



REVIEW ARTICLE

BIO CHEMISTRY

OBESITY: A CRITICAL REVIEW**SUSMITA BAG AND ANAND ANBARASU***

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ABSTRACT

Obesity is a complex interplay of environmental and genetic factors and is associated with significant morbidity and mortality. There are certain detrimental effects to health that are attributed to obesity like metabolic syndrome, cardiovascular disease, diabetes, cancers, high blood pressure. These health consequences associated with obesity result from the cumulative metabolic and physical stress. Obesity is also characterized by an excessively high amount of body fat or adipose tissue. Secretory factors/adipokines released from these adipose tissues undergo abnormal changes with obesity and thus cause a variety of inflammatory conditions. Inherited genetic variation is an important risk factor for obesity and understanding the genetics of obesity will increasingly aid in drug development and better drug targeting to specific patients. This article reviews about factors contributing to obesity, measuring obesity and highlights the need for understanding its prevalence. Also topics on treatment and developing strategies for effective medication are discussed.



KEYWORDS

Obesity; Secretary factors; Adipokines; Drug targeting.

INTRODUCTION

Overweight and obesity is found to be a global epidemic, mentioned by World Health Organization (WHO). It is also depicted as the "New World Syndrome"^{1, 2}. Statistically, the problem of obesity has increased from 12–20% in men and from 16–25% in women over the last ten years³. Obesity is not a single disorder but a heterogeneous group of conditions with multiple causes each of which is ultimately expressed as obese phenotype. Body weight is determined by the interaction of genetic, environmental and psycho-social factors acting through the physiological mediators of energy intake and expenditure⁴. Obesity is often defined as a condition of abnormal or excess fat accumulation in adipose tissue, to the extent that health may be impaired⁵. It is also a chronic and stigmatizing medical condition that has become a major health problem in most industrialized countries because of its high prevalence, causal relationship with serious medical illnesses, and economic impact. Indian Asians have a high prevalence of the metabolic syndrome compared with Europeans and it seems to be highly heritable⁶. It has been reviewed that body mass index (BMI) is a measure of weight (for height) rather than a measure of body fat⁷. Excess fat, rather than excess weight, is linked to obesity-related ill health⁸. Also, BMI does not describe where fat is deposited, and as intra-abdominal fat is thought to be more likely to cause ill health than fat deposited⁹ in other parts of the body; therefore waist circumference (WC) has been undertaken as an obvious measure in consolidating obesity. Obesity is an epidemic of the 21st century, and is a major causative factor for many other metabolic disorders¹⁰. National programmes should carry out for public

awareness, education and improved structural facilities which will undergo to facilitate healthy lifestyle and thus become the keys to alleviate the economic and health care burden of the obesity-related disorders.

SCALE DEPICTING OVERWEIGHT AND OBESITY:

Obesity is usually defined by an indirect measure of body fat, the body mass index (weight (kg)/ (height (m) ²). The international classification of adult weight status was used to classify by body mass index (BMI): (1) underweight (<18.5), (2) normal weight (18.5–24.9), (3) overweight (25.0–29.9), and (4) obese (>30.0)¹¹. Body mass index does not, however, adequately characterize the distribution of body fat, which is important because excess intra-abdominal fat is an independent predictor of health risk¹². Waist circumference correlates with visceral fat and indirectly measure central obesity¹³. An increased risk to health is present when waist circumference exceeds 94 cm (37 inches) for men and 80 cm (32 inches) for women¹.

