipoproteins is also hindered by insulin resistance [31] . The fact that these lipid abnormalities (high triglycerides and LDL, and low HDL) generally improve with weight loss, further supports the idea that obesity is directly involved in the development of this particular type of atherogenic dyslipidemia [32]. There are multiple mechanisms by which obesity leads to atherosclerotic coronary artery disease. These risk factors often cluster in what has been termed the 'metabolic syndrome. The metabolic syndrome is associated with increased risk of death from CVD even in the subset of patients without frank diabetes. In one large study, the overall hazard ratios for CVD mortality in those with metabolic syndrome were 2.26 and 2.78 in men and women, respectively [33]. Obesity is also associated with herosclerosis which is characterized by endothelial damage and dysfunction. Obesity directly contributes to atherogenesis via the effects of some of the adipokines that adipose tissue generates and specifically, IL-6, TNF-α, angiotensin II and leptin, are all pro-inflammatory and are secreted by adipose tissue. IL-6 induces VCAM-1 expression and monocyte chemoattractant protein-1 secretion by endothelial cells, both of which encourage monocytes to attach to and infiltrate into the subendothelial space of the artery wall [32, 34].

Inflammation and oxidative stress also appear to play a role in the vascular calcification that often is a relatively late finding in atherosclerosis [35]. Thus, pro-inflammatory adipokines may also affect this pathologic calcification process. In summation, obesity acts both indirectly and directly on the vasculature promoting atherosclerosis, one of the main pathophysiologic processes leading to coronary artery disease and its clinical sequelae.

OBESITY AND HYPERTENSION

One of the components of the metabolic syndrome that often tracks with obesity, and which is also a risk factor for CVD, is hypertension. Data from population studies suggest that approximately 75% of hypertension can be attributed to obesity [36]. On average, for each increase of 10 kg of body weight there is an associated increase of 3.0 mmHg systolic and a 2.3 mmHg of diastolic blood pressure [32]. Although these blood pressure increases may at first appear minor, they portend a 12% increase in coronary heart disease risk and a 24% increase in stroke risk [37]. The exact mechanisms for the relationship between obesity and hypertension are not completely understood, but it is known that adipose tissue can make angiotensinogen, angiotensin converting enzyme (ACE) and angiotensin receptor 1 (AT-1). Renin activity and aldosterone are also upregulated in obesity [38]. These alterations increase plasma volume and contraction of vascular smooth muscle, both of which may contribute to increased blood pressure. Obesity is also associated with an imbalance in the sympathovagal system, as shown by ganglionic nerve studies, heart rate variability studies and renal norepinephrine spillover studies [39]. This increased activation of the sympathetic nervous system may also contribute to increased blood pressure in the setting of obesity due to the activation of β_1-adrenoreceptors in the myocardium, leading to an increased left ventricular (LV) dp/dt (rate of rise of LV pressure). Increased sympathetic

tone associated with obesity may also increase blood pressure via arterial vasoconstriction due to α_1-adrenoreceptor stimulation. Lastly, obesity is associated with a low-grade systemic inflammatory state. Adipose tissue itself can manufacture the pro-inflammatory cytokines, interleukin-6 (IL-6) and tumor necrosis factor-a (TNF-a), and these can regulate other markers of inflammation, such as C-reactive protein (CRP) [40].

OBESITY AND MYOCARDIAL METABOLISM

Animal studies suggest that alterations in myocardial metabolism contribute to cardiac dysfunction in obesity [41, 42]. Normally, the myocardium is able to utilize multiple substrates for metabolism but in the postnatal, resting, fasted state it primarily uses FAs. In response to an increase in FA delivery, the myocardium typically increases β-oxidation of FAs. Although much of this excess lipid may be stored in a relatively neutral form such as triglycerides, some of the FAs that enter the cell may contribute to apoptosis, via lipotoxicity [41]. This increase in β-oxidation of FAs occurs in animal models of obesity, even before the onset of diabetes [43].

In a study of young women with uncomplicated obesity, it was found that myocardial FA uptake, utilization, and oxidation all were increased as BMI and whole body insulin resistance increased [44]. Excessive myocardial FA metabolism may also contribute to cardiac dysfunction via increased free radical production. In obesity, with its inherent increase in FA oxidation, there is increased myocardial oxidative stress [45].

In addition, left ventricular biopsies from human hearts undergoing LV assist device implantation for heart failure demonstrate that patients with obesity or diabetes and heart failure have more accumulation of lipid within the myocardium than those with heart failure from other causes [46]. In animal studies free radicals appear to impair both vascular and LV systolic and diastolic function, since decomposition of free radicals leads to improvement of these parameters [47]. Supporting this theory that not all of the cardiac dysfunction that is seen with obesity is due to apoptosis-related injury, there are studies showing improvement in cardiac function after significant weight loss [48]. Lastly, increasing BMI is an independent predictor of increasing myocardial oxygen consumption and decreasing efficiency both in animal models and also in a recent study in young obese women [49].

