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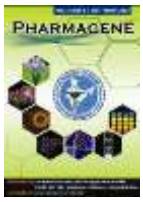

Clinical manifestation of Obesity

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Abstract Obesity is an exaggeration of normal adiposity and is a central player in the pathophysiology of diabetes mellitus, insulin resistance, dyslipidemia, hypertension, sleep apnea and cancer. Renin angiotensin system plays an important role in obesity associated hypertension. Cancer associated with obesity includes breast, colon, endometrial, oesophageal, hepatocellular, renal, and prostate cancer.Because of the accelerating effects that obesity has on the worsening of metabolic syndrome and cancer, it has the potential to be profoundly detrimental to our species if major methods of prevention and/or effective treatment are not realized. As body weight increases, insulin resistance increases that developed type 2 diabetes.

Keywords : Hypertension, type 2 diabetes, cancer

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INTRODUCTION

Obesity is rapidly becoming the most important publichealth problem in industrialized countries. Surveys throughout the world have revealed dramatic increases inthe prevalence of obesity in adults as well as children in many countries, and current estimates indicate that over 1 *billion* people in the world are overweight or obese.[1,2] In China alone, over 200 million people are overweight, and more than 20% of children in major Chinese cities are either clinically overweight or obese, compared to only a 1 to2% prevalence in 1985.[3]The global emergence of obesity has become a major economic challenge as well as the number one public health problem in many countries worldwide.[2] Excess weight gainis an important risk factor for many medical disorders,including hypertension, type II diabetes, sleep apnea, cerebrovascular rdisease, coronary heart disease, kidney disease, and several types of cancer (e.g., breast, colon, kidney, prostate). Currently overweight and obesity are classified using the body mass index (BMI).Table 1 shows the classification of overweight and obesity and the increasing risk for disease and premature mortality associated with increasing BMI.[4]The emerging epidemic of diabetes mellitus appears to be due largely to the increasing prevalence of overweight and obesity, with at least 60% of all cases of diabetes being directly attributable to excess body weight.[5] According to the International Diabetes Federation, diabetes alone accounts for 5 to 10% of the total health care budget in many countries. The American Diabetes Association has estimated that the total cost of diabetes in the United States for 2002 was $132 billion, including direct and indirect costs.Total costs are predicted to rise even further reaching $192 billion in 2020.Coronary heart disease is the major cause of death but cancer rates are also increased in the overweight, especially colorectal cancer in males and cancer of gall bladder, biliary tract, breast, endometrium and cervix in females. Health consequence of obesity are shown in Table 2.[6,7]

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OBESITY AND HYPERTENSION

The majority of patients with high blood pressure are overweight, and hypertension is more frequent in obese subjects.[8] A 10 kg increase in body weight is associated with a 3.0 mm Hg higher systolic and 2.3 mm Hg higher diastolic blood pressure. This rise in blood pressure is greatest when the obesity is of abdominal distribution.[9-13] Factors to be considered in linking obesity to an rise in blood pressure include: (1) hemodynamic changes: increase

Table 1 Classification of Overweight and Obesity By Bmi, Waist Circumference,and Associated Disease Risk[a]

Category	Class	BMI	Disease Risk[b] Men <40 In., Women <35 In.	Men >40 In., Women >35 In.
Underweight		<18.5	-	-
Normal		18.5-24.9	-	-
Overweight		25.0-29.9	Increased	High
Obesity	I	30.0-34.9	High	Very High
Obesity	II	35.0-39.9	Very High	Very High
Extreme obesity	III	>40	Extremely High	Extremely High

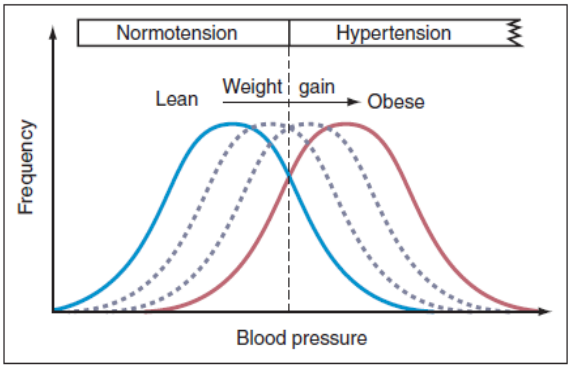
Source: NHLBI Expert Panel 1998.
Relative to normal weight and waist circumference.