HEALTH CONSEQUENCES OF OBESITY:

The increased risk of medical disorders and emotional consequences associated with obesity make the disorder a priority for physicians to assess and treat. Obesity is associated with many diseases that include cardiovascular diseases (CVDs), hypertension, hyperlipidemia, diabetes mellitus, colorectal cancer, breast cancer, and endometrial cancer¹⁰. It has been investigated that the accumulation of adipose tissue predominantly in the visceral



cavity plays a major role in the development of metabolic syndrome and CVD¹⁴. The association of birth weight with body mass index provides an implication for the early origins of both obesity and cardiovascular disease¹⁵. Hypertension and obesity combine to increase the cardiac work significantly. In hypertension the increased myocardial work stems from an increased left ventricular pressure; whereas in obese patients the increased myocardial work is secondary to an increased stroke volume. Thus the obese hypertensive patients suffer from markedly increased stroke work because of a combination of volume and pressure overload state¹⁶. The increase in the prevalence of type 2 diabetes is closely linked to the augmentation in obesity. About 90% of type 2 diabetes is attributable to excess weight¹⁷. It has been implied that preventing weight gain can reduce the risk of many cancers. Even a weight loss of only 5 to 10 percent of total weight can provide health benefits¹⁸. Other diseases associated with obesity include sleep apnea, abdominal hernias, varicose veins, gout, gall bladder disease, respiratory problems including pickwickian syndrome (a breathing blockage linked with sudden death), and liver malfunction¹⁹. Other than the above mentioned conditions, specific historical data that may help to elucidate the factors contributing to a patient's obesity include the following: family history of obesity as quantified by number of first-degree relatives with the condition; lifestyle changes that proclaim the onset of weight gain, such as beginning or graduating college, childbirth, marriage, divorce,

or a job change; and changes in exercise or eating habits²⁰.

HORMONES AND OBESITY:

Obesity is linked to many metabolic disorders and hence the development of obesity can cause changes in metabolic and hormonal conditions, which can result in the storage of excess energy in different forms in the human body²¹. BMI is not considered to be a good estimate of obesity in Asian Indians as they have a characteristic obesity phenotype, with relatively lower BMI but with central obesity. It has been suggested that fat distributed in the abdominal region, particularly visceral fat is more metabolically important than other fat depots. Hence abdominal adiposity assessed using waist circumference is considered to be more appropriate to predict metabolic disorders than generalized adiposity assessed by BMI²². The inflammatory response that emerges in the presence of obesity is that it appears to be triggered which reside predominantly in adipose tissue along with other metabolically critical sites which may also be involved during the course of any metabolic diseases²³. Adipose tissue is now accepted to be an endocrine organ that secretes numerous hormones, growth factors, matrix proteins, enzymes, cytokines, and complement factors that exert multiple effects at both the local and the systemic level. Table 1 provides information of few of the secretory factors and their role in body.



Table 1
Secretary factors of adipose tissue and their role in body.

Adipose tissue secretary factors	Role and function
Leptin ²⁴	16kDa protein, regulates growth, metabolism and behavior, provide message from periphery to CNS, regulates homeostasis, provides signal to negative energy balance and low energy state, triggers IL-6, CNTF and LIF pathways.
Adiponectin ²⁵	30kDa protein, role in homeostasis, insulin resistance, improves whole body insulin sensitivity, stimulate appetite and reduce energy expenditure.
Resistin ²⁶	10kDa protein, secreted from rodents, insulin resistance.
Lipoprotein lipase(LPL) ²⁷	55kDa enzyme, prototype of secreted protein from adipocytes, insulin upregulates LPL at post-translational level and calcium triggers its folding to active dimers.
Acylation stimulating protein (ASP) ²⁸	8.9kDa protein, metabolic link between the local environment of adipocytes, regulation of adipocyte function i.e triglyceride storage, G-protein coupled receptor C5L2 is a functional receptor for ASP.
Visfatin and Vaspin ²⁹	Visfatin (52 kDa) and Vaspin (45 kDa) are the newly added adipokines and whose plasma levels increase during weight gain.

A broad range of protein families as well as fatty acids and prostaglandins, have been reported to be secreted by adipose tissue. These secreted factors play a role in fat mass regulation and regulation of adipocyte differentiation, vascular and blood flow regulation, lipid and cholesterol metabolism, and immune system function³⁰. These factors are not only secreted by mature fat cells but also poorly-identified cells present in the stromal-vascular fraction including macrophages present in extracellular matrix of adipose tissue³¹. Elevated levels of these factors during periods of rapid adipose tissue growth would therefore be expected to increase adipocyte proliferation and differentiation, and potentially programme a permanent increase in adipose tissue mass³².

