Review Article

OBESITY, LEPTIN, AND CORONARY HEART DISEASE

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ABSTRACT

Obesity is an important health problem both in developed and developing countries. Obesity is an abnormal increase in body weight due to fat deposition. The real cause of obesity is unknown but genetic, environmental factors and family eating habits, hormonal, and psychological factors have roles. Regardless of the origin of the disease, obesity develops when caloric intake exceeds the caloric needs of the individual. Adipose tissue is not merely a fat store, it is metabolically active and also has a secretory role. Leptin, synthesized and secreted by adipose tissue, regulates the size of adipose tissue. Obesity is highly associated with the adult onset of diabetes mellitus, coronary heart disease, and hypertension.

Extensive efforts must be made and measures must be taken to educate people in adapting to healthy lifestyles.

Key words: Obesity, Adipose tissue, Leptin.

INTRODUCTION

The terms obesity and overweight refer to excess in body weight relative to height. Ideal body weight (IBW) is associated with the lowest morbidity and mortality. Body weight relative to IBW is called the relative weight. Overweight is defined as relative weight up to 20 % above normal and obesity as over 20 % above IBW. Body weight is continously distributed in populations and it is not easy to define obesity due to great variation in lean body mass among individuals of the same stature.

Reductions in energy expenditure are the main factors responsible for the increase in the prevalance of obesity. Consequences of this increase only become apparent many years later like chronic conditions such as arthritis or conditions related to obesity but occurring later in life such as cerebrovascular events, chronic heart failure or breast cancer in women.

ADIPOSE TISSUE

Adipose tissue (AT) is a specialized connective tissue designed for the synthesis, storage and hydrolysis of triaclyglcerols (TAG). TAG's are stored as liquid droplets in the cytoplasm; the half life of TAG is only a few days. Nearly the entire volume of each adipocyte can be occupied by a droplet of TAG. Adipose tissue is the main organ of cholesterol storage in the body and contains mostly non-esterified cholesterol. Adipocytes first appear late in fetal development preparatory to postnatal life. Adipose lineage arises from the same multipotent stem cell population of mesodermal origin. When appropriately induced with hormonal agents, committed preadipocytes differentiate into adipocytes in culture (1). AT comprises about 10% of the body mass of normal infants at birth. In the first few months of life, adipocytes increase their storage capacity by hypertrophy. In nonobese children fat cells decrease after age one, whereas it remains hypertrophic in obese children. Adipocyte hyperplasia or increase in the number of adipose cells appears to occur from 1 year of age to preadolescence proceeding more rapidly in obese children. Thereafter increase in adipose tissue occurs by hypertrophy. Very obese people have increased number of adipocytes whereas moderate obesity is hypertrophic. The latter respond better to treatment. In early adulthood, nonobese males have 10-15% of body mass as fat, whereas in normal females adipose tissue is 15-20%. In a 70 kg man adipose tissue weighs approximately 14 kg or about half as much as the total muscle mass. In obese individuals AT can constitute up to 70% of body weight (2).

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Adipose tissue is found mostly under the skin, in the abdominal cavity, in skeletal muscle, around blood vessels, and in mammary gland. Although small in quantity compared to white adipose tissue (WAT), brown adipose tissue (BAT) must also be mentioned because of its importance in thermogenesis. Brown adipose tissue which is the site of nonshivering thermogenesis, is reduced or absent in obese people. In fact obesity may be related inpart to a defect in thermogenesis (3).

ETIOLOGY OF OBESITY

Obesity is the state of excess strorage of triglyceride and exerts important effects on metabolic processes in adipose tissue and in other organs. Regulation of triglyceride storage involves both neural and endocrine factors but primarily reflects the net surplus of caloric substrate available to the organism (4).

The cause of most cases of obesity is not known. Genetic factors interact with environmental factors. Family eating patterns especially in infancy and early childhood have important effects (5). However, studies done with identical twins reared apart have shown evidence for substantial genetic determinacy of adipose mass. Studies have also shown that 80% of children with two obese parents will be obese, while only 14% of children of normal weight parents will be obese (6). Endocrine diseases such as Cushing's disease or hypotyhroidism are rare causes. Obesity may also be associated with Klinefelter's and Turner syndromes, male hypogonadism, and castration. Hyperinsulism associated with insulinoma can also lead to obesity. Insulin resistance is almost always associated with obesity. Hypothalamic dysfunction and lesions as well as psychological factors lead to obesity. Prader-Willi, Bardet-Biedl, Alström-Hallgren, Fröhlich's, Cohen's, Carpenter's Syndromes, Hyperostosis Frontalis Interna, and Multiple Lipomatosis are all associated with obesity (7).