Table 2 Complication of obesity

Risk factors	**Outcomes**
'Metabolic syndrome' Type 2 diabetes Hypertension Hyperlipidemia	Coronary heart disease Stroke Diabetes complication
Liver fat accumulation	Non-alcoholics steatohepatitis cirrhosis
Restricted ventilation	Exertional dyspnoea Sleep apnoea Respiratory failure
Mechanical effects of weight	Urinary incontinence Osteoarthritis Varicose veins
Increased peripheral steroid interconversion in adipose tissue	Hormone-dependent cancers(breast, uterus) Polycystic ovary syndrome (infertility, hirsutism)

in blood volume, stroke volume, and cardiac output, and (2) an increase inperipheral vascular resistance: endothelial dysfunction, insulin resistance, sympathetic nervous system, substances released from adipocytes (interleukin [IL]-6, tumor necrosis factor [TNF]-α, etc.), and sleep apnea.[14]One question that often crops up is why some overweight or obese persons are not hypertensive by the usual standards (i.e., blood pressure >140/90) if obesity is a major cause of hypertension? There are several potential explanations. First, it appears that blood pressure in "normotensive" obese people is higher than it would be at a lower body weight because weight loss often reduces their blood pressure. Excess weight gain shifts the frequency distribution of blood pressure toward higher levels, increasing the probability of a person's blood pressure registering in the hypertensive range (Figure 1).

Fig. 1 Effect of weight gain to shift the frequency distribution of blood pressure to higher levels. Not all obese subjects have blood pressures in the hypertensive range (>140/90 mmHg), but excessweight gain raises blood pressure above the baseline level for an individual.



Renin-angiotensin-aldosterone system activation in obesity:

Obese subjects (especially those with visceral obesity)often have mild to moderate increases in plasma renin activity (PRA), angiotensinogen, angiotensin-converting enzyme (ACE) activity, Angiotensin II, and aldosterone levels.[15]Activation of the RAAS in obese subjects responsible for marked sodium retention, extracellular volume expansion,and hypertension—all of which would normally tend to suppress renin secretion, Angiotensin II formation, andaldosterone secretion. Moreover, reduction in weight is usually associated with reductions in plasma renin activity and aldosterone.[16]Potential mechanisms for increased renin secretion and Angiotensin II formation include (1) increased sodium chloride reabsorption and reduced sodium chloride delivery to the macula densa and (2) activation of therenal sympathetic nerves. Increased angiotensinogen formation by adipose tissue has also been suggested to responsible for elevated Angiotensin II levels in obesity,[15] although the importance of this pathway is still unclear. Regardless of the precise mechanisms involved, RAAS systema ctivation appears to contribute to elevated blood pressure in obese subjects.

Role of Angiotensin II in obesity hypertension:

A significant role for Angiotensin II in stimulating sodium reabsorption,impairing renal-pressure natriuresis, and mediating hypertension in obesity is supported by the finding that Angiotensin II receptor blockade (ARB) or ACE inhibition inhibit sodium retention, volume expansion, and increased arterial pressure in obese dogs.[17,18]ARB also reduced blood pressureto a greater extent in obese-prone compared to obese resistant rats fed a high-fat diet.[19] In obese Zucker rats,there is increased sensitivity to the blood pressure effects of Angiotensin II because RAAS blockade lowers blood pressure to a greater extent than in lean rats despite comparable(or perhaps even lower) PRA.[20]Whether the effects of Angiotensin II to raise blood pressure in obesity are due primarily to direct actions on the kidneys,to stimulation of aldosterone secretion, or to SNS activation is unclear.The direct renal sodium-retaining effects of Angiotensin II are well known, as are the direct effects of Angiotensin II to stimulate aldosterone secretion and to increase SNS activity in some conditions.[21] Retrospective analysis of the Anti hypertensive Lipid Lowering Heart Attack Trial (ALLHAT) data should also provide some useful information because there weremany overweight and obese subjects in this trial and anACE inhibitor was compared to other types of antihypertensive therapy.[22]Activation of the RAAS may also contribute to the glomerular injury and nephron loss associated with obesity.By constricting efferent arterioles, increased Angiotensin II formation exacerbates the rise in glomerular hydrostatic pressure caused by systemic arterial hypertension.[21]Studies in type 2 diabetic patients, who are usually overweight or obese, clearly indicate that ACE inhibitors or ARB slow the progression of renal disease.[23-25] However,further studies are needed in nondiabetic obese subjects to determine the efficacy of RAAS blockers compared to other antihypertensive agents in treating hypertension and reducing the risk of renal injury.