GENETICS AND OBESITY:

Obesity results from the interaction of environmental factors (overeating or reduction in physical activity or both) and hereditary factors³³. Obesity, on the basis of genetics, is a multitude of polymorphisms located in genes and candidate regions throughout the genome that regulate an individual's susceptibility to weight

gain in a permissive environment³³. Obesity is associated with many genetic syndromes³⁴. There are 20-30 mendelian disorders in which patients are clinically obese, yet these are additionally distinguished by mental retardation, dysmorphic features, and organ-specific developmental abnormalities. Such cases are referred to as syndromic obesity. These syndromes arise from discrete genetic defects or chromosomal abnormalities and are both autosomal and X-linked disorders³³. The most common disorders known are Prader-Willi syndrome (PWS) and Bardet-Biedl syndrome (BBS), but many others have been reported³⁴. A numerous epidemiological studies carried out in large and different populations (twins brought up together or separately, adopted children, nuclear families, etc³⁵, thus explaining that familial aggregation for obesity was due to genetic factors rather than environment. The effect of environment on the development of overweight or obesity would be very limited, since the genetic predisposition is present. These results show the importance of identifying families at risk and hence prevent the current and future against childhood obesity.



The genetic factors associated to obesity are depicted as follows:

1) Single mutations contribute to the development of obesity (monogenic obesity).

These forms of obesity are rare, very severe and generally start in childhood³⁶. Table 2 represents rare monogenic forms of obesity.

Table 2
Rare monogenic forms of obesity

Gene (References)	Mutation type	Obesity	Associated phenotype
Leptin (LEP) ³⁷	Homozygous mutation.	Severe, from the first days of life.	Gonadotropic and thyrotropic insufficiency.
Leptin receptor (LEPR) ³⁸	Homozygous mutation.	Severe, from the first days of life.	Gonadotropic, thyrotropic and somatotropic insufficiency.
Proopiomelanocortin (POMC) ³⁹	Homozygous or compound heterozygous	Severe, from the first month of life.	ACTH insufficiency, mild hypothyroidie and ginger hair if the mutation leads to the absence of POMC production.
Single-minded 1 (SIM1) ⁴⁰	Translocation between chromosomes 1p22.1 and 6q16.2 in the SIM1 gene.	Severe obesity occurring in childhood.	-----
Neurotropic tyrosine kinase receptor type 2 (NTRK2) ⁴¹	De novo heterozygous Mutation.	Severe from the first months of life.	Developmental delay, behavioral disturbance, blunted response to pain.
Proconvertase 1 (PC1) ³³	Recessive.	Severe, from the first month of life.	Gonadotropic and corticotropic insufficiency, Hyperproinsulinemia and Other dysfunction of gut peptides.
Melanocortin-4 receptor (MC4R) ³³	Dominant.	Early onset, variable severity, large size.	No other phenotype.

2) Polygenic obesity, where many genetic variants interact with the environment in common obesities. The risk for common obesity could be due to large number of loci, each with multiple disease predisposing alleles but of low frequency⁴². The genetic study of common obesity is based on the analysis of variations in genomic DNA (genetic polymorphism or SNP, Single Nucleotide Polymorphism) situated within or near candidate genes⁴³.

Efforts are made to identify candidate genes for obesity concentrating on adipose tissue. In fat, the regulation of thermogenesis by the sympathetic nervous system is mediated by beta- adrenergic receptors⁴⁴. In humans, beta-3- adrenergic receptors (β 3-AR) are modestly expressed in fat and the adipocytes lining the gastrointestinal tract⁴⁵. Leptin plays an important role in polygenic obesity and was first suggested by linkage studies^{46, 47}. A modest reduction of fat-induced leptin secretion may contribute to



weight gain⁴⁸. Polymorphisms within the 5' untranslated region of the human leptin gene were associated with a low leptin level⁴⁹ and with resistance to a low-calorie diet⁵⁰.