Several genes at different loci on human and rodent chromosomes have been associated with obesity. The ob gene is expressed in adipose tissue and plays an important role in regulating body weight in mice. In ob/ob mice which become very obese, the ob gene is mutated so that no leptin is produced, when given leptin the affected mice stop eating and lose weight (7). In humans leptin and leptin receptor gene have shown linkages to obesity. Apart from mutations in leptin and leptin receptor gene, agouti (A) gene, carboxypeptidase E (cpE) and tub genes are implicated in the obesity of rodent. ASIP (gene symbol for human analogous to agouti) has not yet been directly linked to human obesity; agouti related protein (AGRP) gene product may be a potential distal mediator of leptin effects in energy homeostasis. To date no mutations in human tub analog or cpE have been reported in human obesity. Obesity due to compound heterozygoticy for mutations in prohormone convertase has been recently documented in a 47-year old woman (8).

BIOCHEMISTRY OF ADIPOCYTES AND OBESITY

AT is an organ of metabolism that serves as a reservoir of energy rich fatty acids. AT is the main store of TAG in the body, most of the TAG produced by the liver are transported to the adipose tissue for long term storage (9). The TAG stores in the adipose tissue continuously undergo lipolysis and reesterification and these processes are not the forward and the reverse phases of the same reaction (Fig. 1). The resultant of these two processes determine the magnitude of the free fatty acid (FFA) pool in AT and in plasma. It has recently been demonstrated that the release of individual FA from WAT is highly selective and as a rule FA's are preferentially mobilized when they are short, more unsaturated, have double bonds close to the terminal methyl group of the chain (10). Plasma FFA level has important effects on the metabolism of other tissues especially liver and muscle. Most of the FA stored in AT appears to come from circulating triglyceride-rich lipoproteins. The triglycerides of very low density lipoproteins (VLDL) and chylomicrons are hydrolyzed