OBESITY AND HEART FAILURE

Although obesity is a risk factor for coronary artery disease, and hence, ischemic cardiomyopathy, obesity is also a risk factor for nonischemic heart failure. Rarely, obesity is related with a pathologic condition, known as 'Adipositas Cordis' wherein the myocardium is so filled with lipid that it actually floats in water [32]. The lipid in the heart can be from an infiltrative process, with adipocytes strands streaming in from the epicardial fat, and/or a metaplastic process in which myocardial cells are replaced by adipocytes [32]. Obesity has many adverse effects on hemodynamics and cardiovascular structure and

function [50]. Obesity increases total blood volume and cardiac output, and cardiac workload is greater in obesity. Typically, obese patients have a higher cardiac output but a lower level of total peripheral resistance at any given level of arterial pressure [50, 51]. Most of the increase in cardiac output with obesity is caused by stroke volume, although because of increased sympathetic activation, heart rate is typically mildly increased as well [52]. In addition to increasing left ventricular structural abnormalities and the propensity for more frequent and complex ventricular arrhythmias [53], obesity also has adverse effects on diastolic and systolic function [50, 54]. Typically, hypertension leads to thickening of ventricular walls without chamber dilation, a process referred to as concentric remodeling when left ventricular mass is not increased or concentric left ventricular hypertrophy when left ventricular mass is increased, whereas obesity is characterized as increasing chamber dilation without marked increases in wall thickness, a process that leads to eccentric left ventricular hypertrophy [55, 56]. Furthermore, systemic hypertension, which often accompanies obesity, facilitates development of left ventricular dilatation and hypertrophy. Increased left ventricular mass also makes the subendocardium more susceptible to ischemia and increases the risk of sudden cardiac death [50].

PSYCHOSOCIAL FUNCTION

Overweight is stigmatized [57] that is, overweight individuals are exposed to the consequences of public disapproval of their fatness. This stigma occurs in education, employment, health care, and elsewhere. One study that used the Medical Outcomes Study Short-Form Health Survey (SF-36) demonstrated that obese people at a weight management center had profound abnormalities in health-related quality of life [58]. Higher body mass index (BMI) values were associated with greater adverse effects. Obese women appear to be at greater risk of psychological dysfunction than obese men; this is potentially due to increased societal pressures on women to be thin [59]. Intentional weight loss improves the quality of life [60].

SLEEP APNEA

Alterations in pulmonary function have been described in overweight subjects. The chief effect is a decrease in residual lung volume associated with increased abdominal pressure on the diaphragm. Fat distribution, independent of total fat, also influences ventilatory capacity in men, possibly through the effects of visceral fat level. Overweight subjects with obstructive sleep apnea show a number of significant differences from overweight subjects without sleep apnea. Sleep apnea was considerably more common in men than women. People with sleep apnea have an increased snoring index and increased maximal nocturnal sound intensity. Nocturnal oxygen saturation also is significantly reduced. One interesting hypothesis is that the increased neck circumference and fat deposits in the pharyngeal area may lead to the obstructive sleep apnea of obesity. In contrast to the relatively benign effects of excess weight on respiratory function, the overweight associated with sleep apnea can be severe [61].

DISEASES OF THE BONES, JOINTS, MUSCLES, CONNECTIVE TISSUE, AND SKIN

Osteoarthritis is significantly increased in overweight individuals. The osteoarthritis that develops in the knees and ankles may be directly related to the trauma associated with the degree of excess bodyweight [62]. However, the increased osteoarthritis in other nonweight-bearing joints suggests that some components of the overweight syndrome alter cartilage and metabolism independently of weight bearing. Several skin changes are associated with excess weight. Stretchmarks, or striae, are common and reflect the pressures on the skin from expanding lobular deposits of fat. Acanthosis nigricans with deepening pigmentation in the folds of the neck, knuckles, and extensor surfaces occurs in many overweight individuals. Hirsutism in women may reflect the altered reproductive status in these individuals [26].

CONCLUSION

The net effect of overweight and obesity on morbidity and mortality is difficult to quantify. Higher body weight is associated with an increased incidence and prevalence of numerous conditions, including hypertension, diabetes mellitus, dyslipidemia, certain cancers,musculoskeletal disorders, and CVD, and with increased risk of disability.5 Higher body weights are associated with increased risks of cardiovascular mortality and morbidity. In the older age groups, which tend to have the highest mortality and morbidity, there appears to be less of an association of weight with mortality than in younger groups. Although obesity is considered a multifactorial condition, it often is viewed unidimensionally and described and studied as a simple issue of body weight. Considerable attention has been paid to body weight and BMI in epidemiologic studies. Body weight is measured easily and can be obtained through self-report, thus making it feasible for large-scale studies. The social costs of obesity along with the costs of attempts to prevent or to treat obesity are high. In addition, the prevalence of obesity is increasing in most parts of the world and appears likely to continue to increase in the future. The health risks associated with these increases and the risks and benefits of treatment strategies need to be evaluated objectively.

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