The peroxisome proliferator-activated receptor-gamma (PPAR γ) is a nuclear receptor that plays a key role in adipogenesis and which may lead to efficient energy storage⁵¹. A Pro12Ala variation in the PPAR γ gene is shown to be associated with improved insulin sensitivity⁵² and obesity⁵³.

Another approach to identify candidate gene is done by analysis of genome-wide scans in order to detect chromosomal regions showing linkage with obesity in large collections of nuclear families⁵⁴. To identify the gene variant associated with obesity, chromosomal regions of linkage should first be identified using a dense map of bi-allelic single-nucleotide polymorphisms (SNPs). Recently, in a meta-analysis of 32 genome-wide association studies for WHR adjusted for body mass index, 13 new loci has been identified in or near RSPO3, VEGFA, TBX15-WARS2, NFE2L3, GRB14, DNMT3-PIGC, ITPR2-SSPN, LY86, HOXC13, ADAMTS9, ZNRF3-KREMEN1, NISCH-STAB1 and CPEB4⁵⁵. SNPs of adrenoceptors (β 1, β 2 and β 3AR), uncoupling proteins (UCPs 1, 2, 3) and PPAR γ were the markers most frequently evaluated in several populations participating in short- and/or long-term intervention studies. The combined effect of UCP1 and β 3-adrenergic receptor SNPs was found to intensify weight gain in obese individuals during life time³³. The genetic factors (characterized by the combination of multiple allelic variations), environmental factors (diet, exercise, stress and hormones), socio-economical factors and the developmental stage of epigenetic events are the useful predictor that can judge the occurrence, development and maintenance of obesity.

TREATMENT OF OBESITY:

To modify the patient's lifestyle it is necessary to sustain an increase in physical activity and a decrease in food intake. The aim of behavioral therapy is to increase the patient's capacity of self control.

Based on clinical observations, two hypotheses were put forth to explain overeating:

1) Externality theory – A stimulus control which is conditioned to many external food cues (favorite food, time place, etc) beside internal stimuli (hunger)⁵⁶.

2) Obese eating style- It is a modification of act of eating, where eating quickly by taking large mouthfuls of food and fewer bites. There are also some behavioral techniques of obesity like stimulus control, making patient eat slowly, target setting, self-monitoring (recording weight, meal and target behavior), social support (family, friends, public health workers)⁵⁷.

Pharmacological treatment for patients is assessed at high risk and for those whose dietary and physical activity therapy has not been successful is commonly applied to many other chronic disease states treated by the primary care physician, including cholesterol lowering agents, anti-hypertensives, and antidiabetic drugs⁵⁸. According to the National Heart, Lung, and Blood Institute (NHLBI) guidelines on the identification, evaluation, and treatment of overweight and obesity in adults 1 and the US Food and Drug Administration (FDA), pharmacotherapy is indicated for: 1) obese patients with a BMI >30 or 2) overweight patients with a BMI >27 and obesity related risk factors or diseases, such as hypertension, diabetes, or dyslipidemia.

There involve 5 Potential Strategies for Anti-Obesity Drug Action^{59, 60}:

1) Reducing food intake: Either amplifies effects of signals/factors that inhibit food intake or block signals/factors that augment food intake.

2) Acting as appetite suppressants: Blocking nutrient absorption (especially fat or carbohydrates) in the intestine either by



stimulating norepinephrine release (e.g., phentermine, benzphetamine) or block its reuptake into neurons (e.g., mazindol).

3) Increasing thermogenesis: Either increase metabolism and dissipate food energy as heat or increase energy expenditure through the enhancement of physical activity.

4) Modulating fat metabolism/storage: Regulate fat synthesis/breakdown by making appropriate adjustments to food intake or energy expenditure.

5) Modulating the central regulation of body weight: Either alter the internal set point or modulate the signals regarding fat stores.