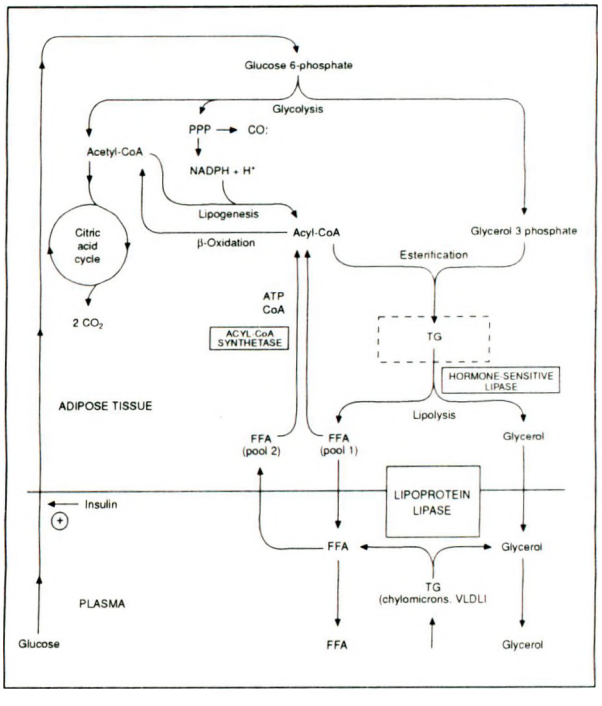

Fig.1: Metabolism of Adipose Tissue

by lipoprotein lipase (LPL) located on the capillary endothelium yielding fatty acids. Insulin induces LPL activity and facilitates entry of glucose into adipocytes where it is converted to glycerol 3-phosphate. Glycerol 3-phosphate provides the glyceryl moiety for the esterification of free fatty acids. Because glycerol kinase is low in activity in AT glycerol cannot be utilized to any great extent in the esterification of FAs. AT can metabolize glucose by hexosemonophosphate pathway producing NADPH essential for fatty acid synthesis. However, human AT is not an important site of lipogenesis. Acetate derived from ethanol can also be converted into fatty acids by the adipose tissue. Glucose also contributes to the synthesis of FAs but to a limited extent. Intracellular hormone sensitive lipase (HSL) hydrolyzes the stored triglycerides in AT and FFAs and glycerol are mobilized into plasma. The first steps in which two moles of FAs are released constitute the rate limiting steps of the hydrolysis which then rapidly completed by monoacylglycerol lipase. Epinephrine, norepinephrine, ACTH, glucagon, and growth hormone stimulate the hydrolysis of triglycerides. However catecholamines either stimulate or inhibit lipolysis in fat cells throught their action on $\beta_{1,2,3}$ -or α_2- adrenoreceptors respectively (11). The sympathetic nervous system plays a central role in the mobilization of FFAs by liberating norepinephrine in AT. Most of these factors increase cAMP which in turn activates a protein kinase that phosphorylates inactive HSL to its active form (12). Inhibition of phoshodiesterase by caffeine and theophylline potentiates the hormonal stimulation of lypolysis. While tyroxine and cortisol have permissive effect on lipolysis, insulin opposes the hormonal and neural stimuli. Insulin promotes storage of fat and inhibits lipolysis when the blood glucose and triglyceride levels rise after a meal. The principal action of insulin is to inhibit the HSL. Fasting and exercise also promote lipolysis. Glucocorticoids promote lypolysis by effecting synthesis of new lipase by a cAMP-independent pathway which may be inhibited by insulin.

AT is a heterogenous metabolic organ and several differences have been observed among various fat depots. For example, visceral adipose tissue has a higher lipolytic activity than subcutaneous adipose tissue due to a combination of increased β_2-adrenoceptor mediated catecholamine-induced lipolysis and reduced antilipolytic action of insulin in the visceral fat depot (11). The fact that visceral fat depot is drained by the portal system to the liver must be kept in mind for the atherosclerotic complications.

Although TAG storage has usually been considered to be the main function of AT, more recently, it has been recognized as a secretory organ. In addition to LPL, adipocytes are also a source of cholesterol ester transfer protein (CETP), apo E, estrogen, angiotensinogen, tumor necrosis factor (TNF) as well as leptin (13). Murine cultured adipocytes have been shown to synthesize and secrete adipsin which is homologous to human plasma factor D and is one of the proteins involved in the alternate complement pathway. Complement C3 and factor B are also expressed and secreted in cultured adipocytes and mouse adipose tissue. Acylation stimulating protein (ASP) is also demonstrated to be produced by cultured human differentiated adipocytes. Apart from having marked effects on adipocyte lipid metabolism as a key regulator of the TAG synthetic pathway, ASP stimulates glucose transport by translocating glucose transporters (GLUT 1, GLUT 4, and GLUT 3). ASP is also produced by mature adipocytes. Neither glucose nor FA s have been shown to have any substantial effect on ASP production. Although insulin increased the ASP production two-fold, addition of chylomicrons to the cell culture medium caused a 150-fold increase (13).

Caloric imbalance-excessive intake or inadequate expenditure-promotes weight gain. The magnitude of weight gain depends on the number of calories not on the source of the calories. Overweight people tend to eat a few infrequent meals. Food intake triggers insulin and glucocorticoid output and this promotes fat accumulation which in turn increases leptin secretion (14,15). In obese humans leptin mRNA in adipocytes is shown to be elevated (16).

LEPTIN

Leptin, a 16 kDa peptide secreted by adipocytes, regulates the size of the adipose tissue mass through effects on satiety and energy metabolism (17). It is a product of the ob (obese) gene on chromosome 7. Leptin is highly conserved in different vertebrates with approximately 85% structral homology in mouse, rat and man (18). Its levels correlate with body fat content in humans but the regulation of leptin levels is poorly understood. In rodents insulin and glucocorticoids seem to regulate the production of leptin but there is only limited evidence that this occurs in humans (19). There are some studies showing that plasma leptin level correlates to insulin secretion (20). Other studies show that leptin levels are not regulated by insulin (21). Leptin is a satiety factor; it controls (supresses) appetite through its widespread distribution of receptors. Leptin receptor (LEPR or Ob-R) is a member of the gp 130 family of cytokine receptors which are known to stimulate gene transcription via activation of cytosolic signal transducer and activator of transcription (STAT) proteins and stimulate