ROLE OF SYMPATHETIC NERVOUS SYSTEM IN OBESITY-RELATED HYPERTENSION

Several observations suggest that increased SNS activity impairs renal-pressure natriuresis and contributes to obesity hypertension:[26-29] (1) obese subjects have elevated SNS activity, especially in the kidneys and in skeletal muscle, as assessed by microneurography and tissue catecholamines pillover, (2) pharmacologic inhibition of adrenergic activity reduces blood pressure to a greater extent in obese than in lean subjects, and (3) renal denervation markedly attenuates renal sodium retention and the development of obesity hypertension associated with a high-fat diet in experimental animals.

Mechanisms of SNS activation in obesity:

Several potential mediators of SNS activation in obesity have been suggested, including (1) hyperinsulinemia, (2) increased levels of free fatty acids, (3) angiotensin II (AngII), (4) impaired baroreceptor reflexes, (5) activation ofchemoreceptor-mediated reflexes associated with sleep apnea, and (6) cytokines released from adipocytes (i.e.,"adipokines"), such as leptin, tumor necrosis factor-α (TNF- α), and interleukin-6 (IL-6). Although these mechanisms have been reviewed previously,[30-33] there is scant evidence supporting cause-and-effect relationships for most of these factors and obesity-induced SNS activation.

OBESITY AND CANCER

Besides the profound effect that obesity has on the manifestations of inflammation in many tissues and organs, it is a major risk factor for many forms of cancer, including breast, colon, endometrial, esophageal, hepatocellular, renal, and prostate cancer. A mechanism for this association was first realized when hyperinsulinemia was found to be a risk factor for colon cancer in obese patients.[34]The combined effects of diabetes, insulin resistance, and increased body-mass index (BMI) were all later determined to contribute to the pathogenesis of colorectal cancer.[35]Obesity accounts for 20–33% of the risk for breast, esophageal, endothelial, and kidney cancer.[36,37] Mechanisms of carcinogenesis or tumor growth include perturbed cellular proliferation, dedifferentiation and/or apoptosis, angiogenesis, and chronic adipokine-associated inflammation, along with the effects of cancer genes and/or environmental toxins that enhance inflammation. Examples of adipose tissue adipokines that promote cancer include stimulating insulin-like growth factor-1 and other growth hormone secretagogues, such as leptin that enhance cellular proliferation and/or dedifferentiation.[38,39]

In a landmark paper, Calle and colleagues[40] determined that among men who did not initially have cancer and who were then followed for 16 years, those with BMIs of 30–34.9 had a 20% higher death rate from prostate cancer, whereas those with BMIs of 35–39.9 had a 34% higher death rate compared with men with normal BMIs. Although testosterone itself is a key prostate growth factor that may enhance cellular proliferation, it was speculated that enzymatic conversion of testosterone to estradiol within cells of benign prostatic hypertrophy caused them to dedifferentiate into prostate cancer cells.[41-43] A meta-analysis of multiple studies showed a relationship between obesity and advanced cancer but not early prostate cancer.[44,45]

Table 3 Time-dependent effect of obesity to increase risk of type 2 diabetes. (Redrawn from data in reference 58.)

BMI	Relative risk of Type 2 diabetes	
	Subject in category <5 years	Subject in category >5 years
<25	1	0
25-27.9	1.8	2.2
28-29.9	2.9	4.9
>30	4.9	8.7

Hepatocellular cancer is also linked to the associated comorbidity of fatty liver in obesity, which, after progressing from steatonecrosis to cirrhosis, becomes a risk factor for hepatocellular cancer. High leptin levels are also found in these obese patients and may be a growth-promoting factor for this cancer.[46] Pancreatic cancer may be linked to obesity as a result of associated inflammatory adipokines, which not only upset glucose transport, causing insulin resistance, but combined with hyperinsulinemia, hyperglycemia, and lipotoxicity, all may lead to pancreatic β-cell inflammation and their exhaustion. It is speculated that the pancreatic dysplasia resulting from chronic inflammation associated with chronic pancreatitis promotes progression to pancreatic adenocarcinoma.[47]Although depression and hypercoagulable states are features of pancreatic cancer, both conditions are enhanced in obese patients with pancreatic cancer.