Body weight undergoes a negative feedback control, which involves peripheral and

central controllers act as a major role⁶⁰. In this system, the peripheral signals from adipose tissue, muscle and liver along with hormonal and gastrointestinal signal, provide inferences to the central controllers in the brain, indicating the state of the external and internal environment as they relate to food, metabolic rates, and activity behavior. The central controllers integrate all the signals and transduce these messages into efferent signals governing the behavioral search for the acquisition of food as well as modulating its subsequent deposition into energy storage compartments such as adipose tissue, liver, and muscle by modulating energy expenditure⁶⁰. Information about currently available drugs for treatment of obesity is given in table 3.

Table 3
Currently Available Agents Indicated for Treatment of Obesity⁵⁹:

Generic/Brand Name	Usual Dose	Mechanism of Action	Side Effects
Orlistat/Xenical	120 mg with each meal	Peripheral: Blocks absorption of about 30% of consumed fat	Gastrointestinal symptoms (oily spotting, flatus with discharge, fecal urgency, oily stools, incontinence)
Sibutramine/Meridia	5-15 mg/d	Central: Inhibits synaptic reuptake of norepinephrine and serotonin	Dry mouth, constipation, headache, insomnia, increased blood pressure, tachycardia
Phentermine/ Adipex, Fastin, Ionamin and others	15-37.5 mg per day as a single or split dose	Central: Stimulates release of norepinephrine	CNS stimulation, tachycardia, dry mouth, insomnia, palpitations

The anti obesity drugs affect appetite, metabolic rate, and/or inhibit caloric absorption, and generally fall into 3 broad classes:

1) Peripherally acting, 2) centrally acting, and 3) combination (i.e., central and peripheral acting).

Peripherally acting drugs mediate their effects by reducing the calorie absorption in the gastrointestinal system or by affecting metabolic and/or control systems outside the central nervous system (CNS). Currently, the only peripherally acting anti-obesity drug globally approved for long-term use is orlistat, a lipase inhibitor. Orlistat has been shown to reduce the

amount of ingested fat absorption by up to 30% in humans⁶¹.

Centrally acting drugs act on the CNS by 3 ways: catecholaminergic noradrenaline and dopamine (e.g., diethylpropion, ethamphetamine, phendimetrazine, and phentermine), 5-hydroxytryptamine (5HT) mediated, or combined (e.g., sibutramine)⁶². Satiety may be regulated through an effect on 5HT, noradrenaline (norepinephrine), or dopamine receptors in the hypothalamus, whereas energy expenditure may be increased directly by thermogenesis and lipolysis or through the stimulation of the



sympathetic nervous system. Sibutramine is the only centrally acting drug currently approved for long-term treatment of obesity in adults.

Rimonabant (Acomplia, Sanofi-Aventis, Paris, France) is a selective endocannabinoid (CB) 1 receptor antagonist that acts both centrally and peripherally to inhibit food intake and to regulate metabolic functions at diverse peripheral organs, including gut, liver, adipose tissue, and skeletal muscle^{63, 64}. Hence, these pharmacological drugs involve the above mentioned mechanisms and thus regulating the body weight.

CONCLUSION

The incidence of obesity and associated co-morbidities is dramatically increasing worldwide in both children and adults. Epidemiologic evidence of rising burden of obesity and associated pathologies has led, to a dramatic increase of research on the role of adipose tissue as an active participant in controlling the body's physiologic and pathologic processes. The current view of adipose tissue is that it acts

as an active secretory organ, sending out and responding to signals that modulate appetite, energy expenditure, insulin sensitivity, endocrine and reproductive systems, bone metabolism, and inflammation and immunity. Also the pattern of inheritance of obesity, suggest a complex mode of inheritance involving multiple genes. Linkage studies represents the best way of mapping genes with unanticipated effects on obesity phenotype and in future this study will increase the power and facilitate replication of existing linkage. It has also been reviewed about the pharmacological anti-obesity drugs that reduce food intake, that increase energy expenditure and drugs that affect nutrient partitioning or metabolism. All of these pharmacological approaches have potential efficacy, but unfortunately serious limitations. To overcome this limitation, the search for novel drug for treatments of obesity in childhood and adolescents is, therefore, both accredited and necessary. The universal prevention of obesity, thus aims to stabilize its level in the population, to reduce the incidence of new cases and, eventually, to reduce its prevalence.

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