transcription through interleukin 6 responsive gene elements (22). The STAT proteins bind to phosphotyrosine residues in the cytoplasmic domain of the ligand-activated receptor where they are phosphorylated. The activated STAT proteins dimerize and translocate to the nucleus where they bind DNA and activate transcription. Linkage of markers flanking LEPR and acute insulin release and obesity have recently been reported. Leptin might be linked to food intake through appetite stimulating hypothalamic peptide neuropeptide Y (NPY). It is known that hypothalamic centers regulate appetite (23). To reach brain, circulating leptin must cross the blood-brain barrier. Studies show that leptin is transported intact from blood to brain by a saturable system (24). In studies done with ob/ob mice showed that leptin deficiency led to hyperglycemia and the overexpression of hypothalamic NPY that is implicated in the pathogenesis of obesity (25). Plasma leptin levels are elevated in most overweight individuals; obesity may be associated with leptin resistance (26). Satiety center is insensitive to endogenous leptin production and this can be one of the fundamental mechanisms in obesity (27). Weight loss reduces serum leptin levels (28).

Leptin administration in the ob/ob mouse resulted in weight loss by reduction of food intake and increased energy expenditure (29).

Leptin diminishes insulin secretion and induces insulin resistance (30). Type II diabetic patients treated with insulin had both raised insulin and leptin concentrations (31). Leptin also appears to regulate thermogenesis (32).

Sex hormones may have an effect on leptin synthesis because obese women have higher ob mRNA levels than obese man (33). Levels are 3 times as high in women as in men. Circulating leptin is inversely related to age (34). Ob/ob mice that have a congenital absence of leptin are infertile. Results of leptin treated mice indicated the role of leptin in stimulating reproductive endocrine system (35).

MEASURING OBESITY

Sophisticated techniques like body density measurement, isotopic compartmentalization, ultrasonography, and magnetic resonance imaging have been used to measure body fat in reseachers (36). More practicle indices express the relationship of weight/height ratio. Weight in kilograms divided by square of height in meters is called the body mass index (BMI or Quetelet index); height divided by cube root of weight is called the ponderal index. The BMI correlates best with body composition. The distribution of adipose mass between the trunk and the gluteal region can be described using the ratio of the circumference at the waist to that at the hips. This ratio falls between 0.7 and 0.85 in normal distrubution. BMI is a measure of general adiposity, whereas waist to hip ratio or regional skinfold thickness are commonly used to mesaure abdominal or visceral adiposity that shows a regional fat distribution. Densitometry is considered as the best method for measuring body fatness and correlation between BMI with densitometry is approximately 0.6 (37). Skinfold thickness when mesaured at the proper sites with constant tension calipers is also a useful index of fat distribution. Adults are considered obese if skinfolds exceed 19 mm for men and 30 mm for women at the midtriceps level or 22 mm for men and 27 mm for women at the subscapular level. However, it must be taken into account that these numbers represent the upper 20% in the United States population (6).

In 1990, WHO accepted obesity as body mass index (BMI) of 30 kg/m^2 or more (38). The average prevalence of obesity among European centers participating in the WHO-MONICA study between 1983 and 1986 was about 15% in men and 22% women (38).

OBESITY AND CORONARY ARTERY DISEASE RISK

Obesity increases the risk of atherosclerosis by influencing the action of insulin and its concentration in blood (39). Obese individuals display some insulin resistance and have increased insulin production and hyperinsulinemia associated with increased concentrations of VLDL and recreased concentration of HDL (40). It has been hypothesized that the insulin resistance associated with visceral fat accumulation is the mediator for excess risk associated with obesity (41). Age related decreases in dehydroepiandosterone sulfate (DHEA) in association with increases in obesity, insulin resistance and atherosclerosis is well known (42).

Obesity is strongly associated with cardiac risk factors including elevated blood pressure, glucose intolerance and dyslipidemia (43). Clinical trials have indicated that weight loss significantly improves these risk profiles. Those patients who are more than 20% above the midrange of desirable weight may benefit from weight reduction, particularly if associated with other risk factors. However, large fluctuations in weight, either up and down, may also increase the risk for CHD (4). All patients following myocardial infarction should be on Step II American Heart Association Diet

with caloric restriction to avoid weight gain. Weight loss can be better maintained with a regular moderate exercise program.