Similarly, multiple etiologies may contribute to both obesity and chronic inflammation that are risk factors for esophageal carcinoma. The chronic inflammatory state related to the chronic esophageal acid reflux common in obesity results in Barrett esophagus, whose pathologic hallmark is intestinal metaplasia. This may also be accentuated by chronic adipokine injury from visceral periesophageal adiposity appearing to enhance the progression of metaplasia to high-grade dysplasia, the premalignant precursor to esophageal carcinoma. Further complications of visceral adiposity include hiatal hernial formation and its associated decreased esophageal sphincter function, which, with increased abdominal pressure from visceral adiposity, further enhances gastric reflux.[48] In addition, increases in the leptin levels seen in obesity may also contribute to cellular proliferation, dedifferentiation, and inhibition of apoptosis in this cancer.[49]

Adipokinesecretagogues such as unbound insulin-like growth factor also enhance angiogenesis, which promotes cancer growth in general.[50]Adiponectin, the adipocyte-secretory proteohormone, protects against angiogenesis, but decreased adiponectin levels in obesity allows the progression from enhanced angiogenesis to cancer.[51,52] Cancer-promoting factors enhanced by estrogenization occur in breast, endometrial, ovarian, and prostate cancers, whereas increased leptin levels have been found in renal, esophageal, and hepatocellular carcinomas. Much more information is needed to explain the molecular biology of obesity that would be responsible for the development of individual cancers, particularly those due to cancer genes and environmental toxins that could compound inflammation engendered by inflammatory adipokines in obesity.

OBESITY AND SLEEP APNEA

The prevalence of sleep disordered breathing and sleep disturbancesrises dramatically in obese subjects,[53] and obesity isby far the most important modifiable risk factor for sleepdisorderedbreathing.[54,55] Obese individuals have an increaseddemand for ventilation and breathing workload,respiratory muscle inefficiency, decreased functional reservecapacity and expiratory reserve volume, and closure ofperipheral lung units. These often result in a ventilationperfusion mismatch, especially in the supine position. Obesityis a classical cause of alveolar hypoventilation. Numeroustreatments are available for sleep apnea but weight loss inobese patients should always be advocated.[53]

OBESITY AND TYPE 2 DIABETES

Obesity is associated with an increased risk of developing insulin resistance and type 2 diabetes.In obese individuals, adipose tissue releases increased amounts of non-esterified fatty acids, glycerol, hormones, pro-inflammatory cytokines and other factors that are involved in the development of insulin resistance. As body weight increases, insulin resistance increases, that is, there is decreased ability of insulin to move glucose into fat and muscle and to shut off glucose release from liver. Weight reduction decrease insulin resistance.When insulin resistance is accompanied by dysfunction of pancreatic islet β-cells that release insulin failure to control blood glucose levels results. Abnormalities in β-cell function are therefore critical in defining the risk and development of type 2 diabetes. This knowledge is fostering exploration of the molecular and genetic basis of the disease and new approaches to its treatment and prevention.[56] Associated with obesity there is hyperinsulinemia, dyslipidaemia, and accelerated development of atherosclerosis. This combination of finding is commonly known as metabolic syndrome or syndrome X.[57] The timedependent effects of obesity on diabetes have been clearly demonstrated (Table 3).When obesity persists for more than five years, the adjusted relative risk for developing diabetes is 8.7 compared to 4.9 if a person has been obese for less than five years.[58] Thus, the health consequences of obesity (including hypertension) are likely to worsen the longer a person is obese, although this is often not considered in cross-sectional studies.

CONCLUSION

There has been an alarming increase in the prevalence of overweight and obesity in most industrialized countries and even in underdeveloped countries, resulting in a worldwide rise in diabetes mellitus, hypertension, and cancer. Excess weight gain is the key risk factor for increased blood pressure in most patients with essential hypertension, and also appears to be a major cause of diabetes. Obesity initially raises blood pressure by increasing renal tubular reabsorption, impairing pressure natriuresis, and causing volume expansion. These changes are due to activation of the SNS and RAAS. Blockade of the SNS and RAAS are therefore effective in reducing bloodpressure in many obese patients. With prolonged obesity, there may be progressive renal dysfunction that worsensthe hypertension Weight reduction is an essential first step in the management of obesity-associated hypertension and diabetes. More emphasis should be placed on lifestyle modifications that help patients maintain a healthier weight and prevent obesity, and consequently hypertension and associated cardiovascular disease and Diabetes. Efforts to prevent the development of obesity are critically needed in populations throughout the world.

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