Some but not all epidemiological studies have shown obesity as an independent risk factor for coronary heart disease both in men and women. Methodologic problems like not taking fat distribution into consideration may account for the contradictory findings (44). Abdominal adiposity confers additional risk for CHD. Abdominal adiposity or w/h is an index of an androgenic fat distribution and strongly correlate with higher insulin levels and insulin resistance. Aging, sex hormone, genetic and dietary factors and physical inactivity may induce visceral fat accumulation (45). Visceral fat is characterized by its high lipogenic activity as well as its accelerated lipolytic activity. High levels of portal free fatty acids may eventually result in an enhancement of hepatic triglyceride synthesis, causing hyperlipidemia. High portal FFA levels would also induce insulin resistance, thereby causing glucose intolerance and diabetes mellitus (46). Obesity is closely associated with multiple lipid abnormalities (47). Higher BMI is associated with lower HDL-cholesterol and higher triglycerides; elevated waist-hip ratio is associated with increased cholesterol, triglycerides, apo B and decreased HDL-c in all age groups of both men and women. Obese people have increased synthetic rates for cholesterol and bile acids. When obese people lose weight triglycerides decrease first, then HDL-c increases (10-20%), LDL-c shows no change (48). W/H has been found to be a stronger predictor of CHD compared to BMI. In a multivariate analysis, women in the highest tertile of W/H were found to have a relative risk of 3.3 for death from CHD. Even after controlling for hypertension and diabetes, W/H remained predictive. Women with noncentral obesity had more favorable blood pressure, fasting glucose, and lipid values than centrally obese women. In men noncentral obesity is also associated with CHD and risk.

MANAGEMENT OF OVERWEIGHT

Treatment of obesity is difficult; patience and persistence is needed. Acceptable weight ranges by height in adults are shown in Table I. A dietician or other nutrition or health professional can play an important role in assisting the patient. The benefits of weight loss should be emphasized. Perscription of a calorie restricted lipid lowering diet will be necessary. It is helpful for the patient to begin a meal with a helping of very low calorie or bulky food, such as clear soup or a mixed or green salad with little or no oil. Energy dense foods must be minimized. For individuals who consume alcoholic beverages, one to two drinks a day may be included as part of the calorie allowance.

Table I. Acceptable Body Weights in Adults

Height in m (Without Shoes)	Acceptable Weight Range in kg (Without Full Clothing)	
	Men	Women
1.46		42-53
1.48		42-54
1.50		43-55
1.52		44-57
1.54		44-58
1.56		45-58
1.58	51-64	46-59
1.60	52-65	48-61
1.62	53-66	49-62
1.64	54-67	50-64
1.66	55-69	51-65
1.68	56-71	52-66
1.70	58-73	53-67
1.72	59-74	55-69
1.74	60-75	56-70
1.76	62-76	58-72
1.78	64-79	59-74
1.80	65-80	
1.82	66-82	
1.84	67-84	
1.86	69-86	
1.88	71-88	
1.90	73-90	
1.92	75-93	
Optimal body mass index (weight in kg/height in m^2)	20.1-25.0	18.7-23.8

Source: Data from the 1992 EAS guidelines.
Note: Desirable waist/hip ratio is <0.9 in men, <0.8 in women; the minimum level for diagnosing obesity is 20% above the upper limit of the acceptable range.

A decrease of about 500 kcal per day will result in the loss of 0.5 kg per week. A deficit about 3500 kcal is needed to lose 0.5 kg.

An exercise program according to the patient's preference and/or level of fitness and health status is necessary. Progressively brisk walking for 30-45 minutes, 5-7 days per week is a useful option to be continued after target weight is attained to assist in weight maintenance. Various surgical treatment methods for obesity are now available when no success with diet and life style modification is attained. The main indication for operative treatment is morbid obesity (BMI>40 kg/m^2) or severe obesity (BMI>35 kg/m^2). The modern surgical methods are aimed at limitation of oral intake per meal-vertical banded gastroplasty and gastric banding, limitation of oral intake and induction of dumping-Roux-en-Y gastric bypass or induction of selective maldigestion and malabsorption, as with biliopancreatic bypass (49). All bariatric surgical treatments have peri or post

absorptive complications related to the operation. Orlistat offers a new therapeutic approach for the treatment of moderate to severe obesity. Orlistat, a chemically synthesized derivative of lipstatin which is a natural product of Steptomyces toxtricini, is a potent inhibitior of intestinal lipases. In humans 400 mg daily dose results in 35% inhibition of dietary fat. Its efficacy has been documented in well controlled, long-term studies. Along with weight loss, Orlistat also favourably affects blood pressure and glucose and insulin levels in obese individuals and in obese type 2 diabetic patients (50).

To conclude: diet, behavior therapy, physical exercise and surgical therapy when implicated are used to deal with obesity which is an increasing health problem in most developed and developing countries.

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